CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761235Orig1s000

PRODUCT QUALITY REVIEW(S)

Priority Review (Rare Pediatric Disease Priority Review Voucher)

Recommendation: Approval

BLA Number: 761235
Assessment Number: 1
Assessment Date: December 8, 2021

Drug Name/Dosage Form	VABYSMO (faricimab-svoa) injection
Strength/Potency	6 mg/0.05 mL[1] solution in a single-dose vial (120 mg/mL)
Route of Administration	Intravitreal injection
Rx/OTC dispensed	Rx
Indication	Neovascular (Wet) Age-Related Macular Degeneration (nAMD), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR)
Applicant/Sponsor	Genentech, Inc.

Product Overview:

VABYSMO (faricimab-svoa) is a recombinant humanized IgG1 bispecific antibody produced in a Chinese Hamster Ovary (CHO) cell line. The antibody selectively binds vascular endothelial growth factor A (VEGF-A) with one arm and angiopoetin-2 (Ang-2) with the other arm, thereby preventing the interactions of these two angiogenic factors with their respective receptors and blocking the modulation of downstream signaling pathways.

VABYSMO (faricimab-svoa) injection is a sterile, preservative-free, clear to opalescent, colorless to brownish-yellow solution in a single-dose glass vial for intravitreal administration. Each vial is designed to deliver 0.05 mL of solution containing 6 mg faricimab-svoa. A 5 µm transfer filter needle is co-packaged with faricimab-svoa drug product and intended for mandatory use for dose preparation. The needle (b) (4) 18 G 1 x 1/2" stainless steel transfer filter needle 5 µm; filter material: (b) (4)) is a class I 510(k)-exempt medical device (b) (4)

Quality Assessment Team:

Discipline	Assessor	Branch / Division
Drug Substance	Dilip Devineni	OBP/DBRRIII
Drug Product	Dilip Devineni	OBP/DBRRIII
Immunogenicity	Mohanraj Manangeeswaran / Daniela Verthelyi	OBP/DBRRIII
Labeling	Jennifer Kim	OBP/IO
Facility	Michael Shanks	OPMA/DBM
Microbiology	Maria Gutierrez-Hoffman	OPMA/DBM
OPMA Team Lead	Madushini Dharmasena	OPMA/DBM
RBPM	Rabiya Haider	OPRO/DRBPMI
Application Team Lead	Nailing Zhang	OBP/DBRRIII
Review Chief	Maria-Teresa Gutierrez-Lugo	OBP/DBRRIII

[1] Expression of strength is under discussion with other disciplines, including OPPQ, DMEPA, OTBB and OBP.

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	Wendy Streight	OND/ORO/DROSM
Signatory Authority	Wiley Chambers	OND/OSM/DO
Cross-disciplinary Team Lead	William Boyd	OND/OSM/DO
Medical Officer	Lucious Lim	OND/OSM/DO
Pharmacology/Toxicology	Maria Rivera	OND/ORDPURM/DPTRDPURM
Clinical Pharmacology	Nisha Kwatra	OTS/OCP/DIIP
Statistics	Solomon Chefo	OTS/OB/DBIV

1. Names:

a. Proprietary Name: VABYSMO
b. Trade Name: VABYSMO™
c. Non-Proprietary Name/USAN: Faricimab-svoa
d. CAS Name: 1607793-29-2
e. Common Name: RO6867461 (company code)
f. INN Name: Faricimab-svoa
g. Compendial Name: Not applicable
h. OBP systematic name: BSMAB: MAB HUMANIZED (IGG1) ANTI P15692 (VEGFA_HUMAN) & ANTI O15123 (ANGP2_HUMAN) [RO6867461]

Submissions Assessed:

Submission(s) Assessed	Document Date
STN 761235/SN 0001 (original submission)	05/28/2021
STN 761235/SN 0004 (Response to OPMA IR)	07/14/2021
STN 761235/SN 0007 (Response to OBP IR)	08/20/2021
STN 761235/SN 0012 (Response to OBP IR)	10/27/2021
STN 761235/SN 0013 (Response to OPMA IR)	11/03/2021
STN 761235/SN 0014 (Response to OPMA IR)	11/19/2021
STN 761235/SN 0016 (Response to OBP IR)	11/24/2021
STN 761235/SN 0017 (Response to OPMA IR)	11/24/2021
STN 761235/SN 0018 (Response to OBP IR)	11/26/2021
STN 761235/SN 0019 (Response to OBP and OPMA IR)	12/01/2021
STN 761235/SN 0020 (Response to OBP and OPMA IR)	12/03/2021
STN 761235/SN 0021 (Response to OBP IR)	12/07/2021

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.

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	N/A	N/A	None
	V			3	N/A	N/A	None
	III			3	N/A	N/A	None

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 are 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	119225	Faricimab (RO6867461)

3. Consults: None.

4. Environmental Assessment of Claim of Categorical Exclusion: A categorical exclusion is claimed from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31(c). The claim of categorical exemption is accepted.

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: **Approval**

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761235 for VABYSMO (faricimab-svoa) manufactured by Genentech, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of VABYSMO (faricimab-svoa) 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: Roche Diagnostics GmbH, Nonnenwald 2, 82377 Penzberg, Germany (FEI: 3002806560)
  - Drug Product: F. Hoffmann-La Roche Ltd, Wurmisweg, CH-4303 Kaiseraugst, Switzerland (FEI: 3003973536)
- Fill size and dosage form: 6 mg/0.05 mL[1] (120 mg/mL) single-dose vial
- Dating period:
  - Drug Product: 30 months: 2°C - 8°C, protected from light
  - Drug Substance: (b) (4) months: (b) (4) (b) (4)
  - For packaged products:
    - VABYSMO drug product vial: 30 months: 2°C - 8°C, protected from light
    - Transfer filter needle (b) (4) storage temperature not specified. (The expiry of the combination product would be limited by the expiry of the drug product.)
  - For stability protocols:
    - We have approved the stability protocol(s) 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: Yes
  Note: VABYSMO is exempted from lot release per FR 95-29960.

[1] Expression of strength is under discussion with other disciplines, including OPPQ, DMEPA, OTBB and OBP.

C. Benefit/Risk Considerations:

VABYSMO (faricimab-svoa) is intended for use in patients with neovascular (wet) age-related macular degeneration (nAMD), diabetic macular edema (DME) and diabetic retinopathy (DR). The information provided in the application demonstrates that the methodologies and processes used for the drug substance (DS) and drug product (DP) manufacturing, release and stability testing are robust and sufficiently controlled to lead to a product that is safe, pure and potent. The overall control strategy for VABYSMO (faricimab-svoa) manufacture incorporates control over raw materials, facilities and equipment, the manufacturing process, and adventitious agents. The manufacturing control strategy coupled with in-process controls, release and stability testing ensures process consistency, and DS and DP that have appropriate quality and are free of adventitious agents.

No approvability issues were identified from a sterility assurance or microbiology product quality perspective. All facilities used for the manufacture and quality control testing were found acceptable for the proposed operations. In lieu of on-site pre-licensing inspections (PLI) for the DS manufacturing facility, Roche Diagnostics GmbH (Penzberg, Germany), a review of requested manufacturing site records under Section 704(a)(4) was conducted and found satisfactory. A PLI waiver was granted for the DP manufacturing facility, F. Hoffmann-La Roche Ltd. (Kaiseraugst, Switzerland), based on its currently acceptable cGMP compliance status and recent relevant inspectional coverage.

The immunogenicity assays are sufficiently sensitive to detect anti-drug antibodies (ADA) in presence of VABYSMO (faricimab-svoa) at concentrations presented in the patient samples. ADAs were not assessed for neutralizing activity. The immunogenicity assays assessment team concluded that neutralizing antibody analysis was not necessary for approval of the BLA because the antibodies are unlikely to neutralize the activity of the product in the intraocular space and there was no observation of effect of ADA positivity on safety or efficacy.

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

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

CQA (type)	Risk	Origin	Control Strategy	Other
Identity by Lys-C Peptide Mapping (identity)	Safety and efficacy	Intrinsic to molecule	(b) (4)	n/a

Anti-Ang2 Potency by Tie-2 Phosphorylation Assay (potency)	Safety and efficacy	Intrinsic to molecule, in-process, and on stability	(b) (4)	(b) (4)
Anti-VEGF-A Potency by VEGF-Reporter Gene Assay (potency)	Safety and efficacy	Intrinsic to molecule, in-process, and on stability		n/a
Appearance (Color, Clarity/Opalescence) (general)	Safety and efficacy	Formulation, contamination, or degradation		n/a
Protein Content (general)	Safety and efficacy	In-process and formulation		n/a
pH (general)	Safety and efficacy	Formulation		n/a
Osmolality (general)	Safety and efficacy	Formulation		n/a
(b) (4) (general)	Safety and efficacy	Intrinsic to formulation and on stability		n/a
Excipient Content (general)	Safety and efficacy	Formulation		n/a
(b) (4) (product related impurity)	Bioactivity, PK, immunogenicity, and safety	Fermentation, in-process, and on stability		n/a
(b) (4) (product related impurity)	Bioactivity and PK	Fermentation, in-process, and on stability		n/a
(b) (4) (product related impurities and substances)	Safety and efficacy	Fermentation, in-process, and on stability		n/a
(b) (4) (product related impurity)	Bioactivity	Fermentation, in-process, and on stability		n/a

(b) (4) (product related impurity)	Bioactivity	Fermentation, in-process, and on stability	(b) (4)	n/a
(b) (4) (product related impurity)	Bioactivity	Fermentation, in-process, and on stability		n/a
(b) (4) (product related impurity)	PK	Fermentation, in-process, and on stability		n/a

B. Drug Substance [Faricimab-svoa] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

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

CQA (type)	Risk	Origin	Control Strategy	Other
Host Cell Protein (process related impurity)	Safety and immunogenicity	Fermentation	(b) (4)	(b) (4)
Host Cell DNA (process related impurity)	Safety	Fermentation		n/a
Leachables (process related impurity)	Safety	Equipment and container closure system		Applicant commits to submit updated leachable stability data in annual report.

(b) (4) (process related impurity)	Safety	Raw material and in-process	(b) (4)	n/a
(b) (4) (process related impurity)	Safety and immunogenicity	Raw material and equipment		n/a
(b) (4) (general)	Safety and efficacy	In-process and formulation		n/a
Raw Materials (general)	Safety	Raw materials		n/a
Viral Safety (contaminant)	Safety	Raw materials and in-process		(b) (4)
Mycoplasma (contaminant)	Safety	Raw materials and in-process		n/a
Bioburden (contaminant)	Safety	Raw materials and in-process		n/a
Endotoxin (contaminant)	Safety	Raw materials and in-process		n/a
(b) (4) (contaminant)	Safety	Raw materials and in-process		n/a

- Description:
  Faricimab-svoa is a humanized bispecific IgG1 antibody that binds vascular endothelial growth factor A (VEGF-A) with one arm and angiopoetin-2 (Ang-2) with the other arm. It is produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology. The antibody consists of two different heavy chains (VEGF-HC with 452 amino acid residues and Ang-2-HC with 462 amino acid residues) and two different light chains (VEGF-LC with 214 amino acid residues and Ang-2-LC with 213 amino acid residues). The CH2 domain of each heavy chain contains N-linked glycosylation at the conserved Asn site that is typical of those observed for CHO-produced antibodies. Faricimab-svoa has a total molecular weight of approximately 146 kDa (peptide chains only).

(b) (4)

(b) (4)

- Mechanism of Action (MoA):
  The clinical efficacy of faricimab-svoa for its indications is mediated by binding both Ang-2 and VEGF-A and preventing the interactions of these two angiogenic factors with their respective receptors. Ang-2 and VEGF-A synergistically increase vascular permeability and stimulate neovascularization. By dual inhibition of Ang-2 and VEGF-A, faricimab-svoa reduces vascular permeability and inflammation, inhibits pathological angiogenesis and restores vascular stability.

- Potency Assay:
  The bindings to Ang-2 and VEGF-A by faricimab-svoa were demonstrated to be independent of each other; therefore, two independent cell-based potency assays were developed to measure the anti-Ang-2 and anti-VEGF-A activities, respectively.

  Anti-Ang-2 by Tie-2 Phosphorylation Assay
  The faricimab-svoa dose-dependent inhibition of Ang-2 induced Tie-2 receptor phosphorylation is quantified as the surrogate measurement for the neutralization of Ang-2. Specifically, serial dilutions of faricimab-svoa standard, control and samples are pre-incubated with a fixed concentration of recombinant human Ang-2 ligand. The faricimab-svoa/Ang-2 solutions are then incubated with the HEK293_Tie-2 cells that stably express Tie-2. Phosphorylation of the Tie-2 receptor in the cell lysate is then measured using a homogeneous time-resolved fluorescence (HTRF) detection system. The results, expressed in fluorescence ratios, are plotted against the faricimab-svoa concentrations. The relative potency of a sample is calculated based on the concentration shift between reference and sample dose-response curve fits.

  Anti-VEGF-A by VEGF Reporter Gene Assay
  The faricimab-svoa dose-dependent inhibition of VEGF-A induced activation of the Luciferase reporter gene is quantified as the surrogate measurement for the neutralization of VEGF-A. Specifically, serial dilutions of faricimab-svoa standard, control and samples are pre-incubated with a fixed concentration of recombinant human VEGF-A ligand (the 165 isoform). The faricimab-svoa/VEGF-A solutions are then incubated with the NFAT-RE-luc2P/KDR HEK293 cells that stably express VEGFR2 and a NFAT-RE-luc2P Luciferase reporter gene. After addition of a luminescent Luciferase substrate, the NFAT-Luciferase reporter gene expression is quantified by measuring luminescence. The results, expressed in relative luminescence units, are plotted against the faricimab-svoa concentrations. The relative potency of a sample is calculated based on the concentration shift between reference and sample dose-response curve fits.

- Reference Materials:
  A two-tiered system comprising of a Primary Reference Standard (PRS) and a Secondary Reference Standard (SRS) is used for the intended commercial faricimab-svoa manufacturing process. (b) (4)

(b) (4)

A protocol to support the qualification of future SRS lots was provided and is acceptable. Future requests to implement a new PRS will be submitted as prior approval supplement (PAS). A description of the stability monitoring program for current and future RS was provided and is acceptable.

- Critical starting materials or intermediates:

(b) (4)

- Manufacturing process summary:

(b) (4)

(b) (4)

- Container closure:

(b) (4)

- Dating period and storage conditions:
  Refer to "Approval Action Letter Language" section.

C. Drug Product [VABYSMO] 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)	Risk	Origin	Control Strategy	Other
Physical State (general)	Safety and efficacy	In-process	(b) (4)	n/a
Particles, visible (general)	Safety, immunogenicity, and efficacy	In-process and container closure system		n/a
Particles, sub-visible (general)	Safety, immunogenicity, and efficacy	In-process and container closure system		(b) (4)
Extractable Volume (general)	Safety and efficacy	In-process		n/a
Extractables / Leachables (process related impurity)	Safety and efficacy	Equipment and container closure system		Applicant commits to submit updated leachable stability data in annual report.

			(b) (4)	
Endotoxin (contaminant)	Safety	Raw materials and in-process		n/a
Sterility (contaminant)	Safety and efficacy	Raw materials and in-process		n/a
Container Closure Integrity (contaminant)	Safety and efficacy	Raw materials, in-process, and on stability		n/a

- Potency and Strength:
  VABYSMO is supplied at a strength of 6 mg/0.05 mL[1] (120 mg/mL).

  Potency is defined as the percent Ang-2 and VEGF-A neutralization activities relative to the current faricimab-svoa SRS. The potency assays are the same as described for DS.

- Summary of Product Design:
  VABYSMO is supplied in a single-dose vial as a sterile, preservative-free, clear to opalescent, colorless to brownish-yellow solution intended for intravitreal injection. Each vial is designed to deliver 0.05 mL of solution containing 6 mg faricimab-svoa. A 5 µm transfer filter needle is co-packaged with VABYSMO drug product for dose preparation to reduce subvisible particles.

- List of Excipients:
  - L-histidine (20 mmol/L)
  - L-methionine (7 mmol/L)
  - Polysorbate 20 (0.4 mg/mL)
  - Sodium chloride (25 mmol/L)
  - D-sucrose (160 mmol/l)
  - Adjusted to pH 5.5 with acetic acid.

- Reference Materials:
  The same reference material is used for DS and DP.

- Manufacturing process summary:

(b) (4)

[1] Expression of strength is under discussion with other disciplines, including OPPQ, DMEPA, OTBB and OBP.

(b) (4)

- Container closure:

(b) (4)

- Dating period and storage conditions:
  Refer to "Approval Action Letter Language" section.

- List of co-package components, if applicable:
  - VABYSMO drug product vial
  - Transfer filter needle (b) (4)

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations: Do not freeze. Do not shake. Protect from light. The co-packaged transfer filter needle should be used for dose preparation to reduce subvisible particles.

F. Establishment Information:

Overall Recommendation: **Approval**					
DRUG SUBSTANCE					
Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DS manufacture, DS in-process control testing (including virus and mycoplasma testing), DS QC testing, DS release, DS stability testing, DS storage, preparation and storage of MCB and WCB	Roche Diagnostics GmbH, (Nonnenwald 2, 82377 Penzberg, Germany)	3002806560 / 323105205	704(A)(4) Assessment Performed with an approval recommendation	N/A	Approve based on 704(a)(4)
Additional site for virus and mycoplasma testing, additional storage site for part of the MCB	Genentech, Inc. (1 DNA Way, South San Francisco, CA 94080, United States)	2917293 / 080129000	Facility history assessment performed with an approval recommendation	N/A	Approved based on Previous History
Additional site for virus and mycoplasma testing	Genentech Inc. (Oceanside)	3006129086 / 146373191	Facility history assessment performed with an	N/A	Approved based on Previous History

	(1 Antibody Way, Oceanside, CA 92056, United States)		approval recommendation		
Additional site for DS storage	F. Hoffmann La Roche Ltd. (Grenzacherstrasse 124, 4070 Basel, Switzerland)	3002807200 / 482242971	Facility history assessment performed with an approval recommendation	N/A	Approved based on Previous History
DRUG PRODUCT					
Function	Site Information	FEI/DUNS Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DP manufacture (including filling/primary packaging), in-process control testing, QC release testing and stability testing except microscopic particle count test, DP release, DP storage, labeling and secondary packaging including co-packaging, release of finished DP	F. Hoffmann-La Roche Ltd. (Wurmisweg, CH-4303 Kaiseraugst, Switzerland)	3003973536 / 485244961	Facility history assessment performed which included a District File Review. An Inspection Waiver was issued with an approval recommendation.	N/A	Approved based on Previous History
QC release testing and stability testing of microscopic particle count test only	(b) (4)		Facility history assessment performed with an approval recommendation	N/A	Approved based on Previous History

G. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Roche Diagnostics GmbH (FEI 3002806560), proposed for DS manufacture. Following a review of requested manufacturing site records under Section 704(a)(4) for the drug substance manufacturing facility, a recommendation of approval was made for this facility. This document review is captured in both eNSpect 204599 and CMS WA 407375. Based on the records review, a post-approval inspection has been requested and this request includes the potential inspection items that have been identified in this memo.

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for F Hoffmann La Roche Limited (FEI 3003973536), proposed for DP manufacture. Based on the site's inspection history an inspection waiver was granted for the DP manufacturing site, and a recommendation of approval was made for this facility.

All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:
   - Verification (b) (4)
   - Verification (b) (4)
   - Verification of drug substance (b) (4)
   - Microbial Hold Time Validation
   - Master Cell Bank and Working Cell Bank stability monitoring
   - Container closure leachables stability study for drug substance
   - Stability protocols for extension of shelf-life of drug substance
   - Post-approval stability protocols for drug substance

ii. Outstanding assessment issues/residual risk: None
iii. Future inspection points to consider: A post-approval inspection request was made through OPQ that included potential inspection items identified in the drug substance manufacturer, Roche Diagnostics GmbH, 704(a)(4) review.

b. Drug Product

iv. Protocols approved:
   - Container closure leachables stability study for drug product
   - Preparation and qualification of future secondary reference standards
   - Stability studies for reference standards
   - Stability protocols for extension of shelf-life of drug product
   - Post-approval stability protocol for drug product

v. Outstanding assessment issues/residual risk: None
vi. Future inspection points to consider: None

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/s/

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