NDA 219713

NDA APPROVAL

Nuvation Bio Inc.
Attention: Elizabeth Hook
Executive Director, Regulatory Affairs
1500 Broadway, Suite 1401
New York, NY 10036

Dear Elizabeth Hook:

Please refer to your new drug application (NDA) received October 23, 2024, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for IBTROZI (taletrectinib) capsules.

This NDA provides for the use of IBTROZI (taletrectinib) capsules for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC).

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 enclosed carton and container labeling submitted on April 15, 2025, 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 219713"** 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 IBTROZI (taletrectinib) capsules for oral administration shall be 36 months from the date of manufacture when stored at USP controlled room temperature conditions: "Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

COMPARABILITY PROTOCOL

The comparability protocol to add a 90-count container configuration submitted as a CBE-0 is acceptable. The comparability protocol to add an alternate drug product manufacturer submitted as a CBE-30 is acceptable. The final decision on the acceptability of the proposed post-approval changes and reporting category will be determined once submitted to your NDA for review.

ADVISORY COMMITTEE

Your application for IBTROZI (taletrectinib) 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.

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 deferring submission of your pediatric study until December 2033, because this product is ready for approval for use in adults and the pediatric studies have 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.

4856-1 Conduct a molecularly targeted pediatric cancer investigation to assess dosing, pharmacokinetics, safety and preliminary efficacy of taletrectinib in pediatric patients with advanced or metastatic solid tumors with NTRK or ROS1 alterations.

Draft Protocol Submission:	09/2025
Final Protocol Submission:	01/2026
Study Completion:	06/2033
Final Report Submission:	12/2033

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.

Submit the protocol(s) to a new pediatric IND, 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.

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 known serious risks of severe hepatotoxicity, interstitial lung disease, and other serious adverse reactions, and to identify unexpected serious risks of increased drug exposure in patients with moderate or severe hepatic impairment and increased drug toxicity when taletrectinib is used concomitantly with sensitive substrates of CYP3A, CYP2D6, BCRP, OATP1B1, and OATP1B3.

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.

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:

4856-2 Conduct a multicenter trial to further characterize known serious risks with taletrectinib including severe hepatotoxicity, interstitial lung disease, other serious adverse reactions, and the risk of gastrointestinal toxicity, by evaluating the safety, activity, and pharmacokinetics of taletrectinib 400 mg daily taken with standard meals, in patients with advanced or metastatic *ROS1*-positive non-small cell lung cancer who are naïve to prior ROS1 tyrosine kinase inhibitors (TKIs) and in patients who have received one prior ROS1 TKI. Include an adequate number of patients from each subgroup (i.e., ROS1 TKI-naïve and previously treated with ROS1 TKI).

The timetable you submitted on May 21, 2025, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	09/2025
Final Protocol Submission:	01/2026
Trial Completion:	12/2027
Final Report Submission:	06/2028

4856-3 Conduct a hepatic impairment clinical trial to evaluate the serious potential risk of increased drug exposure and determine a safe and appropriate dosage of taletrectinib in patients with moderate and severe hepatic impairment. 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 May 21, 2025, states that you will conduct this trial according to the following schedule:

Final Protocol Submission:	08/2025
Trial Completion:	06/2027
Final Report Submission:	12/2027

4856-4 Conduct a clinical drug interaction study to evaluate the effect of taletrectinib on the pharmacokinetics of sensitive substrates of CYP3A, CYP2D6, BCRP, OATP1B1, and OATP1B3 to evaluate the magnitude of exposure change of these substrates and serious potential risk of increased drug toxicity and inform appropriate drug interaction management strategy for coadministration of taletrectinib with these CYP

and transporter substrates. This study should be designed and conducted in accordance with "M12 Drug Interaction Studies."

The timetable you submitted on May 21, 2025, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	12/2025
Final Protocol Submission:	06/2026
Trial/Study Completion:	06/2029
Final Report Submission:	12/2029

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.[3]

Submit clinical protocol(s) to your IND 122347 with a cross-reference letter to this NDA. Submit 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.

[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 COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4856-5 Conduct a clinical drug interaction study to evaluate the effect of taletrectinib on the pharmacokinetics of sensitive substrates of CYP3A and CYP1A2 in healthy subjects to evaluate the magnitude of decreased drug exposure and inform appropriate drug interaction management strategy for coadministration of taletrectinib with these CYP substrates. This study should be designed and conducted in accordance with "M12 Drug Interaction Studies."

The timetable you submitted on May 21, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2025
Final Protocol Submission:	06/2026
Trial Completion:	06/2029
Final Report Submission:	12/2029

4856-6 Conduct a clinical trial to evaluate if staggered administration of an H2-receptor antagonist decreases the exposure of taletrectinib and to inform instructions for taking taletrectinib with H2-receptor antagonists. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled "Evaluation of Gastric pH-Dependent Drug Interactions with Acid-Reducing Agents: Study Design, Data Analysis, and Clinical Implications."

The timetable you submitted on May 21, 2025, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2025
Final Protocol Submission:	04/2026
Trial Completion:	04/2027
Final Report Submission:	12/2027

4856-7 Complete a clinical trial to further characterize the clinical benefit of taletrectinib 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 ROS1 TKI-naive patients with *ROS1*-positive NSCLC and ROS1 TKI-pretreated patients enrolled in TRUST-I and TRUST-II studies. Include updated DOR results for the 139 responders in the response evaluable population of 157 ROS1 TKI-naïve patients and for the 63 responders in the response evaluable population of 113 ROS1 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 May 21, 2025, states that you will conduct this study according to the following schedule:

Trial Completion:	12/2027
Final Report Submission:	06/2028

Submit the datasets with the final report submission.

4856-8 Conduct an appropriate analytical and clinical validation study to support the development of an in vitro diagnostic device using clinical trial data that demonstrates that the device is essential to the safe and effective use of taletrectinib for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer.

The timetable you submitted on May 21, 2025, states that you will conduct this study according to the following schedule:

Final Report Submission:	06/2027

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 122347 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.*[4]

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

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 website[7].

[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.
Deputy 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
- Carton and Container Labeling

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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