CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761123Orig1s000

PRODUCT QUALITY REVIEW(S)

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

LABELS AND LABELING ASSESSMENT

Date of Assessment:	July 29, 2021
Assessor:	Jim Barlow, RPh Labeling Assessor Office of Biotechnology Products (OBP)
Through:	Nailing Zhang, PhD, Product Quality Assessor OBP/Division of Biotechnology Review and Research IV
Application:	BLA 761123
Applicant:	AstraZeneca AB
Submission Date:	July 31, 2020; July 14, 2021 and July 27, 2021
Product:	Saphnelo (Anifrolumab-fnia)
Dosage form(s):	Injection
Strength and Container-Closure:	300 mg/2 mL (150 mg/mL) in a single-dose vial
Purpose of assessment:	The Applicant submitted this biologics license application for the treatment of adult patients with moderate to severe systemic lupus erythematosus (SLE), (b) (4)
Recommendations:	The prescribing information, patient labeling, container labels, and carton labeling are **acceptable** from an OBP labeling perspective.

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

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, patient labeling, container labels, and carton labeling submitted on July 27, 2021 were assessed and found to be acceptable (see Appendix C) from an OBP labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information (submitted on July 31, 2020)
  \\CDSESUB1\evsprod\bla761123\0001\m1\us\nonannotated-draft-label-anifrolumab-sle.docx

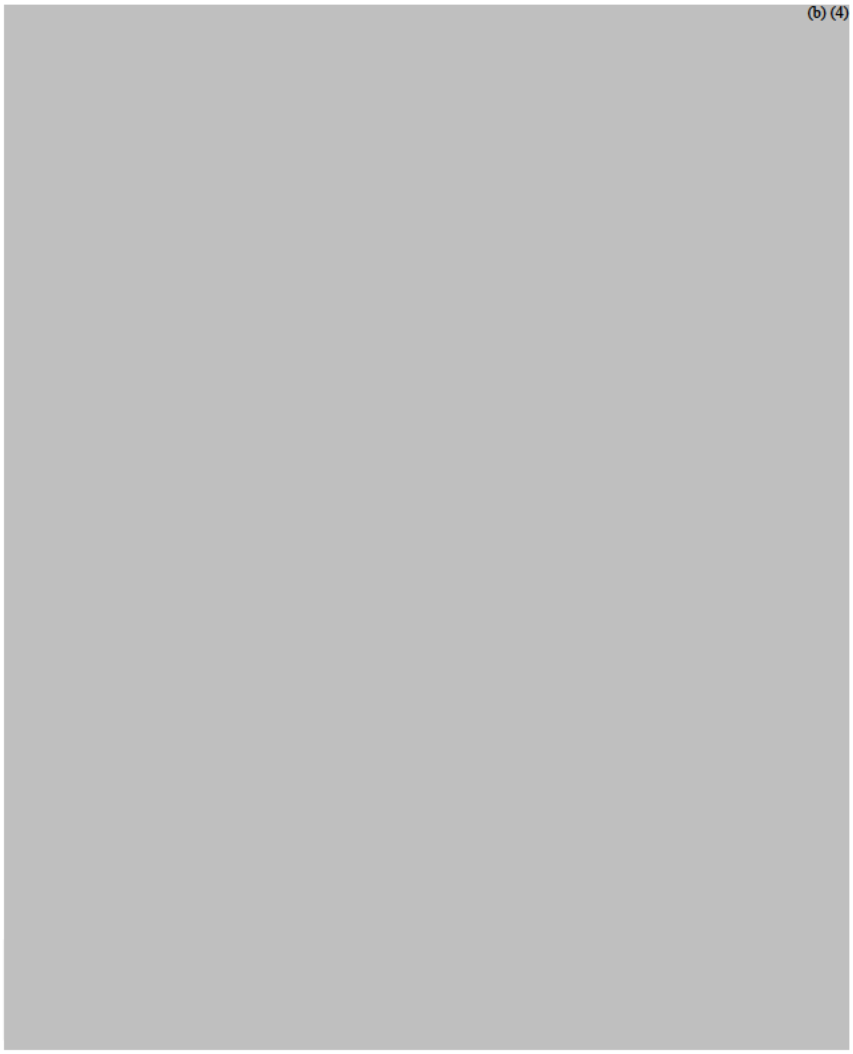
- Patient Information Labeling (submitted on July 31, 2020)
  \\CDSESUB1\evsprod\bla761123\0001\m1\us\nonannotated-draft-label-anifrolumab-sle.docx

- Container Labels (submitted on July 31, 2020)

(b) (4)

- Carton Labeling (submitted on July 31, 2020)

(b) (4)



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

Container[4] Label Evaluation

Proper Name (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	✓ Yes ☐ No ☐ N/A

Manufacturer name, address, and license number (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (U.S license number for container bearing a partial label[5])	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: Acceptable: Considered a partial label so not required

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

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.
[5] Per 21 CFR 610.60(c) *Partial Label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

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

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

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

Multiple-dose containers (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 *(recommended individual dose)*	☐ 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
Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To applicant: Relocate to different area on the PDP to avoid confusion.

Response from Applicant: Revised as requested. Acceptable.

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

	☒ N/A

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**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	✓ Yes ☐ No ☐ N/A

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

Response by the applicant:
AstraZeneca confirms that there is no embossing or printing on the ferrule and cap overseal of the vials.

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

Response from applicant:
AstraZeneca confirms that there is a sufficient area of the container remaining uncovered to allow for visual inspection. There is an approximate 3mm gap vertically on the rear of the vial from the shoulder to the base of the vial when the label is applied. Additionally, there is an approximate 3mm gap from the base of the vial to the base of the label around the circumference of the vial.

Route of administration (container label)	**Acceptable**
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation: Considered a partial label so not necessary.

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

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

Comment/Recommendation: Considered a partial label. Acceptable as is.

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

Comment/Recommendation:

To Applicant: Recommend including the package type term "Single-Dose Vial on label"

Response from the applicant: Revised as requested. Acceptable

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
Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011 *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic*	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation:
Label states 300 mg/2 mL (150 mg/mL). Accepable

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

	☒ N/A

Comment/Recommendation: The label is considered a partial label per 21 CFR 610.60 (c). Thus, the applicant will not be requested to add a statement of dosage.

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

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

Comment/Recommendation: The label is considered a partial label per 21 CFR 610.60 (c). Thus, the applicant will not be requested to add a storage statement.

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

Package[6] Labeling Evaluation

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

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

Manufacturer name, address, and license number (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	✓ Yes ☐ No ☐ N/A

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

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

Comment/Recommendation: States (b)(4) Acceptable

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

Comment/Recommendation: Contains 1 vial per carton

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation: Acceptable. Presented as 300 mg/2 mL (150 mg/mL)

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

Comment/Recommendation: Acceptable

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

Comment/Recommendation: Acceptable

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

Comment/Recommendation: Acceptable – States (b) (4)

Known sensitizing substances (package labeling)	**Acceptable**

Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:
Question to Product Quality Reviewer - Does this utilize Natural Rubber?
Rssponse: It does NOT utilize Natural Rubber.

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

Comment/Recommendation:

To applicant: Revise your ingredient state to read: "Each single-dose vial contains 300 mg (150 mg/mL) of anifrolumab-xxxx, L-histidine (3 mg), L-histidine hydrochloride monohydrate (6 mg), L-lysine hydrochloride (18 mg), polysorbate 80 (1 mg), trehalose dihydrate (98 mg) and water for injection, USP. The pH is 5.9. No preservatives. No U.S. standard of potency. The inactive ingredients are listed in alphabetical order per USP General Chapters <1091> Labeling of Inactive Ingredients, and consistent with the Prescribing Information.

Response from applicant:

Revised as requested. Acceptable

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

Comment/Recommendation: States "No US standard of potency" Acceptable

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

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

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

Comment/Recommendation: Acceptable

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011* *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)*	✓ Yes ☐ No ☐ N/A

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) and 21 CFR 610.61(i)	☐ Yes ☐ No ☒ N/A

Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic *USP General Chapters <7> Labeling*	☐ Yes ☐ No ☒ N/A

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

Comment/Recommendation: Single Dose vial. Acceptable

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

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

Comment/Recommendation:
To applicant:
Revise to read as follows "Recommended Dosage: See Prescribing Information" to be in accordance with OBP labeling practice and PLR formatting.

Reponse from applicant: Revised as requested. Acceptable

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

Other (package labeling)	Acceptable
	☐ 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
Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	✓ Yes ☐ No ☐ N/A

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

Comment/Recommendation:
To QR: Is there any issues with overfill? (b)(4) mL overfill according to the Components and Composition Statement.
Response from QR: Overfill is Acceptable

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv)] *Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*	✓ Yes ☐ No ☐ N/A

Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes) incompatibilities with these components	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To Product Quality Reviewer:
Deleted terminal zeros? Yes
Is this DP stable when diluted in 100 mL Sodium Chloride for Injection? Yes

To Product Quality Reviewer: Are the following acceptable? Yes
If not used immediately after preparation, Store the diluted solution at room temperature for up to 4 hours? Or refrigerated for up to 24 hours? Do not Freeze? Do you need to protect this from light after dilution? Are the 0.2 or 0.22 micron filters adequate to utilize?

Response: All are acceptable, However please add "Protect from light" to this section.

"Protect from light" added by the applicant July 14, 2021 submission.
Acceptable

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Question to Product Quality Reviewer: Are the identifying characteristics of the DP accurate?

"Clear to opalescent, colorless to slight yellow"

Response: Yes

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

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

Comment/Recommendation:
To Product Quality Reviewer confirmed the following-
Sterile? Yes
Preservative Free? Yes
pH is 5.9? Yes
No US standard of potency? Yes
The container/closure is not made with natural rubber? Accurate
Identifying characteristics are accurately described? (section 3).
To Product Quality Reviewer:
Are the amounts of inactive ingredients accurately expressed? Yes
Is this the actual amount per entire content of the vial (2mL) or is it calculated per mL? Yes
Are there any pH adjusters utilized? No
Also do you concur with the rearrangement of the inactive ingredients (alphabetical order)? Yes

To Applicant: Revise to include the MW.
Response: Applicant revised as requested.

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

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

Comment/Recommendation: The Product Quality Reviewer confirmed the following - Refrigerate? Yes In original carton and protect from light? Yes Do not freeze? Yes Do not shake? Yes

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: No comments

Medication Guide Evaluation N/A

Patient Information Labeling Evaluation

PATIENT INFORMATION LABELING	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Recommended Labeling Practices references: To ensure consistency with the product title in the Highlights of Prescribing Information (see Draft Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2018). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).	✓ Yes ☐ No ☐ N/A

PATIENT INFORMATION LABELING	
STORAGE AND HANDLING	**Acceptable**
Recommended labeling practices for Patient Labeling: To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)	✓ Yes ☐ No ☐ N/A

PATIENT INFORMATION LABELING	
INGREDIENTS	**Acceptable**

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

Comment/Recommendation:
To Applicant: Revised the inactive ingredients to be listed in alphabetical order per USP General Chapters <1091> Labeling of Inactive Ingredients, and to be consistent with the Prescribing Information.

Response: Firm revised as requested. Acceptable

PATIENT INFORMATION LABELING	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 201.1, 19 CFR 134.11	✓ Yes ☐ No ☐ N/A
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)	✓ Yes ☐ No ☐ N/A

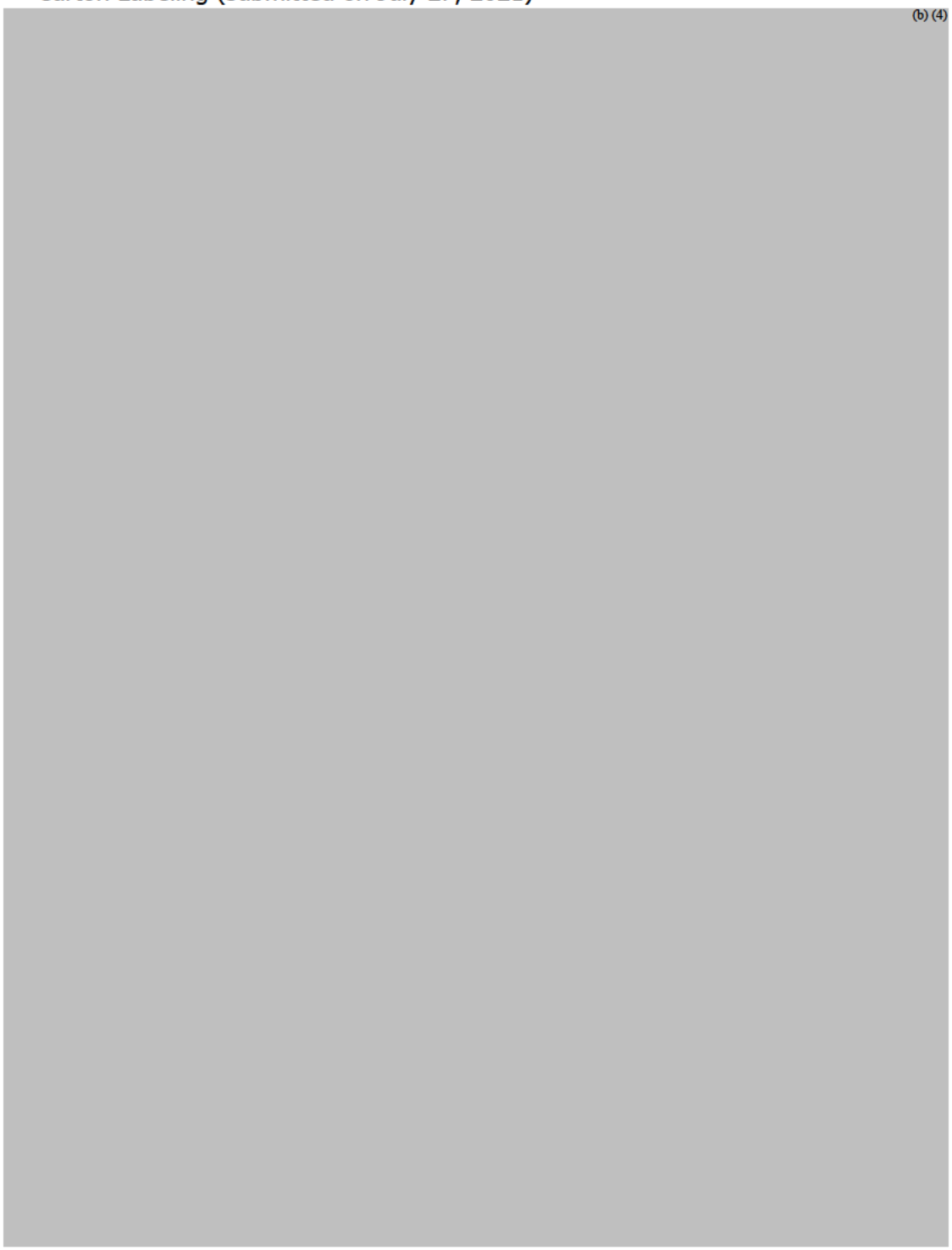
Comment/Recommendation: No comments

Instructions for Use Evaluation N/A

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information (submitted on July 27, 2021)
  \\CDSESUB1\evsprod\bla761123\0048\m1\us\nonannotated-draft-label-anifrolumab-sle.docx
- Patient Information (submitted on July 27, 2021)
  \\CDSESUB1\evsprod\bla761123\0048\m1\us\nonannotated-draft-patient-information-anifrolumab-sle.docx
- Container Labels (submitted on April 20, 2021)

- Carton Labeling (submitted on July 27, 2021)



James Barlow

Digitally signed by James Barlow
Date: 7/29/2021 09:43:30AM
GUID: 508da70800028bcca2d0465dabab258f

Nailing Zhang

Digitally signed by Nailing Zhang
Date: 7/29/2021 10:21:34AM
GUID: 57a4df210075186d6ef8d82accd1f44e

Recommendation: Approval

BLA/NDA Number: 761123
Review Number: 1
Review Date: 6/28/2021

Drug Name/Dosage Form	SAPHNELO™ (anifrolumab-fnia), injection
Strength/Potency	Vial: 300 mg/2 mL (150 mg/mL)
Route of Administration	Intravenous (IV) infusion
Rx/OTC dispensed	Rx
Indication	moderate to severe systemic lupus erythematosus (SLE)
Applicant	AstraZeneca

Product Overview:

Anifrolumab-fnia is a recombinant human immunoglobulin kappa 1 (IgG1) monoclonal antibody targeting subunit 1 of the type I interferon receptor (IFNAR1). It is expressed in mouse myeloma cells (NS0).

SAPHNELO™ (anifrolumab-fnia) injection is a preservative-free, sterile, clear to opalescent and colorless to slightly yellow solution for intravenous infusion after dilution. It is supplied in single-dose vial containing 300 mg/2 mL (150 mg/mL) anifrolumab-fnia.

Quality Review Team:

Discipline	Reviewer	Branch/Division
Drug Substance (DS)	Nailing Zhang	Division of Biotechnology Review and Research (DBRR) IV
Drug Product (DP)	Nailing Zhang	DBRR IV
Immunogenicity Assay	Nailing Zhang	DBRR IV
Labeling	James Barlow	Office of Biotechnology Products (OBP)
Facility	Ziyang Su Michael Shanks	Office of Pharmaceutical Manufacturing Assessment/ Division of Biotechnology Manufacturing (OPMA/DBM)
Facility Team Lead	Zhong Li	OPMA/DBM
Microbiology	Dupeh Palmer Maria Gutierrez-Hoffman	OPMA/DBM
Microbiology Team Lead	Maxwell Van Tassell	OPMA/DBM
Application Team Lead	Haoheng Yan	DBRR IV
RBPM	Rabiya Haider	Office of Program and Regulatory Operations (OPRO)

Multidisciplinary Review Team:

Discipline	Reviewer	Office / Division
RPM	Christine Ford	OND/ORO/DROII
Cross-disciplinary Team Lead	Raj Nair	OND/OII/DRTM
Medical Officer	Amit Golding	OND/OII/DRTM
Pharmacology/Toxicology	Xiaochun Chen	OND/OII/DPTII
Clinical Pharmacology	Lei He	OTS/OCP/DIIP
Statistics	Ling Lan	OTS/OB/DBIII

Names:

a. Proprietary Name: SAPHNELO
b. Trade Name: SAPHNELO™
c. Non-Proprietary Name/USAN: Anifrolumab-fnia
d. CAS Registry Number: 1326232-46-5
e. Common Name: MEDI-546 (company code)
f. INN Name: Anifrolumab-fnia
g. Compendial Name: Not applicable.
h. OBP Systematic Name: MAB HUMAN (IGG1) ANTI P17181 (INAR1_HUMAN) [MEDI546]

Submissions Reviewed:

Submission(s) Reviewed	Document Date
STN 761123/SN 0001,	07/31/2020
STN 761123/SN 0004,	09/28/2020
STN 761123/SN 0006,	10/13/2020
STN 761123/SN 0010	12/15/2020
STN 761123/SN 0011	12/16/2020
STN 761123/SN 0014	01/12/2021
STN 761123/SN 0034	05/18/2021
STN 761123/SN 0036,	05/25/2021
STN 761123/SN 0039	06/02/2021
STN 761123/SN 0040	06/21/2021
STN 761123/SN 0042	06/30/2021
STN 761123/SN 0044	07/09/2021

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 Review Completed	Comments
(b) (4)	III		(b) (4)	3	Adequate	5/1/2020	None
	III			3	Adequate	5/1/2020	None
	V			3	Adequate	5/26/2020	None
	V			3	Adequate	5/26/2020	None
	V			3	Adequate	5/26/2020	None

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: IND101849

3. Consults: None.

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

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761123 for SAPHNELO manufactured by AstraZeneca. The data submitted in this application are adequate to support the conclusion that the manufacture of SAPHNELO 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:

    AstraZeneca Pharmaceuticals LP
    Frederick Manufacturing Center (FMC)
    633 Research Court
    Frederick, MD 21703, USA
    FEI: 3002617771

  - Drug Product:

    MedImmune Pharma B.V.
    Nijmegen Manufacturing Facility
    Lagelandseweg 78
    6545 CG Nijmegen, Netherlands
    FEI: 3003000472

    AstraZeneca AB
    Forskargatan 18
    151 85 Sodertalje, Sweden
    FEI: 3002806411

- Fill size and dosage form:
  - Vial: 300 mg/2 mL (150 mg/mL)

- Dating period:
  - Drug Product: 24 months at 2-8°C.
  - Drug Substance: (b) (4) and (b) (4)
  - Stability:
    - For stability protocols: we have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and drug product under 21 CFR 601.12.

- Exempt from lot release:
  - Yes, SAPHNELO is a specified product and exempted from lot release per FR 95-29960.

C. Benefit/Risk Considerations:

The OPQ assessment 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 manufacturing process is sufficient for inactivation and removal of adventitious agents. All facilities used for the manufacture and quality control testing were found acceptable for the proposed operations. The BLA is recommended for approval from product quality, sterility assurance and facility perspectives.

The immunogenicity assays are sufficiently sensitive to detect anti-drug antibodies (ADA) in presence of at concentrations presented in the patient samples. ADAs were further assessed for neutralizing activity. However, the neutralizing antibody assay is not adequate due to insufficient drug tolerance. The BLA assessment team concluded neutralizing antibody analysis was not necessary for approval of the BLA because the ADA positive rate is extremely low (1.7%, 6 of 352) in the clinical studies and the ADA data alone is sufficient to characterize the immunogenicity profile of drug.

Glycosylation analysis of SAPHNELO showed that it contains (b) (4) % galactose-alpha-1,3-galactose (alpha-gal) on the product Fc domain. Alpha-gal on proteins is a known allergen that may produce anti-alpha-gal IgE mediated anaphylactic and hypersensitivity reaction. Detail analysis of the clinical data, especially the anaphylaxis and hypersensitivity cases, demonstrated that risk of alpha-gal associated hypersensitivity and anaphylaxis for SAPHNELO was low (refer to clinical review memo for detail).

There is one microbiology related post marketing commitment. The additional (b) (4) (b) (4) described in the microbiology related PMC will provide further assurance for consistently producing high quality product.

D. Recommendation on Phase 4 (Post-Marketing) Commitments (draft language)

Implement (b) (4) of anifrolumab drug product and update module 3.2.P.3.4 of the BLA with (b) (4) as a Critical Process Parameter.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

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

CQA (type)	Risk	Origin	Control Strategy	Other
Potency	Efficacy	Intrinsic to the molecule, manufacturing process and storage	(b) (4)	(b) (4)
Disulfide Structure	Efficacy, PK and immunogenicity	Intrinsic to the molecule and introduced during manufacturing process		
N-linked Glycosylation: High Mannose	PK	Intrinsic to the molecule and introduced during manufacturing process		

			(b) (4)	
High molecular weight species	Efficacy, PK and immunogenicity	Manufacturing process and storage		Stability-indicating
Low molecular weight species	Efficacy	Manufacturing process and storage		Stability-indicating
Charge variants	Efficacy and safety.	Intrinsic to the molecule. Manufacturing process and storage		Stability-indicating
Oxidized species	Efficacy and PK	Intrinsic to the molecule. Manufacturing process and storage can affect relative abundance		
Isomerization at LC CDR Asp93 and HC CDR Asp55	Efficacy	Manufacturing process and storage		Stability-indicating
FcRn binding	PK	Intrinsic to the molecule and in process		
High order structure	Efficacy and Immunogenicity	Intrinsic to the molecule, manufacturing process		
Identity	Efficacy and Safety	Intrinsic to molecule		

DS - Drug Substance, DP - Drug Product, (b) (4) LC CDR – Light Chain Complementarity-Determining Region, HC CDR - Heavy Chain Complementarity-Determining Region, Asp - Aspartate.

B. Drug Substance [anifrolumab-fnia] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

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

Category	Type	Risk	Introduction	Control Strategy

Host Cell: (b) (4)	Host cell	Host cell proteins (HCP), host cell DNA, impact patient safety	(b) (4)
(b) (4)	Process related impurity	Patient safety	
	Process related impurity	Patient safety	

(b) (4)

- Description:

Anifrolumab-fnia is an immunoglobulin G1 kappa (IgG1κ) monoclonal antibody directed against subunit 1 of the type I interferon receptor (IFNAR1). (b) (4)

Anifrolumab-fnia is produced in mouse myeloma cells (NS0) by recombinant DNA technology. The molecular weight is approximately 148 kDa. The antibody is composed of two identical heavy chains of 49 kDa each, and two identical light chains of 23 kDa each. Anifrolumab has an N-linked biantennary complex-type and high mannose oligosaccharide attached to each heavy chain at Asn-297.

- Mechanism of Action (MoA):

Anifrolumab-fnia is a human IgG1k mAb directed against subunit 1 of the type I interferon α receptor 1 (IFNAR1). It inhibits the binding of type I interferon to IFNAR1 blocking the biologic activity of type I IFNs.

- Potency Assay:

The potency of anifrolumab-fnia is determined using a cell-based bioassay that measures the ability of anifrolumab to inhibit IFN-α induced signaling resulting from the binding of anifrolumab to IFNAR1. Specifically, 293H-ISRE-Luc cells are human embryonic kidney cells transfected with a plasmid containing an interferon stimulated response element-luciferase (ISRE-Luc) cassette. Binding of IFN-α to the interferon receptor on these 293H-ISRE-Luc cells elicits expression of the luciferase reporter enzyme that is measured by the addition of a chemiluminescent substrate. Sample potency is assessed by comparing the IC50 value of each sample to the IC50 value of the Reference Standard.

- Reference Materials (RM):

AstraZeneca has established a primary reference standard (PRS) to support the commercial product. The current reference standard (b) (4) was prepared (b) (4) A description of the reference standard stability program is included in the BLA. Future RM qualification protocol is included in the BLA.

- Critical starting materials or intermediates:

(b) (4)

- Manufacturing process summary:

Anifrolumab-fnia DS is manufactured in AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center (FMC) in Frederick, Maryland, USA. (b) (4)

(b) (4) Overall, the DS manufacturing process in under adequate control.

- Container closure:

(b) (4)

- Dating period and storage conditions: (b) (4) and (b) (4)

C. Drug Product, (b) (4) 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

Category	Type	Risk	Introduction	Control Strategy
Sterility	Contaminant	Infections in patients, product stability	Accidental during fill, container closure failure	(b) (4)
Endotoxin	Contaminant	Adverse reactions in patients, DP failure	Accidental throughout process	
Appearance (Clarity and color)	General	Product stability	Formulation	
Osmolality	General	Product stability, patient discomfort	Formulation	
pH	General	DP failure, product stability	Formulation	
Visible particles	General	Safety and immunogenicity	Accidental throughout manufacturing process, CCS and stability	
Sub-visible particles				
Container closure	Process related impurities	Negative impact of leachables on product quality.	Filling/storage	

Deliverable volume	General	Inaccurate dosing	Filling/storage
Identity	General	Medication error	Manufacturing process
Protein concentration	General	Inaccurate dosing	Manufacturing process
Excipient		Safety and product stability	Manufacturing process and formulation

(b) (4)

- Potency and Strength:
  - Vial: 300 mg/2 mL (150 mg/mL)
- Summary of Product Design:
  - SAPHNELO (anifrolumab-fnia) injection is supplied in (b) (4) glass vial closed with an elastomeric stopper and capped with aluminum seal.
- List of Excipients:

Name of Excipient	Concentration
(b) (4)	

- Reference Materials: same as DS reference material.
- Manufacturing process summary: anifrolumab-fnia DP is manufactured at MedImmune Pharma B.V. Nijmegen Manufacturing Facility at Nijmegen, Netherlands. The manufacturing process involves the following steps: (b) (4) Accepted vials are labeled and packaged with into cartons at AstraZeneca AB at Sodertalje, Sweden.
- Container closure: (b) (4) clear glass vials with an elastomeric stopper, and aluminum sealing.
- Dating period and storage conditions: 24 months at 2 - 8°C.

- List of co-package components: None

D. Novel Approaches/Precedents: None.

E. Special Product Quality Labeling Recommendations: SAPHNELO should be diluted in 100mL 0.9% Sodium Chloride Injection, USP for administration.

F. Establishment Information:

Overall Recommendation: Approval			
DRUG SUBSTANCE			
Function	**Site Information**	**FEI Number**	**Assessment and Final Recommendation**
Manufacture of DS, release and stability testing, and DS storage. Storage of MCB and WCB	AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center (FMC) 633 Research Court Frederick, MD 21703, USA	3002617771	Approve – based on on-site inspection
	(b) (4)		Approve - Based on Profile
			Approve - Based on Profile
DRUG PRODUCT			
Function	**Site Information**	**FEI Number**	**Assessment and Final Recommendation**
Manufacture of DP, release testing for endotoxin, and DP storage	MedImmune Pharma B.V. Nijmegen Manufacturing Facility, Lagelandseweg 78 6545 CG Nijmegen Netherlands	3003000472	Approve - Based on facility history, Waiver granted by OPMA/OBP
Release and stability testing except sterility and endotoxin	AstraZeneca Pharmaceuticals LP Frederick Manufacturing Center (FMC) 633 Research Court Frederick, MD 21703, USA	3002617771	Approve – based on on-site inspection
Release Testing for Sterility	MedImmune UK Ltd. 6 Renaissance Way Liverpool, L24 9JW, United Kingdom	3004066112	Approve - Based on facility history
Release Testing for Sterility	(b) (4)		Approve - Based on facility history
Primary Labeling; Secondary packaging, DP storage	AstraZeneca AB Forskargatan 18 151 85 Sodertalje, Sweden	3002806411	Approve - Based on facility history

G. Facilities: See the table in F. Establishment Information

H. Lifecycle Knowledge Management:

a. Drug Substance:

   i. Protocols approved:

      1. [redacted] (b) (4) validation, Section 3.2.S.2.5
      2. [redacted] (b) (4) validation, Section 3.2.S.2.5
      3. Future working cell bank qualification, Section 3.2.S.2.3.3.5
      4. Cell bank stability testing, Section 3.2.S.2.3.3.5
      5. Future working reference standard qulification, Section 3.2.S.5.3
      6. Reference standard stability, Section 3.2.S.5.3
      7. Post-approval DS stability testing, Section 3.2.S.7.2

   ii. Outstanding review issues/residual risk: none

   iii. Future inspection points to consider: microbial controls during the DS manufacturing process

b. Drug Product

   i. Protocols approved: Post-approval DP stability testing, Section 3.2.P.8.2

   ii. Outstanding review issues/residual risk: None

   iii. Future inspection points to consider: none

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

/s/

HAOHENG N YAN
07/28/2021 01:57:37 PM

GIBBES R JOHNSON
07/28/2021 02:05:34 PM