

BLA 761342

## BLA ACCELERATED APPROVAL

Janssen Biotech, Inc.  
Attention: Limei Xu, PhD, RAC  
Associate Director, Global Regulatory Affairs  
800/850 Ridgeview Dr.  
Horsham, PA 019044

Dear Dr. Xu:

Please refer to your biologics license application (BLA) dated and received December 9, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for Talvey (talquetamab-tgvs) injection.

### **LICENSING**

We have approved your BLA for Talvey (talquetamab-tgvs) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Talvey under your existing Department of Health and Human Services U.S. License No. 1864. Talvey is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

### **MANUFACTURING LOCATIONS**

Under this license, you are approved to manufacture talquetamab-tgvs drug substance at Janssen Sciences Ireland UC, Cork, Ireland (FEI: 3007029098). The (b) (4) (b) (4) will be manufactured at (b) (4) and the (b) (4) will be manufactured at Janssen Sciences Ireland UC, Cork, Ireland (FEI: 3007029098). The final formulated product will be manufactured, filled, labeled, and packaged at (b) (4). You may label your product with the proprietary name Talvey and market it in 3 mg/1.5 mL and 40 mg/mL injection in single-dose vials.

### **DATING PERIOD**

The dating period for Talvey shall be 18 months from the date of manufacture when stored at  $5 \pm 3$  °C, protected from light. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4).

(b) (4) °C. The dating period for the (b) (4) shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C. The dating period for the (b) (4) shall be (b) (4) months from the date of manufacture when stored at (b) (4) °C.

We have approved the stability protocol in your license application for the purpose of extending the expiration dating period of your (b) (4) drug substance and drug product under 21 CFR 601.12.

### **FDA LOT RELEASE**

You are not currently required to submit samples of future lots of Talvey to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Talvey, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

### **APPROVAL AND LABELING**

We have completed our review of this application, as amended. It is approved under accelerated approval pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and 21 CFR 601.41, effective on the date of this letter, for use as recommended in the enclosed agreed-upon approved labeling. This BLA provides for the use of Talvey for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody.

Marketing of this drug product and related activities must adhere to the substance and procedures of the accelerated approval statutory provisions and regulations.

### **WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS**

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

### **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.<sup>1</sup> Content of labeling must be identical to the enclosed labeling (Prescribing Information and Medication Guide). Information on submitting SPL files using eLIST may be found in the draft guidance for industry *SPL Standard for Content of Labeling Technical Qs and As* (October 2009).<sup>2</sup>

The SPL will be accessible via publicly available labeling repositories.

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

### **CARTON AND CONTAINER LABELING**

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (February 2020, Revision 7)*. For administrative purposes, designate this submission “**Final Printed Carton and Container Labeling for approved BLA 761342.**” Approval of this submission by FDA is not required before the labeling is used.

### **ADVISORY COMMITTEE**

Your application for talquetamab-tgvs was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the biologic in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

### **ACCELERATED APPROVAL REQUIREMENTS**

Pursuant to section 506(c) of the FDCA and 21 CFR 601.41, you are required to conduct further adequate and well-controlled clinical trials intended to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If required postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, including with respect to the conditions set forth below, we may, withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated August 4, 2023. This requirement is listed below.

- 4473-1 Conduct a randomized clinical trial that evaluates the clinical efficacy and safety of talquetamab in patients with relapsed or refractory multiple myeloma. Patients should be randomized to receive a talquetamab-based regimen compared to standard therapy for relapsed or refractory multiple

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<sup>1</sup> <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

<sup>2</sup> When final, this guidance will represent FDA’s current thinking on this topic. 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>.

myeloma. The primary endpoint should be progression-free survival and secondary endpoints should include overall survival and overall response rate. The trial should enroll sufficient numbers of racial and ethnic minority patients and older patients (ages 65-74 years and 75 years and above) to enable an evaluation of talquetamab in a study population that reflects the U.S. population of patients with multiple myeloma.

The timetable you submitted on August 4, 2023, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 12/2023

Trial Completion: 06/2026

Final Report Submission: 12/2026

Submit clinical protocols to your IND 133811 for this product. FDA considers the term final to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.

You must submit reports of the progress of each clinical trial required under section 506(c) (listed above) to this BLA 180 days after the date of approval of this BLA and approximately every 180 days thereafter (see section 506B(a)(2) of the FDCA) (hereinafter “180-day reports”).

You are required to submit two 180-day reports per year for each open study or trial required under 506(c). The initial report will be a standalone submission and the subsequent report will be combined with your annual status report required under section 506B(a)(1) of the FDCA and 21 CFR 601.70. The standalone 180-day report will be due 180 days after the date of approval (with a 60-day grace period). Submit the subsequent 180-day report with your annual status report. Submit both of these 180-day reports annually until the final report for the corresponding study or trial is submitted.

FDA will consider the submission of your annual status report under section 506B(a)(1) and 21 CFR 601.70, in addition to the submission of reports 180 days after the date of approval each year (subject to a 60-day grace period), to satisfy the periodic reporting requirement under section 506B(a)(2).

180-day reports should include:

- date first participant enrolled in each study or trial, if enrollment has started
- anticipated study or trial completion and final report submission dates
- any changes in plans since the last report with rationale for any changes
- the number of participants enrolled to date in each study or trial
- the number of planned participants, per the final protocol

180-day reports, including both the standalone 180-day report submitted 180 days after the date of approval (with 60-day grace period) and the 180-day report submitted with your annual status report, must be clearly designated “**180-Day AA PMR Progress Report.**”

Submit final reports to this BLA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated “**Subpart E Postmarketing Requirement(s).**”

### **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 this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

### **POSTMARKETING REQUIREMENTS UNDER 505(o)**

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of oral toxicity including severe stomatitis, mucositis, and weight loss.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of oral toxicity including severe stomatitis, mucositis, and weight loss.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following trial:

- 4473-2 Conduct a clinical trial to further characterize the serious risk of oral toxicity including severe stomatitis, mucositis, and weight loss, and potential mitigation measures, in patients receiving talquetamab 0.4 mg/kg weekly and talquetamab 0.8 mg/kg every two weeks. Evaluate incidence

rates, time to onset, and outcomes including patient reported outcomes. Include investigation of associations and temporal relationships between incidence and severity of oral toxicity adverse events and other potential risk factors such as age, race and comorbidities, and impact of the mitigation measures evaluated. The study should enroll sufficient numbers of Black/African American patients to enable an evaluation of the serious risk of oral toxicity with talquetamab in this population.

The timetable you submitted on August 4, 2023, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission: 02/2024

Final Protocol Submission: 08/2024

Trial Completion: 03/2027

Final Report Submission: 09/2027

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.<sup>3</sup>

Submit clinical protocol(s) to your IND 133811 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:  
**Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

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<sup>3</sup> See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019)*.  
<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

**POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments:

- 4473-3 Evaluate overall response rate and duration of response with talquetamab 0.4 mg/kg weekly and talquetamab 0.8 mg/kg every two weeks, administered as monotherapy in patients with relapsed or refractory multiple myeloma who have received at least 4 prior lines of therapies including a proteasome inhibitor, immunomodulatory agent, and anti-CD38 monoclonal antibody and have been exposed to T cell redirection therapy, from trial 64407564MMY1001 (MonumenTAL-1).

The timetable you submitted on August 4, 2023, states that you will conduct this study according to the following schedule:

Trial Completion: 09/2024  
Final Report Submission: 03/2025

Submit the datasets with the final report submission.

- 4473-4 Conduct an assessment of neutralizing anti-drug antibody (NAb) responses in all talquetamab treated patients from Study MonumenTAL-1 with a validated assay capable of sensitively detecting NAb responses in the presence of talquetamab concentrations that are expected to be present in the serum at the time of patient sampling. Include information on the concentration of talquetamab in each patient's test sample at each sampling point and an assessment of the effects of NAb on talquetamab exposure, safety, and efficacy.

The timetable you submitted on August 4, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2023

**POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments:

- 4473-5 Develop and validate a sensitive assay for accurate detection of neutralizing antibodies (NAb) to talquetamab in the presence of drug levels that are expected to be present in the serum or plasma at the time of patient sampling. The NAb assay procedures and method validation report will be submitted in the final report to the BLA.

The timetable you submitted on July 10, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2023

- 4473-6 Perform real-time drug product commercial container closure system leachate studies using appropriate test methods to identify and quantify volatile organic compounds (VOC), semi-VOC, non-VOC, and trace metals at regular intervals through the end of shelf life. The study results will be updated annually in the BLA Annual Report. The final results of this study and the toxicology risk evaluation for the levels of leachates detected in the drug product will be provided in the final study report to the BLA.

The timetable you submitted on July 10, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/2024

- 4473-7 Perform a supplemental low endotoxin recovery (LER) study to examine the effects of (b) (4) at (b) (4) °C on endotoxin recovery using 3 batches of both 2 mg/mL and 40 mg/mL talquetamab spiked with RSE or CSE and stored up to (b) (4) days at (b) (4) °C to verify that the (b) (4) has no impact on endotoxin recovery.

The timetable you submitted on July 24, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 04/2024

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 133811 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical

studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

## **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Talvey (talquetamab-tgvs) to ensure the benefits of the drug outweigh the risks of Cytokine Release Syndrome (CRS) and neurologic toxicity including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS).

Your proposed REMS must also include the following:

**Communication Plan:** We have determined that a communication plan targeted to healthcare providers who are likely to prescribe and care for patients treated with Talvey (talquetamab-tgvs) will support implementation of the elements of your REMS. The communication plan provides for the dissemination of information about CRS and neurologic toxicity, including ICANS as well as requirements for prescriber certification and pharmacy or healthcare setting certification.

The communication plan must include, at minimum, the following:

- REMS Letters to Healthcare Providers and Professional Societies
- REMS Factsheet
- Dissemination of the REMS Letters and REMS Factsheet through field-based sales, medical representatives, professional societies, and professional meetings.

**Elements to assure safe use:** Pursuant to 505-1(f)(1), we have also determined that Talvey (talquetamab-tgvs) can be approved only if elements necessary to assure safe use are required as part of the REMS to mitigate the risks of CRS and neurologic toxicity, including ICANS, listed in the labeling of the drug.

Your REMS includes the following elements to mitigate these risks:

- Healthcare providers have particular experience or training, or are specially certified
- Pharmacies or health care settings that dispense the drug are specially certified

**Implementation System:** The REMS must include an implementation system to monitor, evaluate, and work to improve the implementation of the elements to assure

safe use (outlined above) that require pharmacies and health care settings that dispense the drug be specially certified.

Your proposed REMS, submitted on December 9, 2022, amended and appended to this letter, is approved.

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.

Talvey will be subject to a REMS with Tecvayli (BLA 761291) which was approved with a REMS on October 25, 2022. The REMS will be known as the Tecvayli and Talvey REMS. Talvey will be subject to the same REMS assessment plan as Tecvayli.

Your REMS must be fully operational before you introduce Talvey (talquetamab-tgvs) into interstate commerce.

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
  - 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

- i. 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.

If the information provided in an assessment is insufficient to allow FDA to determine whether the REMS is meeting its goals or whether the REMS must be modified, FDA may require the submission of a new assessment plan that contains the metrics and/or methods necessary to make such a determination. Therefore, FDA strongly recommends obtaining FDA feedback on the details of your proposed assessment plan to ensure its success. To that end, we recommend that methodological approaches, study protocols, other analysis plans and assessment approaches used to assess a REMS program be submitted for FDA review as follows:

- i. Submit your proposed audit plan and non-compliance plan for FDA review within 60 days of this letter.
- ii. Submit your proposed protocol for the knowledge survey for FDA review within 90 days of this letter.

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 761342 REMS ASSESSMENT METHODOLOGY**

(insert concise description of content in bold capital letters, e.g.,

**ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)**

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). 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, proposed 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 the 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 a REMS modification, provide a rationale for why the REMS does not need to be modified.*

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 761342 REMS ASSESSMENT**

*or*

**NEW SUPPLEMENT FOR BLA 761342/S-000  
CHANGES BEING EFFECTED IN 30 DAYS  
PROPOSED MINOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR BLA 761342/S-000  
PRIOR APPROVAL SUPPLEMENT  
PROPOSED MAJOR REMS MODIFICATION**

*or*

**NEW SUPPLEMENT FOR BLA 761342/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 761342 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 REVISION FOR BLA 761342**

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, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

**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 additional information on submitting REMS in SPL format, please email [FDAREMSwebsite@fda.hhs.gov](mailto:FDAREMSwebsite@fda.hhs.gov).

**PROMOTIONAL MATERIALS**

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

U.S. Food and Drug Administration  
Silver Spring, MD 20993  
[www.fda.gov](http://www.fda.gov)

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

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*.<sup>4</sup>

## **REPORTING REQUIREMENTS**

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80).

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Compliance Risk Management and Surveillance  
5901-B Amundson Road  
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Compliance Risk Management and Surveillance  
10903 New Hampshire Avenue, Bldg. 51, Room 4207  
Silver Spring, MD 20903

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<sup>4</sup> <https://www.fda.gov/media/128163/download>

## **POSTMARKETING SAFETY REPORTS**

We request that for Talvey, you submit all cases describing a wrong drug error or the potential for a wrong drug error involving Talvey as 15-day “Alert reports” (described under 21 CFR 600.80(c)(1)) through the 3<sup>rd</sup> year following initial U.S. approval.

We request that you provide a separate narrative summary and analysis for the cases of wrong drug error or the potential for a wrong drug error involving Talvey in each required postmarketing periodic safety report (e.g., Periodic Adverse Experience Report [PAER] required under 21 CFR 600.80(c)(2)).

Your narrative summary and analysis should include an interval and cumulative assessment of each wrong drug error or the potential for a wrong drug error involving Talvey, and a line listing of the cases for the reporting interval. Your narrative summary should include an assessment of the following:

- The number of cases reporting that a patient was administered a wrong drug. Include a breakout by the name of the prescribed product and the product administered.
- The number of cases or complaints describing the potential for a wrong drug error (including close call/near miss or intercepted errors, or circumstances capable of leading to a wrong drug error). Include a breakout by the name of the prescribed product and the product that could have inadvertently been administered.
- The reported contributing factors that led to or could lead to a wrong drug error (e.g., products stored next to each other, similar packaging, container label or carton labeling design, incorrect association with step-up dosing schedules, sound alike or look alike names).
- Reporter recommendations or actions taken to mitigate the risk of a wrong drug error involving Talvey.
- Adverse events and outcomes attributed to the wrong drug error involving Talvey.

## **POST APPROVAL FEEDBACK MEETING**

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, please call David Bak, Regulatory Health Project Manager, at 301-796-6299 or email [David.Bak@fda.hhs.gov](mailto:David.Bak@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Marc R. Theoret, MD  
Supervisory Associate Director (Acting)  
Office of Oncologic Diseases  
Office of New Drugs  
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling
- REMS

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**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.**  
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/s/  
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