CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219379Orig1s000
219389Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 139883

MEETING MINUTES

SpringWorks Therapeutics, Inc.
Attention: Candice Durrence, M.S., R.A.C.
Associate Principal Consultant
Regulatory Affairs Halloran Consulting Group
100 Washington Boulevard
Stamford, CT 06902

Dear Candice Durrence:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Mirdametinib.

We also refer to the video conference between representatives of your firm and the FDA on February 27, 2024. The purpose of the meeting was to discuss the recent topline data from Study MEK-NF-201 (ReNeu, NCT03962543, data cut of 20-Sept 2023) and the acceptability of the proposed data package to support a new drug application (NDA) for mirdametinib in adult and pediatric patients with neurofibromatosis type 1-plexiform neurofibromas (NF1-PN).

A copy of the official minutes of the video conference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have any questions, call me at 240-402-4558 or email opeyemi.udoka@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

Opeyemi Udoka DPT, CSM
Senior Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for Division of Oncology 2
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	February 27, 2024, 12:00PM – 1:00PM EST
Meeting Location:	Videoconference
Application Number:	IND 139883
Product Name:	Mirdametinib
Indication:	Treatment of adult and pediatric patients with NF1-associated PNs
Sponsor Name:	SpringWorks Therapeutics
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair:	Amy Barone
Meeting Recorder:	Opeyemi Udoka

FDA ATTENDEES

Martha Donoghue, M.D., Associate Director for Pediatric Oncology, Office of Oncologic Diseases (OOD)
Nicole Drezner, M.D., Deputy Division Director, Division of Oncology 2 (DO2)
Amy Barone, M.D., MSC., Cross Disciplinary Team Leader, DO2
Kristin Wessel, M.D., Clinical Reviewer, DO2
Vishal Bhatnagar, M.D., Associate Director, Patient-Focused Drug Development, Oncology Center of Excellence (PFDD/OCE)
Anup Amatya, Ph.D., Biostatistics Team Leader, DBM
Michelle Marcovitz, Ph.D., Biostatistics Reviewer, DBM
Xing Wang, Ph.D., CMC Team Leader, Division of New Drug Products I (DNDPI)
Tefsit Bekele, Ph.D., CMC Reviewer, DNDPI
Claudia Miller, Ph.D., Nonclinical Team Leader, Division of Hematology, Oncology, and Toxicology (DHOT)
Melissa Pegues, Ph.D., Nonclinical Reviewer, DHOT
Jeanne Fourie Zirkelbach, Ph.D., Master Pharmacokineticist, Division of Cancer Pharmacology II (DCPII)
Hongfei Zhang, Ph.D., Clinical Pharmacology Reviewer, DCPII
Opeyemi Udoka, D.P.T., Senior Regulatory Health Project Manager, Division of Regulatory Operations for Oncologic Diseases (DRO-OD)

SPONSOR ATTENDEES

SpringWorks Therapeutics
James Cassidy, M.D., Ph.D., Chief Medical Officer
Greg Falls, Ph.D., DABT, Senior Director, Toxicology
Thuy Hoang, Ph.D., Associate Director, Clinical Pharmacology
Amy Kranz, Pharm.D., RPh, R.A.C., Global Pharmacovigilance Medical Director

Armend Lokku, Ph.D., Study Statistician
Kristin Patterson, Ph.D., Chief Technical Operations Officer
Wenlin Shao, Ph.D., Senior Vice President, Asset Lead
Irache Visiers, Ph.D., Vice President, Head of Regulatory Affairs
Xiaowei (Sherry) Wang, M.S., R.A.C., Senior Director, Clinical Regulatory Affairs
Michael Weber, Pharm.D., Director, Clinical Development
Halloran Consulting Group
Candice Durrence, M.S., R.A.C., Associate Principal Consultant, Regulatory Affairs

BACKGROUND

On December 29, 2023, SpringWorks submitted a meeting request to discuss the recent topline data from study MEK-NF-201(ReNeu, NCT03962543, data cut of 20-Sept 2023) and the acceptability of the proposed data package to support a new drug application (NDA) for mirdametinib in adult and pediatric patients with neurofibromatosis type 1-plexiform neurofibromas (NF1-PN). The meeting package was received on January 26, 2024.

Regulatory History

SpringWorks was granted Orphan and Fast Track Designation for mirdametinib.

On November 15, 2018, SpringWorks submitted a meeting to obtain FDA feedback regarding the acceptability of the study design to support registration of mirdametinib for both pediatric and adult populations for the treatment of patients NF1-PN. The meeting was cancelled upon receipt of FDA's preliminary comments on January 24, 2019.

On January 28, 2020, SpringWorks submitted a written response only (WRO) meeting request to obtain feedback on the plan to introduce a pediatric formulation ((b) (4) 1mg dispersible tablets) into the ongoing Study MEK-NF-201. FDA issued a final written response on April 9, 2020.

On October 13, 2021, a Type B meeting was held between SpringWorks and FDA to discuss the overall development program, including the clinical pharmacology strategy, and the CMC development plan. FDA expressed concern that the dose of mirdametinib had not been sufficiently optimized for the proposed indication and recommended SpringWorks request an additional meeting to discuss their clinical development program. FDA issued meeting minutes on November 9, 2021.

On November 5, 2021, FDA issued a final written response to a WRO meeting request to discuss thorough QT (TQT) study design and c-QT analysis plan.

On September 2, 2022, SpringWorks submitted a meeting request to seek feedback on their clinical pharmacology proposal to use modeling and simulation to further justify the selected dose of mirdametinib for the treatment of plexiform neurofibroma in adult and

pediatric patients with neurofibromatosis type 1 (NF1-PN). FDA recommended SpringWorks submit a meeting request to discuss dosage justification.

On May 23, 2023, a Type C meeting was held between FDA and SpringWorks Therapeutics to seek feedback on the proposed dose of mirdametinib 2mg/m^2 twice daily (BID) for the intended indication of NF1-PN. FDA stated that the available dose exploration data for mirdametinib was very limited and the 2 mg/m^2 dose has not been compared to other doses using the same administration schedule and recommended an additional dose cohort should be enrolled in the MEK-NF-201 trial with at least 10 adult patients using the same administration schedule and compare the safety and efficacy data to the data from the 2 mg/m^2 cohorts. In the meeting discussion, FDA acknowledged SpringWorks' response and reiterated that the PK/PD model for tumor growth inhibition could be useful for dose selection; however, SpringWorks model is limited by only including data from one nominal dose level of 2 mg/m^2. The model prediction should be confirmed with actual clinical data from an additional dose level. FDA stated that the decision to enroll additional patients to confirm the dose is up to SpringWorks, that a full justification for the selected dose should be provided in the original NDA submission and this will be a review issue.

Nonclinical
Mirdametinib is a small molecule non-ATP competitive inhibitor of mitogen activated protein (MAP) extracellular regulated kinase (MEK) 1/2. The nonclinical program for mirdametinib includes in vitro and in vivo pharmacology and genetic toxicology studies, as well as preliminary embryo-fetal development studies in rats and rabbits, GLP-compliant repeat-dose toxicology studies in rats and dogs up to 13-weeks in duration, and a 6-month carcinogenicity study in transgenic mice. M22 and PD-0315209 are disproportionate human metabolites of mirdametinib, and SpringWorks has submitted summary results of in vitro pharmacology studies evaluating the ability of M22 and PD-0315209 to inhibit MEK1/2 signaling. In a previous communication, SpringWorks stated that they do not plan to conduct additional studies for mirdametinib metabolites, M22 and PD-0315209, or additional carcinogenicity animal studies.

Clinical
Study MEK-NF-201 (ReNeu) is a multicenter, open-label, single-arm study evaluating the safety and efficacy of mirdametinib in patients with inoperable NF1-PNs causing significant morbidity. Patients received mirdametinib capsules or tablets at a dose of 2 mg/m^2 twice daily (BID), on a 3 weeks on/1 week off schedule for each 28-day cycle. The study included treatment phase of 24 cycles, followed by an optional long-term follow up (LTFU) phase. The primary endpoint was objective response rate (ORR) at the end of the treatment phase, with responses defined as a ≥20% reduction in volume consistent with the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria and assessed by blinded independent central review (BICR). Key secondary endpoints included duration of response (DoR), quality of life (QoL) and pain questionnaires, and safety and tolerability of mirdametinib.

Enrollment was completed in December 2021 with 114 patients (58 adult, 56 pediatric).

Efficacy Package

SpringWorks plans to provide data from the ReNeu study to support the efficacy of mirdametinib in the proposed NDA. Updated efficacy data including DoR will be included with the 90/120 day safety update. The integrated summary of efficacy (ISE) will also include data from Study NF-106 (Weiss, 2016), in which patients with NF1-PN (N=19) received mirdametinib at the same dosage as in ReNeu. Due to differences in study design, SpringWorks does not intend on pooling efficacy data; data from Study NF-106 will be summarized separately. SpringWorks intends to provide responder narratives which will include results of patient reported outcome (PRO) assessments.

Top-Line Efficacy Results

Confirmed ORR by BICR during the 24-cycle treatment phase was 41% (24/58) (95% CI: 29, 55) in the adult cohort and 52% (29/56) (95% CI: 38, 65) in the pediatric cohort. Two additional patients in the adult cohort and one additional patient in the pediatric cohort achieved confirmed responses after Cycle 24 in LTFU phase (Table 9 in meeting background package, below).

Table 9. Analysis of Confirmed ORR – Treatment Phase (FAS)

	Pediatric (N=56)	Adult (N=58)
Confirmed ORR		
n	29	24
ORR %	51.8	41.4
95% CI	(38.0, 65.3)	(28.6, 55.1)
p-value	<0.001	<0.001
Best Overall Confirmed Response Status		
CR	0	0
PR	29 (51.8%)	24 (41.4%)
SD	22 (39.3%)	26 (44.8%)
PD	3 (5.4%)	0
Not Evaluable	0	0
Missing	2 (3.6%)	8 (13.8%)

Abbreviations: BICR: blinded independent central review; BOR: best overall response; CI: confidence interval; CR: complete response; FAS: Full Analysis Set; ORR: objective response rate; PD: progressive disease; PR: partial response; SD: stable disease.

For the key secondary endpoint DoR, 75% of adult responses and 76% of pediatric responses were sustained for at least 12 months. Median DoR was not reached at the DCO for the adult and pediatric cohorts. In the adult cohort, there was one event of disease progression by 12 months from the onset of response; no such events occurred in the pediatric cohort. At the time of the data cutoff (DCO), 86% of adult and 88% of pediatric responders had been followed for at least 12 months from initial response. SpringWorks plans to include updated DoR data with the 90/120-day safety update, at which point 100% of the responders will have been followed for at least 12 months from the onset of response.

Key secondary endpoints of QoL and pain were assessed using the Pediatric Quality of Life Inventory (PedsQL), Numeric Rating Scale-11 (NRS-11) and Pain Interference Index (PII) at Cycle 13 and compared to baseline. Improvements in QoL and pain were observed for both adult and pediatric cohorts. Results are summarized in Table 11, below:

Table 11. PRO Results

Study Endpoint	Pediatrics (N=56)		Adults (N=58)
Change from Baseline at Cycle 13 in QoL from PedsQL – Total Score	Self-Report: n = 38 LS mean (SE): 4.01 (2.361) 95% CI: -0.74, 8.76 p = 0.096*	Proxy-Report: n = 43 LS mean (SE): 5.64 (1.939) 95% CI: 1.75, 9.53 p = 0.005*	n = 34 LS mean (SE): 3.94 (1.611) 95% CI: 0.70, 7.17 p = 0.018*
Change from Baseline at Cycle 13 in Pain from NRS-11 (note: assessment only for participants ≥8 years)	n = 17 LS mean (SE): -0.79 (0.243) 95% CI: -1.28, -0.29 p = 0.003*		n = 21 LS mean (SE): -1.33 (0.246) 95% CI: -1.83, -0.84 p < 0.001*
Change from Baseline at Cycle 13 in Pain from PII (note: assessment only for participants ≥6 years)	Self-Report: n = 22 LS mean (SE): -0.46 (0.183) 95% CI: -0.83, -0.09 p = 0.017*	Proxy-Report: n = 20 LS mean (SE): -0.26 (0.112) 95% CI: -0.49, -0.03 p = 0.025*	n = 22 LS mean (SE): -0.70 (0.159) 95% CI: -1.02, -0.38 p < 0.001*

Safety Package

SpringWorks intends to include two separate safety pools in the ISS. Pool 1 (N=133) will include data from the ReNeu study and NF-106. Pool 2 (N=113) will include supportive safety data from two studies (Study A4581001 and Study A4581002) in which adult oncology patients received mirdametinib as a single agent, at dosages differing from that administered in ReNeu and NF-106. SpringWorks also plans to submit supportive safety data from three Phase 1 studies in healthy volunteers and from a global pharmacovigilance database.

Top-Line Safety Results

Among the 114 patients treated in Study MEK-NF-201 and included in the safety population, SpringWorks reports that the most common treatment-emergent adverse events (TEAEs) in ≥30% of patients were dermatitis acneiform, diarrhea, nausea and vomiting. Serious AEs (SAEs) occurred in 14% and 17% of pediatric and adult patients, respectively. TEAEs leading to discontinuation were reported from 9% of pediatric and 22% of adult participants. Dose reductions occurred in 13% and 17% of pediatric and adult participants, and dose interruptions occurred in 30% and 31% of pediatric and adult participants, respectively. One adult patient died of COVID-19; this was assessed as not related to study treatment. FDA sent Preliminary Comments to SpringWorks on

February 22, 2024, on February 26, 2024, SpringWorks provided responses and requested to further discuss Question 2.

SPONSOR QUESTIONS AND FDA RESPONSES

CMC

1. Does the Agency agree with the proposal to submit additional stability data with the Day 90/120 safety update to extend the commercial shelf life of the drug product?

   FDA Response: It is acceptable to submit the original NDA with 18 months stability data for three registration batches of each mirdametinib tablet strength to be followed by an amendment within 90/120 days after the NDA is submitted to provide the 24-month time points. However, there is no commitment by the FDA that any stability data submitted after 30 days will be evaluated. The shelf-life of the drug product will be determined during the NDA review based on the totality of the data submitted in the application.

   SpringWorks Email response on 2/26/24: SpringWorks acknowledges FDA's response. No discussion is needed.

   Discussion During Meeting: No discussion occurred.

Nonclinical

2. Does the Agency agree with the proposed nonclinical package, including request (b) (4)

   FDA Response: No, conduct a 2-year carcinogenicity study in rats with mirdametinib to support a marketing application for the proposed indication. Additional comments regarding your carcinogenicity weight of evidence assessment will be provided by the Executive Carcinogenicity Assessment Committee. We agree with your proposal to initiate this study in August 2024. Please submit a special protocol assessment to the FDA for concurrence before the initiation of carcinogenicity studies. For additional information on submitting a carcinogenicity protocol to FDA, please refer to the FDA Guidance for Industry: Carcinogenicity Study Protocol Submissions available at https://www.fda.gov/media/72270/download.

   In addition to the studies described in the meeting background, include the following information in your original NDA submission:

- A more comprehensive secondary pharmacology assessment, such as a screening panel of kinases, GPCRs, receptors, enzymes, and ion channels, for mirdametinib given that only 27 kinases have been evaluated to date.
- Any available data on levels of PD-0315209 in the in vivo micronucleus assay conducted with the mirdametinib.
- Mirdametinib induced a dose-related increase of micronucleated polychromatic erythrocytes (MNCPE) in the bone marrow of female rats that achieved statistical significance at the high dose. In addition, the study report concludes that mirdametinib may have clastogenic potential. Thus, FDA will consider these data as a positive result unless you provide follow-up testing to verify these results. If you decide to do additional studies, consider measuring the levels of PD-0315209.

We will make a final determination of the acceptability of the data from these studies during review of the original NDA submission.

SpringWorks Email response on 2/26/24: SpringWorks acknowledges FDA's response and will submit a special protocol assessment for the 2-year carcinogenicity study. We will also submit secondary pharmacology assessment information, including screening panels of GPCRs, receptors, enzymes, and ion channels in the NDA. In addition to the panel of 27 kinases, specificity of mirdametinib was evaluated against a panel of 104 kinases, and that data will be submitted in the NDA.

SpringWorks confirms that neither mirdametinib nor its metabolite PD-0315209 were measured in the *in vivo* micronucleus assay. However, exposure levels may be inferred from the Day 1 measurement in the *in vivo* rat toxicology studies where both mirdametinib and PD-0315209 were measured at the same dose levels as those from the *in vivo* micronucleus assay (0.3, 1 and 3 mg/kg/day). The toxicokinetic results for both mirdametinib and PD-0315209 from the rat toxicology studies at dose levels corresponding to those used in the *in vivo* rat micronucleus study are provided in Table 1. The data suggests that sufficient exposure levels of mirdametinib and PD-0315209 were achieved for evaluation in the *in vivo* genetic toxicity studies (approximately 3 times compared to therapeutic exposures in clinical studies).

Table 1. Day 1 Toxicokinetic Parameters of Mirdametinib and PD-0315209 from Rat Toxicology Studies

Dose (mg/kg)	Mirdametinib											
	0.3*		1*		3**		0.3*		1*		3**	
Gender	M	F	M	F	M	F	M	F	M	F	M	F
	Mirdametinib (parent) TK						PD-0315209 (metabolite) TK					

AUC0-24 (ng·h/mL)	936	504	4450	2520	6070	5090	279	865	882	5480	2210	13600
Cmax (ng/mL)	86	95	520	419	1050	997	21	87	64	440	178	1160

*Day 1 values from 3-month rat toxicity study for the 0.3 and 1 mg/kg dose levels.
**Day 1 values from 2-week rat toxicity study for the 3 mg/kg dose level.
Abbreviations: AUC0-24: area under the plasma concentration-time curve from time zero to 24 hours; Cmax: maximum observed plasma concentration; F: female; M: male.

SpringWorks would like to clarify the clastogenic potential of mirdametinib. Data from the rat *in vivo* micronucleus assay suggested mirdametinib was negative for clastogenicity. The mean %MNPCE values for mirdametinib in males were 0.18, 0.18 and 0.32 at 0.3, 1, and 3 mg/kg, respectively, and were not statistically different from the concurrent controls. In females, mean %MNPCE values were 0.22, 0.28 and 0.54 at 0.3, 1, and 3 mg/kg, respectively, with only the 3 mg/kg value statistically greater than control. Although the mean %MNPCE value at 3 mg/kg in females was significantly greater than the vehicle control, the mean value (0.54) and individual values (0.5, 0.4, 0.7, 0.6, and 0.5) of females at 3 mg/kg remained within the historical control reference range. For %MNPCE, the mean historical control reference range was 0.16 – 0.59 in females and the individual animal historical control reference range (minimum to maximum range) was 0.1 – 0.8 in females. Interpretation of the %MNPCE values in these 3 mg/kg females was further complicated by the bone marrow effects of mirdametinib which showed significant decreases in nucleated cells, DNA, and/or RNA in the 3 mg/kg females. Although a statistically significant increase in %MNPCE value was observed at the 3 mg/kg dose level in females, these values did not meet the criteria for a positive response and was further confounded by the bone marrow toxicity observed in these animals.

Mirdametinib *in vivo* genetic toxicology study 745-04155 was inadvertently not submitted to the IND (Oral Gavage Bone Marrow Chromosomal Aberrations Study of PD 325901 in Rats). This study was conducted subsequent to the *in vivo* micronucleus study in rats. Study 745-04155 is included with this response and will be submitted in the NDA. The objective of the study was to provide context to the results obtained in the *in vivo* micronucleus study. The same dose levels of mirdametinib were administered to 5 animals/sex/group at 0.3, 1, and 3 mg/kg/day, once a day for 2 consecutive days with approximately 24 hours in between doses. Toxicokinetic evaluation was not performed but could be inferred from other *in vivo* toxicity studies as provided in Table 1. There were no deaths or clinical signs of toxicity observed in the study. The positive control (cyclophosphamide, 60 mg/kg) induced a statistically significant increase in chromosomal aberrations relative to vehicle controls. Animals treated with mirdametinib at 3 mg/kg had reduction in mitotic index (≤ 1.0%) suggesting bone marrow cytotoxicity. The results showed there were no statistically significant increases in either structural chromosome aberrations or numerical chromosome changes in animals treated with mirdametinib. Hence, this study concluded that

mirdametinib did not produce induction of structural or numerical bone marrow chromosomal aberrations in rats.

Based on the results from these two *in vivo* genotoxicity studies and the negative results from the *in vitro* chromosome aberration assay, SpringWorks believes mirdametinib is negative for clastogenicity.

Discussion During Meeting: FDA reminded SpringWorks that they had stated their position on Study Report # 745-03804. FDA acknowledged SpingWorks' response and the new information provided to support the response. FDA requested SpringWorks submit both Study Report # 745-0384 and Study Report # 745-04155 to the original NDA submission. FDA will review Study Report # 745-04155 and make a final determination of the acceptability of the data from this study, as well as all other new nonclinical data mentioned in the response, during review of the original NDA submission.

Clinical

3. Does the Agency agree that the efficacy and safety data from Study MEK-NF-201(ReNeu), including tumor response, duration of follow up and clinical outcome assessments, are appropriate to support review of the NDA in the proposed indication?

FDA Response: Yes, the data included in the meeting background package appear adequate to support the filing and review of a marketing application; however, a final decision will be based on a comprehensive review of the data submitted to the original NDA.

In the NDA submission, clarify which patients were included in the topline PRO results. For example, the number of patients in each column in Table 11 differ at the same timepoint. As previously communicated, provide complete information about reasons for missingness.

SpringWorks Email response on 2/26/24: SpringWorks acknowledges FDA's response and will clarify which patients were included in the topline PRO results and provide the reasons for missingness in the NDA. No discussion is needed.

Discussion During Meeting: No discussion occurred.

4. Does the Agency agree with the proposed size and scope of the safety database and the proposed plan for safety and responder narratives?

FDA Response: The proposed size and scope of the safety database appears acceptable; however, it will be considered in the context of the overall risk-benefit assessment. We agree with the proposal to include safety narratives for ReNeu

patients who died, discontinued treatment, had an SAE, an adverse event of special interest or any grade of retinal vein occlusion. We may request additional safety narratives during the review cycle.

The proposed plan for responder narratives generally appears acceptable. In the narratives, include a discussion of how any change in function or symptoms correlates with the radiographic response and the timing of response. As part of the summary of the patient's course during the study, also include in the narratives a discussion of the individual patient's safety and tolerability of mirdametinib (e.g., AEs, dose reductions or delays, need for additional supportive care medications for treatment related side effects, etc.) to allow for an individual benefit:risk assessment. If available, include information regarding use of pain medication and response of non-target lesions. For patients with subsequent progression of PN after initial response, please include additional PN-directed therapies received if applicable.

SpringWorks Email response on 2/26/24: SpringWorks acknowledges FDA's feedback and will provide the requested information in the responder's narratives, if available. No discussion is needed.

Discussion During Meeting: No discussion occurred.

5. Does the Agency agree with the scope and content of the Day 90/120 safety update (depending on priority vs. standard review)?

FDA Response: Yes, the proposal for the scope and content of the Day 90/120 day safety update appears acceptable.

SpringWorks Email response on 2/26/24: SpringWorks acknowledges FDA's response. No discussion is needed.

Discussion During Meeting: No discussion occurred.

Biostatistics

6. Does the Agency agree with the ReNeu statistical analysis plan for primary and secondary endpoints, including the proposed sensitivity analyses?

FDA Response: In principle, FDA agrees with the plan to assess ORR by evaluating a 95% confidence interval. Additionally, FDA agrees with the sponsor's plan to analyze DOR using Kaplan-Meier methods and with the proposed sensitivity analysis to evaluate DOR according to REiNS criteria. TTP and PFS are not interpretable in the context of a single-arm trial.

SpringWorks Email response on 2/26/24: SpringWorks acknowledges FDA's response. No discussion is needed.

Discussion During Meeting: No discussion occurred.

7. Does the Agency agree with the proposed strategies for the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS)?

FDA Response: The proposed strategies for the ISE and ISS appear to be acceptable.

SpringWorks Email response on 2/26/24: The proposed strategies for the ISE and ISS appear to be acceptable.

Discussion During Meeting: No discussion occurred.

8. Does the Agency agree with the study data standardization plan?

FDA Response: The study data standardization plan appears to be acceptable; however, please refer to the recently published technical specifications for submitting patient-reported outcome.
https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submitting-patient-reported-outcome-data-cancer-clinical-trials?utm_medium=email&utm_source=govdelivery

SpringWorks Email response on 2/26/24: SpringWorks acknowledges FDA's response. No discussion is needed.

Discussion During Meeting: No discussion occurred.

Clinical Pharmacology

9. Does the Agency agree that the clinical pharmacology studies provide sufficient evidence to support review of the NDA in the proposed indication?

FDA Response: Your plan appears acceptable to support filing; however, as discussed in prior meetings, we have not agreed with the selection of 2 mg/m^2 twice daily with a maximum of 4 mg BID with a 3 weeks on/1 week off schedule in patients with NF1-PN. A full justification for the selected dose should be provided in the original NDA submission and this will be a review issue.

SpringWorks Email response on 2/26/24:
SpringWorks acknowledges FDA's response and will provide a full dose justification in the NDA. No discussion is needed.

Discussion During Meeting: No discussion occurred.

Regulatory

10. Does the Agency agree that the mirdametinib NDA meets the eligibility criteria for priority review?

    FDA Response: We cannot answer this question at this time; a determination regarding eligibility for priority review will be made after receipt of the NDA.

    SpringWorks Email response on 2/26/24: SpringWorks acknowledges FDA's response. No discussion is needed.

    Discussion During Meeting: No discussion occurred.

11. Does the Agency agree that the mirdametinib NDA meets the eligibility criteria for a rare pediatric disease product application to obtain a priority review voucher?

    FDA Response: We note that mirdametinib was granted Rare Pediatric Disease Designation for NF1-associated PN. Please include this designation letter with your voucher request at the time of NDA submission. Whether a priority review voucher will be granted will be a matter of review.

    SpringWorks Email response on 2/26/24: SpringWorks acknowledges FDA's response. No discussion is needed.

    Discussion During Meeting: No discussion occurred.

12. Does the Agency agree with the NDA content for a complete application, including updates during the NDA review, and the proposed rolling review submission timelines?

    FDA Response: The content and proposed timelines appear acceptable.

    SpringWorks Email response on 2/26/24: SpringWorks acknowledges FDA's response. No discussion is needed.

    Discussion During Meeting: No discussion occurred.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- FDA will make a final determination regarding the need for REMS during the review of the NDA.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application: 18 months stability data for three registration batches of each mirdametinib tablet strength to be followed by an amendment within 90/120 days after the NDA is submitted to provide the 24-month time points (see FDA Response to Question 1).

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[2]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology

product development, please refer to FDA.gov.[3]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst

[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[6]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[7]

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.[8]

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the

[6] http://www.fda.gov/ectd
[7] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway
[8] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[9] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[10]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate

[9] https://www.fda.gov/media/84223/download
[10] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[11]

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[12]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- Assessment Aid[13]

[11] https://www.fda.gov/media/85061/download
[12] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[13] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

ISSUES REQUIRING FURTHER DISCUSSION
There were no issues requiring further discussion.

ACTION ITEMS
No action items were identified.

ATTACHMENTS AND HANDOUTS
16 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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