NDA 211810/S-014

SUPPLEMENT APPROVAL

Daiichi Sankyo, Inc.
Attention: Ayako Fujii, M.Sc.
Associate Director, Regulatory Affairs
211 Mount Airy Road
Basking Ridge, NJ 07920

Dear Ayako Fujii:

Please refer to your supplemental new drug application (sNDA) dated and received February 28, 2025, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Turalio (pexidartinib) capsules.

This Prior Approval supplemental new drug application provides proposed modifications to the approved Turalio (pexidartinib) risk evaluation and mitigation strategy (REMS).

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 Turalio (pexidartinib) was originally approved on August 2, 2019, and the most recent REMS modification was approved on April 17, 2023. 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. Your proposed modification to the REMS consists of revising the REMS goal and pertinent REMS materials to include vanishing bile duct syndrome as part of the risks the REMS is intended to mitigate to align with the safety information added to the labeling that occurred with the approval of prior approval supplement 013 on January 3, 2025.

Your proposed modified REMS, submitted on February 28, 2025, amended and appended to this letter, is approved.

The timetable for submission of assessments of the REMS must be revised to submit REMS Assessments annually from the date of the REMS modification approval (August 27, 2025).

Submit a 6-year bridging REMS Assessment Report within 60 days of REMS modification approval. This 6-year bridging REMS assessment report should cover the reporting period from June 4, 2024 (the close of the 5-year REMS assessment reporting period) through one calendar day prior to the approval date of the

modification. Subsequent REMS Assessment Reports must be submitted annually from the date of the REMS modification approval.

The revised REMS assessment plan must include, but is not limited to, the following:

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

REMS Outreach and Communication Plan

1. Communication Plan (provide data for the 7-year and 8-year assessments only)
    a. Indicate whether all required REMS communication materials were disseminated to targeted healthcare providers within the required timeframes
    b. Sources of the distribution lists for healthcare providers
    c. Number of healthcare providers targeted
    d. The date(s), number and medical specialty of healthcare providers who were sent the Letter for Healthcare Providers by the methods of distribution
    e. The date(s), number and names of Professional Societies that were sent the Letter for Professional Societies by the methods of distribution
    f. The number of mailings returned or undeliverable. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients
    g. Professional meetings where Turalio REMS materials were disseminated

REMS Implementation and Operations

2. REMS Certification and Enrollment Statistics
    a. Healthcare Providers
        i. Number of newly certified and active (i.e. who have prescribed at least once during the reporting period) healthcare providers stratified by credentials (e.g., Doctor of Medicine, Doctor of Osteopathic Medicine, Nurse Practitioner, Physician Assistant, Other). If “other” accounts for >10% of respondents for credentials, provide the most common credentials identified.
        ii. Specialty (e.g., Oncology, Orthopedics, Other). If “Other” accounts for >10% of respondents for specialties, provide the most common specialties identified.
        iii. Geographic region
        iv. Method of healthcare provider certification (e.g., online, fax or email)
    b. Pharmacies
        i. Number of newly certified and active (i.e. have received Turalio) pharmacies stratified by geographic region

ii. Number of pharmacies that dispensed Turalio stratified by geographic region
iii. Number of pharmacies that were unable to become certified and reason why

c. Patients
i. Number of newly enrolled patients stratified by age, gender, race, hepatic medical history, and geographic region
ii. Number of patients who have discontinued therapy and the reason for discontinuation

d. Wholesalers/Distributors
i. Number of newly enrolled and active (i.e., have shipped Turalio) wholesalers/distributors

3. Turalio Utilization Data
a. Number of prescriptions (new and refills) dispensed stratified by:
i. Prescriber specialty, provider degree/credentials, geographic region
ii. Patient demographics (age, gender, race, and geographic region)
b. Number of unique patients receiving Turalio, stratified by age, gender, race, and geographic region

4. REMS Infrastructure and Performance
a. REMS Website
i. Number of visits and unique visits to the REMS website
ii. Number of REMS materials downloaded or printed for each material
b. Call Center Report
i. Number of contacts by participant type (patient/caregiver, prescriber, pharmacy, wholesalers/distributors, other)
ii. Summary of reasons for calls (e.g., enrollment question) and by reporter (authorized representative, patient/caregiver, prescriber, other)
iii. If the summary reason for the call(s) indicates a complaint, provide details on the nature of the complaint(s) and whether they indicate potential REMS burden or patient access issues
iv. Summary of frequently asked questions (FAQ) by participant type
v. A summary report of corrective actions resulting from issues identified

5. REMS Compliance
a. Provide a copy of the non-compliance plan, including the criteria for non-compliance for each participant, actions taken to address non-compliance for each case, and which events lead to de-certification from the REMS
b. Provide a copy of the audit plan for each participant
c. Report of audit findings for each participant (REMS Call Center, pharmacies and wholesalers/distributors)

i. The number of audits expected, and the number of audits performed
ii. The number and types of deficiencies noted for each group of audited participants
iii. For those with deficiencies noted, report the number that successfully completed a corrective and preventive action (CAPA) plan within one month of audit
iv. For any that did not complete the CAPA within one month of the audit, describe actions taken
v. Include a unique ID for each participant that had deviations to track deviations by participant over time
vi. Documentation of completion of training for relevant staff
vii. The existence of documented processes and procedures for complying with the REMS
viii. Verification that each audited participant's site that the designated authorized representative remains the same. If different, include the number of new authorized representatives and verification of the site's recertification

d. Provide a summary of non-compliance identified, including but not limited to:
    i. Prescribers (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)
        a) The number of prescribers who were non-compliant with the Turalio REMS requirements
        b) Number of prescribers that were de-certified and reasons for decertification. Include if any prescribers were re-certified
    ii. Patients
        a) Number of patients not enrolled in the REMS or registry who were dispensed Turalio
            1) Provide reason patients are not enrolled, if known
    iii. Pharmacies (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken). Out of all pharmacy non-compliance events provide:
        a) The number and type of pharmacy for which non-compliance with the REMS is detected
        b) The number and type of non-certified pharmacies that dispensed Turalio and the number of incidents for each

c) Number of Turalio prescriptions dispensed that were written by non-certified prescribers and the actions taken to prevent future occurrences
d) Number of Turalio prescriptions dispensed by non-certified pharmacies and the actions taken to prevent future occurrences
e) Number of Turalio prescriptions dispensed to non-enrolled patients and the actions taken to prevent future occurrences
f) Number of times a Turalio prescription was dispensed because a certified pharmacy bypassed REMS authorization processes, to include a description of how the events were identified and any corrective actions taken
g) Number of Turalio prescriptions dispensed for more than a 30 days' supply for each of the first three months of treatment
h) Number of pharmacies decertified, reasons for decertification, and actions to address non-compliance

iv. Wholesalers/distributors (For each non-compliance event, provide the source of the report, a description of the event, the cause of the event, and corrective actions taken)
a) The number of authorized wholesalers/distributors for which non- compliance with the REMS is detected
b) Number of wholesalers de-enrolled, reasons for de-enrollment, and actions to address non-compliance
c) Number of times Turalio was distributed to a non-certified pharmacy or directly to patients

e. Compliance with REMS-required Forms
i. Report on Patient Enrollment Forms
a) The proportion of newly enrolled patients in the REMS that had the Baseline Labs section completed.
1) For those newly enrolled patients with an incomplete Baseline Labs section of the Patient Enrollment Form, provide the reason(s) why and actions taken to obtain the Baseline Labs.

b) For those patients where reported baseline laboratory test values were not WNL, provide a summary analysis of whether these patients experienced an adverse event or laboratory abnormalities suggestive of serious and potentially fatal liver injury, including vanishing bile duct syndrome.

ii. Report on Patient Status Forms
   a) Number of Patient Status Forms expected, received and outstanding as of the report cut-off date
   b) Number of Patient Status Forms not received within 20 calendar days of the date the last Patient Status Form was due. Include description of outreach activities performed to collect the forms
   c) Number and proportion of Patient Status Forms that had missing hepatic monitoring data after outreach attempts completed out of all Patient Status Forms received for the reporting period. Include description of outreach activities performed to ensure completeness of the forms
   d) Number of Patient Status Forms outstanding from previous reporting periods (if applicable)
   e) Number of unique patients that experienced a treatment interruption, duration of the treatment interruption and reason for treatment interruption (e.g. liver toxicity, no status form received)
   f) Number of unique patients whose Turalio was discontinued and the reason treatment was discontinued (e.g. liver toxicity, non-response to therapy, no status form received)

iii. Report on Liver Adverse Event Reporting Forms
   a) Number of Liver Adverse Event Reporting Forms expected due to a "yes" response on the Patient Status Form indicating that a form is required, received, and outstanding as of the report cut-off date
   b) Number of Liver Adverse Event Reporting Forms with missing data and actions taken to obtain the missing data.
   c) Number of unique patients who had a Liver Adverse Event Reporting Form submitted

Health Outcomes and/or Surrogates of Health Outcomes

6. Serious and Potentially Fatal Liver Injury, including Vanishing Bile Duct Syndrome
   a. Using the REMS registry, provide:

i. Number of cases of serious and potentially fatal liver injury, including vanishing bile duct syndrome adverse events reported in the registry.
    a) Estimate the following incidences based on the denominator defined below. Provide the numerator and denominator for each incidence estimate:
    b) Out of total exposed patients during the assessment period:
        1) Calculate the incidence of overall liver injury event.
        2) Calculate the incidence of fatal liver injury.
        3) Calculate the incidence of liver injury requiring liver transplant.
        4) Calculate the incidence of vanishing bile duct syndrome.
    c) Out of cumulative enrolled patients who received at least one Turalio treatment:
        1) Calculate the incidence of overall liver injury event.
        2) Calculate the incidence of fatal liver injury.
        3) Calculate the incidence of liver injury requiring liver transplant.
        4) Calculate the incidence of vanishing bile duct syndrome.
    d) Provide a tabulated stratification of the above incidences by patient exposure duration (e.g., 0-3 months of use, 3-6 months of use, 6-12 months of use, more than 1 year of use).

ii. Trend analysis of how the incidence of adverse events (e.g. overall liver injury, fatal liver injury, injury requiring liver transplant or vanishing bile duct syndrome) changes across reporting periods.

iii. Include a reference list of case identifiers (e.g., manufacturer control numbers) for all cases included in the analysis above.

b. Provide an assessment of whether prescribing information recommendations were followed for baseline and periodic monitoring of liver function testing and what REMS-related factors potentially contributed to the outcome for all known, or suspected U.S. adverse events related to serious and potentially fatal liver injury, including vanishing bile duct syndrome. Sources of the reports to inform your assessment must include but not be limited to: Patient

Enrollment Forms, Patient Status Forms, Liver Adverse Event Forms, and spontaneous adverse event reports.

c. Provide new or updated safety findings, if any, to inform the incidence, severity, and frequency of serious and potentially fatal liver injury including vanishing bile duct syndrome, and an assessment of the effectiveness of the REMS strategy in mitigating the risk.

Knowledge

7. Post-Training Knowledge Assessments
    a. Number of completed post-training Knowledge Assessments for prescribers including method of completion
    b. Summary statistics, including mean/median/range for number of attempts to successfully complete the Knowledge Assessment and score
    c. Summary of the most frequently missed Knowledge Assessment questions
    d. A summary of potential comprehension or perception issues identified with the Knowledge Assessment
8. Prescriber Surveys (provide annually with each assessment report)
    a. Assessment of whether prescribers are educated on the following:
        i. The risk of serious and potentially fatal liver injury including vanishing bile duct syndrome
        ii. The need to counsel patients about the risk of serious and potentially fatal liver injury including vanishing bile duct syndrome, the need for liver monitoring, and the signs and symptoms of liver injury
        iii. The need to monitor patient's liver tests at baseline and periodically during treatment as described in the Prescribing Information

Overall Assessment of REMS Effectiveness

9. 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.

Additionally, we recommend that you submit your proposed audit plan and noncompliance plan for FDA review within 60 days of this letter and that you submit your proposed protocol for the prescriber knowledge survey for FDA review within 90 days of this letter. Prominently identify the submissions containing the assessment instruments and methodology with the following wording in bold capital letters at the top of your cover letter and at the top of the first page of the main submission document **"REQUEST FOR REMS ASSESSMENT METHODOLOGY REVIEW/ AUDIT PLAN AND NONCOMPLIANCE PLAN" or "REQUEST FOR REMS ASSESSMENT METHODOLOGY REVIEW/ SURVEY METHODOLOGIES"**, respectively.

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:

> **NDA 211810 REMS ASSESSMENT METHODOLOGY**
> **(**insert concise description of content in bold capital letters, e.g.,
> **ASSESSMENT METHODOLOGY, PROTOCOL, SURVEY METHODOLOGIES, AUDIT PLAN, DRUG USE STUDY)**

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

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:

> **NDA 211810 REMS ASSESSMENT**
>
> ***or***
>
> **NEW SUPPLEMENT FOR NDA 211810/S-000**
> **CHANGES BEING EFFECTED IN 30 DAYS**
> **PROPOSED MINOR REMS MODIFICATION**
>
> ***or***
>
> **NEW SUPPLEMENT FOR NDA 211810/S-000**
> **PRIOR APPROVAL SUPPLEMENT**
> **PROPOSED MAJOR REMS MODIFICATION**
>
> ***or***

NEW SUPPLEMENT FOR NDA 211810/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 NDA 211810/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 NDA 211810

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.

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 supplement applications, you are exempt from this requirement.

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Stacie Woods, Safety Regulatory Project Manager, at 301-796-4803 or Stacie.woods@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
- 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
08/27/2025 11:36:27 AM