NDA 219389

NDA APPROVAL

SpringWorks Therapeutics, Inc.
Milena Gessica Di Meo, PharmD, MS
Director, Regulatory Affairs
100 Washington Blvd
Stamford, CT 06902

Dear Dr. Di Meo:

Please refer to your new drug application (NDA) dated June 28, 2024, received June 28, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Gomekli (mirdametinib) capsules.

This NDA provides for the use of Gomekli (mirdametinib) capsules 1 mg and 2 mg for the treatment of adults and pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas (PN) not amenable to complete resection.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert) as well as annual reportable changes not included in the enclosed labeling. 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.*[2]

The SPL will be accessible via publicly available labeling repositories.

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

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on December 27, 2024, 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 *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 219389**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Gomekli (mirdametinib) Capsules shall be 36 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from light.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that your request for a rare pediatric disease priority review voucher is denied. This application is not eligible for a rare pediatric priority review voucher because you have been granted a rare pediatric disease priority review voucher under NDA 219379 for Gomekli (mirdametinib) Tablets (PRV NDA 219379) and "no sponsor of a rare pediatric disease product application may receive more than one priority review voucher issued under any section of [the FDCA] with respect to the drug for which the application is made." See section 529(g) of the FDCA.

ADVISORY COMMITTEE

Your application for Gomekli was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected for a drug in the intended population and outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

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 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 identify an unexpected serious risk of carcinogenicity.

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.

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

4785-1 Complete a carcinogenicity study in rats to evaluate the potential serious risk of carcinogenicity.

The timetable you submitted on February 5, 2025, states that you will conduct this study according to the following schedule:

Study Completion:	10/2027
Final Report Submission:	04/2028

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.[3]

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of long-term adverse effects of mirdametinib on growth and development in pediatric patients, to assess known serious risks of ocular toxicity, left ventricular dysfunction, and dermatologic adverse reactions, and to identify an unexpected serious risk of increased drug toxicity in patients with moderate and severe hepatic impairment.

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

[3] 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.

4785-2 Conduct an integrated safety analysis of data from clinical trials to characterize and evaluate the potential serious risk of long-term adverse effects of mirdametinib on growth and development in pediatric patients. Include long-term follow-up data from pediatric patients enrolled on the MEK-NF-201 (ReNeu) trial (NCT03962543) and from ongoing and completed clinical trials of mirdametinib. Pediatric patients must be evaluated for growth and sexual development milestones annually for at least 7 years from initiation of mirdametinib or until a patient has achieved sexual maturity. Evaluations must include growth as measured by weight, height, height velocity, and height standard deviation scores (SDS); if available, include, age at thelarche (females), age at adrenarche (males), age at menarche (females), and Tanner Stage progression.

The timetable you submitted on February 5, 2025, states that you will conduct this trial according to the following schedule:

Study Completion:	12/2028
Final Report Submission:	06/2029

4785-3 Conduct an integrated safety analysis of data from clinical trials to further characterize the long-term incidence, severity, and outcomes of the known serious risks of ocular toxicity, left ventricular dysfunction, and dermatologic adverse reactions. Include the long-term follow-up safety data (minimum of 7 years) from adult and pediatric patients enrolled on the MEK-NF-201 (ReNeu) trial (NCT03962543) and all other ongoing and completed trials of mirdametinib to include an analysis of the following toxicities: ocular toxicity (including but not limited to retinal pigment epithelial detachment and retinal vein occlusion), cardiac toxicity (including but not limited to left ventricular dysfunction), and serious dermatologic toxicity.

The timetable you submitted on February 5, 2025, states that you will conduct this trial according to the following schedule:

Study Completion:	12/2028
Final Report Submission:	06/2029

4785-4 Conduct a clinical pharmacokinetic trial to evaluate the potential serious risk of increased drug toxicity, and to determine an appropriate, safe dose of mirdametinib, in patients with moderate (total bilirubin > 1.5 – 3.0 x ULN, any AST) and severe (total bilirubin > 3 – 10 x ULN, any AST) hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry titled “Pharmacokinetics in Patients with

Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

The timetable you submitted on February 5, 2025, states that you will conduct this trial according to the following schedule:

Final Protocol Submission: 02/2025
Trial Completion: 07/2026
Final Report Submission: 01/2027

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.[4]

Submit clinical protocol(s) to your IND 139883 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. 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 314.81(b)(2)(vii) 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 314.81(b)(2)(vii) 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 314.81(b)(2)(vii). 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.

[4] 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:

4785-5 Complete the MEK-NF-201 (ReNeu) trial (NCT03962543) to further characterize the clinical benefit of mirdametinib in adult and pediatric patients with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas (PN) not amenable to complete resection. To characterize response rate and duration, patients will be followed for at least 24 months from the onset of response.

The timetable you submitted on February 5, 2025, states that you will conduct this study according to the following schedule:

Trial Completion:	12/2028
Final Report Submission:	06/2029

4785-6 Conduct a clinical pharmacokinetic trial with a strong CYP3A4 inducer (that also induces UGTs, P-gp, and CES enzymes) with mirdametinib to evaluate the effect of strong CYP3A4 induction on decreasing the systemic exposure of mirdametinib and to provide dosage recommendations for mirdametinib when used concomitantly with strong CYP3A4 inducers. Design and conduct the trial in accordance with the FDA Guidance for Industry titled “M12 Drug Interaction Studies.”

The timetable you submitted on February 5, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	06/2025
Final Protocol Submission:	10/2025
Trial Completion:	10/2026
Final Report Submission:	04/2027

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 139883 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. 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**."

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.*[5]

As required under 21 CFR 314.81(b)(3)(i), 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.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

REPORTING REQUIREMENTS

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

POST APPROVAL FEEDBACK MEETING

New molecular entities 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.

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

official USP monographs. More information on the USP-NF is available on USP's website[8].

If you have any questions, call Opeyemi Udoka, DPT, Senior Regulatory Health Project Manager, at 240-402-4558 or email opeyemi.udoka@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Paul Kluetz, MD
Supervisory Associate Director (Acting)
Office of Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

[8] https://www.uspnf.com/

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/

PAUL G KLUETZ
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