CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761195Orig1s000

PRODUCT QUALITY REVIEW(S)

Regular Review

Recommendation: Approve

BLA/NDA Number: 761195
Assessment Number: 1
Assessment Date: Nov 15, 2021

Drug Name/Dosage Form	Vyvgart (efgartigimod alfa-fcab) injection
Strength/Potency	20mg/mL
Route of Administration	Intravenous infusion (IV)
Rx/OTC dispensed	Rx
Indication	For the treatment of generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor (AChR) antibody positive.
Applicant/Sponsor	argenx BV

Product Overview:

Vyvgart (efgartigimod alfa-fcab) is a human IgG1-derived Fc fragment targeting the neonatal Fc receptor (FcRn) and designed to compete with binding of circulating IgGs including IgG autoantibodies to the FcRn. When bound to the FcRn, efgartigimod blocks binding of IgG and inhibits the FcRn-mediated recycling of IgG, resulting in a shorter half-life of plasma IgG and, thus, lower plasma IgG levels. The efgartigimod alfa-fcab IgG1 amino acid sequence was engineered with the Abdeg™ mutations (M252Y, S254T, T256E, H433K, N434F) to increase affinity for the FcRn at both neutral and acidic pH, (b) (4)

Vyvgart drug product (DP) is a sterile, preservative-free solution supplied in a single-dose vial. Each DP vial contains 400 mg of efgartigimod alfa-fcab at a concentration of 20mg/mL formulated in a solution containing 25mM sodium phosphate, 100mM sodium chloride, 150mM L-arginine hydrochloride, and 0.02% polysorbate 80. The recommended dose of efgartigimod alfa-fcab is 10 mg/kg as a 1-hour intravenous infusion which would require the use of more than one vial, and up to three vials, per dose.

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Product Quality - Drug Substance	Sang Bong Lee	OPQ/OBP/DBRRIV
Product Quality - Drug Product	Ralph Bernstein	OPQ/OBP/DBRRIV
Labeling	James Barlow	OPQ/OBP
Immunogenicity Assay	Fred Mills	OPQ/OBP/DBRRIV
Facility	Wayne Seifert	OPQ/OPMA/DBM/BI
Microbiology- Drug Substance	Wendy Tan	OPQ/OPMA/DBM/BI
Microbiology- Drug Product	Wayne Seifert	OPQ/OPMA/DBM/BI
Team Leads	Chana Fuchs (product quality) Maxwell Van Tassel (microbiology) Zhong Li (facilities)	OPQ/OBP/DBRRIV OPQ/OPMA/DBM/BI OPQ/OPMA/DBM/BI
Application Team Lead	Chana Fuchs	OPQ/OBP/DBRRIV
RBPM	Kristine Leahy	OPQ/OPRO

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	Michael Matthews	OND/ORO/DRO-N
Cross-disciplinary Team Lead	Laura Jawidzik	OND/ON/DN1

Medical Officer	Rainer Paine	OND/ON/DN1
Non clinical	Barbara Wilcox	OND/ON/DPT-N
Clinical Pharmacology	Gopichand Gottipati Jie Liu Hobart Rogers	OTS/OCP/DNP
DRISK Team Lead	Jacqueline Sheppard	
Medication Error	Celeste Karpow Carlos Mena-Grillasca Beverly Weitzman	OSE/OSE/OMEPRM/DMEPA
Labeling	Tracy Peters	

1. Names:
   a. Proprietary Name: Vyvgart
   b. Trade Name: Vyvgart
   c. Non-Proprietary Name/USAN: Efgartigimod alfa-fcab
   d. CAS registry number: 1821402-21-4
   e. INN Name: Efgartigimod alfa
   f. Other names: ARGX-113, human recombinant immunoglobulin G1 Abdeg™ Fc fragment.
   g. OBP systematic name: MAB FRAG HUMAN (IGG1) ANTI P55899(FCGRN_HUMAN) [ARGX113].

Submissions Assessed:

Submission(s) Assessed	Document Date
eCTD 0002	27 Nov 2020
eCTD 0003	17 Dec 2020
eCTD 0004	18 Dec 2021
eCTD 0007	16 Feb 2021
eCTD 0008	17 Feb 2021
eCTD 0009	26 Feb 2021
eCTD 0010	12 Mar 2021
eCTD 0012	16 Apr 2021
eCTD 0015	23 Jun 2021
eCTD 0022	25 Aug 2021
eCTD 0027	21 Sep 2021
eCTD 0028	27 Sep 2021
eCTD 0029	29 Sep 2021
eCTD 0033	20 Oct 2021
eCTD 0036	17 Nov 2021
eCTD 0037	26 Nov 2021
eCTD 0039	30 Nov 2021
eCTD 0040	9 Dec 2021
eCTD 0041	10 dec 2021
eCTD 0042	13 Dec 2021
eCTD 0043	13 Dec 2021
eCTD 0044	15 Dec 2021
E-mail Response to Information Request (b) (4)	8 Nov 2021
E-mail Response to Information Request (b) (4))	17 Nov 2021

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

Quality Assessment Data Sheet:

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:
   A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code [1]	Status[2]	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	3			
	III			3			
				1	Adequate	03/02/2020	
	V			1			Document reference D029391M05R01.docx
	V			1	Adequate (with information request re products)		
				2			Previously reviewed for a different product.

1. Action codes for DMF Table: 1- DMF Assessed; Other codes indicate why the DMF was not assessed, as follows: 2- Assessed previously and no revision since last assessment; **3- Sufficient information in application;** 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")
2. Action codes for Status column: Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be assessed.

   B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description
IND	132953	Parent IND

3. Consults: None

4. Environmental Assessment of Claim of Categorical Exclusion:
   argenx BV claimed a categorical exclusion from the requirement to prepare and submit an environmental assessment for this BLA in compliance with the categorical exclusion criteria 21 CFR Part 25.31(c). argenx BV claims that it is not aware of any extraordinary circumstance that would require additional environmental assessment per 21 CFR 25.31.
   The claim of a categorical exclusion is accepted.

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality (OPQ), CDER recommends approval of STN 761195 for Vyvgart (efgartigimod alfa–fcab) manufactured by argenx BV. The data submitted in this application are adequate to support the conclusion that the manufacture of Vyvgart 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 location:
  - Drug Substance (DS): (b) (4)
  - Drug Product (DP): (b) (4)
- Fill size and dosage form
  400 mg/20 mL single-dose vial (20 mg/mL)
- Dating period:
  - Drug Product: 36 months at 5 ±3°C, protected from light
  - Drug Substance: (b) (4)
  - Stability Option:
    a. We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12
    b. Results of ongoing stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.
- Exempt from lot release:
  - Yes: Vyvgart is exempted from lot release per FR 95-29960 and 21 CFR 610.2(b).

C. Benefit/Risk Considerations:

The assessment of manufacturing information provided in the application and in the cross-referenced master files (MF) 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 manufacturing processes are robust for removal and control of adventitious agents. No approvability issues were identified from a sterility assurance or microbiology product quality perspective. Manufacturing of the drug substance and drug product, and quality control testing will be performed as summarized in Summary of Quality Assessments of this document below.

In lieu of on-site pre-licensing inspections (PLI) for the DS manufacturing facility, (b) (4) and the release and stability testing facility (b) (4) a review of requested manufacturing site records under Section 704(a)(4) was conducted by OPQ.
A PLI waiver was granted for the DP manufacturing facility, (b) (4) based on its currently acceptable CGMP compliance status and recent relevant inspectional coverage. All facilities used for the manufacture and quality control testing are summarized in Sections E and F of this document.

The OBP DS and DP product quality, OPMA facility, microbiological DS and DP, as well as OBP labeling technical assessments are located as separate documents in Panorama.

Glycosylation of efgartigimod alpha is not controlled through testing and applicant states that glycosylation is not a CQA based on no impact to FcRn binding. However, a molecule of 53kD is too large for renal clearance when intact (cutoff for renal clearance is $\leq$25kD) and therefore, barring other information, it should be assumed that efgartigimod alpha would clear by similar mechanisms as an intact IgG1 for which Fc glycosylation is known to impact PK, such as sialic acid levels and high mannose structures. Therefore, glycosylation should be considered a CQA. Efgartigimod product quality has shown consistency through its manufacturing history, and with manufacturing controls identified in the BLA glycosylation levels should not change in a manner that would impact PK. For future manufacturing changes in the upstream process an analysis of glycoforms as part of comparability should be required.

The immunogenicity assays are sufficiently sensitive to detect anti-drug antibodies (ADA) in presence of efgartigimod alpha at plasma concentrations, however this was not the case for the assay to detect neutralizing antibodies. The immunogenicity assay review is located as separate document in Panorama

D. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable: none

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Tables 1 and 2, below, summarize the critical quality attributes and their control strategy that are relevant specifically to the API and Drug Substance. For additional information, see the OBP drug substance quality technical assessment and the Drug Substance Microbiology technical assessment in Panorama.
Table 1 is a summary of product-related critical quality attributes (CQA), intrinsic to the molecule, that are relevant to the 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)	Risk	Origin	Control Strategy	Other
FcRn binding (potency)	Potency, Efficacy	Intrinsic to the Molecule	(b) (4)	Assay is by competition ELISA
Identity	Efficacy and safety	Intrinsic to the molecule		(by icIEF and competition ELISA)
High Molecular Weight Species (product related impurities)	Efficacy, PK and safety (Immunogenicity)	Manufacturing process, storage and exposure to heat, low pH, and photo stresses		May have an increased affinity to FcRn, mostly through avidity effects, and could trigger FcRn clustering resulting in increased side-effects, shorter PK, and reduced efficacy
Low Molecular Weight Species (product related impurities)	Efficacy and safety (immunogenicity due to new epitope exposures)	Manufacturing process, storage and exposure to heat, low pH, reduction, and photo stresses		Reduced species (single Fc) are dominant LMW species.
Charge variants: Acidic charge variants	efficacy, PK and safety including immunogenicity	Manufacturing process, storage and exposure to heat, low pH, and photo stresses		(b) (4)
Basic charge variants	efficacy, PK and safety including immunogenicity	Manufacturing process, storage and exposure to heat and low pH		
(b) (4) (product related impurity)	efficacy and immunogenicity	Cell line (b) (4		
Glycoform distribution (possible CQA, though identified as non-CQA by applicant)	Potential impact on clearance/PK	Post-translational modification during upstream cell culture.		Glycosylation is not required for FcRn binding. For IgGs - high mannose and sialic acid levels on the Fc impact clearance through specific receptors. It is not clear if/how much these impacts clearance of an IgG Fc fragment
The following were identified as NON-CQAs Based on investigation by the applicant				
Disulfide structure	Potential impact on immunogenicity, efficacy and PK	Intrinsic to the molecule.	(b) (4)	No disulfide bond scrambling

		Manufacturing process (b) (4)		observed for this product
Deamidation (product variant)	Potential impact on efficacy	Upstream cell culture. Manufacturing process, storage and exposure to heat, low pH, and photo stresses	(b) (4)	No impact on FcRn binding
Aspartate (b) (4) isomerization (product variant)	Potential impact on efficacy	Intrinsic to the molecule. Manufacturing process		No changes in (b) (4) isomerization by forced degradation including temperature and pH
Oxidation	Potential impact on efficacy	(b) (4)		100% oxidation showed 80% of potency (low impact on potency)
N-terminal deleted variants (product variant)	Potential impact on efficacy			No impact on FcRn binding
Glycation (product variant)	Potential impact on efficacy	Upstream manufacturing process		No impact on FcRn binding
Effector functions	Safety	Intrinsic to the Molecule		Studies showed no NK cell activation and no cytokine release

- Efgartigimod is a recombinant human IgG1-derived Fc fragment and is composed of 2 identical 227 amino acid heavy chains consisting of the hinge, CH2 and CH3 domains, held together by two interchain disulfide bonds. The IgG1 amino acid sequence has been modified with the Abdeg™ mutations (M252Y, S254T, T256E, H433K, N434F) to increase affinity for FcRn at neutral pH and pH 6.0.

(b) (4) The mass of efgartigimod alpha is 53,915 Da (b) (4) .

Typically for an IgG1 certain quality attributes are usually known CQAs associated with the Fc portion of the molecule. Since efgartigimod alpha is an Fc component of an IgG1, those CQAs associated with IgG1 but identified as non-CQAs for efgartigimod alpha are listed in table 1, above. These were identified as non-CQAs based on studies provided by the applicant.

- **Mechanism of Action (MoA):** efgartigimod binds to the neonatal Fc receptor (FcRn) with increased affinity compared to circulating IgGs resulting 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)

- **Potency Assay:** This assay 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. With the assay format used, absorbance readout is inversely proportional to the concentration of bound efgartigimod. Relative potency is calculated through the comparison of the test sample IC_{50} to the reference standard IC_{50}.

- **Reference Materials:** A two-tiered reference material (RM) system was developed. (b) (4)

- **Critical starting materials or intermediates**: (b) (4)

The long-term stability of MCB and WCB will be assessed per protocol provided in the BLA. A protocol for generation and qualification of future WCBs was included in the BLA.

- **Manufacturing process summary:** (b) (4)

(b) (4)

- **Container closure:** (b) (4)

- **Dating period and storage conditions:** Efgartigimod alpha (b) (4) drug substance is stored (b) (4) A stability protocol is included in the BLA for the purpose of extending shelf life

Table 2: (b) (4) Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management.

CQA (type)	Risk	Origin	Control Strategy	Other
Host Cell DNA	Safety	Production cell viability and viable cell density during upstream cell culture and harvest	(b) (4)	

Host Cell Proteins (HCP)	Safety (immunogenicity)	Production cell viability and viable cell density during upstream cell culture and harvest	(b) (4)	(b) (4)
(b) (4)	Safety (Immunogenicity)	(b) (4)		
(b) (4)	Safety	Component of production bioreactor medium during production cell culture		
(b) (4)	Safety	Component of nutrient feed during production cell culture		
(b) (4)	Safety	Component of cell culture		
Extractables/ Leachables	Safety, product purity and stability (safety and efficacy)	Raw materials, product-contacting equipment and materials including container closure system		
Elemental Impurities	Safety	Trace level components of (b) (4)		

Virus (Adventitious and endogenous)	Safety	Raw material, cell banks. Contamination may be introduced during the DS manufacturing process.	(b) (4)	
Mycoplasma	Safety	Raw materials, contamination may be introduced during the upstream manufacturing process		
Endotoxin (contaminant)	Safety	Raw materials and manufacturing process		
Bioburden	Safety and purity	Raw materials, contamination may be introduced during the DS manufacturing process		
Color (Appearance)	Stability	Variability can be caused by purity of the protein, formulation excipients and protein concentration		
Clarity/turbidity (Opalescence) (Appearance)	Safety and immunogenicity	Intrinsic to the molecule and protein purity, formulation components		
Protein concentration	Efficacy	Formulation (b) (4)		Same protein concentration for DS and DP
pH	Efficacy and stability	Formulation components and manufacturing process		No change during stability study (6.6-6.8)
(b) (4)	Efficacy and safety (Product quality on Stability)	(b) (4) raw material quality, product purity, and manufacturing process		(b) (4)
Osmolality	Efficacy and safety derived through Product quality on Stability	Composition of the formulation		

B. Drug Product [VYVGART] Quality Summary:

CQA Identification, Risk, and Lifecycle Knowledge Management

Table 3, below, 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. For additional information, see the OBP drug product quality technical assessment and the Drug Product Microbiology technical assessment in Panorama.

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

CQA (type)	Risk	Origin	Control Strategy	Other
Sterility (contaminant)	Safety, purity and efficacy	Contamination may be introduced during the DP manufacturing process, or from failure of container closure integrity	(b) (4)	
Endotoxin (contaminant)	Safety, Purity, and Immunogenicity	Raw materials, contamination may be introduced during the DP manufacturing process		For the PPQ lots this was also tested by rabbit pyrogen test.
Container closure integrity	Safety (maintenance of sterility during shelf life)	Storage conditions		
Osmolality	stability	Determined by formulation (osmolality is a surrogate test for excipient levels)		
Extractable volume	Efficacy/dosing	Manufacturing process of the drug product		
Protein Concentration (general)	Efficacy and Safety	(b) (		
Appearance - Visible Particulates (product or process related impurities)	Safety and immunogenicity.	Intrinsic –DS and DP Manufacturing processes, formulation, interaction with the container closure system Extrinsic –manufacturing contact material and container closure components		
Subvisible Particulate Matter (product or process related impurities)	Safety and Immunogenicity	Manufacturing process and CCS. Could be product or foreign particles.		

Appearance - Color of solution (general)	Safety and Efficacy	Formulation, contamination or degradation	(b) (4)	
Polysorbate 80 (general/critical excipient)	Safety and Efficacy	(b) (4)		
Leachables (Process-related impurities)	Safety	Manufacturing equipment and CCS		
pH (General)	Efficacy and Stability	(b) (4) Formulation and interaction with container closure components		N/A
Identity (general)	Safety and Efficacy	Intrinsic to molecule		

- Potency and Strength: 400mg efgartigimod alfa-fcab solution in 20mL (20mg/mL) in a (b) (4) single dose vial.

- Summary of Product Design:
  Efgartigimod alfa-fcab drug product is sterile, non-pyrogenic, and does not include the addition of an anti-microbial preservative, with the drug product (b) (4) filled into 20mL sterile glass vials that are sealed with a sterile stopper and aluminum seal. VYVGART (efgartigimod alfa-fcab) is designed to be diluted in 0.9% Sodium Chloride injection USP to make a total volume of 125mL for administered by IV infusion. The amount of VYVGART to be diluted to the final 125mL is based on patient weight for a final dosage of 10mg/kg, with a maximum of 1200 mg per infusion, requiring use of multiple vials (up to 3) of VYVGART per administration.

- List of Excipients: Each mL of efgartigimod alpha-fcab contains the following excipients:
  - L-arginine hydrochloride - 31.6 mg
  - Polysorbate 80 - 0.2 mg
  - Sodium chloride - 5.8 mg/mL,
  - Sodium phosphate dibasic anhydrous - 2.4 mg
  - Sodium phosphate monobasic monohydrate - 1.1 mg
  - Water for injection, USP

- Reference Materials: the reference material used for release of efgartigimod alpha-fcab drug product is the same as is used for drug substance.

- Manufacturing process summary:
  (b) (4)

(b) (4)

Container closure: Efgartigimod alpha-fcab drug product is filled into a (b) (4) (20 mL) clear glass vial that is stoppered with a (b) (4) 20 mm (b) (4) Gray (b) (4) rubber stopper, with the stopper vial sealed with an aluminum crimp seal with a temper evident white (b) (4) flip-off cap. The vials are placed into a secondary cardboard container to protect from physical damage and light.

- **Dating period and storage conditions:** 36 months when stored at 5 ±3°C. A stability protocol in the BLA would allow extension of expiration for up to 60 months based on additional stability data.

- **Endotoxin** - during process validation, low endotoxin recovery (LER) was identified when using the turbidimetric-kinetic method per <USP 85>. The PPQ batches intended for commercial use were tested according to this method. For DP batches manufactured from 2021 onwards, the test method will be the LAL chromogenic-kinetic method in accordance with USP <85>. The manufactured PPQ lots that were tested using the turbidimetric-kinetic method were also tested by the rabbit pyrogen test which supported absence of pyrogens in these lots.

C. Novel Approaches/Precedents:

Use of authority under Section 704(a)(4) to request records in lieu of performing on-site pre-license inspections from the (b) (4) DS manufacturing facilities (b) (4) and the (b) (4) testing facility (b) (4) Refer to the FDA Staff Manual Guide SMG 9004.1, *Policy and Procedures for Requesting Records in Advance of or in Lieu of a Drug Inspection.*

Rationale:

Sec. 704 (a)(4) (FDASIA Sec. 706) records request for (b) (4) was initiated due to travel restrictions during COVID19 pandemic. This was deemed possible based on satisfactory inspectional history of this site, the similarity of the manufacturing process for efgartigimod alpha to other licensed products manufactured at this site an in the same manufacturing suites. This review was conducted by the OBP and OPMA reviewers of the BLA.

Sec. 704 (a)(4) (FDASIA Sec. 706) records request for (b) (4) was initiated due to travel restrictions during COVID19 pandemic. Although this release and stability testing site had no FDA inspectional history this was deemed possible based on an inspection by

(b) (4) report supportive of FDA assessment using a 704(a)(4). This review was conducted by the OBP reviewers of the BLA and by ORA.

D. Any Special Product Quality Labeling Recommendations:

- Store vials refrigerated at 2°C to 8°C in the original carton
- Do not freeze
- Do not shake
- Prior to administration, vials should be inspected for appearance. Solution should be clear to slightly opalescent and colorless to slightly yellow and free of visible particles.
- Vials are for single-dose only, discard unused portion of the vial.
- Dilution in infusion bag:
  - Diluted in 0.9% Sodium Chloride Injection USP.
  - Diluted solution may be stored at 2°C to 8°C for up to 8 hours, or up to 4 hours at ambient temperature.
  - Protect from light.
  - administer using polyethylene (PE), polyvinyl chloride (PVC), ethylene vinyl acetate (EVA), or ethylene/polypropylene copolymer bags (polyolefins bags), and with PE, PVC, EVA, or polyurethane/polypropylene infusion lines.

E. Establishment Information:

Overall Recommendation: Approve					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
• DS manufacturing and in-process testing, • DS release and stability testing [1] • Creation and storage of master and working cell banks	(b) (4)		Inspection required. .	704 (a) (4) assessment/inspection conducted with a conclusion of adequate.	Approval
DS release and stability testing[1]			Inspection required.	704 (a) (4) assessment/inspection conducted with a conclusion of adequate	Approval
DS release and stability testing[1]			Approve- based on profile	Not Applicable	Approval
Mycoplasma and adventitious agents testing on the			Approve- based on profile	Not Applicable	Approval

unprocessed bulk	(b) (4)				
Storage of master and working cell banks			No evaluation needed.	Not Applicable	Approval

DRUG PRODUCT

Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DP manufacturing including primary packaging and visual inspection. QC testing.[2]	(b) (4)		Approve based on district office recommendation, with facility inspection waived.	Not Applicable	Approval
DP visual inspection and QC testing.[2]			Approve based on file review.	Not Applicable	Approval
DP visual inspection and secondary packaging. QC testing.[2]			Approve based on profile.	Not Applicable	Approval
Visual inspection and CCIT for stability samples.			Approve based on profile.	Not Applicable	Approval
DP Release and stability testing.			Inspection required as supported by alternative inspection tool.	704 (a) (4) assessment/inspection conducted with a conclusion of adequate.	Approval
DP release and stability testing.			Approve based on profile.	Not Applicable	Approval
DP release and stability testing.			Inspection required as supported by alternative inspection tool.	704 (a) (4) assessment/inspection conducted with a conclusion of adequate.	Approval
Secondary packaging.			No evaluation necessary.	Not Applicable	Approval

Rabbit pyrogen testing.	(b) (4)		Approve based on profile.	Not Applicable	Approval
Final disposition.	argenx BV, Belgium	FEI: 301510202398	No evaluation necessary.	Not Applicable	Approval

1 DS release testing:
(b) (4) bioburden, endotoxin, pH, clarity, color, concentration, potency, identity (ELISA and icIEF), rCE-SDS, nrCE-SDS, GP-HPLC, HIC, icIEF, DNA, (b) (4), HCP.

- Quality Assistance– pH, clarity, color, concentration, potency, identity (ELISA and icIEF), rCE-SDS, nrCE-SDS, GP-HPLC, HIC, icIEF, (b) (4)
- (b) (4) pH, clarity, color, concentration, potency, identity (ELISA and icIEF), rCE-SDS, nrCE-SDS, GP-HPLC, HIC, icIEF, (b) (4)

2 In-process testing, release and stability testing and identity testing.
DP release testing for assays used for both DS and DP are done as iden tified for the DS release testing sites. Tests specific to DP are done as follows:
(b) (4) color, clarity, pH, osmolality, extractable volume, visible particles, subvisible particles
Quality Assurance: color, clarity, pH, osmolality, extractable volume, visible particles, subvisible particles
(b) (4) pH,
(b) (4) CCIT
(b) (4) endotoxin, sterility

F. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for (b) (4) DS and DP manufacture, respectively.

Inspection of the DP manufacturing facility, (b) (4) was waived based on the firm's compliance history, current acceptable cGMP status, and the (b) (4) manufacture of other licensed sterile biologic products manufactured by the same process and on the same fill line as Vyvgart.

Due to travel restrictions during COVID19 pandemic, for this BLA, the use of authority under Section 704(a)(4) to request records in lieu of performing on-site pre-license inspections from (b) (4) DS manufacturing facility (b) (4) and the (b) (4) testing facility (b) (4) was implemented based on inspectional histories. For the DS manufacturing facility, (b) (4), this was deemed possible based on satisfactory inspectional history of this site, and the similarity of the manufacturing process for efgartigimod alpha to other licensed products manufactured in the same manufacturing suites. This 704(a)(4) records review was conducted by the OBP and OPMA reviewers of the BLA. For the release and stability testing site, (b) (4) a 704(a)(4) records review was deemed possible based on an inspection by (b) (4) supportive of FDA assessment using a 704(a)(4). This review was conducted by the OBP reviewer of the BLA and by ORA.

All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. This submission is recommended for approval from a facility standpoint.

G. Lifecycle Knowledge Management:

i. Protocols approved:

eCTD Section	Protocol	Brief Summary	Reporting Category
3.2.S.2.2.2.8.1	Reprocessing of: (b) (4)	(b) (4)	CBE-30 Stability data will be reported in the annual report.
3.2.S.2.3.4.9	Protocol for Generation and Characterization of Future Working Cell Banks	Describes criteria and testing when making new working cell banks.	Annual report
3.2.S.2.5 –	Concurrent lifetime validation of (b) (4)	Concurrent validation (b) (4)	Annual report (b) (4)
3.2.S.2.3.3.4.9	Requalification/stability of current primary reference standard	Describes the long-term stability program for the current primary reference standard to demonstrate its stability.	Annual report
	Requalification/stability of current working reference standard	Describes the long-term stability program for the current working reference standard to demonstrate its stability.	Annual Report
3.2.S.5 –	Preparation and qualification of future working reference standard	Describes the release and characterization testing for the future working reference standard.	Annual Report
3.2.S.5 –	Requalification/stability of future working reference standard	Describes the release and characterization testing for the future primary reference standard.	Annual report
3.2.S.7.2 –	Ongoing stability protocol for DS	Long-term (b) (4) and accelerated condition (b) (4) stability studies (b) (4) per specifications listed in 3.2.S.4.1.	Annual report
3.2.S.7.2 –	Annual stability protocol for DS	Long-term (b) (4) and accelerated condition (b) (4) stability studies (b) (4) for one selected batch per year of manufacture per specifications listed in 3.2.S.4.1.	Annual Report

3.2.S.7.2	Ongoing stability protocol for DP	Long-term (5 ± 3°C)) per specifications listed in 3.2.S.4.1.	Annual report
3.2.P.8.2	Annual stability protocol for DP	Long-term (5 ± 3°C) stability study for one commercial batch per year, if production takes place.	Annual Report

ii. Commitments in the BLA

eCTD Section	commitment	Brief Summary	Reporting Category
3.2.S.2.2 (And response to IR3 from 13Dec21)	Commitment to establish definitive control limits after a total of at least 50 batches have been manufactured.	(b) (4) . Applicant will establish definitive control limits after a total of at least 50 batches have been manufactured.	Annual report
3.2.S.2.2	Commitment for stability study of DS batches resulting from reprocessing events	Reprocessing protocols are included as identified in the table above. A commitment is included to place DS batches resulting from reprocessing events on stability per S.7.2 as defined in the reprocessing procedure/protocol	Annual report
3.2.S.2.3.3.4.9	Generation of Future Working Cell Banks	In addition to the specific protocol, in this section applicant committed to place every first efgartigimod drug substance batch manufactured using a new WCB on stability.	Annual report
3.2.S.4.3 (And response to IR2 from 13Dec21)	Potency (b) (4)) validation of stability capabilities (b) (4)	Assess the stability-indicating capability of the potency assay (b) (4) with additional testing of a temperature-stressed sample.	Annual report
3.2.S.7.2	To continue ongoing DS stability studies until completion	For PPQ and other supporting lots on stability, per BLA protocol	Annual report
3.2.S.7.2	To place one selected DS batch per year of manufacture on stability at (b) (4) and at accelerated condition (b) (4)	Confirmation stability study to detect unanticipated changes from manufacturing	Annual report
3.2.P.3.4 (And response to IR2 from 10Dec21)	cumulative ambient hold time processing study	To perform a cumulative ambient hold/processing study whereby a batch will be exposed to ambient temperature conditions (b) (4) for a total duration of ≥250 hours followed by a long-term stability study starting with a batch manufactured in Q1, 2022	Annual report

3.2.P.8.2	To continue ongoing DP stability studies until completion	For PPQ and other supporting lots on stability, through 60 months	Annual report
3.2.P.8.2	To place one selected DP batch per year of manufacture on stability at +5 ± 3°C	Confirmation stability study required by the regulations. To detect unanticipated changes.	Annual report
3.2.P.2.4.4.2.2	Leachables study on drug product (DP) container closure (CC).	Applicant will provide DP Leachable study results for up to 60 months.	Annual report

iii. Outstanding assessment issues/residual risk: none

iv. Future inspection points to consider:

a. For future inspection at (b) (4) – assess the activities when process exceeds the acceptable ranges/limits identified in section 3.2.S.2.2. Rejection limits have not been defined, since edges of failure were not explored for CPPs during process characterization. If the corresponding parameters (both CPPs and non-CPPs) are not within the acceptable range/limit, a deviation record is raised in the (b) (4) quality system. However, it is not clear how these are addressed considering the lack of knowledge of what is the range of failure for CPPs. Note that for this BLA assessment of the facility was done through a 704(a) document review.

Quality Assessment Summary Tables

Table 1: Noteworthy Elements of the Application

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

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/s/

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12/16/2021 09:34:46 AM

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