CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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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	219379 and 219389
PDUFA Goal Date	February 28, 2025
Nexus TTT #	2024-9532 and 2024-8611
Reviewer Name(s)	Ingrid N. Chapman, Pharm.D., BCPS
Team Leader	Naomi Boston, Pharm.D.
Acting Division Director	Laura Zendel, Pharm.D.
Review Completion Date	February 10, 2025
Subject	Evaluation of Need for a REMS
Established Name	Mirdametinib
Trade Name	Gomekli
Name of Applicant	SpringWorks Therapeutics, Inc.
Therapeutic Class	Kinase Inhibitor
Formulation(s)	1 mg and 2 mg capsules for oral administration
	1 mg tablet for oral administration
Dosing Regimen	2 mg/m^2 orally twice 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 Gomekli (mirdametinib) is necessary to ensure the benefits outweigh its risks. SpringWorks Therapeutics, Inc. submitted a New Drug Application (NDA) 219379 and 219389 for mirdametinib with the proposed indication: for the treatment of adult and pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas (PN). The Applicant did not propose any risk management activities for mirdametinib beyond routine pharmacovigilance and labeling.

DRM and the Division of Oncology 2 (DO2) agree that a REMS is not needed to ensure the benefits of mirdametinib outweigh its risks. The efficacy of mirdametinib was evaluated in the ReNeu Study. Results showed an ORR of 24 (41%) in adult subjects and 29 (52%) in pediatric subjects. The DOR at ≥ 12 months was 21 (88%) for adult subjects and 26 (90%) for pediatric subjects. The DOR at ≥ 24 months was 12 (50%) for adult subjects and 14 (48%) for pediatric subjects.

The important safety concerns (risks) associated with mirdametinib include ocular toxicity, left ventricular dysfunction, dermatologic adverse reactions, and embryo-fetal toxicity. We expect prescribers (oncologists) to be familiar with managing the risks associated with mirdametinib because these risks are known toxicities of MEK inhibitors. If approved, mirdametinib would be the 5th MEK inhibitor available. Therefore, we expect labeling is likely to be sufficient to help prescribers manage the risks.

Based on the results of the ReNeu study, the totality of information submitted to this NDA, and the favorable benefit:risk profile for this population with a serious and life-threatening disease, the review team recommends regular approval for mirdametinib for the following indication: for the treatment of adult and pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas not amenable to complete surgical resection.

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 Gomekli (mirdametinib) is necessary to ensure the benefits outweigh its risks. SpringWorks Therapeutics, Inc. submitted a New Drug Application (NDA) for 219379 (tablets) and 219389 (capsules) with the proposed indication: for the treatment of adult and pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas (PN). 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

Gomekli (mirdametinib), a new molecular entity, is a kinase inhibitor.[a] Specifically, mirdametinib inhibits mitogen-activated protein kinase kinases 1 and 2 (MEK1/2). MEK1/2 proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway which is implicated in proliferation, growth, differentiation, cell migration, cell survival, metabolism, and transcription.[1] The proposed indication is for the treatment of adult and pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas (PN).[2] Mirdametinib is proposed as a tablet for oral administration (1 mg) and capsules for oral administration (1 mg and 2 mg). The recommended dosage of mirdametinib is 2 mg/m^2 orally twice daily, with or without food, for the first 21 days of each 28-day cycle. Treatment continues until disease progression or unacceptable toxicity.[b] Currently, mirdametinib is not approved in any jurisdiction.[3]

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 219379 and NDA 219389 relevant to this review:

- **10/03/2018**: Orphan Drug designation granted under IND 139883 for mirdametinib
- **05/28/2019**: Fast track designation granted under IND 139883 for mirdametinib
- **07/24/2023**: Rare Pediatric Disease designation granted under IND 139883 for mirdametinib
- **06/28/2024**: NDA 219379 and NDA 219389 submission for the treatment of adult and pediatric patients 2 years of age and older with NF1 who have symptomatic PN was received.
- **12/30/2025**: A Late-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that no issues related to risk management have been identified to date.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

To determine the need for a REMS, it is necessary to describe the medical condition for which the proposed drug treats. Neurofibromatosis type 1 (NF1), formerly known as von Recklinghausen disease, is an autosomal dominant genetic disorder; 50% of the cases are inherited. The de novo mutations occur primarily in paternally derived chromosomes.[4] The estimated incidence of NF1 is 1:2600 to 1:3000 individuals.[c]

[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.*

The following diverse clinical manifestations present over time and contribute to a decreased quality of life in those affected with NF1:[4,d]

- Café-au-lait macules
- Axillary and/or inguinal freckling
- Lisch nodules (iris hamartomas)
- Tumors: benign and malignant tumors develop at an increased frequency throughout life (e.g. neurofibromas, optic pathway gliomas, central nervous system neoplasms, and soft tissue sarcomas)
- Other tumors
- Bone abnormalities
- Neurologic abnormalities (cognitive deficits, learning disabilities, headaches, seizures, developmental delays, and macrocephaly)
- Hypertension

Focusing on tumors, neurofibromas are the most common type of benign tumor. They are peripheral nerve sheath tumors that are composed of a mixture of Schwann cells, fibroblasts, perineurial cells, mast cells, macrophages, and T cells.[4] Plexiform neurofibromas (PNs) occur in 40% to 50% of patients with NF1. PNs may be associated with significant morbidity including pain, disfigurement, neurologic deficits, and functional impairment. Additionally, PNs may also lead to mortality through compression of vital structures, e.g., airway compression and hemothorax.[5]

3.2. Description of Current Treatment Options

There is no overall treatment for NF1, thus the treatment approach is to manage the clinical manifestations as they present. Because the proposed indication specifically refers to plexiform neurofibromas (PN), this section of the review focuses on the treatment of PN. Non-pharmacologic treatment of NF1-associated PN typically includes surgical resection; however, resection is often not feasible because of the tumor effect on adjacent tissue, nerves, and vasculature.[5]

There is an unmet clinical need for pharmacologic treatment options for PN in adult patients and pediatric patients who cannot swallow capsules. The one FDA-approved treatment for PN includes Koselugo (selumetinib), available as a capsule for oral administration. It is a mitogen-activated protein kinase (MEK) inhibitor that can induce tumor regression.[6] Selumetinib is indicated for the treatment of pediatric patients 2 years of age and older with NF1 who have symptomatic, inoperable PN. It is not indicated for the treatment of adult patients.[7]

4. Benefit Assessment

The efficacy of mirdametinib was evaluated in the MEK-NF-201 Study, also referred to as the ReNeu Study (NCT03962543).[3] It was a Phase 2b, multicenter, open-label, single-arm study in 114 patients ≥ 2 years of age with progressive or symptomatic, inoperable neurofibromatosis type 1 (NF1) associated

[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.*

plexiform neurofibromas (PN) causing significant morbidity (adult patients: n = 58; pediatric patients: n = 56). The dosing regimen was mirdametinib 2 mg/m^2 orally twice daily for the first 21 days of each 28-day cycle until disease progression or unacceptable toxicity.[5]

The major efficacy outcome measure was confirmed overall response rate (ORR), defined as the percentage of patients with complete response (disappearance of the target PN) or partial response (≥ 20% reduction in PN volume).[3] A secondary efficacy outcome measure was duration of response (DOR) for patients who achieved a confirmed response. Results showed an ORR of 24 (41%) in adult patients and 29 (52%) in pediatric patients. The DOR at ≥ 12 months was 21 (88%) for adult patients and 26 (90%) for pediatric patients. The DOR at ≥ 24 months was 12 (50%) for adult patients and 14 (48%) for pediatric patients.[3,e]

The Clinical Team concluded mirdametinib demonstrated a robust and clinically meaningful effect on ORR that is durable and associated with improvements in disease-related morbidities. These factors represent direct clinical benefit to patients and support regular approval.[5]

5. Risk Assessment & Safe-Use Conditions

To assess the safety of this drug, we focused our review on the risks listed in the Warnings and Precautions section of the proposed mirdametinib label. The pooled safety population described in the Warnings and Precautions reflects exposure to mirdametinib in 133 patients (75 adults and 58 pediatric patients). Of these patients, 114 were in the ReNeu study and 19 were in Study NF-106 (NCT 02096471).[3]

Study NF-106

Study NF-106 was a Phase 2, multicenter, open-label, single-arm study in patients ≥ 16 years old to evaluate the confirmed ORR of mirdametinib in patients with NF1 and PN.[5] The dosing regimen was mirdametinib 2 mg/m^2 orally twice daily for the first 21 days of each 28-day cycle.

ReNeu Study

Refer to Section 4 for a description of the ReNeu study. Serious adverse reactions (SARs) occurred in 17% of adult patients. SARs occurring in ≥ 1% of adult patients were COVID-19 (3.4%), nephrolithiasis (3.4%), and in one patient (1.7%) each: acute kidney injury , abdominal pain, ischemic colitis , urinary tract infection, retinal vein occlusion, scoliosis, squamous cell carcinoma of skin, cerebrovascular accident, and chronic obstructive pulmonary disease. One fatal adverse reaction occurred in an adult patient (1.7%) who received mirdametinib, due to COVID-19.[3]

SARs occurred in 14% of pediatric patients. SARs occurring in ≥ 1 % of pediatric patients included viral gastrointestinal infection (3.6%) and in one patient (1.8%) each: diplopia, musculoskeletal pain, seizure, fall, femoral neck fracture, dehydration, and hypertension.[3]

The FDA Clinical Team concluded that the safety profile of mirdametinib is consistent with other MEK inhibitors and is considered acceptable when assessed in the context of a serious and life-threatening disease and with appropriate monitoring as described in labeling.[5] The important safety concerns

[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.*

include ocular toxicity, left ventricular dysfunction, dermatologic adverse reactions, and embryo-fetal toxicity.[5,f]

5.1. Ocular Toxicity

Mirdametinib can cause ocular toxicity including retinal vein occlusion (RVO), retinal pigment epithelium detachment (RPED), and blurred vision.[3] In the pooled safety population, ocular toxicity occurred in 25% of patients treated with mirdametinib (adult patients = 28%; pediatric patients = 19%):

- Grade 1 Adverse Reactions: 20% (adult patients = 21%; pediatric patients = 17%)
- Grade 2 Adverse Reactions: 3.8% (adult patients = 5%; pediatric patients = 1.7%)
- Grade 3 Adverse Reactions: 0.8% (adult patients = 1.3%; pediatric patients = not applicable)

The proposed Warnings and Precautions states the following: "Conduct comprehensive ophthalmic assessments prior to initiating (b) (4) at regular intervals during treatment, and to evaluate any new or worsening visual changes such as blurred vision. Continue, withhold, reduce the dose, or permanently discontinue (b) (4) as clinically indicated."

5.2. Left Ventricular Dysfunction

Mirdametinib can cause left ventricular dysfunction. The adverse reactions in this section are from the ReNeu study. In adult patients, decreased LVEF of 10 to < 20% occurred in 16% of adult patients treated with mirdametinib. In pediatric patients, a decreased LVEF of 10 to <20% occurred in 25%, and decreased LVEF of ≥20% occurred in 1.8% of patients treated with mirdametinib. The median time to onset was 70 days for adult patients and 132 days for pediatric patients.

The proposed Warnings and Precautions states the following: "Before initiating (b) (4) assess ejection fraction (EF) by echocardiogram. Monitor EF every 3 months during the first year and then as clinically indicated. Withhold, reduce the dose, or permanently discontinue (b) (4) based on the severity of adverse reaction."

5.3. Dermatologic Adverse Reactions

Mirdametinib can cause dermatologic adverse reactions including rash. In the pooled safety population, rash occurred in 84% (adult patients = 92%; pediatric patients = 72%) of patients treated with mirdametinib. The most frequent rashes (≥ 2%) included dermatitis acneiform (65%), rash (11%), eczema (8%), maculo-papular rash (4.5%) and pustular rash (3.8%).

- Grade 2 Adverse Reactions 31% (adult patients = 37%; pediatric patients = 22%)
- Grade 3 Adverse Reactions: 6% (adult patients = 8%; pediatric patients = 3.4%)

The proposed Warnings and Precautions states the following: "Initiate supportive care at first signs of dermatologic adverse reactions. Withhold, reduce the dose, or permanently discontinue GOMEKLI based on severity of adverse reaction."

[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.*

5.4. Embryo-Fetal Toxicity

Based on findings from clinical trials, animal studies and its mechanism of action, mirdametinib can cause fetal harm when administered to a pregnant woman. In the ReNeu study, a pregnancy reported 31 days after the last dose of mirdametinib resulted in a first trimester spontaneous abortion.

The proposed Warnings and Precautions states the following: "Verify the pregnancy status of females of reproductive potential prior to the initiation of (b) (4). Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with (b) (4) and for 6 weeks after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with (b) (4) and for 3 months after the last dose."

6. Expected Postmarket Use

If approved, the likely prescribers of mirdametinib are oncologists (including pediatric specialists); it will be administered in the outpatient and inpatient setting. Prescribers are likely to be familiar with the management of adverse reactions associated with mirdametinib as it would be the 5th drug in its class, if approved. Additionally, kinase inhibitors have been prescribed in the oncology setting for over 20 years.

7. Risk Management Activities Proposed by the Applicant

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

8. Discussion of Need for a REMS

The FDA review team recommends regular approval of mirdametinib for the treatment of adult and pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas not amenable to complete surgical resection.[5] The recommendation for approval is primarily supported by the ORR and DOR results from the ReNeu Study.

Treatment options for NF1 and associated PN are limited. Selumetinib is the only FDA-approved treatment for NF1. It is indicated for pediatric patients 2 years of age and older, not adults. Selumetinib's capsule formulation is not accessible to pediatric patients. Because NF1 has an estimated incidence of 1:2600 to 1:3000 individuals, significant morbidity, and decreased quality of life, additional treatment options are needed. If approved, mirdametinib can meet the need to treat adult patients and pediatric patients with NF1 and associated PN.

Labeling is likely to be sufficient to help prescribers manage the risks associated with mirdametinib. The Warnings and Precautions section of the proposed label includes the following safety concerns (risks): ocular toxicity, left ventricular dysfunction, dermatologic adverse reactions, and embryo-fetal toxicity. We expect prescribers (oncologists) to be familiar with managing the risks associated with mirdametinib because these risks are known toxicities of MEK inhibitors. If approved, mirdametinib would be the 5th

MEK inhibitor available. Additionally, kinase inhibitors have been prescribed in the oncology setting for over 20 years.

DRM recommends that, should mirdametinib, be approved, a REMS is not necessary to ensure its benefits outweigh its risks in adult and pediatric patients 2 years of age and older with NF1 who have symptomatic PN not amenable to complete surgical resection.

9. Conclusion & Recommendations

Based on the available data a REMS is not necessary to ensure the benefits outweigh the risks. The safety concerns associated with mirdametinib use are well documented and healthcare providers who will prescribe mirdametinib should be familiar with managing the risks.

Should DO2 have any concerns or questions or if new safety information becomes available, please send a consultation to the Division of Risk Management.

10. References

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NAOMI S BOSTON
02/10/2025 04:11:33 PM

LAURA A ZENDEL
02/10/2025 04:42:27 PM