

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761142Orig1s000

PRODUCT QUALITY REVIEW(S)

Breakthrough Designation
Orphan Drug
Recommendation: Approval

BLA Number: 761142
Review Number: First round
Review Date: March 2, 2020

Drug Name/Dosage Form	UPLIZNA (inebilizumab-cdon)/injection, for intravenous use
Strength/Potency	100 mg/10 mL (10 mg/mL concentration)
Route of Administration	Intravenous
Rx/OTC dispensed	Rx
Indication	For treatment of neuromyelitis optica spectrum disorder (NMOSD)
Applicant/Sponsor	Viela Bio, Inc.

Product Overview:

Inebilizumab-cdon is a humanized, afucosylated IgG1k monoclonal antibody against human CD19. CD19 is a cell surface protein present on pre-B and mature B lymphocytes, including plasmablasts and some plasma cells. Upon binding to CD19, inebilizumab-cdon depletes B-cells through an antibody-dependent cellular cytotoxicity (ADCC) mechanism. The precise mechanism by which Uplizna exerts its therapeutic effects in neuromyelitis optica spectrum disorder (NMOSD) is unknown, but it is presumed to involve B-cell depletion and may include the suppression of antibody secretion, antigen presentation, B cell–T cell interaction, and the production of inflammatory mediators that cumulatively may play role in the pathogenesis of NMOSD.

Inebilizumab-cdon was designed by humanization (b) (4) to have an optimized CD19 binding. Inebilizumab-cdon (b) (4) generates afucosylated antibody with enhanced ADCC activity.

Inebilizumab-cdon drug product, Uplizna, is supplied as a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution, containing 10 mg/mL inebilizumab in 20 mM L-histidine/L-histidine hydrochloride monohydrate, 70 mM sodium chloride, 106 mM trehalose dihydrate, 0.01% (w/v) polysorbate 80, at pH 6.0 and intended for intravenous infusion after dilution.

Quality Review Team:

Discipline	Reviewer	Branch/Division
Drug Substance	Li Lu	OPQ/OBP/DBRR IV
Drug Product	Li Lu	OPQ/OBP/DBRR IV
Immunogenicity	Li Lu	OPQ/OBP/DBRR IV
Labeling	Vicky Borders-Hemphill	OPQ/OBP
Microbiology: Drug Substance Drug Product	Aimee Cunningham Candace Gomez-Broughton	OPQ/OPMA/DBM OPQ/OPMA/DBM
Facility	Amy Devlin	OPQ/OPMA/DBM
Team Leads: Product quality Microbiology Facility	Bazarragchaa Damdinsuren Reyes Candau-chacon Thuy T. Nguyen	OPQ/OBP/DBRR IV OPQ/OPMA/DBM OPQ/OPMA/DBM
CMC RPBM	Anita Brown	OPQ/OPRO
Application Team Lead	Bazarragchaa Damdinsuren	OPQ/OBP/DBRR IV

Multidisciplinary Review Team:

Discipline	Reviewer	Office/Division
RPM	Sandy Folkendt	OND/ORO
Cross-disciplinary Team Lead	Paul R. Lee	OND/ON/DN2
Medical Officer	Lawrence Rodichok	OND/ON/DN2
Pharmacology/Toxicology	Barbara Wilcox	OND/ON/DN2
Clinical Pharmacology	Dawei Li	OND/OCP
Statistics	Xiangmin Zhang	OND/OB

1. Names:

- a. Proprietary Name: UPLIZNA
- b. Trade Name: UPLIZNA
- c. Non-Proprietary Name/USAN: inebilizumab-cdon/inebilizumab
- d. CAS Name: 1299440-37-1
- f. INN Name: inebilizumab
- h. OBP systematic name: MAB HUMANIZED (IGG1) ANTI P15391 (CD19_HUMAN) [MEDI-551]

Submissions Reviewed:

Submission(s) Reviewed	Document Date
STN 761142 / SN0001	6/11/2019
STN 761142 / SN0004 (response to IR #1)	7/17/2019
STN 761142 / SN0005 (response to IR #2)	8/05/2019
STN 761142 / SN0011 (response to IR #3)	9/23/2019
STN 761142 / SN0012 (response to IR #4)	10/08/2019
STN 761142 / SN0016 (response to IR #5)	11/18/2019
STN 761142 / SN0018 (response to IR #6)	1/17/2020
STN 761142 / SN0020 (response to IR #7)	2/04/2020
STN 761142 / SN0022 (response to IR #8)	2/14/2020
STN 761142 / SN0024 (response to IR #9)	2/20/2020

Quality Review Data Sheet:

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code ¹	Status ²	Date Reviewed	Comments
(b) (4)	V	(b) (4)	(b) (4)	3	N/A	N/A	Not reviewed. Sufficient information related to microbial product quality and sterility assurance is in the BLA.
	V			3	N/A	N/A	
	III			3	N/A	N/A	No review was required as all information related to safety and compatibility with the product was provided in the BLA.
	III			3	N/A	N/A	
	III			2	N/A	N/A	
	III			3	N/A	N/A	

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

2. 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 reviewed).

B. Other documents: IND 117295

3. Consults: None

4. Environmental Assessment of Claim of Categorical Exclusion: The applicant claims a categorical exclusion from the requirements of environmental assessment based on 21 CFR 25.15(d) under the provisions of 21 CFR 25.31(b and c). Categorical Exclusion is appropriate for this product.

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The OPQ, CDER, recommends approval of STN 761142 for Uplizna (inebilizumab-cdon) manufactured by Viela Bio. The data submitted in this application are adequate to support the conclusion that the manufacture of Uplizna 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: [REDACTED] (b) (4)
 - Drug Product: [REDACTED] (b) (4)
- Fill size and dosage form: 100 mg/10 mL (10 mg/mL concentration), single-dose vial, injection
- Dating period:
 - Drug Product: 36 months when stored at 2-8 °C
 - Drug Substance: (b) (4) months when stored at [REDACTED] (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.
- Exempt from lot release: Yes
 - Rationale: specified product
Note: Uplizna is exempted from lot release per FR 95-29960.

C. Benefit/Risk Considerations:

Uplizna (inebilizumab-cdon) is indicated for the treatment of adults with neuromyelitis optica spectrum disorders (NMOSD). Inebilizumab-cdon received Orphan drug designation on February 10, 2016 and Breakthrough therapy designation on April 17, 2019 under IND 117295. The pivotal clinical study supporting the BLA showed significant delay of first adjudicated relapse among other improvements with Uplizna in NMOSD patients who are AQP4-IgG seropositive. Some adverse reactions, including urinary tract infection, headache, nasopharyngitis, infusion reaction, are described in the labeling.

The OPQ review of manufacturing has identified that the methodologies and processes used for drug substance and drug product manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The drug substance manufacturing process is robust for inactivation and removal of adventitious agents. The BLA is recommended for approval from a microbiology product quality and sterility assurance perspective. We also recommend approval of the commercial manufacture of inebilizumab-cdon drug substance at [REDACTED] (b) (4) and of drug product at [REDACTED] (b) (4)

(b) (4) and (b) (4) for a labeling and packaging).

The technical assessments for product quality and immunogenicity assay (by OBP), microbiological drug substance and drug product, facility (by OPMA), and OBP labeling are located as separate documents in Panorama.

D. Recommendation on Phase 4 (Post-Marketing) Commitment:

- To perform a shipping study to confirm stability of inebilizumab drug substance during shipping under representative conditions and through a route (b) (4). The study will include monitoring of temperature during three shipments covering the drug substance bag fill range and testing of post-shipment materials for product quality against applicable approved drug substance release acceptance criteria.

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	CQA	Risk	Origin	Control Strategy
Identity	Identity	Safety, Biological activity/DP failure	Intrinsic to the molecule	(b) (4)
Potency	ADCC activity	Biological activity/DP failure	Intrinsic to the molecule, in-process and on stability	(b) (4)
Size Variants (product related impurity)	Aggregates	Immunogenicity and PK	Production and purification processes (b) (4)	(b) (4)
	Fragments	Biological activity	Production and purification processes (b) (4)	(b) (4)
Glycosylation	Afucosylated species	Biological activity/ADCC	Production processes (b) (4)	(b) (4)
	High mannose	ADCC and PK	Production processes (b) (4)	(b) (4)
Post Translational Modifications	Deamidation (b) (4)	Biological activity	Production processes (b) (4)	(b) (4)
	Isomerization (b) (4)	Biological activity	Production processes (b) (4)	(b) (4)
	Oxidation (b) (4)	PK	Production processes (b) (4)	(b) (4)
Structural Variants	Primary sequence variants	Bioactivity, PK, Immunogenicity	Cell line	(b) (4)
	Disulfide bond modifications (increased risk for	Immunogenicity	Production and purification processes (b) (4)	(b) (4)

	aggregation and fragmentation)			(b) (4)
	Higher order structures	Bioactivity, PK, Immunogenicity	Cell line	
Charge Heterogeneity	* Acidic, main and basic species	Bioactivity, Immunogenicity	Cell culture (b) (4)	

DS - drug substance, DP - drug product

* The applicant did not name charge variants as CQA, (b) (4)

B. Drug Substance Inebilizumab Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

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

CQA type	CQA	Risk	Origin	Control Strategy
Process-related impurities	Host Cell DNA	Safety, Immunogenicity	Cell culture (b) (4)	(b) (4)
	Host Cell Proteins	Immunogenicity, Purity Biological activity (b) (4)	Cell culture (b) (4)	
	(b) (4)	Safety, Immunogenicity	Cell culture (b) (4)	
	(b) (4)	Immunogenicity, Safety	(b) (4)	
Adventitious Agents	Viral Safety	Safety	Raw materials and manufacturing process	
	Mycoplasma	Safety	Raw materials and manufacturing process	
Bacterial Endotoxins (contaminant)	Bacterial Endotoxins	Safety, Purity	Raw materials and manufacturing process	
Bioburden (contaminant)	Bioburden	Safety, Purity, Efficacy (degradation or modification of the product)	Raw materials and manufacturing process	
DS Composition	Appearance (color, clarity)	Bioactivity, Safety	Product and formulation	
	Total protein content	Inaccurate dosing impacting PK, efficacy and safety	Manufacturing process (b) (4)	
	Osmolality	Product stability, Patient discomfort	DS formulation (b) (4)	
	pH	Bioactivity, Product stability	Formulation (b) (4)	



- **Container closure:** Inebilizumab-cdon drug substance is stored (b) (4)
- **Datna period and storage conditions:** A shelf-life of (b) (4) months when stored at (b) (4) is acceptable based on available stability data from the process validation lots.

C. Drug Product Uplizna Quality Summary:

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

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

CQA type	CQA	Risk	Origin	Control Strategy
Particles	Visible and Subvisible Particles	Immunogenicity, Safety	Manufacturing process, CCS and product on stability	(b) (4)
Vial Content	Extractable Volume	Inaccurate dosing impacting PK, efficacy and safety	DP manufacturing process (fill)	(b) (4)
Sterility (contaminant)	Sterility	Safety (infection), Efficacy (degradation or modification of the product)	Contamination may be introduced throughout the DP manufacturing process, container closure failure	(b) (4)
Container Closure Integrity	Container Closure Integrity	Safety (loss of sterility), Efficacy (change on product strength due to evaporation or leakage)	Container closure breaches during storage	(b) (4)

Endotoxin (contaminant)	Endotoxin	Safety, Purity, Immunogenicity	Raw materials and manufacturing process	(b) (4)
DP Composition and Strength	Total Protein Content	Inaccurate dosing impacting PK, efficacy and safety	DP manufacturing process (DP formulation)	
	Osmolality	Product stability, Patient discomfort	DP formulation (b) (4)	
	pH	Bioactivity, Product stability	Formulation (b) (4)	
	Polysorbate 80 content	Particle formation, Product stability	(b) (4)	
	Appearance (color, clarity)	Bioactivity, Safety	Product and formulation	

- **Potency and Strength:** 100 mg/10 mL (10 mg/mL concentration)
- **Summary of Product Design:** A sterile, clear to slightly opalescent, colorless to slightly yellow solution for intravenous administration and contains no preservatives. Presented in single-dose vials.
- **List of Excipients:** Histidine, sodium chloride, trehalose dihydrate, polysorbate 80.
- **Reference Materials:** Same as the inebilizumab-cdon drug substance RSs.
- **Manufacturing process summary:** The Uplizna drug product manufacturing includes

(b) (4)

- **Container closure:** (b) (4)
- **Dating period and storage conditions:** A shelf-life of 36 months when stored at 2-8 °C is acceptable based on available stability data from the process validation and clinical lots.

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations: None (see Dr. Borders-Hemphill’s labeling assessment).

F. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DS manufacture, IPC testing, release and stability testing, DS storage, MCB and WCB storage	(b) (4)	(b) (4)	Approve - No action indicated (NAI) according to PLI	None	Approve
DRUG PRODUCT					
Function	Site Information	FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DP manufacture (filling), release testing for endotoxin	(b) (4)	(b) (4)	Approve – Voluntary action indicated (VAI) according to PLI	- Inadequate investigation into (b) (4) - Operators failed to follow procedures (b) (4)	Approve based on facility profile
DS (b) (4) release and stability testing	(b) (4)	(b) (4)	No action indicated (NAI) according to PLI	None	Approve
Labeling and packaging	(b) (4)	(b) (4)	Approve - Based on Previous History	N/a	Approve based on facility profile
Release testing for sterility	(b) (4)	(b) (4)	Approve - Based on Previous History	N/a	Approve based on facility profile
Release testing for sterility	(b) (4)	(b) (4)	Approve - Based on Previous History	N/a	Approve based on facility profile
DP storage	(b) (4)	(b) (4)	Approve - Based on Previous History	N/a	Approve based on facility profile
DP storage	(b) (4)	(b) (4)	Approve - Based on Previous History	N/a	Approve based on facility profile

DS - drug substance, DP - drug product, IPC – in-process control, MCB - Master Cell Bank, WCB - Working Cell Bank

G. Facilities:

A pre-license inspection of the drug substance manufacturing site, (b) (4) was conducted on (b) (4) by Aimee Cunningham (OPQ/OPMA), Ralph Bernstein and Li Lu (both OPQ/OBP). The inspection covered the drug substance upstream and downstream manufacturing and testing laboratories. The inspection was system-based and covered Quality, Production, Laboratory Control, Materials, and Facilities and Equipment Systems. No FDA 483 Form was issued, and the outcome was classified as NAI.

A pre-license inspection of the drug product manufacturing site, (b) (4) was performed by OPQ/OPMA on (b) (4). There was a 2-item FDA Form 483 issued at the conclusion of the inspection, and the outcome was classified as VAI. The firm's responses and corrective actions to the 483 observations were considered adequate.

The compliance recommendations for the other facilities described in the tables (section F), which are not inspected within scope of this BLA, are for approval.

H. Lifecycle Knowledge Management:

a. Drug Substance:

- i. Protocols approved (section):
 - 1. Cell bank storage stability (3.2.S.2.3.3)
 - 2. Future cell bank qualification (3.2.S.2.3.3)
 - 3. (b) (4) verification (3.2.S.2.5.5)
 - 4. (b) (4) validation (3.2.S.2.5.8)
 - 5. Stability of primary reference standard (3.2.S.5.1)
 - 6. Qualification and stability of future reference standards (3.2.S.5.3)
 - 7. Ongoing primary stability study (3.2.S.7.2)
 - 8. Post-approval annual stability (3.2.S.7.2)
- ii. Outstanding review issues/residual risk: None
- iii. Future inspection points to consider: None

b. Drug Product

- i. Protocols approved (section):
 - 1. Ongoing primary stability study (3.2.P.8.2)
 - 2. Post-approval annual stability (3.2.P.8.2)
- ii. Outstanding review issues/residual risk: None
- iii. Future inspection points to consider: None



Bazarragchaa
Damdinsuren

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Date: 3/02/2020 11:29:45PM
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Reyes
Candau-Chacon

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Date: 3/03/2020 12:36:05PM
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Thuy Thanh
Nguyen

Digitally signed by Thuy Thanh Nguyen
Date: 3/03/2020 06:12:19AM
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Christopher
Downey

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BLA STN 761142

UPLIZNA™ (inebilizumab-cdon)

Viela Bio

Li Lu, Ph.D., Primary Reviewer
Bazarragchaa Damdinsuren, M.D., Ph.D., Application Technical Lead
Christopher Downey, Ph.D., Review Chief

Division of Biotechnology Review and Research IV (DBRR IV)
Office of Biotechnology Products (OBP)
Office of Pharmaceutical Quality (OPQ)
Center for Drug Evaluation and Research (CDER)

OBP CMC Review Data Sheet

1. **BLA#:** STN 761142

2. **REVIEW DATE:** 2/20/2020

3. **PRIMARY REVIEW TEAM:**
Medical Officer: Lawrence Rodichok, Paul R. Lee (TL)
Pharm/Tox: Barbara Wilcox, Lois Freed (TL)
Product Quality Team:
 OPQ/OBP: Li Lu (Primary Reviewer), Bazarragcha Damdinsuren (ATL)
 OPQ/OPMA: Aimee Cunningham, Candace Gomez-Broughton and Reyes Candauchacon (TL), Amy Devlin, Thuy Nguyen (TL)
OBP Labeling: Vicky Borders-Hemphill
Clinical Pharmacology: Dawei Li, Angela Men (TL)
Statistics: Xiangmin Zhang, Kun Jin (TL)
RPM: Sandy Folkendt

4. **MAJOR GRMP DEADLINES**
 Filing Meeting: 7/22/2019
 Mid-Cycle Meeting: 11/04/2019
 Wrap-Up Meeting: 2/10/2020
 Primary Review Due: 3/3/2020
 Secondary Review Due: 3/3/2020
 CDTL Memo Due: 4/30/2020
 PDUFA Action Date: 6/11/2020

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

Communication/Document	Date
Teleconference 1	11/18/2019
Information Request #1	7/03/2019
Information Request #2	7/24/2019
Information Request #3	9/16/2019
Information Request #4	9/30/2019
Information Request #5	11/08/2019
Information Request #6	1/08/2020
Information Request #7	1/27/2020
Information Request #8	2/09/2020
Information Request #9	2/14/2020

6. SUBMISSION(S) REVIEWED:

Submission	Date Received	Review Completed (Yes/No)
STN 761142 / SN0001	6/11/2019	Yes
STN 761142 / SN0004 (response to IR #1)	7/17/2019	Yes
STN 761142 / SN0005 (response to IR #2)	8/05/2019	Yes
STN 761142 / SN0011 (response to IR #3)	9/23/2019	Yes
STN 761142 / SN0012 (response to IR #4)	10/08/2019	Yes
STN 761142 / SN0016 (response to IR #5)	11/18/2019	Yes
STN 761142 / SN0018 (response to IR #6)	1/17/2020	Yes
STN 761142 / SN0020 (response to IR #7)	2/04/2020	Yes
STN 761142 / SN0022 (response to IR #8)	2/14/2020	Yes
STN 761142 / SN0024 (response to IR #9)	2/20/2020	Yes

7. DRUG PRODUCT NAME/CODE/TYPE:

- a. Proprietary Name: UPLIZNA
- b. Trade Name: UPLIZNA
- c. Non-Proprietary/USAN: inebilizumab-cdon/inebilizumab
- d. CAS Registry Number: 1299440-37-1
- e. Common name: MEDI-551
- f. INN Name: inebilizumab
- g. OBP systematic name: MAB HUMANIZED (IGG1) ANTI P15391 (CD19_HUMAN) [MEDI-551]

8. PHARMACOLOGICAL CATEGORY: Recombinant humanized monoclonal IgG1 κ antibody against human CD19

9. DOSAGE FORM: Injection, solution in single-dose vial

10. STRENGTH/POTENCY:

- (i) The strength/concentration of the Drug Product: 100 mg/10 mL (10 mg/mL concentration)
- (ii) Type of potency assay(s): ADCC reporter gene bioassay

11. ROUTE OF ADMINISTRATION: Intravenous

12. REFERENCED MASTER FILES:

DMF #	HOLDER	ITEM REFERENCED	Letter of Cross-reference	COMMENTS (STATUS)

(b) (4)	Yes	Defer to the OPMA reviewers
	Yes	
	Yes	No review was required as all information related to safety and compatibility with the product was provided in the BLA
	Yes	
	Yes	
	Yes	

13. INSPECTIONAL ACTIVITIES

A pre-license inspection of the drug substance manufacturing site, (b) (4) was conducted on (b) (4) by Aimee Cunningham (OPQ/OPMA), Ralph Bernstein and Li Lu (both OPQ/OBP). The inspection covered the drug substance upstream and downstream manufacturing and testing laboratories. The inspection was system-based and covered Quality, Production, Laboratory Control, Materials, and Facilities and Equipment Systems. No FDA 483 Form was issued and was classified as NAI.

The pre-license inspection of the drug product manufacturing site, (b) (4) was performed by OPQ/OPMA on (b) (4). There was a 2-item FDA Form 483 issued at the conclusion of the inspection and was classified as VAI; and the approval of BLA 761142/0 was recommended. The firm’s responses and corrective actions to the 483 observations were considered adequate.

14. CONSULTS REQUESTED BY OBP: None

15. QUALITY BY DESIGN ELEMENTS

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

	Design Space
X	Design of Experiments
	Formal Risk Assessment / Risk Management
	Multivariate Statistical Process Control
	Process Analytical Technology
	Expanded Change Protocol

16. PRECEDENTS: None

17. ADMINISTRATIVE

A. Signature Block

Name and Title	Signature and Date
Christopher Downey, Ph.D. Review Chief, DBRR IV/OBP/OPQ	See attached
Bazarragchaa Damdinsuren, M.D., Ph.D. Team Lead, DBRR IV/OBP/OPQ	See attached
Li Lu, Ph.D. Primary Reviewer, DBRR IV/OBP/OPQ	See attached

B. CC Block

Recipient
Sandy Folkendt, Clinical Division BLA RPM
OBP/DBRR IV File/BLA STN 761142

SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The data submitted in this Biologics License Application (STN 761142) support the conclusion that the manufacture of UPLIZNA (inebilizumab-cdon) is well controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents and meets the standards recommended by FDA. The conditions used in the manufacturing process had been adequately validated, and the product had been consistently manufactured from multiple production runs. It is recommended that UPLIZNA (inebilizumab) be approved for human use under conditions specified in the package insert.

II. List Of Deficiencies To Be Communicated:

There are no CMC-related deficiencies precluding approval of this BLA.

III. List Of Post-Marketing Commitments (draft):

- To perform a shipping study to confirm stability of inebilizumab drug substance during shipping under conditions and through a route [REDACTED] (b) (4) [REDACTED]. The study will include monitoring of temperature during three shipments covering the drug substance bag fill range and testing of post-shipping materials for product quality against applicable approved drug substance release acceptance criteria.*

IV. Review Of Common Technical Document - Quality Module 1

A. Environmental Assessment Or Claim Of Categorical Exclusion

Viela Bio claims a categorical exclusion from the requirements of environmental assessment based on 21 CFR 25.15(d) under the provisions of 21 CFR 25.31(b and c). Categorical Exclusion is appropriate for this product and should be granted.

V. Primary Container Labeling Review

The carton and container labels are reviewed by Vicky Borders-Hemphill (OBP labeling). The OBP carton and container labeling review will be uploaded as a separate file in Panorama.

VI. Review Of Common Technical Document - Quality Module 3.2

The review of Module 3.2 is included in this review memorandum.

VII. Review Of Immunogenicity Assays – Module 5.3.1.4

The current immunogenicity assay, an electrochemiluminescent, solution-phase, bridging immunoassay was developed and used for detection, confirmation and titration of anti-drug antibodies (ADA) in patient serum samples. The ADA assay has acceptable accuracy and precision for screening, conformation and titration, intermediate precision, repeatability, selectivity, specificity, and matrix stability. The validation shows that the assay sensitivity is 8.79 ng/mL for goat polyclonal Ab (PAb) and 91.15 ng/mL for mouse

monoclonal clone A4 (MAb A4), and can detect 125 ng/mL PAb when the inebilizumab level is $\leq$ 100-150 μ g/mL and can detect 500 ng/mL MAb A4 when the drug level is $\leq$ 10-25 μ g/mL in the patient sample. The applicant did not develop an assay to test for neutralization capacity of ADAs. Overall, the immunogenicity assays are adequate to use and evaluate the ADAs to inebilizumab. The assessment of the immunogenicity assay is uploaded as a separate file in Panorama.

BLA EDR Location: <\\CDSESUB5\evsprod\BLA761142\761142.enx>

Unless otherwise noted, figures and tables in the review are adapted or copied directly from the submission. Some of the figures and tables in the submission were updated during the review cycle, the review contains only the updated final versions. The Reviewer comments are distinguished by use of italic font.

Contents

S. DRUG SUBSTANCE	10
3.2.S.1 General Information	10
S.1.1 Nomenclature	10
S.1.2 Structure	10
S.1.3 General Properties	11
3.2.S.2 Manufacture	12
S.2.1 Manufacturer(s)	12
S.2.2 Description of Manufacturing Process and Process Controls.....	13
S.2.4 Control of Critical Steps and Intermediates.....	13
S.2.5 Process Validation and/or Evaluation.....	13
S.2.6 Manufacturing Process Development	13
S.2.3 Control of Materials	85
3.2.A.2 Adventitious Agents Safety Evaluation	97
A.2.3 Viral Clearance Assessment	98
3.2.S.3 Characterization.....	102
S.3.1 Elucidation of Structure and Other Characteristics.....	102
S.3.2 Impurities	118
3.2.S.4 Control of Drug Substance	120
S.4.1 Specifications and S.4.5 Justification of Specifications.....	120
S.4.4 Batch Analyses	126
S.4.2 Analytical Procedures and S.4.3 Validation of Analytical Procedures	127
3.2.S.5 Reference Standards or Materials	143
S.5.1 Primary and Working Reference Standards.....	144
S.5.3 Future Reference Standards	145
3.2.S.6 Container Closure System	147
3.2.S.7 Stability	150
S.7.1 Stability Summary and Conclusions	150
S.7.3 Stability Data.....	152
S.7.2 Post-Approval Stability Protocol and Stability Commitment	154
P DRUG PRODUCT	157
3.2.P.1 Description and Composition of the Drug Product.....	157
3.2.P.2 Pharmaceutical Development	158
P.2.1 Components of the Drug Product.....	158
P.2.2 Drug Product.....	158
3.2.P.3 Manufacture	166
P.3.1 Manufacturer(s).....	166
P.3.3 Description of Manufacturing Process and Process Control.....	168
P.3.4 Control of Critical Steps and Intermediates	168
P.2.3 Manufacturing Process Characterization Studies	168
P.3.5 Process Validation	168
3.2.P.4 Control of Excipient.....	185
3.2.P.5 Control of Drug Product	186
P.5.1 Specification(s) and P.5.6 Justification of Specifications	186
P.5.4 Batch Analysis.....	188
P.5.2 Analytical Procedures and P.5.3 Validation of Analytical Procedures.....	189
P.5.5 Characterization of Impurities.....	192
3.2.P.6 Reference Standards or Materials	192

3.2.P.7 Container Closure System 192
3.2.P.8 Stability 195
 P.8.1 Stability Summary and Conclusion..... 195
 P.8.3 Stability Data and Summary 196
 P.8.2 Post-approval Stability Protocol and Stability Commitment 200
3.2.A.1 Facilities and Equipment 200
3.2.R Regional Information (U.S.A.)..... 201

DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT

Inebilizumab is a humanized IgG1 κ monoclonal antibody that binds to CD19 and depletes B-cells through an antibody-dependent cellular cytotoxicity (ADCC) mechanism. Inebilizumab is an engineered-to-be-afucosylated monoclonal antibody, and is expected to have increased ADCC activity. The inebilizumab Drug Product is a sterile, preservative-free, liquid, containing 10 mg/mL inebilizumab in 20 mM L-histidine/L-histidine hydrochloride monohydrate, 70 mM sodium chloride, 106 mM trehalose dihydrate, 0.01% (w/v) polysorbate 80, at pH 6.0 and intended for intravenous infusion after dilution.

S. DRUG SUBSTANCE

3.2.S.1 General Information

S.1.1 Nomenclature

Trade Name:	Uplizna
Company or Laboratory Code	MEDI-551
United States Adopted Name (USAN):	inebilizumab
International Non-Proprietary Name (INN):	inebilizumab
CAS Registration Number:	1299440-37-1

S.1.2 Structure

The amino acid sequences of heavy chain (HC) and light chain (LC) are provided in Figures 1 and 2.

Figure 1 Nucleotide and Amino Acid Sequence of the VH

```

1   E V Q L V E S G G G L V Q P G G S L
   GAG GTG CAG CTG GTG GAG TCT GGG GGA GGC TTG GTC CAG CCT GGA GGG TCC CTG

                                     -----CDR1-----
55  R L S C A A S G F T F S S S W M N W
   AGA CTC TCC TGT GCA GCC TCT GGA TTC ACC TTC AGT AGC TCT TGG ATG AAC TGG

                                     -----CDR2-----
109 V R Q A P G K G L E W V G R I Y P G
   GTC CGC CAG GCT CCA GGG AAG GGG CTG GAG TGG GTT GGC CGG ATT TAT CCT GGA

-----CDR2-----
163 D G D T N Y N V K F K G R F T I S R
   GAT GGA GAT ACT AAC TAC AAT GTG AAG TTC AAG GGC AGA TTC ACC ATC TCA AGA

217 D D S K N S L Y L Q M N S L K T E D
   GAT GAT TCA AAG AAC TCA CTG TAT CTG CAA ATG AAC AGC CTG AAA ACC GAG GAC

                                     -----CDR3-----
271 T A V Y Y C A R S G F I T T V R D F
   ACG GCC GTG TAT TAC TGT GCT AGA TCA GGA TTT ATT ACT ACG GTT CGC GAC TTT

-CDR3--
325 D Y W G Q G T L V T V S S
   GAC TAC TGG GGC CAA GGA ACC CTG GTC ACC GTC TCC TCA

```

Figure 2 Nucleotide and Amino Acid Sequence of the VL

```

1   E I V L T Q S P D F Q S V T P K E K
   GAA ATT GTG CTG ACT CAG TCT CCA GAC TTT CAG TCT GTG ACT CCA AAG GAG AAA

                                     ----- CDR1 -----
55  V T I T C R A S E S V D T F G I S F
   GTC ACC ATC ACC TGC AGA GCC AGC GAA AGT GTT GAT ACT TTT GGC ATT AGT TTT

-CDR1--
109 M N W F Q Q K P D Q S P K L L I H E
   ATG AAC TGG TTC CAG CAG AAA CCA GAT CAG TCT CCA AAG CTC CTC ATC CAT GAG

-----CDR2-----
163 A S N Q G S G V P S R F S G S G S G
   GCA TCC AAT CAA GGA TCC GGG GTC CCC TCG AGG TTC AGT GGC AGT GGA TCT GGG

217 T D F T L T I N S L E A E D A A T Y
   ACA GAT TTC ACC CTC ACC ATC AAT AGC CTG GAA GCT GAA GAT GCT GCA ACG TAT

                                     -----CDR3-----
271 Y C Q Q S K E V P F T F G G G T K V
   TAC TGT CAG CAA AGT AAG GAG GTT CCA TTC ACG TTC GGC GGA GGG ACC AAG GTG

325 E I K
   GAG ATC AAA

```

CDR sequences are labeled and underlined.

S.1.3 General Properties

The physicochemical properties of inebilizumab are summarized in Table 1.

Inebilizumab is composed of two identical HCs of 49,362 Da each, and two identical LCs of 23,836 Da each.

Table 1 Physicochemical Properties of Inebilizumab Drug Substance

Characteristic	Result
Immunoglobulin subclass	IgG1κ
Sequence	Humanized
Molecular Mass	Approximately 149 kDa (including oligosaccharides)
Glycosylation	Afucosylated; N-linked site: Asn-301 Predominantly complex type
Extinction Coefficient (determined experimentally)	1.35 (mg/mL) ⁻¹ cm ⁻¹
pI	7.9 – 8.5
Density	1.022 g/mL

3.2.S.2 Manufacture

S.2.1 Manufacturer(s)

Table 1 Drug Substance Manufacturing and Testing Sites

Name and Address	Facility Identifier	Responsibilities
[Redacted]	(b) (4)	Manufacture of Master and Working Cell Banks
		- Preparation of Future Working Cell Banks - Storage and maintenance of Master and Working Cell Banks - Drug Substance manufacture and storage (Building (b) (4)) (b) (4) Drug Substance (b) (4) - Drug Substance release and stability testing

DUNS= Data Universal Numbering System Number; FEI=Facility Establishment Identifier

Facility and equipment information for [Redacted] (b) (4) is provided in DMF [Redacted] (b) (4)

Reviewer comments: [Redacted] (b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

**S.2.2 Description of Manufacturing Process and Process Controls,
S.2.4 Control of Critical Steps and Intermediates,
S.2.5 Process Validation and/or Evaluation
S.2.6 Manufacturing Process Development**

An overview of the manufacturing process, process validation and process characterization is provided in the following sections. The information source sections are denoted in [].

(b) (4)

P.8.2 Post-approval Stability Protocol and Stability Commitment

Viela Bio commits to continue the stability studies of inebilizumab DP as detailed in Section P.8.1 through their scheduled duration of 36 months and to report the results in the BLA Annual Reports. The applicant also commits to conduct stability testing on a minimum of one commercial DP lot per year for each calendar year during which DP is manufactured. Testing will be performed according to the schedule summarized in Table 1 and results will be evaluated against the criteria summarized in Table 2.

Table 1 Annual Drug Product Stability Tests and Testing Intervals

Tests	Condition: 2-8°C Testing Interval (months)				
	0	6	12	24	36
Appearance–visible particles	●	●	●	●	●
Appearance–color	●	●	●	●	●
Appearance–clarity	●	●	●	●	●
pH	●	●	●	●	●
Capillary isoelectric focusing	●	●	●	●	●
Non-reducing gel electrophoresis	●	●	●	●	●
Reducing gel electrophoresis	●	●	●	●	●
High performance size exclusion chromatography	●	●	●	●	●
ADCC reporter gene bioassay	●	●	●	●	●
Sub-visible Particles	●	●	●	●	●
Container Closure Integrity	●	○	●	●	●

ADCC = antibody dependent cell-mediated cytotoxicity; ● = scheduled; ○ = not performed

Reviewer comments: The end of shelf life specifications are the same as the stability specifications listed in P.5.1 and P.8.3. Both the post-approval stability protocol and the end of shelf life specifications are acceptable.

3.2.A.1 Facilities and Equipment

Reviewer comments: The applicant provided the information of the DP labeling and packaging site - [redacted] (b) (4)

[redacted] Review of information provided on the facilities and equipment is deferred to OPMA reviewers.

Drug Master File (DMF) [redacted] (b) (4)

[redacted], the LOA is provided in the submission. As stated in DP manufacturer, DMF [redacted] (b) (4) is referenced for [redacted] (b) (4)

[redacted] The LOA is provided in the submission.

Note that the identity tests for inebilizumab DS and DP are peptide mapping and lateral flow identity assay. The lateral flow identity assay is based on specific an anti-inebilizumab mAb

immunoreaction. Based on these, the identity tests for inebilizumab are capable to distinguish this product from all other products manufactured in the DS and DP facilities.

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

Method validation reports and Executed Batch Records of DS and DP are provided in this section.

***Reviewer comment:** The method validation reports are reviewed in S.4 and P.5. The batch record for DS batch J2459 was reviewed during the inspection and no discrepancy was identified.*



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Christopher
Downey

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BLA MANUFACTURING FACILITY ASSESSMENT

Application ID	BLA 761142
Drug Product Name	Inebilizumab-cdon, Uplizna®
Strengths	10 mg/mL
Dosage Form	Solution for infusion
Administration Route	Intravenous injection
Indication	Inebilizumab-cdon, treatment of neuromyelitis optica spectrum disorder (NMOSD)
Applicant Name	Viela Bio
US License Number	2129
Application Type	351 (a)

I. Manufacturing Summary

Facility Assessment Recommendation: Approval

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

(b) (4), proposed for inebilizumab-cdon (Uplizna®) DS and DP manufacture, respectively. 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.

Assessment Summary:

List Submissions being assessed (Table):

Document Description (SD #)	Date Received
BLA-761142-1-ORIG	06/11/2019

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Concise Description of Outstanding Issues: None

1. Lifecycle Management Considerations

Post-approval inspection?	No
Lifecycle considerations	No

2. Facilities Table

Facility name and address	FEI	Responsibilities and profile code(s)	Status
(b) (4)	(b) (4)	Preparation of future working cell banks; storage and maintenance of master and working cell banks; Drug Substance manufacture and	Approve- Based on PAI / PLI

(b) (4)	storage; (b) (4) Drug Substance; Drug Substance release and stability testing	
	CBI	
	Manufacture of Drug Product (Filling); release testing for endotoxin	Approve-Based on PAI / PLI
	SVS	
	Release testing for sterility	Approve - Based on Previous History
	LMS	
	Release testing for sterility	Approve - Based on Previous History
	LMS	
Labeling and packaging	Approve - Based on Previous History	
SVS		
Drug product storage	Approve - Based on Previous History	
NEC		
Drug product storage	Approve-Based on Previous History	
NEC		

II. Drug Product Manufacturing

1. Batch Formula



(b) (4)



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Date: February 26, 2020
STN: 761142/0
Reviewer: Candace Gomez-Broughton, Ph.D. Microbiologist CDER/OPQ/OPF/DMA/Branch IV
Endorsed: Reyes Candau-Chacon, Ph.D. CDER/OPQ/OPF/DMA/Branch IV
Subject: Original BLA
Applicant: Viela Bio
Facilities: (b) (4)
Product: UPLIZNA™ (inebilizumab-cdon)
Dosage: Solution of intravenous infusion (10 mg/mL)
Indication: Treatment of neuromyelitis optica spectrum disorder
Action Date: June 11, 2020

Recommendation: This BLA is recommended for approval from a sterility assurance perspective.

Introduction

Viela Bio has submitted a biological license application BLA for the approval of UPLIZNA™ (inebilizumab-cdon) for treatment of patients with neuromyelitis optica spectrum disorder. The inebilizumab drug product (DP) is a solution filled into vials for intravenous infusion.

This review covers the manufacturing processes for the drug product. The drug substance process is covered in a separate review completed by Aimee Cunningham, Ph.D.

Amendments Reviewed

- Sequence 0008 submitted 05 Aug 2019
- Sequence 0022 submitted 14 Feb 2020
- Sequence 0024 submitted 20 Feb 2020

Module 1

1.14 Labeling

UPLIZNA is administered intravenously at a recommended dose of 300mg. The contents of three vials (10 mL from each) are transferred into a 250 mL intravenous (IV) bag containing 0.9% sodium chloride and mixed. The diluted drug product is to be administered immediately or stored at 2-8°C for 24 hours or 4 hours at room temperature. The prepared solution is to be administered through an IV line containing a sterile, low-protein binding 0.2 or 0.22µm inline filter.

Reviewer comment: The proposed storage conditions for diluted drug product are supported by microbial challenge studies discuss in Section P.2.6.4 of this document.

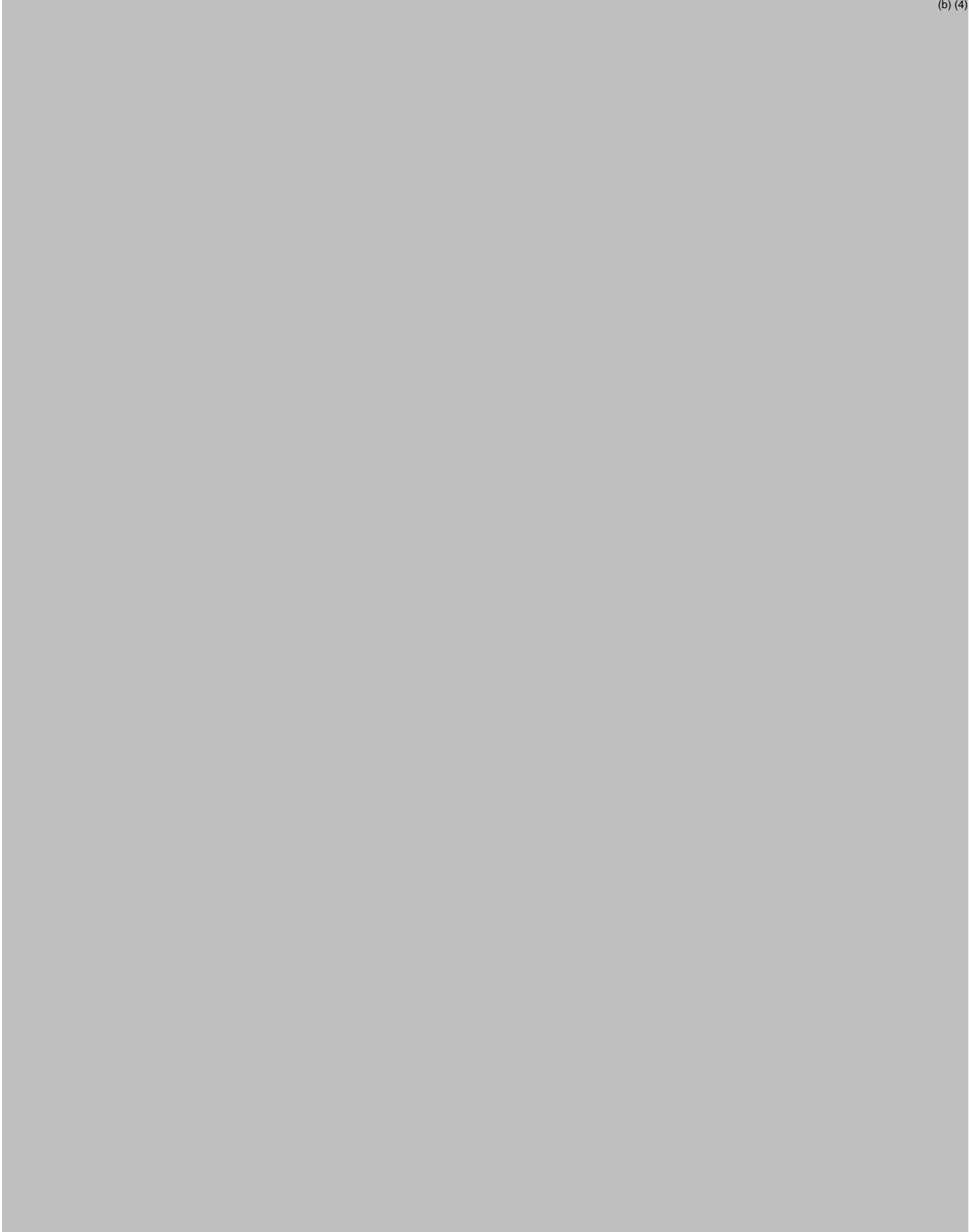
P.1 Description and Composition of the Drug Product

The inebilizumab drug product is a sterile preservative-free solution. The liquid dosage is filled into single-use vials at a concentration of 100 mg/10 mL. The commercial dose of 300 mg requires the use of three drug product (DP) vials. The DP formulation consists of 10 mg/mL inebilizumab, 20 mM L-histidine, 70 mM sodium chloride, 106 mM trehalose dihydrate, and 0.01% (w/v) polysorbate 80, pH 6.0.

The final container for inebilizumab is a (b) (4) glass vial closed with rubber stopper and aluminum seal. The vials are packed into cartons (3 vials in each).

P.2 Pharmaceutical Development

(b) (4)



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P.8 Stability**P.8.2 Post-Approval Stability Commitment**

The applicant plans to add a minimum of one batch per presentation to the long-term stability program each year at the recommended storage temperature of 2-8°C for 36 months. Samples placed on stability will be tested for container closure integrity (dye ingress) initially and annually through expiry.

Reviewer comment: The plan to test samples for CCIT annually through expiry is acceptable.

CONCLUSION

- I. This BLA supplement is recommended for approval from a sterility assurance perspective.

- II. Information and data in this BLA not related to microbial control of the drug product should be reviewed by the OBP reviewer.
- III. Refer to Panorama for GMP status of the relevant facilities.

Information Requests

(b) (4)



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Reyes
Candau-Chacon

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

PRODUCT QUALITY MICROBIOLOGY REVIEW AND EVALUATION

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

BLA: 761142/0
Applicant: Viela Bio
US License Number: 2129
Submission Reviewed: Original BLA
Product: Uplizna (inebilizumab-cdon)
Indication: neuromyelitis optica spectrum disorder (NMOSD)
Dosage Form: solution for i.v. injection (10 mg/mL)
Manufacturing Sites: [REDACTED] (b) (4)
[REDACTED]
FDA Receipt Date: 06/11/2019
Action Date: 12/11/2019

Conclusion and Approvability Recommendation

The drug substance portion of the BLA was reviewed from a microbial control and product quality microbiology standpoint and is recommended for approval.

Product Quality Microbiology Assessment: Drug Substance

Viela Bio has submitted BLA 761142 to license inebilizumab-cdon and its associated drug substance and drug product manufacturing processes. BLA 761142 was submitted via eCTD on June 11, 2019. This review contains the assessment of the manufacturing process of inebilizumab bulk drug substance from a microbiological quality perspective. For review of drug product aspects of this application, please see the review by Dr. Candace Gomez-Broughton.

Drug Substance Quality Microbiology Information Reviewed

Sequence number	Date	Description
0001	06/11/2019	Original BLA
0011	09/23/2019	IR responses

Module 3.2

S.1 General Information

Uplizna (inebilizumab-cdon) is a 149 kD humanized IgG1κ monoclonal antibody against CD19. It depletes B-cells through ADCC and ADCP mechanisms.

SATISFACTORY

S.2 Manufacture

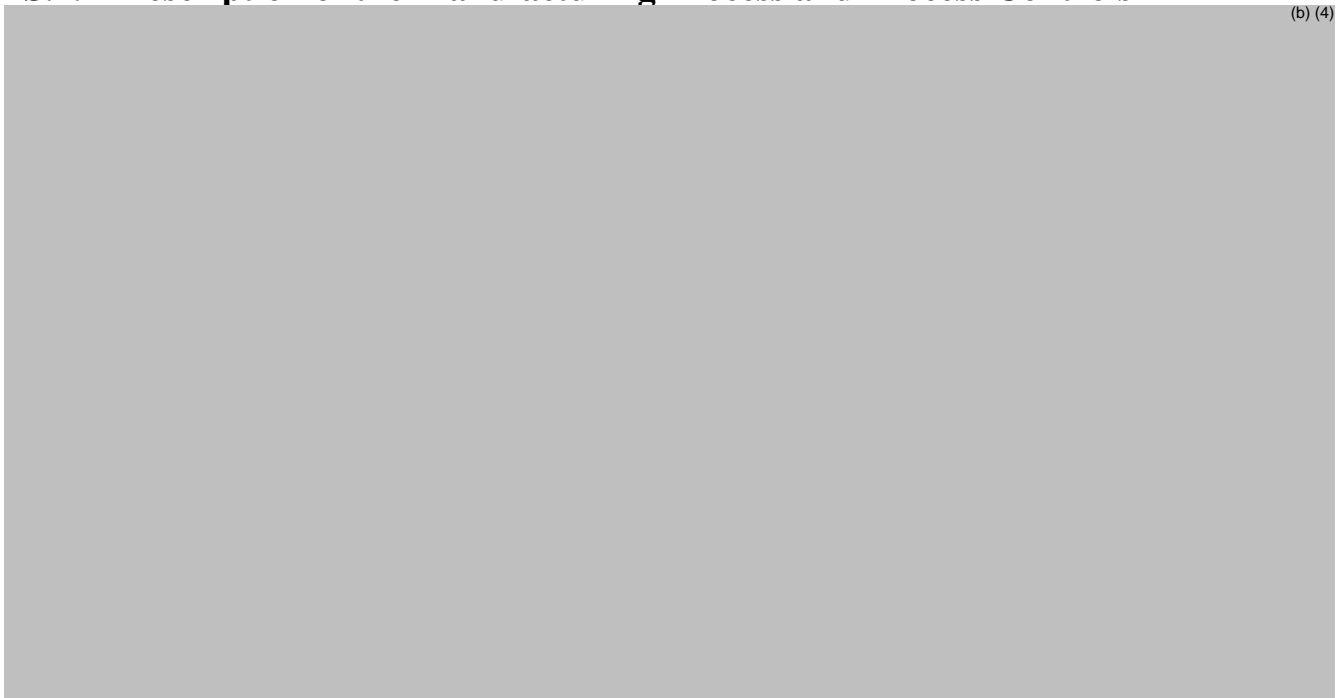
S.2.1 Manufacturers

	Responsibilities
(b) (4)	Manufacture of MCB and WCB
(b) (4)	Preparation of future WCB, storage and maintenance of MCB and WCB, DS manufacture and storage (bldg (b) (4) DS (current bldg. (b) (4) DS release and stability testing

SATISFACTORY

S.2.2 Description of the Manufacturing Process and Process Controls

(b) (4)



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(b) (4)

SATISFACTORY

S.7 Stability

The proposed DS shelf life [REDACTED] (b) (4)
[REDACTED]. All 3 PPQ batches have been

placed on stability in support of both storage conditions. Stability is also monitored under accelerated (b) (4) and stressed (b) (4) conditions as well as after 3 freeze/thaw cycles. Bioburden and endotoxin are not monitored. Post-approval, Viela Bio commits to continue primary stability studies (b) (4) with data reported annually in ARs. In addition, the Sponsor commits to place a minimum of one commercial lot on stability annually for each year DS is manufactured; samples will be stored at long-term, short-term, and accelerated conditions.

Reviewer's Comment: Aspects of the stability program not related to microbial control are deferred to OBP.

SATISFACTORY

Conclusions

1. The drug substance portion of this BLA was reviewed from a microbial control and product quality microbiology perspective and is recommended for approval.
2. Product quality aspects other than microbiology should be reviewed by OBP.
3. Refer to Panorama for the updated status of all facilities.

DS Quality Microbiology Information Requests Sent and Date

IR #1, sent 09/16/2019





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Reyes
Candau-Chacon

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Review Memorandum

STN	BLA761142
Subject	Immunogenicity Assay Review
Submission Date:	June 11, 2019
Review/Revision Date	October 28, 2019; January 31, 2020
Primary Assessor	Li Lu, PhD, Product Quality Reviewer, OPQ/OBP/DBRR IV
Secondary Assessor	Bazarragchaa Damdinsuren, MD, PhD, Team Leader
Tertiary Assessor	Christopher Downey, PhD, Review Chief
Applicant	Viela Bio
Product	Inebilizumab
Indications	Treatment of neuromyelitis optica spectrum disorder (NMOSD)
Action Due Date	June 11, 2020

Summary

Inebilizumab (also known as MEDI-551) is a humanized, (b) (4) afucosylated immunoglobulin G1 kappa monoclonal antibody that binds to B cell-specific surface antigen CD19 that leads to depletion of B cells through antibody-dependent cellular cytotoxicity mechanism.

To evaluate the immunogenicity of inebilizumab, an electrochemiluminescent, solution-phase, bridging immunoassay that employs Meso Scale Discovery technology was developed and used for detection, confirmation and titration of anti-drug antibodies (ADA) in patient serum samples (per SOP (b) (4) (b) (4)).

The applicant did not develop an assay to test for neutralization capacity of ADAs. Written responses of type C meeting dated on 8/12/2016 stated that the Agency agreed with the applicant's planned assessments of the effect of ADAs on MEDI-551 clearance and B-cell depletion in the absence of a neutralizing antibody (Nab) assay. However, the Agency recommended assessing the effect of ADAs on efficacy and safety.

The ADA assay validation evaluated specificity, precision, linearity, robustness, stability and drug tolerance. The results support that the ADA assay has acceptable accuracy and precision for screening, conformation and titration, intermediate precision, repeatability, selectivity, specificity, and matrix stability. The validation results also show that the assay sensitivity is 8.79 ng/mL for goat polyclonal Ab (PAb) and 91.15 ng/mL for mouse monoclonal clone A4 (MAb A4), both are the ADA positive controls, in serum matrix without MEDI-551. The assay sensitivity data also show that in order to detect 125 ng/mL PAb, the MEDI-551 drug level should be $\leq 100\text{-}150 \mu\text{g/mL}$ in the patient sample, and to detect 500 ng/mL MAb A4, the drug level should be $\leq 10\text{-}25 \mu\text{g/mL}$. This information is relayed to clinical pharmacology reviewers to support their assessment of the clinical immunogenicity data.

Overall, the immunogenicity assays are adequate to use and evaluate the ADAs to inebilizumab.

Review

Testing Strategy

Multi-tiered testing approach is used to evaluate ADAs against inebilizumab (MEDI-551) that includes an ADA screening, confirmatory and titer assays. Nab assay was not developed.

Assessor's comments: Rationale for not developing a specific method for the characterization of neutralizing ability of ADA-positive samples was provided to the Agency in a Type C meeting package in June 2016 (under IND 117295). The Agency agreed with the applicant's plan (see written response of the type C meeting of 8/12/2016).

We communicated the absence of the NAb assay in the application to the BLA review team. My review is for the validation of the ADA screening, confirmatory and titer assay.

ADA Assay Format

The ADA assay format is an electrochemiluminescence (ECL)-based bridging assay performed per SOP CT-050319 "Detection, Confirmation, and Titration of anti-MEDI-551 Antibodies in Human Serum by MSD ECL Assay". Briefly, in the screening assay, equimolar amounts of biotin- and sulfo-tag-labeled inebilizumab form a complex with ADA in diluted serum samples during an overnight incubation. The bridging complex is captured on a streptavidin coated microplate and signal measured by MSD Sector® Imager. The signal intensity is proportional to the amount of anti-inebilizumab antibodies present in the samples. The sample signal values are compared to a screening cut-off ECL value to determine sample positivity. The samples positive in the screening assay are tested in confirmatory assay. This assay is a competitive inhibition assay where serum samples are spiked with inebilizumab and compared with un-spiked samples. Samples with signal inhibition levels at or above the confirmatory cut point are defined as confirmed ADA positive.

All patient samples confirmed as positive are analyzed in titer assay, each sample is subjected to serial 1:2 dilution with pooled normal human serum (NHS) followed by the screening assay.

The acceptance criteria for ADA assay runs are summarized in Table 1.

Reviewer's Table 1. System Suitability and Sample Suitability Criteria for ADA Screening, Confirmatory and Titer Assays

Controls	Acceptance Criteria	Comment
Screening, confirmatory and titer assay		
Negative Quality Control (NQC)	1) The mean of a minimum of 6 of 8 wells must have a %CV $\leq$ 25% 2) The mean ECL value should be $\leq$ the upper limit of the NQC established during validation	Acceptable
Positive Quality Control (PQC, includes low [LQC] and high [HQC])	1) All LQC and HQC samples measure positive. At least 50% of the PQCs at each level must have %CVs $\leq$ 25%. 2) The ECL values of at least 50% of the PQCs at each level and at least 66.7% overall measure are within the ranges established during validation.	Acceptable
Screening Assay		

Sample acceptance	The %CV for each sample must be $\leq 25\%$ unless both replicates measure either $<$ the cut point (are negative), or $\geq$ the cut point of the assay (are positive).	<i>Acceptable. The acceptance criterion allows %CV $\geq 25\%$ when the replicates are either positive or negative, which is acceptable considering that the screening assay is qualitative assay.</i>
Confirmatory Assay		
Confirmatory Controls	1) NQC: The mean of a minimum of 6 of the 8 wells must have a %CV $\leq 25\%$, and the inhibition level of the NQC mean must be $<$ the confirmatory cut point established during assay validation 2) PQCs: at least 50% of the QCs at each level and 3 of 4 (or at least 66.7% overall if there are additional QCs) must have %CVs $\leq 25\%$, and have inhibition levels $\geq$ to the lower limit of inhibition determined during assay validation.	<i>Acceptable</i>
Sample acceptance	1) The assays must meet the confirmatory controls acceptance criteria 2) The %CV for a buffer treated (no drug) sample is $\leq 25\%$ 3) A MEDI-551 treated (+ drug) sample needs to be repeated only when %CV is $> 25\%$ and the duplicates are confirmed positive and negative. If both replicates produce the same confirmatory result, the sample does not need to be repeated even if the CV $> 25\%$.	<i>Acceptable</i>
Titer Assay		
Sample acceptance	A sample is to be re-titered if the %CV is $> 25\%$ and one of its duplicates is above the assay cut point and the other is below.	<i>Acceptable. Note, the assay allows variation of the positive samples (%CV$>25\%$).</i>

Note: details for the controls and qualifications of the cut points are discussed in the Validation section below.

Assessor's comment: *Overall the assay controls appear acceptable.*

The evaluation of inebilizumab immunogenicity in the BLA is based on data from the following 3 clinical studies:

- Phase 1 study MI-CP200 (study CP200) in adult subjects with systemic sclerosis (SSc),
- Phase 1 study CD-IA-MEDI-551-1102 (study 1102) in adult subjects with relapsing forms of multiple sclerosis (MS),
- Phase 2/3 study CD-IA-MEDI-551-1155 (study 1155) in adult patients with NMOSD.

Validation of ADA Screening, Confirmatory and Titer Assays

Validation of the MSD ECL Assay for the detection, confirmation, and titration of anti-MEDI-551 antibodies in human serum is provided in validation report CTVR-0070. Addendum 2 (CTVR-0070.ADD2) evaluates the assay's specificity and selectivity in serum samples from subjects with NMOSD and Addendum 3 (CTVR-0070.ADD3) provides additional information on determination of screening and confirmatory cut points in the NMOSD samples.

The assay validation is performed in Clinical Testing Laboratory at (b) (4). The system suitability for each of the MSD instruments and plate washers employed in the validation assays was established prior to data collection.

1) Selectivity and Qualification of normal human serum (NHS)

This was evaluated from 12 normal individuals of mixed gender and 3 different pools of NHS matrixes. Each sample and serum pool were tested both unspiked and spiked with anti-MEDI-551 antibodies (at the Low Quality Control level (LQC) 50 ng/mL). The results showed that unspiked 3 NHS matrix pools and samples of individuals had comparable mean responses (OD450 absorbance respectively 104, 101, 110 and 106, results are in report CTVR-0070, Table 11-1). Thus, the applicant chose NHS pool #2 for use as an assay matrix, as the pools are qualified for use in the ADA assays. The results show that all individual samples spiked with anti-MEDI-551 antibody at LQC levels measured positive, and the signals of 10 out of 12 samples (>80%) were within 30% of the spiked pool #2 signal. The applicant concludes the selectivity of the method is acceptable.

Assessor's comments: I agree with the applicant's conclusion that the selectivity of the method is acceptable and the NHS pool (#2) is used as negative control and assay matrix.

Addendum 2 shows that 4 of 5 (80%) unspiked NMOSD samples were correctly classified as negative in both the screening and confirmatory tiers. All 5 NMOSD samples spiked with anti-MEDI-551 antibody at LQC level screened positive, and the ECL responses of 4 of 5 samples (80%) were within 30% of the mean response of the spiked pool #2. Furthermore, all spiked NMOSD samples were confirmed positive by confirmatory assay with % inhibition values ranging from 79.5 to 92.1%.

Assessor's comment: Acceptable selectivity is shown for NMOSD patient serum samples.

2) Quality Controls (QCs)

Goat anti-MEDI-551 polyclonal antibody (PAb) was used as positive control [REDACTED] (b) (4) [REDACTED] at concentration 1.57 mg/mL). Mouse monoclonal antibody (MAb) A4 was used as positive control to determine the assay sensitivity in the presence of drug. Positive controls at low (LQC=50 ng/mL) and high (HQC=2500 ng/mL) levels were prepared by adding the PAb in NHS pool #2.

The qualification of the negative QC (NQC), LQC and HQC was performed using the screening assay procedure. A standard curve was prepared by 2-fold serial dilutions of the PAb in pool #2 in 8000 ng/mL - 15.63 ng/mL concentrations. Six replicates (12 wells) of each QC level (from the 10 standard concentrations) were tested in each assay. *The standard curve is tight (each concentration sample resulted in %CV ≤ 20% and %Bias (% of a measured value compared to the target) within ± 20%).*

Assessor's comments: The raw data presented in Table 11-2 of the report, and my analysis shows that all QCs (NQC, LQC, HQC) are classified correctly, the standard curve has a good regression covering wide positive range. I agree with the definitions of the LQC, HQC and NQC.

3) Screening and Confirmatory Cut Points

The screening and confirmatory cut points were determined using 25 female and 25 male individual NHS samples that were tested using the confirmatory assay procedure. Each sample was analyzed in duplicate wells, both with and without of excess MEDI-551, in 4 independent assays performed by 2 analysts using different MSD instruments. Each test plate included 4 NQC, 2 LQC, and 2 HQC sets each with and without MEDI-551 as required by the confirmatory method. The applicant stated that all

16 plates met the assay acceptance criteria as defined in SOP CT-050319 and evaluated for cut point determination.

For the **screening assay cut point** determination, the individual "no-drug" sample mean ECL values were normalized relative to the mean NQC value on each plate, and the values were expressed as signal to background (S:B) ratios (Tables 11-3 and 11-4 of the report). The data set consisted of 199 normalized values and were used to calculate cut point factor (CPF). The screening cut point was calculated using 3 inter-quartile ranges (3IQR) outlier criterion and was set to provide a 5% false-positive rate. Details of the analysis are described in the statistical report CTL-MEDI551-LMZ-001 "Screening Cut Point Factor Determination for the MSD ECL Anti-MEDI-551 Antibody Assay in Normal Human Serum Validated at MedImmune". Briefly, the 199 data points were tested for normality to assess the suitability of using a parametric method. The test indicated that the data violated an assumption of normality ($P < 0.001$) after the log-transformation. Subsequently, CPF was determined to be 1.21 using nonparametric approach on the log-transformed data.

For all screening ADA assays, a plate specific screening cut point value is determined by multiplying the mean ECL value of the NQC matrix blank by the CPF.

Assessor's comments: The applicant's approach for and determination of the screening cut point is acceptable.

In addition, the applicant submitted statistical report (CTL-MEDI551-JZ-003) that says the screening CPF identified from normal serum samples is considered statistically equivalent to the screening CPF identified from NMO samples (i.e. 1.12).

The **confirmatory assay cut point** was calculated from % inhibition using the % differences between the "no drug" and "+ drug" values from the 50 NHS samples (from the same experimental setting described above), as the % inhibition were calculated using the following equation:

The confirmatory cut point was calculated to be 26.3% inhibition using 1.5 inter-quartile ranges (1.5IQR) outlier criterion and was set to provide a false-positive rate of 1%.

$$\% \text{ Inhibition} = \left(1 - \frac{\text{ECL signal of sample with MEDI - 551}}{\text{ECL signal of sample without MEDI - 551}} \right) \times 100$$

Assessor's comments: The applicant's approach for and determination of the confirmatory assay cut point is acceptable.

4) Precision

Intra-assay precision (repeatability) was evaluated using the data generated in the 4 intra-assay accuracy (confirmatory) assays performed by 2 analysts. Each assay contained six 2-well determinations of each QC level without and with excess drug (i.e., NQC, LQC, HQC and NQC+drug, LQC+drug, HQC+drug). The intra-assay %CVs at all QC levels in the 4 assays ranged from 1.4% to 6.8% in the absence of drug and from 2.6% to 6.5% in the presence of drug.

Inter-assay precision was evaluated based on the %CV of the mean values of each QC from all acceptable runs (43 runs). For the screening assay, the %CVs of the mean ECL values of the LQC and HQC were 7.9% and 8.7%, respectively. For the confirmatory assay, the inter-assay %CVs of the +drug

QCs at each level were $\leq 15.5\%$, and the %CV of positive control inhibition levels was $\leq 4.1\%$ (provided in Tables 11-13 and 11-14).

Assessor's comment: The intra-assay precisions and the inter-assay precisions for the ADA assays are within the FDA Guidance for Industry (Immunogenicity Testing of Therapeutic Proteins - Developing and Validating Assays for Anti-Drug Antibody Detection) recommended limit of %CV of $\leq 20\%$, thus acceptable.

The validation shows the assay sensitivity as 8.79 ng/mL for PAb and 91.15 ng/mL for MAb A4 in serum matrix without MEDI-551, which are adequate per the guidance.

5) Robustness

Robustness was determined, in part, by evaluating the performance of confirmatory assays across analysts. The data from the 8 assay runs that were performed by the 2 analysts for determination of cut point values (described in section 3 above), were used for this evaluation. Based on the results provided in Table 11-15 of the report, the inter-analyst %CV of QCs were $\leq 5.8\%$. The overall pass rate of the assay was also evaluated. Of the 66 assay plates performed during the validation, 62 were evaluable for final assay acceptance; experiments 1 and 9 were not included since the assay plates did not include QCs, runs 3 and 4 of experiment 5 failed validation acceptance criteria and were excluded from the final evaluation (the cause was identified as the time (15 mins) after the addition of read buffer (must be read within 10 mins)). Of the 62 evaluable assays, all 62 met the final screening assay acceptance criteria, and the overall assay pass rate of the screening assay was 94% (Table 11-13) which met the acceptance criterion of $\geq 75\%$. The overall assay pass rate of the confirmatory assay was 100% (Table 11-14).

Assessor's comments: The results support that the screening and confirmatory assays are reproducible within normal variations (i.e., analysts, days, instruments and multi-plate runs). The data presented in sections 10-12 below with different variations support the assay robustness from analyte and test sample stability, and plate lot variation perspectives.

6) Accuracy and Precision of Titration

The ability of the titration assay to measure ADA titer values in human serum that are ADA positive was evaluated in 3 assays performed by 2 analysts. In each assay, the LQC and HQC samples were serially diluted (2-fold) in NHS pool #2. The results provided in Table 11-16 show that the titers of both QCs were measured within one dilution step of the estimated titer of the cut point/sensitivity of 8.79 ng/mL (see Table 11-24) on all 3 plates: For the HQC, the last positive responses were measured at 9.77 ng/mL or 4.88 ng/mL for HQC dilutions, and at 6.25 ng/mL for LQC dilutions).

Assessor's comment: These results show that the titer assay has acceptable accuracy and precision for titration results.

7) Linearity and Hook Effect

The hook effect of the ADA assay was tested by assessing the dilution responses of the ultra-high QC (80,000 ng/mL) in the titration experiment. The results show that ECL signal continuously increases up through the highest ADA concentration, and no apparent hook effect in the dose response curve.

Assessor's comment: The evaluation of the hook effect is acceptable.

When I plotted the raw data of ECL signal to QC concentration data covering from 15 to 8000 ng/mL, the data showed good linearity (with R^2 of 0.99).

8) Specificity of Detection

Specificity of the method to measure ADAs to MEDI-551, with minimal cross reactivity to unrelated antibodies, was evaluated using the anti-MEDI-551 antibodies (PAb) in LQC and HQC levels in NHS pool #2 matrix in the following combinations:

- PAb alone (control)
- PAb + unrelated ADA at the same QC level (nonspecific binding)
- PAb + excess MEDI-551 drug (specific competition)

In the presence of excess MEDI-551 drug, measured levels of PAb were by an average of 66.7% less at the LQC level and by an average of 96.0% less at the HQC level, relative to their respective controls. In the presence of an unrelated ADA, the differences of mean measured levels to the control were 1.5% at LQC and 6.8% at HQC level.

The specificity and selectivity in patient samples were evaluated in 5 serum samples from individuals diagnosed with NMOSD and in a NHS pool (CTVR-0070.ADD2). Each of the individual samples and serum pool were tested both unspiked and spiked with PAb at the LQC level. Specificity and selectivity evaluation data for NMOSD samples is presented in Table 8.2 of the report. Four of 5 (80%) unspiked NMOSD samples correctly classified as negative in both the screening and confirmatory tiers. All 5 spiked NMOSD samples screened positive and the ECL responses of 4 samples (80%) were within 30% of the mean response of the spiked NHS pool. All spiked NMOSD samples also confirmed positive upon addition of excess drug with % inhibition values ranging from 79.5 to 92.1 %.

Assessor's comments: The specificity for positive control PAb in presence of other antibody is acceptable, while drug tolerance is discussed in the following section.

The selectivity and specificity of the assay when tested NMOSD patient samples met the protocol acceptance criteria, and support that the method CT-050319 is suitable for testing of the ADAs in NMOSD patient serum.

9) Drug Tolerance

The effect of MEDI-551 drug on the measurement of ADAs to MEDI-551 in the assay was evaluated in two assays using PAb. The NHS pool #2 aliquots were spiked with MEDI-551 drug at twice the desired final concentrations of 100, 75, 50, 25, 10 and 0 ug/mL, and another set of pool aliquots was spiked with PAb at twice the desired final concentrations of 1000, 500, 250, 125, 62.5 and 0 ng/mL. The drug-ADA mixtures were prepared by combining equal volumes of the designated drug-spiked and antibody spiked serum pool. The mixture samples were incubated at room temperature for ~1 hour and measured for ECL signal. The results are provided in Table 11-18. The results show that PAb level of at least 62.5 ng/mL is detectable in the presence of 100 µg/mL of MEDI-551.

Additional experiments were performed to further evaluate the drug tolerance of the assay using Mab A4 with known binding affinity ($K_D=0.18nM$) and PAb controls. In this case, MEDI-551 drug final concentrations were 150 to 5 µg/mL with Mab A4 or PAb concentrations from 3.91 to 32,000 ng/mL. The results are summarized in Table 11-25.

Based on the data provided, the assay sensitivity is 125 ng/mL and 1000 - 2000 ng/mL respectively for PAb and Mab A4 in the presence of 150 µg/mL and 100 µg/mL MEDI-551 respectively. The assay sensitivity is 15.63 - 31.25 ng/mL and 500 - 1000 ng/mL respectively for PAb and Mab A4 in the presence of 25 µg/mL MEDI-551.

Assessor's comments: When we look at the data from the positive ADA control concentrations point, the results show that the MEDI-551 drug level should be $\leq 100-150$ µg/mL in the patient sample in order to detect 125 ng/mL PAb with the ADA assay, and the drug level should be $\leq 10-25$ µg/mL to detect 500 ng/mL MAb A4.

At the time of our assessment, a conclusive information on drug levels in patient samples (e.g., C_{trough}) was not available from the pharmacology reviewers to enable an assessment whether the above determined drug tolerance levels of the ADA assay are adequate for the patient samples. Therefore, we relayed the drug tolerance results and deferred the assessment of the suitability the drug tolerance for interpreting the clinical data to the clinical pharmacology reviewers.

On the other hand, the proposed inebilizumab dose is 300 mg to be administered on day 1 and day 15 and every 6 months thereafter. Blood concentration of the drug immediately after an infusion may reach the maximum of 60 µg/mL (300 mg/5 L). Considering the dosing scheme and potential highest concentration of the drug, the determined drug tolerance might be sufficiently high depending on the immunogenicity sampling points after infusion, but we are deferring the assessment of the clinical immunogenicity data to the clinical pharmacology reviewers.

10) Analyte Stability

Freeze-thaw stability:

The NQC, LQC, HQC samples stored at $\leq -70^{\circ}\text{C}$ were exposed to 1, 3, 5, and 7 freeze-thaw cycles (thawed at room temperature and then refrozen for >12 hours at $\leq -70^{\circ}\text{C}$). The freeze-thawed and freshly thawed QC samples were then analyzed together in screening assay.

Assessor's comment: The results provided in Table 11-19 show that all QC samples at each freeze-thaw cycle were correctly classified (i.e., either negative or positive) and the values were acceptable: %CVs $\leq 7.6\%$, $\leq 7.1\%$ and $\leq 5\%$ respectively for NQC, LQC and HQC samples, and the positive QC samples are measured within 25% of the mean value of the non-freeze-thaw controls.

Room temperature stability:

The NQC, LQC and HQC samples were analyzed for stability after being stored at room temperature for 1, 4, and ~20 hours. At the time of analysis, all QC samples were analyzed together with sets of freshly thawed control QCs.

Assessor's comments: The results provided in Table 11-20 show that all RT stored QC samples were correctly classified (i.e., either negative or positive) and the values were acceptable: %CVs $\leq 7.8\%$, $\leq 20\%$ and $\leq 7.8\%$ respectively for NQC, LQC and HQC samples, and the positive QC samples are measured within 25% of the mean value of the fresh controls.

Refrigerator stability:

The NQC, LQC, and HQC samples were analyzed for stability after being stored at $5 \pm 3^{\circ}\text{C}$ for 1, 7, and 14 days. On the day of analysis, all QCs were analyzed together with sets of freshly thawed control QCs.

Assessor's comments: The results provided in Table 11-21 show that all refrigerator stored QC samples were correctly classified and the values were acceptable: %CVs $\leq 4.4\%$, $\leq 2.4\%$ and $\leq 5\%$ respectively for NQC, LQC and HQC samples, and the positive QC samples are measured within 25% of the mean value of the fresh controls.

Overall, the analyte stability results support that QCs in NHS are stable as been exposed to up to 7 freeze-thaw cycles, stored at room temperature for up to 20 hours, or in the refrigerator for up to 14 days.

11) Stability of Measurement

The signal stability after addition of MSD read buffer to assay plates was evaluated in 4 confirmatory assay plates each containing 4 duplicates of all QC levels. The wait times after addition of read buffer were ≤ 5 , 10, 15 and 30 minutes. Based on the results provided in Table 11-22, ECL values of the plate measured within 15 minutes met the assay acceptance criteria ($\geq 66.7\%$ of the QCs at each level measured within $\pm 25\%$ of the values of initial read within 5 minutes), however, were outside of the ECL ranges established from testing the QC in Table 11-13. The longer waited plates failed the acceptance criteria.

Assessor's comment: The study results support the measurement to run within 10 minutes after addition of read buffer.

12) Meso Scale Discovery Plate Lot Variability

Three different lots of MSD high bind plates were tested for variability of performance in a typical confirmatory assay with 4 duplicates of each QC. All the plates were set up using a single batch of master mix and other critical reagents. The results provided in Table 11-23 show that the relative% differences in both ECL signals and S:B values for all QCs were under 25% across all 3 plate lots.

Assessor's comment: These results support assay robustness for MSD plate lots.

Assessor's Additional Comment: Overall, the screening, confirmatory and titer ADA assays are adequately validated for their intended use. When assessing the clinical immunogenicity results the drug presence levels should be accounted against the assay drug tolerance.



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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	June 11, 2020
Assessor:	Vicky Borders-Hemphill, PharmD Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Li Lu, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research IV
Application:	BLA 761142
Applicant:	Viela Bio, Inc.
Submission Date:	June 11, 2019
Product:	Uplizna (inebilizumab-cdon)
Dosage form(s):	injection
Strength and Container-Closure:	100 mg/10 mL (10 mg/mL) solution in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for Agency assessment
Recommendations:	The prescribing information/medication guide, container labels, and carton labeling are acceptable from an OBP labeling perspective.

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

n/a = not applicable for this assessment

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/medication guide (final versions agreed upon June 4 and June 11, 2020), container labels and carton labeling (submitted March 3, 2020) were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

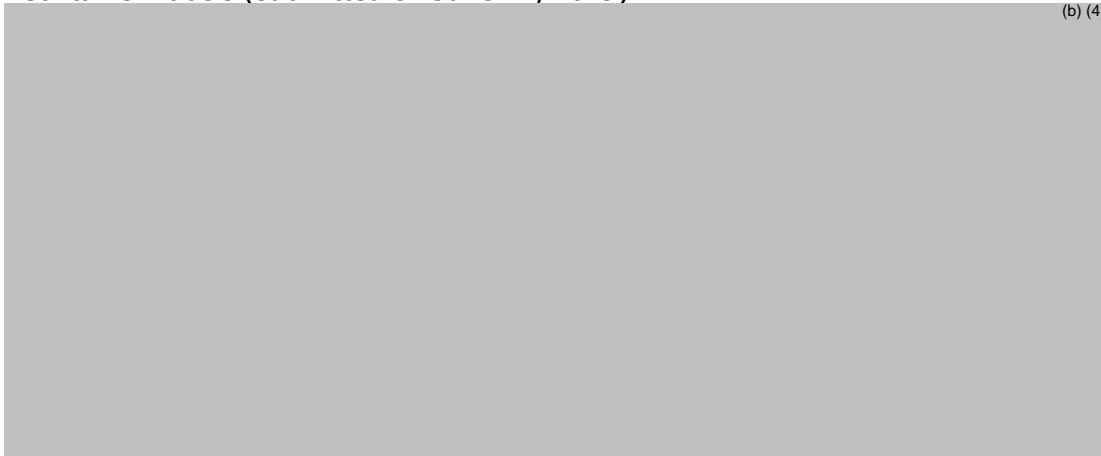
APPENDICES

Appendix A: Proposed Labeling

Prescribing Information/Medication Guide (submitted on September 5, 2019

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Container Labels (submitted on June 11, 2019)



Appendix B: Evaluation Tables

Evaluation Tables: Label^{1,2} and Labeling³ Standards

Container⁴ 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
<i>Recommended labeling practices (placement of dosage form below the proper name)</i>	☒ Yes ☐ No ☐ N/A

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
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☐ Yes ☐ No ☒ N/A
<i>Recommended labeling practices (U.S license number for container bearing a partial label)</i>	☒ Yes ☐ No ☐ N/A

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

Expiration date (container label)	Acceptable
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: USP General Chapters <7> Labeling, Draft Guidance Safety Considerations for Container Labels and</i>	☒ Yes

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.

<i>Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic</i>	☐ No ☐ N/A

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

Product Strength (container label)	Acceptable
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	☒ Yes ☐ No ☐ N/A
<i>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</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the strength presentation to include a parenthetical strength/mL as follows: "100 mg/10 mL (10 mg/mL)"
The Applicant revised as requested

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

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

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

Comment/Recommendation: partial label

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

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

Ferrule and cap overseal (for vials only)	Acceptable
<i>Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)</i>	☒ Yes ☐ No ☐ N/A

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

Applicant response: The Drug Product lot number is printed on the ferrule. There is no text on the cap overseal.

OBP labeling finds the response acceptable since per United States Pharmacopeia (USP) General Chapters: <7> Labeling, other statements or features including, but not limited to, identifying numbers or letters, such as code numbers, lot numbers, company names, logos, or product names, etc., may appear on the side (skirt) surface of the ferrule on vials containing injectable products, but not on the top (circle) surface of the ferrule or cap overseal.

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

Comment/Recommendation: 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 response: We confirm that sufficient area of the container remains uncovered to allow for visual inspection as the label does not wrap completely around the vial. Please see the photo below.



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

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

Comment/Recommendation: Add the NDC number to the container, if space permits
The Applicant provided as requested.

Preparation instructions (container label)	Acceptable
Regulation: 21 CFR 201.5(g)	☒ Yes ☐ No ☐ N/A
<i>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</i>	☐ Yes ☐ No ☒ N/A

Package type term (container label)	Acceptable
<i>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</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Consider adding the package-type term for this product, "single-dose" to the container label. Include the statement "Discard unused portion." As follows: "Single-dose vial. Discard unused portion."
The Applicant revised as requested

Misleading statements (container label)	Acceptable
Regulation: 21 CFR 201.6	☐ Yes ☐ No ☒ N/A
Prominence of required label statements (container label)	Acceptable
Regulation: 21 CFR 201.15	☒ Yes ☐ No ☐ N/A

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

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

Bar code label requirements (container label)	Acceptable
Regulations: 21 CFR 201.25, 21 CFR 610.67	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011</i> <i>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</i>	☒ Yes ☐ No ☐ N/A

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

Net quantity (container label)	Acceptable
Regulation: 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
<i>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</i> <i>Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ Yes ☐ No ☐ N/A

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

Inactive ingredients (container label)	Acceptable
Regulation: 21 CFR 201.100	☐ Yes ☐ No ☒ N/A
<i>Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling</i>	☐ Yes ☐ No

	☒ N/A

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

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

Package⁵ 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

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
<i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the manufacturer statement using the following qualifying phrase "Manufactured by:" - the licensed manufacturer must appear as: Manufactured by: Viela Bio, Inc. Gaithersburg Maryland 20878 US License No. xxxx <i>The Applicant revised as requested</i>	

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

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

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

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

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

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

Comment/Recommendation: Consider revising the number of containers in the carton to read as follows: "Contents: 3 single-dose vials"
The Applicant revised as requested

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
<i>Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize</i>	☒ Yes ☐ No

Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic USP General Chapters: <7> Labeling	☐ N/A

Comment/Recommendation: Revise the strength presentation to include a parenthetical strength/mL as follows: "100 mg/10 mL (10 mg/mL)"
The Applicant revised as requested

Storage temperature/requirements (package labeling)	Acceptable
Regulation: 21 CFR 610.61(h)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements</i>	☒ Yes ☐ No ☐ N/A

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	Acceptable
Regulation: 21 CFR 610.61(i)	☒ Yes ☐ No ☐ N/A

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

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

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

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

Comment/Recommendation: Revise the ingredient statement to read as follows: Each single-dose vial contains 100 mg of inebilizumab-cdon in 10 mL of solution. Each mL of solution contains 10 mg of inebilizumab-cdon, L-histidine (1.4 mg), L-histidine hydrochloride monohydrate (2.3 mg), polysorbate 80 (0.1 mg), sodium chloride (4.1 mg), α,α -trehalose dihydrate (40.1 mg), and Water for Injection, USP.
The Applicant revised as requested

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

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

Rx only (package labeling)	Acceptable
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	☒ Yes ☐ No ☐ N/A
<i>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</i>	☒ Yes ☐ No ☐ N/A

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

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

Bar code (package labeling)	Acceptable
Regulations: 21 CFR 610.67, 21 CFR 201.25	☒ Yes ☐ No ☐ N/A
Recommended labeling practices references: <i>Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011</i> <i>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)</i>	☒ Yes ☐ No ☐ N/A

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

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

Preparation instructions (package labeling)	Acceptable
Regulation: 21 CFR 201.5(g)	☒ Yes ☐ No ☐ N/A
<i>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</i>	☐ Yes ☐ No ☒ N/A

Package type term (package labeling)	Acceptable
<i>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</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Add the package-type term for this product, "single-dose". Include the statement "Discard unused portion." As follows: "Single-dose vial. Discard unused portion." Remove the statement (b) (4) " since the package type term (b) (4) " does not apply to your product (see 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 Guidance for Industry)
The Applicant revised as requested

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

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

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

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

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

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

Net quantity (package labeling)	Acceptable
Regulation: 21 CFR 201.51	☒ Yes ☐ No ☐ N/A
<i>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</i> <i>Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)</i> <i>USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: see inactive ingredient comment above

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

Comment/Recommendation: Add the following statement of dosage (per 21 CFR 201.55):
 "Dosage: See Prescribing Information"
The Applicant revised as requested

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

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

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	Acceptable
Regulation: 21 CFR 201.57(a)(2)	☒ Yes ☐ No ☐ N/A
<i>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</i>	☒ Yes ☐ No ☐ N/A

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

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
<i>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)</i> <i>USP chapter <659> Packaging and Storage Requirements</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: identifying characteristics of the dosage form are not required to appear in highlights dosage form and strengths.
The Applicant revised as requested

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	Acceptable
Regulation: 21 CFR 201.57(c)(3)(iv)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products</i>	☒ Yes ☐ No ☐ N/A

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	Acceptable
Regulation: 21 CFR 201.57(c)(4)	☒ Yes ☐ No ☐ N/A
<i>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)</i> <i>USP chapter <659> Packaging and Storage Requirements</i> <i>USP General Chapters: <7> Labeling</i>	☒ Yes ☐ No ☐ N/A

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

Comment/Recommendation: We deleted the proprietary name from the first paragraph since this paragraph discusses the drug substance.
The Applicant revised as requested

The pharmacological class has been added per 21 CFR 201.57(c)(12)
The Applicant revised as requested

The mechanism of action ("targeting CD19+ B cells") has been deleted since it is not required information for this section and is stated in section 12.1.
The Applicant revised as requested

The word "(b) (4)" has been deleted since it is ambiguous and not helpful for the healthcare professional.

Applicant response: This terminology is aligned with the drug product release specification.
OBP labeling response: We recommend deletion of the analytical test terminology (b) (4) for consistency with the instructions provided in section 2 of full PI for the healthcare provider to contact Viela Bio if the solution "contains discrete particulate matter". We think that describing the solution as (b) (4) may present confusion for healthcare providers.
Applicant revised as requested

Dosing information is required for section 2 and how supplied information is required for section 16 and has been removed from this section ("(b) (4) was deleted).
The Applicant revised as requested

Added the pH per 3.2.P.1 submission
The Applicant revised as requested

Full Prescribing Information	
15 Cytotoxic Drug reference	Acceptable
Regulation: 21 CFR 201.57(c)(17)(iv) xxxx is a cytotoxic drug. Follow applicable special handling and disposal procedures.1 1.OSHA Hazardous Drugs. OSHA. [Accessed on June 9, 2017, from http://www.osha.gov/SLTC/hazardousdrugs/index.html]	☐ Yes ☐ No ☒ N/A

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	Acceptable
Regulation: 21 CFR 201.57(c)(17)	☒ Yes ☐ No ☐ N/A
<i>Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products</i>	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: This (" (b) (4)) was deleted since it is redundant information that is included in the bullet point below
The Applicant revised as requested

Full Prescribing Information	
MANUFACTURER INFORMATION	Acceptable
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	☒ Yes ☐ No ☐ N/A
<i>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)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the manufacturer statement using the following qualifying phrase "Manufactured by:"
The Applicant revised as requested

Medication Guide Evaluation

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

MEDICATION GUIDE	
<u>STORAGE AND HANDLING</u>	<u>Acceptable</u>
Regulation for Medication Guide: 21 CFR 208.20(a)(2)	☐ Yes ☐ No ☒ N/A

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

MEDICATION GUIDE	
<u>MANUFACTURER INFORMATION</u>	<u>Acceptable</u>
21 CFR 208.20(b)(8)(iii)	☒ Yes ☐ No ☐ N/A
<i>21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)</i>	☒ Yes ☐ No ☐ N/A

Comment/Recommendation: Revise the manufacturer statement using the following qualifying phrase "Manufactured by:" <i>The Applicant revised as requested</i>

Patient Information Labeling Evaluation (N/A)

Instructions for Use Evaluation (N/A)



Vicky
Borders-Hemphill

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