

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

219713Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	219713
PDUFA Goal Date	June 23, 2025
Nexus TTT #	2024-11557
Reviewer Name(s)	Somya Dunn, MD
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Division Director (Acting)	Laura Zendel, PharmD
Review Completion Date	June 11, 2025
Subject	Evaluation of Need for a REMS
Established Name	Taletrectinib
Trade Name	Ibuprofen
Name of Applicant	Nuvation Bio., Inc.
Therapeutic Class	Kinase inhibitor
Formulation(s)	200 mg capsules for oral administration
Dosing Regimen	600 mg once daily

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Ibrozi (taletrectinib) is necessary to ensure the benefits outweigh its risks. Nuvation Bio, Inc. submitted a New Drug Application (NDA) 219713 for taltrectinib with the proposed indication for the treatment of adult patients with locally advanced or metastatic c-ros oncogene 1 positive (ROS1-positive) non-small cell lung cancer (NSCLC). The applicant did not submit a proposed REMS or risk management plan with this application.

DRM and the Division of Oncology 2 (DO2) determined a REMS is not needed to ensure the benefits of taltrectinib outweigh its risks. The primary evidence for efficacy for the application came from data from patients with ROS1-positive NSCLC (including patients previously treated with a ROS1 TKI and those naïve to a ROS1 TKI) from two studies (AB-106-C203 [TRUST-I or Study C203] and AB-106-G208 [TRUST-II or Study G208]). The review team determined that response rate of the patients provides evidence of a clinically meaningful benefit of taltrectinib in patients with ROS1-positive NSCLC. The pooled safety population from these studies included 352 patients with solid tumors who received at least one dose of taltrectinib 600 mg daily. The ROS1-positive NSCLC 600 mg once daily safety cohort included 337 patients with ROS1-positive NSCLC who received at least one dose taltrectinib 600 mg. Analysis of this data led to the determination that taltrectinib has an acceptable safety profile when evaluated in the context of patients with a cancer diagnoses.

The clinical review team concluded the risk-benefit of taltrectinib is favorable for this population with a serious, life-threatening disease. The risks of hepatotoxicity, ILD/pneumonitis, QTc prolongation, hyperuricemia, myalgia with CPK elevation, skeletal fractures, and embryo-fetal toxicity will be included in the Warnings and Precautions section of the label. The likely prescribers will be oncologists who are expected to have experience monitoring, identifying, and managing the adverse events that may occur with taltrectinib.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Ibrozi (taletrectinib) is necessary to ensure the benefits outweigh its risks. Nuvation Bio, Inc. submitted a New Drug Application (NDA) 219713 for taltrectinib with the proposed indication for the treatment of adult patients with locally advanced or metastatic c-ros oncogene 1 positive (ROS1-positive) non-small cell lung cancer (NSCLC). This application is under review in the Division of Oncology 2 (DO2). The applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Taletrectinib, a new molecular entity^a, is a selective, central nervous system (CNS)-penetrant next-generation ROS1 tyrosine kinase inhibitor (TKI) with activity against both wild-type ROS1 fusion and ROS1 resistance mutations. Taletrectinib also demonstrated a 10-fold selectivity over tropomyosin receptor kinase B (TRKB), a target reportedly linked to CNS effects. Fusion proteins that include ROS1 domains can drive tumorigenic potential through hyperactivation of downstream signaling pathways leading to unconstrained cell proliferation. Taletrectinib inhibited growth of cancer cells expressing ROS1 fusion genes and mutations.

Taletrectinib is proposed to be supplied as 200 mg tablets. The proposed dosing regimen of 600 mg is to be taken orally once daily without food, until disease progression or unacceptable toxicity.^{b,1} Dose reductions may be needed for adverse reactions.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 219713 relevant to this review:

- 08/01/2022: Breakthrough Therapy Designation granted with advanced or metastatic ROS1-positive NSCLC who are ROS1 TKI treatment naïve or previously treated with crizotinib.²
- 07/16/2024: Orphan drug designation granted for taletrectinib.
- 09/30/2024: Applicant submitted NDA 219713 for taletrectinib with the proposed indication for the treatment of adult patients with locally advanced or metastatic ROS1-positive NSCLC.
- 05/23/2025: Applicant informed at Late Cycle Meeting that no issues related to REMS or risk management have been identified.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

In the United States lung cancer is the leading cause of cancer-related deaths, accounting for almost 25% of all cancer deaths 2021.¹ There are more than 235,000 new diagnoses of lung cancer per year in the US and the estimated number of deaths for 2025 is almost 125,000.^{2c} Non-small cell lung cancer (NSCLC) accounts for approximately 80-90% of respiratory system cancers.³ Approximately 1% to 2% of patients with NSCLC harbor a ROS1 rearrangement (ROS1+) causing a modified receptor tyrosine kinase.⁴ Overall survival for patients with NSCLC at five years has been reported as 22% and patients

^a Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

^b Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

^c Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

with ROS1+ NSCLC have similar outcomes.^{5d} This molecular subtype is associated with brain metastasis, particularly in the advanced clinical setting.⁶ TKIs are a class of drugs that target these tyrosine kinase pathologies and have been proven to be effective antitumor agents. Taletrectinib is a next generation, selective TKI in that it penetrates the central nervous system (CNS) and targets ROS1+ rearrangements.

3.2. Description of Current Treatment Options

There are currently three ROS1 TKIs approved in the US: crizotinib (XALKORI®), entrectinib (ROZLYTREK®) and repotrectinib (AUGTYRO™). In spite of these treatments, there is significant medical need for patients with NSCLC as not all patients respond to these treatments and most patients will experience tumor progression due to development of resistance to ROS1 TKI. Tumor progression can include brain metastases. While both entrectinib and repotrectinib have intracranial activity to treat brain metastases, they cause inhibition of tropomyosin receptor kinases which results in neurological adverse events. These adverse events can affect patient compliance to their treatments and their general quality of life.⁷ Over 75% treated with repotrectinib developed a wide range of treatment-emergent neurological AEs, including dizziness, ataxia, dysgeusia, and peripheral neuropathy.⁸

Table 1 summarizes the current available treatments.

Table 1 Applicant - Summary of Treatments Approved for ROS1-Positive NSCLC⁹

Product (s) Name	Relevant Indication	Year of Approval and Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Crizotinib XALKORI®	Adult patients with metastatic NSCLC whose tumors are ALK or ROS1+ as detected by an FDA-approved test	Initial US accelerated approval: 2011 US approval in ROS1+: 2016	Metastatic NSCLC: 250 mg PO twice daily	PROFILE 1001 Multicenter, single-arm, open-label ORR by BICR (95% CI): 66% (51, 79) mDOR, months by BICR (95% CI): 18.3 (12.7, NR) IC-ORR by BICR (95% CI): NA	Hepatotoxicity, ILD/pneumonitis, QT interval prolongation, bradycardia, severe visual loss, gastrointestinal toxicity, and embryo-fetal toxicity
Entrectinib ROZLYTREK®	Adult patients with ROS1+ metastatic NSCLC as detected by an FDA-approved test	Initial US approval: 2019	Recommended dosage for ROS1+ NSCLC: 600 mg PO once daily	ALKA, STARTRK-1, STARTRK-2 Multicenter, single-arm, open-label cORR by BICR (95% CI): 74% (64, 83) Observed DOR, by BICR (%) ≥9 months, 75%	Congestive heart failure, CNS effects, skeletal fractures, hepatotoxicity, hyperuricemia, QT interval prolongation, visual disorders, and embryo-fetal toxicity

^d Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

Product (s) Name	Relevant Indication	Year of Approval and Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
				≥12 months, 57%	
Reprotrectinib AUGTYRO®	Adult patients with locally advanced or metastatic ROS1+ NSCLC	Initial US approval: 2023	Recommended dosage: 160 mg PO once daily for 14 days, then increase to 160 mg twice daily, with or without food	TRIDENT-1 Multicenter, single-arm, open-label, multi-cohort cORR by BICR (95% CI) ROS1 TKI-naïve: 79% (68, 88) ROS1 TKI-pretreated: 38% (25, 52) mDOR (months) by BICR (95% CI) ROS1 TKI-naïve: 34.1 (25.6, NE) ROS1 TKI-pretreated: 14.8 (7.6, NE) Observed DOR, by BICR (%) ≥12 months, 70% (naïve) 48% (pretreated) IC-ORR by BICR (% , n/N): ROS1 TKI-naïve: 88% (7/8) ROS1 TKI-pretreated with no prior platinum-based chemotherapy: 42% (5/12)	CNS effects, ILD/pneumonitis, hepatotoxicity, myalgia with CPK elevation, hyperuricemia, skeletal fractures, and embryo-fetal toxicity

Abbreviations: ALK, anaplastic lymphoma kinase; BICR, Blinded Independent Central Review; CI, confidence interval; CNS, central nervous system; cORR, confirmed objective response rate; CPK, creatine phosphokinase; DOR, duration of response; FDA, Food and Drug Administration; IC-ORR, intracranial objective response rate; ILD, interstitial lung disease; mDOR, median duration of response; n, number of subjects in the category; N, number of subjects; NA, not applicable; NE, not evaluable; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; ROS1, c-ros oncogene 1; SFM, solvent front mutation; TKI, tyrosine kinase inhibitor; US, United States.

4. Benefit Assessment

The primary efficacy analysis population included 270 subjects in two key studies described below. The Response Evaluable Population (REP) was defined as all ROS1+ NSCLC subjects with at least one measurable lesion at baseline per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 by Independent Review Committee (IRC). These patients had received at least one dose of taletrectinib with a starting dose of 600 mg once daily. The two key studies were:

Study G208 or TRUST-II, [NCT 04919811] a Phase 2, global, multicenter, open-label, single-arm study to evaluate the efficacy and safety of taletrectinib were ROS1+. Patients were either TKI treatment-naïve or treated with prior ROS1 TKI(s).

Study C203 or TRUST-I, [NCT 04395677] a Phase 2, multicenter, single-arm, open-label study of taletrectinib which took place in China. Adult patients with either ROS1 fusion gene positive,

locally advanced, or metastatic NSCLC who had either not received any ROS1-TKI treatment or previously treated with crizotinib were enrolled in this study.

The 270 REP patients were evaluated as two separate cohorts:

- ROS TKI Treatment-naïve REP (N=157): This cohort consists of 54 subjects from Cohort 1 of Study G208 and 103 subjects from the ROS1 TKI-naïve cohort of Study C203.
- ROS TKI-Pretreated REP (N=113): This cohort consists of 47 subjects from Cohort 2 of Study G208 and 66 subjects from the ROS1 TKI-pretreated cohort of Study C203.

Of the 157 ROS1 TKI-naïve patients across both studies, 15 had measurable CNS metastases at baseline and had not received radiation therapy to the brain within two months prior to study entry, and responses in intracranial lesions were observed in 11 patients.^e See Table 2.

Table 2: Efficacy Results in ROS1-Positive TKI-Naïve NSCLC Patients per BICR Assessment¹⁰

Efficacy Parameters	ROS1 TKI-Naïve N=157	
	TRUST-I	TRUST-II
	n=103	n=54
Response Rate, % (95% CI)	90% (83, 95)	85% (73, 93)
Complete Response	5%	7%
Partial Response	85%	78%
Duration of Response (DOR)	n= 93	n= 46
Median DOR (95% CI)	NR (30.4, NR)	-- ^a
Range (months)	1.1, 46.9+	1.4+, 30.4+
% with DOR ^b ≥12 months	72	63

BIRC=blinded independent central review; CI = Confidence interval; +indicating ongoing response; DOR=duration of response

Among the 113 ROS1 TKI-pretreated patients in both studies, 24 had measurable CNS metastases at baseline and had not received radiation therapy to the brain within two months prior to study entry, and responses in intracranial lesions were observed in 15 patients.^e See Table 3.

^e Section 505-1 (a) of the FD&C Act: *FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

Table 3: Efficacy Results in *ROS1*-Positive TKI-Pretreated NSCLC Patients per BICR Assessment¹¹

Efficacy Parameters	ROS1 TKI-Pretreated N=113	
	TRUST-I	TRUST-II
	n=66	n=47
Response Rate, % (95% CI)	52% (39, 64)	62% (46, 75)
Complete Response	0%	11%
Partial Response	52%	51%
Duration of Response (DOR)	n= 34	n= 29
Median DOR (95% CI)	13.2 (7.7, 24.9)	--
Range (months)	1.4, 38.7+	1.7+, 30.4+
% with DOR $\geq$ 6 months	74	83
% with DOR $\geq$ 12 months	44	45

BIRC=blinded independent central review; CI = Confidence interval; +indicating ongoing response; DOR=duration of response

The review team determined that response rate of the patients provides evidence of a clinically meaningful benefit of taletrectinib in patients with *ROS1*-positive NSCLC.

5. Risk Assessment & Safe-Use Conditions

The review team has determined that taletrectinib has an acceptable safety profile when evaluated in the context of patients with life-threatening cancer diagnoses. The pooled safety population included 352 patients with solid tumors who received at least one dose of taletrectinib 600 mg once a day. In these 352 patients 337 had *ROS1*-positive NSCLC the other 15 patients had other solid tumors. The following sections summarize relevant safety information to date for taletrectinib.

Deaths

In the 600 mg once daily group, 30.4% of participants died from all causes, regardless of the number of days after the last dose of taletrectinib. Patient deaths that occurred within 30 days after the last dose of treatment occurred in 9.1% of participants. The majority of deaths occurred more than 30 days after the last dose of study drug. In general, regardless of timing of last dose, the most common reason of death was disease progression.⁹

Serious Adverse Events

The most frequently reported serious adverse events (SAEs) (in $\geq$ 2% of participants) were pleural effusion (4.5%), pneumonia (4.0%), and abnormal hepatic function (2.3%). In the 600 mg once daily group, the only treatment-related SAE reported in $\geq$ 2% of participants was abnormal hepatic function (2.3%). Other treatment-related SAEs reported in more than 1 participant included ILD (1.1%), asthenia

(0.6%), dizziness (0.6%), and pneumonia (0.6%).^{9f}

The *Warnings and Precautions* section of the proposed taletrectinib label includes the following risks: interstitial lung disease (ILD)/pneumonitis, hepatotoxicity, QTc interval prolongation, myalgia with increased creatinine phosphokinase, hyperuricemia, skeletal fractures, and embryo-fetal toxicity. Although medications of this class can affect various organs differently, these adverse events are expected for TKI products. For this review hepatotoxicity and ILD/pneumonitis will be discussed in detail.²

5.1. Hepatotoxicity

The most frequent hepatic laboratory abnormalities in the 600 mg once daily treated group were increased AST and increased ALT. In this group, 36.1% and 31.8% of subjects had increases of $\geq 3\times$ upper limit of normal (ULN) in ALT and AST, respectively. Most hepatic enzyme abnormalities were $< 5\times$ ULN. Only four patients had increases of $\geq 3\times$ ULN in hepatic enzymes that was also in conjunction with $\geq 2\times$ ULN increases in total bilirubin. Most of the hepatic enzyme values were Grade 1 and 2 and outside the range for Hy's Law. Two subjects (0.6%) had hepatic enzyme levels that were consistent with potential Hy's Law cases (ALT, AST $> 3\times$ ULN]; bilirubin $\geq 2\times$ ULN; alkaline phosphatase $< 2\times$ ULN). These elevations were determined to be related to taletrectinib and led to treatment discontinuation.⁹ Both events resolved after discontinuation of treatment.

The review team assessed that liver toxicity is a potential risk of the drug and will include hepatotoxicity in the *Warnings and Precautions* of the proposed label in section 5.1. The label recommends monitoring liver function tests including ALT, AST, and total bilirubin at baseline and every two weeks during the first two months of treatment and then monthly afterwards. Patients that may warrant more frequent hepatic testing if liver elevations continue. The label also advises to withhold, reduce the dose, or permanently discontinue taletrectinib based on the severity of hepatic elevations.¹²

5.2. Interstitial Lung Disease/Pneumonitis

Taletrectinib can cause severe interstitial lung disease (ILD)/pneumonitis. Eight subjects (2.3%) experienced an adverse event of ILD/pneumonitis of any Grade in the 600 mg once daily group. No specific timing of onset pattern was noted. ILD or pneumonitis was observed even after several months and or years after initiation of taletrectinib treatment. The median time to first onset of ILD/pneumonitis was 3.8 months (range: 12 days to 11.8 months). Four subjects (1.1%) were noted to have Grade ≥ 3 ILD/pneumonitis. Five subjects (1.4%) were reported to have an SAE of pneumonitis. The AE of ILD/pneumonitis resulted in dose interruption in four patients (1.1%), dose reduction in two subjects (0.6%), and drug discontinuation in two subjects (0.6%).⁹

^f Section 505-1 (a) of the FD&C Act: FDAAA factor (E): *The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

ILD/Pneumonitis is listed second in the *Warnings and Precautions* section in the draft label. The label advises healthcare providers to monitor patients for new or worsening pulmonary symptoms that may indicate that patients have ILD/pneumonitis. In these patients, taletrectinib should be withheld, then the dose should be reduced or permanently discontinued if Grade ≥ 2 ILD/pneumonitis is confirmed.¹²

6. Expected Postmarket Use

If approved, taletrectinib will primarily be used in outpatient settings, self-administered by patients, or administered from patients' caregivers, or inpatient settings depending on the disease progression. We expect this product will be dispensed from either inpatient or outpatient pharmacy settings. The likely prescribers will be oncologists who are specialized in the treatment and management of ROS1+ NSCLC.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities beyond labeling and routine pharmacovigilance.

8. Discussion of Need for a REMS

The review team recommends regular approval of taletrectinib on the basis of the efficacy and safety information currently available for the treatment of adult patients with locally advanced or metastatic ROS1-positive NSCLC. The recommendation for approval is based on efficacy data from two well controlled studies and safety data from these studies.

In the United States lung cancer is the leading cause of cancer-related deaths with NSCLC accounting for approximately 80-90%. Survival for patients with NSCLC at five-years has been reported as 22% with patients with ROS1+ NSCLC having similar outcomes. There is a need for treatments for these patients with this life threatening disease, to improve quality of life and survival. The review team did not identify significant safety concerns requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS). Serious risks are planned to be listed in the *Warnings and Precautions* of the label. Taletrectinib will be prescribed by oncologists who are familiar with monitoring, identifying, and managing the toxicities described in the label, and the label also contains guidelines to address the risks. The review team has determined that a postmarketing requirement (PMR) is needed to further evaluate the safety and efficacy of taletrectinib at the dosage of 400 mg daily, to evaluate the safety of the drug in patients with moderate or severe hepatic impairment, and to address the potential for drug-drug interactions. This reviewer agrees that a REMS is not necessary to ensure the benefits outweigh the risks of taletrectinib.

9. Conclusion & Recommendations

Based on the clinical review, the benefit-risk profile for taletrectinib is favorable in this life-threatening condition of NSCLC therefore, a REMS is not necessary to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. The management of the risks associated with taletrectinib can be communicated through labeling. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10. References

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