NDA 217677

CORRECTED APPROVAL

SpringWorks Therapeutics, Inc.
Attention: Cory Ferguson, M.H.A.
Executive Director, Regulatory Affairs
Halloran Consulting Group
3040 Science Park Road, Suite 1300
San Diego, CA 92121

Dear Cory Ferguson:

Please refer to your new drug application (NDA), received December 27, 2022, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ogsiveo (nirogacestat), tablets, for oral use.

We acknowledge receipt of your major amendment dated May 26, 2023, which extended the goal date by three months.

We also refer to our approval letter dated November 27, 2023, which contained the following error: The original approval letter contained an incorrect shelf life of 36 months. The correct shelf life is 48 months when stored at 20°C-25° C (68°F-77°F). Excursions are permitted between 15°C-30°C (59°F-86°F). See USP Controlled Room Temperature.

This corrected action letter incorporates the correction of the error. The effective action date will remain November 27, 2023, the date of the original letter.

This NDA provides for the use of Ogsiveo (nirogacestat), tablets, for oral use for adult patients with progressing desmoid tumors who require systemic treatment.

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.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling and carton and container labeling submitted on October 20, 2023, 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 217677**." 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 Ogsiveo (nirogacestat), tablet shall be 48 months from the date of manufacture when stored at 20ºC-25ºC (68ºF-77ºF). Excursions are permitted between 15ºC-30ºC (59ºF-86ºF). See USP Controlled Room Temperature.

ADVISORY COMMITTEE

Your application for Ogsiveo (nirogacestat), tablets, for oral use 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/biologic of this class or in the intended population for which external input was necessary.

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.

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[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.

We are waiving the pediatric study requirement for patients 0 to < 24 months of age because the necessary studies would be impossible or highly impracticable due to the rarity of progressive, surgically unresectable desmoid tumors in this population.

We are also deferring submission of your pediatric study until post approval, because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required under section 505B(a) of the FDCA is a required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. This required study is listed below.

4550-1 Complete clinical Study ARST1921, “A Safety, Pharmacokinetic and Efficacy Study of a gamma -Secretase Inhibitor, Nirogacestat (PF-03084014), in Children and Adolescents with Progressive, Surgically Unresectable Desmoid Tumors” in pediatric patients to further characterize the safety, pharmacokinetics, and anti-tumor activity of nirogacestat in pediatric patients 2 to 17 years with desmoid tumors. The study will include long-term monitoring to characterize epiphyseal disorders and ovarian toxicity in pediatric patients.

Study Completion:	09/2025
Final Report Submission:	09/2026

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]

Submit the protocol(s) to your IND 138207 with a cross-reference letter to this NDA. Reports of this required pediatric postmarketing study must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

[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.

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 ovarian toxicity.

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 ovarian toxicity.

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

4550-2 Conduct a prospective, open-label, single-arm clinical trial in adult premenopausal females with desmoid tumor to further characterize the incidence and severity of ovarian toxicity after a minimum of 12 months of nirogacestat treatment. Ensure that ovarian safety assessments after 12 months of continuous treatment are available from a minimum of 40 subjects. Post-treatment follow-up assessments including reproductive hormone measurements should be obtained at regularly scheduled intervals and after treatment cessation to assess time to ovarian function recovery.

The timetable you submitted on November 17, 2023, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	07/2024
Final Protocol Submission:	10/2024
Trial Completion:	12/2028
Final Report Submission:	06/2029

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]

[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.

Submit clinical protocol(s) to your IND 138207 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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4550-3 Conduct physiologic-based pharmacokinetic (PBPK) modeling study and subsequently a clinical pharmacokinetic trial if needed, to evaluate the effect of proton pump inhibitors (PPIs) on the bioavailability of nirogacestat. Design and conduct the trials and modeling analyses in accordance with the FDA guidance for industry, “Evaluation of Gastric pH-Dependent Drug Interactions with Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications” and “Physiologically Based Pharmacokinetic Analyses — Format and Content Guidance for Industry.”

The timetable you submitted on November 17, 2023, states that you will conduct this study according to the following schedule:

Interim Report Submission (Final PBPK Analysis):	06/2024
Draft Protocol Submission:	01/2025
Final Protocol Submission:	04/2025
Trial Completion:	02/2026
Final Report Submission:	08/2026

Submit your draft analysis plan prior to conducting and submitting the final results from the PBPK modeling study for FDA review.

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 138207 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).

[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

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

If you have any questions, call Autumn Zack-Taylor, M.S., Senior Regulatory Health Project Manager, at (240) 402-5913.

Sincerely,

{See appended electronic signature page}

Paul Kluetz, M.D.
Deputy Center Director
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- Carton and Container Labeling

[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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