BLA 761291/S-004

SUPPLEMENT APPROVAL

Janssen Biotech, Inc.
c/o Janssen Research & Development, LLC
Attention: Raja Agnihotram
Director, Global Regulatory Affairs
920 US Highway 202, P.O. Box 300
Raritan, NJ 08869-0602

Dear Raja Agnihotram:

Please refer to your supplemental biologics license application (sBLA) dated and received June 14, 2023, and your amendments, submitted under section 351(a) of the Public Health Service Act for Tecvayli (teclistamab-cqyv) injection.

This Prior Approval sBLA provides for updating the risk evaluation and mitigation strategy (REMS) name from TECVAYLI REMS to TECVAYLI and TALVEY REMS in the labeling and proposed modifications to the approved TECVAYLI REMS to form a combined REMS with talquetamab.

We have completed our review of this supplemental application, as amended. It is approved effective on the date of this letter.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

The REMS for Tecvayli (teclistamab-cqyv) was originally approved on October 25, 2022. The REMS consists of a communication plan, elements to assure safe use, an implementation system, and a timetable for submission of assessments of the REMS.

In accordance with section 505-1 of the FDCA, we have determined that the following REMS modifications are necessary to minimize burden on the healthcare delivery system of complying with the REMS:

- Changes to the REMS document to:
  - add an additional BLA number to include Talvey (talquetamab-tgvs) – BLA 761342
  - change the name of the REMS to the 'Tecvayli and Talvey REMS'
  - update to include Talvey (talquetamab-tgvs)

- update the REMS goal

In addition, this REMS modification updates the format and content of the REMS document consistent with the FDA guidance for industry *Format and Content of a REMS Document*[1] and changes the REMS materials to incorporate Talvey (talquetamab-tgvs) – BLA 761342.

Your proposed modified REMS, submitted on June 14, 2023, amended and appended to this letter, is approved. The modified REMS consists of a communication plan, elements to assure safe use, implementation system, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments of the REMS must be revised to annually from the date of approval of the Tecvayli and Talvey REMS.

The 12-month Tecvayli REMS assessment report must be submitted by October 25, 2023, using the REMS assessment plan described in our October 25, 2022, letter. The 12-Month Tecvayli REMS Assessment Report will contain information from October 25, 2022, through one calendar day prior to the Tecvayli and Talvey REMS approval. Subsequent assessment reports will be submitted annually from the date of the Tecvayli and Talvey REMS approval.

The Tecvayli and Talvey REMS assessment plan must include, but is not limited to, the following:

For each metric, the two previous, current, and cumulative reporting periods (where applicable) unless otherwise noted will be reported.

Program Outreach and Communication

1. REMS communication plan activities (provide data for the 1-year and 2-year assessments only):

    a. Sources of the distribution lists for healthcare providers

    b. Number of healthcare providers targeted stratified by specialty if known

    c. Number of healthcare professional societies targeted, and which healthcare professional societies reported distribution of the REMS letter to their respective members

    d. The number of packets of REMS materials sent by date, attempt, and method of distribution

[1] This guidance represents the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

e. The number and percentage of emails successfully delivered, opened, and unopened

f. The number and percentage of mail successfully delivered and returned as undeliverable

g. The number of REMS Fact Sheets distributed to targeted healthcare providers during the 12 months after TECVAYLI and TALVEY REMS is approved

h. Date and name of the key scientific meetings attended and corresponding information on the REMS materials displayed

Program Implementation and Operations

2. Program Implementation (*provide data at the 1-year assessment only):

   a. *Date of first commercial availability of TECVAYLI

   b. *Date of first commercial availability of TALVEY

   c. Date the REMS Website went live

      i. Number of total visits and unique visits to the REMS Website
      ii. Number and type of REMS materials downloaded or accessed

   d. *Date the REMS Coordinating Center was fully operational

   e. Date prescribers and pharmacies/healthcare settings were able to complete the REMS certification process (online and by fax)

   f. *Date of the first prescriber certification

   g. *Date of the first pharmacy/healthcare setting certification

3. REMS Certification and Enrollment Statistics

   a. Healthcare Providers

      i. Number of certified healthcare providers that were initially certified in the TECVAYLI REMS and subsequently transitioned to the TECVAYLI and TALVEY REMS (to be provided at the 2-year assessment only)

      ii. Number of newly certified healthcare providers and the number and percentage of active (i.e., for whom a REMS Dispense Authorization for

TECVAYLI or TALVEY has been generated at least once during the reporting period), stratified by:

1) Credentials (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Nurse Practitioner, Physician Assistant, other)

2) Specialty (e.g., Oncology, Hematology, Internal Medicine/Family Medicine, Other). If "other" accounts for >10% of respondents for specialties, provide the most common specialties identified.

3) Geographic region as defined by the US Census

4) Method of enrollment (e.g., online, fax, e-mail) for newly certified healthcare providers only

iii. Number of incomplete prescriber enrollments, and summary of reported reason(s) for not completing

b. Pharmacies and Healthcare Settings

i. Number of certified pharmacies/healthcare settings that were initially certified in the TECVAYLI REMS and subsequently transitioned to the TECVAYLI and TALVEY REMS (to be provided at the 2-year assessment only)

ii. Number of newly certified pharmacies/healthcare settings and the number and percentage of active (i.e., who have dispensed or ordered the drug at least once during the reporting period) pharmacies/healthcare settings stratified by:

1) Type of pharmacy/healthcare setting (e.g., Inpatient Hospital Pharmacy, Outpatient Hospital Pharmacy, Oncology Infusion Center, Community Oncology Physician Office, Other). If "other" accounts for > 10% of respondents for type, provide the most common type(s) identified.

2) Geographic region as defined by the US Census

3) Method of enrollment (e.g., online, fax, e-mail) for newly certified pharmacies/healthcare settings only

iii. Number of incomplete pharmacy/healthcare setting enrollments, and summary of reported reason(s) for not completing

c. Wholesalers/distributors

i. Number of wholesalers/distributors contracted to ship and number of active (i.e., have shipped) wholesalers/distributors

4. Utilization Data

a. Number of vials sent to certified pharmacies/healthcare settings, stratified by each drug and by type of pharmacy/healthcare setting

b. Number and percentage of healthcare providers for whom at least one REMS Dispense Authorization was generated, stratified, for each drug, by medical specialty (e.g., oncology) and provider credentials (e.g., Doctor of Medicine)

c. Number of dispense authorizations stratified by pharmacy/healthcare setting type

d. Number of RDAs rejected, stratified by each drug:

i. Reasons and number of denials (numerator) divided by all denials (denominator)

1) Healthcare provider not certified
2) Pharmacy or Healthcare Setting not certified
3) Other reasons for denial not categorized above

e. The percentage of dispensed prescriptions that were authorized by the REMS prior to dispense. REMS authorization for dispense requires both the prescriber and the pharmacy/healthcare setting be certified

5. REMS Compliance

a. Audits

i. A copy of the audit plan

ii. Report of audit findings for each stakeholder

iii. Number of audits expected, and the number of audits performed

iv. Documentation of completion of training for relevant staff

v. Documentation of processes and procedures in place for complying with the REMS

vi. Verification for each audited stakeholder's site that the designated Authorized Representative remains the same. If different, include the number of new Authorized Representatives

vii. Number and type of deficiencies (e.g., critical. major, or minor findings) noted for each group of audited stakeholders as a percentage of audited stakeholders

viii. Confirmation of documentation of completion of training for relevant staff after audit findings indicated training was necessary

ix. A comparison of the findings to findings of previous audits and an assessment of whether any trends are observed

b. A copy of the Noncompliance Plan which addresses the criteria for noncompliance for each stakeholder (healthcare providers, pharmacies/healthcare settings and wholesalers-distributors), actions taken to address noncompliance for each event, and under what circumstances a stakeholder would be suspended or decertified from the REMS

i. For those with deficiencies noted, report the number that successfully completed a Corrective and Preventive Actions (CAPA) plan within the timeframes specified in the Noncompliance Plan

ii. For any that did not complete the CAPA within the timeframe specified in the Noncompliance Plan, describe actions taken

iii. Number of instances of noncompliance accompanied by a description of each instance and the reason for the occurrence (if provided). For each instance of noncompliance, report the following information:

1) Unique ID(s) of the stakeholder(s) associated with the noncompliance event or deviation to enable tracking over time

2) Source of the noncompliance data

3) Results of root cause analysis

4) Action(s) that were taken in response

iv. Pharmacies/healthcare settings

1) Number of pharmacies/healthcare settings for which non-compliance with the REMS is detected (numerator) divided by all pharmacies/healthcare settings dispensing TECVAYLI or TALVEY (denominator)

2) Number and description of pharmacies/healthcare settings that dispensed TECVAYLI or TALVEY to non-certified prescribers, and any corrective and preventative actions taken to prevent future occurrences

3) Number of non-certified pharmacies/healthcare settings that dispensed TECVAYLI or TALVEY (numerator) divided by all pharmacies/healthcare settings that dispensed TECVAYLI or TALVEY

4) Number of prescriptions dispensed by non-certified pharmacies/healthcare settings (numerator) divided by all TECVAYLI and TALVEY prescriptions dispensed (denominator) and the actions taken to prevent future occurrences

5) Summary of audit findings and any action taken and outcome of actions to prevent future occurrences

6) Summary of findings for monitoring conducted during the reporting period, including any CAPA

v. Wholesalers/Distributors

1) Number and description of non-certified pharmacies/healthcare settings that were shipped TECVAYLI or TALVEY, and the number of these that subsequently became certified

2) The number of authorized wholesalers-distributors for which non-compliance with the REMS is detected (numerator) divided by the number of contracted wholesalers-distributors (denominator)

3) The number and type of wholesalers-distributors not contracted with Janssen that shipped TECVAYLI or TALVEY, the number of incidents for each, actions taken to remove TECVAYLI or TALVEY from these entities, actions taken to prevent future occurrences, and outcomes of such actions

4) The number of contracted wholesalers-distributors suspended and/or unauthorized to distribute for non-compliance with REMS requirements, reasons for such actions and actions taken to prevent distribution or removal of TECVAYLI or TALVEY from these entities

c. Any other TECVAYLI and TALVEY REMS noncompliance, source of report and resulting CAPA

6. REMS Coordinating Center Report

   a. Number of contacts by stakeholder type (patient/caregiver, certified prescriber, pharmacy/healthcare setting authorized representative or staff, other HCP, wholesaler/distributor, other)

   b. Summary of the reasons for the call(s) by stakeholder type. Limit the summary to the top five reasons for calls by stakeholder group

   c. Description of each call, including stakeholder credentials, that may indicate an issue with product access due to the REMS program, REMS program burden or adverse event

   d. If the summary reason for the call(s) indicates an adverse event related to Cytokine Release Syndrome (CRS) or neurologic toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS) include details and the outcome of the call(s)

   e. Provide an assessment for any reports to the REMS Coordinating Center indicating a burden to the healthcare system or barrier(s) to patient access. Include in the assessment whether the burden or access issue is attributable to the REMS, insurance, health care availability, other

   f. Summary of frequently asked questions (FAQ) by stakeholder credentials type. Limit the summary to the top five FAQs for calls by stakeholder group

   g. Summary of any noncompliance that is identified through coordinating center contacts, source of report and resulting CAPA

   h. Summary of CAPAs resulting from issues identified

   i. Percentage of calls to the REMS Coordinating Center that were answered within 20 minutes

   j. The shortest wait time for a call to be answered, the longest wait time for a call to be answered and the median time for a call to be answered

   k. Percentage of calls to the REMS Coordinating Center where the caller abandoned the call before the call was answered

   l. The shortest wait time at which a call was abandoned, the longest wait time before the call was abandoned and the median wait time for a call to be abandoned

Knowledge

7. Knowledge Assessment

    a. Number of completed healthcare provider Knowledge Assessments, including the method of completion

    b. Summary statistics, including mean number of attempts, score, and range of scores and number of attempts to successfully complete the Knowledge Assessment

    c. Summary of most frequently missed questions on the Knowledge Assessment

    d. A summary of potential comprehension or perception issues identified with the Knowledge Assessment

8. Periodic Survey of Certified Prescribers (beginning with the 1-Year REMS Assessment Report and thereafter with each assessment report)
   A Knowledge, Attitude and Behavior (KAB) Survey will be conducted with random samples of healthcare providers who prescribe TECVAYLI or TALVEY

    a. Evaluation of understanding of the risks for CRS and neurologic toxicity including ICANS associated with Tecvayli and Talvey use and mitigation strategies of the TECVAYLI and TALVEY REMS as well as compliance with the mitigation strategies

    b. An evaluation of prescriber's knowledge on the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS

    c. Provide the proportion of KAB prescriber survey respondents that demonstrated knowledge of the importance of monitoring patients for signs and symptoms of CRS and neurologic toxicity including ICANS

Health Outcomes and/or Surrogates of Health Outcomes

9. A summary analysis of all reported cases of CRS and neurologic toxicity including ICANS, stratified by source of report (i.e., spontaneous)

    a. Include the following stratifications by grade/severity in the analysis

        i. Step-up dosing was initiated in the hospital setting (For those reports that indicate initiation outside of the hospital setting provide the setting if known)

ii. Pre-medication was administered

Overall Assessment of REMS Effectiveness

10. The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use, as described in section 505-1(g)(2)(A) of the FDCA. This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication.

b) A determination of the implications of a change in the benefit-risk profile for the current REMS.

c) *If the new indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of that last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing*

REMS modifications, provide a rationale for why the REMS does not need to be modified.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

BLA 761291 REMS ASSESSMENT METHODOLOGY
(insert concise description of content in bold capital letters, e.g.,
ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

BLA 761291 REMS ASSESSMENT

or

NEW SUPPLEMENT FOR BLA 761291/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761291/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION

or

NEW SUPPLEMENT FOR BLA 761291/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 761291/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISIONS FOR BLA 761291

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, or website screenshots are only in PDF format, they may be submitted as such, but Word format is preferred.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format using the FDA automated drug registration and listing system (eLIST). Content of the REMS document must be identical to the approved REMS document. The SPL will be publicly available.

Information on submitting REMS in SPL format may be found in the guidance for industry *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling.*

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[2] that is identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

[2] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[3]

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

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[3] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] For the most recent version of a guidance, check the FDA guidance web page athttps://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, contact Jessica Kim, Safety Regulatory Project Manager, at 240-402-0883, or via email at Jessica.Kim1@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Shan M. Pradhan, M.D.
Associate Director for Safety
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- REMS

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/

SHAN PRADHAN
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