CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219379Orig1s000
219389Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 27, 2025

To: Opeyemi Udoka, Senior Regulatory Health Project Manager, DO2

Barbara Scepura, Associate Director for Labeling, DO2

From: Mispa Ajua-Alemanji, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, Team Leader, OPDP

Subject: OPDP Labeling Comments for GOMEKLI™ (mirdametinib) capsules, for oral use and GOMEKLI™ (mirdametinib) tablets for oral suspension

NDA: 219379; 219389

Background:
In response to DO2's consult request dated August 5, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI)/Instructions for Use (IFU), and carton and container labeling for the original NDA submission for GOMEKLI™ (mirdametinib) capsules, for oral use and GOMEKLI™ (mirdametinib) tablets for oral suspension. SpringWorks Therapeutics is seeking the approval of GOMEKLI™ (mirdametinib) for proposed treatment of adults and pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas (PN).

PI:
OPDP's comments on the proposed labeling are based on the draft labeling emailed to OPDP on January 13, 2025, and later revised on January 22, 2025, and our comments are provided below.

PPI /IFU:
A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed and comments on the proposed PPI and IFU were sent under separate cover on January 16, 2025.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on December 23, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Mispa Ajua-Alemanji at Mispa.Ajua-Alemanji@fda.hhs.gov.

29 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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/

MISPA L AJUA-ALEMANJI
01/27/2025 02:44:03 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	January 16, 2025
To:	Opeyemi Udoka DPT, CSM Senior Regulatory Health Project Manager **Division of Oncology II (DO2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Laurie Buonaccorsi, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Adesola Adejuwon, PharmD, MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	GOMEKLI (mirdametinib)
Dosage Form and Route, Application Type/Number:	NDA 219389: capsules, for oral use NDA 219379: tablets for oral suspension
Applicant:	SpringWorks Therapeutics, Inc.

1 INTRODUCTION

On June 28, 2024, SpringWorks Therapeutics, Inc. submitted for the Agency's review an original New Drug Application (NDA) 219389 for GOMEKLI (mirdametinib) capsules and NDA 219379 for GOMEKLI (mirdametinib) tablets for oral suspension. The Applicant proposes an indication for the treatment of adults and pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas (PN).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology II (DO2) on August 5, 2024, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for GOMEKLI (mirdametinib) capsules and GOMEKLI (mirdametinib) tablets for oral suspension and the proposed Instructions for Use (IFU) for GOMEKLI (mirdametinib) tablets for oral suspension.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on October 21, 2024.

2 MATERIAL REVIEWED

- Draft GOMEKLI (mirdametinib) capsules and tablets for oral suspension PPI received on June 28, 2024, revised by the review division throughout the review cycle, and received by DMPP and OPDP on January 13, 2025.
- Draft GOMEKLI (mirdametinib) tablets for oral suspension IFU received on June 28, 2024, revised by the review division throughout the review cycle, and received by DMPP and OPDP on January 13, 2025.
- Draft GOMEKLI (mirdametinib) capsules and tablets for oral suspension Prescribing Information (PI) received on June 28, 2024, revised by the review division throughout the review cycle, and received by DMPP and OPDP on January 13, 2025.
- Approved KOSELUGO (selumetinib) capsules comparator labeling dated January 24, 2024.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI and IFU, the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more

accessible for patients with vision loss. We reformatted the PPI and IFU using Arial font.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that they are free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFU meets the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)
- ensured that the PPI and IFU are consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/

LAURIE J BUONACCORSI
01/16/2025 02:55:24 PM

ADESOLA F ADEJUWON
01/16/2025 02:59:36 PM

LASHAWN M GRIFFITHS
01/16/2025 03:36:37 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	January 10, 2025
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 219379 and NDA 219389
Product Name, Dosage Form, and Strength:	Gomekli (mirdametinib) Tablets for Oral Suspension, 1 mg Gomekli (mirdametinib) Capsules, 1 mg, and 2 mg
Applicant Name:	SpringWorks Therapeutics
FDA Received Date:	December 27, 2024
TTT ID #:	2024-8610-1 and 2024-9529-1
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Tingting Gao, PharmD

1 PURPOSE OF MEMORANDUM

SpringWorks Therapeutics submitted revised container labels and carton labeling received on December 27, 2024 for Gomekli. The Division of Oncology 2 (DO2) requested that we review the revised container labels and carton labeling for Gomekli (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

SpringWorks Therapeutics implemented all our recommendations and we have no additional recommendations at this time.

13 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[a] Stewart, J. Label and Labeling Review for Gomekli (NDA 219379 and NDA 219389). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 OCT 21. TTT ID: 2024-8610 and 2024-9529.

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/

JANINE A STEWART
01/10/2025 04:10:10 PM

TINGTING GAO
01/10/2025 06:21:18 PM

Clinical Inspection Summary

Date	January 2, 2025
From	Lee Pai-Scherf, MD Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) DCCE, OSI
To	Kristin Wessel, MD, Medical Officer Jeannette Nashed, Clinical Analyst Amy Barone, MD, Team Leader (CDTL) Division of Oncology 2 (DO2), Office of Oncology Products
NDA #	NDA 219379
Applicant	SpringWorks Therapeutics Inc.
Drug	Mirdametinib capsule
NME (Yes/No)	Yes
Therapeutic Classification	Kinase inhibitor of MEK1/2
Proposed Indication(s)	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)
Consultation Request Date	August 6, 2024
Summary Goal Date	January 11, 2025
Action Goal Date	February 11, 2025
PDUFA Date	February 28, 2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study MEK-NF-201 were submitted to the Agency in support of New Drug Application (NDA 219379) for 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 (PN). Three clinical investigators (CIs), Drs. David Viskochil (Site # 11), Christopher Moertel (Site # 12), and Eric Creed (Site # 3), and the imaging contract research organization (CRO), [redacted] (b) (4) were inspected.

Inspections of the CIs, Drs. Viskochil, Moertel, and Creed, did not find significant concerns regarding the study conduct, data integrity, Good Clinical Practice (GCP), or regulatory compliance. The inspection of the imaging CRO, [redacted] (b) (4), revealed no significant data discrepancies, GCP or regulatory violations. Based on these inspections, Study MEK-NF-201 appears to have been conducted adequately and the data generated by the inspected clinical investigators and the imaging CRO and submitted by the Applicant appear acceptable in support of the proposed indication.

II. BACKGROUND

SpringWorks Therapeutics Inc. submitted NDA 219379 seeking approval for mirdametinib for the above indication based on the efficacy and safety results from Study MEK-NF-201, a single-arm, phase 2b study to evaluate the efficacy, safety, and tolerability of mirdametinib in participants ≥ 2 years of age with an inoperable NF1-associated PN causing significant morbidity. The study enrolled subject into 2 cohorts: Cohort 1, age 2 to 17 years of age (pediatric cohort) and Cohort 2, age ≥ 18 years of age (adult cohort).

Eligible subjects received mirdametinib orally at a dose of 2 mg/m^2 twice daily (BID) with a maximum dose of 4 mg BID. Dosing was on a 28-day cycle (4-week course) with a 3-week on/1-week off schedule for up to 24 cycles, disease progression (confirmed by central review), intolerable event, pregnancy, non-compliance, or subject withdraw from study. Subjects who completed cycle 24 of the treatment phase and did not meet withdrawal criteria were eligible to participate in the long-term follow-up phase.

The primary efficacy endpoint was confirmed objective response rate (ORR), defined as the proportion of participants who had a confirmed ≥ 20% reduction in target tumor volume compared to baseline as assessed by a Blinded Independent Central Review (BICR). The key secondary efficacy endpoint was duration of response (DoR) by BICR.

Patient consent must be obtained prior to any study procedures being performed. Baseline clinical assessment and laboratory tests were to be performed up to 45 days prior to the 1st study treatment and at the protocol specified time points. Clinical assessment must include ophthalmic exam by an ophthalmologist, 12-lead ECG, echocardiogram to assess left ventricular ejection fraction and motor function assessment (strength, range of motion, 6-minute walk tests).

Tumor volume was measured by MRI and all scans are to be submitted for independent, blinded central radiologic review throughout the study. Baseline MRI were to be obtained up to 45 days before Day 1, at weeks 19 (cycle 5), 35 (cycle 9), 61 (cycle 13), 67 (cycle 17), 83 (cycle 21), and 96 (cycle 24), or at the time of early termination.

The population of interest to support the proposed indication consist of 114 subjects (56 pediatric and 58 adults) enrolled in Study MEK-NF-201. Subjects were enrolled across 50 study centers across the US.

III. RESULTS (by site)

1. **Dr. David Viskochil (Site # 11)**
   421 Wakara Way, Suite 360
   Salt Lake City, UT 84108

   Inspection dates: September 23 -26, 2024

   Dr. Viskochil was inspected as a BIMO review-based inspection for Study MEK-NF-201. This was the first FDA inspection for this investigator.

   At the time of the inspection, the site had screened 11 subjects and had enrolled 5 subjects in the MEK-NF-201study. Of the 5 subjects enrolled, 3 subject completed the study treatment, 1 subject was in long term follow-up phase, and 1 subject was lost to follow-up.

   Source records for all 5 enrolled subjects were reviewed. Records reviewed included, but were not limited to, informed consent form, inclusion and exclusion criteria, protocol deviations, concomitant medications, protocol-required study visits and procedures, and adverse events were compared with data listings. Records were compared with the line listings and were found to be generally consistent with the data submitted to the NDA.

   The inspection verified that MRI scans to assess the primary efficacy endpoint were performed according to protocol specified time points and all scans were submitted to the for central read. No discrepancies were observed when compared to the data submitted to the NDA.

   Additional records reviewed included but were not limited to, IRB approval documentation, screening and enrollment logs, financial disclosures, investigational drug storage and accountability, case report forms, site monitoring documents. No issues were observed.

   Based on the results of the inspection, the data generated at Dr. Viskochil's site appear acceptable in support of the proposed indication in the NDA.

2. **Dr. Christopher Moertel (Site # 12)**
   L 2450 Riverside Ave
   Minneapolis, MN 55454

   Inspection dates: October 28 -31, 2024

   Dr. Moertel was inspected as a BIMO review-based inspection for Study MEK-NF-201. This was the first FDA inspection for this investigator.

   At the time of the inspection, the site had screened 8 subjects and had enrolled 7 subjects

in the study, of these, 3 subjects completed study, 3 subjects were in long-term follow-up phase, and 1 subject withdrew consent.

Source records for 7 enrolled subjects were reviewed and compared with data listings submitted to the NDA. Records reviewed included, but were not limited to, informed consent forms, inclusion/exclusion criteria, treatment initiation dates, and adverse events. Additional selected records reviewed include ECG, laboratory tests, echocardiogram, ophthalmic examinations, bone plate radiograph reports (for subjects 2 – 17 years of age), progress notes, protocol deviations and follow-up visits. The source documentation at the site was compared against data line listings and no significant discrepancies were observed.

Radiographic scans to evaluate the efficacy endpoint were performed as specified in the protocol and all scans were submitted for central review. No discrepancies were found when compared with the listings submitted to the NDA.

Additional records reviewed during the inspection included, but were not limited to, IRB approvals, financial disclosure forms, staff training, site monitoring documents, and investigational product accountability. No issues were observed.

Based on the results of the inspection, the data generated at Dr. Moertel' s site appear acceptable in support of the proposed indication in the NDA.

3. **Dr. Eric Creed (Site # 3)**
   170 Manning Drive
   University of North Carolina
   Chapel Hill, NC 27599-7025

   Inspection dates: September 9 – 13, 2024,

   Note: Dr. Jamie K. Capal was the previous Principal Investigator for Study MEK-NF-201 at the site. Dr. Capal left the site in June 2024 and Dr. Eric Creed has since assumed full investigator responsibilities for Study MEK-NF-201.

   Dr. Creed was inspected as a BIMO review-based inspection for Study MEK-NF-201. This was the first FDA inspection for this investigator.

   At the time of the inspection, the site had screened 11 subjects and had enrolled 9 subjects in the study. Of the 9 subjects enrolled, 8 had completed study and 1 subject had been transferred away from the site.

   Source records for all 9 enrolled subjects were reviewed. Records reviewed included, but were not limited to, informed consent forms, eligibility criteria, protocol deviation, concomitant medications, and adverse events. No discrepancies were observed between

the source documents at the site and data line listings provided by the Applicant.

The inspection verified that MRI scans to evaluate tumor status were performed as specified in the protocol and all scans were submitted for central review for efficacy endpoint determination. Source records were consistent with the information submitted in the NDA.

Additional documents reviewed during the inspection included, but were not limited to, financial disclosures, IRB approval and communications, investigational product accountability records, staff training records, and site monitoring documents. No issues were observed.

Based on the results of the inspection, the study data generated at Dr. Creed's site appear acceptable in support of the proposed indication in the NDA.

1. (b) (4)

Inspection dates: (b) (4)

(b) (4)
.

This inspection reviewed (b) (4) responsibilities to perform an independent central imaging review for Study MEK-NF-201. Records reviewed included, but were not limited to, imaging source data, overview of electronic systems, written agreements, meeting minutes, standard operating procedures, manuals, and training records. The review found the processes adequate.

The inspection verified the accuracy of imaging time points per protocol and charter, that readers were blinded to the subject data and the other radiologist's imaging reads, and the procedures for receipt, evaluation, and data transfer to the sponsor were according to the data transfer agreement.

Tumor measurements for 48 out of 114 subjects in the efficacy population (28 pediatric and 20 adult subjects) enrolled in study MEK-NF-201 were compared with the data listing submitted to the NDA. The data were found to be accurate, verifiable, and collected and disseminated according to protocol, agreements charters and manuals.

The ID of the subjects whose tumor measurement data were verified during the inspection are as follow:

SUBJECT ID	
PEDIATRIC SUBJECTS	ADULT SUBJECTS
	(b) (6)

Based on the results of the inspection, the imaging review data generated by (b) (4) appear acceptable in support of the proposed indication in the NDA.

{See appended electronic signature page}

Lee Pai-Scherf, MD
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Michele Fedowitz, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {*See appended electronic signature page}*

Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

Review Division /Project Manager/Opeyemi Udoka
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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/

LEE HONG PAI SCHERF
01/02/2025 03:12:51 PM

MICHELE B FEDOWITZ
01/02/2025 03:16:34 PM

JENN W SELLERS
01/02/2025 03:20:21 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 219379 and 219389
Submission Number	2
Submission Date	6/28/2024
Date Consult Received	9/16/2024
Drug Name	Mirdametinib
Indication	Treatment of adults and pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas (PN).
Therapeutic Dose	2 mg/m2 BID first 21 days out of each 28-day cycle
Clinical Division	DO2
Protocol Review	Link

Note: Any text in the review with a light background should be considered as copied from the Applicant's document.

This review responds to your consult dated 9/16/2024 regarding the Applicant's QT evaluation. We reviewed the following materials:

- Previous IRT review under IND 139883 dated 11/03/2021 in DARRTS;
- TQT study report (MEK-NF-102) (NDA 219379 / SDN 002; link);
- Concentration QTc study report (NDA 219379 / SDN 002; link);
- Investigator's brochure (IND 139883 / SDN 144; link); and
- Highlights of clinical pharmacology and cardiac safety (NDA 219379 / SDN 004; link).

1 SUMMARY

Mirdametinib did not prolong the QTcF interval in this thorough QT study – see Table 1 for overall results. The supratherapeutic dose (15 mg, single dose) provided 5.7-fold the steady state clinical exposure for mirdametinib and covered the high clinical exposure for PD-0315209 when administered to subjects with moderate renal impairment. The high clinical exposure for mirdametinib is still pending the results of the hepatic impairment study.

The clinical study MEK-NF-102 was a double-blind, randomized, 4-treatment, 4-period crossover TQT study in healthy adults to evaluate the effects of mirdametinib and its primary metabolite (PD-0315209) on cardiac repolarization as detected by QTc prolongation. Data were analyzed with exposure-response analysis as the primary analysis,

which did not suggest that mirdametinib is associated with significant QTc prolonging effect (refer to section 4.3). The findings of the primary analysis are further supported by the lack of QTc prolongation in nonclinical data, by-time analysis (section 4.3) and categorical analysis (section 4.4).

Table 1: Summary of findings

<table>
<tr><td>QT assessment pathway</td><td>☒ Thorough QT study
☐ Substitute for thorough QT study (5.1)
☐ Alternative QT study when a thorough QT study is not feasible (6.1)</td></tr>
<tr><td>Clinical QT study findings</td><td>• Currently the tentative high clinical exposure is in moderate renal impairment. High clinical exposure scenario will be known after a hepatic impairment study (section 3.1).
• The highest dose in the TQT study covers the tentative high clinical exposure of PD-0315209 and covers 5.7-fold the steady state clinical exposure for mirdametinib (section 3.1).
<table>
<tr><th>ECG parameter</th><th>Treatment</th><th>Concentration</th><th>ΔΔQTcF (msec)</th><th>90% CI (msec)</th></tr>
<tr><td>QTc</td><td>Mirdametinib 2 mg/m^2 BID</td><td>202.2 ng/mL</td><td>-0.4</td><td>-0.9 to 0.1</td></tr>
<tr><td>QTc</td><td>Mirdametinib 14 mg single dose</td><td>1,158.6 ng/mL</td><td>-0.7</td><td>-2.3 to 0.9</td></tr>
</table></td></tr>
<tr><td>In vitro and In vivo findings</td><td>Integrated nonclinical risk assessment was not performed.</td></tr>
</table>

2 RECOMMENDATIONS

Below are proposed edits to the label submitted to SDN 004 (link).

Our changes are highlighted (addition, ~~deletion~~). Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At approximately 6 times the steady-state exposure associated with the recommended dose of 2 mg/m^2, clinically significant QTc interval prolongation was not observed.

Reviewer's comment: *The Applicant's proposed labelling language for this product is consistent with the labelling guidance, i.e., "QTc Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry"(link).*

3 APPLICANT'S SUBMISSION

3.1 OVERVIEW

The Applicant (Springworks Therapeutics, Inc.) is proposing mirdametinib (GOMEKLI) for the treatment of adult and pediatric patients 2 years of age or older with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas (PN).

The proposed therapeutic dose is 2 mg/m^2 BID for the first 21 days of each 28-day cycle.

We previously reviewed the protocol for the TQT study and overall found it acceptable but recommended that the Applicant used 8 sequences instead of 4 sequences to maintain blinding because moxifloxacin is open-label. We also provided recommendations related to the concentration-QTc and by-time analysis. (DARRTS 11/03/2021)

The Applicant has modified the study protocol to address our comment related to the number of sequences. Otherwise, the study protocol has not been significantly altered.

3.1.1 Clinical Pharmacology

See highlights of clinical pharmacology and cardiac safety.

In a mass balance study, mirdametinib and metabolites PD-0315209 and M22 exhibited exposure >10% of total radioactivity in plasma. In the QT study and five clinical studies used for population PK model development, mirdametinib and PD-0315209 were measured.

No clinical DDI studies have been performed. Mirdametinib (482.19 g/mol) is metabolized by UGT and CES enzymes and is a substrate of P-gp and BCRP. PD-0315209 is a substrate of UGT enzymes and BCRP.

Table 2. Summary of Dose and Exposure Assessment

		Mean Cmax (ng/mL)
Highest therapeutic or clinical trial dosing regimen	2 mg/m^2 BID first 21 days out of each 28-day cycle, oral tablets, or capsules	Mirdametinib: 202[a] PD-0315209: 75.7[a]
Applicant's High clinical exposure scenario[b]	Moderate renal impairment[b] leading to 1.1- and 1.67-fold higher Cmax	Mirdametinib: 222.2 PD-0315209: 126.4
Highest dose in QT assessment	Single dose of 14 mg in healthy adults	Mirdametinib: 1160 PD-0315209: 111
Cmax Ratio	Mirdametinib: 1150 / 222.2 = 5.2 PD-0315209: 111 / 126.4 = 0.9	

[a]Mean predicted Cmax_ss in adults and pediatric participants in the popPK analysis. [b]This is the tentative high clinical exposure scenario, pending completion of a hepatic impairment study. Also, per the DO2 Clinical Pharmacology reviewer, there is a possibility that PMRs may be issued for DDI studies.

A proposed hepatic impairment PK study has not yet been conducted.

In a food effect study (5 mg capsule formulation), mirdametinib Cmax was reduced 43% and PD-0315209 Cmax decreased 27% upon fed-state administration.

A dedicated renal impairment study has not been conducted. In a popPK analysis (n=260 participants), 60 participants had mild renal impairment and 10 had moderate renal impairment. In those with moderate renal impairment vs normal renal function, predicted mirdametinib Cmax was increased ~10% and PD-0315209 Cmax increased ~67% (popPK report, figure 33).

In the popPK analysis, no effect of age, sex, or race was observed on the PK of mirdametinib or PD-0315209.

Reviewer's comment: *M22 is a secondary O-glucuronide metabolite of mirdametinib that represented 14.7% of total plasma radioactivity in single dose mass balance study MEK-NF-101. M22 was not measured in the QT study or other PK studies. The Applicant cites FDA guidance for safety testing of drug metabolites for why M22 was not evaluated, specifically "Phase 2 conjugation reactions generally render a compound more water soluble and pharmacologically inactive, thereby eliminating the need for further evaluation."*

3.1.2 Nonclinical Safety Pharmacology Assessments

hERG: The Applicant evaluated the effects of mirdametinib and its metabolite (PD-0315209) on hERG current in the study report (SWT-21-01, link). The hERG current was assessed at near physiological temperature (36±1°C)] using manual patch clamp assay.

The reduction in hERG current at the highest concentration of mirdametinib 100 µM tested was 39.5%. This concentration provides 21701-fold (MW: 482.2 g/mol; PB: 99%) the high clinical exposure scenario (Table 2). Assuming a hill coefficient of 1 this corresponds to an IC_{50} of 153.2 µM and a safety margin of 33238-fold.

There was an increase in the hERG current at the highest concentration tested of PD-0315209 (100 µM) of 25.6%. However, PD-0315209 at 100 µM increased the hERG ramp current but did not affect the step current, as shown in the example traces shown in Figure 2 of the study report. Additionally, the ratio of ramp current amplitude to step current amplitude in the example trace is relatively small (~1x) compared to the typical ~2x ratio reported in the literature and observed in FDA lab using the same voltage protocol at near-physiological temperature. Therefore, it is unclear whether the increase in hERG ramp current is a result of the drug effect or an artifact.

In vivo QT: The in vivo QT study (rr-745-03782, link) assessed the effects of mirdametinib on ECG parameters following single oral doses to conscious telemeterized male monkeys (n=4) at 0, 3, or 10 mg/kg. Three additional non-instrumented monkeys were given 3 and 10 mg/kg for toxicokinetic assessment.

The free Cmax of the highest dose in the study is 3820 ng/mL and 143 ng/mL for mirdametinib and PD-0315209, respectively. Protein binding is similar between monkeys and humans for mirdametinib. PD-0315209 is highly bound (>99%) in humans and information about protein binding in monkeys is not available. Assuming similar protein binding for PD-0315209 the highest dose in the study provides 17- and 1-fold coverage of the high clinical exposure (Table 2). No changes in mean HR were reported in the study. Mean changes for other ECG intervals were not evaluated.

3.2 APPLICANT'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for mirdametinib was based on exposure-response analysis, please see section 3.2.3 for additional details.

Applicant presented by-time analysis results for all intervals. Central-tendency, and diagnostic statement analyses were all consistent with absence of a clinically significant effect of mirdametinib at supratherapeutic exposures (up to 6x the therapeutic exposure).

Reviewer's comment: *Reviewer's analysis results are similar to the Applicant's analysis results. Please see section 4.3 for additional details.*

3.2.1.1 Assay Sensitivity

The results of the Applicant's analysis shows that assay sensitivity was established by the moxifloxacin arm.

Reviewer's comment: *Both by-time and exposure-response analyses show that assay sensitivity was established by the moxifloxacin arm.*

3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted by the Applicant.

3.2.2 Categorical Analysis

There were no significant outliers per the Applicant's analysis for QTc (i.e., >450 msec or >60 msec over baseline), PR (>220 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline).

The only observed outlier was a single participant with HR > 100 bpm at Hour 6 in the placebo and both mirdametinib treatments (Participant 900138, placebo and mirdametinib 6 mg; Participant 900915, mirdametinib 14 mg).

Reviewer's comment: *Reviewer's analysis results are similar to the Applicant's analysis results. Please see section 4.4 for additional details.*

3.2.3 Exposure-Response Analysis

The Applicant used the model recommended in the white paper. The results of the Applicant's analysis show an absence of significant QTc prolongation.

Reviewer's comment: *The Applicant's and reviewer's analyses had similar results.*

3.2.4 Safety Analysis

There were no deaths or serious adverse events in the study. Seven participants discontinued due to a treatment emergent adverse event. None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias, or sudden cardiac death) occurred in this study.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The Applicant used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| >10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Digital ECG waveforms were submitted for review. The ECGs were read semi-automatically by a central reader blinded to treatment. Compared to the ECG warehouse

algorithm, we did not observe significant bias in QT measurements and the ECG acquisition and interpretation for this study is therefore acceptable.

4.3 By-Time Analysis

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG. The statistical reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and baseline as a covariate. The model also includes subject as a random effect and an unstructured covariance matrix to explain the associations among repeated measures within the period.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTcF for different treatment groups. The maximum ΔΔQTcF values by treatment are shown in Table 3.

Figure 1. Mean and 90% CI of ΔΔQTcF Time-Course (Unadjusted CIs)

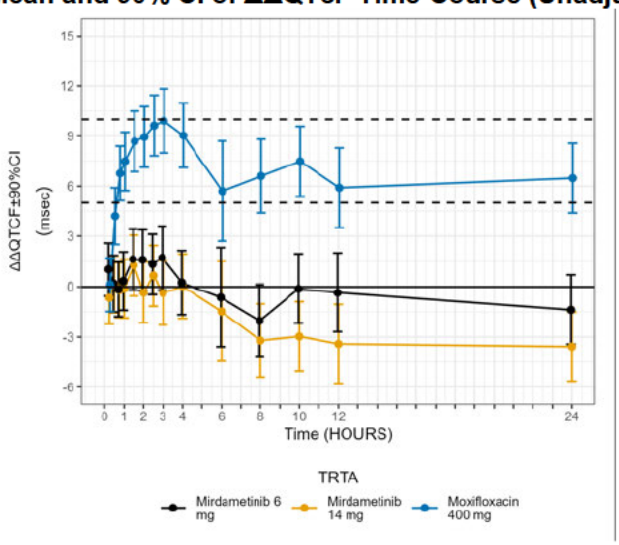


Table 3. Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTcF

Actual Treatment	Nact / Npbo	Time (HOURS)	ΔΔQTCF (msec)	90.0% CI (msec)
Mirdametinib 14 mg	52 / 49	1.5	1.2	(-0.6 to 3.1)
Mirdametinib 6 mg	54 / 49	3.0	1.7	(-0.2 to 3.6)

4.3.1.1 Assay Sensitivity

The statistical reviewer used the same linear mixed model as treatment arm to analyze the moxifloxacin effect by time for each biomarker (e.g., ΔQTcF, ΔHR). The time-course of changes in ΔΔQTcF is shown in Figure 1 and includes the expected time-profile with a mean effect of >5 msec after Bonferroni adjustment for 4 time points (Table 4).

The primary method for establishing assay sensitivity for this study was based on exposure-response analysis—see section 4.5.1.1 for details.

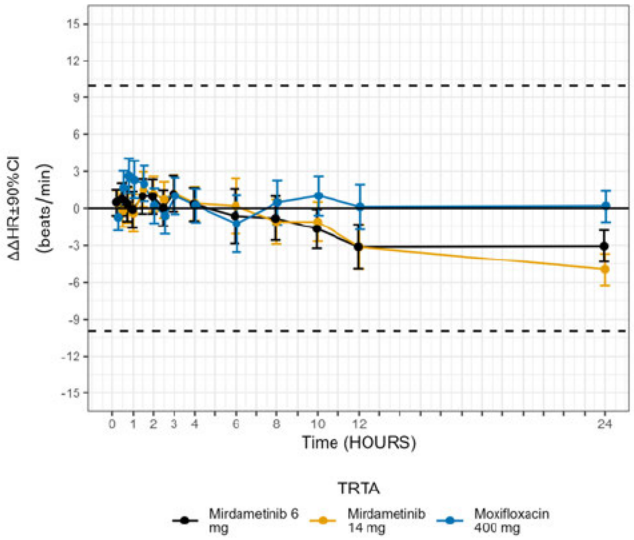
Table 4. The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for ΔΔQTcF

Actual Treatment	Nact / Npbo	Time (HOURS)	ΔΔQTCF (msec)	90.0% CI (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	50 / 49	3.0	9.9	(8.0 to 11.8)	(7.3 to 12.5)

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different treatment groups.

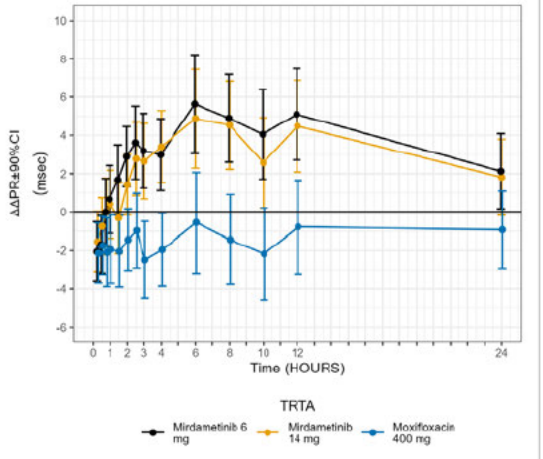
Figure 2. Mean and 90% CI of ΔΔHR Time-Course



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different treatment groups.

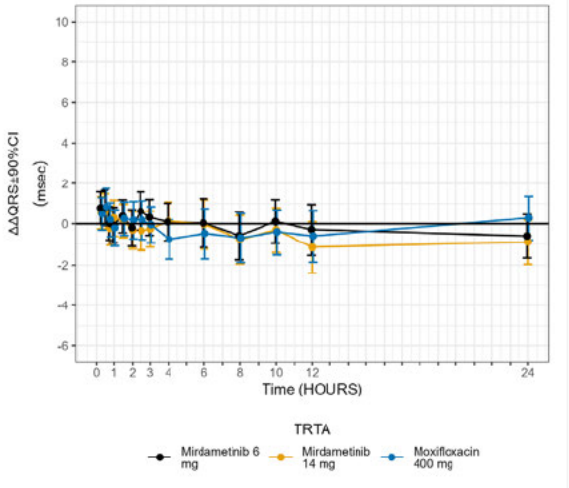
Figure 3. Mean and 90% CI of ΔΔPR Time-Course



4.3.4 QRS

Figure 4 displays the time profile of ΔΔQRS for different treatment groups.

Figure 4. Mean and 90% CI of ΔΔQRS Time-Course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

None of the subjects experienced QTcF values >450 msec with or without a change from baseline >60 msec and/ or ΔQTcF >60 msec for any dose levels of mirdametinib.

4.4.2 HR

Table 5 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). One subject in mirdametinib 6 mg group and one subject in mirdametinib 14 mg group experienced HR >100 beats/min.

Table 5: Categorical Analysis for HR

Actual Treatment	Total (N)		Value <=100 beats/min		Value >100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Mirdametinib 6 mg	54	756	53 (98.1%)	755 (99.9%)	1 (1.9%)	1 (0.1%)
Mirdametinib 14 mg	52	728	51 (98.1%)	727 (99.9%)	1 (1.9%)	1 (0.1%)

4.4.3 PR

None of the subjects experienced PR >220 msec with 25% increase over baseline for any dose levels of mirdametinib.

4.4.4 QRS

None of the subjects experienced QRS >120 msec for any dose levels of mirdametinib.

4.5 EXPOSURE-RESPONSE ANALYSIS

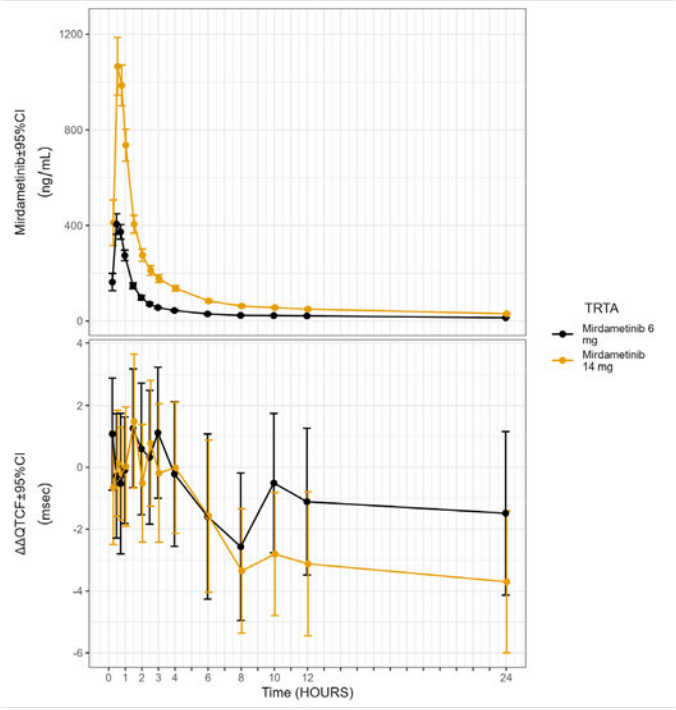
Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK.

4.5.1 QTc

Prior to evaluating the relationship between drug concentration and QTcF using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) absence of delay between plasma concentration and ΔΔQTcF; and 3) absence of a nonlinear relationship.

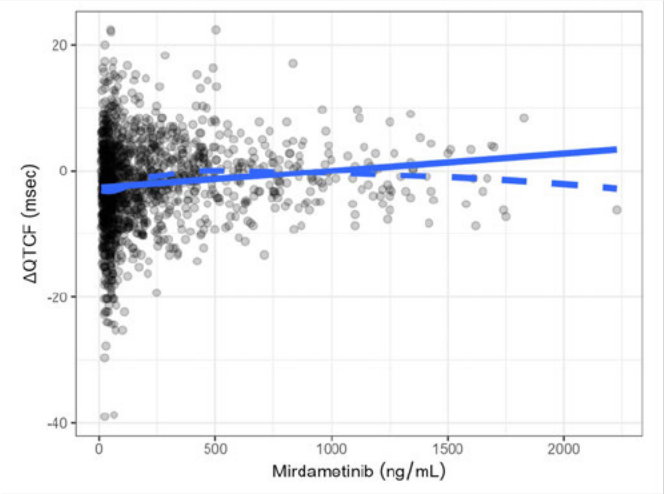
Figure 2 shows the time-course of ΔΔHR, with an absence of significant ΔΔHR changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and ΔΔQTcF, with no appearance of significant hysteresis. Figure 6 shows the relationship between drug concentration and ΔQTcF and supports the use of a linear model.

Figure 5. Time-Course of Drug Concentration (Top) and QTcF (Bottom)[1]



[1] ΔΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

Figure 6. Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 6.

Figure 7. Goodness-of-Fit Plot for QTcF

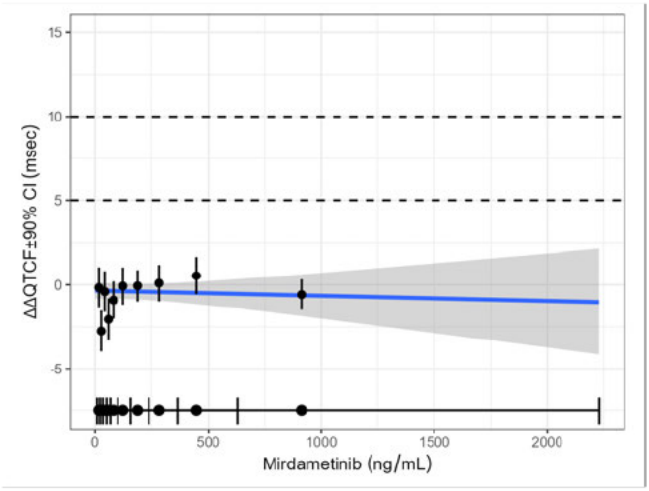


Table 6. Predictions From Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	Mirdametinib (ng/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
Mirdametinib 6 mg	1	428.4	-0.5	(-1.1 to 0.2)
Mirdametinib 14 mg	1	1,158.6	-0.7	(-2.3 to 0.9)

4.5.1.1 Assay Sensitivity

The time course of moxifloxacin concentration and ΔΔQTcF is shown in Figure 8. When the same linear mixed effect model is applied, the goodness-of-fit plot for moxifloxacin is shown in Figure 9, and the predicted QTcF at the geometric mean Cmax is listed in Table 7.

Figure 8. Time-Course of Moxifloxacin Concentration (Top) and QTcF (Bottom)

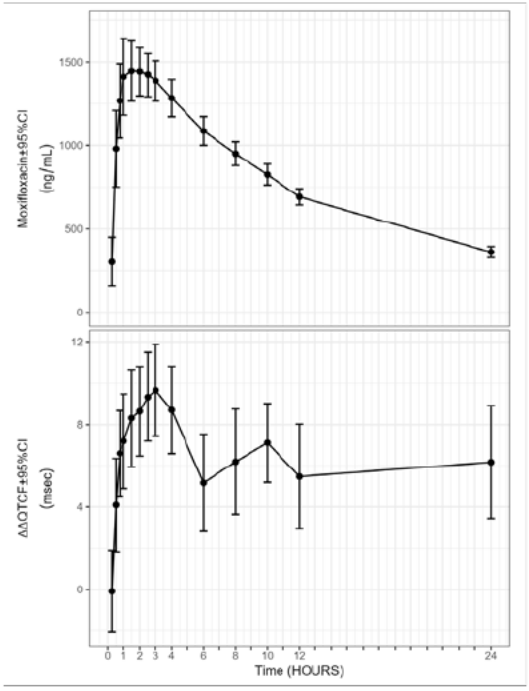


Figure 9. Goodness-of-Fit Plot of ΔΔQTcF for Moxifloxacin

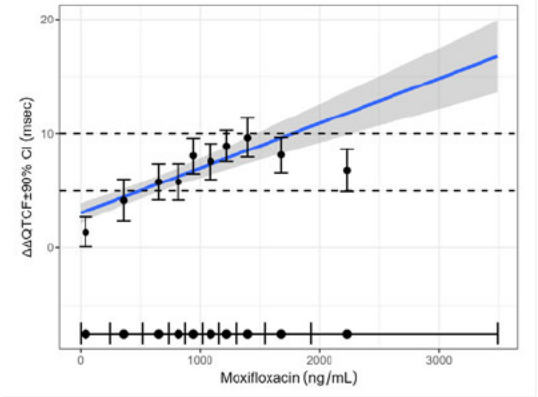


Table 7. Predictions From Concentration-QTcF Model for Moxifloxacin

Actual Treatment	Analysis Nominal Period Day (C)	Moxifloxacin (ng/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
Moxifloxacin 400 mg	1	1,807.4	10.1	(8.6 to 11.6)

4.6 Safety assessments

See section 3.2.4. No additional safety analyses were conducted.

5 APPENDIX

5.1 Evaluation of the Applicant's Clinical QT Studies

Previously reviewed (IND 139883 - 11/03/2021)

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/

FERDOUSE BEGUM
10/30/2024 03:17:16 PM

DALONG HUANG
10/30/2024 04:58:02 PM

MARIO SAMPSON
10/31/2024 12:08:41 AM

ELIFORD N KITABI
10/31/2024 08:10:32 AM

DONGLIN GUO
10/31/2024 09:59:24 AM

MICHAEL Y LI
10/31/2024 10:00:48 AM

LARS JOHANNESEN
10/31/2024 10:04:25 AM

CHRISTINE E GARNETT
10/31/2024 10:14:04 AM

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 21, 2024
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 219379 and NDA 219389
Product Name, Dosage Form, and Strength:	Gomekli (mirdametinib) Tablets for Oral Suspension, 1 mg Gomekli (mirdametinib) Capsules, 1 mg, and 2 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	SpringWorks Therapeutics
FDA Received Date:	June 28, 2024
TTT ID #:	2024-8610 and 2024-9529
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Tingting Gao, PharmD

1 INTRODUCTION

As part of the approval process for Gomekli (mirdametinib) tablets for oral suspension (NDA 219379) and Gomekli (mirdametinib) capsules (NDA 219389), the Division of Oncology 2 (DO2) requested that we review the proposed Gomekli Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), container label(s), and carton labeling for areas of vulnerability that may lead to medication errors. The NDAs cross-reference each other and both dosage forms are labeled in a shared PI.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 219379.

Table 1. Materials Considered for this Label and Labeling Review	
Material(s) Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B

3 CONCLUSION

We evaluated the proposed Gomekli Patient Package Insert (PPI) and carton labeling and determined that they are acceptable from a medication error perspective.

However, the proposed Gomekli Prescribing Information (PI), Instructions for Use (IFU), and container label(s) may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Oncology 2 (DO2) in Section 4 and for SpringWorks Therapeutics in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF ONCOLOGY 2 (DO2)

A. Prescribing Information

1. Highlights of Prescribing Information

a. Consider revising the statement [redacted] (b) (4) to read "Continue treatment with GOMEKLI until disease progression or unacceptable toxicity" to use customary language.

2. Section 2 Dosage and Administration

a. Consider revising the statement in section 2.1 [redacted] (b) (4) to read "Continue treatment with GOMEKLI until disease progression or unacceptable toxicity" to use customary language.

b. Consider revising the information regarding available dosage forms, preparation, and administration into separate subsections as follows:

2.3 GOMEKLI DOSAGE FORM OVERVIEW

GOMEKLI is available as two dosage forms: capsules or tablets for oral suspension.

GOMEKLI capsules must be swallowed whole. Do not open, break or chew capsules.

GOMEKLI tablets for oral suspension can be swallowed whole or they can be dispersed in drinking water and administered orally as a liquid [see Dosage and Administration (2.4)].

(b) (4)

(b) (4)

2.5 GOMEKLI PREPARATION AND ADMINISTRATION INSTRUCTIONS

GOMEKLI Capsules

- Swallow GOMEKLI capsules whole with or without food. If more than one capsule is required for a dose, swallow one capsule at a time.
- Do not open, break or chew capsules. Do not administer to patients who are unable to swallow a whole capsule.

GOMEKLI Tablets for Oral Suspension

- GOMEKLI tablets for oral suspension can be swallowed whole. If more than one tablet is required for a dose, swallow one tablet at a time.
- For patients who are not able to swallow tablets, GOMEKLI tablets for oral suspension can be dispersed in drinking water and administered orally as a liquid *[see Instructions for Use]*.

Preparation and Administration of GOMEKLI Tablets for Oral Suspension

- Add the prescribed number of tablets to a dosing cup containing approximately 5 mL to 10 mL of drinking water.
- Gently swirl the water and tablets until the tablets are fully dispersed and an oral suspension is obtained. It may take at least [X] minutes to fully disperse the tablets. Once the tablets are dispersed, the oral suspension will appear white and cloudy.

- Administer the oral suspension immediately after preparation from a dosing cup or oral syringe. Discard the oral suspension if not administered within 30 minutes after preparation.
- After administration of the prepared suspension, add approximately 5 mL to 10 mL of drinking water to the dosing cup and gently swirl to resuspend any remaining particles. Administer the suspension to ensure the full dose is taken.

3. Section 16 How Supplied/Storage and Handling
    a. Consider revising Section 16 for improved readability and brevity as follows:

How supplied

GOMEKLI Capsules are supplied as follows:

Capsule Strength	Capsule Description	Package Configuration	NDC
1 mg	Light green body and cap with "MIR 1 mg" printed on the cap in white ink.	Bottle of 42-capsules	82448-130-42
2 mg	White body and a blue green cap with "MIR 2 mg" printed on the cap in white ink.	Bottle of 42-capsules	82448-260-42
		Bottle of 84-capsules	82448-260-84

GOMEKLI Tablets for Oral Suspension are supplied as follows:

Tablet Strength	Tablet Description	Package Configuration	NDC
1 mg	White to off-white, oval tablet, debossed with "S" on one side.	Bottle of 42-tablets	82448-134-42
		Bottle of 84-tablets	82448-134-84

Storage and Handling

Store capsules and tablets for oral suspension at 20°C to 25°C (68°F to 77°F). Excursions permitted between 15°C to 30°C (59°F to 86°F). See USP Controlled Room Temperature. Protect from light.

B. Instructions for Use (IFU)

1. We note the IFU does not include instructions for how to dispose of unused or expired Gomekli tablets or oral suspension nor does it include instructions for how to clean up spilled Gomekli oral suspension. Consider requesting the Applicant to include this information in the IFU to support safe handling.
2. Consider the following IFU revisions for improved clarity and to support safe and effective use:

4 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

5 RECOMMENDATIONS FOR SPRINGWORKS THERAPEUTICS

A. Container Labels – Gomekli Tablet for Oral Suspension Formulation (NDA 219379)

1. To improve readability and reduce clutter on the side panel, consider revising the layout of the product information by relocating the "Each tablet contains # mg mirdametinib." statement to appear above the company name and contact information on the opposite side panel. Ensure there is sufficient white space between the Recommended Dosage statement and the storage information to improve readability.

B. Container Labels – Gomekli Capsule Formulation (NDA 219389)

1. For the 1 mg container labels, consider revising the layout of the product information by relocating the "Each capsule contains # mg mirdametinib." statement to appear above the company name and contact information on the opposite side panel to improve readability and reduce clutter on the side panel. Ensure there is sufficient white space between the Recommended Dosage statement and the storage information.

2. As currently presented, the statement "Do not open, break, or chew capsules." is expressed as a negative statement. Post-marketing reports have shown that negative statements (e.g., do not) may have the opposite of the intended meaning because the word "not" can be overlooked and misinterpreted as an affirmative action. We recommend revising this statement to "Swallow capsules whole. Do not open, break, or chew capsules." to present the affirmative instruction first, followed by the negative statement.

3. For the 2 mg container labels, ensure that the "Do not open..." statement appears on one line instead of broken up into two lines to minimize the risk of the negative statement being misinterpreted as affirmative action. For example:

> Recommended Dosage:
> See Prescribing Information.
> Swallow capsules whole. Do not open,
> break, or chew capsules.

APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Gomekli received on June 28, 2024 from SpringWorks Therapeutics.

<table>
<tr><th colspan="2">Table 2. Relevant Product Information for Gomekli</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Active Ingredient</td><td>mirdametinib</td></tr>
<tr><td>Indication</td><td>GOMEKLI is indicated 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).</td></tr>
<tr><td>Dosage Form</td><td>Dispersible Tablets
Capsules</td></tr>
<tr><td>Strength</td><td>Dispersible Tablet: 1 mg
Capsule: 1 mg and 2 mg</td></tr>
<tr><td>Route of Administration</td><td>Oral</td></tr>
<tr><td>Dose and Frequency</td><td>The recommended dosage is 2 mg/m^2 orally twice daily (approximately every 12 hours) for the first 21 days of each 28-day cycle. The maximum dose is 4 mg twice daily.
<table>
<tr><th>Body Surface Area*(m^2)</th><th>Recommended Dosage for Capsules or Tablets for Oral Suspension</th></tr>
<tr><td>0.40 to 0.69</td><td>1 mg twice daily</td></tr>
<tr><td>0.70 to 1.04</td><td>2 mg twice daily</td></tr>
<tr><td>1.05 to 1.49</td><td>3 mg twice daily</td></tr>
<tr><td>≥1.50</td><td>4 mg twice daily</td></tr>
</table>
*The recommended dosage for patients with a BSA less than 0.40 m^2 has not been established.</td></tr>
<tr><td>How Supplied</td><td>42-count and 84-count bottles</td></tr>
<tr><td>Storage</td><td>Store at 20°C to 25°C (68°F to 77°F). Excursions permitted between 15°C to 30°C (59°F to 86°F). See USP Controlled Room Temperature. Protect from light.</td></tr>
<tr><td>Container Closure</td><td>High density polyethylene (HDPE) bottles with (b) (4) closures with a foil induction seal.</td></tr>
</table>

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Gomekli labels and labeling submitted by SpringWorks Therapeutics.

- Prescribing Information received on June 28, 2024, available from \\CDSESUB1\EVSPROD\nda219379\0004\m1\us\clean-mirda-uspi-for-final-nda-submission.docx
- Patient Package Insert received on June 28, 2024, available from \\CDSESUB1\EVSPROD\nda219379\0004\m1\us\clean-mirda-uspi-for-final-nda-submission.docx
- Instructions for Use received on June 28, 2024, available from \\CDSESUB1\EVSPROD\nda219379\0004\m1\us\clean-mirda-uspi-for-final-nda-submission.docx
- Container label(s) received on June 28, 2024
- Carton labeling received on June 28, 2024

B.2 Container Label(s) and Carton Labeling Images

B.2.1 NDA 219379- Gomekli (mirdametinib) Tablets for Oral Suspension 1 mg

(b) (4)

[redacted]

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

13 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

---

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/

JANINE A STEWART
10/21/2024 12:27:44 PM

TINGTING GAO
10/21/2024 01:18:07 PM