CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761388Orig1s000

PRODUCT QUALITY REVIEW(S)

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Product Quality Assessment III

LABELS AND LABELING ASSESSMENT

Date of Assessment:	June 20, 2024
Assessor:	Diana Pei, PharmD Jennifer Kim, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	YanYan Cao, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XV
Application:	BLA 761388
Applicant:	Genentech, Inc.
Submission Date:	June 19, 2023
Product:	Piasky (crovalimab-akkz)
Dosage form(s):	Injection
Strength and Container-Closure:	340 mg/2 mL in a single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application for the use of crovalimab-akkz in the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH).
Recommendations:	The prescribing information, medication guide, container labels, and carton labeling are **acceptable** from an OPQA III 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, container labels, and carton labeling submitted on June 20, 2024, were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information (submitted on June 20, 2023)
  \\CDSESUB1\EVSPROD\bla761388\0001\m1\us\annotated-draft-labeling-text.docx
- Medication Guide (submitted on June 20, 2023)
  \\CDSESUB1\EVSPROD\bla761388\0001\m1\us\draft-medication-guide.docx
- Instructions for Use (submitted on June 20, 2023)
  \\CDSESUB1\EVSPROD\bla761388\0001\m1\us\draft-ifu.docx
- Container Labels (submitted on June 20, 2023)

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

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: *The label is small and could be considered a partial label. Thus, the qualifying phrase "Manufactured by" and manufacturer address may be omitted per 21 CFR 610.60(c).*	

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

[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."

	☐ N/A

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ 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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ 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: *The label is small and could be considered a partial label. Thus, a medication guide statement is not required per 21 CFR 610.60(c).*	

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
Comment/Recommendation: *The product contains a container label.*	

Ferrule and cap overseal *(for vials only)*	**Acceptable**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: Confirm there is no text on the ferrule and cap overseal of the vials. *The applicant confirms that there is no text 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. *The applicant confirms there is sufficient area of the container to allow for visual inspection. The label is placed around the circumference of the vial. A sufficient area of the container remains uncovered for the label's full length or circumference to permit full inspection of the vial contents. The viewing window between the two ends of the vial labels is approximately 3 mm (0.12 in).*	

(b) (4)

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:

The route of administration should appear prominently directly under the strength statement.

TRADENAME
(crovalimab-xxxx)
Injection
340 mg/2 mL
(170 mg/mL)
For intravenous use after dilution or subcutaneous use

Applicant's response March 25, 2024: *The Applicant intentionally omitted the route of administration from the vial label due to space constraints. Adding "For intravenous use after dilution or subcutaneous use" would reduce the font size for all text, which will affect the overall legibility of the container label. Omitting the route of administration on the vial label and adding it on the carton labeling is compliant with 21 CFR 201.10 (i).*

Agency response: We acknowledge your response regarding omission of the route of administration statement, "For intravenous infusion after dilution or subcutaneous use" due to space constraints. However, we identified space on the container label under the statement "Discard unused portion." Additionally, you may consider relocating the statement "Discard unused portion" to immediately after the statement with the package type term on the line above to further accommodate the route of administration statement. Thus, we recommend you add the route of administration "For intravenous infusion after dilution or subcutaneous use" in accordance with 21 CFR 201.100(b)(3).

Applicant's response May 2, 2024: *The applicant agrees to update the vial label according to FDA's comment.*

Agency response: Relocate the route of administration statement to appear directly underneath the strength statement as follows:

Piasky

(crovalimab-akkz)
Injection
340 mg/2 mL (170 mg/mL)
For Intravenous Infusion After dilution or Subcutaneous Use
Single-Dose Vial. Discard Unused Portion.

Applicant's response June 20, 2024: *The applicant revised as requested.*

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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	☐ Yes ☐ No ☒ N/A

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:
The correct package type term is "single-dose" as per FDA's guidance "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".

Applicant's response March 25, 2024: *The Applicant prefers to use the term "single-use" on the labeling. Reasons include but are not limited to:*

• Comprehension - More understandable from a lay user perspective. The term "single-use" reinforces that each vial should only be used once.

• Reduce risk of medication errors and underdosing - depending on the total prescribed dose, the number of vials will be either 1, 2 or 3 to receive a full dose. For example, 3 vials are required for a total prescribed dose of 1020 mg. The proposed carton and container label would state "single use vial". The term "single-dose" in this example may be interpreted to mean only 1 vial is needed for a complete dose instead of 3 vials. The Applicant notes the recent approval of Evenity (romosozumab-aqqg) which similarly requires two separate syringes to administer the total dose. The labeling for Evenity states "single-use prefilled syringe".

Agency response: The term "single-dose" container does not imply the entire content of the container constitute a single dose. It may contain more drug than is required or multiple vials may be needed to obtain a single dose. See 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) Page 5. Although the term "single-use" was used in Evenity to reduce confusion in describing 2 co-packaged prefilled syringes that are required for intended dose as "single-dose", the same concern does not apply for Piasky, as the dose and required number of vials can vary. The term "single-dose" also describes a container of a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirement. Furthermore, "single-use" is package type term that is no longer used in FDA labeling. In the past, "single-use" was used to describe a container that allowed for multiple doses in a single patient. **Applicant's response April 26, 2024**: *The applicant agrees to revise package type term from "single-use" to "single-dose".*

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
Comment/Recommendation: *The label does not display text in Spanish.*	

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: *The drug product does not contain FD&C Yellow No. 5 or 6.*	

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) Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ 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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) Guidance for Industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015) *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: The net quantity statement does not appear on the principal display panel of the container label. We recommend including a net quantity statement (i.e., 2 mL) on the principal display panel and ensure it is located away from and less prominent than the product strength. Additionally, ensure the net quantity is placed away from and less prominent than the product strength. See Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022). **Applicant's response March 25, 2024**: The Applicant prefers to omit the net quantity as a standalone statement from the vial label because of space constraints. Adding it would require the font size of the surrounding text to be decreased, which in turn would impact legibility. Additionally, the net quantity of 2 mL is captured in the horizontal strength color bar, which makes it recognizable and easily distinguishable. *The label is small and could be considered a partial label. Thus, applicant's response to omit net quantity is acceptable from OPQA III labeling perspective.*	

Statement of Dosage (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A
Comment/Recommendation: *The label is small and could be considered a partial label. Thus, a dosage statement is not required per 21 CFR 610.60(c).*	

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: *The label is small and could be considered a partial label. Thus, inactive ingredients are not required per 21 CFR 610.60(c).*	

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 small and could be considered a partial label. Thus, storage information is not required per 21 CFR 610.60(c).*	

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

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

[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.

	☐ 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

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

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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters: <7> Labeling*	✓ Yes ☐ No ☐ N/A

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: Consider adding a "Date removed from refrigerator (___/___/___)" under the storage information. *The applicant revised as requested.*	

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
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	✓ 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
Comment/Recommendation: *The drug product is not made with latex (natural rubber latex, dry natural rubber or synthetic derivatives of natural rubber latex).*	

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

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: Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with OPQA III Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for crovalimab products (i.e., there is no specific test method described in regulation for crovalimab products that establishes an official standard of potency) and 2) Product Quality assessors have determined that potency is not a factor within the meaning of § 610.61(r) for Piasky because lot variability is not a concern as the manufacturing process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling. Remove the statement "No U.S. standard of potency" from the container and carton labeling because our view is that 21 CFR 610.61(r) is not applicable. *The applicant revised as requested.*	

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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ 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: Guidance for Industry *Bar Code Label Requirements Questions and Answers* (August 2011) Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	✓ 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: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *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*	✓ Yes

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*	☐ No ☐ N/A

Comment/Recommendation:
The correct package type term is "single-dose" as per FDA's guidance "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".
Applicant's response March 25, 2024: *The Applicant prefers to use the term "single-use" on the labeling. Reasons include but are not limited to:*
• Comprehension - More understandable from a lay user perspective. The term "single-use" reinforces that each vial should only be used once.
• Reduce risk of medication errors and underdosing - depending on the total prescribed dose, the number of vials will be either 1, 2 or 3 to receive a full dose. For example, 3 vials are required for a total prescribed dose of 1020 mg. The proposed carton and container label would state "single use vial". The term "single-dose" in this example may be interpreted to mean only 1 vial is needed for a complete dose instead of 3 vials. The Applicant notes the recent approval of Evenity (romosozumab-aqqg) which similarly requires two separate syringes to administer the total dose. The labeling for Evenity states "single-use prefilled syringe".
Agency response: The term "single-dose" container does not imply the entire content of the container constitute a single dose. It may contain more drug than is required or multiple vials may be needed to obtain a single dose. See 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) Page 5. Although the term "single-use" was used in Evenity to reduce confusion in describing 2 co-packaged prefilled syringes that are required for intended dose as "single-dose", the same concern does not apply for Piasky, as the dose and required number of vials can vary. The term "single-dose" also describes a container of a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirement. Furthermore, "single-use" is package type term that is no longer used in FDA labeling. In the past, "single-use" was used to describe a container that allowed for multiple doses in a single patient.
Applicant's response April 26, 2024: *The applicant agrees to revise package type term from "single-use" to "single-dose"*

No 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
Comment/Recommendation: *The label does not display text in Spanish.*	

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: *The drug product does not contain FD&C Yellow No. 5 or 6.*	

Phenylalanine as a component of aspartame (package labeling)	**Acceptable**
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: *The drug product does not contain phenylalanine.*	

Sulfites; required warning statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A
Comment/Recommendation: *The drug product does not contain sulfites.*	

Net quantity (package labeling)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) Guidance for Industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products (June 2015)* *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

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: The correct package type term is "single-dose" as per FDA's guidance "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.*	

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: "Tradename is for single use only" was revised to "Tradename is for one-time use in only one patient" for clarity and to mitigate confusion with the package type term no longer used in FDA labeling, "single-use", which in the past was used to describe a container that allowed for multiple doses in a single patient. *The applicant revised as requested.* Revised to include the required verbatim statement per 21 CRF 201.57(c)(3)(iv). *The applicant revised as requested.* During product quality review, it was determined there was no data to support the (b) (4) thus it was deleted. *The applicant revised as requested.*	

We revised the storage information language for consistency with other product labeling.
Applicant's response June 13, 2024*: The applicant rejected the revision to use "or" instead of "and" to describe two different storage conditions of diluted solution at refrigerator and room temperature based on their stability data provided. Microbiology reviewer from OPMA found this to be acceptable based on the applicant's Information Request response and this is acceptable from OPQA III labeling perspective.*

We revised the diluent name to comply with USP nomenclature.
The applicant revised as requested.

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: To Applicant: The correct package type term is "single-dose" as per FDA's guidance "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.* To Applicant: Consider deleting "(b) (4)" as it may present the healthcare provider with ambiguity when deciding to discard the product. *The applicant revised as requested.*	

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 Applicant: The second paragraph discusses the drug product and includes both the proprietary name and the proper name.
The applicant revised as requested.

To Applicant: Consider deleting (b) (4)" as it may present the healthcare provider with ambiguity when deciding to discard the product.
The applicant revised as requested.

To Applicant: The name of the pH adjuster was added.
The applicant revised "L-aspartic acid" to "aspartic acid" to align with other USPIs. This is acceptable from OPQA III labeling perspective.

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: To Applicant: We added the proper name. *The applicant revised as requested.* To Applicant: We revised the package type term. *The applicant revised as requested.* To Applicant: Please clarify if the unopened vial that has been kept in room temperature (up to 30 C) in its outer carton should be discarded after 7 days. If so, consider adding further instructions for the storage such as the statement provided.	

Applicant's response May 21, 2024*: The applicant added additional text to clarify that once removed from the refrigerator, the vial can be later returned to refrigerator provided that the time at room temperature does not exceed 7 days: "Prior to administration, if needed, unopened vials of PIASKY may be stored out of the refrigerator at room temperature and then returned to refrigeration. The total combined time out of refrigeration should not exceed 7 days and the temperature should not exceed 30°C (86°F). Discard if stored out of the refrigerator at room temperature for longer than 7 days." The product quality reviewer confirmed that stability data supports this information, and the revision is acceptable from OPQA III labeling perspective.*

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

Medication Guide Evaluation

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

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

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

MEDICATION GUIDE	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 208.20(b)(8)(iii)	✓ 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

Patient Information Labeling Evaluation: NA

Instructions for Use Evaluation: NA

APPENDIX C. Acceptable Labels and Labeling

To note, additional non-product quality-related revisions may be submitted at a future date within this review cycle. Product quality-related information in this version of the labeling is acceptable from OPQA III labeling perspective.

- Prescribing Information (submitted on June 20, 2024)

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

Jennifer Kim

Digitally signed by Jennifer Kim
Date: 6/20/2024 11:55:48AM
GUID: 5e5438d2008138bdbae1db8d4abc0580

Ian McWilliams

Digitally signed by Ian McWilliams
Date: 6/20/2024 12:27:45PM
GUID: 5d8bbaa900b13f329712ebc94d4e8daa

BLA Executive Summary
Assessment Date: April 30, 2024

1. Application/Product Information

BLA number	761388
Submission Type	Original submission
Regulatory Pathway	NME 351(a), orphan designation
Associated IND/BLA	IND 131343
Review Designation	Standard review
Applicant	Genentech, Inc.
Indication	Paroxysmal Nocturnal Hemoglobinuria (PNH)
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name: PIASKY
	Non-proprietary Name/Code Name: crovalimab-akkz
	OPQA III Naming: MAB HUMANIZED (IGG1) ANTI P01031 (CO5_HUMAN) [RO7112689]
Drug Product Description	Piasky (crovalimab-akkz) is supplied as 340 mg/2 mL solution formulated in 30 mM L-histidine/L-aspartic acid buffer, 100 mM L-arginine hydrochloride, and 0.5 mg/mL poloxamer 188 at pH 5.8. Piasky (crovalimab-akkz) is a recombinant humanized anti-complement component 5 (C5) monoclonal antibody (mAb) based on a human IgG1 framework containing heavy chain (HC) VH3 and light chain (LC) VLκ1 subgroup sequences. The antibody is engineered for pH-dependent C5 binding, enhanced neonatal Fc receptor (FcRn) binding to increase half-life, and reduced Fc effector function. Crovalimab is produced in the Chinese hamster ovary (CHO) cell substrate. Piasky (crovalimab-akkz) is developed for the treatment of paroxysmal nocturnal hemoglobinuria (PNH). It binds to C5 with high affinity and blocks its cleavage into subunits C5a and C5b, thus preventing the formation of the membrane attack complex (MAC), membrane disruption, and consequent cell lysis.
Dosage Form	Liquid
Strength	340 mg/2 mL
Route of Administration	Intravenous and subcutaneous

Primary Container Closure System	Single-dose, (b) (4) glass 2 mL vial with a (b) (4) rubber stopper and aluminum seal with (b) (4) flip-off cap.		
Device Information	Not applicable.		
Co-packaged Product Information	Not applicable.		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	Zhen Ren	Ian McWilliams
	Drug product	Yanyan Cao	Ian McWilliams
	Immunogenicity Assay	Rachel Lokanga	Ian McWilliams
	Facility	Michael Shanks	Virginia Carroll
	Microbiology	Reyes Candau-Chacon	Virginia Carroll
	RBPM	Kelly Ballard	
	ATL	Ian McWilliams	
OPQ Issued Consults	None		

2. Recommendation and Conclusion on Approvability
Recommendation: Approval with PMCs/PMRs

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761388 for Piasky (crovalimab-akkz) manufactured by Roche Diagnostics GmbH and Genentech, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Piasky (crovalimab-akkz) is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

3. CMC Information for Action Letter
   a. Manufacturing Location:
      - Drug Substance:
        - Roche Diagnostics GmbH
          Nonnenwald 2
          82377 Penzberg
          Germany
          FEI: 3002806560
      - Drug Product:
        - Genentech, Inc.
          1 DNA Way
          South San Francisco, CA 94080
          United States
          FEI: 2917293

- Roche Diagnostics GmbH
  Sandhofer Strasse 116,
  68305 Mannheim
  Germany
  FEI: 3002806559

b. Fill size and dosage form:
PIASKY is supplied as a 340 mg/2 mL (170 mg/mL) solution in a single-dose 2 mL glass vial.

c. Dating Period:
- Drug Product: 36 months at 2 to 8°C. This dating period may include a single period up to 7 days at a maximum of 30°C protected from light.
- Drug Substance: (b) (4)
- For packaged products: Not packaged.
- Stability Option: Not applicable

d. Exempt from lot release:
- Yes
- Crovalimab is exempted from lot release per FR 95-29960.

e. Draft Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, as applicable:
- Develop and validate a competitive ligand binding neutralizing antibody (NAb) assay with adequate sensitivity and drug tolerance to test inhibition of crovalimab. This NAb assay will be used to test available confirmed anti-drug antibody positive samples from banked and ongoing clinical studies. Provide a final validation report detailing the performance of the NAb assay.

4. Basis for Recommendation

a. Summary:
Piasky (crovalimab-akkz) is proposed for the treatment of paroxysmal nocturnal hemoglobinuria (PNH). Crovalimab is a recombinant humanized anti-complement component 5 (C5) IgG1 that is engineered for pH-dependent C5 binding, enhanced neonatal Fc receptor (FcRn) binding to increase half-life, and reduced Fc effector function. It binds to C5 with high affinity and blocks its cleavage into subunits C5a and C5b, thus preventing the formation of the membrane attack complex (MAC), membrane disruption, and consequent cell lysis.

Crovalimab potency is monitored by the liposome immunoassay where liposomes presenting dinitrophenyl (DNP) are incubated with goat anti-DNP antibodies, C5-deficient human serum supplemented with human C5 protein, and increasing concentrations of crovalimab. Complement proteins in the human serum bind to the anti-DNP antibodies bound to the liposome surface to initiate the complement cascade. Liposome lysis releases G6PDH into the

supernatant that is quantified spectroscopically. The dose-dependent inhibition of the liposome lysis by crovalimab is quantified as a measure of potency. All potency results are reported as percentage relative to a qualified reference material.

(b) (4)

The overall crovalimab control strategy incorporates controls over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the drug substance and drug product and sterility assurance of the drug product. The manufacturing processes and overall control strategies for Piasky (crovalimab-akkz) as described in the license are appropriately established to ensure consistent quality and safety of the final product; therefore, lot variability is not a concern. Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for Roche Diagnostics GmbH (FEI 3002806560) crovalimab DS manufacturing site, and additional sterility assurance controls were provided for Genentech, Inc. (FEI 2917293) and Roche Diagnostics GmbH (FEI 3002806559) DP manufacturing sites. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage.

The antidrug antibodies (ADA) assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose for samples at (b) (4) The ADA assay performed at (b) (4) is adequately validated and suitable for their intended purpose for samples with ≤ 250 µg/mL crovalimab. Neither of the neutralizing antibody assays performed at (b) (4) or Roche (Basel, Switzerland) are suitable for use because of drug

tolerance issues (< 10 µg/mL crovalimab). An immunogenicity PMC is provided to develop a NAb assay with improved sensitivity and drug tolerance.

The BLA is recommended for approval from a product quality, facility, microbiology and sterility assurance perspectives

b. Subdiscipline Recommendation:

Drug Substance	-	Adequate
Drug Product	-	Adequate
Immunogenicity Assay	-	Adequate with PMCs/PMRs
Facilities	-	Adequate
Microbiology	-	Adequate

c. Environmental Assessment (EA):
Categorical exclusion is claimed by the applicant and deemed acceptable.

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

5. Life-Cycle Considerations
   a. Established Conditions based on ICH Q12 principles: No

   b. Drug Substance:
      i. Protocols approved:
         1. Cell bank stability monitoring
         2. Verification of (b) (4) and regeneration
         3. Verification of (b) (4) and regeneration
         4. Microbial Hold Time Validation
         5. Verification of DS (b) (4)
         6. Homogeneity of (b) (4)
         7. Container closure leachables stability study through the end of DS shelf-life
         8. Post-approval stability protocol and stability commitment

ii. Residual risk: None
iii. Future inspection points to consider: None

c. Drug Product:
   i. Protocols approved:
      1. Container closure leachables stability study through the end of DP shelf-life
      2. Preparation and qualification of future secondary reference standards (RS)
      3. Stability studies for RS
      4. Post-approval stability protocol and stability commitment
   ii. Residual risk: None
   iii. Future inspection points to consider: None

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

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

/s/

IAN L MCWILLIAMS
04/30/2024 05:57:26 PM

MARIA T GUTIERREZ LUGO
04/30/2024 05:59:20 PM