

NDA 220185

NDA APPROVAL

Nuvalent, Inc.
Attention: Virginia Vetter
Vice President, Global Regulatory Affairs
One Broadway, 14th Floor
Cambridge, MA 02142

Dear Virginia Vetter:

Please refer to your new drug application (NDA) received September 19, 2025, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Jideytro (zidesamtinib) tablets.

This NDA provides for the use of Jideytro (zidesamtinib) tablets for the treatment of adult patients with locally advanced or metastatic ROS 1-positive non-small cell lung cancer (NSCLC) who received a prior ROS1 kinase inhibitor.

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 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 enclosed carton and container labeling and carton and container labeling submitted on April 9, 2026, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to 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 220185.**” 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 Jideytro (zidesamtinib) tablets shall be 30 months from the date of manufacture when stored at 20°C-25°C (68°F-77°F); excursions permitted from 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Results of ongoing stability studies should be submitted throughout the dating period in your annual report, as they become available, including the results of stability studies from the first three production lots.

ADVISORY COMMITTEE

Your application for Jideytro (zidesamtinib) 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 of this class; the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease; and outside expertise was not necessary, and 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.

We are waiving the pediatric study(ies) requirement for this application because necessary studies are impossible or highly impracticable due to the very small number of potentially eligible pediatric patients with ROS1-positive pediatric cancers.

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 unexpected serious potential risks of increased drug toxicity due to elevated drug levels when zidesamtinib is taken concomitantly with sensitive P-gp and BCRP substrates and moderate CYP3A inhibitors, and in patients with moderate and severe hepatic impairment or severe renal impairment.

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 these serious risks.

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 these serious risks.

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

- 5032-1 Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of zidesamtinib on the single dose pharmacokinetics of sensitive P-gp and BCRP substrates, assess serious potential risk of increased drug toxicity due to elevated drug levels, and inform appropriate management strategies for clinically relevant drug interactions. Design and conduct the trial in accordance with the ICH Harmonized Guidance for Industry entitled "M12 Drug Interaction Studies."

The timetable you submitted on July 20, 2026, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	10/2026
Final Protocol Submission:	02/2027
Trial Completion:	08/2027
Final Report Submission:	02/2028

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>.

- 5032-2 Conduct a clinical drug-drug interaction trial or conduct a physiologically-based PK (PBPK) modeling to evaluate the effect of moderate CYP3A inhibitors on the pharmacokinetics of zidesamtinib and its active metabolite M9 to assess the serious potential risk of increased drug toxicity due to elevated drug levels. Design and conduct the modeling in accordance with the ICH Harmonized Guidance for Industry entitled "M12 Drug Interaction Studies."

The timetable you submitted on July 20, 2026, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	10/2026
Final Protocol Submission:	02/2027
Trial Completion:	04/2028
Final Report Submission:	10/2028

- 5032-3 Conduct a hepatic impairment clinical trial to determine a safe and appropriate dose of zidesamtinib in patients with moderate and severe hepatic impairment and to assess the serious potential risk of increased drug toxicity due to elevated drug levels. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

The timetable you submitted on July 20, 2026, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	10/2026
Final Protocol Submission:	02/2027
Trial Completion:	12/2027
Final Report Submission:	04/2028

- 5032-4 Conduct a renal impairment clinical trial to evaluate the serious potential risk of increased drug toxicity and to determine a safe and appropriate dose of zidesamtinib in patients with severe renal impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

The timetable you submitted on July 20, 2026, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	10/2026
Final Protocol Submission:	02/2027
Trial Completion:	12/2027

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.⁴

Submit clinical protocol(s) to your IND 154781 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:

- 5032-5 Complete a clinical study (ARROS-1) to further characterize the clinical benefit of zidesamtinib for the treatment of adult patients with ROS1 fusion-positive metastatic NSCLC by providing a more precise estimation of the BICR-assessed overall response rate (ORR) and duration of response (DOR) in the 117 ROS1 TKI-pretreated patients with measurable disease enrolled on ARROS-1. Include updated DOR results for the 51 responders in the efficacy evaluable population of 117 ROS1

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>.

TKI-pretreated patients, after all responders have been followed for at least 18 months from the date of initial response.

The timetable you submitted on July 20, 2026, states that you will conduct this study according to the following schedule:

Trial Completion:	08/2026
Final Report Submission:	12/2026

- 5032-6 Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of strong or moderate CYP3A4 inducers on the single dose pharmacokinetics of zidesamtinib and inform appropriate management strategies for clinically relevant drug interactions. Design and conduct the trial in accordance with the ICH Harmonized Guidance for Industry entitled "M12 Drug Interaction Studies."

The timetable you submitted on July 20, 2026, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	10/2026
Final Protocol Submission:	02/2027
Trial Completion:	08/2027
Final Report Submission:	02/2028

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 154781 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 guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs*.

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.⁵ Information and Instructions for completing the form can be found at FDA.gov.⁶

METHODS VALIDATION

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

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 official USP monographs. More information on the USP-NF is available on USP's website⁷.

⁵ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>

⁶ <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>

⁷ <https://www.uspnf.com/>

If you have any questions, contact Raniya Al-Matari, Regulatory Health Project Manager, at 301-796-1755 or Raniya.Al-Matari@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, M.D.
Director
Office of Oncologic Diseases
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
 - Prescribing Information
 - Patient Package Insert

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/

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