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RESEARCH**

APPLICATION NUMBER:

219379Orig1s000

219389Orig1s000

MULTI-DISCIPLINE REVIEW

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	NDA
Application Number(s)	219379 and 219389
Priority or Standard	Priority
Submit Date(s)	June 28, 2024
Received Date(s)	June 28, 2024
PDUFA Goal Date	February 28, 2025
Division/Office	Division of Oncology 2/Office of Oncologic Diseases
Review Completion Date	See DARRTS signature
Established Name	Mirdametinib
(Proposed) Trade Name	GOMEKLI
Pharmacologic Class	Kinase inhibitor
Code name	PD-0325901
Applicant	SpringWorks Therapeutics
Formulation(s)	Tablets and capsules
Dosing Regimen	2 mg/m ² orally twice daily, with or without food, for the first 21 days of each 28-day cycle. Continue treatment with GOMEKLI until disease progression or unacceptable toxicity.
Applicant Proposed Indication(s)/Population(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).
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	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) not amenable to complete resection.

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OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
DPV= Division of Pharmacovigilance
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRM=Division of Risk Management

Glossary

ADME	absorption, distribution, metabolism, and excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AME	absorption, metabolism, and excretion
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration-time curve
AUC _{0-12,ss}	steady-state AUC from dosing to 12 hours postdose
AUC ₀₋₂₄	area under the concentration-time curve from time 0 to 24 hours
AUC _{inf}	AUC from dosing extrapolated to infinity
AUC _{last}	area under the concentration time curve from time zero to last measurable concentration
BCRP	breast cancer resistance protein
BICR	blinded independent central reviewer
BID	twice daily
BLA	biologics license application
BOR	best overall response
BRA	Benefit-Risk Assessment
BSA	body surface area
C _{avg,ss}	average concentration in each dosing interval at steady state
CES	carboxylesterase
CFR	Code of Federal Regulations
CL/F	apparent clearance
CLCR	creatinine clearance
CL _m /F	apparent clearance of the metabolite
C _{max}	maximum observed concentration
C _{max,ss}	steady-state maximum concentration
C _{min,ss}	steady-state minimum concentration
CNS	central nervous system
COA	clinical outcome assessment
CPK	creatine phosphokinase
CR	complete response
CRF	case report form
CRO	contract research organization

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CRT	clinical review template
CSF	cerebrospinal fluid
CSR	clinical study report
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DMC	data monitoring committee
DoR	duration of response
E50	half maximum effect
ECG	electrocardiogram
ECHO	echocardiogram
eCRF	electronic case report form
eCTD	electronic common technical document
EFD	embryo-fetal development
Emax	maximum effect
ePRO	electronic patient reported outcomes
E-R	exposure-response
ERK	extracellular signal-regulated kinase
ESRD	end-stage renal disease
FAS	full analysis set
FDA	Food and Drug Administration
Fm	fraction metabolized
GCP	good clinical practice
GD	gestation day
geomean	geometric mean
GLMR	geometric least squares mean ratio
GLP	good laboratory practice
GTPase	guanosine triphosphate hydrolase
IC50	half-maximal inhibitory concentration
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IIV	interindividual variability
IND	Investigational New Drug
IRB	Institutional Review Board
ISE	Integrated Summary of Effectiveness
ISS	Integrated Summary of Safety
IV	intravenous
Ki	inhibition constant
KM	Kaplan-Meier
LLN	lower limit of normal
LOAEL	lowest observed adverse effect level
LS	least-squares

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LTFU	long term follow up
LVEF	left ventricular ejection fraction
MAPK	mitogen-activated protein kinase
MAPK	mitogen-activated protein kinase
MATE	multidrug and toxin extrusion protein
MCT	meaningful change threshold
MedDRA	Medical Dictionary for Regulatory Activities
MED	minimally effective dose
MEK	mitogen-activated protein kinase kinase
MMRM	mixed model repeated measures
MPNST	malignant peripheral nerve sheath tumors
MPNSTs	malignant peripheral nerve sheath tumors
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multigated acquisition scan
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NDA	New Drug Application
NF1	neurofibromatosis type 1
NIH	National Institute of Health
NOAEL	no-observed-adverse-effect level
NSCLC	non-small cell lung cancer
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCS	Office of Computational Science
OCT	organic cation transporter
OPQ	Office of Pharmaceutical Quality
ORR	objective response rate
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	Progressive Disease
PDx	pharmacodynamic
pERK	phosphor-extracellular signal-regulated kinase
PFS	progression free survival
P-gp	P-glycoprotein
PI	prescribing information
PK	pharmacokinetic
PKPDx	pharmacokinetic-pharmacodynamic
PMC	postmarketing commitment
PMR	postmarketing requirement
PN	plexiform neurofibroma

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PN	plexiform neurofibroma
PO	orally
PopPK	population pharmacokinetic
popPKPDx	population pharmacokinetic pharmacodynamic
PR	partial response
PRO	patient reported outcome
PT	preferred term
QD	once daily
QoL	quality of life
ReiNS	Response Evaluation in Neurofibromatosis & Schwannomatosis
REMS	risk evaluation and mitigation strategy
RP2D	recommended phase 2 dose
RVO	retinal vein occlusion
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOC	System Organ Classification
t _{1/2}	terminal elimination half-life
TEAE	treatment emergent adverse event
TGI	tumor growth inhibition
T _{last}	time of the last quantifiable concentration
T _{max}	Time of the maximum concentration
TTP	time to progression
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal
US	United States

1 Executive Summary

1.1. Product Introduction

Mirdametininb is a small molecule inhibitor of mitogen-activated protein kinases 1 and 2 (MEK1/2). MEK1/2 proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway. Activation of this signaling pathway leads to cell proliferation and is involved in various types of cancer (Yaeger and Corcoran, 2019).

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder with variable expressivity caused by germline mutations in the NF1 gene. Plexiform neurofibromas (PNs) are benign tumors of the peripheral nerve sheath which occur in 40-50% of patients with NF1. PNs may be associated with significant morbidity including pain, disfigurement, neurologic deficits, and functional impairment; and mortality from malignant transformation to malignant peripheral nerve sheath tumors (MPNST) and compression of vital structures (Ly and Blakeley, 2019). In a mouse model of neurofibromatosis type 1 (NF1), oral dosing of mirdametininb inhibited ERK phosphorylation and reduced neurofibroma tumor volume and proliferation.

In this new drug application (NDA), the Applicant proposed the following indication for mirdametininb:

- Adult and pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas.

The review team recommends approval for adult and pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas (PN) not amenable to complete resection.

The recommended dosage of mirdametininb is 2 mg/m² orally twice daily with or without food for the first 21 days of each 28-day cycle, until disease progression or unacceptable toxicity.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends regular approval of mirdametininb for the treatment of adult and pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas not amenable to complete surgical resection. The recommendation for approval is primarily supported by overall response rate (ORR) and duration of response (DOR) results from Study MEK-NF-201 (which will be referred to as the ReNeu study in the review). In this study, mirdametininb demonstrated a robust and clinically meaningful effect on ORR that is durable and associated with improvements in disease-related morbidities. These factors represent direct clinical benefit to patients and support regular

approval. The safety profile for mirdametinib is consistent with other MEK inhibitors and is acceptable in the context of a serious and life-threatening disease.

The ReNeu study is a multicenter, single-arm trial investigating mirdametinib in adult and pediatric patients with NF1 and progressive or symptomatic plexiform neurofibromas not amenable to complete surgical resection. Eligible patients were at least 2 years of age with PN causing significant morbidity, and a target PN that was evaluable by volumetric analysis. Patients were enrolled by age group into pediatric and adult cohorts. Treatment consisted of mirdametinib at a dosage of 2 mg/m² orally twice daily for the first 21 days of each 28-day cycle. The study included a treatment phase lasting 24 cycles and an optional long-term follow-up phase. The primary endpoint to demonstrate the efficacy of mirdametinib for this population was confirmed ORR, defined as PN decrease ≥20% compared to baseline in consecutive scans within 2-6 months, using independent central review of MRI volumetric analysis. DOR was a key secondary endpoint.

The primary efficacy population consisted of 114 patients, including 56 pediatric and 58 adult patients. The confirmed BICR-assessed ORR in pediatric patients was 52% (95% CI: 38, 65); the median DOR was not reached. A total of 90% of responders had a DOR of ≥12 months and 48% of responders had a DOR of ≥24 months. The confirmed ORR as assessed by BICR in adult patients was 41% (95% CI: 29, 55); the median DOR was not reached. A total of 88% of responders had a DOR of ≥12 months and 50% of responders had a DOR of ≥24 months. Supportive data for the application were derived from the observed ORR in 19 patients treated with mirdametinib on Study NF-106 [32% (95% CI: 13, 57)], a single arm, multicenter trial of adolescent and adult patients with an unresectable PN with progression within the past year.

In addition to radiographic tumor shrinkage, the ReNeu study evaluated mirdametinib effects on PN-related functional impairment, symptoms and disfigurement using various clinical outcome assessment (COA) measures as well as longitudinal photographic evaluations. Despite the limitations of the single-arm trial design, small sample size, heterogeneity of associated morbidities and interpretation of the COA measures, a general trend toward an association between a reduction in tumor volume and durable improvement in clinical outcomes was observed.

Given the benign, albeit morbid, nature of NF1-PN, the Applicant submitted reports from the literature indicating that a key characteristic of NF1 PN is the uncommon occurrence of spontaneous regression, supporting the conclusion that the observed tumor responses in ReNeu are due to the effect of the drug. This supportive information includes reports from the placebo control arm of the National Cancer Institute (NCI) Study 01-C-0222, a randomized, placebo-controlled trial of tipifarnib in pediatric patients with NF1 and progressive PNs; and NCI Study 08-C-0079, a natural history study of children, adolescents, and adults with NF1.

FDA considers ORR, supported by DOR, to be an appropriate endpoint for regular approval for this rare patient population given that their clinical meaningfulness is associated with improved clinical outcome assessment data from the ReNeu study. Furthermore, while rare instances of spontaneous PN volume decrease have been observed, the magnitude of these reductions are not comparable to the tumor regression observed with mirdametinib treatment. There are no approved therapies for adults with NF1-PN. Selumetinib is a MEK inhibitor that is approved for pediatric patients with symptomatic, inoperable NF1-PN; however, the approval of mirdametinib addresses an unmet need for pediatric patients with NF1-PN who are unable to swallow capsules.

The observed ORR and DOR with mirdametinib are robust and clinically meaningful and the tumor shrinkage results are associated with a positive trend in improved clinical outcomes in patients with symptomatic NF1-PN not amenable to surgical resection, and provide substantial evidence of effectiveness. The safety findings support a favorable benefit:risk assessment, and the review team recommends regular approval.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder with variable expressivity caused by germline mutations in the NF1 gene. Plexiform neurofibromas (PNs) are benign tumors of the peripheral nerve sheath which occur in 40-50% of patients with NF1. More than 50% of NF1-PNs are detected in early childhood, and the fastest growth rate is typically during the first decade of life. PNs may be associated with significant morbidity including pain, disfigurement, neurologic deficits, and functional impairment (Ly and Blakely, 2019; Dombi et al, 2007). PNs may also lead to mortality through compression of vital structures, e.g., airway compression and hemothorax (Prada et al, 2012). Malignant transformation to malignant peripheral nerve sheath tumors (MPNST) can occur in 8-16% of patients with NF1-PN.

Treatment typically includes surgical resection; however, resection is often not feasible due tumor effect on adjacent tissue, nerves, and vasculature. The only FDA-approved therapy for NF1-PN is the MEK inhibitor selumetinib, for pediatric patients 2 years of age and older with NF1 who have symptomatic, inoperable PN. The reported ORR for selumetinib is 44% (95% CI: 30, 59) according to Response Evaluation in Neurofibromatosis and Schwannomatosis (REINS) criteria (i.e. PN decrease $\geq 20\%$ compared to baseline in consecutive scans within 3-6 months) by independent central review (Koselugo USPI). Selumetinib is currently only available in a capsule formulation and is therefore not accessible to pediatric patients who cannot swallow capsules. There are currently no approved systemic therapies for adult patients with NF1-PN.

This NDA for mirdametinib is primarily supported by results from the ReNeu study, a multicenter, single-arm trial investigating mirdametinib in adult and pediatric patients with NF1 and progressive or symptomatic plexiform neurofibromas not amenable to complete surgical resection. The primary efficacy population included 114 patients, including 56 pediatric and 58 adult patients with NF1-PN. All patients in the study had measurable disease and received mirdametinib at a dosage of 2 mg/m² orally twice daily for the first 21 days of each 28-day cycle, for up to 24 cycles in the treatment phase.

The primary endpoint to demonstrate the efficacy of mirdametinib for this population was confirmed ORR defined as PN decrease $\geq 20\%$ compared to baseline in consecutive scans within 2-6 months, using independent central review of MRI volumetric analysis. Because the study calendar required end-of-study imaging at 3 months (+/- 10 days) from the second to last imaging timepoint, these modified criteria were used to capture responses that occurred late in the study with less than 3 months between consecutive scans. DOR was a key secondary endpoint. The confirmed BICR-assessed ORR in the primary efficacy population of pediatric patients was 52% (95% CI: 38, 65); the median DOR was not

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reached. A total of 90% of responders had a DOR of ≥ 12 months and 48% of responders had a DOR of ≥ 24 months. The confirmed ORR as assessed by BICR in the primary efficacy population of adult patients was 41% (95% CI: 29, 55); the median DOR was not reached. A total of 88% of responders had a DOR of ≥ 12 months and 50% of responders had a DOR of ≥ 24 months.

The primary safety population for this NDA comprises a pooled population of 133 patients (58 pediatric and 75 adult) treated with mirdametinib at the recommended dosage on the ReNeu study or Study NF-106. The most common adverse events in the ReNeu study in adult patients ($>40\%$) were rash, diarrhea, nausea and musculoskeletal pain, and the most common adverse events in pediatric patients ($>40\%$) were rash, diarrhea, and musculoskeletal pain. Serious adverse reactions in the ReNeu study occurred in 17% of adult patients; serious adverse reactions occurring in $\geq 1\%$ of adult patients were COVID-19 (3.4%), nephrolithiasis (3.4%), acute kidney injury (1.7%), abdominal pain (1.7%), ischemic colitis (1.7%), urinary tract infection (1.7%), retinal vein occlusion (1.7%), scoliosis (1.7%), squamous cell carcinoma of skin (1.7%), cerebrovascular accident (1.7%) and chronic obstructive pulmonary disease (1.7%). Serious adverse reactions in the ReNeu study occurred in 14% of pediatric patients; serious adverse reactions occurring in $\geq 1\%$ of patients included viral gastrointestinal infection (3.6%), diplopia (1.8%), musculoskeletal pain (1.8%), seizure (1.8%), fall (1.8%), femoral neck fracture (1.8%), dehydration (1.8%), and hypertension (1.8%). One fatal adverse reaction occurred in an adult patient (1.7%) due to COVID-19. No additional safety signals were identified in the pooled population. The safety profile of mirdametinib is consistent with that of other MEK inhibitors, and important safety concerns include ocular toxicity, left ventricular dysfunction, dermatologic adverse reactions, and embryo-fetal toxicity. These safety concerns will be addressed in the Warnings and Precautions section of the USPI. The safety profile for mirdametinib is considered acceptable when assessed in the context of a serious and life-threatening disease and with appropriate monitoring as described in the product label. Postmarketing requirements (PMRs) will be issued for an integrated safety analysis of data to further characterize the long-term incidence, severity, and outcomes of known serious risks including ocular toxicity, left ventricular dysfunction, and dermatologic adverse reactions as well as to further characterize the potential serious risk of long-term adverse effects of mirdametinib on growth and development in pediatric patients. PMRs are described in further detail in Section 13.

The results of the ReNeu study demonstrate substantial evidence of effectiveness for the treatment of adult and pediatric patients 2 years of age or older with NF1 who have symptomatic PN not amenable to complete surgical resection. The magnitude of the observed treatment effect on ORR and DOR is clinically meaningful and is supported by a positive trend in COA data. Given the rarity of NF1-PN and the associated morbidity in this patient population, a randomized trial is not considered feasible.

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

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- NF1 is a progressive multi-system disease caused by loss of NF1 function and characterized by progressive cutaneous, neurological, skeletal, and neoplastic manifestations early in life and which can be associated with severe morbidity. - PNs are benign nerve sheath tumors that occur in 40-50% of patients with NF1. PNs may develop along nerves throughout the body and may be located around the orbit, face, upper and lower limbs, back, thorax, abdomen, neck brachial plexus and/or lumbosacral plexus, which result in clinical symptoms such as disfigurement, motor dysfunction, pain, respiratory impairment, visual dysfunction, and neurological dysfunction. - Malignant transformation to malignant peripheral nerve sheath tumors (MPNST) can occur in 8-16% of patients with NF1-PN.	NF1 is a rare, progressive, and highly morbid condition that can lead to fatal outcomes depending upon the location of the tumor. It is a serious and life-threatening disease.
Current Treatment Options	- Selumetinib is approved for pediatric patients 2 years of age and older with symptomatic, inoperable NF1-PN, and demonstrated an ORR of 44% as assessed by independent central review. Selumetinib is available in a capsule formulation. - There are no available systemic therapies for adult patients	There is an unmet medical need for adult patients with progressive or symptomatic NF1-PN, and for pediatric patients who are unable to swallow capsules.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	with progressive or symptomatic NF1-PN not amenable to complete surgical resection.	
<u>Benefit</u>	- The efficacy of mirdametinib was evaluated in the ReNeu study, a multicenter, single-arm trial investigating mirdametinib in adult and pediatric patients with NF1 and progressive or symptomatic plexiform neurofibromas not amenable to complete surgical resection. The primary efficacy population included 114 patients, including 56 pediatric and 58 adult patients with NF1-PN. - In the pediatric cohort, the confirmed ORR per volumetric analysis was 52% (95% CI: 38, 65); the median DOR was not reached. A total of 90% of responders had a DOR of ≥ 12 months and 48% of responders had a DOR of ≥ 24 months. - In the adult cohort, the confirmed ORR per volumetric analysis was 41% (95% CI: 29, 55); the median DOR was not reached. A total of 88% of responders had a DOR of ≥ 12 months and 50% of responders had a DOR of ≥ 24 months.	The submitted evidence meets the statutory evidentiary standard for regular approval for the indicated population. The magnitude of the treatment effect and durability of responses, coupled with supportive COA data, provide evidence of a clinically meaningful treatment effect.
<u>Risk and Risk Management</u>	- The pooled safety population from the ReNeu study and supportive Study NF-106 included 133 patients (58 pediatric and 75 adult) with NF1 PN who were treated with 2 mg/m² BID (maximum 4 mg BID); 3 weeks on/1 week off. - The most common adverse events in the ReNeu study in adult patients (>40%) were rash, diarrhea, nausea and musculoskeletal pain, and the most common adverse events in pediatric patients (>40%) were rash, diarrhea, and	The safety profile for mirdametinib is acceptable for the treatment of adult and pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have progressive or symptomatic plexiform neurofibromas (PN) not amenable to complete resection. Important safety concerns include ocular toxicity, left

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	musculoskeletal pain.	ventricular dysfunction, dermatologic adverse reactions, and embryo-fetal toxicity. These safety concerns will be addressed in the Warnings and Precautions section of the USPI. Postmarketing requirements will be issued to further characterize the long-term incidence, severity and outcomes of ocular toxicity, left ventricular dysfunction and dermatologic adverse reactions. A risk evaluation and mitigation strategy (REMS) is not recommended for mirdametinib given that the current safety profile is consistent with the known safety profile of MEK inhibitors and the experience of the medical community in managing MEK inhibitor toxicities. Given the intended chronic use of the drug for pediatric patients with NF-1 PN, postmarketing requirements will be issued for long-term monitoring of patients to include evaluations for safety, growth, and development.

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1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application, include:			Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		Section 8.1, Efficacy Results – Secondary of exploratory COA (PRO) endpoints
		X	Patient reported outcome (PRO)	Section 8.1, Efficacy Results – Secondary of exploratory COA (PRO) endpoints
		☐	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerFO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	X	Patient-focused drug development or other stakeholder meeting summary reports		Section 2.1 Analysis of Condition and Section 8.4 Conclusions and Recommendations
	☐	Observational survey studies designed to capture patient experience data		
	X	Natural history studies		Section 8.1, External control data
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		

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☐	Other: (Please specify)	
☐	Patient experience data that was not submitted in the application, but was considered in this review.	

X

Cross-Disciplinary Team Leader
Amy Barone, MD

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Neurofibromatosis is classified into three major clinically and genetically distinct forms: neurofibromatosis type 1 (NF1), neurofibromatosis type 2, and schwannomatosis. NF1, also known as von Recklinghausen disease, is the most common form of neurofibromatosis. NF1 is a rare, autosomal dominant genetic disorder with an annual birth incidence of approximately 1 in 2500 individuals ([Children's Tumor Foundation 2023](#); [Lee 2023](#)). Approximately one-half of cases are inherited with the remainder being the result of de novo mutations in the NF1 tumor suppressor gene, located at chromosome 17q11.2 ([Evans 2010](#); [Ledbetter 1989](#); [Feldkamp 1998](#)).

Neurofibromin, the protein product encoded by the NF1 gene, belongs to a family of guanosine triphosphate hydrolase (GTPase)-activating proteins that down-regulate the cellular proto-oncogene p21-ras (21 kD rat sarcoma viral oncogene homologs) ([Martin 1990](#); [Weiss 1999](#); [Gutmann 2013](#)). Ras activates numerous signaling pathways, including the mitogen-activated protein kinase (MAPK) pathways. Ras has been implicated in the control of cell growth and differentiation, and the ability of neurofibromin to down-regulate p21-ras suggests that the loss of neurofibromin may lead to uncontrolled cellular growth or tumor formation.

Mutations in the NF1 gene result in loss of production or reduced function of neurofibromin, causing the wide spectrum of clinical findings, including NF1-associated tumors (Shen 1996). Penetrance, or the likelihood that the individual carrying the mutation will manifest the disorder, is complete. The loss of neurofibromin in malignancy supports the notion that neurofibromin is a tumor-suppressor protein ([Bergoug 2020](#)).

NF1 is characterized by diverse, progressive cutaneous, neurological, skeletal, and neoplastic manifestations. The manifestation of the NF1 clinical diagnostic criteria typically appear in the order of café-au-lait macules, axillary and/or inguinal freckling, Lisch nodules (iris hamartomas), and finally neurofibromas ([DeBella 2000](#)). Most importantly, patients with NF1 develop both benign and malignant tumors at increased frequency throughout life ([Gutmann 1997](#); [Seminog 2013](#)). The diagnostic criteria for NF1 were defined at a National Institute of Health (NIH) consensus development conference in 1987 (NIH Consensus Development Conference Statement 1987) and updated in 2021. In most cases, the diagnosis of NF1 is made on clinical grounds, requiring 2 or more clinical features to be present from the defined list of diagnostic criteria for NF1 presented below:

- Six or more café-au-lait-macules*

- > 5mm in pre-pubertal children
 - > 15mm in post-pubertal individuals
- Freckling in axilla (armpit) or groin*
- Two or more neurofibroma tumors of any type, or 1 PN
- Two or more Lisch nodules (iris hamartomas) or two or more choroidal abnormalities – defined as bright, patchy nodules imaged by optical coherence tomography /near-infrared reflectance imaging
- Optic pathway glioma
 - A distinctive osseous lesion such as a sphenoid dysplasia, anterolateral bowing of tibia, or pseudarthrosis of a long bone
- A heterozygous pathogenic *NF1* variant with a variant allele fraction of 50% in apparently normal tissue such as white blood cells
- A child of a parent who meets the diagnostic criteria specified above merits a diagnosis of NF1 if one or more of the criteria above are present

*At least one of the two pigmentary findings (café-au-lait macules or freckling) should be bilateral. ([Legius 2021](#))

Neurofibromas are benign peripheral nerve sheath tumors that are comprised of a mixture of Schwann cells, fibroblasts, perineural cells, and mast cells ([Tucker 2011](#)). When a neurofibroma extends longitudinally along a nerve and involves multiple fascicles, it is classified as a plexiform neurofibroma (PN). PNs grow most rapidly during the first decade of life and while the growth rate is highly variable between patients, the growth rate of PN in younger children is generally much greater compared to older children or adults ([Dombi 2007](#), [Nguyen 2012](#), [Tucker 2009](#)). A Natural History study of NF1 conducted by the National Cancer Institute (NCI) Pediatric Oncology Branch demonstrated that, although spontaneous PN shrinkage occurred in a small number of PNs in older adolescent and adult patients, the shrinkage is very slow, taking place over many years, and no patient had spontaneous PN shrinkage $\geq 20\%$ within a year ([Dombi 2007](#), [Gross 2018](#)). As such, PNs rarely regress spontaneously, and in many patients their growth is relentless. PNs occur in 30%-50% of patients with NF1 and represent a major cause of morbidity and disfigurement in individuals with NF1, and when symptomatic, are associated with increased mortality ([Prada 2012](#); [Miller 2019](#)). As tumor growth progresses, PNs produce dysfunction, pain, and cosmetic disfigurement and can compress vital structures such as the airway or spinal cord. Once a clinical morbidity develops in patients with PN that are growing, it is extremely unlikely for the morbidity to resolve spontaneously ([Gross 2018](#)). Chronic pain in NF1 can be associated with PN, as well as subcutaneous neurofibroma and bony deformations (scoliosis and pseudoarthrosis), and as such, can occur anywhere in the body or multiple sites at the same time ([Bellampalli 2019](#)). Furthermore, PNs have the potential to undergo malignant transformation into malignant peripheral nerve sheath tumors (MPNSTs), which occur in an estimated 8%-16% of patients with NF1 ([Evans 2002](#); [Hirbe 2014](#)). MPNSTs are aggressive tumors that can metastasize, with a 5-year survival rate of 20%-30% ([Imura 2021](#)).

The FDA's Assessment:

FDA agrees with the Applicant's description of the condition. FDA also notes that during the NF1 Natural History study conducted at the NCI, spontaneous gradual tumor volume was confirmed in 10/113 (8.8%) of PNs, with a median decrease from maximum volume of 19% and a median decrease per year of 3.6% (Akshintala et al, 2020).

On June 13, 2019, FDA hosted a listening session for patients with NF, which included those affected by PN, and their caregivers. During this session, patients described the symptoms, daily burden, and impact of living with NF. Common themes in their narratives included the physical burden of chronic pain, multiple surgeries, motor dysfunction, side effects of chemotherapy, and the social and emotional toll of disfigurement. For example, one 19-year-old male with NF1 and multiple PNs, including a tumor which compressed his spinal cord, described undergoing over twenty surgeries and receiving chemotherapy for 17 years to control PN growth. He also described bullying by classmates that required him to change schools.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

The approach to treatment of the various tumors associated with NF1 depends upon the type of tumor, its effect on adjacent tissues, and related complications. PNs usually involve multiple nerve fascicles, with serpiginous growth and significant vascularity. These lesions can represent a significant challenge in surgical treatment and pain management, especially with progressive growth along the spinal column that may result in compression of the spinal cord (Gold 2013).

The management of these complex lesions varies. Patients were more likely to benefit from surgery when the indications were airway compression or disfigurement (Canavese 2011). However, up to 44% of tumors progress after the first surgery, most commonly in patients younger than 10 years of age, with head and neck tumors that could not be completely resected (Needle 1997). Surgical resection is often limited to debulking of a specific area of a large lesion, for example, when a component is impinging on the spinal cord or airway, or a large soft tissue component is removed to improve cosmesis. Investigational studies of various tyrosine kinase inhibitors, mTOR inhibitors, a farnesyl transferase inhibitor, and fibroblast inhibitors have not demonstrated meaningful or durable objective responses in patients with progressive PN (Jakacki 2017, Robertson 2012, Weiss 2014, Widemann 2014, Widemann 2014b). One treatment option, selumetinib (Koselugo®), an oral selective MAPK inhibitor, is currently approved in the United States (US) for the treatment of pediatric patients ≥ 2 years with NF1 who have symptomatic, inoperable PNs (Koselugo 2024). However, Koselugo does not have an age-appropriate formulation and cannot be administered to patients who have difficulty swallowing a capsule whole.

The pivotal study in support of the selumetinib approval was a Phase 2 study (SPRINT) that enrolled 50 participants aged 3 to < 18 years with inoperable, morbid NF1 PNs. The primary endpoint was objective response rate (ORR) per the Response Evaluation in Neurofibromatosis & Schwannomatosis (REINS) per a single reviewer and resulted in an ORR of 66% (95% CI: 51, 79); using the same dataset, an independent centralized review of the final tumor response best overall response (BOR) per the REINS criteria resulted in an ORR of 44% (95% CI: 30, 59) (Koselugo 2024). Common side effects ($\geq 40\%$) were vomiting, rash, abdominal pain, diarrhea, nausea, dry skin, fatigue, musculoskeletal pain, pyrexia, acneiform rash, stomatitis, headache, paronychia, and pruritus. Serious adverse reactions occurred in 24% of participants with the most common AEs including anemia, hypoxia, and diarrhea. Permanent discontinuation due to an adverse reaction occurred in 12% of participants. Dose interruptions and dose reductions due to adverse reactions occurred in 80% and 24% of participants, respectively (Koselugo 2024).

There is no curative treatment for NF1 and there are no approved pharmacological treatments for adult patients ≥ 18 years of age with NF1 PN, which represents approximately 81% of the total patient population (Ejerskov 2023). Mirdametinib was studied in both adults and pediatric patients with NF1 PN aged 2 years and above. Mirdametinib not only provides as a treatment option in pediatric patients and addresses the medical need in children with difficulty swallowing given its dispersible tablet formulation, it also addresses the unmet need in the adult population with NF1 PN.

The FDA's Assessment:

FDA agrees with the Applicant's position, and that there is an unmet medical need for adults with symptomatic, inoperable NF1 PN as well as pediatric patients who are unable to swallow capsules.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

The following regulatory designations were granted to mirdametinib:

- Orphan Drug: 30Oct2018
- Fast Track: 28May2019
- Rare Pediatric Disease: 24Jul2023

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Mirdametinib is not currently registered (or approved) in the US or in any other part of the world. The current application was submitted by the Sponsor as a new drug application (NDA) on 28Jun2024.

The FDA's Assessment:

FDA agrees with the Applicant's position.

3.2. Summary of Presubmission/Submission Regulatory Activity

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The Applicant's Position:

Table 1: Regulatory History of Mirdametinib Development Program (IND 139883)

Date	Interaction	Summary
29-Aug-2018	Pre-IND Meeting	Meeting objectives: - To obtain agreement on overall chemistry, manufacturing and controls development plan - To obtain feedback on adequacy of current nonclinical data package to support conducting Phase 2b pivotal clinical trial and submission of NDA for treatment of NF1 - To obtain feedback regarding proposed Phase 2b study design, including primary, secondary, and exploratory endpoints, and use of patient-reported outcome (PRO) tools - To obtain feedback on plan to submit Proposed Pediatric Study Request for Agency to issue Written Request
30-Oct-2018	Orphan Drug Designation Granted Letter	Treatment of neurofibromatosis type 1
29-Jan-2019	Type C Meeting	Meeting objective: To align on the modified Phase 2b study design and to gain consensus if the study would support labeling for both pediatric and adult populations.
26-Apr-2019	Study May Proceed Letter	Study MEK-NF-201 cleared to proceed
28-May-2019	Grant Fast Track Letter	Treatment of patients ≥ 2 years of age with NF1-associated inoperable PNs that are progressing or causing significant morbidity
13-Jun-2019	Advice/Information Request Letter	Feedback on Study MEK-NF-201

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Date	Interaction	Summary
09-Apr-2020	Type C WRO Meeting	Meeting objective: To align on introduction of pediatric formulation into Study MEK-NF-201
02-Jul-2020	Executive CAC Protocol Meeting	CAC review of protocol for the definitive 6-month carcinogenicity study in transgenic mice: Dose levels of 0 (b) (4), 2, 5, and 15 mg/kg/day selected for both male and female mice.
13-Oct-2021	Type C Meeting	Meeting objectives were to gain Agency's feedback on: - Clinical pharmacology development plan - Aspects of CMC development plan including designation of starting materials, plan to evaluate formulation palatability, and test method for monitoring drug release for the tablet - Clinical strategy for initial NDA submission
05-Nov-2021	Type C WRO Meeting	Meeting objective: To obtain feedback on study design and analysis plan for thorough QT Study MEK-NF-102
16-Nov-2022	Type C Meeting	Meeting objectives: - To seek feedback on current study that could support registration and proposed statistical analysis plan for primary analysis of pivotal Study MEK-NF-201 (ReNeu) - To request feedback on clinical pharmacology proposal to use modeling and simulation to further justify selected dose - To discuss overall clinical development plan
24-Feb-2023	Email	FDA agreed that further reproductive toxicology studies are not warranted based on dose range finding study results in rats and rabbits.
11-May-2023	Advice/Information Request Letter	Mirdametinib NDA is exempt from requirements under Section 505B of Food, Drug, and Cosmetic Act as amended by Title V of FDA Reauthorization Act of 2017.

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Date	Interaction	Summary
		Mirdametinib's orphan drug designation exempts requirements to conduct pediatric assessments under Pediatric Research Equity Act
23-May-2023	Type C Meeting	Meeting Objective: To gain Agency's alignment on the dose justification and proposed modeling analysis plan.
24-Jul-2023	Rare Pediatric Disease Designation Granted Letter	Mirdametinib for treatment of NF1 is designated as drug for a rare pediatric disease.
16-Oct-2023	Email	FDA requested that SpringWorks submit two separate mirdametinib NDAs, one for tablet formulation and one for capsule formulation.
06-Feb-2024	Rolling Review Granted	Agency agreed with proposed M3 eCTD structure for both mirdametinib formulations (tablet and capsule).
27-Feb-2024	Pre-NDA Meeting	Meeting objectives: - To seek agreement on suitability of clinical data, as well as content and format of application to support full approval for mirdametinib in treating adult and pediatric patients with NF1 PN - To request for Agency's feedback on content strategy (CMC, nonclinical, clinical, pooling strategy for ISS, narratives, biostatistics, and clinical pharmacology).
11-Mar-2024	Response to Request – Carcinogenicity	FDA indicates that a 2-year rat carcinogenicity study is warranted for intended population.
27-Mar-2024	Biopharmaceutics Information Request	In response to BCS Class 1 Designation and Biowaiver Request (SN0150), FDA stated biowaiver is unnecessary because PK is similar for 2 mirdametinib formulations and review of BCS classification will be conducted as part of NDA review.

(b) (4)

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BCS: biopharmaceutics classification; CAC: Carcinogenicity Assessment Committee; CMC: chemistry, manufacturing, and controls; eCTD: electronic common technical document; FDA: Food and Drug Administration; ISS: integrated summary of safety; M: module; NDA: new drug application; WRO: written response only

The FDA's Assessment:

FDA agrees with the Applicant's timeline, with the following additional comments regarding the discussion at selected meetings:

- **Pre-IND meeting August 29, 2018**

- FDA stated that the Applicant would need to conduct a full battery of GLP-compliant reproductive toxicology studies and carcinogenicity studies and recommended that the Applicant submit carcinogenicity protocols for special protocol assessment review by FDA prior to initiation of studies (subsequently reviewed by FDA on June 25, 2024). The Applicant confirmed that an embryo-fetal study was conducted in the rabbit, however FDA noted that the data from the EFD study were not submitted. FDA recommended that the Applicant submit the results of the study and ask for FDA feedback regarding whether pre and post-natal development and pivotal EFD studies are necessary.
- FDA stated that the single-arm MEK-NF-201 study, with a primary endpoint of radiographic response, might support an application seeking marketing approval, provided that the natural history of the disease has been adequately established. FDA also stated that the study should demonstrate a clinically meaningful magnitude of response rate, that response rates are sufficiently durable, and unequivocal evidence of an important treatment effect that is supported by data showing an improvement in physical function or an improvement in specific symptoms related to progressive PN disease that correlates with radiographic tumor shrinkage.

- **Type C meeting Jan 29, 2019**

- FDA agreed with the Applicant's plan to analyze age-based cohorts independently given the age-dependent differences in tumor growth rate.
- FDA stated that the primary analysis for ORR should be based on all treated patients who received at least one dose of mirdametinib; the Applicant indicated agreement.
- FDA requested that the Applicant provide detailed plans for the analysis of Clinical Outcome Assessment Data; the Applicant agreed to provide this information in the Statistical Analysis plan prior to the start of study enrollment.

- **Type C meeting October 13, 2021**

- FDA strongly recommended that the Applicant request a meeting to discuss the overall clinical development program for mirdametinib, specifically regarding the approach to dosage optimization and the clinical outcome assessments and patient reported outcomes being used to support the primary endpoint of Study MEK-NF-201.

- **Type C meeting November 16, 2022**

- FDA recommended that for the data submitted in an original NDA submission, all or nearly all responders should be followed for 12 months after their initial response. FDA also recommended providing patient-level data from Study NF-106 and including this data in the pooled safety population. The Applicant acknowledged this advice.
- FDA provided comments regarding the submitted SAP for the analysis of PROs/COAs. The Applicant acknowledged this advice.
- FDA recommended that the Applicant use a dual-reader paradigm with adjudication for assessment of imaging responses rather than a single-reader paradigm and requested a revised independent review charter.

- **Pre-NDA meeting February 27, 2024**

- FDA disagreed with the Applicant's request (b) (4)
[REDACTED]
The Applicant agreed to submit a special protocol assessment for the 2-year carcinogenicity study.
- FDA requested that the Applicant clarify which patients were included in the topline PRO data and provide complete information about reasons for missingness. The Applicant agreed to provide this information in the NDA.
- FDA requested that a full justification for the selected dose be provided in the original NDA submission and that the selection of the proposed dosage would be a review issue. The Applicant acknowledged and agreed to provide a full dose justification in the NDA.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Three clinical investigators and the imaging contract research organization (CRO) were inspected. Inspections of the clinical investigators did not find significant concerns regarding the study conduct, data integrity, Good Clinical Practice (GCP) or regulatory compliance. The inspection of the imaging CRO revealed no significant data discrepancies, GCP or regulatory violations. See Clinical Inspection Summary for full details (uploaded in DARRTS, 1/2/2025) .

4.2. Product Quality

The Integrated Quality Assessment Template (uploaded in DARRTS 12/30/24) supports approval. The review noted that the original NDA submission contained CMC information for (b) (4) 1 mg tablets; (b) (4) keeping the 1 mg strength is acceptable based on the dosing regimen. NDA 219389, submitted simultaneously, contains relevant data to support the capsule formulation and cross references all other modules in mirdametinib tablet NDA 219379 for supporting data. The Applicant's requests to designate mirdametinib tablets for oral suspension and capsules as a BCS Class 1 drug substance/drug product were granted. For routine quality control testing of mirdametinib tablets, the Applicant's proposal to use disintegration testing (instead of dissolution testing) is acceptable. The Applicant provided sufficient information to assure the identity, strength, purity, and quality of the proposed drug product (tablets and capsules). All associated manufacturing, testing, packaging facilities were deemed acceptable.

4.3. Clinical Microbiology

See Section 4.2.

4.4. Devices and Companion Diagnostic Issues

N A

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Mirdametinib is an orally bioavailable small molecule non-ATP competitive inhibitor of mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinases 1 and 2 (MEK1/2). MEK1/2 proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway. Both MEK and ERK are critical components of the RAS-regulated RAF-MEK-ERK pathway, which is often activated in different types of cancers. The proposed indication for mirdametinib is the treatment of adult and pediatric patients with neurofibromatosis type 1 (NF1)-related tumors. Neurofibromin (encoded by NF1) contains a RAS-GTPase activating domain. Mutations in the NF1 gene result in loss of production or reduced function of neurofibromin, causing hyperactive Ras signaling, that results in a wide spectrum of clinical findings, including benign or malignant NF1-associated tumors.

The established pharmacological class of mirdametinib is kinase inhibitor. In biochemical assays, mirdametinib inhibited the kinase activity of MEK1 and MEK2 with inhibitory constant (Ki) values of 1.1 nM and 0.79 nM, respectively. In a cell-free signaling cascade assay, mirdametinib inhibition of MEK reduced the level of phosphorylated ERK1 (pERK1) with a Ki value of 0.9 nM. Mirdametinib and its pharmacologically active unique human metabolite, M22, reduced the levels of pERK in cells in vitro, but M22 demonstrated considerably lower ability to reduce the levels of pERK (>91-times lower). In addition, the carboxylic acid metabolite of mirdametinib, PD-0315209, demonstrated inhibitory activity against MEK1 phosphorylation in a cell-based assay (IC₅₀=1.3 μM) but was less active compared to mirdametinib (IC₅₀=0.59 nM). The Applicant further demonstrated the antitumor activity of mirdametinib in a transgenic mouse model of NF1 neurofibroma (*Nf1^{fl/fl};Dhh-Cre*). The Applicant cites literature [Jessen (2013), Jousma (2015)] to support the claim that in this model, deletion of *Nf1* gene in Schwann cells exhibits similar neurofibroma growth and histology to human neurofibromas. In this model, spontaneous neurofibromas are detected by magnetic resonance imaging (MRI) at approximately 4 months of age. Daily treatment of animals with mirdametinib for two months (from 7 to 9 months of age) resulted in reduced tumor growth compared to untreated animals. Protein lysates of tumor tissue harvested from mice treated with mirdametinib showed reduced levels of pERK, a downstream target of MEK signaling. The results of the pharmacology studies support the proposed mechanism of action of mirdametinib and proof-of-concept for the proposed indication.

In a panel of 104 kinases, mirdametinib at a concentration of 1 μM resulted in >70% inhibition of 4 kinases (MEK1, B-Raf, B-RafV600E, and C-Raf). The effect of mirdametinib on MEK2 was not evaluated in this study. In a separate panel of 87 receptors, enzymes, ion channels, and transporters, mirdametinib at a concentration of 10 μM resulted in >50% inhibition of

peroxisome proliferator activated receptor gamma (PPAR γ) and the L-type calcium channel (phenylalkylamine). Although the Applicant did not conduct follow up assays to determine IC₅₀ values, the 1 μ M concentration of mirdametininib tested in secondary pharmacology assays is approximately 800-fold higher than the free C_{max}. Additionally, the inhibition noted on B-Raf and C-Raf kinases may be a consequence of MEK inhibition and not a direct effect on targets considering that the Applicant used a linked kinase cascade assay format, containing other kinases of the MAPK signaling cascade in the reaction.

In safety pharmacology studies, mirdametininib did not affect cardiovascular parameters in monkeys at single oral doses $\leq$ 10 mg/kg. Mirdametininib or its metabolite, PD-0315209, did not affect hERG current in an in vitro assay at clinically relevant concentrations (<10% inhibition at 10 mM). Mirdametininib did not affect CNS parameters in rats after single IV doses $\leq$ 150 mg/kg, but a single oral dose of 100 mg/kg resulted in reduced locomotor activity 24 hours post-dose. In an in vitro assay, mirdametininib reduced action potential amplitude, but not resting membrane potential, at a concentration of 100 mM in isolated canine Purkinje fibers. Increased respiratory rate and decreased tidal volume occurred in rats after single oral doses of 30 or 100 mg/kg mirdametininib but no effect was noted at 10 mg/kg.

Mirdametininib was highly bound in plasma from humans ($\geq$ 99.7%), mice, rats, and dogs. Following a single oral dose of 10 mg/kg, [¹⁴C]-mirdametininib-derived radioactivity distributed widely to rat tissues, with greatest uptake in the liver, followed by kidney, blood, adrenal, lung, salivary gland, heart, and pancreas. Radioactivity was not retained in pigmented tissues, suggesting no affinity for melanin. The highest concentrations of [¹⁴C]-mirdametininib-derived radioactivity were noted 4 hours after oral administration and radioactivity was undetectable by 48 hours post-dose. Following oral administration to rats, the primary excretion route was the feces. PD-0315209 (a carboxylic acid metabolite) and M22 (a glucuronide conjugate; a unique human metabolite) have been identified as major human metabolites (>10%) of mirdametininib. Both metabolites are pharmacologically active, though activity is significantly lower than mirdametininib. PD-0315209 was detected in rats and dogs in the 3-month repeat-dose toxicology studies with exposure up to 20-times higher in animals than clinical exposure. Because M22 is a Phase 2 glucuronide conjugate and Phase 2 conjugation reactions generally render a compound more water soluble and pharmacologically inactive, and consistent with FDA Guidance for Industry Safety Testing of Drug Metabolites, further evaluation is not warranted.

Mirdametininib was shown to absorb light in the 290 to 700 nm range, indicating probable phototoxicity.

The Applicant is developing a tablet for dissolution formulation (NDA 219379) for pediatrics and a capsule formulation (NDA 219389) for adults. Based on discussion with the clinical pharmacology review team, the exposure to mirdametininib in pediatric and adults, using either

formulation, is not significantly different. Therefore, animal to human exposure multiples were calculated using human pharmacokinetic (PK) parameters of C_{max} of 189 ng/mL and AUC_{last} of 445 ng•h/mL.

The toxicity profile of mirdametinib administered orally, the intended route of administration, was evaluated in GLP-compliant general toxicology studies of up to 3-months duration in rats and dogs. Though mortalities did not occur in rats at doses ≤ 1 mg/kg in the 1- or 3-month studies or dogs at doses ≤ 0.3 mg/kg in the 1-month study, two male and two female dogs at the high dose level of 0.4 mg/kg in the 3-month study were euthanized in moribund condition on Days 37 to 50. Common clinical signs in early death dogs included diarrhea, emesis, and soft stools that correlated with decreased food consumption and body weight loss. Other findings in early death dogs suggestive of a systemic inflammatory response included neutrophilic infiltrates/inflammation in the tongue, stomach, and/or esophagus as well as lymphoid depletion in multiple lymphoid organs and myeloid cell hyperplasia in the bone marrow; increases in circulating leukocytes and neutrophils were noted in individual animals. Due to severe clinical signs in the high dose group, dosing in the surviving male and female dogs at 0.4 mg/kg was stopped early on Days 51 and Day 57, respectively. Clinical signs of emesis, abnormal stools were also noted at doses ≥ 0.1 mg/kg in dogs in the 3-month study.

Signs of skin toxicity were noted in rats at doses ≥ 0.1 mg/kg and in dogs at 0.3 mg/kg in the 1- and 3-month studies and included clinical signs of skin sores that correlated with minimal to mild neutrophilic inflammation, crust, and/or ulceration of the epidermis. Consistent with nonclinical findings, dermatitis acneiform, non-acneiform rashes, and exfoliative rash were reported in patients, leading to a warning and precautions for skin toxicity in the label. In general, dermatologic adverse events are associated with other MEK inhibitors and are consistent with the role of MEK1/2 in the epidermis [Scholl (2007)].

Hematologic changes in animals were noted at doses ≥ 0.8 -times the human exposure at the clinical dose of 2 mg/m² twice daily based on area under the curve (AUC). Decreases in red blood cell parameters, including red blood cells, hemoglobin, and hematocrit, occurred at doses ≥ 0.1 mg/kg in rats and at ≥ 0.05 mg/kg in dogs. Increases in circulating monocytes, neutrophils, and/or large unstained cells were noted in rats at ≥ 0.3 mg/kg and dogs at ≥ 0.05 mg/kg. These findings correlated with histologic signs in the lymph nodes in the 3-month studies in rats and dogs, including minimal to moderate lymphoid hyperplasia, lymphoid depletion, and increases in plasma cells, as well as hypocellularity in rats.

Ocular findings in rats administered 1 mg/kg included minimal conjunctiva mineralization in the 1-month study and corneal mineralization in the 3-month study. Minimal atrophy and thinning of the cornea were also noted at doses ≥ 0.3 mg/kg (≥ 2 -times the clinical dose of 2 mg/m² twice daily based on AUC) in the 3-month study in rats. In the 3-month toxicology study in dogs, corneal opacity was noted during ophthalmic examinations in one male each at 0.05 mg/kg and

0.4 mg/kg and correlated with histologic signs of minimal neutrophilic inflammation and mild corneal atrophy in the 0.4 mg/kg male. Mineralization and atrophy of the cornea were added to section 13.2 of the label because they differed from the ocular toxicity listed (retinal vein occlusion, retinal pigment epithelium detachments and blurred vision) in the warning and precautions of the GOMEKLI label.

In rats, minimal to mild mineralization was observed at doses ≥ 0.3 mg/kg (≥ 2 -times the human exposure at the clinical dose of 2 mg/m² twice daily based on AUC) in the 1-month and 3-month studies in multiple organs, including major arteries (pulmonary, renal, and/or mesenteric), kidney, liver, stomach, and GALT. Though signs of mineralization were not noted in dogs, increases in phosphorus occurred at all dose levels in rats (increased up to 37% compared to controls) and at ≥ 0.05 mg/kg in dogs (increased up to 49% compared to controls) and improved after a drug-free period in the 1-month studies, suggesting reversibility. Minimal and transient increases in calcium were noted during the first week of dosing in the 1-month rat study, but no changes in calcium were noted in the 1-month study in rats or the 3-months studies in rats and dogs. Hyperphosphatemia and mineralization findings in animals were not added to section 13.2 of the label because the clinical relevance of these findings is unclear.

Findings in the bone were noted in rats at 1 mg/kg in the 1-month study and at ≥ 0.3 mg/kg in the 3-month study (≥ 2 -times the human exposure at the clinical dose of 2 mg/m² twice daily based on AUC), including minimal to mild thickening of trabeculae and dysplasia of the epiphysis and compact bone. Bone toxicity is relevant given the pediatric population, with growing bones, included in this indication; therefore, bone findings in the repeat-dose studies in rats were added to section 8.4 of the label.

There were slight but statistically significant increases in liver enzymes (ALT, AST, ALP) that correlated with minimal to mild mixed cell inflammation and/or hepatocyte vacuolation at doses ≥ 0.1 mg/kg in the 1-month rat study and ≥ 0.3 mg/kg in the 3-month rat study. Increases in liver enzymes were also noted in dogs at 0.3 mg/kg in the 1-month study and at 0.4 mg/kg in the 3-month study but lacked any histologic correlate. Additionally, increased liver enzymes in the 28-day study in mice correlated with dose-dependent increases in incidence of hepatocellular necrosis. Of note, liver had the highest drug uptake in tissue distribution studies. Considering the totality of nonclinical data, including increases in liver enzymes, marked liver vacuolation, and necrosis in other toxicology studies (3-month rat and 1-month mouse), which were also the cause of death in the 6-month carcinogenicity mouse study, mirdametininib induced hepatotoxicity at exposures ≥ 2 -times the human exposure at the clinical dose of 2 mg/m² based on AUC.

Mirdametininib was negative in an in vitro bacterial reverse mutation test (Ames assay) and an in vitro human lymphocyte chromosomal aberration assay. The rat in vivo micronucleus assay showed equivocal results with mirdametininib. In a separate, follow-up assay, mirdametininib was

negative for clastogenic potential in an in vivo chromosomal aberration assay in rats; however, this study did not rule out aneugenicity. Considering the totality of the data from both in vivo genotoxicity studies, the FDA has determined mirdametinib to be positive for aneugenicity. Though genetic toxicity of the PD-0315209 metabolite was not directly tested, it is expected that rats were exposed to PD-0315209 in the in vivo genetic toxicology tests as rats can generate PD-0315209. As discussed above, because M22 is a Phase 2 glucuronide conjugate, it is not expected to have an increased risk of carcinogenicity and further evaluation is not warranted.

Plexiform neurofibromas with NF-1 are generally slow growing and depending on location are not immediately life-threatening but can be debilitating. Because of the potential for prolonged treatment and long-term survival in the proposed patient population, the Applicant conducted a carcinogenicity study and a dedicated fertility and early embryonic development study. In a 6-month carcinogenicity study in CByB6F1/Tg rasH2 hemizygous mice, the FDA concluded that no carcinogenic effect related to mirdametinib administration was observed at any dose level tested (up to 5 mg/kg/day). The Applicant is currently conducting a 2-year carcinogenicity study in rats and a post-marketing requirement (PMR) will be issued for the submission of the final study report.

The effects of mirdametinib on fertility were assessed in a dedicated fertility study, where male rats were treated with mirdametinib at doses of 0.1, 0.3, or 1 mg/kg/day for 28 days before mating with untreated females to Gestational Day 1. In a separate cohort, female rats were treated with mirdametinib at doses of 0.1, 0.3, or 1 mg/kg/day for 14 days before mating with untreated males to Gestational Day 7. Though mirdametinib did not affect fertility in this study, findings from the repeat-dose toxicology studies indicate that mirdametinib may impair female fertility at exposures ≥ 2 -times the human exposure at the clinical dose of 2 mg/m² twice daily based on AUC. In the 3-month repeat-dose toxicology studies that did not include a recovery period, follicular cysts associated with decreased corpora lutea were noted in female rats at ≥ 0.3 mg/kg and correlated with decreased ovarian organ weight. Based on findings from repeat-dose toxicology studies, FDA included an infertility section under 8.3 Females and Males of Reproductive Potential of the GOMEKLI label to inform infertility risk.

Male reproductive organ findings noted at 1 mg/kg (≥ 8 -times the human exposure at the clinical dose of 2 mg/m² twice daily based on AUC) in the 3-month study in rats included inflammation of the prostate in individual animals and marked hypoplasia of the spermatogenic epithelium in the testis and marked decreased content in the epididymis in one male. Additionally, degeneration of the testes was noted in a 28-day repeat-dose study in mice. Though the results of the dedicated fertility study were negative, male reproductive findings in rats may only be apparent when dosed at very high drug concentrations and/or after a longer duration of dosing due to differences in physiology compared to humans. Dose-dependent increases were noted in the incidence and severity of findings in male reproductive organs in

the 3-month toxicology study in rats, despite low overall incidence. The potential for these findings to impair male fertility was discussed during the review. Considering all available data and literature supporting a role for MEK in spermatogenesis [Hasegawa (2013)], the possibility that male reproductive findings noted in animals were related to mirdametinib could not be ruled out. Therefore, male reproductive organ findings in rats were included in section 13.1 of the GOMEKLI label; however, the potential for impairment of male fertility was not included in section 8.3 of the GOMEKLI label given that the clinical impact of these findings is unclear.

Based on the mechanism of action of mirdametinib and findings in animals, the pharmacology/toxicology team recommends a warning for embryo-fetal toxicity in the label for GOMEKLI. Embryo-fetal developmental (EFD) studies were conducted as dose range finding studies in rats and rabbits. Toxicokinetic evaluations were not included in the rat study; thus, for consistency, animal to human dose comparisons were made based on body surface area (BSA). Mirdametinib showed signs of maternal toxicity in rats at 5 mg/kg (30 mg/m²), including decreases in body weight gain and food consumption, as well as scabs, sores, and abrasions in the skin. Embryo-fetal toxicity at ≥3 mg/kg (≥5-times the clinical dose of 2 mg/m² twice daily based on BSA) included post-implantation loss and decreased fetal body weights. At 3 mg/kg (5-times the clinical dose of 2 mg/m² twice daily based on BSA), multiple malformations, including shortening of limbs and absence or shortening of digits, were observed in one fetus and another fetus had a limb hyperflexion variation. In rabbits, maternal toxicity was evident at ≥1 mg/kg (≥3-times the clinical dose of 2 mg/m² twice daily based on BSA) and included decrease in body weight gain and moribundity leading to early sacrifice of all animals at ≥3 mg/kg. Embryo-fetal toxicity in rabbits was observed at doses as low as 0.3 mg/kg (approximately equivalent to the clinical dose of 2 mg/m² based on BSA) and included post-implantation loss and decreases in fetal body weight. Two animals had spontaneous abortions at the 1 mg/kg dose on Days 20 and 23 and total early fetal resorptions were reported at ≥3 mg/kg. Based on the clear evidence of embryofetal lethality and teratogenicity in the dose range finding studies, the FDA agreed that no further reproductive toxicology testing (i.e., GLP embryo-fetal development and pre-and post-natal development studies) was warranted.

FDA recommends advising females of reproductive potential to use effective contraception during treatment with GOMEKLI and for 6 weeks after the last dose and male patients with female partners of reproductive potential to use effective contraception during treatment with GOMEKLI for 3 months after the last dose. The recommendation is consistent with drugs that are teratogenic or embryo-fetal lethal and aneugenic and takes into consideration the half-life of 28 hours for mirdametinib. Because of the potential for serious adverse effects of GOMEKLI in a breastfed child, the review team recommends advising patients not to breastfeed during treatment with GOMEKLI and for 1 week after the last dose.

Recommendation:

From a pharmacology/toxicology perspective, the nonclinical data are adequate to support the

approval of GOMEKLI for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

There are no referenced NDAs, BLAs, or DMFs related to nonclinical pharmacology or toxicology for mirdametininib.

The FDA's Assessment:

FDA agrees.

5.3. Pharmacology

The Applicant's Position:

Mirdametininib (PD-0325901) has been evaluated in numerous in vitro and in vivo nonclinical studies that were designed to characterize the pharmacology, safety pharmacology, pharmacokinetics (PK) and toxicology of the compound. The pharmacological properties of mirdametininib have been studied using enzyme and cell-based assays and evaluated in tumor xenograft models and in an NF1 mouse model. Biochemical assays have shown that mirdametininib is a selective, noncompetitive, allosteric inhibitor of mitogen-activated protein kinase kinase (MEK)-1 and MEK2 and thereby inhibits phosphorylation of the extracellular signal-regulated kinase (ERK)1 and ERK2, which in turn impairs tumor cell growth through the MAPK pathway.

Primary Pharmacology

As a potent MEK inhibitor, mirdametininib has an inhibition constant (K_i) for the activated forms of MEK1 and MEK2 of ≤ 1.1 nM. In a cell-based assay measuring inhibition of phosphorylated ERK1 as a measure of MEK inhibition of the Ras/Raf/MEK/ERK pathway, the K_i for mirdametininib was 0.90 nM.

The specificity for various species was determined by comparing the potency of mirdametininib in cell-based assays using Colon-26 (mouse), MDCK (dog), and HCT-116 (human) cancer cell lines. The pharmacodynamic properties of mirdametininib are summarized in [Table 2](#).

Table 2: Pharmacodynamic Properties of Mirdametininib Across Different Assay Types

Property	Value
Biochemical activity in vitro	
MEK enzyme IC50 (nM) ^a	15
Cellular IC50 (nM) ^b	
Colon-26 (mouse)	0.34
MDCK (dog)	0.31
HCT-116 (human)	0.28
Pharmacodynamic activity – in vivo target engagement	
IC50 (nM) ^c	34.2
IC90 (nM) ^c	179.4
Ex vivo % pERK inhibition at 24 h ^d	
Colon-26	76
HT-29	79
MiaPaCa-2	93
Antitumor activity in vivo^e	
Percent of animals with complete tumor response with daily dose of 25 mg/kg	70%
Tumor growth delay (in days) at dose of 25 mg/kg	15.4

Abbreviations: Colon-26: mouse colon adenocarcinoma cell line; HCT-116: human colorectal carcinoma cell line; HT-29: human colorectal adenocarcinoma cell line; IC50: 50% inhibitory concentration; IC90: 90% inhibitory concentration; MDCK: Madin-Darby canine kidney cell line; MEK: mitogen-activated protein kinase kinase; MiaPaCa-2: human pancreatic carcinoma cell line; pERK: phospho-extracellular signal-regulated kinase.

^a A cascade assay with Raf-1, MEK1, and ERK1 (DELTA readout) was used to measure enzyme inhibition of MEK1.

^b Western blots were used to measure MEK inhibition in cultured cells exposed to the indicated compound for 1 hour.

^c Mice bearing Colon-26 tumors were treated with various oral doses of mirdametininib and the plasma concentrations along with decreases pERK levels in excised tumors were determined. From these values, the plasma concentrations required to inhibit ERK phosphorylation by 50% and 90% (IC50 and IC90) were calculated.

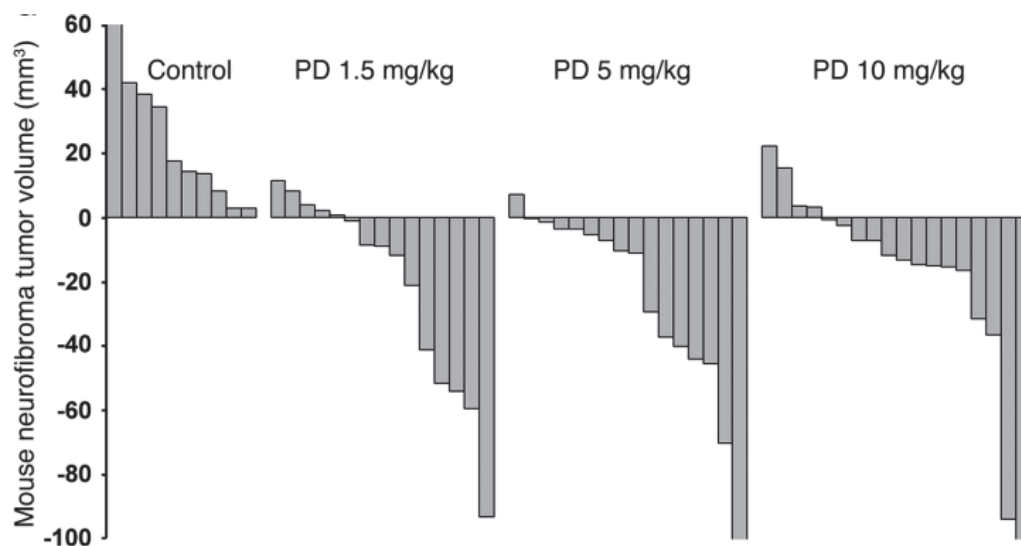
^d Tumor-bearing mice were treated orally with mirdametininib at 25 mg/kg; 24 hours postdose, pERK levels in excised tumors were measured by western blot analysis.

^e Mice bearing the C26 tumor were treated orally with 25 mg/kg/day mirdametininib for 14 days. A complete tumor response represents a decrease in tumor mass below the level of detection. Tumor growth delay is the difference in median days for the control and treated tumors to reach a specified evaluation size.

Mirdametininib was shown to be highly efficacious in the *Nf1^{fl/fl};Dhh-Cre* mouse model of NF1 neurofibroma, in which *Nf1* gene deletion in Schwann cells exhibited similar neurofibroma growth and histology to human neurofibromas. These mice were treated with mirdametininib at

1.5, 5.0, or 10 mg/kg/day or vehicle via oral gavage once daily (QD) for 60 to 90 days, and small-animal magnetic resonance imaging (MRI) was used to evaluate tumor growth (Jessen 2013). Tumors measured by volumetric MRI analysis responded to a similar degree, with pronounced tumor reduction at all 3 dose levels ($p < 0.001$) in $> 80\%$ of mice (Figure 1), which correlated with associated reductions in biomarkers for cell proliferation (Ki67+) and blood vessels (MECA+ endothelial cells). Additionally, phosphor-extracellular signal-regulated kinase (pERK) was reduced in NF1 neurofibromas at both the high- (10 mg/kg) and low-dose groups (1.5 mg/kg): pERK disappeared by 30 minutes after dosing and remained low at 6 hours post dose; at 24 hours post dose, a sustained reduction in pERK was noted only in the low-dose group while pERK levels in the high-dose group had recovered.

Figure 1: Mirdametininib Inhibits Neurofibroma Growth in NF1 Mouse Model



Reference: Jessen 2013, Figure 2G.

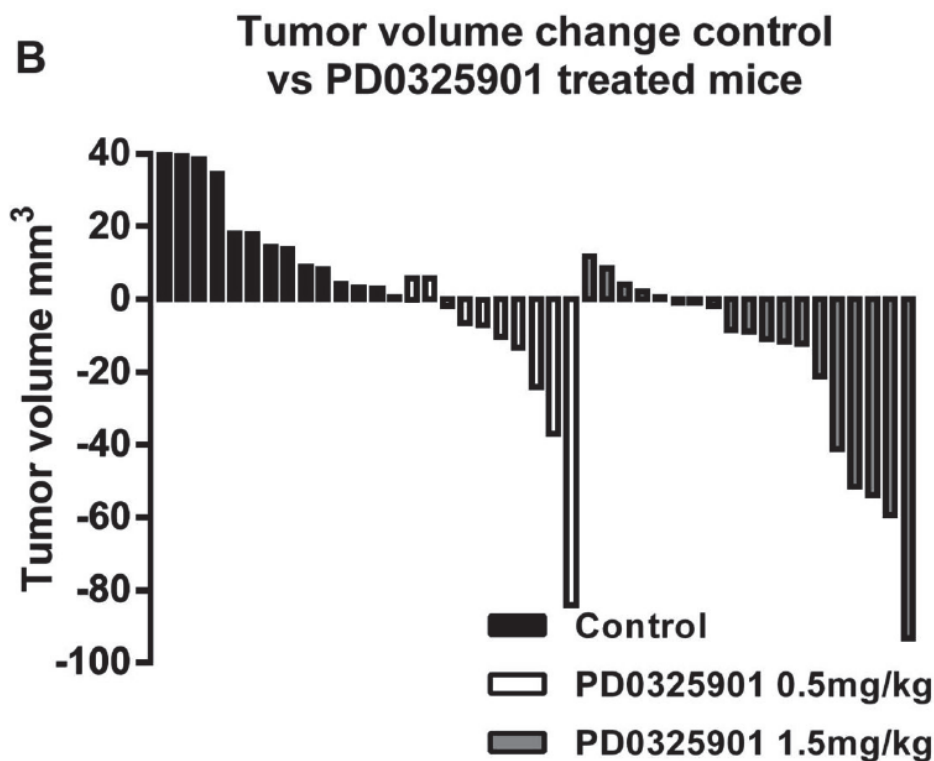
Abbreviations: PD: as abbreviation for mirdametininib, also known as PD-0325901, in X axis of this figure.

Notes: Volumetric measurements of vehicle-treated or mirdametininib-treated *Nf1^{fl/fl};Dhh-Cre* NF1 mice indicate a decrease in neurofibroma volume treated with 1.5 mg/kg, 5 mg/kg, or 10 mg/kg PD 0325901 for 2 months. The y axis shows tumor volume in mm³ quantified by measurements of MRI scans. Each bar represents the difference in tumor volume in an individual animal from Day 0 (7 months) to Day 60 (9 months). Mixed effects model analysis indicated statistical significance for each dose ($p < 0.001$).

The minimally effective dose (MED) of mirdametininib was evaluated in NF1 mice by treating mice with established tumors at the relatively low doses 0.5 and 1.5 mg/kg/day (Jousma 2015). In this study, 0.5 mg/kg dose group (human equivalent dose of approximately 2.5 mg twice daily [BID]) led to statistically significant neurofibroma shrinkage as compared to vehicle-treated mice. As shown in Figure 2, the extent of shrinkage seen in the 0.5 mg/kg mirdametininib group was comparable to the shrinkage of tumors from mice treated with mirdametininib at 1.5 mg/kg (dose was noted to provide a concentration similar to 8 mg BID in humans) (Jessen 2013). The low dose (0.5 mg/kg) of mirdametininib led to comparable reductions in tumor

volume, blood vessel/area, and pERK levels with slightly higher frequencies of proliferating cells compared to 1.5 mg/kg dose (Figure 3).

Figure 2: Low-Dose Mirdametinib Shrinks Neurofibromas

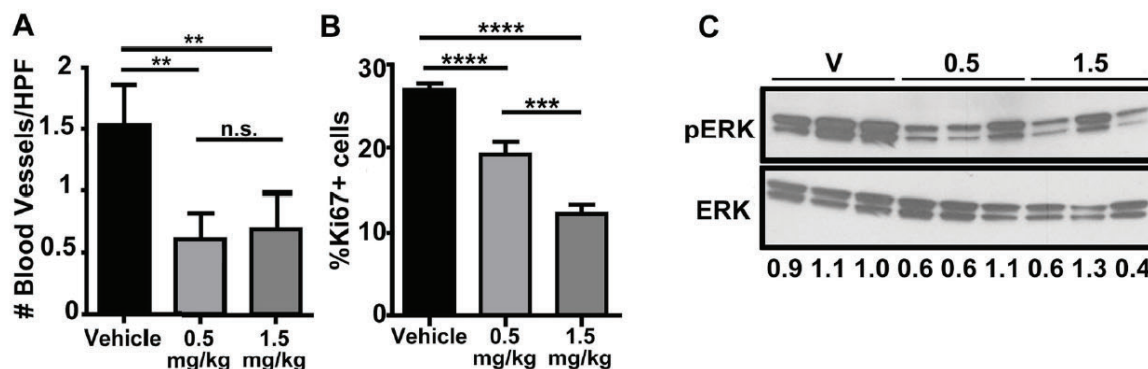


Reference: Jousma 2015, Figure 4B.

Abbreviations: PD0325901: mirdametinib.

Notes: Change in neurofibroma volume from 7 to 9 months of age in mice exposed to vehicle, PD0325901 at 0.5 mg/kg, or PD0325901 at 1.5 mg/kg. Each bar displays the absolute difference in neurofibroma volume between 7 and 9 months in a single mouse based on serial MRI imaging. A positive value indicates neurofibroma size increase; a negative value indicates neurofibroma shrinkage. Mean neurofibroma volume remained significantly lower in both PD0325901 treatment groups compared to vehicle-treated controls.

Figure 3: MEK Inhibitor Retains Efficacy at Low Doses



Reference: Jousma 2015, Figure 5A, B, and C.

Abbreviations: HPF: high-powered field; n.s.: not significant; SD: standard deviation; V: vehicle.

Notes: (A) Bars represent blood vessels per area of neurofibroma tissue detected with an anti-MECA-32 antibody (endothelial cell marker) (mean $\pm$ SD). Vessels per field were significantly reduced ($p < 0.05$) in the 0.5 and 1.5 mg/kg-treated groups, as compared to the vehicle-treated group. There was no significant difference in blood vessels/area between the mirdametinib-treated groups. (B) The percentage of Ki67+ proliferating cells were significantly different ($p < 0.0001$) between vehicle-treated and 0.5 and 1.5 mg/kg mirdametinib-treated groups. Mice exposed to 1.5 mg/kg dose showed fewer proliferating cells than the 0.5 mg/kg-treated group ($p < 0.0005$). (C) In protein lysates from tumors, the level of pERK quantified as a fraction of total ERK, was decreased in tumors harvested from mice treated with 0.5 and 1.5 mg/kg mirdametinib. Numbers are the ratio of pERK to total ERK for each sample. **, $p < 0.05$; ***, $p < 0.0005$; ****, $p < 0.0001$.

Mirdametinib is a potent MEK inhibitor, as demonstrated in a variety of species and nonclinical models. Evaluation in mouse models of NF1 that have similar histopathology and growth rates as human NF1 PNs demonstrated antitumor activity of mirdametinib treatment in NF1. Dose-ranging studies in NF1 mouse models also support the use of low doses of mirdametinib in achieving tumor reductions and demonstrate that NF1 neurofibromas have high sensitivity to MEK inhibition.

The FDA's Assessment:

In general, FDA agrees with the Applicant's conclusions. However, the Applicant uses terminology such as "selectively and efficiently inhibits," "superior," "clear," and "potent" to describe study results; such terms should be avoided as they are vague, subjective, and promotional. In addition to these findings, the FDA notes the following results:

M22, a unique human metabolite of mirdametinib, demonstrated considerably lower ability to reduce ERK phosphorylation in HCT-116 cells (IC_{50} values of 362 nM to 835 nM). A carboxylic acid metabolite of mirdametinib, PD-0315209, also demonstrated activity as assessed by inhibition of MEK1 phosphorylation in a cell-based assay (IC_{50} =1.3 μ M); however, activity was lower compared to mirdametinib (IC_{50} =0.59 nM).

In a mouse model of NF1 neurofibromas (*Nf1^{fl/fl};Dhh-Cre* mouse), intended to recapitulate

neurofibroma growth and histology of human neurofibromas [Jessen (2013), Jousma (2015)], oral mirdametinib at doses as low as 0.5 mg/kg/day (1.5 mg/m²) reduced tumor growth in approximately 66% to 93% of neurofibroma-bearing animals.

Secondary Pharmacology

The Applicant's position:

In a kinase selectivity assay with a select panel of 104 kinases (FR0950040003), 100 kinases were not inhibited after treatment with 1 μ M mirdametinib. The other 4 kinases showed little to no kinase activity, including human MEK1 (21% activity), human B-Raf (0% activity), human B-Raf V599E (-1% activity), and human C-Raf (0% activity). Of note, the MEK1, B-Raf, B-Raf(V599E), and C-Raf kinases are linked assays exploiting kinase cascades in which the reaction mixtures contain components of the MAPK pathway, including MEK1. Therefore, B-Raf and C-Raf inhibition is consistent with the nature of the linked assay format for on-target inhibition by a MEK inhibitor.

In addition, an in vitro safety screening assay (TW04-0016273) comprising 87 targets (receptors, enzymes, ion channels, and transporters) was conducted with 1 and 10 μ M mirdametinib. At 10 μ M, mirdametinib inhibited only 2 targets which included the L-type calcium channel (phenylalkylamine) inhibited by 54% and the peroxisome proliferator activated receptor gamma inhibited by 53%. Mirdametinib did not inhibit any targets at 1 μ M.

The screening assays covered a sufficient range of targets and did not demonstrate significant mirdametinib-mediated activity against proteins other than MEK1/2. The 1 μ M concentration of mirdametinib tested in these assays is approximately 250-fold higher than the clinically observed unbound maximum observed concentration (C_{max}; 0.0039 μ M) for mirdametinib in the MEK-NF-201 clinical study.

The FDA's Assessment:

FDA generally agrees with the Applicant's assessment, except that based on a human plasma binding of 99.7% and a C_{max} of 189 ng/mL (392 nM), the free C_{max} is 1.2 nM. Thus, the 1 μ M concentration of mirdametinib tested in secondary pharmacology assays is approximately 800-fold higher than the free C_{max}.

Safety Pharmacology

The Applicant's position:

Safety pharmacology studies with mirdametinib assessed potential cardiac effects in good laboratory practice (GLP)-compliant in vitro human ether-a-go-go-related gene (hERG) and isolated Purkinje fiber assays, in GLP-compliant neurofunctional and respiratory studies in rats, and in a GLP-compliant cardiovascular study in telemetered monkeys, as outlined in [Table 3](#).

NDA/IND Multi-disciplinary Review and Evaluation NDA 219379/219389
Mirdametinib (GOMEKLI)

Table 3: Safety Pharmacology

Organ Systems Evaluated	Species/ Strain	Method of Admin.	Doses or Concentration	No. per Group	and Noteworthy Findings	Study No.
Cardiovascular	hERG-transfected HEK293 cells	In vitro	10 and 100 μ M	NA	Mirdametinib reduced hERG current amplitude by <10% and by 39.5% at 10 and 100 μ M, respectively. The primary metabolite, PD-0315209 at 10 μ M did not affect hERG current amplitude, and at 100 μ M increased hERG current amplitude by 25.6%; the increase could be reversed upon washout. The assay positive control compound (dofetilide) blocked hERG current by 98% at 20 nM.	SWT-21-01
Cardiovascular	Isolated Canine Purkinje Fibers	In vitro	1, 10 and 100 μ M	NA	There was no meaningful effect on resting membrane potential at any dose. Mirdametinib produced a statistically significant ($p < 0.01$) reduction in action potential amplitude at 100 μ M (-4.3%) and caused a statistically significant ($p < 0.05$) reduction in V_{max} (-22.8%) at a concentration of 100 μ M; the effects were smaller at 10 μ M, while 1 μ M had no effect.	PD325901/IC/001/022
Central Nervous System	Rat/ Sprague-Dawley	Oral	30 or 100 mg/kg	M/8	No treatment-related effects were observed in grip strength, acoustic startle, catalepsy, hindlimb foot splay, analgesia, air-righting, or visual placing at 30 mg/kg. At 100 mg/kg, vertical movements and total distance covered decreased by 45% and 30%, respectively, at 24 hours postdose. The decreased locomotor activity at 100 mg/kg could not be differentiated between general toxicity and CNS effects. No CNS effects were observed at 30 mg/kg. Mirdametinib had no effect on corneal or pupillary reflexes.	745-03552

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Mirdametinib (GOMEKLI)

Organ Systems Evaluated	Species/ Strain	Method of Admin.	Doses or Concentration	and No. per Group	Noteworthy Findings	Study No.
Central Nervous System	Rat/ Sprague-Dawley	IV	30 or 150 mg/kg	M/8	No effect on observational assessments, neurofunctional and reflex parameters, or body temperature.	745-03690
Respiratory	Rat/ Sprague-Dawley	Oral gavage	10, 30, or 100 mg/kg	M/8	No effects on respiratory rate or tidal volume were observed at 10 mg/kg dose. At 30 and 100 mg/kg, respiratory rate was slightly increased, and the associated tidal volume was decreased.	745-03809
Cardiovascular	Monkey/ cynomolgus	Oral gavage	3 or 10 mg/kg	M/4	Doses of mirdametinib up to 10 mg/kg had no effect on blood pressure, body temperature, heart rate, or any of the ECG parameters, including QT interval.	745-03782

Abbreviations: Admin: administration; CNS: central nervous system; GLP: good laboratory practice; ECG: Electrocardiogram; hERG: human Ether-á-go-go Related Gene; IV: Intravenous; M: Male; NA: Not applicable; No: number

The FDA's Assessment:

FDA agrees with the results presented by the Applicant. The increased respiratory rate and decreased tidal volume noted in rats (Study# 745-03809) were up to 39% and 20%, respectively. Of note, the Applicant did not include females in the stand-alone safety pharmacology studies; however, effects on CNS, cardiovascular, and respiratory parameters were evaluated in the repeat-dose toxicology studies in rats and dogs that included both males and females. There were no effects on CNS parameters in rats at doses up to 1 mg/kg or dogs at doses up to 0.4 mg/kg after repeated dosing for up to 3 months. Mineralization of the arteries was noted in rats at 1 mg/kg in the 1-month and 3-month studies, but no cardiovascular effects were noted in dogs at doses up to 0.4 mg/kg. Though minimal to mild foamy macrophage infiltrates were noted in the lungs of rats at 1 mg/kg in the 3-month study, clinical signs of changes in respiratory parameters were not noted in rats or dogs.

5.4. ADME/PK

The Applicant's Position:

Data:

Absorption

2-Week Oral Dose Range-Finding Study of PD-0325901 in Rats (745-03478)

2-Week Oral Dose Range-Finding Study of PD-0325901 in Dogs (745-03537)

Single Dose Pharmacokinetics and Oral Bioavailability of PD-0325901 in Fasted, Male Sprague-Dawley Rats Following Intravenous or Oral Administration of PD-0325901-0000 (764-04243)

Single Dose Pharmacokinetics and Oral Bioavailability of PD-0325901 in Fasted, Male Beagle Dogs Following Intravenous or Oral Administration of PD-0325901-0000 (764-04241)

Single Dose Pharmacokinetics and Oral Bioavailability of PD-0325901 in Fasted, Cynomolgus Monkeys Following Intravenous or Oral Administration of PD-0325901-0000 (764-04242)

In dose range finding studies in rats (745-03478) and dogs (745-03537), orally administered mirdametininib was rapidly absorbed and increased in a dose proportional manner. Time of the maximum concentration (T_{max}) was reached by 1 hour in rats and ranged from 1 to 4 hours in dogs, with most animals reaching T_{max} by 2 hours on Day 14. Plasma levels were similar between males and females at all doses. PK of mirdametininib was evaluated following oral and intravenous (IV) administration to male Sprague-Dawley rats (764-04243), male and female beagle dogs (764-04241), and male cynomolgus monkeys (764-04242). The absolute bioavailability was moderate to high (29.5%, 103%, and 43.7% in the rat, dog, and monkey, respectively).

Distribution

In Vitro Evaluation of Protein Binding by Equilibrium Dialysis and Red Blood Cell Partitioning of [¹⁴C] PD-0325901 in Plasma and Red Blood Cells of Mouse, Rat, Dog, Monkey, Human and to Protein Solutions (HSA and AAG) (764-04271)

Determination of Plasma, Brain, and Cerebrospinal Fluid (CSF) Concentrations of PD-0325901 and Metabolite PD-0325209 Following Intravenous Administration in Male Sprague-Dawley Rats (19SPRWP11R1)

[¹⁴C] PD-0325901 Tissue Distribution in Male Rats Following a Single 10-mg/kg orally (PO) Dose or a Single 2-mg/kg IV Dose (764-04029)

Binding to Human Plasma Proteins Human Blood to Plasma Partitioning (19SPRWP2R1)

Plasma protein binding for [¹⁴C] mirdametinib was high (≥ 98.7%) in mouse, rat, dog, monkey, and human and did not appear to be saturated over the concentration range studied of 5 to 100 µg/mL (764-04271). In the same study, binding to human serum albumin was determined to be ≥99.7% and did not appear to be saturated over the concentration range studied, whereas binding to α1-acid glycoprotein ranged from 17.2% to 54.3% suggesting the binding was saturable. Human plasma protein binding for the PD-0315209 metabolite was also high (99.975% at 1 µg/mL) (19SPRWP2R1). Whole blood to plasma ratios were generally similar across species and did not show meaningful variability with increasing drug concentration (764-04271).

Mirdametinib is preferentially distributed to plasma. The distribution of mirdametinib and PD-0315209 into brain and CSF was evaluated in male rats following IV infusion of 1 mg/kg over 30 minutes (19SPRWP11R1). The half-life of mirdametinib in the rat brain was longer than in plasma and the brain to plasma ratio increased over time. PD-0315209 did not appear to enter the rat brain.

A whole-body autoradiography study (764-04029) showed that radioactivity derived from [¹⁴C] mirdametinib is widely distributed throughout the body with [¹⁴C] mirdametinib equivalents in most tissues lower than in blood. For all tissues, the highest measured concentrations were observed within 4 hours and 0.5 hours postdose for the oral and IV routes, respectively. Drug equivalents were not retained in pigmented tissues. Distribution of [¹⁴C] mirdametinib equivalents in brain demonstrated distinct regional localization with highest levels in striatum, hippocampus, and olfactory bulb. [¹⁴C] mirdametinib equivalents in thoracic duct was approximately equal to blood through 24 hours after dosing, suggesting that drug equivalents may be recycled via intestinal lymphatics. Following IV administration of [¹⁴C] mirdametinib to male Long Evans rats, the distribution of [¹⁴C] mirdametinib equivalents was similar to that seen after oral dose administration. Evidence of recirculation was not as distinct. In both oral- and IV-dosed animals, high [¹⁴C] mirdametinib equivalents were present in bile ducts through the 24-hour collection

time point, suggesting that biliary excretion is the main route of elimination. Renal excretion plays a minor role in elimination of mirdametininib as evidenced by low levels of [¹⁴C] mirdametininib equivalents in the bladder.

Metabolism

In Vitro Metabolism of [¹⁴C] PD-0325901 by Rat, Dog, Monkey, and Human Liver Microsomes and Hepatocytes (76404904)

Metabolic Stability in Human Liver Microsomes and Reaction Phenotyping in Recombinant Uridine diphosphate glucuronosyltransferase (UGT) Enzymes of Mirdametininib and Primary Metabolite (PD-0315209) (2009107_2009108)

Reaction Phenotyping of PD-0325901 (Mirdametininib) in Human Recombinant Carboxylesterase (CES) Enzyme Supersomes (2102065)

Urine, Bile, and Plasma Metabolic Profiling and Identification in Sprague-Dawley Rats Following a Single 3 mg/kg Oral Administration of [¹⁴C] PD-0325901 (764-05091)

Fecal and Plasma Metabolic Profiling and Identification in Beagle Dogs Following a Single 0.5 mg/kg Oral Administration of [¹⁴C] PD-0325901 (764-05213)

In vitro metabolism of mirdametininib is consistent across nonclinical species and humans. All circulating metabolites observed in human liver microsomes were also present in rat, dog, and monkey liver microsomes and hepatocytes (764-04904). [¹⁴C] mirdametininib undergoes both glucuronidation and oxidation of the parent compound. A carboxylic acid metabolite of mirdametininib (PD-0315209) was detected in microsomal incubations without the addition of NADPH as well as following preincubation with aminobenzotriazole, suggesting that this metabolite can be formed by non-CYP enzyme(s) with very little contribution by a single CYP isoform being identified in an in vitro study with recombinant enzymes. In vitro studies assessing the contribution of UGT to the metabolism of mirdametininib (showed that metabolism of mirdametininib was significant for UGT isoforms 1A6 (27.1%) and 2B7 (39.4%) (2009107_2009108). The percent contribution to metabolism of the primary metabolite was most significant for UGT isoform 1A6 (57.9%). A reaction phenotyping assay explored the contribution of CES to the metabolism of mirdametininib (2102065). Production of PD-0315209 was highest with CES1b followed by CES1c, indicating that these enzymes may contribute to the conversion of mirdametininib to the primary metabolite, PD-0315209.

Mass balance and metabolite identification studies were conducted in both rat (764-05091) and dog (764-05213). Following oral administration of 3 mg/kg to rats, [¹⁴C] mirdametininib underwent extensive metabolism via glucuronidation and oxidation. Combined parent drug and PD-0315209 accounted for approximately 80% to 90% of the total circulating radioactivity found in the rat. Beagle dogs (male and female) were

administered a single 0.5 mg/kg oral dose of [¹⁴C] mirdametinib and metabolism was primarily through oxidation to PD-0315209. Mirdametinib and PD-0315209 accounted for 97% to 100% of circulating radioactivity. The major plasma circulating drug-derived components in rat and dog consisted of mirdametinib and PD-0315209, thus the metabolism of [¹⁴C] mirdametinib was extensive and similar across species.
Excretion <i>Determination of Radiolabeled Routes of Excretion of [¹⁴C] PD-325901 in Sprague-Dawley Rat (PDMK2005-0012PR)</i> <i>Determination of Radiolabeled Mass Balance and Routes of Excretion Of [¹⁴C] PD-325901 in Beagle Dogs (PDMK2005-030PR)</i>
Excretion Routes: Following oral administration of [¹⁴C] mirdametinib to intact rats (PDMK2005-0012PR), the primary route of excretion was via the feces (≥ 82%), with approximately 11% of the radioactivity recovered in the urine. In bile-duct cannulated rats, the total recovery in the bile was 85% and 70% for males and females, respectively. In intact dogs, approximately 95% and 89% were recovered in the feces of male and female dogs, respectively, whereas the amount recovered in urine accounted for approximately 2% for both male and female dogs (PDMK2005-030PR).
Toxicokinetic data from general toxicology studies <i>A GLP 5-Day and 28-Day Range-Finding Study of PD-0325901 by Oral Gavage in CByB6F1 Hybrid Mice (20196649)</i> <i>1-Month Oral Toxicity Study of PD-325901 in Rats (745-03826)</i> <i>3-Month Oral Toxicity Study of PD-325901 in Rats (05067)</i> <i>1-Month Oral Toxicity Study of PD-325901 in Dogs (745-03833)</i> <i>3-Month Oral Toxicity Study of PD-325901 in Dogs (05039)</i>
In a 28-day study, mice were administered 10, 30, or 100 mg/kg PO mirdametinib QD (20196649). Mirdametinib maximum concentration (C_{max}) and AUC from dosing to last quantifiable concentration (AUC_{last}) for were higher in females than males on Day 1 and Day 28. T_{max} was observed within 1 hour and increases in C_{max} and AUC_{last} on Day 1 were generally greater than dose proportional. Mirdametinib exposures were similar on Day 1 and Day 28, suggesting no accumulation. Exposure to PD-0315209 was similar in both sexes, with metabolite representing 20-43% of parent exposure in males and 15-27% in females. Accumulation of PD-0315209 was not observed. AUC₀₋₂₄ for mirdametinib and PD-0315209 at the lowest observed adverse effect level (LOAEL) (10 mg/kg) and their safety margins relative to human exposure are provided in Table 4.

In a 4-week study, rats were administered 0.1, 0.3, or 1 mg/kg PO mirdametinib QD (745-03826). Mirdametinib C_{max} and area under the plasma concentration-time curve over the last 24-h dosing interval (AUC₀₋₂₄) for were similar between females and males on Day 1 and Day 22 and mirdametinib plasma AUC₀₋₂₄ increased in a dose proportional manner. Mirdametinib exposures were similar on Day 1 and Day 22, suggesting no accumulation. Exposure to PD-0315209 was greater in females than in males, with metabolite representing 27-50% of parent exposure in males and 134-174% in females. Accumulation of PD-0315209 was not observed. AUC₀₋₂₄ for mirdametinib and PD-0315209 at the no observed adverse effect level (NOAEL) (0.1 mg/kg) and their safety margins relative to human exposure are provided in [Table 4](#).

In a 13-week study, rats were administered 0.1, 0.3, or 1 mg/kg PO mirdametinib QD (05067). Mirdametinib C_{max} and AUC_{last} for were similar between females and males on Day 1 and Day 89 and mirdametinib plasma AUC₀₋₂₄ increased in a dose-related manner. T_{max} was observed within 3.25 hours for males and 1.75 hours for females. Mirdametinib exposures were similar on Day 1 and Day 89, suggesting no accumulation. Exposure to PD-0315209 was higher in females than in males. Accumulation of PD-0315209 was not observed. AUC₀₋₂₄ for mirdametinib and PD-0315209 at the NOAEL (0.1 mg/kg) and their safety margins relative to human exposure are provided in [Table 4](#).

In a 4-week study, dogs were administered 0.05, 0.1, or 0.3 mg/kg PO mirdametinib QD (745-03833). Mirdametinib C_{max} and AUC_{last} for were similar between females than males on Day 1 and Day 28 and increased in a dose-dependent manner. Exposure to PD-0315209 was similar in both sexes, with metabolite representing 23-34% of parent exposure in males and 22-35% in females. Accumulation of mirdametinib and PD-0315209 was not observed. AUC₀₋₂₄ for mirdametinib and PD-0315209 at the NOAEL (0.1 mg/kg) and their safety margins relative to human exposure are provided in [Table 4](#).

In a 13-week study, dogs were administered 0.05, 0.1, or 0.4 mg/kg PO mirdametinib QD (05039). PK at Day 90 for the high dose was not obtained due to mortality. Mirdametinib C_{max} and AUC_{last} for were similar between females than males on Day 1, Day 41 and Day 90 and increased in a dose-dependent manner. T_{max} was observed within 1.67 hours. Exposure to PD-0315209 was similar in both sexes and accumulation was not observed for mirdametinib or PD-0315209. AUC₀₋₂₄ for mirdametinib and PD-0315209 at the NOAEL (0.1 mg/kg) and their safety margins relative to human exposure are provided in [Table 4](#).

Toxicokinetic data from carcinogenicity studies

A 26-week Carcinogenicity Study of PD-0325901 by Oral Gavage in CByB6F1/Tg ras H2 Hemizygous Mice (20196651)

In a 26-week study, mice were administered 2, 5, or 15 mg/kg PO mirdametinib QD (20196651). PK at Day 180 for the high dose was not obtained due to early termination of

the group. Mirdametinib C_{max} and AUC_{last} were higher in females than males on Day 1 and Day 180. T_{max} was observed within 1 hour and increases in C_{max} and AUC_{last} were slightly less than dose proportional. Mirdametinib exposures were similar on Day 1 and Day 180, suggesting minimal or no accumulation. Exposure to PD-0315209 was generally greater in females than in males. Overall, AUC_{last} for PD-0315209 was 12.4-32.1% of what was observed for mirdametinib. Accumulation of PD-0315209 was not observed. AUC₀₋₂₄ for mirdametinib and PD-0315209 at the maximum tolerated dose (MTD) (5 mg/kg) and their safety margins relative to human exposure are provided in [Table 4](#).

Toxicokinetic data from reproductive toxicology studies

Oral Dose Range-Finding Study of PD 0325901 in Pregnant Rabbits (2005-0052)

In an embryo-fetal toxicity study, pregnant female rabbits were administered 0.3, 1, 3, or 6 mg/kg PO mirdametinib QD during gestation days 7 through 19 (2005-0052). PK at the 3 and 6 mg/kg dose levels were not obtained due severe toxicity. Mirdametinib exposure increased in a generally dose proportional manner. T_{max} was observed within 2.7 hours. The metabolite (PD-0315209) to parent ratio was 0.8 and 0.6 at the 0.3 and 1 mg/kg dose levels, respectively. AUC₀₋₂₄ for mirdametinib and PD-0315209 at the LOAEL (0.3 mg/kg) and their safety margins relative to human exposure are provided in [Table 4](#).

Table 4: Calculated Safety Margins from Definitive Repeat-Dose Toxicity Studies

Study	Mirdametinib Dose (mg/kg/day)	Mirdametinib AUC0-24 (ng·h/mL) ^a	Margin for Mirdametinib ^b	PD-0315209 AUC0-24 (ng·h/mL) ^a	Margin for PD-0315209 ^c
Repeat-dose general toxicity studies					
1-Month mouse	10 (LOAEL)	13,250	7.1	3680	2.7
1-Month rat	0.1 (NOAEL)	213	0.11	182	0.13
3-Month rat	0.1 (LOAEL)	342	0.18	380	0.27
1-Month dog	0.1 (NOAEL)	655	0.35	218	0.16
3-Month dog	0.1 (NOAEL)	633	0.34	213	0.16
Carcinogenicity					
6-Month mouse	5 (MTD)	6720	3.6	1105	0.81
Developmental and reproductive toxicity					
Rat fertility ^d	1 (NOAEL)	2440	1.3	2315	1.7
Rat EFD ^d	0.3 (LOAEL)	769	0.41	824	0.60
Rabbit EFD	0.3 (LOAEL)	763	0.41	621	0.46

Abbreviations: AUC0-24: area under the plasma concentration-time curve from 0 to 24 hours; BID: twice daily; EFD: embryo-fetal development; LOAEL: lowest-observed-adverse-effect level; MTD: maximum tolerated dose, NOAEL: no -observed-adverse-effect level; popPK: population pharmacokinetic; TK: toxicokinetics.

^a The AUC values are an average of the reported male and female values at the end of the dosing period.

^b The PopPK report presents a mean steady-state AUC0-24 of 1862 ng·h/mL at 2 mg/m² bid with a maximum of 4 mg BID for mirdametinib.

^c The PopPK report presents a mean steady-state AUC0-24 of 1362 ng·h/mL for metabolite PD-0315209 when administered mirdametinib at 2 mg/m² BD with maximum of 4 mg BID.

^d TKs were not assessed in this study; therefore, the exposure was derived from the 1-month rat study.

Mirdametinib is rapidly absorbed, with T_{max} typically being observed within 1 to 2 hours of oral administration. Exposure increases with dose in a generally dose proportional manner and minimal accumulation is observed following repeat dosing for either mirdametinib or its primary metabolite, PD-0315209. Absolute bioavailability of mirdametinib ranged from moderate (rat and monkey) to high (dog). Mirdametinib showed high protein binding in all evaluated species and was also found to be widely distributed into tissues, including exposure in the brain. Mirdametinib is extensively metabolized and primarily undergoes glucuronidation and oxidation of the parent compound. UGT1A6 and UGT2B7 are heavily involved in the metabolism of mirdametinib and its most abundant metabolite, PD-0315209, is produced by carboxylesterase variants CES1b and CES1c. The majority of the drug was excreted in the feces

as metabolites, with only small amounts of unchanged mirdametinib found in urine or feces.

The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment of the nonclinical ADME/PK data. FDA notes that following a single oral dose of 10 mg/kg, [¹⁴C]-mirdametinib-derived radioactivity distributed widely to rat tissues, with greatest uptake in the liver, followed by kidney, blood, adrenal, lung, salivary gland, heart, and pancreas.

Because the FDA calculated animal to human exposures based on their own analysis of nonclinical and clinical PK data, the FDA did not verify the results presented by the Applicant for Table 4 titled Calculated Safety Margins from Definitive Repeat-Dose Toxicity Studies.

Toxicokinetics (TK)

Exposure to mirdametinib and its metabolite, PD-315209, were measured in repeat-dose toxicology studies in mice, rats, and dogs. The tables below show sex combined TK values used for FDA's analyses.

Table 5 TK Parameters in the 28-Day Repeat-Dose Study in Mice

Mirdametinib			
Day	Dose (mg/kg)	C _{max} (ng/mL)	AUC ₀₋₂₄ (ng·h/mL)
1	10	2535	67645
	30	9155	39800
	100	63450	216000
28	10	2155	13250
	30	8190	33450
Metabolite PD-315209			
Day	Dose (mg/kg)	C _{max} (ng/mL)	AUC ₀₋₂₄ (ng·h/mL)
1	10	333	3325
	30	1100	11565
	100	4145	39050
28*	10	436	3680
	30	963	9765

*Day 28 data not available for 100 mg/kg animals due to early deaths; H = hours

Table 6 TK Parameters in the 1-Month Repeat-Dose Study in Rats

Mirdametinib				
Day	Dose (mg/kg)	C _{max} (ng/mL)	AUC ₀₋₂₄ (ng·h/mL)	T _{max} (h)

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1	0.1	22.6	181	1
	0.3	81.15	609.5	1
	1	552	2510	1
Week 4	0.1	26.9	213	1
	0.3	106	769	1
	1	372	2440	1
Metabolite PD-315209				
Day	Dose (mg/kg)	C_{max} (ng/mL)	AUC₀₋₂₄ (ng·h/mL)	T_{max} (h)
1	0.1	14.37	143.6	3
	0.3	43.3	626	1.5
	1	207.85	2309	3
Week 4	0.1	16.595	183	1.5
	0.3	66.95	823.5	1.5
	1	232.05	2315	3

H = hours

Table 7 TK Parameters in the 1-Month Repeat-Dose Study in Dogs

Mirdametinib				
Day	Dose (mg/kg)	C_{max} (ng/mL)	AUC₀₋₂₄ (ng·h/mL)	T_{max} (h)
1	0.05	25.3	187.5	1
	0.1	59.25	455	1.125
	0.3	361.5	1650	1
28	0.05	30.3	215	1.125
	0.1	116.85	655	1
	0.3	396	1495	1.125
Metabolite PD 315209				
Day	Dose (mg/kg)	C_{max} (ng/mL)	AUC₀₋₂₄ (ng·h/mL)	T_{max} (h)
1	0.05	2.585	24.2	7.9
	0.1	8.19	141.5	8.5
	0.3	31	463	4.25
28	0.05	4.31	57.5	2.75
	0.1	14.4	217.5	2.875
	0.3	28.95	348.5	2.5

H= hours

Table 8 TK Parameters in the 3-Month Repeat-Dose Study in Rats

Mirdametinib

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Mirdametinib (GOMEKLI)

Day	Dose (mg/kg)	C _{max} (ng/mL)	AUC ₀₋₂₄ (ng·h/mL)	T _{max} (h)
1	0.1	24.55	230.5	2.125
	0.3	90.3	720	1.75
	1	469.5	3485	2.5
89	0.1	43.65	342	1.25
	0.3	161.5	1084	1.375
	1	599.5	3415	1.125
Metabolite PD 315209				
Day	Dose (mg/kg)	C _{max} (ng/mL)	AUC ₀₋₂₄ (ng·h/mL)	T _{max} (h)
1	0.1	20.29	244.35	3.75
	0.3	53.5	572	2.75
	1	252.05	3181	4.125
89	0.1	26.7	380	3.25
	0.3	76.15	893	2.875
	1	394.5	4230	2.625

H= hours

Table 9 TK Parameters in the 3-Month Repeat-Dose Study in Dogs

Mirdametinib				
Day	Dose (mg/kg)	C _{max} (ng/mL)	AUC ₀₋₂₄ (ng·h/mL)	T _{max} (h)
1	0.05	36.6	264	1.165
	0.1	61.8	378.5	1
	0.4	378.5	1885	1.5
41	0.05	39	283	1
	0.1	100.15	571.5	1
	0.4	520	2575	1.165
90*	0.05	55.85	360	1
	0.1	115.5	633	1.165
Metabolite PD 315209				
Day	Dose (mg/kg)	C _{max} (ng/mL)	AUC ₀₋₂₄ (ng·h/mL)	T _{max} (h)
1	0.05	4.775	70.45	2.67
	0.1	8.73	138	3.67
	0.4	37.45	495	3.335
41	0.05	6.78	105	1.835
	0.1	15.4	201	2.17
	0.4	50.6	675.5	4.335
90*	0.05	7.815	107.65	1.835
	0.1	16.1	213	2

*Day 90 data not available for 0.4 mg/kg animals due to early deaths and stopping of dosing; H = hours

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:

Mirdametininib was assessed in a series of nonclinical toxicology studies in alignment with applicable International Conference on Harmonization (ICH) guidance documents. The oral route of exposure was selected for these studies as the oral route is the intended clinical route of administration. The rat and dog were selected as the general toxicology species based on mirdametininib PK and metabolism properties compared across species. The definitive studies were performed in the US in accordance with the US Department of Health and Human Services, FDA, US Code of Federal Regulations, Title 21, Part 58: GLP for Nonclinical Laboratory Studies.

Exploratory studies were conducted in mice, rats, dogs, and monkeys, while definitive toxicity studies were conducted in rats and dogs. Studies were based on daily oral (gavage) dosing with a limited number of studies involving IV administration. Mirdametininib was administered to rats and dogs in repeat-dose general toxicology studies up to 3 months. The 1-month studies in rats and dogs were followed by a 1-month recovery period. A 1-month mouse study was conducted to support a 6-month carcinogenicity study in transgenic mice. A 2-year rat carcinogenicity study will be conducted as a postmarketing commitment. Preliminary embryo-fetal development (EFD) toxicity studies were conducted in rats and rabbits, and a definitive fertility study was conducted in male and female rats. Juvenile animal studies were not conducted.

Table 10: 5- and 28-Day Mouse Study

Test Article: Mirdametininib (PD-0325901) Study Number: 20196649 Study Title: A GLP 5-day and 28-day Range-Finding Study of PD-0325901 by Oral Gavage in CByB6F1 Hybrid Mice eCTD Location: 4.2.3.2 Key Drug-related Adverse Findings: • Mortality at 100 mg/kg/day. • Target organ effects were noted in bone marrow, the large intestine (cecum, colon, rectum), liver, and stomach. • Microscopic changes were also noted in the adrenals, pancreas, testes, thymus, and mesenteric lymph nodes. • The NOAEL was not established. The LOAEL was 10 mg/kg/day. GLP compliance: Yes	
Dose and frequency of dosing:	0, 10, 30, and 100 mg/kg/day given once daily for 28 days

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Route of administration:	oral gavage							
Formulation/Vehicle:	(b) (4) cellulose (b) (4) in Ultra Pure Water							
Species/Strain:	Mouse/CByB6F1 Hybrid							
Number/Sex/Group:	10 male and 10 female in main study, 36 male and 36 female in TK treatment groups, 6 males and 6 female TK control group							
Age:	8 weeks							
Satellite groups:	Toxicokinetic group							
Toxicokinetics								
Daily Dose (mg/kg)	0 (Control)		10		30		100	
Number of TK Animals	M:6	F:6	M:36	F:36	M:36	F:36	M:36	F:36
PD-0325901 – Day 28								
C _{max} (ng/mL)	NA	NA	2000	2310	6410	9970	NE ^a	NE ^a
AUC _(tlast) (ng*hr/mL)	NA	NA	10200	16300	26900	40000	NE ^a	NE ^a
PD-0315209- Day 28								
C _{max} (ng/mL)	NA	NA	371	501	977	949	NE ^a	NE ^a
AUC _(tlast) (ng*hr/mL)	NA	NA	3060	4300	8830	10700	NE ^a	NE ^a
Findings								
Died or Sacrificed Moribund	Mortality was observed at 100 mg/kg/day beginning on Day 5, with all main phase and TK animals found dead, euthanized moribund, or subjected to unscheduled euthanasia by the end of Day 7.							
Body Weight and Food Consumption	Body weight gain was increased in male rats at 10 and 30 mg/kg/day and increased in female rats at 10 mg/kg/day compared to controls. Mean body weight gain and Day 28 body weights were similar in females at the 30 mg/kg/day dose. Differences in food consumption were inconsistent. Due to early death or euthanasia, the 100 mg/kg/day mice were only weighed on Day 4.							
No Noteworthy Findings	Gross findings							
Clinical Observations	Dehydration, abnormal respiratory rate, hunched posture, closed eyes, cold to the touch, and decreased activity in the 100 mg/kg/day dose group. There were no mirdametininib related clinical observations in the 10 and 30 mg/kg/day groups.							
Hematology	Increases in neutrophils and large unstained cells in males and females and increases in monocytes in males at 10 and 30 mg/kg/day. Minimal to mild decreases in red cell mass, hemoglobin, and hematocrit, coupled with increases in mean corpuscular volume, red cell distribution width, platelets and reticulocytes at 30 mg/kg/day in males and females.							
Clinical Chemistry	Non-adverse increases in ASP, ALT, ALP, globulin at 10 and 30 mg/kg/day males and females. Decreases in albumin in females at 30/mg/kg/day and non-adverse decreases in the albumin/globulin ratio in males and females at 10 and 30 mg/kg/day							
Organ Weight	Increased thyroid gland weights in males and females at 30 mg/kg/day, increased spleen weights in males and females at 30 mg/kg/day, decreased ovary weights at 10 and 30 mg/kg/day, and increased uterus weights at 10 and 30 mg/kg/day.							

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Histopathology	- Decreased cellularity or necrosis of the bone marrow in males at 100 mg/kg/day - Adrenal cortical degeneration/necrosis in males at 100 mg/kg/day or females at ≥ 30 mg/kg/day - Epithelial degeneration/necrosis or erosion/ulceration throughout the gastrointestinal tract in males and females at ≥ 30 mg/kg/day - Inflammatory cell infiltrates throughout the GI tract in males and females at ≥ 10 mg/kg/day - Hepatocellular necrosis in males at ≥ 30 mg/kg/day and females at ≥ 10 mg/kg/day - Pancreatic secretory depletion in males and females at 100 mg/kg/day - Testicular degeneration/necrosis at ≥ 10 mg/kg/day - Decreased lymphoid cellularity of the thymus (males at 100 mg/kg/day and females at ≥ 30 mg/kg/day) and/or mesenteric lymph node (males and females at 100 mg/kg/day)
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Abbreviations: AUC: area under the curve; Cmax: maximum plasma concentration; eCTD: electronic Common Technical Document; F: female; M: male; GLP: Good Laboratory Practice; NOAEL: no observed adverse effect level; LOAEL: lowest observed adverse effect level; NA: not applicable; NE: not evaluated.

^a PD-0325901 related mortality was observed at 100 mg/kg/day beginning on Day 5, with all main phase and toxicokinetic animals found dead, euthanized moribund, or subjected to unscheduled euthanasia by the end of Day 7.

Table 11: 1 Month Rat Study

Test Article: Mirdametinib (PD-0325901) Study Number: 745-03826 Study Title: 1-Month Oral Toxicity Study of PD-325901 in Rats eCTD Location: 4.2.3.2 Key Drug-related Adverse Findings: - Target organ effects were systemic mineralization, skin sores, and localized bone injury. - Microscopic changes consisted of systemic mineralization in the stomach, kidney, and major blood vessels, along with alterations in skin, bone, and bone marrow. - Most changes were reversible during the recovery period with the exception of systemic mineralization. - The NOAEL was 0.1 mg/kg/day for males and 0.3 mg/kg/day in females	
GLP compliance: Yes	
Dose and frequency of dosing:	0, 0.1, 0.3, 1mg/kg/day given once daily for 4 weeks followed by a 4-week recovery period
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4) cellulose/0.2% Tween 80 at 2 mL/kg
Species/Strain:	Rat/Sprague-Dawley
Number/Sex/Group:	10/sex/dose in the main group, 6/sex/dose in the TK group, 5/sex/dose in the recovery group
Age:	7-8 weeks
Satellite groups:	Toxicokinetic group
Toxicokinetics	

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Daily Dose (mg/kg)	0 (Control)		0.1		0.3		1	
Number of TK Animals	M:6	F:6	M:6	F:6	M:6	F:6	M:6	F:6
PD-0325901 – Week 4								
C _{max} (ng/mL)	NA	NA	23.3	30.5	105	107	310	434
AUC ₀₋₂₄ (ng•h/mL)	NA	NA	231	195	733	805	2820	2060
PD-0315209- Wee 4								
C _{max} (ng/mL)	NA	NA	8.29	24.9	24.9	109	37.1	367
AUC ₀₋₂₄ (ng•h/mL)	NA	NA	102	261	247	1400	1400	3230
Findings								
Died or Sacrificed Moribund	Due to gavage error, one female each at 0.1 and 1 mg/kg/day were sacrificed moribund on Days 12 and 9, respectively.							
No Noteworthy Findings	Compound related mortality, body weight and food consumption, organ weight							
Clinical Observations	Skin sores occurred in a dose dependent fashion at ≥ 0.1 mg/kg/day. Lesions were first observed on Day 8 and were present throughout the body. Alopecia was associated with skin sores in 1 male each at 0.1 and 1 mg/kg/day, and in 1 female at 0.3 mg/kg/day. The following clinical signs occurred sporadically at all doses: reduced feces, red staining of muzzle and hair coat, dermatopathy, and chromodacryorrhea.							
Hematology	Increase in WBCs at 1 mg/kg/day, due to increased neutrophils and monocytes and consistent with an inflammatory response related to the skin sores. Increase in megakaryocytes in 1 mg/kg females.							
Clinical Chemistry	Dose dependent increases in phosphorous and decreases in albumin at ≥ 0.1 mg/kg/day in males. Increases in phosphorous and decreases in albumin at ≥ 0.3 mg/kg/day were observed in females. Minor increases in serum calcium were observed in both sexes at ≥ 0.3 mg/kg/day on Day 2 and in males at 1 mg/kg/day on Day 8. Plasma PTH decreased in males at 0.3 and 1 mg/kg/day and in females at 1 mg/kg/day. Serum osteocalcin decreased in both sexes at ≥ 0.1 mg/kg/day. Terminal urine phosphorus levels were increased in males at 1 mg/kg/day. Increases in urine calcium were observed at 0.3 and 1 mg/kg/day in females.							
Histopathology	- Mineralization of gastric fundic mucosa was present in 1 male at 0.3 mg/kg, and in all males and 1 female at 1 mg/kg/day. - Mineralization of the tunica media of the aorta, pulmonary artery, mesenteric artery, and/or renal arteries/tubules was present in up to 4 males at 1 mg/kg/day, whereas mineralization of the pulmonary artery was observed in 1 female at 1 mg/kg/day. - Locally extensive hypocellularity of the metaphyseal region (bone and bone marrow) of distal femur and/or proximal tibia was present in males at 1 mg/kg/day. - Sternal bone marrow myeloid hypercellularity was present in both sexes at 1 mg/kg.							

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Recovery	Toxicity was reversible except for mineralization. Although systemic mineralization was not reversible, this toxicity resulted in minimal effects on the clinical condition of the animals. Systemic mineralization likely arose due to increases in serum phosphorus and calcium.
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Abbreviations: AUC: area under the curve; Cmax: maximum plasma concentration; eCTD: electronic Common Technical Document; F: female; M: male; NOAEL: no observed adverse effect level; GLP: Good Laboratory Practice; NA: not applicable.; WBC: white blood cells

Table 12: 3-Month Rat Study

Test Article: Mirdametininb (PD-0325901) Study Number: 05067 Study Title: 3-Month Oral Toxicity Study of PD-325901 in Rats eCTD Location: 4.2.3.2 Key Drug-related Adverse Findings: - Target organ effects were systemic mineralization, corneal opacities, skin ulcers or crusts, changes in female reproductive tract, dysplasia in epiphyseal growth plate, thickening of bone trabeculae and metaphyseal hypocellularity of the bone marrow. - Males were more sensitive than females despite similar exposure to mirdametininb. - Systemic mineralization characterized by mineralization of various soft tissues (stomach, renal cortex, heart) and arteries at ≥ 0.3 mg/kg/day, notably more pronounced in males and accompanied by elevated phosphorus (hyperphosphatemia) and decreased albumin with unchanged calcium values. - A NOAEL was not defined. The LOAEL is 0.1 mg/kg/day.								
GLP compliance: Yes								
Dose and frequency of dosing:	0, 0.1, 0.3, or 1 mg/kg/day given once daily for 12 weeks							
Route of administration:	Oral gavage							
Formulation/Vehicle:	(b) (4) cellulose/0.2% Tween 80 at 2 mL/kg							
Species/Strain:	Rat/Sprague-Dawley							
Number/Sex/Group:	10/sex/dose in the main group, 4/sex/dose in the TK group							
Age:	7 weeks							
Satellite groups:	Toxicokinetic group							
Daily Dose (mg/kg)	0 (Control)		0.1		0.3		1	
Number of TK Animals	M:4	F:4	M:4	F:4	M:4	F:4	M:4	F:4
Toxicokinetics								
PD-0325901 – Day 89								
Cmax (ng/mL)	NA	NA	42.5	44.8	126	197	468	731
AUC0-24 (ng•h/mL)	NA	NA	382	302	1190	978	3860	2970
PD-0315209- Day 89								
Cmax (ng/mL)	NA	NA	10.5	42.9	26.3	126	114	675
AUC0-24 (ng•h/mL)	NA	NA	151	609	366	1420	1430	7030
Findings								
Died or Sacrificed Moribund	There were no unscheduled deaths or morbidity.							
Ophthalmology	Focal corneal opacities at all dose levels, mainly in males							

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No Noteworthy Findings	Body weight and food consumption
Clinical Observations	Pinpoint skin lesions at 1 mg/kg/day.
Hematology	Slight decreases in RBC count, hemoglobin and hematocrit occurred in males at ≥ 0.3 mg/kg/day and in females at 1 mg/kg/day, and changes in WBC parameters in both sexes at ≥ 0.3 mg/kg/day.
Clinical Chemistry	Increases in globulin in both sexes at 1 mg/kg/day, and slight increases in urea and creatinine (males only) at ≥ 0.3 mg/kg/day. Elevated phosphorus (hyperphosphatemia) and decreased albumin
Organ Weight	Decreased ovarian weights
Histopathology	- Focal corneal opacities observed during ophthalmologic exams correlated with histopathologic focal minimal mineralization in the basement membrane of the corneal epithelium in only 2/10 males at 1 mg/kg/day. Atrophy or thinning of the corneal epithelium was noted in rats from 0.3 mg/kg/day. - Epidermal ulcers and crusts were evident microscopically at 1 mg/kg/day and correlated with macroscopic wounds/scars/scabs. - There was an increased proportion of females staged in diestrus (9/10 females) at 1 mg/kg/day and the ovaries of several females (6/10) had increased numbers of follicular cysts associated with a reduction in the number of corpora lutea. This correlated with decreased ovarian weights. - Bone effects comprised dysplasia in femoral epiphyseal growth plate and metaphyseal hypocellularity of the bone marrow of long bones from 0.3 mg/kg/day, and metaphyseal thickening of bone trabeculae of long bones at 1 mg/kg/day. - Systemic mineralization characterized by mineralization of various soft tissues (stomach, renal cortex, heart) and arteries was observed from 0.3 mg/kg/day. - Minimal mineralization of the renal medulla occurred at ≥ 0.1 mg/kg/day.

Abbreviations: AUC: area under the curve; Cmax: maximum plasma concentration; eCTD: electronic Common Technical Document; F: female; GLP: Good Laboratory Practice; M: male; NOAEL: no observed adverse effect level; LOAEL: lowest observed adverse effect level; NA: not applicable; RBC: red blood cells.

Table 13: 1-Month Dog Study

Test Article: Mirdametininib (PD-0325901) Study Number: 745-03833 Study Title: 1-Month Oral Toxicity Study of PD 325901 in Dogs eCTD Location: 4.2.3.2 Key Drug-related Adverse Findings: - The skin was the primary target for toxicity. - The NOAEL was 0.1 mg/kg/day GLP compliance: Yes	
Dose and frequency of dosing:	0, 0.05, 0.1, 0.3 mg/kg/day once daily for 4 weeks followed by a 4-week recovery
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4) cellulose/0.2% Tween 80 at 1 mL/kg
Species/Strain:	Dog/Beagle

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Number/Sex/Group:		3/sex/dose in the Main group, 1/sex/dose in the recovery group						
Age:		19-21 months						
Satellite groups:		None						
Daily Dose (mg/kg)	0 (Control)		0.05		0.1		0.3	
Number of Animals	M:4	F:4	M:4	F:4	M:4	F:4	M:4	F:4
Toxicokinetics								
PD-0325901 – Day 28								
C _{max} (ng/mL)	NA	NA	28.3	32.3	95.7	138	446	346
AUC ₀₋₂₄ (ng•h/mL)	NA	NA	208	222	567	743	1550	1440
PD-0315209- Day 28								
C _{max} (ng/mL)	NA	NA	3.40	5.22	11.6	17.2	32.2	25.7
AUC ₀₋₂₄ (ng•h/mL)	NA	NA	47.5	67.5	174	261	374	323
Findings								
Died or Sacrificed Moribund	None							
No Noteworthy Findings	Ophthalmology, blood pressure, electrocardiographic parameters, food consumption, body weight, organ weights, urinalysis							
Clinical Observations	Skin sores were observed on Days 28 and 29 in 1 male (midline dorsal) and 1 female (head) at 0.3 mg/kg. Hypoactivity was seen periodically during the dosing period in 3 males and 2 females at 0.3 mg/kg.							
Hematology	Minimal hematology changes including decreases in red blood cells, hemoglobin, and hematocrit in Week 4 were seen in males at ≥0.1 mg/kg. These parameters were also in females at 0.3 mg/kg. Absolute reticulocytes were decreased in males at ≥0.1 mg/kg. Fibrinogen was increased in males at ≥0.1 mg/kg and in females at 0.3 mg/kg. Changes in hematology and coagulation parameters were reversible by Week 9.							
Clinical Chemistry	Clinical chemistry changes included increases in serum phosphorus in males and females at all dose levels; the changes in phosphorus were reversible and not considered toxicologically significant because systemic mineralization did not occur. Albumin was decreased and 1,25-dihydroxyvitamin D was increased in a dose-dependent fashion.							
pMAPK/pERK	Inhibition of pMAPK/pERK was observed in colon and lung in a dose-dependent manner.							
Histopathology	One male at 0.3 mg/kg had a skin lesion consisting of a focal epidermal ulcer with neutrophilic inflammation and surface crusts containing bacterial colonies, which correlated with a focal skin sore observed grossly (midline dorsal).							
Recovery	No findings after the recovery period.							

Abbreviations: AUC: area under the curve; C_{max}: maximum plasma concentration; eCTD: electronic Common Technical Document; F: female; GLP: Good Laboratory Practice; M: male; NA: not applicable; NOAEL: no observed adverse effect level; pERK:phospho-extracellular signal-regulated kinase; pMAPK: phospho-mitogen-activated protein kinase.

Table 14: 3-Month Dog Study

Test Article: Mirdametinib (PD-0325901) Study Number: 05039 Study Title: 3-Month Oral Toxicity Study of PD 325901 in Dogs eCTD Location: 4.2.3.2 Key Drug-related Adverse Findings: • Mortality occurred at 0.4 mg/kg/day. • Target organ was mucosa of the tongue and esophagus at 0.4 mg/kg/day. • The NOAEL was 0.1 mg/kg/day. GLP compliance: Yes								
Dose and frequency of dosing:			0, 0.05, 0.1, or 0.4 mg/kg/day given once daily for 12 weeks					
Route of administration:			Oral gavage					
Formulation/Vehicle:			(b) (4) cellulose/0.2% Tween 80 at 2 mL/kg					
Species/Strain:			Dog/Beagle					
Number/Sex/Group:			3/sex/dose group					
Age:			9 months					
Satellite groups:			N/A					
Daily Dose (mg/kg)	0 (Control)		0.05		0.1		0.4 ^a	
Number of Animals	M:3	F:3	M:3	F:3	M:3	F:3	M:3	F:3
Toxicokinetics								
PD-0325901 – Day 90								
Cmax (ng/mL)	NA	NA	53.6	58.1	115	116	NA ^a	NA ^a
AUC0-24 (ng•h/mL)	NA	NA	359	361	632	634	NA ^a	NA ^a
PD-0315209- Day 90								
Cmax (ng/mL)	NA	NA	7.07	8.56	14.2	18.0	NA ^a	NA ^a
AUC0-24 (ng•h/mL)	NA	NA	96.3	119	200	226	NA ^a	NA ^a
Findings								
Died or Sacrificed Moribund	At 0.4 mg/kg/day, 2 males and 2 females were euthanized between Days 33 and 50 due to their moribund status. Treatment for the remaining male was suspended on Day 51 and for the female on Day 57 until the end of the study							
No Noteworthy Findings	Urinalysis, organ weights, ophthalmology, electrocardiograms							
Clinical Observations	At 0.4 mg/kg/day clinical signs included decreased activity, tremors, titubation/impaired balance, arched back with rigid extended limbs, stiff neck and low head resulting in prostration, low food consumption, diarrhea, emesis, and soft stool. Additional clinical signs at 0.4 mg/kg/day were splashed coloration of the tongue surface and buccal mucosa.							

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Hematology	A moderate increase in leucocytes, fibrinogen and globulin combined with a decrease in albumin were suggestive of an inflammatory process and were correlated with macroscopic findings and microscopic findings of minimal multifocal neutrophilic inflammation of the mucosa of the tongue and esophagus in the 0.4 mg/kg/day group. Decrease in reticulocytes, erythrocytes and RBC counts at 0.4 mg/kg/day.
Clinical Chemistry	Moderate increase in globulin and a decrease in albumin at 0.4 mg/kg/day.
Microscopic Observations	- Minimal multifocal neutrophilic inflammation of the mucosa of the tongue and esophagus at 0.4 mg/kg/day. - Decrease in erythroid elements in bone marrow at 0.4 mg/kg/day.

Abbreviations: AUC: area under the curve; Cmax: maximum plasma concentration; eCTD: electronic Common Technical Document; F: female; GLP: Good Laboratory Practice; M: male; NA: not applicable; NOAEL: no observed adverse effect level.; RBC: red blood cells

^a Two males and 2 females at the 0.4 mg/kg/day dose were euthanized between Days 33 and 50 due to moribund health status that included adverse clinical signs (decreased activity, tremor, titubation/impaired balance, low head resulting in prostration, decreased food consumption, diarrhea, emesis and soft stool). Treatment was suspended for the remaining high dose male on Day 51 and the high dose female on Day 57 until the end of the study.

The primary mirdametinib toxicities in exploratory and definitive nonclinical studies were to the gastrointestinal tract, skin, cornea, liver, bone, and systemic mineralization. Many of these target organ effects can be attributed to the pharmacological mechanism of mirdametinib. Intestinal toxicity was present in rats, dogs, monkeys, and rabbits. In dogs and monkeys, erosions or ulcerations of the intestinal mucosa, or both, was dose limiting. These effects are related to the requirement of the MEK pathway on normal intestinal function; MEK inhibition manifests in ulcerations in intestinal mucosa in dogs and monkeys and translates to intestinal toxicities in humans treated with MEK inhibitors (Mourad 2019). Skin lesions, characterized microscopically as epidermal ulceration, were observed in rats in the 1- and 3-month studies. Similar skin lesions were observed in the 1-month dog study, and in an exploratory 14-day monkey study. These skin effects are expected based on the role of MEK on skin keratinocyte survival (Jost 2001) and is a class effect with skin lesions noted in all approved MEK inhibitors.

Mirdametinib caused several toxicities that were specific to the rat. For example, in the 3-month rat study, corneal opacities were detected mainly in males with the incidence being dose dependent. The fact that corneal opacities were detected almost exclusively in male rats in the 3-month study suggests that tissue mineral deposition was the likely cause. Despite inhibition of pERK in the repeat dose dog studies, corneal opacities were not observed. Mineralization of vasculature and various soft tissues (systemic mineralization) was observed in toxicology studies in rats in a time- and dose-dependent manner. However, these effects were not seen in the dog or monkey. The stomach appears to be the most sensitive tissue since mineralization of gastric fundic mucosa occurs prior to the onset of mineralization in other tissues. Male rats were consistently more sensitive to this toxicity compared to female rats and the effect was reversible. Administration of mirdametinib to rats resulted in bone lesions that

included necrosis of the metaphysis and the ossifying zone of the physis and thickening of the zone of hypertrophying cartilage of the physis. These changes were characterized by localized injury to bone that appear to be due to local ischemia and/or necrosis. In the 1- and 3-month rat studies, hypocellularity in the metaphyseal region of the distal portion of the femur and/or proximal portion of the tibia occurred in males and was reversible following cessation of dosing in the 1-month study. In addition, thickening of the bony trabeculae in the femoral/tibial metaphyseal region was evident in males in the 3-month study. Bone lesions, like those observed in rats, have not been seen in mice, dogs, or monkeys administered mirdametininib.

Safety margins are presented in [Table 4](#).

The FDA's Assessment:

FDA's assessment is limited to repeat-dose general toxicology studies, and other studies, such as carcinogenicity and embryo-fetal development, are discussed in the appropriate sections. FDA did not verify the monkey findings discussed by the Applicant because this study had limited number of animals and was non-GLP.

Studies # 20196649, 745-03826, 05067, 745-03833, and 05039 were previously reviewed by FDA under IND 139883. In general, FDA agrees with most of the Applicant's assessment of the results of the GLP-compliant toxicity studies in rats and dogs. FDA notes that Study# 05039 in dogs was 13-weeks in duration. The following summarizes FDA's perspective of repeat-dose studies results and indicates additional findings or differences of interpretation of results from the Applicant, where appropriate.

Common clinical signs in early death dogs at 0.4 mg/kg in the 3-month study included diarrhea, emesis, and soft stools that correlated with decreased food consumption and body weight loss; clinical signs of emesis, abnormal stools were also noted at doses ≥ 0.1 mg/kg in the 3-month dog study. Additionally, neutrophilic infiltrates/inflammation in the tongue, stomach, and/or esophagus, as well as lymphoid depletion in multiple lymphoid organs and myeloid cell hyperplasia in the bone marrow were noted in early death dogs, suggesting a systemic inflammatory response.

Skin sores were noted in rats at ≥ 0.1 mg/kg in the 3-month study and at 1 mg/kg in the 1-month study and correlated with histologic signs of minimal to mild neutrophilic inflammation, crust, and/or ulceration of the epidermis. In the 1-month study in dogs, microscopic findings of minimal to mild ulceration or necrosis of the epidermis were noted in individual animals at ≥ 0.1 mg/kg and correlated with clinical signs of skin sores at 0.3 mg/kg. Additionally, skin redness occurred at ≥ 0.1 mg/kg in the 3-month dog study but lacked any histologic correlate. These findings trended toward improvement during the recovery phase in the 1-month studies. Recovery periods were not included in the 3-month studies.

Hematologic changes included decreases in red blood cell parameters, including red blood cells, hemoglobin, and hematocrit, in the 3-month rat study at doses ≥ 0.1 mg/kg and in the 1- and 3-month dog studies at doses ≥ 0.05 mg/kg. Increases in circulating monocytes, neutrophils, and/or large unstained cells were noted in the 1- and 3-month studies in rats at ≥ 0.3 mg/kg and dogs at ≥ 0.05 mg/kg. These findings correlated with histologic signs in the lymph nodes in the 3-month studies in rats and dogs, including minimal to moderate lymphoid hyperplasia, lymphoid depletion, and increases in plasma cells, as well as hypocellularity in the 3-month rat study.

In addition to the mineralization findings described above by the Applicant, mineralization of the renal corticomedullary junction was noted in female rats at ≥ 0.3 mg/kg in the 1-month study and mineralization of the medulla and/or corticomedullary junction in the kidney was observed in both sexes at all doses in the 3-month study. Signs of mineralization were not noted in dogs; however, mirdametinib increased phosphorus levels at all doses tested in rats (up to 37% compared to controls) and dogs (up to 49% compared to controls) in the 1-month and 3-month studies. Though the 3-month studies did not include a recovery phase, increases in phosphorous improved after a drug-free period in the 1-month studies in rats and dogs, but mineralization findings, including mineralization of the gastric fundus, were irreversible in rats. Additionally, minimal increases in calcium (up to 6% compared to controls) occurred during the first week of dosing in the 1-month rat study but improved by the second week of dosing; increases in calcium were not noted in the 1-month study in dogs or the 3-month studies in rats and dogs.

Findings in the eye were noted in rats and dogs. Ocular findings in rats administered 1 mg/kg included minimal conjunctiva mineralization in the 1-month study and minimal corneal mineralization in the 3-month study. Minimal atrophy and thinning of the cornea were also noted at doses ≥ 0.3 mg/kg in the 3-month study in rats. In the 3-month toxicology study in dogs, corneal opacity was noted during ophthalmic examinations in one male each at 0.05 mg/kg and 0.4 mg/kg and correlated with histologic signs of minimal neutrophilic inflammation and mild corneal atrophy in the 0.4 mg/kg male.

Signs of liver toxicity were noted in rats and dogs. Increases in liver enzymes, including AST (up to 107%) and ALT (up to 66%), were noted in rats at ≥ 0.1 mg/kg in the 1-month study and at ≥ 0.3 mg/kg in the 3-month study and correlated with histologic signs of minimal to mild mineralization, mixed cell inflammation, and/or vacuolation in male rats at ≥ 0.3 mg/kg in the 3-month study. In dogs, increases in AST (up to 81%), ALT (up to 90%), and/or ALP (up to 119%) were noted at 0.3 mg/kg in the 1-month study and at 0.4 mg/kg in the 3-month study but lacked any histologic correlate in either study. These findings improved during the recovery phases in the 1-month studies. Additionally, FDA disagrees with the Applicant's assessment that increases in liver enzymes were non-adverse in the 28-day study in mice considering that these findings correlated with dose-dependent increases in incidence of hepatocellular necrosis and

that signs of liver toxicity occurred in toxicology studies in rats and dogs. Of note, tissue distribution studies with radiolabeled-mirdametinib showed greatest radioactivity in the liver.

Bone findings in rats at 1 mg/kg in the 1-month study included minimal to moderate hypocellularity of the metaphyseal region of the femur and distal tibia and findings at ≥ 0.3 mg/kg in the 3-month study, included minimal to mild dysplasia and thickening of the trabeculae. While these bone findings occurred in both sexes, males appeared to be more sensitive to these effects. Findings in long bone are relevant considering the intended population includes pediatric patients and were included in section 8.4 of the GOMEKLI label. These findings were not noted at the end of the recovery period in the 1-month study in rats.

Male and female reproductive organs were target organs in the 3-month study in rats. See Section 5.5.4 for details. Findings noted in male reproductive organs (epididymis, prostate, and testis) in the 3-month study in dogs were not added to the label as the relationship of these findings to mirdametinib was uncertain given that descriptions of these findings in the study report did not clearly distinguish differences in severity.

Table 15 Histopathology Findings in the 13-Week Toxicology Study in Rats

Organ/tissue	Finding	Severity	Male				Female			
			0 mg/kg	0.1 mg/kg	0.3 mg/kg	1 mg/kg	0 mg/kg	0.1 mg/kg	0.3 mg/kg	1 mg/kg
			N=10	N=9	N=10	N=10	N=10	N=10	N=10	N=10
Artery, pulmonary	Mineralization	Minimal	5	5	6	2	3	4	6	6
		Mild				3				
Artery, renal	Mineralization	Minimal				2				
		Mild				1				
Artery, mesenteric	Mineralization	Mild				2				
Heart	Degeneration, myocardium	Minimal	2	1	2	4	1			
	Fibrosis	Minimal		1						
	Ossification, endocardium	Minimal				3				
Pituitary gland	Cyst					1				
	Hypertrophy, pituicyte	Minimal				2				
Esophagus	Infiltrate, mononuclear cell	Minimal						1		
	Granuloma	Mild		1						
Large intestine, cecum	Hyperplasia, epithelial	Mild				1				

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Organ/tissue	Finding	Severity	Male				Female			
			0	0.1	0.3	1	0	0.1	0.3	1
			mg/kg N=10	mg/kg N=9	mg/kg N=10	mg/kg N=10	mg/kg N=10	mg/kg N=10	mg/kg N=10	mg/kg N=10
Liver	Mineralization	Mild				1				
	Extramedullary hematopoiesis	Minimal				1				
	Inflammation, mixed cell	Minimal				1		1		
	Vacuolation, hepatocyte	Minimal	3			4	1		3	2
Stomach	Mineralization, glandular stomach	Minimal			1	1				2
		Mild				6				2
		Mod				3				
	Hyperkeratosis, nonglandular stomach	Mild		1						
Tongue	Infiltrate, neutrophilic	Minimal							1	
Bone marrow	Hypocellularity, pancytic	Minimal			5				2	2
		Mild			4	1				1
		Mod			1	9				
	Hypocellularity, myeloid	Minimal								1
Thrombus					1					
Lymph node, inguinofemoral	Hyperplasia, lymphoid	Minimal		1		6				1
	Increased plasma cells, medullary cord	Minimal	1	1	1	1		1	1	3
		Mild				5				2
		Mod				2				
Lymph node, mesenteric	Increased plasma cells, medullary cord	Minimal	1	1	1	2	1	2	1	
		Mild			1	3				
	Hyperplasia, lymphoid	Minimal				1		1		
	Cystic dilatation	Mild				1				
GALT	Mineralization	Minimal	1	3	3	2		1	1	4
		Mild		1	1	1		1		
Skin	Infiltrate, mononuclear cell	Minimal					1	1		
		Minimal								1
	Inflammation, neutrophilic	Mild				1				
		Crust	Minimal				1			
	Mild					1				
	Ulcer, epidermis	Minimal								1
Mild					2				6	
Bone	Dysplasia, epiphysis	Minimal			2	2			2	1
		Mild							1	3
	Dysplasia, compact bone	Minimal				1				
		Thick trabecula	Minimal				3			
Mild					7					
Brain	Dilatation, ventricle	Mild				1				

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Organ/tissue	Finding	Severity	Male				Female			
			0	0.1	0.3	1	0	0.1	0.3	1
			mg/kg N=10	mg/kg N=9	mg/kg N=10	mg/kg N=10	mg/kg N=10	mg/kg N=10	mg/kg N=10	mg/kg N=10
Epididymis	Decreased content	Marked				1				
	Granuloma, sperm			1						
Ovary	Follicular cyst with decreased corpora lutea						1		2	6
Prostate	Inflammation	Minimal	1			4				
Testis	Hypoplasia, spermatogenic epithelium	Minimal	1							
		Marked				1				
Lung	Infiltrate, mononuclear cell	Minimal	1	1	2		1	1		2
	Infiltrate, foamy macrophages	Minimal	3	3	5	3	3	4	3	7
		Mild				6				
Eye	Mineralization, cornea	Minimal				2				
	Atrophy, corneal epithelium	Minimal			1	6			2	5
	Vesicle, corneal epithelium					1				
Kidney	Infiltrate, mononuclear cell	Minimal	1			1	1			
		Mild				1				
	Abnormal content	Minimal						2		
	Hydronephrosis	Mild			1					
	Inflammation, neutrophilic	Minimal	2	2			1			1
		Mild					1			2
	Mineralization, cortex	Minimal	1			7				
		Mild				2				
	Mineralization, corticomedullary junction	Minimal						1	1	
Ureter	Mineralization, medulla	Minimal		1	3			2	3	2
	Infiltrate, mononuclear cell	Minimal								1

Mod = moderate

Table 16 Histopathology Findings in the 13-Week Toxicology Study in Dogs

Organ/tissue	Finding	Severity	Male				Female			
			0	0.05	0.1	0.4	0	0.05	0.1	0.4
			mg/kg N=3	mg/kg N=3	mg/kg N=3	mg/kg* N=3	mg/kg N=3	mg/kg N=3	mg/kg N=3	mg/kg* N=3
Adrenal gland	Increased coarse vacuoles	Minimal				1	1	1	2	1
		Mild						1		1
Pituitary	Cyst		1	1		1		1	3	3
Thyroid	Cyst			1				1		1
Esophagus	Inflammation, neutrophilic	Minimal				1				1

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Organ/tissue	Finding	Severity	Male				Female			
			0 mg/kg	0.05 mg/kg	0.1 mg/kg	0.4 mg/kg*	0 mg/kg	0.05 mg/kg	0.1 mg/kg	0.4 mg/kg*
			N=3	N=3	N=3	N=3	N=3	N=3	N=3	N=3
	Infiltrate, mononuclear cell	Minimal				1				
	Cyst									1
Large intestine, cecum	Necrosis, fibrinoid, artery	Minimal				1				
Large intestine, colon	Inflammation, neutrophilic	Minimal				1				
	Hemorrhage	Minimal				1				
Liver	Congestion	Mild								1
	Infiltrate, mononuclear cell	Minimal					1	3		1
	Thrombus									1
Pancreas	Decreased granules, acinar cell	Minimal				2				1
	Degeneration, acinar cell	Mild							1	
Salivary gland, mandibular	Infiltrate, mononuclear cell	Minimal		1		1		1	2	
Small intestine, duodenum	Abnormal content	Minimal								1
Stomach	Hemorrhage	Minimal				1				
	Infiltrate, neutrophilic	Minimal								1
	Secretory depletion, pyloric region	Mild				1				
Tongue	Inflammation, neutrophilic	Minimal				1				1
		Mild				1				1
Bone marrow	Decreased erythroid cellularity	Minimal				1				1
	Hyperplasia, myeloid	Minimal				1				1
Lymph node, mediastinal	Hemorrhage	Mild				1				
	Pigment, hemosiderin	Minimal				1				
Lymph node, mesenteric	Hemorrhage	Minimal		1						
	Lymphoid depletion	Minimal				1				
		Mod								1
Lymph node, popliteal	Hemorrhage	Minimal								1
	Lymphoid depletion	Minimal				1				
	Lymphoid hyperplasia	Minimal						2		
		Mild			1					
		Minimal	1		2			3		1

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Organ/tissue	Finding	Severity	Male				Female			
			0 mg/kg	0.05 mg/kg	0.1 mg/kg	0.4 mg/kg*	0 mg/kg	0.05 mg/kg	0.1 mg/kg	0.4 mg/kg*
			N=3	N=3	N=3	N=3	N=3	N=3	N=3	N=3
	Increased plasma cells, medullary cord	Mild				1	1		1	1
		Mod		1	1	1			1	1
GALT	Lymphoid depletion	Minimal				2				
		Mild								1
	Increased plasma cells	Minimal			1					
	Abscess	Minimal								1
Spleen	Adhesion, fibrous	Minimal				1				
	Lymphoid depletion	Minimal				1				
	Plaque	Minimal	1					2		1
		Mild				1				
Thymus	Lymphoid depletion	Mild								1
Brain	Infiltrate, mononuclear cell	Minimal			1	1				
Cervix, uterus	Infiltrate, mixed cell	Minimal							1	
Epididymis	Abnormal content	Minimal				2				
Prostate	Atrophy	Minimal			1					
		Mild		1						
	Cystic dilatation	Minimal		1	1					
		Mild		1	1					
Testis	Degeneration, spermatogenic epithelium	Minimal		1		1				
Vagina	Infiltrate, mixed cell	Mild							1	
Lung	Infiltrate, mononuclear cell	Minimal								2
	Hemorrhage	Minimal				1				
	Infiltrate, foamy macrophages	Mild			1					
Trachea	Infiltrate, neutrophilic	Minimal							1	1
Eye	Inflammation, neutrophilic	Minimal				1				
	Atrophy, corneal epithelium	Mild				1				
Urinary bladder	Necrosis, fibrinoid, artery	Mild				1				

*Includes early death animals. Dosing for the surviving 0.4 mg/kg male and female was stopped on Days 51 and 57, respectively; Mod = moderate

The GLP-compliant 28-day toxicology study in non-transgenic mice (Study #: 20196649) presented by the Applicant was used to select the recommended dose levels for the 6-month carcinogenicity study of PD-0325901 in transgenic mice (Study #:20196651). Toxicology findings in the 28-day study in mice were generally consistent with findings noted in rats and dogs, with the additional finding that mirdametinib caused minimal to moderate degeneration/necrosis in the testes at doses ≥ 10 mg/kg. Signs of gastrointestinal toxicity, including minimal to severe epithelial degeneration/necrosis, erosion/ulceration, and inflammatory cell infiltrates throughout the gastrointestinal tract were also noted at doses ≥ 10 mg/kg.

5.5.2. Genetic Toxicology

The Applicant's Position:

Data:

The genotoxicity of mirdametinib was assessed in a battery of genotoxicity studies as summarized in [Table 10](#). Mirdametinib was not mutagenic in bacteria (745-03535) and was not clastogenic in human lymphocytes in vitro (745-03511). In an in vivo rat micronucleus study mirdametinib was not clastogenic (745-03804). Additionally, in a rat bone marrow chromosomal aberration assay, mirdametinib was negative for induction of structural or numerical chromosome breaks in the treatment groups (745-04155).

Table 17: GLP Genotoxicity Studies Conducted with Mirdametinib (PD-0325901)

Study Type	Study Title / Study No	Key study findings	Test System	Assessment of test validity
Reverse mutation in bacterial cells	Bacterial Mutagenicity Assay of PD 325901/ 745-03535	Cytotoxic Effects: For the definitive assay, cytotoxicity was observed in the absence of metabolic activation at ≥ 800 $\mu\text{g}/\text{plate}$ (TA-1537), 1600 $\mu\text{g}/\text{plate}$ (TA-98, TA-100, and TA-1535), and at 5000 $\mu\text{g}/\text{plate}$ (WP2uvrA pKM101). Cytotoxicity was observed with metabolic activation at ≥ 1250 $\mu\text{g}/\text{plate}$ (TA-98), 1600 $\mu\text{g}/\text{plate}$ (TA-1537), ≥ 2500 $\mu\text{g}/\text{plate}$ (TA-100 and TA-1535), and at 5000 $\mu\text{g}/\text{plate}$ (WP2uvrA pKM101). Genotoxic Effects: None	Salmonella typhimurium strains TA 98, TA 100, TA 1535 and TA 1537 and Escherichia coli strain WP2uvrA pKM101	The positive and negative controls confirmed sensitivity, while phenotypic analysis confirm bacterial strains maintained expected phenotype.

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Study Type	Study Title / Study No	Key study findings	Test System	Assessment of test validity
Chromosome aberrations	Chromosomal Aberrations in Cultured Human Peripheral Blood Lymphocytes with PD 325901/ 745-03511	Cytotoxic Effects: $\geq 603 \mu\text{g/mL}$ with or without S9 Genotoxic Effects: None. There was no significant increase in chromosome damage, polyploidy, or endoreduplication at any concentration evaluated under any test condition.	Human peripheral blood lymphocytes	The positive and negative controls confirmed sensitivity.
Micronuclei	In Vivo Micronucleus Study of PD 325901 in Sprague-Dawley Rats / 745-03804	Toxic/Cytotoxic Effects: Statistically significant and dose-dependent decreases in total nucleated cells and increases in total erythrocytes were observed in both sexes as compared to concurrent controls, indicative of mild bone marrow cytotoxicity. Changes in bone marrow may be related to local hypocellularity of the metaphyseal region, which has been observed in rats administered PD-0325901 for 4 weeks and considered a consequence of localized injury rather than a generalized bone marrow effect. Genotoxic Effects: PD-0325901 was not clastogenic to the bone marrow of rats at doses up to 1 mg/kg. Although 3 mg/kg did not meet the criteria for a positive response, the slight increase at 3 mg/kg/day could be related to the bone marrow toxicity (significant decrease total nucleated cells) seen at this dose level in females.	Bone marrow from femur from Rat/Sprague-Dawley	Evidence of bone marrow toxicity confirmed adequate exposure to the bone marrow and validity for this study. The positive control also confirmed the sensitivity of the assay.
Chromosome aberrations	Oral Gavage Bone Marrow Chromosomal Aberrations Study of PD-325901 in Rats/ 745-04155	Toxic/Cytotoxic Effects: At 3 mg/kg reductions of mitotic index was present ($\leq 1\%$) suggesting cytotoxicity. Genotoxic Effects: PD-0325901 was not clastogenic to the bone marrow of rats at doses up to 3 mg/kg.	Bone marrow from tibia from Rat/Sprague-Dawley	Evidence of bone marrow toxicity confirmed adequate exposure to the bone marrow and validity for this study. The positive control also confirmed the sensitivity of the assay.

Based on the totality of data from the genotoxicity studies, mirdametinib is not genotoxic.

The FDA's Assessment:

FDA does not agree with the Applicant's interpretation of the in vivo micronucleus assay. In this study, female rats treated with mirdametinib showed dose-related increases in percent of micronucleated polychromatic erythrocytes (%MNPCE) compared to concurrent controls and achieved statistical significance at the high dose of 3 mg/kg, suggesting that mirdametinib may have clastogenic potential. However, the results of the 3 mg/kg dose level did not meet the criteria for a positive response because the results were within the levels of historical controls albeit closer to the higher limit (historical control range % MNPCE = 0.16 to 0.59; at 3 mg/kg % MNPCE = 0.54). The Applicant attributes this increase to be potentially related to bone marrow toxicity, but this endpoint was not measured in the study. Overall, the FDA considered the results of the micronucleus assay to be equivocal. Follow-up testing demonstrated mirdametinib was negative for clastogenicity in the in vivo chromosomal aberration assay in rats, but this study did not rule out the potential for aneugenicity. Therefore, FDA determined that mirdametinib is genotoxic with an aneugenic mode of action.

See section 5.5.1 Other Toxicology Studies for discussion of genetic toxicology of metabolites.

5.5.3. Carcinogenicity

The Applicant's Position:

Data:

The carcinogenic potential of mirdametinib was assessed in a 6-month study in transgenic rasH2 mice (20196651). The dose levels established for this study (0, 2, 5, 15 mg/kg/day) were based on findings in the 28-day mouse study and feedback provided by the Carcinogenicity Advisory Council at FDA.

Based on microscopic evaluation, there were no carcinogenic effects of mirdametinib at any dose level in this study.

A 2-year rat carcinogenicity study (20435943) will be conducted (start of dosing planned in Aug2024), and the Applicant intends to submit the results post-approval.

Table 18: 6-Month Mouse Carcinogenicity Study

Test Article: Mirdametinib (PD-0325901) Study Number: 20196651 Study Title: A 26-week Carcinogenicity Study of PD 0325901 by Oral Gavage in CByB6F1/Tg rasH2 Hemizygous Mice eCTD Location: 4.2.3.4 Key Drug-related Adverse Findings: No carcinogenic effect related to mirdametinib administration was observed at any dose level. GLP compliance: Yes								
Dose and frequency of dosing:	0, 2, 5, and 15 mg/kg/day administered once daily for 24/26 weeks							
Route of administration:	Oral							
Formulation/Vehicle:	(b) (4) cellulose (b) (4) in Ultra Pure Water							
Species/Strain:	Mouse/CByB6F1-Tg(HRAS)2Jic Hemizygous							
Number/Sex/Group:	Main study group: 25/sex/group Positive control group: 15/sex at 75 mg/kg							
Age:	9 weeks							
Satellite groups:	Toxicokinetic groups consisting of non-transgenic animals; Positive control group							
Mirdametinib Daily Dose (mg/kg)	0 (Control)		2		5		15	
Number of Animals								
Carcinogenicity	M:25	F:25	M:25	F:25	M:25	F:25	M:25	F:25
Toxicokinetic	M:12	F:12	M:36	F:36	M:36	F:36	M:36	F:36
Toxicokinetics								
PD-0325901 – Day 180								
Cmax (ng/mL)	NA	NA	359	607	765	1140	3180	NE
AUC0-24 (ng•h/mL)	NA	NA	2190	4330	5540	7900	NE	NE
Metabolite PD-0315209 – Day 180								
Cmax (ng/mL)	NA	NA	36.6	71.6	69.9	134	457	NE
AUC0-24 (ng•h/mL)	NA	NA	441	1030	690	1670	NE	NE
Findings								

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Died or Sacrificed Moribund	There were mirdametininib-related effects on survival in males and females at 15 mg/kg/day. Females at 15 mg/kg/day were terminated early (Day 164) as per FDA recommendation due to poor survivability. A definitive cause of death or moribundity could not be determined in 13 early death females at ≥ 5 mg/kg/day. The cause of death or moribundity in 10 early death females at ≥ 5 mg/kg/day was attributed to moderate to marked hepatocellular necrosis. The cause of death or moribundity in 4 males at 15 mg/kg/day was attributed to microscopic changes in the urogenital tract, including mixed cell inflammation of the prostate gland and adjacent urethra and preputial gland abscesses. Survival at 2 or 5 mg/kg/day of mirdametininib was 100% in males and ranged from 92% to 100% in females and was comparable to controls, while survival at 15 mg/kg/day was reduced to 84% in males on Day 176 (study termination at 26 weeks) and 16% in females on Day 164 (early group termination at 24 weeks).
Body Weight and Food Consumption	There were significant increases in mean body weight gains for 2, 5, and 15 mg/kg/day males and 2 and 5 mg/kg/day females as compared to controls from Day -1 to Day 183. Mean body weight increases were observed in the 15 mg/kg/day females from Days -1 to 162 with increased mean body weights on Day 162 (69%) as compared to controls prior to early termination on Day 164. A general dose-dependent trend of increased food consumption generally corresponded to increased mean body weight during the study.
Clinical Observations	There were no mirdametininib-related clinical observations at 2 or 5 mg/kg/day during the study. Clinical observations were generally related to the early mortality in the 15 mg/kg/day males and females and included breathing abnormalities, prostrate, erected fur, cold to touch, decreased activity, dehydration, and hunched posture.
Non-Neoplastic Changes	- Increased lymphoid cellularity and/or epithelial hyperplasia of the thymus in males and females at ≥ 2 mg/kg/day - Increased hematopoietic cells in the spleen in males and females at ≥ 2 mg/kg/day - Hepatocellular vacuolation in males at ≥ 2 mg/kg/day and females at 2 and 5 mg/kg/day - Hepatocellular necrosis in males at 2 and 15 mg/kg/day and females at ≥ 5 mg/kg/day - epithelial degeneration/necrosis or erosion/ulceration throughout the GI tract in males and females at ≥ 5 mg/kg/day - Epithelial hyperplasia of the non-glandular stomach in males at ≥ 5 mg/kg/day - Epithelial hyperplasia of the crypt in the intestine in 1 male at 15 mg/kg/day and females at ≥ 5 mg/kg/day - Preputial gland abscess in males at ≥ 2 mg/kg/day - Mixed cell inflammation of the prostate gland in males and clitoral gland in females at 15 mg/kg/day. - Multiple non-neoplastic microscopic findings were considered secondary to stress/inanition (Everds 2013, Travlos 2006) in males at 15 mg/kg/day and females at ≥ 5 mg/kg/day. These findings included minimal to mild decreased cellularity in the sternal bone marrow, minimal to severe decreased cellularity of lymphoid tissues (white pulp of the spleen, germinal center of the lymphoid follicles of mandibular and mesenteric lymph nodes, and cortex of thymus), and minimal to moderate secretory depletion of the acinar cells in the pancreas and mandibular salivary glands.

Neoplastic Changes	- Based on microscopic evaluation, no carcinogenic effect related to mirdametinib administration was observed at any dose level in this study. - In both sexes, the NMU positive control group exhibited the expected neoplastic (increased incidence of malignant lymphoma, squamous cell papilloma, and squamous cell carcinoma) and non-neoplastic (retinal atrophy) changes, thereby validating the CByB6F1/Tg rasH2 hemizygous model used in this study.
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Abbreviations: AUC: area under the curve; Cmax: maximum plasma concentration; eCTD: electronic Common Technical Document; F: female; FDA: Food and Drug Administration; GLP: Good Laboratory Practice; M: male; NA: not applicable; NE: not evaluated.

Mirdametinib showed no evidence of carcinogenicity in the 6-month CByB6F1/Tg rasH2 hemizygous mice study.

The FDA's Assessment:

The FDA previously reviewed the 6-month carcinogenicity study in CByB6F1/Tg rasH2 hemizygous mice under IND 139883. The review focused on neoplastic findings. FDA agrees with the Applicant's conclusion that no carcinogenic effects related to administration of mirdametinib were observed at any dose level tested in the 6-month mouse study.

The Applicant submitted a special protocol assessment (SPA) for the 2-year rat study under IND 139883, which was reviewed by the FDA on June 25, 2024. The final study report will be submitted to the NDA as a post marketing requirement (PMR).

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

The developmental and reproductive toxicology assessment of mirdametinib consisted of a definitive fertility study in male and female rats and preliminary EFD toxicity studies in pregnant rats and rabbits.

Given the significant EFD toxicities observed in both the rat and rabbit range-finding studies, and the requirement for MEK in embryonic development ([Giroux 1999](#)), neither definitive embryo-fetal toxicity studies nor pre- and post-natal development studies were conducted for mirdametinib; this was agreed upon with the FDA (email, 24Feb2023).

Table 19: Fertility and Early Embryonic Development in Male and Female Rats

Test Article: Mirdametinib (PD-0325901) Study Number: 01953001 Study Title: An Oral Gavage Administration Study of the Effects of PD-325901 on Fertility and Early Embryonic Development to Implantation in CD® (Sprague Dawley) IGS Rats eCTD Location: 4.2.3.5.1 Key Drug-related Adverse Findings: The NOAEL was 1 mg/kg/day for male and female systemic and reproductive toxicity and embryonic development GLP compliance: Yes	
Dose and frequency of dosing:	0, 0.1, 0.3, 1 mg/kg/day once daily.
Dosing period	Male rats were dosed for 28 days before mating with naïve females and dosing continued through Gestation Day (GD) 1 day before euthanasia. Female rats were dosed for 14 days before mating with naïve sexually mature male rats and continued through Gestation Day (GD) 7
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4) cellulose in Ultra Pure Water
Species/Strain:	Rat/CD® (SD) IGS
Number/Sex/Group:	22/sex/dose
Age:	11 weeks (treated rats)
Day of C-Section	GD 13
Toxicokinetics (not assessed in this study)	
Treated Male Findings (treated males mated with naïve breeding females)	
Died or Sacrificed Moribund	None
Body Weight and Food Consumption	Higher mean body weight gains were noted with statistical significance in the 0.1, 0.3, and 1 mg/kg/day group males, but the mean absolute body weights in these groups were generally comparable to the control group throughout the study. Mean food consumption in the 0.1, 0.3, and 1 mg/kg/day groups was unaffected by test article administration.
Clinical Observations	Scabbing on various surfaces or skin lesion were noted at increasing incidences with increasing dose level in the 0.1, 0.3, and 1 mg/kg/day group males.
Males Fertility Indices	No test article-related effects on reproductive performance (mating, fertility, and pregnancy indices) were observed at any dose level when treated males were mated with naïve females. No statistically significant differences were noted between the control and test article-treated groups. All males sired a litter.
Untreated Female Findings	There were no test article-related effects on implantation sites or intrauterine survival when test article-treated males were mated with untreated females.
Sperm Analysis	No test article-related effects were observed on sperm parameters (mean testicular sperm numbers and sperm production rate, motility, and morphology) in males at any dose level.

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Microscopic Observations	Gross findings at necropsy of skin scabs in males at 1 mg/kg/day were characterized microscopically by mild focal epidermal ulceration, epidermal hyperplasia, mixed cell inflammation, epidermal crust, subcorneal (under the stratum corneum) neutrophil pustules, and/or follicular pustule, and were considered nonadverse.
Treated Female Findings (treated females mated with naive sexually mature males)	
Died or Sacrificed Moribund	None
Body Weight and Food Consumption	Higher mean body weight gains were noted with statistical significance in the 1 mg/kg/day group females but were generally comparable to control throughout the gestation period. The mean absolute body weight as well as food consumption was not affected at 1 mg/kg/day.
Clinical Observations	Scabbing on various surfaces or skin lesion were noted at increasing incidences with increasing dose level in the 0.1, 0.3, and 1 mg/kg/day group females.
Female Estrous Cycle	There were no test article-related effects on mean number of days between pairing and coitus and the mean lengths and number of estrous cycles at any dose level.
Female Fertility Indices	No test article-related effects on reproductive performance (mating, fertility, and pregnancy indices) were observed at any dose level when treated females were mated with naive males. No statistically significant differences were noted between the control and test article-treated groups.
Microscopic Observations	There were no microscopic findings for the ovaries (the only organ microscopically evaluated in females) of pregnant females at 1 mg/kg/day.
Uterine Findings	Mean numbers of corpora lutea, implantation sites, and intrauterine survival were unaffected by administration of the test article to the females at dose levels of 0.1, 0.3, and 1 mg/kg/day. No statistically significant differences from the control group were noted.

Abbreviations: AUC: area under the curve; Cmax: maximum plasma concentration; eCTD: electronic Common Technical Document; F: female; GD: gestation day; GLP: Good Laboratory Practice; M: male; NA: not applicable; NOAEL: no observed adverse effect level.

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Table 20: Reproductive and Development Non-Pivotal Studies Conducted with Mirdametinib (PD-0325901)

Test Article: Mirdametinib (PD-0325901)						
Species/ Strain	Method of Administration (Vehicle/Formulation)	Dosing Period	Doses mg/kg/day	No. per Group	Noteworthy Findings	Study Number
Rat/Sprague Dawley	Oral (b) (4) cellulose, 0.2% Tween 80/suspension)	12 days (GD 6 through GD 17)	0, 0.3, 1, 3, 6	6 pregnant rats	Maternal toxicity was limited to the 6 mg/kg/day group and consisted of decreased body weights and food consumption, along with hair loss, skin scabs/sores/abrasions, ocular and nasal staining. Fetal effects at ≥ 3 mg/kg/day included decreased fetal body weights, decreased number of live fetuses, increases in resorptions and postimplantation loss. A single fetal at 3 mg/kg/day had malformations consisting of micromelia, adactyly, brachydactyly and blunt-tipped tail. The NOAEL for maternal toxicity was 3.0 mg/kg/day and the NOAEL for developmental toxicity was 1 mg/kg/day. Systemic exposures were not measured in this study.	2005- 0017
Rabbit/New Zealand White	Oral (b) (4) cellulose, 0.2% Tween 80/suspension)	13 days (GD 7 through GD 19)	0, 0.3, 1, 3, 6	6 pregnant rabbits	Early maternal deaths at 3 and 6 mg/kg/day. At 1 mg/kg/day, 2 out of 6 in the 1 mg/kg/day group aborted (GD20 and 23). Maternal toxicity in this group included decreased body weights, decreased food consumption, decreased feces, and urine. Fetal toxicities at 0.1 mg/kg/day included resorptions, increased postimplantation loss and decreased fetal body weights. At 0.3 mg/kg/day, there were no maternal toxicities; however, fetal toxicities included increased resorptions and increased postimplantation loss. The PD-0325901 C_{max} and AUC_{0-24} at 0.3 mg/kg/day were 86.6 ng/mL and 763 ng*hr/mL, respectively. Metabolite PD-0315209 C_{max} and AUC_{0-24} at 0.3 mg/kg/day were 60.8 ng/mL and 621 ng*hr/mL, respectively.	2005- 0052

Abbreviations: AUC: area under the curve; C_{max} : maximum plasma concentration; GD: gestation day; NOAEL: no-observed-adverse-effect level.

In the definitive male and female rat fertility and early embryonic development study, mirdametinib did not have any effects on male reproductive parameters, female reproductive parameters, or embryonic development at any dose level. However, mirdametinib induced EFD toxicities (early resorptions, post-implantation loss, dose-dependent decreased fetal weights) in both rat and rabbit dose-range finding preliminary studies. Because of these EFD effects, no additional developmental toxicity studies were conducted per agreement with the FDA (email, 24-Feb-2023). Of note, EFD toxicity is considered a class effect of MEK inhibitors.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of the findings of the GLP-compliant fertility study in male and female rats and dose range finding embryo-fetal development (EFD) toxicity studies in rats and rabbits. The FDA previously reviewed the EFD studies and concluded that mirdametinib showed clear evidence of embryo-fetal toxicity. Based on the positive results of the dose range finding studies and mechanism of action, the FDA agreed that further GLP-compliant reproductive toxicology studies were not warranted.

In the EFD study in rats, actual doses administered were 0.25, 0.6, 3, and 5.0 mg/kg based on formulation analysis for the 0.3, 1, 3 and 6 mg/kg groups. One rat at 0.6 mg/kg (1 mg/kg) was found dead on GD21 and necropsy results indicated 15 late resorptions and no live fetuses; the cause of death was considered due to fetal necrosis.

While we agree that mirdametinib did not affect mating performance or fertility under the conditions tested in the dedicated fertility study, FDA notes that repeat-dose toxicology studies with mirdametinib had reproductive organ findings that may impair female fertility. In a 3-month repeat-dose toxicology study in rats, mirdametinib caused follicular cysts associated with decreases in the number of corpora lutea at doses ≥ 0.3 mg/kg/day (≥ 2 -times the human exposure at the clinical dose of 2 mg/m² twice daily based on AUC) that correlated with decreased organ weight. Male reproductive organ findings in rats at 1 mg/kg (8-times the human exposure at the clinical dose of 2 mg/m² twice daily based on AUC) included inflammation of the prostate in individual males and marked hypoplasia of the spermatogenic epithelium in the testis and decreased content in the epididymis in one male. In a 1-month repeat-dose toxicology study in mice, mirdametinib caused testicular degeneration and/or necrosis at doses ≥ 10 mg/kg/day (≥ 23 -times the human exposure at the clinical dose of 2 mg/m² twice daily based on AUC). The reversibility of effects on ovary and testes were not assessed. Given differences in incidence and severity of male reproductive organ findings between control and mirdametinib-treated groups and literature supporting a role for MEK in spermatogenesis [Hasegawa (2013)], the possibility that findings in male reproductive organs in animals were related to administration of mirdametinib could not be eliminated; however, the clinical impact on male fertility is unclear given the low incidence of findings.

Additional relevant data is presented below:

In an EFD study, administration of mirdametinib to pregnant rats caused decreases in maternal body weight gains and food consumption at the dose of 5 mg/kg (approximately 8-times the human clinical dose of 2 mg/m² twice daily based on BSA). A summary of the Cesarean section data in rats is shown in Table 20. The increases in percentage mean post-implantation loss and decrease in mean number of live fetuses and fetal body weights were observed at doses ≥3 mg/kg (≥5-times the human clinical dose of 2 mg/m² twice daily based on BSA). One fetus at the 3 mg/kg dose had multiple malformations including micromelia, adactyly, brachydactyly, and blunt-tipped tail and another one had a limb hyperflexion variation.

Table 21 Summary of Cesarean Section Data in Rats

	Dose (mg/kg/day)				
	0	0.25	0.6	3.0	5.0
# of Females not pregnant	2	4	2	1	1
# of Females pregnant	4	2	3	5	5
# of Corpora Lutea	56	32	41	75	61
Mean # of corpora lutea	14.0	16.0	13.7	15.0	12.2
# of Implantations	50	27	39	72	56
Mean # of implantations	12.5	13.5	13.0	14.4	11.2
Mean Pre-implantation Loss (%)	9.1	15.5	4.4	3.9	8.1
# of Early Resorptions	2	2	1	19	32
Mean #early resorptions	0.5	1.0	0.3	3.8	6.4
Mean Post-implantation Loss (%)	4.6	7.5	2.6	26.2	59.0
# of Females with Pre-implantation Loss	3	2	1	3	3
# of Females with Post-implantation Loss	1	2	1	5	5
# of Females with Complete Post-implantation Loss	0	0	0	0	2
# of Live Fetuses	48	25	38	53	24
Mean #live fetuses	12.0	12.5	12.7	10.6	4.8
Mean Body Weight of Live Fetuses (g)					
Male	6.2 (4)	5.8 (2)	5.5 (3)	4.7 (5)	4.7 (3)
Female	5.8 (4)	5.5 (2)	5.2 (3)	4.6 (5)	4.5 (3)

Numbers in parenthesis represent the number of fetuses

In rabbits, administration of mirdametinib caused decreases in maternal body weight gains and food consumption at the dose of ≥1 mg/kg (≥3-times the human clinical dose of 2 mg/m² twice daily based on BSA). Moribundity leading to unscheduled euthanasia occurred in all animals at ≥3 mg/kg/day (≥9-times the human clinical dose of 2 mg/m² twice daily based on BSA). A summary of the Cesarean section data in rabbits is shown in Table 21. Increases in percentage mean post-implantation loss and decrease in mean number of live fetuses were observed at

doses ≥ 0.3 mg/kg (approximately equivalent to the clinical dose of 2 mg/m² twice daily, based on BSA). Decreases in fetal body weight were observed at 1 mg/kg/day (3-times the clinical dose of 2 mg/m² twice daily based on BSA).

Table 22 : Summary of Cesarean Section Data in Rabbits

	Dose (mg/kg/day)		
	0	0.3	1.0
# of Females pregnant	6	6	4
# of Corpora Lutea	64	60	43
Mean # of corpora lutea	10.7	10.0	10.8
# of Implantations	50	43	39
Mean # of implantations	8.3	7.2	9.8
Mean Pre-implantation Loss (%)	19.5	25	9.6
# of Early Resorptions	0	4	8
Mean # of early resorptions	0	0.7	2.0
# of late Resorptions	1	4	5
Mean # of late resorptions	0.2	0.7	1.3
# of Total Resorptions	1	8	13
Mean # of total resorptions	0.2	1.3	3.3
Mean Post-implantation Loss (%)	1.7	19.2	32.8
# of Females with Pre-implantation Loss	4	4	3
# of Females with Post-implantation Loss	1	5	4
# of Live Fetuses	49	35	26
Mean # of live fetuses	8.2	5.8	6.5
Mean Body Weight of Live Fetuses (g)			
Male + Female	42.7	41.3	36.8

5.5.5. Other Toxicology Studies

The Applicant's Position:

Data:

Phototoxicity

Mirdametinib absorbs light in the 290 to 700 nm range; therefore, an in vitro phototoxicity study was conducted (05075). In the in vitro Balb/c 3T3 mouse fibroblast neutral red uptake assay, mirdametinib exhibited a weak positive signal. However, mirdametinib was not retained in the skin or eye based on the [¹⁴C] mirdametinib tissue distribution study in rats.

Metabolites

Separate toxicity studies of mirdametinib metabolites have not been conducted. However, the carboxylic metabolite, PD-0315209, was measured in the pivotal toxicology studies in both rats

and dogs (Table 5, Table 6, Table 7, Table 8, and Table 9) and in the 6-month carcinogenicity study conducted in transgenic rasH2 mice; results are shown in Table 11.

Overall, the nonclinical toxicology profile of mirdametinib is considered to be acceptable for the proposed indication.

The FDA's Assessment:

Phototoxicity: Although the Sponsor concludes that mirdametinib has little risk of phototoxicity given that it is not retained in the eye or skin, there were two cases of photosensitivity and one case of photophobia reported clinically. In animals, there was skin toxicity (sores, crust, neutrophilic infiltrates) observed in repeat-dose toxicology studies, but it is unclear if these were related to phototoxicity. In the clinic, dermatologic reactions, such as dermatitis acneiform and non-acneiform rashes, were also reported; however, these findings are consistent with MEK inhibitors class effects, suggesting that the majority of dermatologic disorders in patients may be related to a pharmacological effect.

Metabolites: Two major metabolites of mirdametinib with pharmacological activity have been identified (M22 and PD-0315209) that represent >10% of mirdametinib in human plasma. M22 (O-glucuronide conjugate) is a unique human metabolite while PD-0315209 (carboxylic acid) was detected in repeat dose studies in mice, rats, and dogs. M22 is a Phase 2 glucuronide conjugate and Phase 2 conjugation reactions generally render a compound more water soluble and pharmacologically inactive; thus, M22 is not expected to have an increased risk of carcinogenicity and further evaluation is not warranted. Genetic toxicity of PD-0315209 was not directly tested; however, it is expected that rats were exposed to PD-0315209 in the in vivo micronucleus test as rats can generate PD-0315209, though levels PD-0315209 were not measured in this study. FDA clarifies that toxicokinetics analyzing PD-0315209 levels during the 6-month carcinogenicity study were conducted in non-transgenic littermates.

Impurities: The CMC review team inquired if the level of (b) (4) was qualified based on a limit of NMT (b) (4)%. The (b) (4) was present in the mirdametinib batch # XH451101, used in the 13-week toxicology studies at (b) (4)%. Based on the highest dose of 1 mg/kg of mirdametinib tested in the 13-week toxicology study in rats, which did not cause deaths, the (b) (4) present in the clinical dose of mirdametinib was qualified by toxicology studies.

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X

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Supervisor

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6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

The clinical pharmacology key review questions focused on the evaluations of the proposed dosage (including the two dosage forms and the unified dosing nomogram), food effect, and drug-drug interactions and organ impairment.

The primary evidence for efficacy and safety was obtained from Study MEK-NF-201 which evaluated mirdametininib in patients ≥ 2 years of age with an inoperable NF1-associated PN causing significant morbidity. The proposed recommended dosage is 2 mg/m² BID (with or without food) for the first 21 days of each 28-day cycle (maximum dose is 4 mg BID) until disease progression or unacceptable toxicity. The proposed dosage forms are capsules (1, 2 mg) and tablets for oral suspension (1 mg). The tablets may be swallowed whole or dispersed in water to be administered as an oral suspension to facilitate administration in patients who cannot swallow pills.

The proposed recommended dosage is acceptable, based on the observed benefit-to-risk profiles of mirdametininib from pivotal Study MEK-NF-201 and supportive Study NF-106. Based on the clinical pharmacology review, the proposed dosage forms of capsules (1, 2 mg) and tablets (1 mg) are acceptable given the overlapping PK observed between adult and pediatric patients following administration of 2 mg/m² BID via tablets or capsules, including comparable PK in the overlapping ages of pediatric patients who received tablets vs. capsules (age 5 to 14 years). Efficacy was observed across pediatric age groups (2 to < 12, 12 to < 18 years), while differences in TEAEs by dosage form appear attributable to age-related development differences. The proposed dosing nomogram is acceptable, based on the PPK simulation which showed no expected clinically meaningful differences in systemic exposures.

Based on the clinical pharmacology review of the in vitro and clinical studies, administration with regard to food, DDIs and organ impairment were adequately addressed, except for the following:

- The effects of moderate and severe hepatic impairment on the PK of mirdametininib is not known, and a post-marketing requirement (PMR) will be issued to provide dosage recommendations for mirdametininib in patients with moderate and severe hepatic impairment.
- The effect of concomitant strong CYP3A4 inducers on the PK of mirdametininib is not known. A post-marketing commitment (PMC) will be issued to provide dosage recommendations for mirdametininib when used concomitantly with strong CYP3A4

inducers.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 219379 (tablets) and NDA 219389 (capsules). The key review issues with specific recommendations and comments are summarized below:

REVIEW ISSUE	RECOMMENDATIONS / COMMENTS
Pivotal or supportive evidence of effectiveness	See Executive Summary (above) and Section 8 (Statistical and Clinical Evaluation).
General dosing instructions	2 mg/m ² BID (with or without food) for the first 21 d of each 28-d cycle (maximum dose is 4 mg BID).
Dosing in patient subgroups (intrinsic and extrinsic factors)	No restrictions or dose adjustments are needed in patient subgroups at this time.
Labeling	Overall, the proposed labeling recommendations are acceptable upon Applicant's agreement to FDA's revisions.
Bridge between the clinical trial and to-be-marketed formulations	N/A (the to-be-marketed capsules (1, 2 mg) and tablets (1 mg) were used in the pivotal Study MEK-NF-201).

Post-Marketing Requirement (PMR) or Commitment (PMC)

The following outstanding issues should be addressed as a PMR and a PMC (see Section 13):

PMR

1. Conduct a clinical pharmacokinetic trial to evaluate a serious potential risk of increased drug toxicity and to determine an appropriate, safe dose of mirdametinib in patients with moderate (total bilirubin > 1.5 – 3.0 x ULN, any AST) and severe (total bilirubin > 3 – 10 x ULN, any AST) hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry titled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

PMC

2. Conduct a clinical pharmacokinetic trial with a strong CYP3A4 inducer (that also induces UGTs, P-gp, and CES enzymes) with mirdametinib to evaluate the effect of strong CYP3A4 induction on decreasing the systemic exposure of mirdametinib and to provide dosage recommendations for mirdametinib when used concomitantly with strong CYP3A4 inducers. Design and conduct the trial in accordance with the FDA Guidance for Industry titled "M12 Drug Interaction Studies."

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

Mirdametininib PK has been evaluated in 7 clinical studies as a single agent either as a single dose (4 to 20 mg) or multiple doses (1 mg QD or BID up to 30 mg BID). Single dose PK studies were conducted in healthy adult participants to evaluate the effects of food on mirdametininib PK (Study A4581004), metabolism and elimination via radiolabeled mass balance (Study MEK-NF-101), and effects of mirdametininib and PD-0315209 on QT interval (Study MEK-NF-102). Dose-ranging studies and pharmacodynamic (PDx) data were collected in adult participants with advanced cancers (Study A4581001) and with non-small cell lung cancer (NSCLC; Study A4581002). PK and PDx data were collected from adult and pediatric participants with NF1 PN at the target dose of 2 mg/m² BID in Studies NF-106 and MEK-NF-201.

Collectively, these studies were used to characterize the PK of mirdametininib with population PK (PopPK) and population pharmacokinetic pharmacodynamic (PopPKPDx) models to evaluate exposure-response relationships with safety and efficacy endpoints. The exposure-efficacy and exposure-safety analyses were used to support the recommendation of 2 mg/m² BID, with a maximum of 4 mg BID, administered orally for 3 weeks on and 1 week off (treatment for the first 21 days of a 28- day cycle) as an optimal regimen of mirdametininib for the treatment of NF1 PN.

No clinical drug-drug interaction studies were conducted due to the absence of expected risk based on nonclinical evaluations. Studies of the effects of severe renal impairment and moderate or severe hepatic impairment have also not been conducted.

Mirdametininib has two major metabolites and both show less pharmacological activity than mirdametininib. PD-0315209, a carboxylic acid metabolite representing 24% of circulating drug-related material, was significantly less effective than mirdametininib (approximately 2200-fold difference) at reducing ERK phosphorylation in tumor cells grown in culture. PD-0315209 transiently suppressed pERK in tumor bearing mice; however, the PopPK predicted steady-state maximum concentration (C_{max,ss}) for PD-0315209 at the proposed target dose of 2 mg/m² BID is approximately 8-fold lower than the half-maximal inhibitory concentration (IC₅₀) for pERK suppression. M22, a secondary *O*-glucuronide representing 14.7% of circulating drug-related material, was significantly less effective than mirdametininib (greater than 75-fold difference) at reducing ERK phosphorylation in tumor cells grown in culture. Neither metabolite is expected to have contributions to clinical efficacy.

The Applicant's Position:

The clinical pharmacology studies support the recommended dose for mirdametininib of 2 mg/m² BID with cycles of 3 weeks on followed by 1 week off treatment (treatment for the first 21 days

of a 28-day cycle). The BSA-driven dosing guidance ensures that PK between adult and pediatric populations are similar. The metabolites are not expected to have clinically relevant pharmacological activity.

The FDA's Assessment:

FDA agrees with the Applicant's position.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

The selection of mirdametinib at 2 mg/m² BID, with a maximum dose of 4 mg BID, on a 3 weeks on/1 week off schedule as the Recommended Phase 2 Dose (RP2D) was made using the totality of evidence from nonclinical data in the human tumor xenograft and mouse NF1 neurofibroma models, tolerability assessment, PK and PDx measurements from clinical studies A4581001 and A4581002 in advanced cancer patients, and findings from a Phase 2 investigator-initiated study (NF-106) in NF1 PN.

The nonclinical PKPDx relationship was evaluated using mouse and human tumor xenograft models, including an NF1 neurofibroma model. These models demonstrated human exposures at the proposed dose of 2 mg/m² BID were consistent with doses associated with pERK inhibition in nonclinical models, which demonstrated tumor volume reductions in 85% of treated mice in the NF1 mouse model.

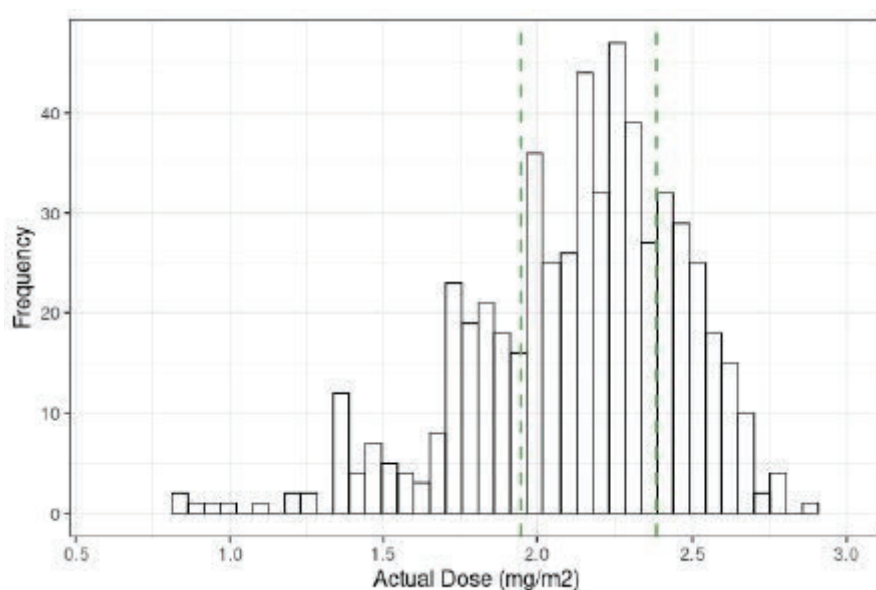
In clinical studies of advanced cancer populations (Studies A4581001 and A4581002), mirdametinib was assessed at various dose levels (1 mg QD to 30 mg BID) and schedules (continuous, intermittent). Based on the occurrence of late-onset adverse events (AEs), dose de-escalation, inclusive of both reduction of the total daily dose as well as the utilization of different administration schedules, was explored. Due to challenges with tolerability at the initial RP2D (15 mg BID) preventing long-term administration, full evaluation of mirdametinib efficacy in participants with advanced cancers could not be performed. It was concluded that an intermittent administration schedule using doses between 2 and 10 mg BID should be explored to identify a recommended dose for long-term treatment with mirdametinib (LoRusso 2010). In Study NF-106, participants ≥16 years of age with NF1 and progressing and/or morbid PN received mirdametinib at a 2 mg/m² dose (maximum 4 mg BID) on a 3 weeks on/1 week off schedule. In this study, mirdametinib was well tolerated and resulted in a confirmed ORR >30%. Based on these supportive data, a mirdametinib dose of 2 mg/m² (maximum 4 mg BID) on a 3 weeks on/1 week off schedule was selected for the pivotal Phase 2b Study MEK-NF-201.

The results of exposure-response analyses identified a clear relationship between exposure and tumor growth, with increasing average concentration at steady-state being predictive of

increasing reduction in tumor volume, increasing probability of response, and reduced time to response. Exposure-safety analyses identified relationships between mirdametinib and PD-0315209 exposure and incidence of several AEs. No relationships with AEs of Grade ≥ 2 severity were identified.

The actual body surface area (BSAs) and doses used in the PopPK and PKPDx modeling datasets were of a sufficiently wide range to support simulation of PK and tumor response across a range of doses. The median (minimum, maximum) of actual doses was 2.52 mg/m² (0.424, 18.6) in the PopPK model development and 2.21 mg/m² (0.806, 2.86) in participants with NF1 PN in Studies MEK-NF-201 and NF-106, which provided tumor volume measurements (Figure 4). Therefore, the range of actual doses administered in the studies used to develop these models supports their predictive ability to estimate safety and efficacy responses at target mirdametinib doses ranging from approximately 1.0 to 3.0 mg/m².

Figure 4: Distribution of Actual Doses in Studies MEK-NF-201 and NF-106



Histogram includes all non-zero actual doses corresponding to a tumor volume scan in Study MEK-NF-201 and NF-106 participants. The dashed vertical green lines indicate the interquartile range of actual doses.

Source: Derived from ADEX

Population and trial simulations were conducted using exposure-efficacy and exposure-safety models to predict the impact of various target dose levels from 1.0 to 3.0 mg/m² BID (1.0, 1.5, 2.0, 2.2, and 3.0 mg/m²). The simulations support that exposures associated with the 2 mg/m² dose of mirdametinib provide an optimal balance of robust efficacy for patients with NF1 PN with a tolerable incidence of low severity exposure-related AEs.

Population simulations were also conducted to evaluate the impact of a simplified nomogram for use with both tablet and capsule formulations. Study MEK-NF-201 used separate

nomograms for the 2 formulations, with the tablet nomogram using a 0.5 mg step. No meaningful differences from observed clinical study results for PK, efficacy, or safety were predicted using a single unified nomogram for both formulations. Therefore, the unified nomogram (Table 14) is proposed for marketing approval of both the tablet and capsule formulations of mirdametinib.

Table 23: Unified Mirdametinib Dosing Nomogram

Both Formulations (Tablet and capsule)	
BSA Range (m ²)	Unit Dose (mg BID)
0.4 to <0.7	1
0.7 to <1.05	2
1.05 to <1.5	3
≥1.5	4

Abbreviations: BID: twice daily; BSA: body surface area

The Applicant's Position:

The recommended mirdametinib dose regimen of 2 mg/m² BID, with a maximum dose of 4 mg BID, administered on a 3 weeks on/1 week off schedule for NF1 PN patients is supported by safety, tolerability, efficacy, PopPK, and exposure-response analyses. Mirdametinib has a concentration-dependent impact on PN tumor growth. Exposure-safety relationships were only significant for low severity AEs, namely lab elevations that do not correlate with clinical tolerability findings. Simulations of tumor growth and AE incidence conducted using the PopPK and PKPDx models to predict the responses over a range of target doses of 1.0, 1.5, 2.0, and 3.0 mg/m² indicated that exposures associated with the 2 mg/m² BID dose of mirdametinib provide an optimal balance of robust efficacy for patients with NF1 PN with a tolerable incidence of low severity exposure-related AEs.

Simulations from PopPK and PKPDx models also predict negligible changes to exposure and response when using the same nomograms for the tablet and capsule dose forms. Thus, mirdametinib may be dosed using a single unified nomogram, for both tablet and capsule dose forms, using 1 mg increments for each BSA band without altering the anticipated clinical outcomes for patients with NF1 PN. This unified nomogram compared with what was used in Study MEK-NF-201 will prevent errors in dose calculation that may arise from having different instructions for the two dose forms.

The FDA's Assessment:

FDA agrees with the Applicant's position. The proposed unified dosing nomogram for capsules (1, 2 mg) and tablets (1 mg) is acceptable.

6.2.2.2. Therapeutic Individualization

Data:

Body weight scaled allometrically with clearance and volume of distribution in a PopPK analysis. BSA, however, was not identified as a covariate that affects mirdametinib PK. The lack of association with BSA is expected based on the use of BSA-based guidance for selecting the administered dose. Simulations of PK by administered dose identified that PK is largely overlapping regardless of administered dose.

The age range in the PopPK analysis was from 2 through 86 years of age, however few participants over the age of 65 were enrolled in the studies. No clinically meaningful effects on mirdametinib PK were identified for age, sex, race, or baseline liver function tests. No meaningful relationships were identified for participants with creatinine clearance values consistent with mild or moderate renal impairment or for participants with bilirubin values consistent with mild hepatic impairment based on the NCI-organ dysfunction working group (ODWG) criteria.

The Applicant's Position:

Therapeutic individualization based on BSA is proposed using the simplified nomogram supported by the PopPK and PKPDx simulations (Table 14). Individualization of dosing is not required for other demographic factors (age, sex, race), for patients with mild or moderate renal impairment, or for patients with mild hepatic impairment (based on NCI-ODWG). Effects of severe renal impairment or end stage renal disease (ERSD) cannot be estimated from the PopPK analysis. Potential effects of moderate or severe hepatic impairment will be studied in a planned hepatic impairment study.

The FDA's Assessment:

FDA agrees with the Applicant's position. A PMR for renal impairment is not needed, given that mirdametinib is minimally renally eliminated (<1.5% mirdametinib and PD-0315209 recovered in the urine).

6.2.3. Outstanding Issues

The presented clinical pharmacology program adequately characterizes the PK of mirdametinib and evaluates the need for dosing guidance based on intrinsic/extrinsic factors. Nonclinical evaluations of drug-drug interaction potential suggest low clinical risk for major CYP-mediated interactions or transporters of clinical interest.

An additional clinical study is planned to evaluate the impacts of moderate or severe hepatic impairment on mirdametinib PK.

The Applicant's Position:

The impact of moderate and severe hepatic impairment on mirdametinib exposure is outstanding and will be addressed as a postmarketing commitment (PMC).

The FDA's Assessment:

FDA agrees with the Applicant's position, however notes that the effect of moderate and severe hepatic impairment on mirdametinib PK will be addressed as a PMR (instead of a PMC, as stated by the Applicant above).

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

The PK of mirdametinib is comparable between healthy adults, adults with advanced solid malignancies, and adults and children 2 years of age and older with NF1 PN. Therefore, observations and conclusions from the clinical pharmacology evaluations in healthy adults and patients without NF1 PN are of direct relevance to NF1 PN adult patients and pediatric patients. An overview of absorption, distribution, metabolism, and excretion (ADME) properties, clinical PK, and drug-drug interaction (DDI) characteristics of mirdametinib are provided below. For a list of clinical studies referenced in this section, refer to [Table 15](#).

Absorption: Mirdametinib was rapidly absorbed, with a median T_{max} of approximately 1 hour following administration of tablet or capsule formulations. Differences in T_{max} were not observed between healthy adults and patients with NF1 PN or between adult and pediatric patients.

Human absolute bioavailability was not evaluated in clinical studies. Mirdametinib is highly soluble and shows high permeability in in vitro assays. As such, a Biopharmaceutics Classification System Class I compound designation request was submitted for mirdametinib.

Distribution: The mirdametinib apparent volumes of distribution estimated from a PopPK analysis using data across clinical studies was 16 L for central compartment and 22.4 L and 54.3 L for shallow and deep peripheral compartments, respectively. Following administration of a single oral 4 mg dose to healthy male participants in the mass balance study (Study MEK-NF-101), the mean apparent volume of distribution (% coefficient of variation [CV]) was 255 L (13.4%).

Mirdametinib is highly bound to protein in human plasma. The mean unbound fraction for mirdametinib in human plasma ranged from 0.176% to 0.254% and is independent of mirdametinib concentration.

Metabolism: Mirdametinib undergoes oxidation and glucuronidation and forms predominantly the metabolites PD-0315209 (a carboxylic acid metabolite) and M22 (a secondary O-glucuronide metabolite of mirdametinib). In the mass balance study (Study MEK-NF-101), mirdametinib was highly metabolized, with <10% of mirdametinib excreted unchanged by either route (0.7% and 8% of the dose in urine and in feces, respectively). Mirdametinib and PD-0315209 represented 35.3% and 24.0% of total plasma radioactivity, respectively. M22 represented 14.7% of total plasma radioactivity. In vitro experiments indicate that the metabolism of mirdametinib involves UGT and CES enzymes.

PD 0315209 was significantly less effective than mirdametinib (approximately 2200-fold difference) at reducing ERK phosphorylation in tumor cells grown in culture. PD-0315209 also transiently suppressed pERK in tumor bearing mice; however, the PopPK predicted C_{max,ss} for PD-0315209 at the proposed target dose of 2 mg/m² BID is approximately 8-fold lower than the IC₅₀ for pERK suppression. M22 was significantly less effective than mirdametinib (> 75-fold difference) at reducing ERK phosphorylation in tumor cells grown in culture and, as a Phase 2 conjugation reaction generally renders a compound more water soluble and pharmacologically inactive, no further evaluation was warranted. Neither metabolite is expected to have a substantial contribution to pharmacological activity of mirdametinib.

Excretion: In the mass balance study (Study MEK-NF-101), renal excretion of glucuronide metabolites was found to be the major route of elimination for mirdametinib in humans; a mean of 67.7% of the radiolabel was recovered in urine and 27.3% in feces. The urinary excretion of unchanged parent drug was minor, at approximately 0.7%. In the Phase 1/2 study in advanced cancers, urinary excretion of unchanged parent drug was minor (approximately 2% to 6%), and <1% was excreted as PD-0315209 (Study A4581001).

Clinical Pharmacokinetics: In participants with advanced cancer, mirdametinib was rapidly absorbed and exposure generally increased proportional to dose from 1 mg QD/BID to 30 mg BID (Study A4581001). The mean t_{1/2} was 28 hours following a single dose of 4 mg in the mass balance study that was conducted in healthy male participants (Study MEK-NF-101). The observed intersubject variability (coefficient of variation [CV%]) for cold mirdametinib AUC and C_{max} in the mass balance study was 12.0 % and 16.5%, respectively. Following multiple oral BID doses, mirdametinib mean accumulation ratio on Day 21 ranged from 1.1 to 1.9 across different dose levels in participants with solid tumors (Study A4581001). The PopPK model predicted mean accumulation ratio for participants with NF1 PN receiving a mirdametinib dose of 2 mg/m² BID, with a maximum dose of 4 mg BID, in Study MEK NF 201 ranged from 1.88 to 2.09.

Gastric acid modifying agents: The solubility of mirdametinib exceeds 16 µg/mL (4 mg/250 mL) across the physiological pH range (1.2 to 7.5). Dissolution data also support rapid dissolution of all strengths of (b) (4) capsule dose forms across the physiological pH range. Therefore, drugs that modify gastric pH are not expected to impact the dissolution or solubility

of mirdametinib and represent a low risk of altering its clinical exposure.

Renal Impairment: Total urinary elimination of mirdametinib and PD-0315209 was 1.3% of the administered drug (Study MEK-NF-101). In the regulatory guidance on PK in renal impairment (FDA 2020), a drug is considered to be substantially eliminated by the renal route when the fraction of systemically available drug or active metabolite eliminated in the urine is >30%. Therefore, effects of renal impairment on the PK of mirdametinib have not been evaluated in a dedicated clinical study. Of note, the enrollment of participants with CLCR indicative of mild renal impairment was allowed in Study MEK NF-201. Additionally, participants with moderate renal impairment were included in Studies A4581001 and A4581002. Covariate analysis for baseline creatinine clearance (CLCR) was conducted in the PopPK analysis. The PopPK analysis population contained 60 participants with CLCR consistent with mild impairment and 10 participants with moderate impairment. No relationship between mirdametinib PK and CLCR was observed. A statistically significant effect was found for CLCR on the clearance of PD-0315209 (CL_m/F), suggesting a decrease in CL_m/F with increasing severity of renal impairment. PopPK model predicted exposures of PD-0315209 for participants with normal function, mild renal impairment, or moderate renal impairment suggest an increase in exposure to PD-0315209 in participants with moderate renal impairment; however, the exposures remain far below concentrations associated with pERK inhibition. Participants with severe renal impairment and ESRD were not represented in the PopPK analysis and expected effects to mirdametinib and PD-0315209 exposure cannot be extrapolated.

Hepatic Impairment: The effects of hepatic impairment on the PK of mirdametinib have not been evaluated in a dedicated clinical study. Covariate analysis for baseline liver function tests was conducted in the PopPK analysis. Based on baseline bilirubin values and the NCI-ODWG classification system, 19 participants in the PopPK analysis population were consistent with mild impairment (Group B2) and 6 were consistent with moderate impairment (Group C). No clinically meaningful relationships were observed between mirdametinib or PD-0315209 PK and baseline liver enzymes levels (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and Bilirubin). The effects of moderate and severe hepatic impairment cannot be inferred from the PopPK analysis. A dedicated clinical study in these populations is planned as a PMC.

Victim DDI: Mirdametinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). PD-0315209 is a substrate of BCRP. Concomitant use of P-gp inhibitors showed no impact on PopPK model predicted exposures of mirdametinib and PD-0315209. No dedicated clinical studies have been conducted to assess the risk of victim DDIs from P-gp or BCRP inhibitors.

Nonclinical studies suggest minimal risk for DDIs from inhibitors or inducers of CYP-mediated metabolism. Mirdametinib is a substrate of UGT and CES enzymes. PD-0315209 is a substrate of UGT enzymes. Concomitant use of UGT1A6 inhibitors and inducers, UGT2B7 inhibitors and inducers, and CES inhibitors showed no impact on PopPK model predicted exposures of

mirdametinib. An effect of UGT2B7 inducers was observed on the fraction metabolized (F_m) to PD-0315209, leading to a 19% increase in F_m. Model predicted exposures for PD-0315209 were still comparable in participants with and without concomitant use of UGT2B7 inducers.

Perpetrator DDI: No clinical DDI studies have been performed. In vitro studies suggest a low potential to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 at the highest anticipated clinical dose (4 mg BID). There is also low induction potential for CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP2C19. Mirdametinib induced CYP3A4 mRNA expression with apparent maximum effect (E_{max}) and apparent half-maximum effect (EC₅₀) values of ~> 3.17 to ~> 5.74 (fold) and ~> 10uM. The calculated R₃ value of 0.98 does not indicate that mirdametinib has induction potential in vivo. Mirdametinib also showed no detectable or limited (< 50%) inhibition of UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15.

There is also low potential for mirdametinib and PD-0315209 to perpetrate DDIs involving inhibition of efflux and uptake transporters (P-gp, BCRP, multidrug and toxin extrusion protein [MATE]1, MATE2K, organic anion transporting polypeptide [OATP]1B1, OATP1B3, organic anion transporter [OAT]1, OAT3, and organic cation transporter [OCT]2) at clinically relevant free plasma concentrations.

QTc: Based on a dedicated thorough QT study (MEK-NF-102), mirdametinib does not prolong the QTc interval in healthy subjects and does not have any adverse effect on cardiac repolarization at concentrations well above steady-state peak exposures.

The Applicant's Position:

The clinical pharmacology of mirdametinib and PD-0315209 has been adequately characterized by clinical evaluations. The primary metabolites in humans were identified, results from nonclinical assays demonstrate that contribution of the metabolites to pharmacological activity is not clinically relevant. No clinical evaluations of DDIs were conducted, however, in vitro assessments support low risk of clinically relevant interactions with major CYP enzymes or transporters. The PopPK analysis was sufficient to evaluate expected effects from mild and moderate renal impairment and mild hepatic impairment. No dose adjustments are necessary in these populations and a clinical study is planned to further evaluate the effects of moderate and severe hepatic impairment. The overall evaluation of clinical pharmacology supports the selection of 2 mg/m² BID as an appropriate dose for adult and pediatric patients with NF1 PN.

The FDA's Assessment:

FDA agrees with the Applicant's position. FDA notes that the effect of moderate and severe hepatic impairment on mirdametinib PK will be addressed as a PMR (instead of a PMC, as stated by the Applicant above). The DDI assessment based on the PopPK model alone is considered inadequate due to many patients who take multiple medications together at the same time. Regarding DDI evaluations, mirdametinib is not likely to be affected by concomitant

inhibitors to a clinically relevant extent, given that mirdametinib is metabolized via multiple pathways and enzymes. The effect of concomitant strong CYP3A4 inducers (that also co-induce UGTs, P-gp, and CES enzymes) on mirdametinib PK is currently unknown and will be addressed as a PMC.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

Yes. The exposure-response analyses identified a clear relationship between mirdametinib exposure and response within the range of actual doses used in the NF1 PN clinical studies. Mirdametinib has a concentration-dependent impact on PN tumor growth and overall response. The final tumor growth inhibition (TGI) model was used to generate simulations to evaluate target doses (1, 1.5, 2, and 3 mg/m²) of mirdametinib BID by comparing efficacy (response rate, with response defined as tumor volume reduction from baseline exceeding 20%, or percent change from baseline). Desirable clinical efficacy is predicted at target doses as low as 1 mg/m² BID; however, substantial increases in both magnitude and time of response are predicted at the recommended starting dose of 2 mg/m² BID. As the starting dose allows for potential reduction due to tolerability, this relationship ensures high probability of response at the initial dose and confidence that a clinically active dose is still expected in the event of individual reductions.

The Applicant's Position:

The mirdametinib clinical pharmacology program supports that exposure resulting from the proposed regimen 2 mg/m² dose (maximum 4 mg) BID on a 3 weeks on/1 week off schedule provides effective reduction in tumor volume in both adult and pediatric patients with NF1 PN.

The FDA's Assessment:

FDA agrees with the Applicant's position. Additionally, the proposed dosage forms of capsules (1, 2 mg) and tablets (1 mg) are acceptable based on overlapping PK observed between adult and pediatric patients following administration of 2 mg/m² BID via tablets or capsules, including comparable PK in the overlapping ages of pediatric patients who received tablets vs. capsules (age 5 to 14 years). Efficacy was observed across pediatric age groups (2 to < 12, 12 to < 18 years), while differences in TEAEs by dosage form appear attributable to age-related development differences. The proposed unified dosing nomogram is also acceptable, based on the PPK simulation which showed no expected clinically meaningful differences in systemic exposures.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Data:

Yes. In the PopPK analysis, no clinically meaningful covariate effects for sex, race, or disease status were found. An allometric effect for weight on the clearance and volumes of distribution for mirdametinib and PD-0315209 was found; the BSA-driven dosing adequately controls for substantial variance across the range of actual doses administered. Most AEs were managed by standard supportive care measures and/or dose modifications based on BSA.

The Applicant's Position:

The proposed BSA-based dosing regimen of 2 mg/m² BID, with a maximum dose of 4 mg BID, on a 3 weeks on/1 week off schedule is suitable for both adult and pediatric patients with NF1 PN.

The FDA's Assessment:

FDA agrees with the Applicant's position. The proposed recommended dosage is acceptable, based on the observed benefit-to-risk profiles of mirdametinib from pivotal Study MEK-NF-201 and supportive Study NF-106.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

Data:

The effects of hepatic impairment on the PK of mirdametinib were not evaluated in a dedicated clinical study. Covariate analysis for baseline liver function tests was conducted in the PopPK analysis. Based on baseline bilirubin values and the NCI-ODWG classification system, 19 participants in the PopPK analysis population were consistent with mild impairment (Group B2) and 6 were consistent with moderate impairment (Group C). No clinically meaningful relationships were found between mirdametinib PK and baseline liver enzymes levels (AST, ALT, and bilirubin). The effects of moderate and severe hepatic impairment cannot be inferred from the PopPK analysis. A dedicated clinical study in these populations is planned.

The effects of renal impairment on the PK of mirdametinib have not been evaluated in a dedicated clinical study. Covariate analysis for baseline CLCR was conducted in the PopPK analysis. The PopPK analysis population contained 60 participants with CLCR consistent with mild impairment and 10 participants with moderate impairment. No relationship between mirdametinib PK and CLCR was observed. PopPK-predicted C_{max}, C_{trough}, and AUC for mirdametinib were not meaningfully different between participants with normal function, mild renal impairment, or moderate renal impairment. No evaluations have been conducted with

participants with severe renal impairment or ESRD. Due to high plasma protein binding, dialysis is unlikely to affect systemic mirdametinib exposure and is unlikely to be beneficial to treat mirdametinib overdose.

The Applicant's Position:

Based on intrinsic patient factors in the PopPK analyses, no alternative dosing regimen or management strategy is required based on demographic factors or for patients with mild hepatic impairment (NCI-ODWG Group B1 and B2), mild renal impairment, or moderate renal impairment. The potential impact to mirdametinib PK from severe renal impairment or ESRD and for moderate or severe hepatic impairment cannot be described at this time.

The FDA's Assessment:

FDA agrees with the Applicant's position. A PMR will be issued to evaluate the effect of moderate and severe hepatic impairment on mirdametinib PK.

NF1 Genotype

Enrollment in MEK-NF-201 was based on a patient having either a clinical diagnosis of NF1 using the NIH Consensus Conference criteria or a pathogenic documented *NF1* variant. In the FAS, 27/58 (47%) adult patients and 25/56 (45%) pediatric patients were enrolled based on documented *NF1* variant status (Table 28). Subject level genotype and type of *NF1* variant was not collected as part of study MEK-NF-201. In response to FDA IR dated 21 August 2024, the Applicant provided available subject level *NF1* variant data for 19/56 (34%) pediatric and 6/58 (10%) adult patients from the FAS. Given the complexity of the *NF1* locus, the Applicant grouped variants into the following categories: deletion, duplication, indel, missense, nonsense, or splice. In pediatric patients, the distribution of *NF1* variants was as follows: nonsense (N = 6, 31.6%), splice (N = 5, 26.3%), duplications (N = 4, 21.0%), deletions (N = 3, 15.8%), and missense (N = 1, 5.3%). In the group of adult patients, 3 patients had *NF1* deletions (50%), 1 patient had an indel variant (16.7%), 1 patient had a missense variant (16.7%), and 1 patient had a nonsense variant (16.7%). In general, the types and distribution of variants across the *NF1* locus were consistent with estimates from the literature (PMID: 34566848, PMID: 38095723, PMID: 23244495). The ORRs in pediatric and adult patients with available *NF1* variant data were similar to the ORRs in the FAS (Table 15, Table 16). In terms of best confirmed objective responses, PRs were observed across all *NF1* variant categories with data from ≥1 patient per category. Of note, one adult patient with a deletion encompassing the full coding sequence of *NF1*, which is associated with larger numbers and earlier appearance of cutaneous and PNs (PMID: 34566848, PMID: 38095723), achieved a confirmed PR of the target PN. This exploratory analysis suggests that treatment with mirdametinib induces objective responses in patients carrying different types of pathogenic *NF1* variants.

Table 24. Confirmed objective response rates and best objective responses by *NF1* variant category.

	Pediatric (N=19)						
	Deletion (N=3)	Duplication (N=4)	Indel (N=0)	Missense1 (N=1)	Nonsense (N=6)	Splice Variant (N=5)	Total (N=19)
Confirmed Objective Response Rate							
n	3	3	0	1	2	1	10
%	100%	75.0%	0	100%	33.3%	20.0%	52.6%
95% CI	(29.2, 100.0)	(19.4, 99.4)	NA	(2.5, 100.0)	(4.3, 77.7)	(0.5, 71.6)	(28.9, 75.6)
p-value	<0.001	0.006	NA	0.046	0.414	1.000	<0.001
Best Overall Confirmed Response Status							
Complete Response	0	0	0	0	0	0	0
Partial Response	3 (100%)	3 (75.0%)	0	1 (100%)	2 (33.3%)	1 (20.0%)	10 (52.6%)
Stable Disease	0	1 (25.0%)	0	0	4 (66.7%)	2 (40.0%)	7 (36.8%)
Progressive Disease	0	0	0	0	0	2 (40.0%)	2 (10.5%)
Not Evaluable	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0

Source: Applicant response to FDA IR received 20 September 2024.

CI: Confidence interval; CR: Complete Response; PR: Partial Response. Target lesion baseline occurs at Screening.

N represents the number of participants in the corresponding cohort. n is the number of confirmed objective responders. Confirmed objective response is defined as two consecutive assessments of PR or CR assessed by a BICR within 2-6 months during the Treatment Phase.

95% CIs are derived using the Clopper-Pearson approach.

P-values are calculated using a one-sample two-sided binomial test compared to the minimally clinically relevant response rates of 20% for the pediatric cohort.

Participants who had no post-baseline MRI assessment or no confirmed objective response are treated as non-responders. Best overall confirmed response status is defined as the best confirmed response prior to disease progression during the Treatment Phase. Missing contains participants who have no post-baseline assessments.

[1] GTPase activating domain.

Table 25. Confirmed objective response rates and best objective responses by *NF1* variant category.

	Adult (N=6)						Total (N=6)
	Deletion (N=3)	Duplication (N=0)	Indel (N=1)	Missense ¹ (N=1)	Nonsense (N=1)	Splice Variant (N=0)	
Confirmed Objective Response Rate							
n	2	0	1	0	1	0	4
%	66.7%	0	100%	0	100%	0	66.7%
95% CI	(9.4, 99.2)	NA	(2.5, 100.0)	(0.0, 97.5)	(2.5, 100.0)	NA	(22.3, 95.7)
p-value	0.072	NA	0.067	0.585	0.067	NA	0.011
Best Overall Confirmed Response Status							
Complete Response	0	0	0	0	0	0	0
Partial Response	2 (66.7%)	0	1 (100%)	0	1 (100%)	0	4 (66.7%)
Stable Disease	1 (33.3%)	0	0	1 (100%)	0	0	2 (33.3%)
Progressive Disease	0	0	0	0	0	0	0
Not Evaluable	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0

Source: Applicant response to FDA IR received 20 September 2024.

CI: Confidence interval; CR: Complete Response; PR: Partial Response. Target lesion baseline occurs at Screening.

N represents the number of participants in the corresponding cohort. n is the number of confirmed objective responders. Confirmed objective response is defined as two consecutive assessments of PR or CR assessed by a BICR within 2-6 months during the Treatment Phase.

95% CIs are derived using the Clopper-Pearson approach.

P-values are calculated using a one-sample two-sided binomial test compared to the minimally clinically relevant response rates of 23% for the adult cohort.

Participants who had no post-baseline MRI assessment or no confirmed objective response are treated as non-responders. Best overall confirmed response status is defined as the best confirmed response prior to disease progression during the Treatment Phase. Missing contains participants who have no post-baseline assessments.

[1] GTPase activating domain.

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:

Food Effect: Study A4581004 evaluated the effect of a high-fat, high-calorie meal on mirdametinib PK in healthy adult participants receiving a single oral 20 mg dose of mirdametinib. The dose evaluated in this study is higher than the proposed dose of 2 mg/m² BID for NF1 PN because it was conducted at a dose hypothesized to be relevant to the advanced cancer indication under development at the time. PopPK analysis supports dose proportionality up to at least 20 mg, indicating that results from this study are applicable to the 2 mg/m² dose level. Consumption of a high-fat, high-calorie meal reduced and delayed the rate of absorption (43% reduction in C_{max}; T_{max} delayed by 2 hours). The extent of absorption was slightly reduced (AUC_{inf} reduced by 7%), but the confidence intervals of the geometric least-squares mean ratio (GLMR) remained within standard bioequivalence limits. Mirdametinib was dosed without regard to food in Study MEK-NF-201 and NF-106.

Exposure-response analyses concluded that average concentration, or AUC, is the primary driver of efficacy for mirdametinib. Therefore, a reduction in C_{max} with maintenance of the overall extent of exposure is not considered clinically meaningful for mirdametinib. Mirdametinib may be dosed without regard to food.

Gastric acid modifying agents: Mirdametinib is highly soluble across the physiological pH range. Dissolution data also support rapid dissolution of all strengths of both tablet and capsule dose forms across the physiological pH range. Therefore, drugs that modify gastric pH are not expected to impact the dissolution or solubility of mirdametinib and represent a low risk of altering its clinical exposure. Mirdametinib may be taken concomitantly with gastric acid reducing agents.

Victim DDI: Mirdametinib is a substrate of P-gp and BCRP. PD-0315209 is a substrate of BCRP. Concomitant use of P-gp inhibitors showed no impact on PopPK model predicted exposures of mirdametinib and PD-0315209. No dedicated clinical studies have been conducted to assess the risk of victim DDIs from P-gp or BCRP inhibitors.

Nonclinical studies suggest minimal risk for DDIs from inhibitors or inducers of CYP-mediated metabolism. Mirdametinib is a substrate of UGT and CES enzymes. PD-0315209 is a substrate of UGT enzymes. Concomitant use of UGT1A6 inhibitors and inducers, UGT2B7 inhibitors and inducers, and CES inhibitors showed no impact on PopPK model predicted exposures of mirdametinib. An effect of UGT2B7 inducers was observed on the F_m to PD-0315209, leading to a 19% increase in F_m. Model predicted exposures for PD-0315209 were still comparable in participants with and without concomitant use of UGT2B7 inducers.

Taken together, mirdametinib is unlikely to be susceptible to CYP- or transporter-mediated DDIs

in a clinically meaningful capacity.

Perpetrator DDI: No clinical DDI studies have been performed. In vitro studies suggest a low potential to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 at the highest anticipated clinical dose (4 mg BID). There is also low induction potential for CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP2C19. Mirdametinib induced CYP3A4 mRNA expression with apparent E_{max} and apparent EC₅₀ values of ~> 3.17 to ~> 5.74 (fold) and ~> 10uM. The calculated R₃ value of 0.98 does not indicate that mirdametinib has induction potential in vivo. Mirdametinib also showed no detectable or limited (< 50%) inhibition of UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15.

Taken together, mirdametinib is unlikely to result in CYP- or transporter-mediated DDIs at clinically relevant exposures.

The Applicant's Position:

Based on in vitro and clinical studies, management strategies for food, gastric PH, and DDIs are not required.

The FDA's Assessment:

FDA agrees with the Applicant's position. A PMC will be issued to evaluate the effect of concomitant a strong CYP3A4 inducer (that also co-induce UGTs, P-gp, and CES enzymes) on mirdametinib PK.

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Jeanne Fourie Zirkelbach

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Hezhen Wang

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X

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7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

Safety and efficacy studies relevant to this NDA are provided in [Table 26](#). In addition to the studies provided in [Table 26](#), data from 8 additional non-pooled interventional studies and the compassionate use program were used as supportive safety information, for a total of 577 patients exposed to mirdametinib.

NDA/IND Multi-disciplinary Review and Evaluation NDA 219379/219389
Mirdametininib (GOMEKLI)

Table 26: Listing of Clinical Trials Relevant to this NDA

Study Identifier / NCT Number / eCTD location	Study Design	Regimen/ schedule/ route	Primary Objective	Study Population	Number of Participants Enrolled, Centers, and Countries
Pool 1: Studies to Support Safety and Efficacy					
MEK-NF-201 / NCT03962543 / Module 5.3.5.2	Phase 2b, open-label, multi-center, longitudinal study	2 mg/m ² BID/ 4-week cycle (3 weeks on / 1 week off) / Oral capsule and oral tablet	To evaluate the confirmed CR and PR rates of mirdametininib using volumetric MRI analysis, as assessed by BICR, in participants with an inoperable NF1-associated PN that is causing significant morbidity.	Participants with NF1-associated inoperable PNs that cause significant morbidity (Age ≥2 years)	114 participants (58 Adult, 56 Pediatric) / 50 centers / 1 country
NF-106 / NCT02096471 / Module 5.3.5.2	Phase 2, open-label, multi-center study	2 mg/m ² BID/ 4-week cycle (3 weeks on / 1 week off) / Oral capsule	To evaluate the confirmed ORR (CR + PR) of mirdametininib using volumetric MRI analysis, in participants with a NF1 and PN	Participants with NF1-associated inoperable morbid or progressing PNs (Age ≥16 years)	19 participants / 10 centers / 1 country
Pool 2: Studies to Support Safety					
A4581001 / NCT00147550 / Module 5.3.5.2	Phase 1-2, multicenter, open-label, noncomparative study Phase 1: Dose escalation, PK, and PD	Phase 1: 1 mg QD to 30 mg BID / 4-week cycle (3 weeks on / 1 week off) / Oral solution 10 to 20 mg BID / cont / Oral Solution 10 mg BID (5 days on/2 days off)/ Oral Solution	Phase 1: To determine the safety profile, including DLTs, MTD, RP2D, PK profile, and preliminary antitumor activity. Phase 2: To determine the antitumor activity.	Participants with Advanced Cancer (Age ≥18 years)	Phase 1: 66 participants Phase 2: 13 participants / 10 centers / 1 country

NDA/IND Multi-disciplinary Review and Evaluation NDA 219379/219389
Mirdametinib (GOMEKLI)

Study Identifier / NCT Number / eCTD location	Study Design	Regimen/ schedule/ route	Primary Objective	Study Population	Number of Participants Enrolled, Centers, and Countries
		Phase 2: 15 to 20 mg BID / 4-week cycle (3 weeks on / 1 week off) / Oral Solution			
A4581002 / NCT00174369 / Module 5.3.5.2	Phase 2, single-arm, multicenter, open-label study	15 mg BID / 28-day cycle with 3 weeks on / 1 week off (Schedule 1) 28-day cycle with 5 days on / 2 days off for 3 weeks, followed by 1 week off (Schedule 2)/ Oral capsule	To determine the activity of mirdametinib in advanced non-small cell lung cancer participants as measured by ORR, CR, and PR by RECIST.	Participants with Advanced Non-Small Cell Lung Cancer (Age ≥18 years)	34 participants / 8 centers / 1 country
Healthy Volunteer Studies					
A4581004 / Module 5.3.3.1	Phase 1, single-arm, 2-stage, open-label PK Food Effect Study	20 mg / single dose / Oral capsule	To assess the effect of a high-fat, high-calorie meal and fasting on mirdametinib PK, and the effect of timing of meals relative to dosing of mirdametinib PK following a	Healthy participants between 21 and 55 years old, inclusive.	23 participants/ 1 center/ 1 county

NDA/IND Multi-disciplinary Review and Evaluation NDA 219379/219389
Mirdametininib (GOMEKLI)

Study Identifier / NCT Number / eCTD location	Study Design	Regimen/ schedule/ route	Primary Objective	Study Population	Number of Participants Enrolled, Centers, and Countries
			single oral dose in healthy volunteers.		
MEK-NF-101/ Module 5.3.3.1	Phase 1, single arm, single-center, open-label PK, metabolism, mass balance study	4 mg / single dose / [¹⁴ C] mirdametininib Oral solution	To evaluate the mass balance, routes of elimination, pharmacokinetics, and safety and tolerability of a single oral dose of mirdametininib, in healthy male volunteers	Healthy males between 18 and 50 (inclusive).	8 participants/ 1 center/ 1 country
MEK-NF-102/ Module 5.3.3.1	Phase 1 QT/QTc Study	Placebo, mirdametininib 6 mg or 14 mg, or moxifloxacin 400 mg/ single dose / oral solution	To evaluate the relationship between mirdametininib plasma concentrations and time-matched, placebo-corrected, baseline-adjusted difference in QTc using Fridericia's formula (QTcF) ($\Delta\Delta\text{QTcF}$).	Healthy participants between 18 and 55 (inclusive).	57 participants /1 center/ 1 country

The FDA's Assessment:

FDA agrees with the Applicant's position and notes that the primary analysis of efficacy and safety was based on results from Study MEK-NF-201. The Applicant submitted a complete data set for this study, using a data cut date of September 20, 2023, at the time of the initial NDA submission. The Applicant submitted an updated data set, with DCO of June 12, 2024, at the time of the 90-day safety update (submitted September 26, 2024, to SDN 19). The updated data from Study MEK-NF-201 will form the basis for this review.

Efficacy from Study NF-106 was evaluated as supportive evidence given differences in the study design that did not allow for full evaluation of ORR and DOR, with patients being required to discontinue treatment if they did not have a response by a certain timepoint. Results from this trial were not independently verified during the review of this application.

Study MEK-NF-201 was open-label and did not include a comparator arm; therefore, the analyses of efficacy and safety are descriptive only. Where possible, confidence intervals are provided to assist in the interpretation of the efficacy data. For additional statistical methodologies, see Section 8.1.1.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

Studies MEK-NF-201 and NF-106 are the relevant studies used to support efficacy.

8.1.1. Study MEK-NF-201

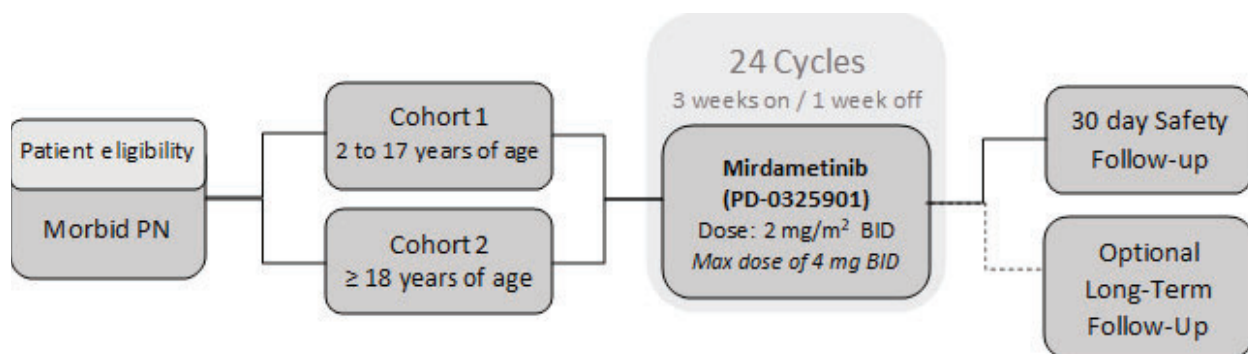
Study Design

The Applicant's Description:

Study MEK-NF-201 is an open-label, multi-center, Phase 2b study being conducted to determine the efficacy and safety of mirdametinib in participants ≥ 2 years old with symptomatic inoperable NF1-associated PNs. A total of 113 participants enrolled and stratified by age (approximately 50 participants 2 to 17 years of age and 50 participants ≥ 18 years of age). Mirdametinib was orally administered at a dose of 2 mg/m² BID (maximum 4 mg BID) in 4-week cycles on an intermittent (3 weeks on/1 week off) schedule. This study consists of two phases: the Treatment Phase (24 cycles) and the optional Long Term Follow Up (LTFU) Phase.

Participants who completed Cycle 24 of the Treatment Phase and did not meet withdrawal criteria were eligible to participate in the LTFU Phase. Withdrawal criteria included the participant having met the definition of progressive disease, occurrence of a medical condition or circumstance that exposed participant to substantial risk or prevented the participant from adhering to protocol requirements, any SAE which the investigator considered was not in the best interest of the participant to continue, pregnancy, prohibited concomitant medication, failure to comply with protocol requirements, or termination of the study by the Sponsor, IRB or regulatory authority. Eligible participants will continue taking the last dose assigned in the Treatment Phase. Participants will remain in the LTFU Phase until a withdrawal criterion is met or mirdametinib is commercially available. The treatment phase of the study is completed; the LTFU phase of the study is currently ongoing.

Figure 5: Schema



The primary endpoint was confirmed ORR, defined as the proportion of participants who had a confirmed $\geq 20\%$ reduction in target tumor volume compared to baseline as assessed by a blinded independent central reviewer (BICR). The response needed to be confirmed in a consecutive tumor assessment within 2 to 6 months during the treatment phase. All tumor volume measurements were independently determined by 2 reviewers. In the case that the two measurements represented different tumor response statuses, as defined above, an independent adjudicator made the final decision on which response category is recorded at that visit. The primary endpoint analysis was performed using the adjudicator-selected reader for those visits where the two BICR readers did not agree. Magnetic resonance imaging (MRI) was performed approximately every 4 cycles throughout the Treatment Phase and the LTFU Phase.

Key secondary endpoints included duration of response (DoR), quality of life (QoL) and pain questionnaires, and safety and tolerability of mirdametinib.

Administrative Structure

This study utilized an independent data monitoring committee (DMC) and operated according to an established charter. The committee was composed of 3 members including physicians knowledgeable in the treatment of NF1 and an independent statistician. Sponsor employees were not members of the DMC. The DMC was responsible for ongoing monitoring of the safety, efficacy and benefit/risk profile of participants in the Treatment Phase of the study. Reviews included aggregate safety, targeted medical events of special interest, serious AE data and aggregate endpoint data.

Study Location

A total of 50 sites were opened across the US.

External Control Data

As the natural history of NF1 PN is incompletely described in the published literature, notably for the adult population, NF1 natural history data were gathered and analyzed to serve as an external historical control to support this application.

Two historical controls studies were included in these analyses: the placebo control arm of Study 01-C-0222 and the natural history Study 08-C-0079; both studies were conducted by the NCI.

Study 01-C-022

Study 01-C-0222 was an NCI-sponsored Phase 2 randomized, flexible crossover, double-blinded, placebo-controlled study of tipifarnib, a farnesyltransferase inhibitor, in children and young adults (aged 3-25 years) with NF1 and progressive PNs at baseline with the potential to cause significant morbidity. The study started in Jul2001 and was completed in Feb2009. To be eligible for this study, participants must have had tumors that were measurable, defined as ≥ 3 cm in one direction, and progressive, defined as either a $\geq 20\%$ increase in target PN volume, $\geq 13\%$ increase in 2-D, or $\geq 6\%$ increase in 1-D measurement over last 2 consecutive MRI scans or within approximately 1 year prior to screening.

Participants were randomized in a double-blinded fashion to receive tipifarnib or placebo (Phase A) and crossed over to the opposite treatment arm at the time of tumor progression (Phase B) after a 2-week washout period following Phase A. Participants remained in Phase B until tumor progression or they met other criteria for treatment discontinuation. Tipifarnib (200 mg/m²/dose orally every 12 hours) or placebo was administered twice daily for 21 days followed by a 7-day rest period between cycles. The primary endpoints were time to progression (TTP), ORR, and the incidence of AEs. QoL was also monitored by the NIH Impact of Pediatric Illness Scale. PN volumes were measured with MRI at the start of Cycles 1, 4, 7, and 10, followed by every 6 cycles. Progression was defined as $\geq 20\%$ volume increase in at least 1 target PN compared with baseline; a response was defined as $\geq 25\%$ reduction in the sum of the volume of all index lesions for ≥ 4 weeks.

Participants in this study could have had up to 3 target lesions with volumetric measurements. All lesions with an adequate number of sequential measurements were analyzed, with the date of progression being the first date that the criteria for progression was met by any lesion.

Study 08-C-0079

Study 08-C-0079 is an NCI-sponsored observational and longitudinal analysis of participants with clinically confirmed NF1 or a known NF1 mutation to characterize the natural history of NF1. New participants evaluated at the NIH were ≤ 35 years and there was no upper age limit for participants previously enrolled in clinical trials at NIH or for participants diagnosed with MPNST, with clinical concern for MPNST, or with infrequent or unusual NF1-related manifestations. Participants in the study were allowed to undergo clinically indicated surgeries and medical treatments and concurrently enroll in clinical trials for PNs. Participants remained on study until they met the criteria for discontinuation (including withdrawal of consent, serious protocol violation, lost to follow-up, or completed study objectives per the principal investigator).

Diagnostic Criteria

Children and adults with NF1 and PN, with a PN-related morbidity at enrollment as determined by the site PI.

Eligibility Criteria

Key inclusion criteria included:

- Participant must be ≥ 2 years of age inclusive, at the time of signing the informed consent/assent; participant must have weighed ≥ 10 kg with a body surface area of ≥ 0.4 m²
- Participant had EITHER the clinical diagnosis of NF1 using the NIH Consensus Conference criteria OR have a constitutional NF1 mutation documented in a Clinical Laboratory Improvement Amendments/College of American Pathologists certified lab.
- Participants must have a target PN that is causing significant morbidity, such as (but not limited to) head and neck lesions that are compromising the airway or great vessels, brachial or lumbar plexus lesions that are causing nerve compression and loss of function, lesions causing major deformity or are significantly disfiguring, lesions of the extremity that cause limb hypertrophy or loss of function, and painful lesions.
- Participant has a target PN that is deemed inoperable, defined as a PN that cannot be completely surgically removed without risk for substantial morbidity due to: encasement of or close proximity to vital structures, invasiveness, or high vascularity of the PN, or the participant refuses surgery.
- Participants must have a target PN, defined as the clinically most relevant PN, amenable to volumetric MRI analysis. For the purpose of this study, the target PN must be seen on at least 3 consecutive MRI slices and the field of view must contain the entire tumor of interest.
- Participants ≥ 16 years of age must have had a Karnofsky performance level of $\geq 50\%$, and participants < 16 years must have had a Lansky performance level of $\geq 50\%$

Key exclusion criteria included:

- Participant had a Screening ALT value of > 2.0 x upper limit of normal (ULN);
- Participant had a Screening total bilirubin value of > 1.5 x ULN (isolated bilirubin > 1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin $< 35\%$);
- Any clinically significant active or known history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones);
- Participants with evidence of an active optic glioma or other low-grade glioma, requiring treatment with chemotherapy or radiation therapy. Participants not requiring treatment were eligible. Ophthalmological findings secondary to long-standing optic pathway glioma (such as visual loss, optic nerve pallor or strabismus) or long-standing orbito-

temporal PN (such as visual loss, strabismus) will NOT be considered a significant abnormality for the purposes of the study;

- Pregnant or breast-feeding females
- Participant recorded a left ventricular ejection fraction (LVEF) < 55% at Screening or within 3 years of signing informed consent/assent, OR has a history of congestive heart failure;
- Participant had a history of, or evidence of, retinal pathology on ophthalmologic examination that is considered a risk factor for central serous retinopathy, retinal vein occlusion (RVO), or neovascular macular degeneration. Participants were excluded from study participation if they have any of the following risk factors for RVO at Screening:
 - Intraocular pressure > 21 mmHg;
 - Serum cholesterol > 300 mg/dL;
 - Serum triglycerides > 300 mg/dL;
 - Hyperglycemia (fasting blood glucose > 125 mg/dL or random blood glucose > 200 mg/dL);
 - Age specific hypertension
 - Participants ≥ 13 years of age with a blood pressure ≥ 140/90 mm Hg
 - Participants ≤ 12 years of age with a blood pressure ≥ 95th percentile for age + 12 mmHg
- Participant had a history of glaucoma;
- Participant had received NF1 PN-targeted therapy (e.g., farnesyltransferase inhibitors, kinase inhibitors, etc.) within 45 days of first dose of study treatment (or 5.5 half-lives, whichever is longer). All toxicities from prior therapy must resolve to ≤ Grade 1 or Baseline;
- Participant previously received or is currently receiving therapy with mirdametinib or any other MEK1/2 inhibitor (e.g., selumetinib, trametinib, cobimetinib, binimetinib, etc.).

Dose Selection

Mirdametinib was administered orally at a dose of 2 mg/m² BID with a maximum dose of 4 mg BID on a 28-day Cycle (4-week course) with a 3 week on/1 week off schedule. The nomograms used for the capsule and dispersible tablet formulation are described in Table 27 and Table 28.

Table 27: Study MEK-NF-201 Capsule dosage form

BSA (m ²)	0.4 to 0.69	0.7 to 1.04	1.05 to 1.49	≥ 1.5
BID unit dose	1 mg	2 mg	3 mg	4 mg

BSA = body surface area; mg = milligrams

All study dosing will be administered on a 3 weeks on/1 week off intermittent schedule

Table 28: Study MEK-NF-201 Dispersible tablet dosage form (pediatric formulation)

BSA (m ²)	0.4 to 0.59	0.6 to 0.79	0.8 to 0.99	1 to 1.39	1.4 to 1.59	1.6 to 1.69	≥ 1.7
BID unit dose	1 mg	1.5 mg	2 mg	2.5 mg	3 mg	3.5 mg	4 mg

BSA = body surface area; mg = milligrams

All study dosing will be administered on a 3 weeks on/1 week off intermittent schedule

Dose Modifications

In the event of significant toxicity, dosing must have been interrupted and/or dose reduced as described in Table 29.

Table 29: Criteria For Dose Modification For Study Drug Related Adverse Events

RELATED ADVERSE EVENTS	INTERVENTION
OCULAR/VISUAL	
Any Grade ≤ 2 event.	Continue dosing and perform ophthalmologic exams every 2 to 4 weeks until resolution to Grade ≤ 1 or baseline.
Any Grade ≥ 3 event except RVO.	Interrupt dosing; if resolution to Grade ≤ 1 or baseline occurs within 14 days, re-start study treatment at the next lower dose following Tables 30 and 31 . Consider ophthalmologic exams every 2 to 4 weeks.
Grade ≥ 3 RVO	Permanently discontinue study treatment
NEUROLOGICAL	
Grade ≤ 2 events such as hallucination, confusion or delirium lasting more than 24 hours AND after ruling out other possible causes.	Interrupt dosing; if resolution to Grade ≤ 1 or baseline occurs within 14 days, re-start study treatment at the next lower dose following Tables 30 and 31 .
Any Grade ≥ 3 event.	Withhold dose and discuss with the Medical Monitor. Consider permanent discontinuation after re-evaluating the benefit risk of ongoing study drug treatment
MUSCULOSKELETAL	
Grade ≥ 3 muscle weakness (symptomatic and interfering with activities of daily living).	Interrupt dosing; if resolution to Grade ≤ 1 or baseline occurs within 14 days, re-start study treatment at the next lower dose following Tables 30 and 31 .
DERMATOLOGICAL	

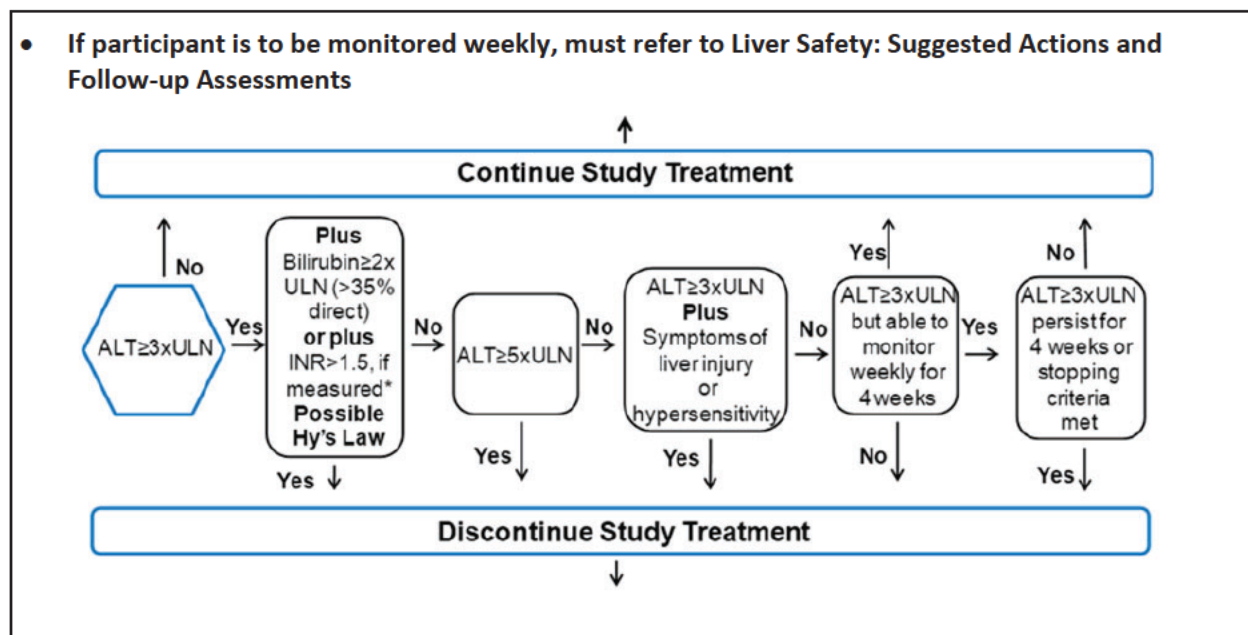
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Grade ≥ 3 acneiform rash.	Interrupt dosing; if resolution to Grade ≤ 1 or baseline occurs within 14 days, restart study treatment at the next lower dose following Tables 30 and 31
CARDIAC	
Asymptomatic, absolute decrease in LVEF of $\leq 10\%$ from baseline and is below institutional lower limit of normal (LLN).	Interrupt dosing; if LVEF value improves to above the institutional LLN or baseline, resume at the same dose, if supported by the investigator's assessment of the benefit-risk ratio. If LVEF does not improve to above the institutional LLN or baseline within 14 days, permanently discontinue study treatment.
Asymptomatic, absolute reduction in LVEF of $> 10\%$ to $\leq 19\%$ from baseline and is below institutional lower limit of normal (LLN).	Interrupt dosing; if LVEF value improves to above the institutional LLN or baseline within 14 days, resume at the next lower dose level following Table 5. If LVEF does not improve to above the institutional LLN or baseline within 14 days, permanently discontinue study treatment.
Symptomatic congestive heart failure. Absolute decrease in LVEF of greater than 20% from baseline.	Permanently discontinue study treatment.
LIVER (Refer to Figure 6)	
OTHER	
Grade ≥ 3 hematologic toxicities or clinically significant Grade 2 hematologic abnormalities, that do not resolve within 72 hours after initiation of medical management.	Interrupt dosing; if resolution to Grade ≤ 1 occurs within 14 days, restart study treatment at the next lower dose following Tables 30 and 31 .
Grade ≥ 3 nonhematologic toxicity that is not controlled by optimal supportive medication.	Interrupt dosing; if resolution to Grade ≤ 1 or baseline occurs within 14 days, restart study treatment at the next lower dose following Tables 30 and 31 .
Other Grade 2 toxicity that is subjectively intolerable (except alopecia) and not controlled by optimal supportive medication.	Interrupt dosing; if resolution to Grade ≤ 1 or baseline occurs within 14 days, re-start study treatment at the same dose.
Recurrent subjectively intolerable toxicity (at least a week interruption on 2 occasions) that is not controlled by optimal supportive medication.	Interrupt dosing; if resolution to Grade ≤ 1 or baseline occurs within 14 days, restart study treatment at the next lower dose using Tables 30 and 31 . If toxicity is still intolerable, permanently discontinue study treatment

	(unless otherwise discussed with the Medical Monitor or Sponsor).
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CHF=congestive heart failure; LLN=lower limit of normal; LVEF=left ventricular ejection fraction

Figure 6: Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm



Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal

Table 30: Capsule dosage form dose modification table

Dose at the time of the event	Reduced dose
1 mg BID	1 mg AM
2 mg BID	2 mg AM; 1 mg PM
3 mg BID	2 mg BID
4 mg BID	3 mg BID

BID = twice daily; mg= milligrams

Table 31: Tablet dose modification table

Dose at the time of the event	Reduced dose
1 mg BID	1 mg AM; 0.5 mg PM
1.5 mg BID	1 mg BID
2 mg BID	1.5 mg BID
2.5 mg BID	2 mg AM; 1.5 mg PM
3 mg BID	2.5 mg AM; 2 mg PM
3.5 mg BID	2.5 mg BID
4 mg BID	3 mg AM; 2.5 mg PM

BID = twice daily; mg= milligrams

Procedures and Schedule

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Table 32: Treatment Phase Schedule of Activities

Cycle (Treatment Phase)	Screening	Cycle 1		Cycle 2	Cycles 3, 4, 6, 7, 11, 15, 19, 23	Cycles 5, 9, 13, 17, 21	Cycle 24 (End of Treatment Phase)	Early Termination (ET)	Safety Follow-Up (SFU)
Visit		Baseline Week 1	Week 3	Week 7	Weeks 11, 15, 23, 27, 43, 59, 75, 91	Weeks 19, 35, 51, 67, 83	Week 96		
Cycle Day (Visit Window)	Up to 45 days before Day 1	Day 1 (Up to 48 hours prior to 1st dose)	Day 15 (±2 d)	Day 15 (±2 d)	Day 15 (±5 d)	Day 15 (±5 d)	Day 21 (±5 d)		30 days (+5 days) after last dose
Informed consent/assent	X								
Inclusion/exclusion review	X	X							
Demographics	X								
Medical history	X								
Karnofsky/Lansky performance status criteria	X	X		X		X	X	X	X
Weight/height	X	X			X (C3, C7, C11, C15, C19 and C23 only)	X	X	X	X
Physical examination	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X
Post 6-minute walk test blood pressure & heart rate		X				X	X	X	
Laboratory									
Blood for serology	X								
Blood for serum pregnancy test (WOCBP only)	X								
Monthly urine pregnancy test (WOCBP only)		X	X	X	à (monthly)	à (monthly)	àX (monthly)	X	X
Blood for hematology and serum chemistry	X	X	X	X	X	X	X	X	X

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Cycle (Treatment Phase)	Screening	Cycle 1		Cycle 2	Cycles 3, 4, 6, 7, 11, 15, 19, 23	Cycles 5, 9, 13, 17, 21	Cycle 24 (End of Treatment Phase)	Early Termination (ET)	Safety Follow-Up (SFU)
Visit		Baseline Week 1	Week 3	Week 7	Weeks 11, 15, 23, 27, 43, 59, 75, 91	Weeks 19, 35, 51, 67, 83	Week 96		
Cycle Day (Visit Window)	Up to 45 days before Day 1	Day 1 (Up to 48 hours prior to 1st dose)	Day 15 (±2 d)	Day 15 (±2 d)	Day 15 (±5 d)	Day 15 (±5 d)	Day 21 (±5 d)		30 days (+5 days) after last dose
Urinalysis	X	X	X	X		X	X	X	X
Blood for PK sampling		X (pre-dose, 1- and 2-hours post dose)	X (serial sampling)	X (pre-dose)	X (pre-dose)	X (pre-dose)	X		
Tumor Assessment									
MRI for tumor volume	X					X	X	X	
Target tumor biopsy		X					X	X	
Other Clinical Assessments									
Ophthalmic assessments	X			X		X	X	X	X
12-Lead ECG	X	X (pre-and post-dose)	X (post dose)	X		X	X	X	X
Echocardiogram	X			X		X	X	X	X
Strength assessment		X				X	X	X	
Range of motion assessment		X				X	X	X	
6-minute walk test	X	X				X	X	X	
Photography of PN		X				X	X	X	
Bone plate radiographs		X				X (C13 only)	X	X	
Patient Reported Outcomes (PROs)									

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Cycle (Treatment Phase)	Screening	Cycle 1		Cycle 2	Cycles 3, 4, 6, 7, 11, 15, 19, 23	Cycles 5, 9, 13, 17, 21	Cycle 24 (End of Treatment Phase)	Early Termination (ET)	Safety Follow- Up (SFU)
Visit		Baseline Week 1	Week 3	Week 7	Weeks 11, 15, 23, 27, 43, 59, 75, 91	Weeks 19, 35, 51, 67, 83	Week 96		
Cycle Day (Visit Window)	Up to 45 days before Day 1	Day 1 (Up to 48 hours prior to 1st dose)	Day 15 (±2 d)	Day 15 (±2 d)	Day 15 (±5 d)	Day 15 (±5 d)	Day 21 (±5 d)		30 days (+5 days) after last dose
ePRO device training	X								
PedsQL (paper)		X			X (C3 and C7 only)	X	X	X	X
PII		X (and daily for 6 days prior to visit)			X (C3 and C7 only and the 6 days prior to the C3 and C7 visits)	X (and daily for 6 days prior to visits)	X (and daily for 6 days prior to visit)	X	X (and daily for 6 days prior to visit)
NRS-11		X (and daily for 6 days prior to visit)			X (C3 and C7 only and the 6 days prior to the C3 and C7 visits)	X (and daily for 6 days prior to visits)	X (and daily for 6 days prior to visit)	X	X (and daily for 6 days prior to visit)
PROMIS-Physical Function/Mobility/Upper extremity		X			X (C3 and C7 only)	X	X	X	X
PGIS		X			X (C3 and C7 only)	X	X	X	X
PGIC					X (C3 and C7 only)	X	X	X	X
P-OMAQ (paper)					X	X	X	X	
Study Treatment									
Assign study treatment using IRT and first dose		X							
Study treatment dispensing (every 2 Cycles)		X			X (C3, C7, C11, C15, C19 and C23 only)	X	X		

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Cycle (Treatment Phase)	Screening	Cycle 1		Cycle 2	Cycles 3, 4, 6, 7, 11, 15, 19, 23	Cycles 5, 9, 13, 17, 21	Cycle 24 (End of Treatment Phase)	Early Termination (ET)	Safety Follow- Up (SFU)
Visit		Baseline Week 1	Week 3	Week 7	Weeks 11, 15, 23, 27, 43, 59, 75, 91	Weeks 19, 35, 51, 67, 83	Week 96		
Cycle Day (Visit Window)	Up to 45 days before Day 1	Day 1 (Up to 48 hours prior to 1st dose)	Day 15 (±2 d)	Day 15 (±2 d)	Day 15 (±5 d)	Day 15 (±5 d)	Day 21 (±5 d)		30 days (+5 days) after last dose
Study treatment administration		Xà	à	à	à	à			
Study treatment accountability					X (C3, C7, C11, C15, C19 and C23 only)	X	X	X	
Study treatment diary		Xà	à	à	à	à	àX		
Ongoing Monitoring									
Monthly wellness checks					Xà	à	àX		
Concomitant medication review	Xà	à	à	à	à	à	à	à	àX
AE / SAE review	Xà	à	à	à	à	à	à	à	àX

AE = adverse event; C = cycle; d = day(s); ECG = electrocardiogram; ePRO = electronic patient reported outcome; ET = early termination; IRT = interactive response technology; MRI = magnetic resonance imaging; NSR-11: 11-point numeric rating scale; PD = pharmacodynamic; PedsQL = Pediatric Quality of Life Inventory; PGIC = patient global impression of change; PGIS = patient global impression of severity; PII = pain interference index; PK = pharmacokinetic; PN = plexiform neurofibroma; P-OMAQ = Pediatric Oral Medicines Acceptability Questionnaire; PRO = patient reported outcome; PROMIS = Patient-Reported Outcomes Measurement Information System; SAE = serious adverse event; SFU = safety follow-up; WOCBP = women of childbearing potential

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Table 33: Long-Term Follow-up Phase Schedule of Activities

Cycle (LTFU)	Cycle 28 & Every 4 Cycles	End of Treatment (EOT) ¹⁷	Safety Follow- Up (SFU) ¹⁸
Cycle Day (Visit Window)	Day 15 (±5 d)		30 days (+5 days) after last dose of study treatment
Karnofsky/Lansky performance status criteria ¹	X	X	X
Weight/height ²	X	X	X
Physical examination	X	X	X
Vital signs ³	X	X	X
Laboratory			
Monthly urine pregnancy test ⁴ (WOCBP only)	X ^a (monthly)	X ^a (monthly)	X
Blood for hematology and serum chemistry ⁵	X	X	X
Urinalysis ⁵	X	X	X
Tumor Assessment			
MRI for tumor volume ⁶	X	X ^{6a}	
Other Clinical Assessments			
Ophthalmic assessments ⁷	X	X ^{7a}	X
12-Lead ECG ⁸	X	X	X
Echocardiogram ⁹	X	X ^{9a}	X
Photography of PN ¹⁰	X	X	
PedsQL (paper) ¹¹	X	X	
P-OMAQ (paper) ¹²	X	X	
Study Treatment¹²			
Study treatment dispensing ^{13a}	X		
Study treatment administration ^{13b}	X	X	

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Cycle (LTFU)	Cycle 28 & Every 4 Cycles	End of Treatment (EOT) ¹⁷	Safety Follow- Up (SFU) ¹⁸
Cycle Day (Visit Window)	Day 15 (±5 d)		30 days (+5 days) after last dose of study treatment
Study treatment accountability ^{13c}	X	X	
Ongoing Monitoring			
Monthly wellness checks ¹⁴	Xà	àX	
Concomitant medication review ¹⁵	Xà	à	àX
AE / SAE review ¹⁶	Xà	à	àX

AE = adverse event; d = day(s); ECG = electrocardiogram; EOT = end of treatment; IRT = interactive response technology; LTFU = Long-Term Follow-up; MRI = magnetic resonance imaging;
PedsQL = Pediatric Quality of Life Inventory; PN = plexiform neurofibroma; P-OMAQ = Pediatric Oral Medicines Acceptability Questionnaire; SAE = serious adverse event; SFU = safety follow-up;
WOCBP = women of childbearing potential

Study Endpoints

The Applicant's Description:

Primary Endpoint:

- The primary efficacy endpoint was confirmed ORR at the end of the Treatment Phase (defined as PN decrease $\geq 20\%$ compared to baseline in consecutive scans within 2-6 months) using centrally read MRI volumetric analysis.

The target PN was selected by the local investigator as the most clinically relevant PN, amenable to volumetric MRI analysis. Tumor response was evaluated at screening and during Cycles 5, 9, 13, 17, 21, and 24 during the Treatment Phase. For participants that elected to continue mirdametinib administration in the Long-Term Follow-up Phase, additional tumor evaluations were conducted during Cycle 28 and every 4 cycles thereafter.

All tumor volume measurements were independently calculated by two BICR readers. In the case that the two readers generated measurements representing different categorical tumor response statuses, an independent adjudicator made the final decision on which reader's assessment was the best representation of tumor response and the selected response category was recorded at that visit. The primary endpoint analyses were performed using the adjudicator-selected reader for those visits where the two BICR readers did not agree.

To determine the level of target tumor response (complete response [CR], partial response [PR], stable disease [SD], or progressive disease [PD]) which are described below, post-baseline measurement scans are compared to the target PN volume in the pre-treatment MRI scan using volumetric data analysis:

- CR: A complete resolution of the target PN
- PR: A $\geq 20\%$ reduction in the volume of the target PN lesion compared to baseline
- SD: Between a $< 20\%$ increase and $< 20\%$ decrease in the volume of the target PN lesion compared to baseline
- PD: A $\geq 20\%$ increase in the volume of the target PN compared to baseline.
(Radiographic disease progression)

Secondary Endpoints:

- Safety endpoints included incidence of treatment emergent adverse events (TEAEs), changes in laboratory parameters, vital signs, physical examination findings, and electrocardiograms (ECGs). Incidence of TEAEs was assessed by dose formulation. Tolerability was assessed according to toxicities graded by NCI CTCAE v5.0.
- DoR for participants whose best overall confirmed response was CR or PR using centrally

read MRI volumetric analysis.

- Change from baseline at Cycle 13 in QoL assessed by the age-specific PedsQL.
- Change from baseline at Cycle 13 in pain severity and pain interference assessed using the NRS-11 and PII.

Key Exploratory Endpoints:

- Change from baseline in physical function status (PROMIS – Physical Function/Mobility/Upper Extremity Scale) in the Treatment Phase.
- Patient global impression of change (PGIC) and patient global impression of severity (PGIS) scores throughout the Treatment Phase.
- Change from baseline in localized strength (dynamometer and Medical Research Council Muscle Scale), range of motion, and endurance (6-minute walk test) of PN-associated functional impairment in the Treatment Phase.
- Time to progression (TTP) and progression free survival (PFS) in progressive PN
- Pediatric Oral Medicines Acceptability Questionnaire (P-OMAQ) scores recorded as self-report and by caregiver.
- Change from baseline in target tumor volume by centrally read MRI volumetric analysis. Best volumetric percentage change from baseline as well as the time to the best volumetric percentage change from baseline.
- DCR (defined as a confirmed BOR of SD or better post-baseline during the Treatment Phase) measured by centrally read MRI volumetric analysis.
- Time to response for participants whose best overall confirmed response was CR or PR using centrally read MRI volumetric analysis.

The FDA's Assessment:

FDA generally agrees with the description of the trial design and endpoints. Notably, under Response Evaluation in Neurofibromatosis and Schwannomatosis (REINS) criteria, a partial response (PR) is defined as a decrease in the volume of the target lesion by 20% or more compared to baseline and confirmed within 3-6 months, and sustained when the response is maintained for at least 6 months. In contrast, the Applicant considered a $\geq 20\%$ decrease in PN from baseline across consecutive scans within 2–6 months. A sensitivity analysis was conducted, which showed minimal impact on the ORR outcome in pediatric cohort and slightly larger impact in adult cohort. The details of the rationale for the modified criteria and the sensitivity analysis are provided in section 8.1.1.1.

FDA considers the external control data to be supportive in a descriptive manner and as such the data from the placebo arm of Study 01-C-0222 and the natural history Study 08-C-0079 were not independently confirmed and will not be included in FDA's assessment of efficacy.

Statistical Analysis Plan and Amendments

The Applicant's Description:

Two draft versions of the statistical analysis plan (SAP) dated 20Sep2022 and 31Jan2023 were submitted to FDA for review and feedback. The final SAP (v1.0) was dated 02Nov2023.

Primary Efficacy Endpoint

The primary efficacy endpoint was the confirmed ORR by the end of Treatment Phase (i.e., Cycle 24). The primary endpoint was based on the full analysis set (FAS), defined as the set of all participants who received at least one dose of mirdametininib. The confirmed ORR was defined as the proportion of participants who had a confirmed $\geq 20\%$ reduction in target tumor volume as compared to baseline as assessed by a blinded independent central review (BICR), and the response needs to be confirmed by BICR in a consecutive tumor assessment within 2- 6 months.

All tumor volume measurements were independently calculated by two BICR readers. In the case that the two readers generated measurements representing different categorical tumor response statuses, an independent adjudicator made the final decision on which reader's assessment was the best representation of tumor response and the selected response category was recorded at that visit. The primary endpoint analyses were performed using the adjudicator-selected reader for those visits where the two BICR readers did not agree.

Only tumor assessments during the Treatment Phase were considered for the determination of confirmed response. Participants who did not achieve a confirmed response were categorized as non-responders. Participants who did not have a post-baseline MRI assessment were also categorized as non-responders and their best overall response was deemed as 'Missing'.

To assess the primary efficacy endpoint, confirmed ORRs by the end of the Treatment Phase as assessed by BICR were presented as percentages alongside the corresponding 2-sided 95% Clopper-Pearson CIs and the p-values from one-sample two-sided binomial tests for the confirmed ORR compared to the minimum clinically relevant response rates (23% in adult participants and 20% in pediatric participants). The overall assessment of the endpoint was based on the exclusion of the minimum clinically relevant response rates by the lower tail of the 95% CIs.

A sensitivity analysis was performed that mirrored this primary efficacy analysis but used the per-protocol set (PPS), defined as the set of all participants in the FAS who had completed at least one post-baseline disease evaluation and who did not have any major CSR reportable deviations, including but not limited to efficacy assessments or compliance, rather than the FAS.

Secondary Efficacy Endpoints

Duration of Response

Duration of response was defined as the time in months between the first instance of response that was subsequently confirmed, until the date of radiographic disease progression or death,

whichever occurred first. The DoR was summarized in months as follows: (date of event [i.e., radiographic disease progression or death] or censoring – date of first response + 1) / 365.25 × 12.

For participants who entered the LTFU Phase, all MRI assessments in both the Treatment Phase and LTFU Phase were used to determine DoR. Those who achieved a DoR of at least 12 months were considered to have experienced a durable response.

Participants without radiographic disease progression or death while on study had their results censored to their most recent adequate (i.e., evaluable) tumor assessment date.

DoR was analyzed using Kaplan-Meier (KM) methods, with the median, lower, and upper quartile estimates of DoR and their associated 95% CIs using the Brookmeyer and Crowley method.

Patient Reported Outcomes

All PROs analyzed in this study were assessed using the mean change from baseline as well as by the proportion of participants who achieved a clinically meaningful change from baseline at the Cycle 13 visit. Cycle 13 was selected as the timepoint that will best allow the treatment effect to be captured in PRO scores. It was projected that a strong majority of participants who present a response would do so at or before Cycle 13, with the median time of response expected to be Cycle 5 to Cycle 9, so any associated pain or QoL improvements should be captured at the Cycle 13 visit. Choosing a later cycle would have captured few additional responses, but may have been susceptible to increased amounts of missing data.

For PedsQL, distribution-based thresholds were $>0.5 \times \text{StD}$, where StD was calculated from the baseline scale data. MCTs were defined separately for adult, pediatric self-report, and pediatric parent proxy data.

For NRS-11, distribution-based thresholds were presented using change from baseline of ≤ -1 (this cut point has previously been researched and assessed as a meaningful change in pediatric populations), representing a clinically meaningful improvement, as well as change from baseline greater than the within-patient MCT.

Distribution-based MCTs were applied to interpret the change from baseline results as well as the number and percentage of participants with a clinically meaningful change for PII. Distribution-based thresholds were $< -0.5 \times \text{StD}$ (using StD from the baseline scores).

Exploratory Efficacy Endpoints

Change from Baseline in physical function status (PROMIS)

Actual values and change from baseline were summarized by visit and confirmed objective response status for each PROMIS Scale, with self-report and parent proxy records summarized

separately.

Strength

The strength measured by the dynamometer by each area location was summarized and the percent change from baseline using standard summary statistics was summarized by age cohort and by visit.

Range of Motion

The range of motion for that location was summarized and the percent change using standard summary statistics was summarized by age cohort and by visit.

6-Minute Walk Test

Standard summary statistics of length walked and the pre-/post vitals were summarized by each visit.

Patient Global Impression of Change/Severity

The absolute count and percentage of participants in each of the PGIS and PGIC categories were summarized separately by visit and by confirmed objective response status.

Pediatric Oral Medicines Acceptability Questionnaire

Descriptive statistics were used to summarize P-OMAQ. P-OMAQ-P (parent) and P-OMAQ-C (child) individual question scores and total scores were summarized separately.

Disease Control Rate

The number and percentage of participants who achieved disease control (i.e. BOR of SD or better) by the end of the treatment phase were presented by age cohort, alongside the corresponding 2-sided Clopper-Pearson 95% CIs.

Time to Response

Time to response was summarized for confirmed responders by age cohort and is defined as the time in months from the start of treatment to the date of first response that was subsequently confirmed. The time to response was summarized for the primary endpoint and by each of the two readers separately for the FAS.

Change from Baseline in Target tumor volume

Change from baseline in tumor volume, and percentage change from baseline in tumor volume was summarized descriptively by visit for each age cohort separately. Results were presented by averaged tumor volumes across the two readers (unless response adjudication was

performed) and reported separately for each reader. A Mixed Models for Repeated Measures (MMRM) was fit separately by age cohort with change from baseline in tumor volume as the dependent variable, visit as a fixed effect and baseline tumor volume as a covariate. LS Means estimates were presented with associated standard errors, 95% CIs and p-values by visit.

Best Volumetric Percentage Change from Baseline

Best volumetric percentage change from baseline as well as the time, in months, to the best volumetric percentage change from baseline was summarized descriptively using averaged tumor volumes across the two readers (unless response adjudication was performed) and reported separately for each reader.

Time to Progression and Progression-Free Survival

Time to progression (TTP) and progression-free survival (PFS) were analyzed separately for each age cohort using the Kaplan-Meier (KM) method; with median, lower, and upper quartile estimate and associated 95% CIs (using the Brookmeyer-Crowley method), the number of participants with events or who are censored, as well as reason for censoring being summarized.

External Control

Yearly Percentage Change from Baseline in Target PN Volume

For each cohort, an analysis of covariance (ANCOVA) model was applied for treatment comparison between participants in MEK-NF-201 and the historical control at each year. Comparisons of this endpoint were made at each year up to 3 years. Since the 2 studies for historical controls did not have the same assessment timepoints as in MEK-NF-201, a window of ± 6 months was used for the comparison timepoints at months 12, 24, 36, etc. This rule created the following windows in months for comparison:

- Month 12: (6, 18]
- Month 24: (18, 30]
- Month 36: (30, 42]
- Last assessment time point.

Within each window, the assessment timepoint closest to the yearly comparison timepoint was selected to calculate the percentage change from baseline in target PN volume. Comparisons were performed if each treatment group has at least 5 participants for yearly percentage change from baseline in target PN volume after propensity score matching. In the model, the yearly percentage change from baseline in target PN volume was the dependent variable, and age and target PN volume at baseline were the covariates.

For each comparison, the assessment time from baseline in months [= (time in

days) $\times(12/365.25)]$ and percentage change in tumor volume per-year was summarized with and without modeling.

Time to Progression

TTP for each cohort was analyzed using the KM method, with quartiles and associated 95% CI calculated using the log-log transformation, if estimable. Survival curves for both treatment groups in the same cohort were presented. Within each cohort, the p-value for treatment comparison was calculated using a log rank test; the hazard ratio and its 95% CI for Study MEK-NF-201 versus Studies 01-C-0222 and 08-C-0079 were estimated with a Cox regression model using treatment group, age, and target PN volume at baseline as covariates. Participants not experiencing radiographic disease progression were censored on the last adequate MRI assessment that verified lack of disease progression.

Progression Free Survival

Progression free survival (PFS) was analyzed using the KM method, with quartiles and associated 95% CI calculated using the log-log transformation, if estimable. Survival curves for both treatment groups in the same cohort were presented. Within each cohort, the p-value for treatment comparison was calculated using a log rank test; the hazard ratio and its 95% CI for the Study MEK-NF-201 versus Studies 01-C-0222 and 08-C-0079 were estimated with a Cox regression model using treatment group, age, and target PN volume at baseline as covariates. Participants not experiencing radiographic disease progression or death were censored on the last adequate MRI assessment that verified lack of disease progression or death.

The FDA's Assessment:

FDA generally agrees with the Applicant's description of study endpoints.

FDA did not use inferential procedures to evaluate the results of this single arm trial. Instead, FDA relied on overall benefit: risk assessment to evaluate the outcome across primary and secondary endpoints. This evaluation included both the magnitude of BICR-assessed confirmed ORR as well as sufficiently mature duration of response and whether the observed confirmed response rate and durability of the response outweigh any concerns over toxicity and safety in the context of other available therapies.

Due to the benign nature of NF1-PN, FDA considered it important to capture improvement in PN-related symptoms correlating with radiographic responses. The ReNeu study utilized various COA measures to evaluate changes in PN-related functional impairment, symptoms, and disfigurement. See section 8.1 for discussion of COA results.

FDA considered the external control data as supplementary information, appropriate only for cautious descriptive interpretation. The analyses of exploratory endpoints using external control were not verified by the FDA.

Protocol Amendments

The Applicant's Description:

The original study protocol was finalized on 06March2019 and amended 4 times; the final protocol (Protocol Amendment 4) was dated 17May2022. [Table 34](#) provides a summary of each amendment.

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Table 34: MEK-NF-201 Protocol Amendments Summary

Number (Date of approval)	Number Of Participants Who Were Consented Under Amendment	Key changes
Amendment 1 (17May2019)	63	• A safety run-in cohort was added to the pediatric stratum (stratum 1). • Changed the MRC grading assessment from option to a required strength assessment. • The 6-minute walk test was added as an assessment for participants that have a target PN causing airway or lower extremity motor dysfunction. • The entry criterion based on progression of target PN was removed and any associated instruction or language pertaining to a progressing target PN prior to study entry. • The minimum Karnofsky performance level for participants ≥ 16 years of age and Lansky performance score for participants < 16 years was decreased from 60% to 50%. • The following was removed: "If participant enrolls with progression and no associated morbidities, NF1-targeted therapy must not be administered after the observed progression" • Dose modification language was changed to clarify that a maximum of 1 dose reduction will be allowed due to AE and dose re-escalation after resolution of an AE will not be permitted. • Specific study stopping criteria was added. The definition of an overdose was changed from > 12 mg to $> 150\%$ of the scheduled dose, within a 24-hour period. • The collection of whole blood for PBMC pharmacodynamic analysis was removed and subsequently the approximate amount of blood required from each participant over the course of the study was decreased. • Triglycerides and total cholesterol were added to the required clinical laboratory assessments. • The size of the DMC was changed from '3 to 4 members' to specifically state '3 members.'
Amendment 2	110	• Mirdametinib was incorporated as the study treatment generic name. • The screening period was extended from 28 days to 45 days prior to first dose of study

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Number (Date of approval)	Number Of Participants Who Were Consented Under Amendment	Key changes
(05Jun2020)		treatment. • The window for collection of the pre-treatment biopsy was extended to accommodate site logistics. • The tablet formulation was added along with general guidance for this formulation. • Inclusion Criteria #5 was updated to clarify that the tumor assessment is based on the REiNS criteria. • Inclusion Criterion #9 was updated to eliminate global requirement of swallowing a capsule for entry due to the introduction of tablet formulation. • Exclusion Criterion #11 was updated to limit assessment of echocardiogram history to the 3 years prior to enrollment. • Exclusion Criterion #12.1 was modified to exclude participants with intraocular pressure > 21 mm Hg. • Exclusion Criteria #16 and #17 were modified to clarify that previous treatment with a MEK inhibitor at any time was not allowed. • The dosing window was extended from 2 to 6 hours. • Dose modifications in response to an ocular AE were updated to align with current MEK inhibitor class guidance. • The criteria for skin disorders to be reported as an AESI were changed from Grade ≥ 2 to Grade ≥ 3. • Language was added to permit the use of local laboratories for assessment with sponsor approval in extenuation circumstances (e.g., pandemic, site closure). • Sample size determination was updated to provide clarity on the trial statistical assumptions for the pediatric and adult strata.
Amendment 3	14	• The LTFU Phase and LTFU Phase-specific SoA were added to the protocol. • Inclusion Criterion #13 was modified to describe that a WOCBP partner of a male study

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Number (Date of approval)	Number Of Participants Who Were Consented Under Amendment	Key changes
(14Jun2021)		participant should utilize a referenced form of contraception and the length of contraceptive use after discontinuation of study treatment and the length of time before egg donation after discontinuation of study treatment were reconciled. • Exclusion Criterion #18 was modified to explicitly exclude inhaled glucocorticoid therapy. • Dose modified instructions were clarified to state that resumption of treatment after an interruption should occur if the AE has returned to Grade ≤ 1 or baseline within 14 days of a dose interruption. Cardiac dose modification language was also updated to provide optimal guidance to the investigator and to align with CTCAE v5 grading criteria. • Text referencing a Continued Access Program was removed with the addition of the LTFU Phase. • Text was added to provide guidance on conducting study assessments impacted by a public health emergency. • Analysis set populations were clarified and optimized to align with a single-arm study analysis.
Amendment 4 (17May2022)	0	• The primary endpoint language was modified to clarify when the ORR is assessed (i.e., by the end of the Treatment Period). • The P-OMAQ was added as an exploratory endpoint for participants ≥ 8 years and caregivers of all participants and incorporated as a single administration PRO to assess acceptability of the tablet (pediatric formulation). • Dose modification language was updated: ○ Updated to allow for an increase in dose of study treatment due to an increase in BSA, at the discretion of the treating investigator, utilizing an alternative dosing nomogram for participants that have previously reduced their dose of study treatment. ○ Language was modified to support more frequent ocular safety monitoring in the

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Number (Date of approval)	Number Of Participants Who Were Consented Under Amendment	Key changes
		presence of an observed ocular-related AE. ○ Alternative dosing nomograms for participants that have reduced their dose of study treatment were added. • Sample size determination text was simplified to clarify sample size required for analysis and remove redundancies. • Text was added to clearly state the independent analysis of the pediatric and adult cohorts. To this end, the use of 'strata/stratum' was changed to 'cohort' to reflect the independence of populations. • The confidence interval for the primary efficacy analysis was updated to reflect hypothesis testing and clarified handling of data from discontinued participants.

AE: adverse event; AESI: adverse event of special interest; BSA: body surface area; CTCAE: Common Terminology Criteria for Adverse Events; DMC: data monitoring committee; LTFU: long term follow up; MEK: mitogen-activated protein kinase kinase; MRC: Medical Research Council; NF1: neurofibromatosis type 1 ; PN: plexiform neurofibromas; P-OMAQ: Pediatric Oral Medicines Acceptability Questionnaire; REiNS: Response Evaluation in Neurofibromatosis and Schwannomatosis; SoA: schedule of activities

The FDA's Assessment:

The Applicant's description of the protocol amendments is consistent with what was provided in the submission. FDA notes that in Amendment 1, the inclusion criteria were revised so that patients with progressive PN and no associated morbidities were not eligible to enroll. We also note that while inclusion criterion number 5 was modified in Amendment 2 to specify that the PN must be analyzable by volumetrics using the REiNS criteria, a modified version of REiNS criteria was utilized in this study as described in Section 8.1, Efficacy results. As described by the Applicant in Amendment 4, the primary endpoint language was modified to specify that the ORR will be assessed at the end of the Treatment Phase, therefore, patients with objective responses during the long-term follow-up phase were not included in FDA's analysis.

8.1.1.1. Study Results

Compliance with Good Clinical Practices

Data:

This study was designed and monitored in accordance with sponsor procedures, which comply with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

The Applicant's Position:

Study MEK-NF-201 is GCP compliant.

The FDA's Assessment:

FDA acknowledges the Applicant's statement of compliance with GCP requirements.

Data Quality and Integrity

Data:

All participant data relating to the study were entered into the electronic case report forms (eCRFs) unless transmitted to the sponsor or designee electronically (e.g., laboratory data).

The investigator was responsible for verifying that data entries were accurate and correct by electronically signing the eCRF. The investigator maintained accurate documentation (source data) that supported the information entered in the eCRF. The investigator permitted study-related monitoring, audits, Institutional review board (IRB)/Independent ethics committee (IEC) review, and regulatory agency inspections and provided direct access to source data documents.

Monitoring details describing strategy methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) were indicated in the monitoring plan to ensure the protocol and GCP was followed.

The sponsor or designee was responsible for the data management of this study including quality checking of the data. The sponsor assumed accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Study monitors performed ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel were accurate, complete, and verifiable from source documents; that the safety and rights of participants were being protected; and that the study was being conducted in accordance with the currently approved protocol and any other study agreements, International Conference on Harmonization (ICH) GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study were retained by the investigator according to specifications in the ICH guidelines, local regulations, or as specified in the clinical trial agreement, whichever was longer. No records were to be destroyed during the retention period without the written approval of the sponsor. No records were to be transferred to another location or party without written notification to the sponsor.

SpringWorks conducts clinical studies according to procedures that incorporate the ethical principles of GCP. To ensure compliance with these procedures and to assess the adequacy of quality control procedures, SpringWorks undertakes a GCP audit program.

Audits were performed by SpringWorks Quality Assurance (or designees) operating independently of the study monitors. The audits within the clinical program were aimed at study documentation, investigator sites, and clinical study reports (CSRs).

The audit program, together with SpringWorks' internal quality control procedures, provide reassurance that study conclusions were based on valid procedures for data management and analysis, and that the clinical study program was carried out in accordance with GCP guidelines.

The Applicant's Position:

The study conduct, quality and integrity were appropriate to allow adequate assessment of the data.

The FDA's Assessment:

FDA did not identify quality or integrity issues in the data. The data submitted were organized and adequate to perform a complete review of the efficacy of mirdametinib.

Financial Disclosure

The Applicant's Position:

All investigators have been researched for conflicts of interest. None were identified as having financial interests/arrangements with the sponsor.

The FDA's Assessment:

In accordance with 21 CFR Part 54, the Applicant submitted Form FDA 3454 (Financial Interests and Arrangements of Clinical Investigators) certifying that as the sponsor of the submitted studies, they did not enter into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study. All investigators were assessed for equity interest, significant payments of other sorts, and other compensation by the sponsor or proprietary interest. The Applicant certified that none of the financial interests or arrangements described in 21 CFR Part 54 existed for any of the investigators who participated in Study MEK-NF-201. The Applicant provided a list of all investigators for Study MEK-NF-201 in Appendix 16.1.4 of the CSR.

FDA reviewed the financial disclosure information provided by the Applicant and agrees that the integrity of the study data was not affected by the financial interest of the investigators.

Patient Disposition

Data:

The data cutoff for the CSR was 20Sep2023. A summary of the disposition of all participants enrolled is presented in Table 35.

Table 35: MEK-NF-201 Participant Disposition

	Pediatric (N = 56)	Adult (N = 58)	Total (N = 114)
Participants in the Safety Analysis Set	56 (100%)	58 (100%)	114 (100%)
Participants in the FAS	56 (100%)	58 (100%)	114 (100%)
Participants in the PPS	51 (91.1%)	47 (81.0%)	98 (86.0%)
Completed the Treatment Phase	33 (58.9%)	31 (53.4%)	64 (56.1%)
Ongoing in the Treatment Phase	4 (7.1%)	0	4 (3.5%)
Discontinued/Withdrawn from Study Prior to Completing the Treatment Phase	19 (33.9%)	27 (46.6%)	46 (40.4%)
Primary Reason for Discontinuation/Withdrawal from Study Prior to Completing the Treatment Phase			
Death	0	1 (1.7%)	1 (0.9%)
Radiographic PD	9 (16.1%)	3 (5.2%)	12 (10.5%)
Withdrawal by participant	3 (5.4%)	0	3 (2.6%)
AE	3 (5.4%)	12 (20.7%)	15 (13.2%)
Participant decision	3 (5.4%)	8 (13.8%)	11 (9.6%)
Lost to follow-up	1 (1.8%)	2 (3.4%)	3 (2.6%)
Other	0	1 (1.7%)	1 (0.9%)
Ongoing Treatment in Treatment Phase	4 (7.1%)	0	4 (3.5%)
Discontinued Treatment Prior to Completing the Treatment Phase	19 (33.9%)	27 (46.6%)	46 (40.4%)
Primary Reason for Discontinuing Treatment Prior to Completing the Treatment Phase			
Radiographic PD	9 (16.1%)	3 (5.2%)	12 (10.5%)
AE	4 (7.1%)	13 (22.4%)	17 (14.9%)

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	Pediatric (N = 56)	Adult (N = 58)	Total (N = 114)
Non-compliance	1 (1.8%)	2 (3.4%)	3 (2.6%)
Participant decision	5 (8.9%)	8 (13.8%)	13 (11.4%)
Other	0	1 (1.7%)	1 (0.9%)
Withdrawing Consent from the Study Prior to Completing the Treatment Phase	3 (5.4%)	0	3 (2.6%)
Reason for Withdrawing Consent from the Study Prior to Completing the Treatment Phase			
Inability or refusal to complete study procedures	1 (1.8%)	0	1 (0.9%)
Intolerable side effects	1 (1.8%)	0	1 (0.9%)
Participant refusal to continue study medication	1 (1.8%)	0	1 (0.9%)
Eligible for LTFU Phase	33 (58.9%)	31 (53.4%)	64 (56.1%)
Entering LTFU Phase	28 (84.8%)	26 (83.9%)	54 (84.4%)
Did Not Enter LTFU phase	5 (15.2%)	5 (16.1%)	10 (15.6%)

Abbreviations: AE: adverse event; FAS: Full Analysis Set; PD: progressive disease; PPS: Per-protocol Set; LTFU: Long-term Follow-up.

The Safety Analysis Set and FAS was defined as the set of all participants who took at least one dose of mirdametinib.

The PPS was defined as the set of all participants in the FAS who completed at least one post-baseline disease evaluation and who did not have any major CSR-reportable deviations, including but not limited to efficacy assessments or compliance.

Participants were considered to have completed the Treatment Phase if they completed the Cycle 24 visit (End of Treatment Phase) or have entered the LTFU Phase.

Percentages were calculated out of the number of participants eligible for LTFU Phase for 'entering LTFU Phase/did not enter LTFU Phase' and reasons for not entering, and out of all participants in the cohort for all other rows.

Source: ADSL

The Applicant's Position:

A total of 56 participants in the pediatric cohort were exposed to at least one dose of study treatment. During the Treatment Phase, 19 (34%) participants prematurely discontinued treatment; the most common (> 10%) reason for premature treatment discontinuation was radiographic PD (9 [16%] participants). Of the 33 (59%) participants in the pediatric cohort eligible for the LTFU Phase, 28 (85%) participants entered the LTFU Phase. As of the data cutoff, 24 (86% of those who entered the LTFU Phase) participants are ongoing treatment in the LTFU

Phase and 4 (14%) discontinued treatment; reasons for treatment discontinuation included radiographic PD, AE, non-compliance, and other (sponsor request) in 1 [4%] participant each.

A total of 58 participants in the adult cohort were exposed to at least one dose of study treatment. During the Treatment Phase, 27 (47%) participants prematurely discontinued treatment. The most common (> 10%) reasons for premature treatment discontinuation were AE (13 [22%] participants) and participant decision (8 [14%] participants). Of the 31 (53%) participants in the adult cohort eligible for the LTFU Phase, 26 (84%) participants entered the LTFU Phase. As of the data cutoff, 22 (85% of those who entered the LTFU Phase) are ongoing treatment in the LTFU Phase and 4 (15%) discontinued treatment in the LTFU Phase; reasons for treatment discontinuation included participant decision (2 [8%] participants), non-compliance (1 [4%] participant), and other (1 [4%] participant). There was 1 death in the adult cohort during Study MEK-NF-201.

The FDA's Assessment:

FDA generally agrees with the description of patient disposition in MEK-NF-201 presented in Table 35. There appears to be differential rates of treatment discontinuation prior to completion of the treatment phase between the pediatric and adult cohorts, particularly for reasons of radiological progression: pediatric cohort (16.1%) compared to the adult cohort (5.2%) and adverse events: pediatric cohort (9%) compared to the adult cohort (22.4%). The higher rate of discontinuation due to PN progression in the pediatric may be attributable to the more rapid growth rate in childhood as compared to adulthood.

Protocol Violations/Deviations

Data:

In the pediatric cohort, 3 (5%) participants had at least 1 major protocol deviation and were therefore excluded from the per-protocol set. These deviations included study eligibility; 1 participant did not meet inclusion criterion #5 (their target PN volume at baseline was < 5 mL) and 2 participants did not meet inclusion criterion #3 (reported no morbidity at baseline) and both were enrolled in the study.

In the adult cohort, 6 (10%) participants had at least 1 major protocol deviation and were therefore excluded from the per-protocol set. These deviations included study inclusion (2 [3%] participants; both participants did not meet inclusion criterion #5 and were enrolled in the study with baseline target PN volumes measured < 5 mL) and investigational product (4 [7%] participants; all 4 participants received < 60% prescribed study treatment during the Treatment Phase).

The Applicant's Position:

A CSR-reportable protocol deviation is considered a significant deviation that may impact the accuracy, and/or reliability of the study data or participants rights, safety, or well-being. A

major CSR-reportable protocol deviation would exclude the participant from the per-protocol population and include participants that did not meet inclusion/exclusion criteria, mis-randomizations, mis-stratifications, or may impact accuracy and reliability of the study data.

The 3 participants in the pediatric cohort with major CSR -reportable protocol deviations excluded from the per-protocol set were not expected to impact the data integrity for the analysis. Two additional participants in the pediatric cohort were excluded from the per-protocol set due to not having at least 1 post-baseline disease evaluation. The ORR for the per-protocol set supports the results from the primary analysis for the pediatric cohort (ORR from per-protocol set: 56.9% [95% CI: 42.2 to 70.7] vs ORR from primary analysis: 51.8% [38.0 to 65.3]). These data demonstrate that the lower limit of the 95% CI excludes the null hypothesis of ORR = 20%.

The 6 participants in the adult cohort with major CSR -reportable protocol deviations excluded from the per-protocol set were not expected to impact the data integrity for the analysis. Eight additional participants in the adult cohort were excluded from the per-protocol set due to not having at least 1 post-baseline disease evaluation. The ORR for the per-protocol set supports the results from the primary analysis for the adult cohorts (ORR from per-protocol set: 46.8% [32.1 to 61.9] vs ORR from primary analysis: 41.4% [28.6 to 55.1]). These data demonstrate that the lower limit of the 95% CI excludes the null hypothesis of ORR = 23%.

The FDA's Assessment:

FDA generally agrees with the description of protocol violations and deviations and that they are not likely to have impacted the interpretability of the study results.

Table of Demographic Characteristics

Data:

A summary of the demographic characteristics of the FAS is presented in [Table 36](#).

In the pediatric cohort, the median (min, max) age at the time of consent was 10.0 (2, 17) years. Most participants were White (66%) and approximately half were female (54%).

In the adult cohort, the median (min, max) age at the time of consent was 34.5 (18, 69) years. Most participants were White (85%) and female (64%).

Table 36: Summary of Demography and Baseline Characteristics (FAS)

	Pediatric (N = 56)	Adult (N = 58)	Total (N = 114)
Age at time of consent (years)			
n	56	58	114

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	Pediatric (N = 56)	Adult (N = 58)	Total (N = 114)
Mean (StD)	10.1 (4.50)	35.0 (13.17)	22.8 (15.94)
Median	10.0	34.5	18.0
Min, Max	2, 17	18, 69	2, 69
Sex			
Male	26 (46.4%)	21 (36.2%)	47 (41.2%)
Female	30 (53.6%)	37 (63.8%)	67 (58.8%)
Childbearing Potential at Screening			
Yes	15 (50.0%)	29 (78.4%)	44 (65.7%)
No	15 (50.0%)	8 (21.6%)	23 (34.3%)
Race			
Black or African American	11 (19.6%)	5 (8.6%)	16 (14.0%)
White	37 (66.1%)	49 (84.5%)	86 (75.4%)
Asian	2 (3.6%)	2 (3.4%)	4 (3.5%)
American Indian or Alaska Native	1 (1.8%)	0	1 (0.9%)
Native Hawaiian or Other Pacific Islander	0	0	0
Other	5 (8.9%)	2 (3.4%)	7 (6.1%)
Ethnicity			
Hispanic or Latino	8 (14.3%)	1 (1.7%)	9 (7.9%)
Not Hispanic or Latino	44 (78.6%)	52 (89.7%)	96 (84.2%)
Missing/Not Reported/Unknown	4 (7.1%)	5 (8.6%)	9 (7.9%)
Karnofsky/Lansky Score			
n	56	58	114
Mean (StD)	94.5 (9.33)	87.1 (7.73)	90.7 (9.29)
Median	100.0	90.0	90.0
Min, Max	50, 100	70, 100	50, 100

Abbreviations: FAS: Full Analysis Set; Max: maximum; Min: minimum; StD: standard deviation.

Childbearing potential percentages were calculated using the number of female participants in the corresponding cohort as the denominator.

Source: ADSL

The Applicant's Position:

Demographic characteristics were consistent with the general population with NF1 PN.

The FDA's Assessment:

FDA generally agrees that the demographic characteristics were largely consistent with the general population with NF1-PN in the U.S., however patients of Hispanic or Latino ethnicity were underrepresented (7.9% of patients in ReNeu vs. 19.5% per 2024 U.S. Census data).

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

150

Version date: June 2022 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as "Data" and "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Data:

A summary of the baseline disease characteristics of the FAS is presented in [Table 37](#).

In the pediatric cohort, half of participants (50%) had their tumor in the head and neck, and most participants had a progressing PN at study entry (63%) by local investigator assessment. The median (min, max) time since target PN diagnosis was 43.0 (2.0, 183.0) months. The most common ($\geq 50\%$) reported morbidities were pain (70%) and disfigurement or major deformity (50%).

In the adult cohort, the most common target tumor location was the head and neck (48%) and lower extremities (26%), and approximately half of the participants had a progressing PN at study entry (53%) by local investigator assessment. The median (min, max) time since target PN diagnosis was 82.8 (3.0, 598.5) months. The most common ($\geq 50\%$) reported morbidities were pain (90%) and disfigurement or major deformity (52%).

Table 37: Summary of Baseline Disease Characteristics (FAS)

	Pediatric (N = 56)	Adult (N = 58)	Total (N = 114)
Target Tumor Location			
Head & Neck	28 (50.0%)	28 (48.3%)	56 (49.1%)
Lower Extremities	4 (7.1%)	15 (25.9%)	19 (16.7%)
Other	8 (14.3%)	3 (5.2%)	11 (9.6%)
Paraspinal	4 (7.1%)	5 (8.6%)	9 (7.9%)
Chest Wall	2 (3.6%)	4 (6.9%)	6 (5.3%)
Mesentery & Pelvis	5 (8.9%)	1 (1.7%)	6 (5.3%)
Upper Extremities	4 (7.1%)	2 (3.4%)	6 (5.3%)
Abdominal Wall	1 (1.8%)	0	1 (0.9%)
Target Tumor Type (Reader A)			
Nodular	11 (19.6%)	15 (25.9%)	26 (22.8%)
Solitary Nodular	2 (3.6%)	4 (6.9%)	6 (5.3%)
Typical	43 (76.8%)	39 (67.2%)	82 (71.9%)
Time Since Target PN Diagnosis (Months)			
N	42	22	64

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	Pediatric (N = 56)	Adult (N = 58)	Total (N = 114)
Mean (StD)	55.97 (50.714)	157.45 (169.241)	90.85 (116.540)
Median	42.96	82.83	59.35
Min, Max	2.0, 183.0	3.0, 598.5	2.0, 598.5
Documented NF1 Mutation (CLIA/COA testing)			
Yes	25 (44.6%)	27 (46.6%)	52 (45.6%)
No	19 (33.9%)	18 (31.0%)	37 (32.5%)
Unknown	12 (21.4%)	13 (22.4%)	25 (21.9%)
Target PN Progressing at Study Entry			
Yes	35 (62.5%)	31 (53.4%)	66 (57.9%)
No	21 (37.5%)	27 (46.6%)	48 (42.1%)
Any Reported Morbidities			
Motor Dysfunction or Weakness	15 (26.8%)	23 (39.7%)	38 (33.3%)
In Lower Extremity	10 (17.9%)	15 (25.9%)	25 (21.9%)
In Upper Extremity	5 (8.9%)	8 (13.8%)	13 (11.4%)
Airway Dysfunction	7 (12.5%)	3 (5.2%)	10 (8.8%)
Pain	39 (69.6%)	52 (89.7%)	91 (79.8%)
Disfigurement or Major Deformity	28 (50.0%)	30 (51.7%)	58 (50.9%)
Other	12 (21.4%)	10 (17.2%)	22 (19.3%)
Optic Glioma			
Yes	16 (28.6%)	11 (19.0%)	27 (23.7%)
No	40 (71.4%)	47 (81.0%)	87 (76.3%)
Prior PN Treatments			
Yes	8 (14.3%)	11 (19.0%)	19 (16.7%)
No	48 (85.7%)	47 (81.0%)	95 (83.3%)
Prior PN Surgery			
Yes	20 (35.7%)	40 (69.0%)	60 (52.6%)
No	36 (64.3%)	18 (31.0%)	54 (47.4%)

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	Pediatric (N = 56)	Adult (N = 58)	Total (N = 114)
Prior PN Radiotherapy			
Yes	0	1 (1.7%)	1 (0.9%)
No	56 (100%)	57 (98.3%)	113 (99.1%)

Abbreviations: CLIA: Clinical Laboratory Improvement Amendments; COA: Certificate of Accreditation; NF1: neurofibromatosis type 1; PN: plexiform neurofibroma; StD: standard deviation. Percentages were calculated using the number of participants in the corresponding cohort as the denominator. Morbidities were not mutually exclusive; a participant may have had more than one reported morbidity. Optic glioma was not a reason for enrollment in the study and was not assessed on study for changes to treatment.

Note: The exclusion criteria were modified in Protocol Amendment 2 to not allow prior MEK inhibitors.

Source: ADSL

External Control Data

Participant baseline disease characteristics were generally similar between MEK-NF-201 and external control data included for comparison. As Study 01-C-022 only included pediatric participants with a progressive PN, these data were compared against pediatric participants with progressive PN in Study MEK-NF-201 to provide the most accurate comparison. All adult and pediatric participants in Study MEK-NF-201 were compared against adult and pediatric participants enrolled in the external Study 08-C-0079, but disease severity and rate of progression in the external controls were not known, which is a limitation to this evaluation. For comparisons to natural history data, only participants in Study MEK-NF-201 who had both a baseline and post-baseline scan were included for analysis. The Study MEK-NF-201 cohorts for comparison were:

- Pediatric participants with progressive PN: n=34
- Pediatric Participants: n=54
- Adult participants: n=50.

The Applicant's Position:

Disease characteristics were consistent with the disease under study.

The FDA's Assessment:

FDA generally agrees that the baseline disease characteristics of patients in the ReNeu study are consistent with the general population of patients with NF1-PN

The FDA views the external control data as supportive in a descriptive manner. The data from Studies 01-C-022 and 08-C-0079 were not independently confirmed and will not be included in FDA's assessment of the efficacy results for the ReNeu study.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Participant compliance with study treatment was assessed at each visit where study treatment was dispensed. Compliance was assessed by counting returned capsules/tablets in addition to reviewing the dosing diary entries from the home electronic patient-reported outcome (ePRO) device used in the Treatment Phase (participants were trained on the home ePRO device at the Screening Visit). Study treatment exposure is presented in [Table 38](#).

A total of 54 (96%) participants in the pediatric cohort received at least 1 concomitant medication during the Treatment Phase. The most frequently reported (> 30%) Anatomical Therapeutic Chemical (ATC) classifications were anilides (46%), serotonin antagonists (39%), propionic acid derivatives (38%), anti-infectives for the treatment of acne (32%), and other antibiotics for topical use (32%).

A total of 57 (98%) participants in the adult cohort received at least 1 concomitant medication during the Treatment Phase. The most frequently reported (> 30%) ATC classifications were anti-infectives for the treatment of acne (74%), tetracyclines (59%), and other viral vaccines (47%).

Table 38: Summary of Exposure to Study Treatment (Safety Analysis Set)

	Pediatric (N = 56)	Adult (N = 58)	Total (N = 114)
Duration of Exposure (Months)			
N	56	58	114
Mean (StD)	21.0 (10.82)	19.8 (13.79)	20.4 (12.38)
Median	22.0	21.8	21.8
Min, Max	1.6, 40.0	0.4, 45.6	0.4, 45.6
Total Duration of Exposure (Patient Years)	97.96	95.66	193.62
Actual Dose Intensity (mg/day)			
N	55	56	111
Mean (StD)	5.3 (1.62)	6.7 (1.70)	6.0 (1.79)
Median	5.1	7.3	6.3
Min, Max	2.6, 8.7	0.3, 9.3	0.3, 9.3
Relative Dose Intensity (%)			
N	55	56	111
Mean (StD)	95.3 (14.96)	89.2 (18.72)	92.2 (17.17)
Median	96.8	95.2	95.9
Min, Max	49.1, 128.8	4.8, 116.0	4.8, 128.8

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	Pediatric (N = 56)	Adult (N = 58)	Total (N = 114)
BSA Adjusted Actual Dose Intensity (mg/m ² /day)			
N	55	56	111
Mean (StD)	4.2 (0.76)	3.9 (1.02)	4.0 (0.91)
Median	4.4	4.0	4.2
Min, Max	2.2, 5.8	0.2, 5.5	0.2, 5.8
BSA Adjusted Relative Dose Intensity (%)			
N	55	56	111
Mean (StD)	83.9 (37.12)	51.9 (13.36)	67.8 (32.00)
Median	73.1	52.9	59.3
Min, Max	30, 223	4, 79	4, 223
Time to First Dose Reduction (Months)			
N	7	10	17
Mean (StD)	4.2 (4.5)	6.0 (5.9)	5.2 (5.3)
Median	2.9	2.5	2.8
Min, Max	1, 14	1, 15	1, 15
Participants with at least 1 Dose Modification	39 (69.6%)	31 (53.4%)	70 (61.4%)
Due to Change in BSA	25 (44.6%)	5 (8.6%)	30 (26.3%)
Due to AE	18 (32.1%)	23 (39.7%)	41 (36.0%)
Due to Other	16 (28.6%)	6 (10.3%)	22 (19.3%)
Participants with at least 1 Dose Reduction	7 (12.5%)	10 (17.2%)	17 (14.9%)
Related to the Treatment	7 (12.5%)	10 (17.2%)	17 (14.9%)
Participants with at least 1 Dose Interruption	25 (44.6%)	25 (43.1%)	50 (43.9%)
Due to AE	18 (32.1%)	22 (37.9%)	40 (35.1%)
Related to the Treatment	8 (14.3%)	5 (8.6%)	13 (11.4%)
Due to Change in BSA	13 (23.2%)	0	13 (11.4%)
Interruption Due to Other	13 (23.2%)	6 (10.3%)	19 (16.7%)

Abbreviations: AE: adverse event; BSA: body surface area; CRF: case report form; StD: standard deviation.

Note: The reason for dose modifications and dose interruptions of AE also contains the CRF field of COVID-19.

Note: Unit dose changes as a result of BSA changes were not considered a dose modification and were intended to maintain the prescribed dose (2 mg/m²).

Actual dose intensity = cumulative dose received/number of prescribed dosing days.

Relative dose intensity = $100 \times (\text{cumulative dose received} / \text{planned dose})$.

Dose reduction was defined as re-assignment of dose where the new dose was less than the original dose as a result of an AE.

Participants could have had multiple reasons for dose modifications, reductions, or interruptions, and thus could be counted in multiple rows corresponding to reasons.

Source: ADSL, ADEX, ADEX2

The Applicant's Position:

A total of 56 (100%) participants in the pediatric cohort received at least 1 dose of study treatment. The median duration of study treatment exposure was almost 2 years with a maximum duration of over 3 years, suggesting sustained tolerability over an extended period of treatment in the pediatric cohort.

A total of 58 (100%) participants in the adult cohort received at least 1 dose of study treatment. The median duration of study treatment exposure was almost 2 years with a maximum duration of almost 4 years, suggesting sustained tolerability over an extended period of treatment in the adult cohort.

The FDA's Assessment:

FDA agrees with the Applicant's description of concomitant medication use and treatment compliance.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

A summary of the confirmed ORR by the end of the Treatment Phase is provided for the FAS in [Table 39](#). Waterfall plots of best percent change from baseline in tumor volume are provided in [Figure 7](#) (pediatric cohort) and [Figure 8](#) (adult cohort).

The confirmed ORR (95% CI) by BICR was 51.8% (38.0, 65.3) in the pediatric cohort, with no CRs and 29 confirmed PRs. The median (min, max) time to onset of first response that was subsequently confirmed was 7.90 (4.1, 18.8) months for the pediatric cohort. In addition, 1 participant achieved a confirmed PR in the LTFU Phase. Inclusive of this response, the confirmed ORR (95% CI) in the pediatric cohort was 53.6% (39.7, 67.0).

The confirmed ORR (95% CI) by BICR was 41.4% (28.6, 55.1) in the adult cohort, with no CRs and 24 confirmed PRs. The median (min, max) time to first response that was subsequently confirmed was 7.75 (4.0, 19.0) months for the adult cohort. In addition, 2 participants each achieved a confirmed PR in the LTFU Phase. Inclusive of these responses, the confirmed ORR (95% CI) in the adult cohort was 44.8% (31.7, 58.5).

Table 39: Analysis of Confirmed ORR by BICR – Treatment Phase (FAS)

	Pediatric (N = 56)	Adult (N = 58)
Confirmed ORR by BICR		
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; CI: confidence interval; CR: complete response; FAS: Full Analysis Set; ORR: objective response rate; PD: progressive disease; PR: partial response; SD: stable disease. N represents the number of participants in the corresponding cohort. n is the number of confirmed objective responders.

Confirmed objective response was defined as two consecutive assessments of PR or CR assessed by a BICR within 2-6 months during the Treatment Phase.

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p-values were calculated using a one-sample two-sided binomial test compared to the minimally clinically relevant response rates of 23% for the adult cohort and 20% for the pediatric cohort.

Participants who had no post-baseline MRI assessment or no confirmed objective response were treated as non-responders.

Best overall confirmed response status was defined as the best confirmed response prior to disease progression during the Treatment Phase.

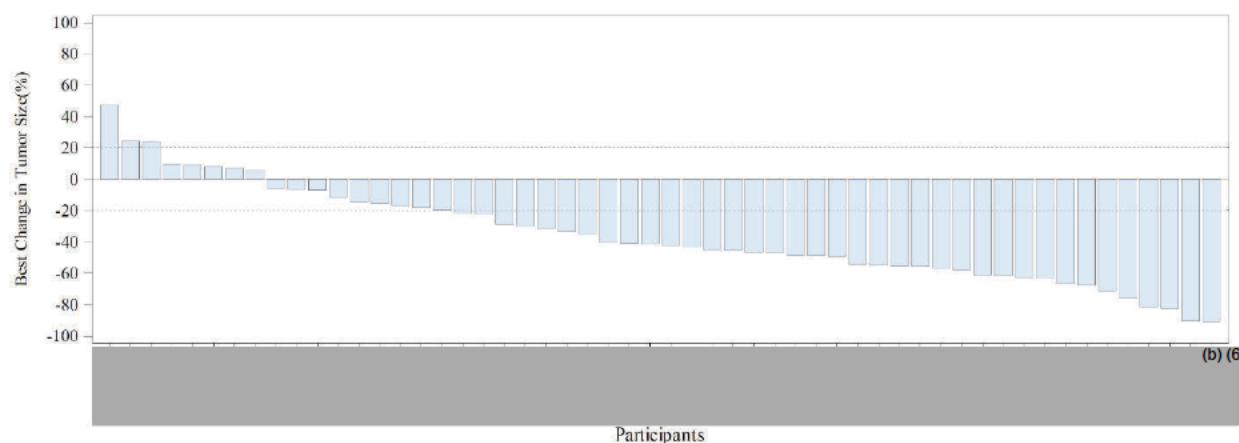
Missing contains participants who had no post-baseline assessments.

Source: ADSL, ADEFF

In the pediatric cohort, responses were deep with a median best average percentage change from baseline in target PN tumor volume of -42% and a maximum reduction of 91% (Figure 7). The median (min, max) time to best percentage change from baseline in tumor volume was 13.45 (4.0, 32.7) months.

In the adult cohort, responses were deep with a median best average percentage change from baseline in target PN tumor volume of -41% and a maximum reduction of 90% (Figure 8). The median (min, max) time to best percentage change from baseline in tumor volume was 15.23 (4.0, 40.0) months.

Figure 7: Waterfall Plot of Best Percent Change from Baseline in Tumor Volume – Pediatric Cohort (FAS)



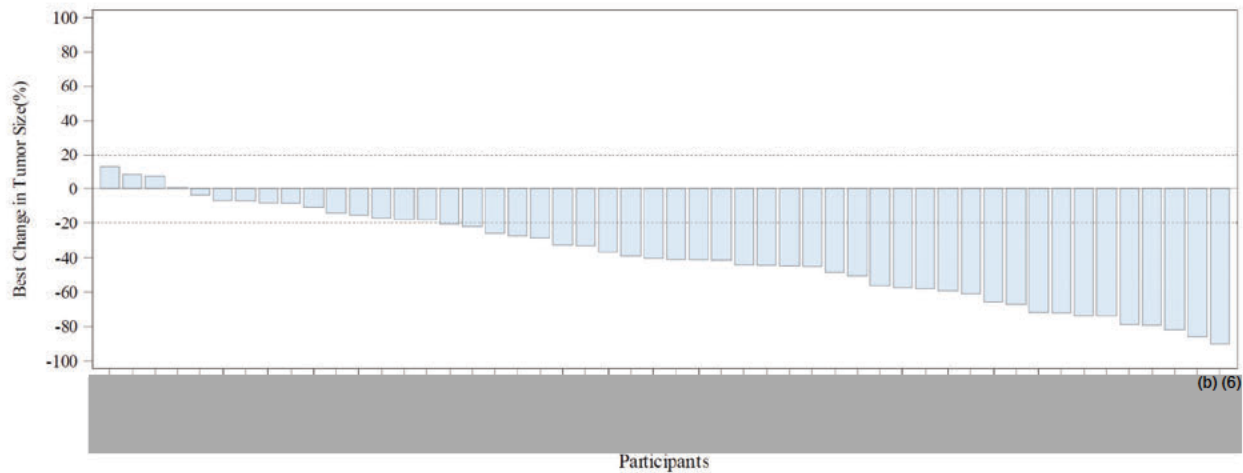
Abbreviations: FAS: Full Analysis Set; PN: plexiform neurofibroma.

Tumor volume measurements were taken for target PN tumors and independently calculated by two reviewers.

The two calculated volumes were averaged to give the visit volume assessment, unless they represented different response statuses, in which case the reader assessment confirmed by the adjudicator was used.

Source: ADEFF

Figure 8: Waterfall Plot of Best Percent Change from Baseline in Tumor Volume – Adult Cohort (FAS)



Abbreviations: FAS: Full Analysis Set; PN: plexiform neurofibroma.

Tumor volume measurements were taken for target PN tumors and independently calculated by two reviewers.

The two calculated volumes were averaged to give the visit volume assessment, unless they represented different response statuses, in which case the reader assessment confirmed by the adjudicator was used.

Source: ADEFF

The results of sensitivity analyses of confirmed ORR are provided in [Table 40](#). The confirmed ORR for the per-protocol set in the pediatric cohort was 56.9% (42.2, 70.7) for Reader A and 54.9% (40.3, 68.9) for Reader B and in the adult cohort was 48.9% (34.1, 63.9) for Reader A and 44.7% (30.2, 59.9) for Reader B.

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Table 40: Confirmed ORR Sensitivity Analyses

	Pediatric					Adult				
	FAS (N = 56)		PPS (N = 51)			FAS (N = 58)		PPS (N = 47)		
	Reader A	Reader B	Reader A	Reader B	Ave ^a	Reader A	Reader B	Reader A	Reader B	Ave ^a
Confirmed ORR										
N	29	28	29	28	29	25	23	23	21	22
ORR %	51.8	50.0	56.9	54.9	56.9	43.1	39.7	48.9	44.7	46.8
95% CI	38.0, 65.3	36.3, 63.7	42.2, 70.7	40.3, 68.9	42.2, 70.7	30.2, 56.8	27.0, 53.4	34.1, 63.9	30.2, 59.9	32.1, 61.9
p-value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	0.003	< 0.001	< 0.001	< 0.001
Best Overall Confirmed Response Status										
CR	0	0	0	0	0	0	0	0	0	0
PR	29 (51.8%)	28 (50.0%)	29 (56.9%)	28 (54.9%)	29 (56.9%)	25 (43.1%)	23 (39.7%)	23 (48.9%)	21 (44.7%)	22 (46.8%)
SD	21 (37.5%)	23 (41.1%)	18 (35.3%)	20 (39.2%)	19 (37.3%)	24 (41.4%)	26 (44.8%)	23 (48.9%)	25 (53.2%)	25 (53.2%)
PD	4 (7.1%)	3 (5.4%)	4 (7.8%)	3 (5.9%)	3 (5.9%)	0	1 (1.7%)	0	1 (2.1%)	0
NE	0	0	0	0	0	1 (1.7%)	0	1 (2.1%)	0	0
Missing	2 (3.6%)	2 (3.6%)	0	0	0	8 (13.8%)	8 (13.8%)	0	0	0

Abbreviations: Ave: average; BICR: blinded independent central review; CI: confidence interval; CR: complete response; FAS: Full Analysis Set; NE: not evaluable; ORR: objective response rate; PD: progressive disease; PPS: Per Protocol Set; PR: partial response; SD: stable disease.

N represents the number of participants in the corresponding cohort. n is the number of confirmed objective responders.

p-values were calculated using a one-sample two-sided binomial test compared to the minimally clinically relevant response rates of 23% for the adult cohort and 20% for the pediatric cohort.

Participants who had no post-baseline MRI assessment or no confirmed objective response were treated as non-responders.

Missing contains participants who had no post-baseline assessments.

^a In the case that the two measurements represented different tumor response statuses, as defined above, an independent adjudicator made the final decision on which response category was recorded at that visit.

Source: ADSL, ADEFF

Yearly Percentage Change from Baseline in Target PN Compared to External Control Data

For efficacy analyses, one-to-one propensity score matching was used as the balancing method. After one-to-one propensity score matching, variance ratios became within the recommended range of 0.5 to 2, which supports that the groups are well balanced with respect to the selected demographic characteristics (Rubin 2001).

In Cohort 1 (Study MEK-NF-201 pediatric participants with progressive PN and Study 01-C-0222 pediatric participants with progressive PN), participants in Study MEK-NF-201 had a significant decrease in yearly percentage change in the target PN volume while participants from Study 01-C-0222 had increases in PN volume at all the time intervals. After adjusting for potential differences in baselines covariates using one-to-one propensity score matching, the LS mean percentage differences (standard errors) were -43.72 (8.816), -23.76 (5.812), -21.91 (7.874), and -38.72 (8.331), at Year 1, 2, 3, and the last assessment, respectively. This improvement remained significant and robust even after a sensitivity analysis comparing alternative target lesion at baseline.

In Cohort 2 (Study MEK-NF-201 pediatric participants and Study 08-C-0079 pediatric participants), participants in Study MEK-NF-201 had a significant decrease in yearly percentage change in the target PN volume while participants from Study 08-C-0079 had increases in PN volume at all time intervals. After adjusting for potential differences in baselines covariates using one-to-one propensity score matching, the LS mean percentage differences (standard errors) were -40.63 (6.699), -36.62 (3.891), -27.53 (4.471), and -24.28 (5.701), at Year 1, 2, 3, and the last assessment, respectively.

In Cohort 3 (Study MEK-NF-201 adult participants and Study 08-C-0079 adult participants), participants in Study MEK-NF-201 had a substantial decrease in yearly percentage change in the target PN volume as compared to an increase in the yearly percentage change in the target PN volume in participants from Study 08-C-0079 at all-time intervals. All results were statistically significant except for Year 3 after propensity score matching. Since only 38% of participants from Study MEK-NF-201 were matched with participants from Study 08-C-0079 after one-to-one propensity score matching without replacement, treatment comparisons based on this matching result need to be interpreted with caution. After adjusting for potential differences in baselines covariates, using IPTW, the LS mean percentage differences (standard errors) were -26.74 (6.470), -24.96 (4.628), -19.79 (5.067), and -27.14 (6.189), at Year 1, 2, 3 and the last assessment, respectively.

The Applicant's Position:

In the pediatric cohort, there was an ORR of 51.8% (29 of 56 participants dosed; 95% CI 38.0%, 65.3%), as assessed by BICR, during the 24 cycle Treatment Phase. The ORR inclusive of additional responses confirmed in the LTFU Phase was 53.6% (39.7, 67.0). These data demonstrate that the lower limit of the 95% CI excluded the null hypothesis of confirmed ORR =

20%. Responses were deep with a median best average percentage change from baseline in target PN tumor volume of -42% and a maximum reduction of 91%. These data demonstrate treatment effect when compared against the external control data from both Study 08-C-0079 and Study 01-C-022 where comparable participants from each external control study demonstrated mean increases in PN volume at all time intervals assessed.

In the adult cohort, there was an ORR of 41.4% (24 of 58 participants dosed; 95% CI 28.6%, 55.1%), as assessed by BICR, during the 24 cycle Treatment Phase. The ORR inclusive of additional responses confirmed in the LTFU Phase was 44.8% (31.7, 58.5). These data demonstrate that the lower limit of the 95% CI excluded the null hypothesis of confirmed ORR = 23%. Responses were deep with a median best average percentage change from baseline in target PN tumor volume of -41% and a maximum reduction of 90%. These data demonstrate treatment effect when compared against the external control data from Study 08-C-0079 where participants demonstrated mean increases in PN volume at all time intervals assessed.

Sensitivity analyses of ORR for the per protocol set support the results of the primary analysis. Sensitivity analyses of ORR by reader for the full analysis set and per protocol set also demonstrate consistency between readers and support the results of the primary analysis.

The FDA's Assessment:

FDA agrees with the results for ORR presented in this section, noting that as a single arm trial with no control for multiplicity in any of the hypothesis tests presented in Table 39 and Table 40, the p-values reported by the Applicant should be interpreted with caution. In addition, there were no complete responses which should be acknowledged when describing responses as "deep."

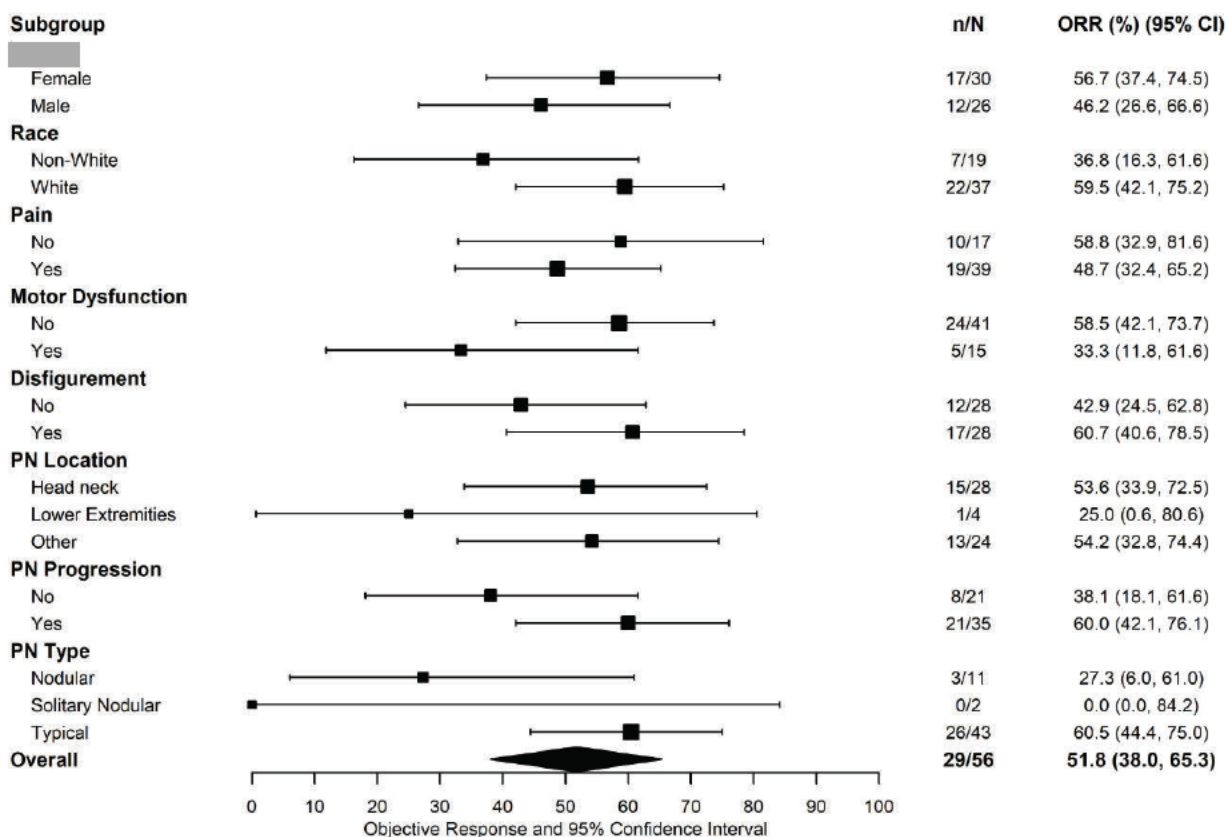
The primary endpoint is defined as confirmed ORR at the end of the treatment phase, using centrally read MRI volumetric analysis, where a confirmed response is specified as a PN decrease of $\geq 20\%$ compared to baseline on consecutive scans within 2-6 months. This differs from the REiNS criteria for partial response, which defines confirmed PR based on consecutive scans within 3-6 months. The rationale for this modification was primarily to account for patients in whom a first response observed at Cycle 21 would be confirmed at Cycle 24 (end of Treatment Phase) which, per protocol, could occur at 3 months +/- 10 days. Ultimately, three adult patients had a first response at Cycle 21 with a confirmatory scan at 91, 91, and 86 days, falling short of strict REiNS criteria. All three patients continued to have a confirmed response in the long-term follow-up phase. Two patients, one adult, and one pediatric, had unscheduled MRI assessments which led to confirmatory scan intervals of 70 days. The adult patient had an MRI assessment at the scheduled time; however, it was missing the PD/T2 sequence; because this sequence was required according to the Imaging Review Charter v8.0, an unscheduled MRI was conducted at a later date to meet study imaging criteria for volumetric evaluation of the target PN. This patient went on to have progressive disease. The pediatric patient had an

unscheduled assessment due to an adverse event of upper respiratory infection and the MRI assessment for that cycle was conducted later in the cycle following recovery. This patient went on to have a confirmed response in the long-term follow-up phase. In response to an FDA information request (October 7, 2024), the Applicant provided a sensitivity analysis of confirmed ORR per REiNS for both the pediatric and adult cohorts (Table 41). Applying the REiNS criteria strictly would remove the 4 adult patients and resulted in confirmed ORR of 35% (95% CI: 22, 48) for the adult cohort. Applying the REiNS criteria to remove the pediatric responder resulted in a change in confirmed ORR from 52% (95% CI: 38, 65) to 50% (95% CI: 36,64).

Sensitivity analyses of confirmed ORR across BICR readers as well as between FAS and PPS populations provide reassurance that trial results are robust.

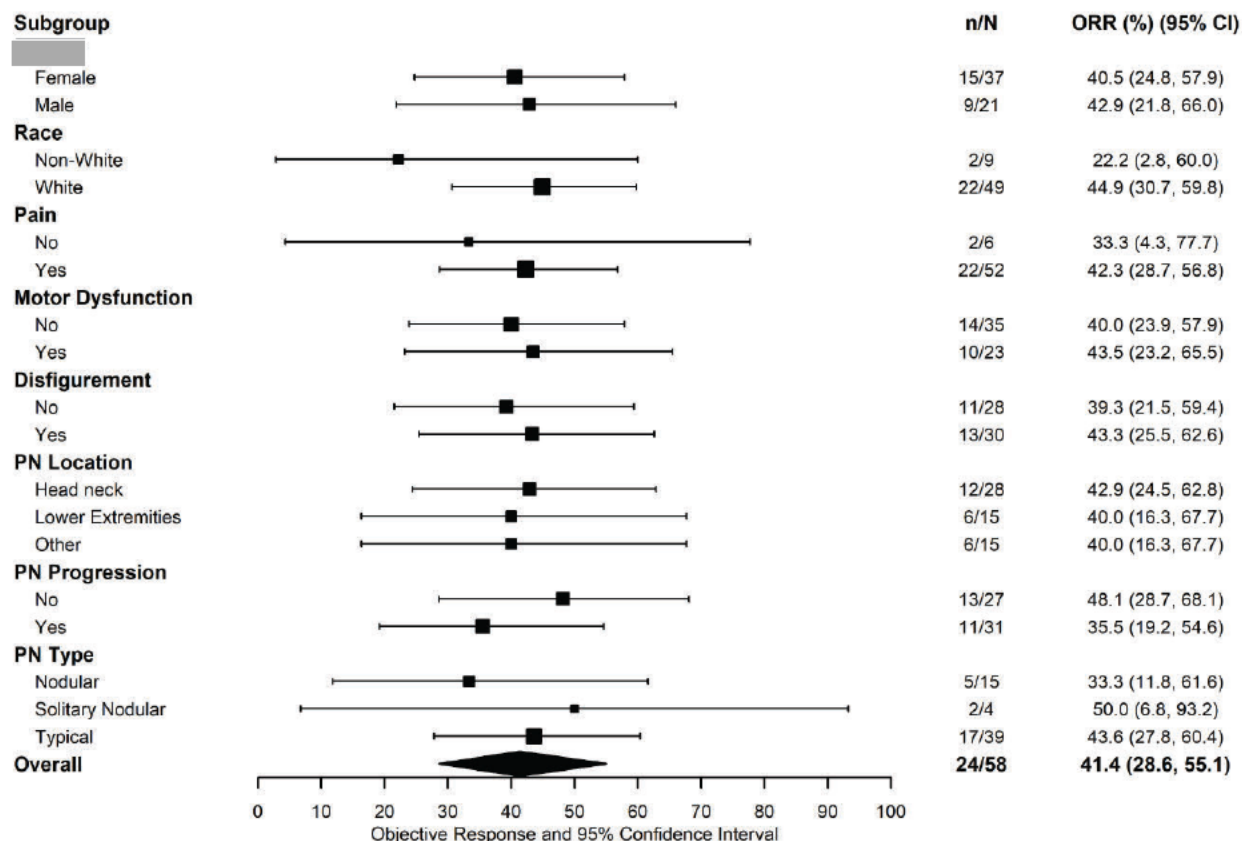
The ORR outcomes are generally consistent across subgroups based on demographic and clinical characteristics in both pediatric and adult cohorts, Figure 9 and Figure 10, respectively.

Figure 9: ORR Subgroup Analysis in Pediatric Cohort



Source: FDA generated analysis based on Applicant submitted data [ADSL, ADEFF]

Figure 10: ORR Subgroup Analysis in Adult Cohort



Source: FDA generated analysis based on Applicant submitted data [ADSL, ADEFF]

Table 41 Sensitivity Analysis of Confirmed ORR per Strict REiNs Criteria- Treatment Phase Only

Confirmed ORR per REiNs	Pediatric (N=56)	Adult (N=58)
Responders	28	20
Overall Response Rate, (95% CI)	50% (36, 64)	35% (22, 48)

Source: Adapted from Applicant response to FDA Information request (10/7/24)

Of note, the yearly percentage change from baseline in target PN, compared to external control data, was not the primary efficacy endpoint in the ReNeu study.

Efficacy Results – Secondary and other relevant endpoints

Data:

As of the data cut of 20-Sept-2023, the majority of responders (88% of pediatric responders and 86% of adult responders) were followed for at least 12 months from the onset of response, unless they discontinued earlier. A KM analysis of DoR for participants whose best confirmed response was a CR or PR is provided in [Table 41](#). Swimmer plots of duration of treatment are provided in [Figure 11](#) for the pediatric cohort and [Figure 12](#) for the adult cohort.

In Study MEK-NF-201, the KM estimated median DoR was not reached for the pediatric cohort due to no events (i.e., PDs or deaths) occurring after a confirmed response as of the data cutoff of 20-Sept-2023 ([Table 41](#)). The responses were durable, with 22 (76%) of pediatric responders maintaining a confirmed response for at least 12 months, and no disease progression or deaths being observed ([Figure 11](#)). Most participants (27 [93%]) were censored due to no PD/death post response confirmation, 1 (3%) participant was censored due to no adequate tumor assessment post confirmed response, and 1 (3%) participant was censored due to undergoing PN therapy/surgery prior to PD/death. Since 4 out of the 29 pediatric responders had an onset of response less than 12 months from the data cut, updated DoR with a later data cut will be provided as an addendum to the CSR.

Similar to the pediatric cohort, the Kaplan-Meier estimated median DoR was not reached for the adult cohort due to only 1 event of PD after achieving a confirmed objective response as of the data cutoff ([Table 41](#)). The responses were durable, with 18 (75%) of adult responders maintaining an observed response for at least 12 months; 1 PD and no deaths were observed ([Figure 12](#)). Of the remaining responders, most participants (20 [87%]) were censored due to no PD/death post response confirmation and 3 (13%) participants were censored due to no adequate tumor assessment post confirmed response. Since 3 out of the 24 adult responders had an onset of response less than 12 months from the data cut, updated DoR with a later data cut will be provided as an addendum to the CSR.

Table 42: Kaplan-Meier Analysis of DoR (FAS)

	Pediatric (N = 56)	Adult (N = 58)
Number of Participants with Confirmed Response	29 (51.8%)	24 (41.4%)
Number of Participant Events	0	1 (4.2%)

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	Pediatric (N = 56)	Adult (N = 58)
PD	0	1 (100%)
Death	0	0
Number of Censored Participants	29 (100%)	23 (95.8%)
Reason for Censoring		
No adequate tumor assessment post confirmed response	1 (3.4%)	3 (13.0%)
No PD/death post response confirmation	27 (93.1%)	20 (87.0%)
Underwent PN therapy/surgery prior to PD/death	1 (3.4%)	0
Two or more consecutive missing/non-adequate assessments	0	0
Duration of Response (Months):		
1 st Quartile	NE	NE
95% CI	(NE, NE)	(6.1, NE)
Median	NE	NE
95% CI	(NE, NE)	(NE, NE)
3 rd Quartile	NE	NE
95% CI	(NE, NE)	(NE, NE)
At 8 Months		
Number of Events Experienced by This Point	0	1 (4.2%)
Number Still Maintaining Response at This Point (At Risk)	25 (86.2%)	18 (75.0%)
Kaplan-Meier Response Rate Estimate	1.00	0.95
95% CI	(1.00, 1.00)	(0.71, 0.99)
At 12 Months		
Number of Events Experienced by This Point	0	1 (4.2%)
Number Still Maintaining Response at This Point (At Risk)	22 (75.9%)	18 (75.0%)
Kaplan-Meier Response Rate Estimate	1.00	0.95
95% CI	(1.00, 1.00)	(0.71, 0.99)

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	Pediatric (N = 56)	Adult (N = 58)
At 16 Months		
Number of Events Experienced by This Point	0	1 (4.2%)
Number Still Maintaining Response at This Point (At Risk)	18 (62.1%)	13 (54.2%)
Kaplan-Meier Response Rate Estimate	1.00	0.95
95% CI	(1.00, 1.00)	(0.71, 0.99)
At 20 Months		
Number of Events Experienced by This Point	0	1 (4.2%)
Number Still Maintaining Response at This Point (At Risk)	10 (34.5%)	11 (45.8%)
Kaplan-Meier Response Rate Estimate	1.00	0.95
95% CI	(1.00, 1.00)	(0.71, 0.99)
At 24 Months		
Number of Events Experienced by This Point	0	1 (4.2%)
Number Still Maintaining Response at This Point (At Risk)	4 (13.8%)	9 (37.5%)
Kaplan-Meier Response Rate Estimate	1.00	0.95
95% CI	(1.00, 1.00)	(0.71, 0.99)

Abbreviations: CI: confidence interval; CR: complete response; DoR: duration of response; FAS: Full Analysis Set; LTFU: long-term follow-up; NE: not evaluable; PD: progressive disease; PN: plexiform neurofibroma; PR: partial response; SAP: statistical analysis plan; SD: stable disease.

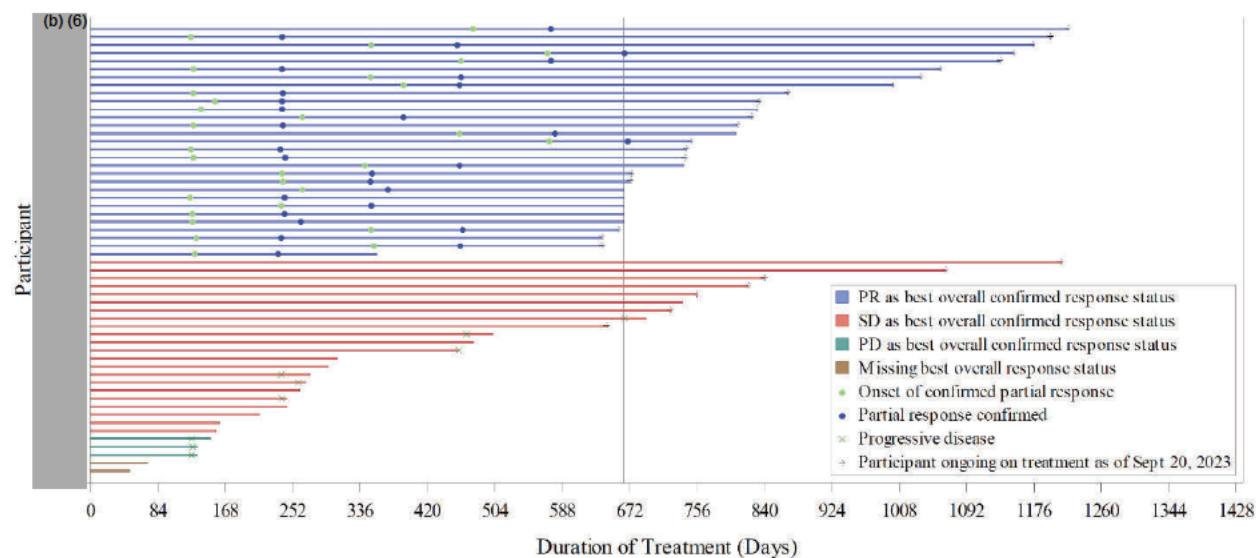
DoR was defined as the time in months between that first instance of response that was subsequently confirmed, until the date of radiographic disease progression or death, whichever occurred first.

Percentages were calculated out of the number of participants with a confirmed response for the number with PD/censored, number of events experienced by this point, and number of participants still event-free by this point.

Percentages for event type were based on the total number of events and out of the number censored for the reasons for censoring.

Source: ADSL, ADTTE

Figure 11: Swimmer Plot of Duration of Treatment – Pediatric Cohort (FAS)

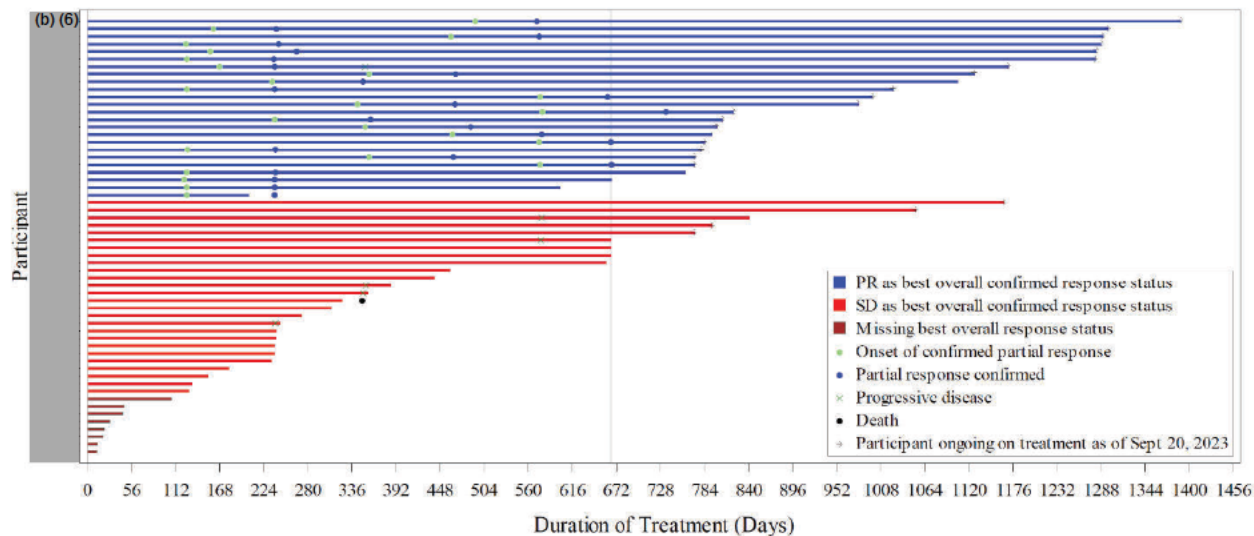


Abbreviations: BICR: blinded independent central review; C: Cycle; D: Day; FAS: Full Analysis Set; PD: progressive disease; PR: partial response; SD: stable disease.

The gray vertical line corresponds to the hypothetical date of the end of Treatment Phase on C24D21 (D665), assuming the study visit schedule was followed.

Source: ADSL, ADEFF, ADRS

Figure 12: Swimmer Plot of Duration of Treatment – Adult Cohort (FAS)



Abbreviations: BICR: blinded independent central review; C: Cycle; D: Day; FAS: Full Analysis Set; PD: progressive disease; PR: partial response; SD: stable disease.

The gray vertical line corresponds to the hypothetical date of the end of Treatment Phase on C24D21 (D665), assuming the study visit schedule was followed.

Source: ADSL, ADEFF, ADRS

The Applicant’s Position:

At the time of the data cut-off in Study MEK-NF-201 (20Sep2023) 88% of pediatric participants with a confirmed objective response during the 24 cycle Treatment Phase had been followed for at least 12 months from the onset of response, or discontinued study. The K-M estimated median DoR was not reached for the pediatric cohort due to no events occurring as of the data cutoff. The responses were durable, with 22 (76%) of pediatric responders maintaining a confirmed response for at least 12 months, and no disease progression or deaths were observed following a confirmed response. These data demonstrate continuing effect of mirdametininib over time in pediatric participants with NF1-PN.

At the time of the data cut-off in Study MEK-NF-201 (20Sep2023) 86% of adult participants with a confirmed objective response during the 24 cycle Treatment Phase had been followed for at least 12 months from the onset of response, or discontinued study. The K-M estimated median DoR was not reached for the adult cohort due to a low number of events after achieving a confirmed objective response as of the data cutoff (1 event of PD). The responses were durable, with 18 (75%) of adult responders maintaining an observed response for at least 12 months; 1 PD and no deaths were observed following a confirmed response. These data demonstrate continuing effect of mirdametininib over time in adult participants with NF1-PN.

The FDA’s Assessment:

FDA generally agrees with the description of secondary and other relevant endpoints.

The median DOR was not reached in either the pediatric or adult cohorts due to lack of events. Therefore, the Applicant provided DOR estimates for 8-, 12-, 16- and 24-month landmarks based on the KM rate as shown in Table 41. The Applicant has also included DOR based on observed time which provides additional critical information, as it reflects the conservative estimate.

A 90-day safety update for DOR, based on a data cut of June 12, 2024, indicates the Kaplan-Meier estimated DOR was still not reached in either pediatric or adult cohorts. Additionally, there was no change in estimated ORRs for both cohorts. A summary of the updated efficacy results including observed DOR is provided in Table 42.

Table 43: Efficacy results by Cohort based on 90-day safety update

	Pediatric (N=56)	Adult (N=58)
Overall Response Rate, (95% CI)	52% (38, 65)	41% (29, 55)

	Pediatric (N=56)	Adult (N=58)
Duration of Response (DOR)		
DOR ≥ 12 months ^a	26 (90%)	21 (88%)
DOR ≥ 24 months ^a	14 (48%)	12 (50%)

^a Duration of response was assessed based on observed time.

Source: FDA generated analysis based on Applicant submitted data [ADSL, ADTTE]

The DOR estimates, based on observed time, indicate that 90% of patients in the pediatric cohort and 88% of patients in the adult cohort are still in response at 12 months or longer. Additionally, 48% of patients in the pediatric cohort and 50% of patients in the adult cohort remain in response for 24 months or longer.

Dose/Dose Response

The Applicant's Position:

Mirdametinib was dosed in Studies MEK-NF-201 and NF-106 by BSA. The median (minimum, maximum) of actual doses received by participants with NF1 PN was 2.21 mg/m² (0.806, 2.86) (Figure 4).

In addition, population and trial simulations were conducted using exposure-efficacy and exposure-safety models to predict the impact of alternative target dose levels from 1.0 to 3.0 mg/m² BID (1.0, 1.5, 2.0, 2.2, and 3.0 mg/m²). The simulations support that exposures associated with the proposed marketing dose of 2 mg/m² of mirdametinib provide an optimal balance of robust efficacy with a tolerable incidence of low severity exposure-related AEs for patients with NF1 PN. Please refer to Section 6.2.2.1 for additional simulation details in support of the proposed 2mg/m² dose used in Study MEK-NF-201, Figure 4.

The FDA's Assessment:

Refer to Section 6, 19.4.2, and 19.4.3 for clinical pharmacology review details.

Durability of Response

Data:

Refer to Table 41, Figure 11, and Figure 12.

The Applicant's Position:

Refer to the secondary endpoint position.

The FDA's Assessment:

FDA generally agrees with the Applicant, adding that with the 90-day safety update the number of patients remaining in response after 12 months (90% in the pediatric cohort and 88% in the

adult cohort) and 24 months (48% in the pediatric cohort and 50% in the adult cohort) indicate that the majority of responders experienced durable response (Table 42).

Persistence of Effect

Data:

Refer to efficacy results – secondary and other relevant endpoints above.

The Applicant's Position:

The study demonstrated persistence of effect over time based on the observed duration of response.

The FDA's Assessment:

FDA generally agrees with the Applicant, adding that with the original data submission no deaths were observed in the pediatric cohort and only one death was observed in the adult cohort. These findings remained the same with no additional deaths or progressions with the 90-day safety update report.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

PRO assessments evaluated as part of the secondary endpoints included quality of life as assessed by PedsQL, pain severity as assessed by NRS-11, and pain interference as assessed by PII, and were assessed at the prespecified Cycle 13 timepoint (Figure 11):

Pediatric participants:

- For the PedsQL PRO assessment, the LS mean change from baseline in total score at Cycle 13 was 4.01 (n=38; 95% CI: -0.74, 8.76; p = 0.096) by self-report and 5.64 (n=43; 95% CI: 1.75, 9.53; p = 0.005) by parent proxy, demonstrating improvement in quality of life.
- For the NRS-11 PRO assessment, the LS mean change from baseline at Cycle 13 was -0.79 (n=17; 95% CI: -1.28, -0.29; p = 0.003), demonstrating a decrease in pain severity.
- For the PII PRO assessment, the LS mean change from baseline at Cycle 13 was -0.46 (n=22; 95% CI: -0.83, -0.09; p = 0.017) by self-report and -0.26 (n=20; 95% CI: -0.49, -0.03; p = 0.025) by parent proxy, demonstrating a decrease in pain interference.

Adult participants:

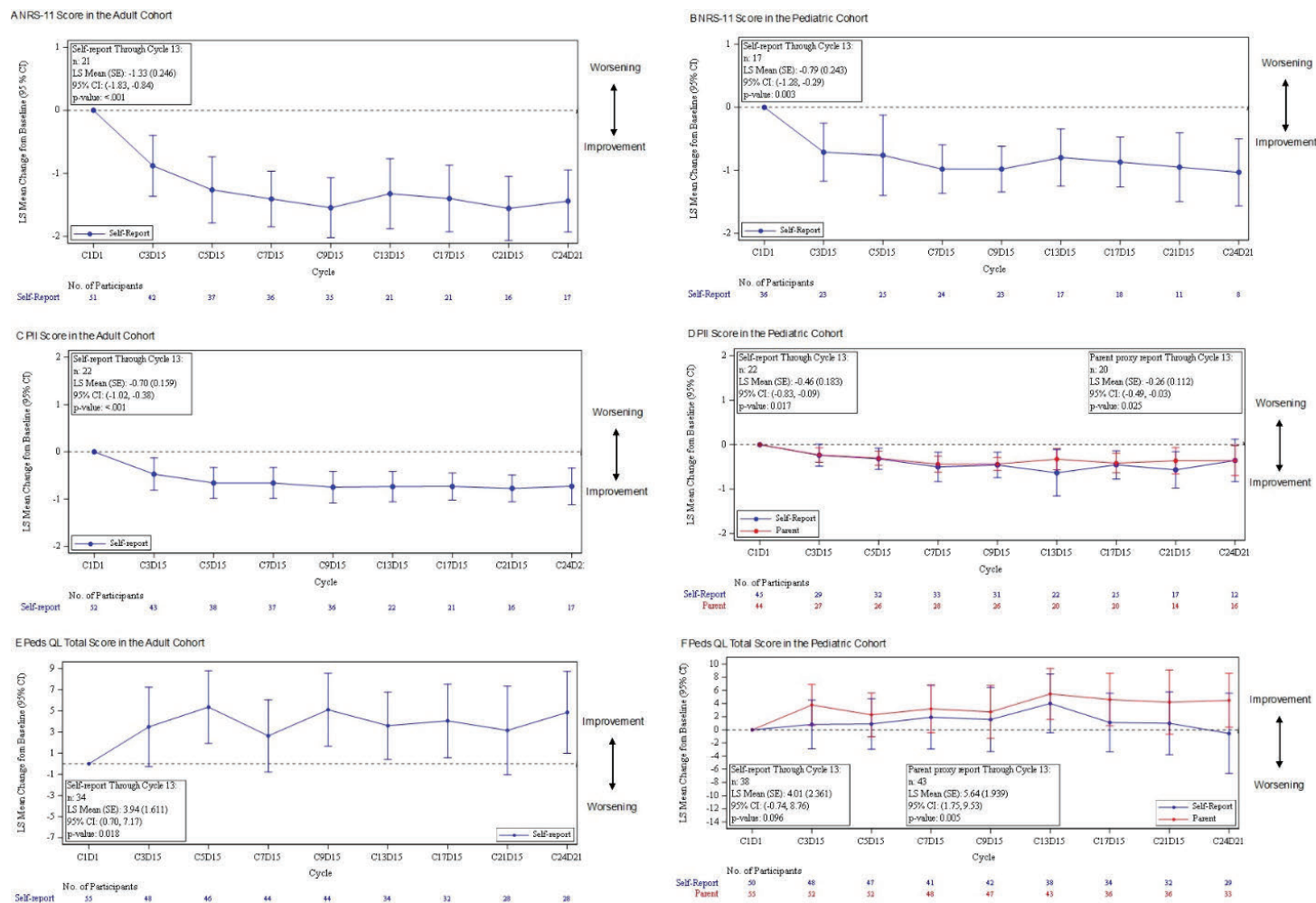
- For the PedsQL PRO assessment, the LS mean change from baseline in total score at Cycle 13 was 3.94 (n=34; 95% CI: 0.70, 7.17; p = 0.018), demonstrating improvement in quality of life.
- For the NRS-11 PRO assessment, the LS mean change from baseline at Cycle 13 was -1.33 (n=21; 95% CI: -1.83, -0.84; p < 0.001), demonstrating a decrease in pain severity.
- For the PII PRO assessment, the LS mean change from baseline at Cycle 13 was -0.70 (n=22; 95% CI: -1.02, -0.38; p < 0.001, demonstrating a decrease in pain interference.

Least Squares (LS) mean change from Cycle 1 Day 1 (baseline) over time in PRO estimated from the MMRM analysis through all cycles in pediatric participants showed a significant improvement in parent proxy-reported PedsQL total score, durable and significant reductions from baseline in patient-reported NRS-11 and patient/parent proxy-reported PII, beginning early (at Cycle 3 or 5), and sustained through most cycles ([Figure 11](#)). Similarly, in adult participants a significant improvement in PedsQL total score, durable and significant reductions from baseline in NRS-11 and PII, beginning early and sustained throughout the cycles, were observed.

Additionally, meaningful change threshold (MCT) analyses were performed for each PRO assessment to further describe clinical benefit of mirdametininib using a distribution -based approach and generally demonstrated that the statistically significant PRO findings were associated with clinically meaningful improvements.

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Figure 13: Mixed Model Repeat Measures: Change from Baseline in PRO Assessments



Abbreviations: C: cycle; D: day; NRS-11: Numeric Rating Scale-11; PedsQL: Pediatric Quality of Life Inventory; PII: Pain Interference Index

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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Source: ADSL, ADQS

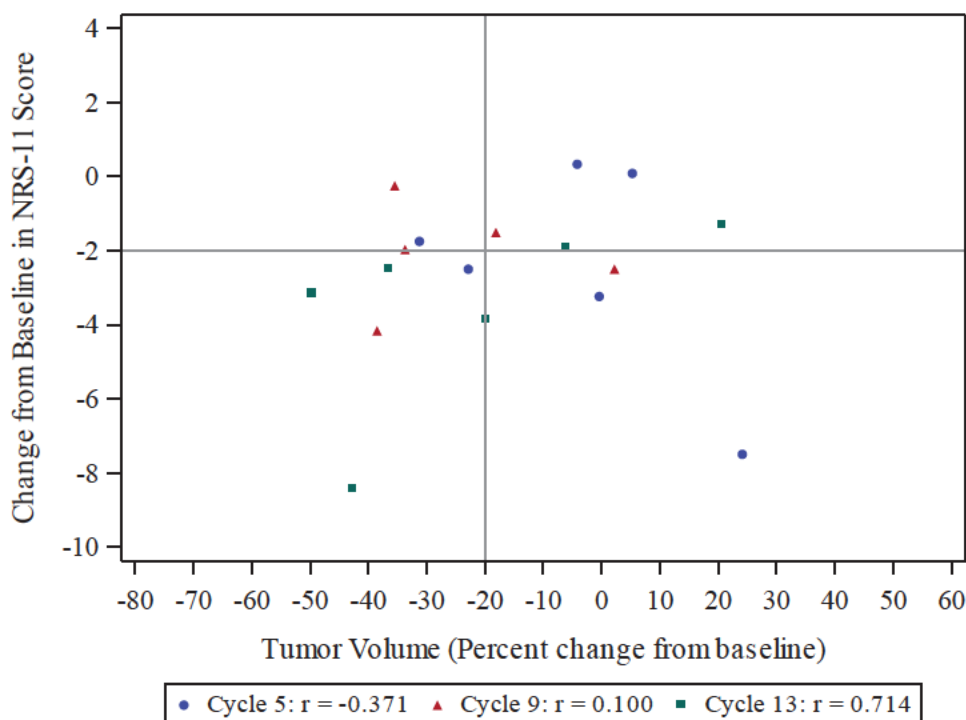
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A post-hoc exploratory analysis was conducted to assess the correlation of change from baseline in NRS-11 score and percent change from baseline in tumor volume, by cycle, in participants with a baseline NRS-11 score ≥ 2 . The Spearman rank correlation coefficient (r) was used to measure the strength of this relationship and was assessed as per Cohen (Cohen 1988) using the following ranges (for both positive and negative correlations): $r = 0$ to 0.3 indicates a weak correlation, $r = 0.3$ to 0.5 indicates a moderate correlation, and $r = 0.5$ to 1.0 indicates a strong correlation.

In the pediatric cohort, a strong positive correlation was observed between percentage change from baseline in tumor volume and change from baseline in NRS-11 score at Cycle 13 ($n = 6$, $r = 0.714$) (Figure 14). However, small sample sizes at this time point limit the interpretation of these data.

In the adult cohort, a weak positive correlation was observed between percent change from baseline in tumor volume and change from baseline in NRS-11 score at Cycle 13 ($n = 11$, $r = 0.164$) (Figure 15). However, small sample sizes at this time point limit the interpretation of these data.

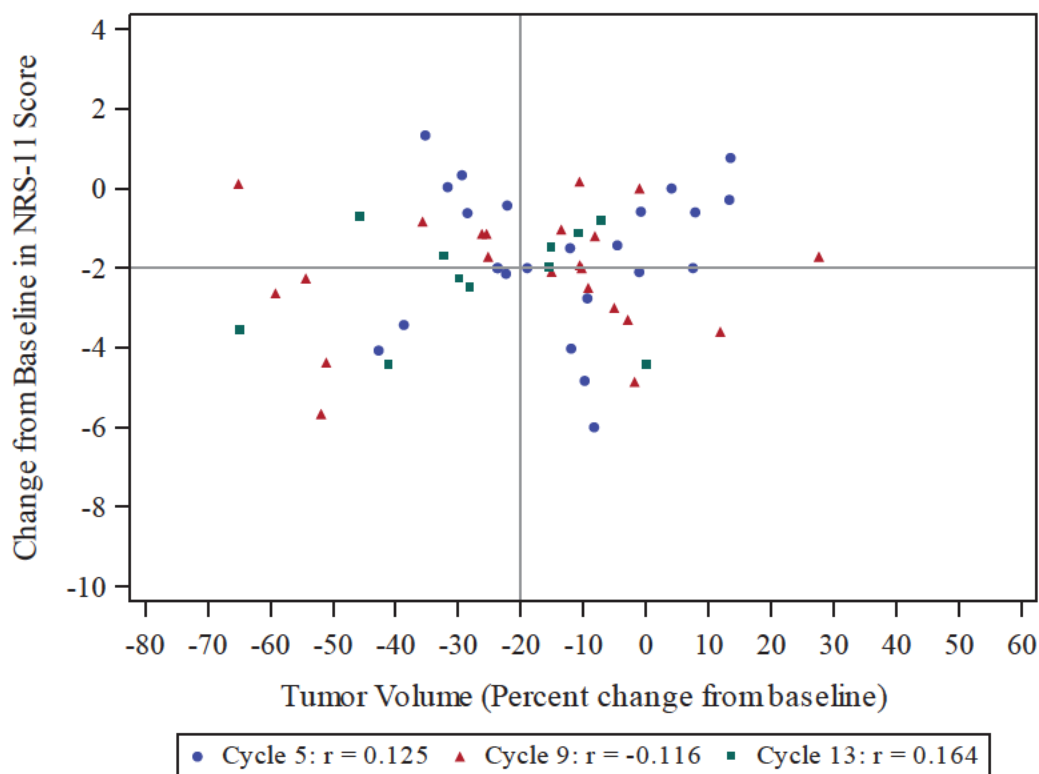
Figure 14: Spearman Rank Correlation Plot of Change from Baseline in NRS-11 Score with Percentage Change of Tumor Volume by Cycle in Participants with a Baseline NRS-11 Score ≥ 2 – Pediatric Cohort



Abbreviations: NRS-11: Numeric Rating Scale-11.

Source: ADQS, ADTR

Figure 15: Spearman Rank Correlation Plot of Change from Baseline in NRS-11 Score with Percentage Change of Tumor Volume by Cycle in Participants with a Baseline NRS-11 Score ≥ 2 – Adult Cohort



Abbreviations: NRS-11: Numeric Rating Scale-11.

Source: ADQS, ADTR

In addition, the P-OMAQ was a clinical outcome assessment conducted as a self-report by pediatric participants (P-OMAQ-P), with an associated adult caregiver observer report (P-OMAQ-C) assessing the acceptability of the tablet dosage formulation.

The P-OMAQ-P was completed by 13 pediatric participants aged ≥ 8 years who received the tablet formulation of mirdametinib. The median (min, max) P-OMAQ-P (pediatric) overall score was 4.7 (3, 5), indicating very good acceptability. A median of 5 (highest score) was achieved for most categories, including number of medicines per day, size/amount of medication, smell of medication, acceptability, and taste.

The P-OMAQ-C was completed by 17 adult caregivers of participants aged 6 months to 17 years who received the tablet formulation of mirdametinib. The median (min, max) P-OMAQ-C

(caregiver) overall score was 4.8 (3.1, 5), indicating very good acceptability. A median of 5 (highest score) was achieved for all categories, including number of medicines per day, size/amount of medication, smell of medication, acceptability, and taste.

The Applicant's Position:

Statistically significant and clinically meaningful improvements were observed in PRO measures at the pre-specified timepoint of Cycle 13.

Pediatric Participants:

- For the parent-proxy PedsQL PRO assessment, the LS mean change from baseline in total score at Cycle 13 indicated improved quality of life.
- For the NRS-11 PRO assessment, the LS mean change from baseline at Cycle 13 indicated decreased pain severity.
- For the PII PRO assessment, the LS mean change from baseline at Cycle 13 indicated decreased pain interference.
- The tablet formulation was acceptable as indicated by the P-OMAQ-P (pediatric) overall score of 4.7 (3, 5) and P-OMAQ-C (caregiver) overall score of 4.8 (3.1, 5).

Adult participants:

- For the PedsQL PRO assessment, the LS mean change from baseline in total score at Cycle 13 indicated improved quality of life.
- For the NRS-11 PRO assessment, the LS mean change from baseline at Cycle 13 indicated decreased pain severity.

For the PII PRO assessment, the LS mean change from baseline at Cycle 13 indicated decreased pain interference.

The FDA's Assessment:

FDA does not use inferential testing procedures to assess single arm trial results, including for PRO-based endpoints. There was no control for multiplicity in any of the hypothesis tests included in this report, therefore, claims of statistical significance reported by the Applicant should be interpreted with caution.

FDA notes some observed improvements in functioning relative to baseline in patients treated with mirdametinib, however notes the following limitations in the PRO data:

- The PRO data from a single arm trial with a small, heterogenous (age, location of PN targets) population may be difficult to accurately interpret.
- Compliance at Cycle 13 for all PROs except the PedsQL was below 70%. In the pediatric population, compliance with the NRS-11 was 41% at cycle 13 and for pain interference it was 57%. Compliance rate for the PedsQL was high at cycle 13 for all patients (>90%).

- Patients in the adult cohort were administered the PedsQL, which is not designed for patients age greater than 18 however the PedsQL scoring manual does include instructions on scoring for adult patients.
- The magnitude of change from baseline for adult patients was greater than observed for pediatric patients, but as noted above, there was more missing data in the pediatric cohort.
- P-OMAQ was included in protocol amendment #4 and the sample size of patients is too small to draw any conclusions.

Overall, these exploratory results generally support the primary clinical findings however have some substantial limitations that should be considered when interpreting these results.

Additional Analyses Conducted on the Individual Trial

Data:

Analysis of exploratory endpoints showed the following for the pediatric cohort:

- The overall median (min, max) change from baseline at Cycle 13 for the PROMIS mobility scale score was 7.0 (3, 11) by self-report and 3.0 (-3, 11) by parent proxy.
- The median (min, max) change from baseline at Cycle 13 for the PROMIS upper extremity scale score was 11.5 (9, 14) by self-report and 9.5 (7, 12) by parent proxy.
- The median (min, max) change from baseline at Cycle 13 was 4.7 (1, 95) lbs in strength assessment using MicroFET2 dynamometer. The median (min, max) change from baseline at Cycle 13 in strength assessment using MRC grading was 0.1 (0, 1); given the median score at baseline was 4.4 out of 5, there was not much room for improvement in this assessment.
- The median (min, max) change from baseline at Cycle 13 in range of motion was 15.0 (-189, 70) degrees.
- The median (min, max) change from baseline at Cycle 13 in the 6-minute walk test distance was 15.0 (-99, 55) meters.
- The median TTP was not reached for all participants or for participants with a progressive tumor at baseline due to few events of disease progression.
 - External Control Data: Cohort 1
 - There were substantially more events in Study 01-C-0222 and the median was reached; the medians of TTP (95% CI) in months were 13.40 (8.50, 18.80) before matching, 12.80 (8.50, 18.80) after propensity score matching, and 13.40 (8.50, 18.80) after IPTW.
 - The HR for TTP comparing participants from Study MEK-NF-201 to those in Study 01-C-0222 showed statistically significant

improvements in disease progression favoring Study MEK-NF-201 (p-value <0.0001). The HR (95% CI) was 0.13 (0.052, 0.338) before matching, 0.14 (0.049, 0.392) after propensity score matching, and 0.12 (0.062, 0.250) after IPTW.

- External Control Data: Cohort 2
 - There were substantially more events in participants from Study 08-C-0079 and the median was reached; the medians TTP (95% CI) in months were 19.71 (16.13, 24.15) before matching, 21.75 (16.36, 32.30) after propensity score matching, and 20.63 (16.36, 30.62) after IPTW.
 - The HR for TTP comparing participants from Study MEK-NF-201 to from Study 08-C-0079 showed statistically significant (p-value <0.001) improvements in disease progression favoring Study MEK-NF-201. The HR (95% CI) was 0.22 (0.107, 0.456) before matching, 0.24 (0.110, 0.507) after propensity score matching, and 0.26 (0.161, 0.416) after IPTW.
- The median PFS was not reached for all participants or for participants with a progressive tumor at baseline in Study MEK-NF-201 or in Study 01-C-0222.
 - External Control Data: Cohort 2
 - In contrast, there were substantially more events in the historical control and the median was reached; the median PFS (95% CI) in months were 19.71 (16.13, 24.15) before matching, 21.75 (16.36, 32.30) after propensity score matching, and 20.63 (16.36, 30.62) after IPTW.
 - The average assessment intervals in Study 08-C-0079 were much longer compared to Study MEK-NF-201, which could be a bias in favor of the historical control. However, there was still a statistically significant reduction in the risk of disease progression or death for participants from Study MEK-NF-201 compared to participants from Study 08-C-0079. The HR (95% CI) was 0.22 (0.106, 0.455) before matching, 0.24 (0.110, 0.508) after propensity score matching, and 0.26 (0.160, 0.415) after IPTW.
- The DCR was 91% (95% CI: 80.4, 97.0). Results were similar by reader.
- The tablet formulation was acceptable as indicated by the P-OMAQ-P (pediatric) overall score of 4.7 (3, 5) and P-OMAQ-C (caregiver) overall score of 4.8 (3.1, 5).

Analysis of exploratory endpoints showed the following for the adult cohort:

- The overall median (min, max) change from baseline at Cycle 13 for the PROMIS physical function scale score was 1.00 (-10.9, 20.6).
- The median (min, max) change from baseline at Cycle 13 was 14.5 (-31, 468) lbs in strength assessment using MicroFET2 dynamometer. The median (min, max) change from baseline at Cycle 13 in strength assessment using MRC grading was 0 (0, 1); given the median score at baseline was 4.5 out of 5, there was not much room for improvement in this assessment.
- The median (min, max) change from baseline at Cycle 13 in range of motion was 9.5 (-49, 102) degrees.
- The median (min, max) change from baseline at Cycle 13 in the 6-minute walk test distance was 5.5 (-161, 79) meters.
- The median TTP was not reached for all participants or for participants with a progressive tumor at baseline.
 - External Control Data: Cohort 3

One-to-one propensity score also yielded a substantially reduced sample size. Only 19 adult participants from Study MEK-NF-201 (38%) were matched with adults from Study 08-C-0079. The remaining participants were not matched due to differences in their propensity score after adjusting for age, MEK inhibitor treatment, and lesion type. The reduced sample size and the small number of events make interpretation of the TTP difficult, and the results of this analysis in Cohort 3 are thus inconclusive.
- The median PFS was not reached for all participants or for participants with a progressive tumor at baseline.
 - External Control Data: Cohort 3
 - One-to-one propensity score also yielded a substantially reduced sample size. Only 19 adult participants from Study MEK-NF-201 (38%) were matched with adults from Study 08-C-0079. The remaining participants were not matched due to differences in their propensity score after adjusting for age, MEK inhibitor treatment, and lesion type. The reduced sample size and the small number of events make interpretation of the PFS difficult, and the results of this analysis in Cohort 3 are thus inconclusive.
- The DCR was 86.2% (95% CI: 74.6, 93.9).

The Applicant's Position:

The exploratory PRO endpoints demonstrated improvements in mobility, upper extremity function, strength, range of motion, and 6-minute walk test within the pediatric cohort. Median TTP and PFS were both not reached. Additionally, the tablet formulation achieved high scores on the P-OMAQ-P and P-OMAQ-C, indicating high acceptability among the pediatric cohort.

Exploratory efficacy endpoints also supported clinical benefit of mirdametinib in the adult cohort. The exploratory PRO endpoints demonstrated improvements in mobility, upper extremity scores, strength, range of motion, and 6-minute walk test. Median TTP and PFS were both not reached.

The FDA's Assessment:

FDA did not independently verify results for some exploratory endpoints including DCR, time to progression or progression-free survival.

As described above, there were observed general improvements in clinical outcome assessments however the same limitations apply: these results should be interpreted with caution given the small sample size, single arm design of the study, heterogenous population in terms of age and tumor location, and compliance rate at cycle 13. Because of these limitations and to better assess the clinical meaningfulness of tumor shrinkage, FDA also reviewed individual patient narratives submitted by the Applicant for all responders, given the heterogeneity in target PN location and associated morbidities. On review of the individual narratives, the majority of responders had improvement in at least one symptom or clinical outcome measure. Key information from the responder narratives for patients in the pediatric and adult cohorts, including evidence of clinical benefit for each patient, in ReNeu is summarized in Table 43 and Table 44, respectively.

Table 44 Summary of Responder Narratives for ReNeu Pediatric Cohort (Source: CSR)

Patient ID	Sex	Age	Progressive (Y/N)	Target PN Location	Morbidity	Best Response, Timepoint	DOR at DCO (20 Sep 2023)	Reviewer Notes
(b) (6)	F	15	N	Head and neck	Disfigurement/Major Deformity	-48.9%, C5D15	7.3 months	Discontinued after 11.7 months due to participant decision. Improvement in PedsQL pediatric self-report total score beginning C3D15 and maintained through C13D15.
	M	2	Y	Head and neck	Optic disfigurement, vision decline, disfigurement/major deformity	-35.11%, C17D15	13.2 months	Completed treatment phase and did not enroll in LTFU. Initial improvement in PedsQL parent proxy total score beginning C3D15 with fluctuations observed throughout the study. No improvement in optic disfigurement or vision decline.

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Patient ID	Sex	Age	Progressive (Y/N)	Target PN Location	Morbidity	Best Response, Timepoint	DOR at DCO (20 Sep 2023)	Reviewer Notes
(b) (6)	M	8	N	Head and neck	Disfigurement/major deformity	-82.34%, C24D21	17.8 months	Patient reported “moderately better” or “a little better” at all PGIC assessments on study. Discontinued due to participant decision after 21.8 months.
	F	4	Y	Upper limb	Motor dysfunction or weakness in the upper extremity, pain, disfigurement/major deformity	-91.01%, C36D15	28.4 months	Patient remains on treatment in LTFU. Demonstrated increased ROM throughout study.
	F	12	Y	Mesentery and pelvis	Motor dysfunction, weakness in lower extremity, pain	-62.58%, C21D15	21.2 months	Patient remains on treatment in LTFU. Initial improvement in PedsQL pediatric self-report total score observed at C3D15, further improvements through C28D15. Improvement in PGIS from “moderate” at baseline to “mild” at C21. Gabapentin 300 mg QD PO at baseline, discontinued on study day 330.
	M	10	Y	Head and neck	Pain, disfigurement/major deformity	-45.25%, C24D21	20.8 months	Patient remains on treatment in LTFU. Improvement from baseline in NRS-11.
	F	10	N	Head and neck	Pain, motor dysfunction, weakness in upper extremity, disfigurement or major deformity, airway dysfunction	-67.66%, C28D15	16.8 months	Patient remains on treatment in LTFU. Improvements in PROMIS Pediatric and Parent Proxy Short Form v2.0 – Upper extremity 8a initially observed at C5D15, further improvements observed through C24D21
	M	9	Y	Paraspinal	Pain, disfigurement or major deformity	-40.86%, C9D15	14.6 months	Patient remains on treatment in the Treatment Phase. PGIC score of “moderately better” starting at C5D15 and “very much better” starting at C7D15.
	M	10	Y	Mesentery and pelvis	Pain	-46.55%, C28D15	24.4 months	Patient remains on treatment in LTFU. No clear improvement in COA.
	M	7	N	Abdominal wall	Pain	-49.26%, C28D15	32.8 months	Patient remains on treatment in LTFU. Improvement in PGIC, “very much better” at C24.
	M	6	Y	R peritoneum and R flank	Pain	-66.70%, C17D15	21.2 months	Patient remains on treatment in LTFU. PGIC “very much better” starting at C3 and continuing for all subsequent visits.
	M	15	Y	Head and neck	Airway dysfunction	-71.42%, C17D15	14.1 months	Patient discontinued treatment on Study Day 701 due to participant decision. Improvement in 6-minute walk test at C5D15 that was

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Patient ID	Sex	Age	Progressive (Y/N)	Target PN Location	Morbidity	Best Response, Timepoint	DOR at DCO (20 Sep 2023)	Reviewer Notes
								maintained throughout the study.
(b) (6)	F	9	Y	Head and neck	Pain, ongoing hearing loss in L ear, airway dysfunction	-75.55%, C24D21	17.7 months	Completed treatment phase, did not enroll in LTFU and discontinued due to participant decision. Improvement in 6-minute walk test at C5D15 maintained throughout study. PGIC "very much better".
	F	16	N	Head and neck	Pain	-63.06%, C24D21	20.2 months	Patient remains on treatment in LTFU. Improvement in NRS-11 starting at C3D15, further improvements through C24D21.
	M	17	Y	Head and neck	Disfigurement or major deformity	-55.63%, C32D15	21.4 months	Patient remains on treatment in LTFU. Improvement in PedsQL pediatric self-report and parent proxy total scores starting at C3D15, further improvements observed throughout study.
	F	15	Y	Mesentery and pelvis	Constipation, pain	-55.10%, C17D15	14.2 months	Patient remains on treatment in LTFU. PGIC "a little better" C7D15, "very much better" starting C9D15. Improvement in constipation starting C7D15.
	F	17	N	Upper limb	Disfigurement or major deformity	-28.56%, C13D15	10.3 months	Patient remains on treatment in LTFU. No improvements in COA.
	M	10	Y	Head and neck	Pain, disfigurement or major deformity	-33.72%, C9D15	10.2 months	Discontinued in LTFU due to concomitant procedure that resected some of the target PN. Improvement in NRS-11 starting C3D15, further improvements through C21D15.
	F	6	Y	Walls of bladder, vagina, uterus and colon	PN encompassing large portion of patient's lower abdomen causing displacement of bladder	-56.87%, C13D15	17.7 months	Patient completed treatment phase and did not enroll in LTFU due to physician's decision. Patient had prior treatment with selumetinib and progressed. PGIC "very much better" starting C21D15. At C4D15 it was noted that lesion was no longer palpable. Patient had a decrease in hematuria during treatment.
	F	13	Y	Head and neck	Airway dysfunction, disfigurement or major deformity	-43.40%, C32D15	17.7 months	Patient remains on treatment in LTFU. Variable improvement in 6-minute walk test.
	F	14	Y	Head and neck	Pain	-61.5%, C36D15	Not provided, initial response	Patient remains on treatment in LTFU. No clear improvement with COA data with many missing assessments. Patient

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Patient ID	Sex	Age	Progressive (Y/N)	Target PN Location	Morbidity	Best Response, Timepoint	DOR at DCO (20 Sep 2023)	Reviewer Notes
							observed at C32D15.	discontinued amitriptyline for PN pain on study day 449.
(b) (6)	F	6	Y	Chest wall	Pain	-40.15%, C13D15	21.3 months	Patient remains on treatment in LTFU. Minimal improvements in PII by self-report and parent proxy. PGIC of "very much better" starting at C7D15.
	F	14	Y	Hip/sacrum	Motor dysfunction or weakness in lower extremity, pain, disfigurement or major deformity	-44.87%, C21D15	7.7 months	Patient receiving treatment in treatment phase. Improvements in PedsQL self-report and parent proxy total scores starting at C3D15 and continuing through C21D15. Improvement in NRS-11 starting at C3D15 and continuing through C24D21. Improvement in PII parent proxy starting C5D15 and continuing through C17D15. Improvement in strength and 6-minute walk throughout study. Slight increase in ROM. PGIC "very much better" starting at C5D15 and continuing through DCO.
	F	5	N	Mediastinum, with intrathoracic involvement to right upper extremity and cervical spine	Risk of spinal cord compression, motor dysfunction or weakness in upper extremity, disfigurement or major deformity	-61.25%, C32D15	24.9 months	Patient remains on treatment in LTFU. Increase in range of motion and strength starting C5D15 and continuing throughout study.
	F	4	Y	Head and neck	Pain, disfigurement or major deformity	-81.50%, C25D21	17.7 months	Patient remains on treatment in LTFU. Improvement in PedsQL parent proxy total score.
	M	2	Y	Head and neck	Pain, disfigurement or major deformity	-90.56%, C28D15		Patient remains on treatment in LTFU. Slight improvement in PedsQL parent proxy total score.
	F	17	N	Lower limb	Pain	-58.14%, C21D15	11.1 months	Patient remains on treatment in LTFU. Improvement in NRS-11 starting at C3D15 and continuing through C13D15 (no scores available after this). PGIC of "very much better" from C13D15 through DCO.
	M	6	Y	Head and neck	Airway dysfunction, disfigurement or major deformity	-46.98%, C24D21	17.8 months	Patient remains on treatment in LTFU. Improvements in PedsQL self-report and parent proxy starting at C3D15 and C7D15, respectively. Improvement in 6-minute walk starting C5D15. PGIC score "very much better" starting C3D15 and continuing through C24.

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Patient ID	Sex	Age	Progressive (Y/N)	Target PN Location	Morbidity	Best Response, Timepoint	DOR at DCO (20 Sep 2023)	Reviewer Notes
(b) (6)	F	6	Y	Upper limb	Pain	-31.54%, C13D15	3.3 months	Patient remains on treatment in LTFU. Slight improvement in PII by self-report and parent proxy. PGIC "very much better" or "moderately better" at all assessments.
	F	6	Y	Head and neck	Pain, disfigurement or major deformity	-48.92%, C21D15	7.4 months	Patient in treatment phase. No improvement in PII. PGIC "moderately better" starting at C13D15 through DCO.

Table 45 Summary of Responder Narratives for ReNeu Adult Cohort (Source: CSR)

Patient ID	Sex	Age	Progressive (Y/N)	Target PN Location	Morbidity	Best Response, Timepoint	DOR at DCO (20 Sep 2023)	Reviewer Notes
(b) (6)	M	48	N	Lower limb	Pain, motor dysfunction or weakness in lower extremity	-59.18%, C24D21	25.5 months	Patient remains on treatment in LTFU. Improvement in NRS-11 and PII scores starting C3D15 and continuing through C21D15. Improvement in PROMIS Short Form v2.0 Physical Function 8b starting C3D15, further improvements through C24D21.
	F	22	N	Lower limb	Motor dysfunction, weakness in lower extremity, pain	-89.74%, C21D15	15.6 months	Patient did not complete the treatment phase due to participant decision. Total treatment duration 19.7 months. Improvement in PedsQL total score starting C3D15, further improvements observed though C21D15. Increased ROM starting at C5.
	M	35	Y	Lower limb	Motor dysfunction, weakness in lower extremity, pain	-60.82, C17D15	34.0 months	Patient remains on treatment in LTFU. Improvement in NRS-11 starting C3D15 through C17D15. PGIC "very much better" at C24.
	F	64	N	Paraspinal	Pain	-79.19, C36D15	26.2 months	Entered LTFU but discontinued due to noncompliance. Improvements in NRS-11 and PII starting at C3D15, further improvements though C21D15.
	F	47	N	Head and neck	Pain and disfigurement or major deformity	-85.74%, C32D15	6.1 months	Patient remains on treatment in LTFU. PGIS "severe" at baseline to "moderate" starting at C3D15.
	M	24	N	Left flank	Pain	-57.50%, C40D15	Not provided, PR onset	Patient remains on treatment in LTFU. Improvement in PII noted at C3D15, continued through C13S15.

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Patient ID	Sex	Age	Progressive (Y/N)	Target PN Location	Morbidity	Best Response, Timepoint	DOR at DCO (20 Sep 2023)	Reviewer Notes
							C32D15 during LTFU	PGIS "moderate" at baseline to "mild" at C24; PGIC "a little better" at C3, "moderately better" at C9, "very much better" at C17.
(b) (6)	M	39	N	Head and neck	Pain, disfigurement or major deformity	-44.19%, C9D15	3.7 months	Patient did not complete study treatment due to AEs of nausea and diarrhea. Treatment duration 6.7 months.
	F	22	N	Paraspinal	Pain	-73.30%, C9D15	19.4 months	Patient discontinued after 21.9 months due to physician decision. No clear indication of clinical benefit on COA.
	F	36	N	Lower limb	Motor dysfunction or weakness in lower extremity, pain	-56.30%, C44D15	34.9 months	Patient remains on treatment in LTFU. Improvements in NRS-11 and PII scores starting C3D15 and continuing through C24D21. Increase in ROM and improvement in 6-minute walk starting C5D15.
	M	39	N	Head and neck	Pain, motor dysfunction or weakness in upper extremity, disfigurement or major deformity	-78.77%, C36D15	35.8 months	Patient remains on treatment in LTFU. Improvement in strength throughout study.
	F	38	Y	Head and neck	Pain, disfigurement or major deformity	-58.06%, C32D15	24.6 months	Patient remains on treatment in LTFU. PGIS from "mild" at baseline to "none" at C24. PGIC "a little better" at all non-missing assessments.
	F	27	N	Head and neck	Pain, disfigurement or major deformity	-65.49%, C28D15	32.1 months	Patient remains on treatment in LTFU. Improvement in PedsQL total score, starting at C3D15, further improvements through C40D15.
	M	69	Y	Head and neck	Stable hearing loss, pain	-73.42%, C40D15	24.9 months	Patient remains on treatment in LTFU. NRS-11 and PII scores 0 at baseline. Improvement in PedsQL total score starting C3D15, further improvements through C44D15.
	M	36	N	Head and neck	Airway dysfunction	-32.15%, C13D15	15.1 months	Patient remains on treatment in LTFU. Improvements in PedsQL total score and NRS-11 starting C3D15. Improvement in PII starting at C5D15. PGIS "moderate" at baseline to "mild" starting C13. PGIC "moderately better" or "a little better" at all non-missing assessments. No improvement in 6-minute walk.

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Patient ID	Sex	Age	Progressive (Y/N)	Target PN Location	Morbidity	Best Response, Timepoint	DOR at DCO (20 Sep 2023)	Reviewer Notes
(b) (6)	F	18	Y	Chest wall	Pain, disfigurement or major deformity	-81.83%, C32D15	28.5 months	Patient remains on treatment in LTFU. Improvement in NRS-11 starting C3D15. PGIS "moderate" at baseline to "mild" on treatment. PGIC of at least "a little better" at all assessments, "very much better" at last assessment, C24.
	M	40	N	Head and neck	Pain, motor dysfunction or weakness in upper extremity, disfigurement or major deformity	-44.58%, C17D15	21.2 months	Patient remains on treatment in LTFU. Improvement in PedsQL total score starting C3D15. Improvement in NRS-11 and PII scores starting C3D15. Improvement in ROM. Improvement in PROMIS Short Form v2.0 Physical Function 8b score starting C5D15. Improvement in PGIS from "moderate" at baseline to "mild" on treatment. PGIC at least "moderately better" on all non-missing assessments.
	M	38	Y	Head and neck	Disfigurement or major deformity	-48.16%, C36D15	Not provided. PR onset C28D15.	Patient remains on treatment in LTFU. PGIS "mild" at baseline to "none" at all on-treatment assessments. PGIC "a little better" at C3D15 to "very much better" at C24D21.
	F	41	Y	Head and neck	Pain, disfigurement or major deformity	-38.95%, C32D15	13.9 months	Patient remains on treatment in LTFU. Improvements in NRS-11 and PII starting C3D15.
	M	50	Y	Upper limb	Motor dysfunction or weakness in upper extremity, disfigurement or major deformity	-41.13%, C24D21	17.7 months	Patient remains on treatment in LTFU. Improvement in NRS-11 starting C3D15. Improvement in strength and ROM. PGIS "mild" at baseline to "none" starting at C13. Improvement in PGIC starting at C7, "very much better" at C24.
	F	36	Y	Lower limb	Motor dysfunction or weakness in the lower extremity, pain, disfigurement or major deformity	-40.28%, C17D15	6.6 months	Discontinued treatment in LTFU due to withdrawal of consent. Improvement in PedsQL total score starting C3D15. Improvement in PROMIS Short Form v2.0 Physical Function 8b starting C5D15. PGIS "mild" at baseline to "none" on study. PGIC of "moderately better" starting C5 and "very much better" starting C9. Reduction in pain medication on study.
	M	29	N	Mesentery and pelvis	Stable neuropathic pain, bowel	-50.16%, C24D21	14.1 months	Patient remains on treatment in LTFU. Leg pain resolved and bowel dysfunction improved from baseline.

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Patient ID	Sex	Age	Progressive (Y/N)	Target PN Location	Morbidity	Best Response, Timepoint	DOR at DCO (20 Sep 2023)	Reviewer Notes
(b) (6)					dysfunction, pain			PGIC "very much better" from C13 through last assessment at C24. Discontinued gabapentin for tumor pain.
	F	24	Y	Head and neck	Pain	-44.06%, C24D21	6.5 months	Patient remains on treatment in LTFU. Improvement in NRS-11 starting C7D15. Improvement in PII score starting C3D15.
	F	31	N	Head and neck	Pain	-32.58%, C21D15	5.2 months	Patient remains on treatment in LTFU. Improvement in NRS-11 starting C5D15. PGIS "moderate" at baseline to "mild" starting C5. PGIC of "a little better" or "moderately better" at all non-missing PGIC assessments from C5 to last assessment.
	M	38	Y	Paraspinal	Pain, motor dysfunction or weakness in the lower extremity, disfigurement or major deformity	-71.33%, C24D21	21.2 months	Discontinued treatment in LTFU due to withdrawal of consent. Improvement in strength throughout study.
	F	51	Y	Head and neck	Pain, disfigurement or major deformity	-44.89%, C24D21	3.0 months	Patient remains on treatment in LTFU. Improvement in PedsQL total score starting C3D15. Improvement in NRS-11 and PII starting C3D15.
	F	56	Y	Lower limb	Motor dysfunction or weakness in lower extremity, pain, disfigurement or major deformity	-71.59%, C24D21	13.6 months	Patient remains on treatment in LTFU. Improvement in PedsQL total score starting C3D15. Improvement in strength. Improvement in PROMIS Short Form v2.0 Physical Function 8b Score starting C3D15. PGIS "moderate" at baseline to "mild" from C13 to last assessment. PGIC "moderately better" or "very much better" at all non-missing PGIC assessments.

8.1.2. Study NF-106

Study Design

The Applicant's Description:

Study NF-106 was an investigator-initiated, open-label, multi-center, Phase 2 study to evaluate safety and efficacy of mirdametinib in participants ≥ 16 years old with NF1 and symptomatic or progressing PN. This study has been completed. The primary endpoint was confirmed ORR based on volumetric MRI analysis. Key secondary objectives included evaluation of QoL and pain, characterization of the single dose PK profile of mirdametinib in the NF1 population, and the evaluation of safety and tolerability of chronic mirdametinib administration. Mirdametinib was orally administered at a dose of 2 mg/m² BID (maximum 4 mg BID) in 4-week cycles on an intermittent (3 weeks on/1 week off) schedule, for up to 24 cycles. Participants were required to have $\geq 15\%$ reduction in target tumor volume at the end of Cycle 8 of therapy to continue to receive treatment up to Cycle 12. If a participant had $\geq 20\%$ reduction in target tumor volume at the end of Cycle 12 of therapy, they could continue on study up to Cycle 24. Evaluations were performed every 4 cycles of treatment for the first year, followed by every 6 cycles thereafter.

The FDA's Assessment:

The NF-106 study is a supportive study, and the efficacy results were not verified by FDA. The efficacy portion of the label for marketing application is solely based on the MEK-NF-201 study results.

Eligibility Criteria

The Applicant's Description:

Key inclusion criteria included:

- Participants must be ≥ 16 years of age at the time of study entry.
- Participants must have EITHER the clinical diagnosis of NF1 using the NIH Consensus Conference criteria OR have a constitutional NF1 mutation documented in a CLIA/CAP certified lab.
- Participants must have a target PN that is progressive OR causing significant morbidity, such as (but not limited to) head and neck lesions that are compromising the airway or great vessels, brachial or lumbar plexus lesions that are causing nerve compression and loss of function, lesions causing major deformity or are significantly disfiguring, lesions of the extremity that cause limb hypertrophy or loss of function, and painful lesions.
 - For subjects enrolled for tumor progression, progression is defined as presence of new plexiform neurofibroma on MRI or CT OR a measurable increase in plexiform neurofibroma size ($\geq 20\%$ increase in the volume, or a $\geq 13\%$ increase in the product of the two longest perpendicular diameters, or a $\geq 6\%$ increase in the longest diameter) documented by comparison of two

scans (MRI or CT) in the time period of approximately one year or less prior to evaluation for this study.

- Participants must have a target PN this is deemed inoperable, defined as a PN that cannot be completely surgically removed without risk of substantial morbidity, or if the participant with surgical option refuses surgery.
- Participants must have measurable PN amenable to volumetric MRI analysis. For the purpose of this study, the target lesion must be seen on at least 3 consecutive MRI slices and the field of view must contain the entire tumor of interest.
- Participants must have had a Karnofsky performance level of $\geq 50\%$

Key exclusion criteria included:

- Active optic glioma or low-grade glioma requiring treatment.
- Subjects with glaucoma, intraocular pressure >21 mmHg, or any other significant abnormality on ophthalmic examination (performed by an ophthalmologist).
- Chronic treatment with systemic steroids or another immunosuppressive agency.
- Prior treatment with a MEK inhibitor of any kind.

The FDA's Assessment:

FDA agrees with the description of the inclusion and exclusion criteria for the NF-106 study.

Study Endpoints

The Applicant's Description:

Primary Endpoint:

- The primary efficacy endpoint was confirmed ORR defined as the proportion of participants who have a BOR of PR or CR by the end of treatment with ≥ 4 weeks duration.

Secondary Endpoints:

- Safety endpoints included TEAEs, serious adverse events (SAEs), adverse event of special interest (AESIs), changes from baseline in laboratory parameters, vital signs and retinal exam abnormalities
- Duration of response for participants whose best response was CR or PR
- Change in pain and quality of life scores from baseline as measured by NRS-11, BPI, and PedsQL NF1 module.

The FDA's Assessment:

FDA acknowledges the Applicants description of study endpoints and notes that the primary endpoint of ORR differs from that of MEK-NF-201 in that patients were discontinued from treatment if they did not achieve at least a 15% or 20% reduction in target tumor volume at Cycle 8 and 12, respectively, precluding a full evaluation of ORR and DOR.

Statistical Analysis Plan and Amendments

The Applicant's Description:

There were 2 versions of the SAP that were submitted to the FDA. The initial SAP (v1.0) was approved on 18 May 2023. The final SAP (v2.0) was approved 03 December 2023.

The results of this study are presented overall and by pediatric and adult cohorts.

Primary Efficacy Endpoint

The primary efficacy endpoint was confirmed ORR defined as the proportion of participants who had a BOR of CR or PR by the end of Cycle 24 with ≥ 4 weeks duration.

The target PNs were centrally evaluated by MRI by a single reader at the [REDACTED]

(b) (4)

Level of target PN response was defined as follows:

- CR: A complete resolution of the target PN for ≥ 4 weeks
- PR: A $\geq 20\%$ reduction in the volume of the target PN lesion compared to the pretreatment volume for ≥ 4 weeks
- Stable Disease (SD): Between a $<20\%$ increase, and $<20\%$ decrease in the volume of the target PN lesion compared to the pretreatment volume for ≥ 4 weeks
- PD: A $\geq 20\%$ increase in the volume of the target PN compared to the pretreatment volume

To assess the primary efficacy endpoint, the confirmed ORR was presented alongside the corresponding 2-sided 95% Clopper-Pearson CIs and the p-values from a one-sample two-sided binomial test evaluating the null hypothesis that the ORR = 5%. Best overall confirmed response was summarized according to the categories presented above. Tumor volume (mL), change from baseline in tumor volume, and percentage change from baseline in tumor volume were summarized. Additionally, the best observed percentage volumetric change from baseline was also summarized.

For calculation of the ORR, all participants with missing data who were not previously presented as confirmed PR or CR were imputed as non-responders for the primary endpoint

analysis. Any participants who terminated study treatment early without a confirmed PR or CR were also imputed as non-responders.

Secondary Efficacy Endpoints

Duration of Response

A secondary efficacy objective was to determine the DoR for participants who attained a best overall confirmed response of CR or PR using MRI volumetric analysis. The DoR was defined as the time (in months) between the first instance of response that was subsequently confirmed, until the date of radiographic disease progression or death, whichever occurred first.

In the absence of radiographic progression or death, participants had their results censored to the date of their most adequate tumor assessment date prior to the start of any surgery to the target PN or the start of any anti-cancer/PN medication (e.g., chemotherapy, immunology, biologic therapy, or radiation therapy).

DoR was analyzed using the Kaplan-Meier method based on participants with a confirmed CR or PR. Additionally, the KM estimates with corresponding 95% CIs (using the log-log transformation) and number of participants at risk will be estimated at the following time points: 2, 4, 8, 12, 18, and 24 months.

Time to response was summarized descriptively for confirmed responders and focused on the evaluation of outcomes within each treatment arm.

Patient Reported Outcomes

Absolute values and changes from baseline in NRS-11 scores were summarized. Summaries by ORR status (i.e., participants with confirmed objective response herein denoted as ‘responders’ versus participants who did not achieve confirmed objective response or ‘non-responders’) were provided.

Additionally, a MMRM was fit for overall and adult participants only with change from baseline in NRS-11 score as the dependent variable, visit as a fixed effect and baseline NRS-11 score as a covariate. Covariance structures were trialed in the order of decreasing complexity, with the first structure which converges without error used. The structures tested were as follows: Unstructured, Heterogenous Toeplitz, Heterogenous Autoregressive, Autoregressive, Heterogenous Compound Symmetry, Compound Symmetry, Variance Components.

Absolute values and changes from baseline in BPI-Pain Interference Subscale scores were summarized descriptively by visit for the corresponding domains and total scores. Summaries by ORR status (responder versus non-responder) were also presented.

Absolute values and changes from baseline in PedsQL NF1 Total Scale scores were summarized descriptively by visit for the corresponding domains and total scores. Summaries by ORR status (responder versus non-responder) were also presented.

The FDA's Assessment:

FDA acknowledges the Applicant's description of the statistical analysis plan.

Protocol Amendments

The Applicant's Description:

The original study protocol was finalized on 13Jan2014 and amended twice; the final protocol (Protocol Amendment 2) was dated 20Jul2018. [Table 45](#) provides a summary of each amendment.

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Table 46: NF-106 Protocol Amendments Summary

Number (Date of approval)	Key changes
Amendment 1 (03Dec2014)	• Use of nasogastric tube was removed and participants were required to swallow the capsules whole • Mirdametinib handling instructions were added with noted caution for any forms of contact exposure, and it was reinforced that capsules should not be crushed or chewed • Windowing was added for the retinal examination • Windowing of PRO assessments after Cycle 4 were changed from +1 to +2 weeks • The total research samples in Cycle 1 were updated to include 1 additional 10mL blood sample • Clarification was added to describe that all PROs will be reviewed centrally at NCI in a real time manner to monitor for serious emotional distress • Additional MRI collection details were added based on PN size/location • Language was added to require MRI review during screening to confirm the lesion is measurable and amenable to volumetric analysis • Text was added to summarize/clarify biopsy collection procedure • Text was added to summarize blood processing for cytokine and growth factor analysis • Text was added as administrative changes to text in protocol deviations
Amendment 2 (20Jul2018)	• “To assess quality of life and pain in patients on PD-0325901” was changed from an Exploratory Objective to a Secondary Objective. Additional endpoints were recategorized from Secondary Objectives to Exploratory Objectives. Exclusion Criterion #11 was updated to limit assessment of echocardiogram history to the 3 years prior to enrollment.

The FDA's Assessment:

FDA acknowledges the Applicant's description of the protocol amendments noting that quality of life and pain objectives were changed from exploratory to secondary objectives with Amendment #2.

8.1.2.1. Study Results

Compliance with Good Clinical Practices

Data:

This study was designed and monitored in accordance with sponsor procedures, which comply with the ethical principles of GCP as required by the major regulatory authorities.

The Applicant's Position:

Study NF-106 is GCP compliant.

The FDA's Assessment:

FDA acknowledges the Applicant's statement of compliance with GCP requirements.

Data Quality and Integrity

Data:

The study investigator and clinical coordinator reviewed the study progress regularly. Participants entered on the study and AEs were reviewed to ensure that the study was conducted as outlined in the protocol. Monthly reports were generated by the NF Consortium to assess completeness of data. There were monthly phone conferences between the NF Consortium and the investigator to address quality assurance issues. A Data Safety Monitoring Board was established for the purpose of ensuring data compliance and regular monitoring of the study.

The Applicant's Position:

No issues were identified that could potentially impact data integrity, prevent an adequate assessment of the data, or change the conclusions drawn.

The FDA's Assessment:

FDA did not identify quality or integrity issues in the data. The data submitted were organized and adequate to perform a complete review of mirdametinib.

Financial Disclosure

The Applicant's Position:

The NF-106 study was sponsored by University of Alabama. Consistent with University of Alabama requirements, no investigators were identified as having financial interests/arrangements with the sponsor.

The FDA's Assessment:

In accordance with 21 CFR Part 54, the Applicant submitted Form FDA 3454 (Financial Interests and Arrangements of Clinical Investigators) certifying that as the sponsor of the submitted studies, they did not enter into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study. All investigators were assessed for equity interest, significant payments of other sorts, and other compensation by the sponsor or proprietary interest. The Applicant certified that none of the financial interests or arrangements described in 21 CFR Part 54 existed for any of the investigators who participated in Study NF-106. The Applicant provided a list of all investigators for Study NF-106 in Appendix 16.1.4 of the CSR.

FDA reviewed the financial disclosure information provided by the Applicant and agrees that the integrity of the study data was not affected by the financial interest of the investigators.

Patient Disposition

Data:

A summary of participant disposition is presented in [Table 46](#).

Table 47 Summary of Participant Disposition (Enrolled Set)

	Pediatric (N=2)	Adult (N=17)	Total (N=19)
Participants Who Received At Least One Dose of Study Treatment	2 (100%)	17 (100%)	19 (100%)
Participants Who Completed Treatment	1 (50.0%)	5 (29.4%)	6 (31.6%)
Participants Who Prematurely Discontinued Treatment	1 (50.0%)	12 (70.6%)	13 (68.4%)
Reason for Treatment Discontinuation			
Progressive Disease	0	1 (5.9%)	1 (5.3%)
<15% target tumor volume reduction after Cycle 8	0	5 (29.4%)	5 (26.3%)
<20% target tumor volume reduction after Cycle 12	0	1 (5.9%)	1 (5.3%)
Refusal of further protocol therapy	1 (50.0%)	3 (17.6%)	4 (21.1%)
Non-compliance	1 (50.0%)	1 (5.9%)	2 (10.5%)
Physician determines not in the subject's best interest	0	0	0

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	Pediatric (N=2)	Adult (N=17)	Total (N=19)
Participant becomes pregnant	0	0	0
Participant prescribed non-allowed concomitant medication	0	0	0
Withdrawal of protocol consent	0	1 (5.9%)	1 (5.3%)
Any surgical procedure on a target PN	0	0	0
Study treatment-related toxicity requiring removal	0	1 (5.9%)	1 (5.3%)
Participants Who Completed the Study	1 (50.0%)	11 (64.7%)	12 (63.2%)
Participants Who Prematurely Discontinued the Study	1 (50.0%)	6 (35.3%)	7 (36.8%)
Primary Reason for Study Discontinuation			
Death	0	0	0
Lost to follow-up	0	2 (11.8%)	2 (10.5%)
Withdrawal of consent for any further data submission	0	1 (5.9%)	1 (5.3%)
Other	1 (50.0%)	2 (11.8%)	3 (15.8%)
Missing	0	1 (5.9%)	1 (5.3%)
Participants Who Entered the Off Treatment Follow-Up Period	2 (100%)	15 (88.2%)	17 (89.5%)
Participants Who Completed the Study During Off Treatment Follow-Up	2 (100%)	8 (47.1%)	10 (52.6%)
Participants Who Discontinued the Study During Off Treatment Follow-Up	0	7 (41.2%)	7 (36.8%)
Reason for Study Discontinuation During Off Treatment Follow-up			
Initiation of other medical treatment towards PN	0	0	0
Initiation of medical treatment towards other NF1 tumor	0	0	0
Death	0	0	0
Lost to follow-up	0	2 (11.8%)	2 (10.5%)
Withdrawal of consent for any further data submission	0	1 (5.9%)	1 (5.3%)
Other	0	4 (23.5%)	4 (21.1%)

Abbreviations: NF1: Neurofibromatosis type 1; PN: Plexiform neurofibroma.

Percentages are calculated using the enrolled participants in the corresponding cohort as the denominator.

Multiple reasons could be selected for treatment discontinuation and study discontinuation during off treatment follow-up. A participant is considered to have completed the study if they have completed the Cycle 24 visit, entered the off-treatment follow-up period, or have not been recorded to have prematurely withdrawn from the study. A participant will be considered to have completed treatment if their case report form (CRF) entry for 'Reason for Treatment discontinuation' was 'Completion of Cycle 24 of the therapy'.

Source: ADSL

The Applicant's Position:

Most participants prematurely discontinued treatment: the most common reasons for treatment discontinuation were <15% target tumor volume reduction at the end of Cycle 8, refusal of further protocol therapy, and non-compliance.

The FDA's Assessment:

FDA acknowledges the Applicant's position noting that one third of patients discontinued treatment as a result of not meeting target tumor reduction thresholds by cycles 8 and 12. The results of this trial are considered supportive, but the efficacy review of mirdametinib did not rely on these results and they were not independently verified during the review of this application.

Protocol Violations/Deviations

Data:

A total of 17 (90%) participants had at least 1 protocol deviation, with the majority (79%) of deviations occurring in the protocol assessment/procedure category. One participant had a deviation that resulted in an AE or an AE and impacted participant safety, which was 'noncompliance with contraception, fathered a pregnancy'. The majority of recorded deviations describe missed doses within a given cycle, and sporadically missed vitals, cytokine blood draws, and PRO assessments. No deviations were determined to affect the scientific integrity of study.

The Applicant's Position:

The deviations were reviewed and GCP compliance was maintained. None of the observed protocol deviations impacted the primary objective of the study and did not affect the overall safety and efficacy outcomes of the study.

The FDA's Assessment:

FDA agrees with the description of one patient that resulted in protocol deviation with a partner pregnancy reported on Day 330 with a resolution of Day 606.

Table of Demographic Characteristics

Data:

The median (min, max) age at the time of consent was 24 (16, 39) years. Most participants were female (63%) and approximately half were White (42%). The most common target PN locations (>20%) were head and neck (5 participants [26%]) and mesentery and pelvis (4 participants [21%]).

The Applicant's Position:

Demographic characteristics were consistent with the general population with NF1 PN.

The FDA's Assessment:

FDA acknowledges the Applicant's description of demographic characteristics. Demographics for this population are characterized as part of the pooled safety population (see Section 8.2).

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

The most common target PN locations (>20%) were head and neck (5 participants [26%]) and mesentery and pelvis (4 participants [21%]).

The Applicant's Position:

Disease characteristics were consistent with the disease under study.

The FDA's Assessment:

FDA acknowledges the Applicant's description. Baseline characteristics for this population are captured as part of the pooled safety population (see Section 8.2).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment compliance was assessed by a participant diary. The diary was reviewed with the treating physician at the history/physical visit after completion of Cycles 1, 2, 3, 4, 8, 12, 18 and 24. Study treatment exposure is presented in [Table 47](#).

A total of 19 (100%) participants received at least 1 concomitant medication. The most common concomitant medications were doxycycline (9 [47%]) participants and clindamycin (8 [42%]) participants.

Table 48 Summary of Exposure to Study Treatment (Safety Analysis Set)

Parameter	Pediatric (N=2)	Adult (N=17)	Total (N=19)
Duration of Exposure (months)			
N	2	17	19
Mean (StD)	17.26 (6.528)	12.06 (7.469)	12.61 (7.392)
Median	17.26	7.69	7.82
Minimum, Maximum	12.6, 21.9	3.4, 22.8	3.4, 22.8
Actual Dose Intensity (mg/day)			
N	2	17	19
Mean (StD)	5.00 (1.410)	6.11 (1.029)	5.99(1.084)
Median	5.0	6.0	6.0
Minimum, Maximum	4.0, 6.0	4.1, 8.0	4.0, 8.0
Relative Dose Intensity (%)			
N	2	17	19
Mean (StD)	99.95 (0.070)	95.61 (11.302)	96.07 (10.743)
Median	99.95	97.62	97.88
Minimum, Maximum	99.9,100.0	58.6, 114.3	58.6, 114.3
Actual Dose Intensity – BSA Adjusted (mg/m ² /day)			
N	2	17	19
Mean (StD)	3.81 (0.312)	3.75 (0.534)	3.75 (0.510)
Median	3.81	3.70	3.70
Minimum, Maximum	3.6, 4.0	2.8, 4.7	2.8, 4.7

Parameter	Pediatric (N=2)	Adult (N=17)	Total (N=19)
Relative Dose Intensity – BSA Adjusted (%)			
N	2	17	19
Mean (StD)	99.95 (0.070)	95.72 (11.247)	96.17 (10.687)
Median	99.95	97.63	97.87
Minimum, Maximum	99.9, 100.0	58.8, 114.2	58.8, 114.2

Abbreviations: BSA: Body Surface Area; StD: standard deviation.

Duration of exposure in months was calculated as: (last dose date – first dose date + 1)/30.4375.

Actual Dose intensity (mg/day) was calculated as: cumulative dose received/number of prescribed dosing days.

Relative Dose intensity is calculated as: $100 \times (\text{cumulative dose received} / \text{planned dose})$.

Source: ADSL, ADEX

The Applicant's Position:

Mirdametinib was tolerated by the majority of participants, as only 1 participant discontinued treatment due to toxicity.

The FDA's Assessment:

FDA agrees with the Applicant's description of treatment compliance and concomitant medication use.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

There was a total of 19 participants dosed with mirdametinib. Confirmed ORR was defined as the proportion of participants who have a BOR at the end of the Treatment Phase of PR or CR for ≥ 4 weeks duration. The ORR for the total population was 31.6% (95% CI: 12.58, 56.55; $p < 0.001$); 6 participants had a best overall confirmed response of PR. The remaining 13 participants had SD as their best overall confirmed response.

The median (min, max) best percentage change from baseline in tumor volume was -17.14% (-28.0, 17.9).

The Applicant's Position:

Mirdametinib was effective as demonstrated by the confirmed ORR of 32%. No participants had a best objective response of PD. Of note, participants discontinued treatment unless the participant had at least a 15% or 20% reduction in volume of the target tumor at Cycle 8 and 12, respectively. Due to these required efficacy benchmarks that caused participants to discontinue treatment, some participants were withdrawn from study treatment that may have achieved an objective response with longer duration of administration.

The FDA's Assessment:

FDA acknowledges the Applicant's position noting that one third of patients discontinued treatment as a result of not meeting target tumor reduction thresholds by cycles 8 and 12. The results of this trial are considered supportive, but the efficacy review of mirdametinib did not rely on these results and they were not independently verified during the review of this application.

Efficacy Results – Secondary and other relevant endpoints

Data:

Of the 6 (32%) confirmed responders, the median (95% CI) DoR was not reached because all 6 responders were censored due to no PDs/deaths following a confirmed response. Of these 6 responders, 5 participants maintained their response for ≥ 8 months. The onset of response was at Cycle 8 for 1 participant and at Cycle 12 for 5 participants; 4 of these participants had an onset of response at Cycle 12 and maintained this response through Cycle 24, at which point they were censored. The 2 remaining responders discontinued treatment early due to non-compliance and refusal of further therapy.

The median time to onset of response for all participants was 10.92 (7.16, 11.66) months.

The Applicant's Position:

The DoR suggest that treatment with mirdametinib at 2 mg/m² BID results in long-term durability. Participants were discontinued from treatment unless they had at least a 15% or 20% reduction in volume of the target tumor at Cycle 8 and 12, respectively. Due to these required efficacy benchmarks that caused participants to be discontinued from treatment, some participants were withdrawn from study treatment that may have achieved an objective response with continued administration.

The FDA's Assessment:

FDA acknowledges the Applicant's position but did not rely on or verify these results.

Dose/Dose Response

The Applicant's Position:

Mirdametinib was dosed in Studies MEK-NF-201 and NF-106 by BSA. The median (minimum, maximum) of actual doses received by participants with NF1 PN was 2.21 mg/m² (0.806, 2.86) (Figure 4).

In addition, population and trial simulations were conducted using exposure-efficacy and exposure-safety models to predict the impact of alternative target dose levels from 1.0 to 3.0 mg/m² BID (1.0, 1.5, 2.0, and 3.0 mg/m²). The simulations support that exposures associated with the proposed marketing dose of 2 mg/m² of mirdametinib provide an optimal balance of

robust efficacy with a tolerable incidence of low severity exposure-related AEs for patients with NF1 PN. Please refer to [Section 6.2.2.1](#) for additional simulation details in support of the proposed 2mg/m² dose used in Study MEK-NF-201, [Figure 4](#).

The FDA's Assessment:

Refer to Section 6, 19.4.2, and 19.4.3 for clinical pharmacology review details.

Durability of Response

Data:

Median DoR for participants with a confirmed response was not reached.

The Applicant's Position:

Response was durable among participants with a confirmed response.

The FDA's Assessment:

Among the 19 patients in NF-106, only 6 (32%) had a confirmed response of PR. The small number of patients, lack of events and follow-up limit the ability to interpret DOR and durability of response.

Persistence of Effect

Data:

Refer to efficacy results – secondary and other relevant endpoints above.

The Applicant's Position:

The study demonstrated persistence of effect over time.

The FDA's Assessment:

Persistence of effect cannot be verified.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

Of 19 participants, 9 completed the NRS-11 at Cycle 12 and 4 participants completed the NRS-11 at Cycle 24. The median (min, max) change in score from baseline at Cycle 12 for the FAS was -1 (-9, 0). At Cycle 24, the median (min, max) change from baseline was 0 (-3, 1). There was statistically significant improvement in the mean NRS-11 change from baseline at Cycle 12 (LS mean=-1.81; p=0.030), indicating decreased pain severity. At Cycle 24, the LS mean change from baseline was -0.30 (p=0.740).

At Cycle 12, 9 participants completed the BPI. There were improvements found in the BPI with a median (min, max) change from baseline total score of -0.86 (-4.57, 0.86), indicating decreased pain interference.

At Cycle 24, 4 participants completed the BPI. There were improvements found in the BPI with a median (min, max) change from baseline total score of -1.21 (-5.86, 2), indicating decreased pain interference.

At Cycle 12, 9 participants completed the PedsQL NF1 module. The median (min, max) change from baseline at Cycle 12 in PedsQL NF1 module total score was 3.6 (-20, 29), indicating an improvement in NF1-related QoL. All 6 responders completed Cycle 12.

At Cycle 24, 4 participants completed the PedsQL NF1 module. The median (min, max) change from baseline at Cycle 24 in PedsQL NF1 total score was 15.6 (-8, 34), indicating an improvement in NF1-related QoL.

The Applicant's Position:

Secondary PRO endpoints showed meaningful improvements in QoL and pain:

- At Cycle 12 there was statistically significant improvement in the mean NRS-11 change from baseline, indicating decreased pain severity.
- At Cycle 12 and Cycle 24, improvement in pain interference score was observed in the median BPI change from baseline, indicating decreased pain interference.
- At Cycle 12 and Cycle 24, improvement in the PedsQL NF1 module total score, indicating improved QoL, was observed in the median (min, max) change from baseline.

The FDA's Assessment:

As stated above under "Trial Design" FDA did not independently analyze the results of Study NF-106. Based on the Applicant's presentation of this data, the PRO data is not interpretable given the sample size of 19 patients in this study and only 9 patients responding to the BPI and PedsQL at cycle 12.

Additional Analyses Conducted on the Individual Trial

Data:

Analysis of secondary PK endpoints showed the following:

- Mirdametinib was absorbed rapidly, with a median Tmax of 1.0 hour. Following attainment of Cmax, the disposition of mirdametinib exhibited biphasic decline with a median Tlast of 9.98 hours.
- Mirdametinib exposures as measured by geometric mean (geometric CV%) AUClast, AUC0-8, and Cmax were 387.1 ng·h/mL (24.18%), 368.1 ng·h/mL (25.59%), and 188.3 ng/mL (50.46%), respectively.

- Formation of PD-0315209 was rapid to moderate with median (min, max) Tmax values of 2.00 hours (1.00, 6.00). Median Tlast was 9.98 hours. Following attainment of Cmax, disposition of PD-0315209 appeared to be 1.
- PD-0315209 exposures as measured by geometric mean (geometric mean CV%) AUClast, AUC0-8, and Cmax were 117.3 ng·h/mL (102.98%), 103.4 ng·h/mL (107.55%) and 18.0 ng/mL (110.34%).

The Applicant's Position:

Analysis was done on first dose pharmacokinetics. These data are in alignment in the adult cohort of MEK-NF-201.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

The ReNeu study is a single arm, multi-center study which served as the primary basis for establishing the efficacy of mirdametinib in the treatment of patients with NF1 PN. Study NF-106, an open-label, single arm study that included 2 pediatric and 17 adult patients, provided supportive evidence of mirdametinib's efficacy.

All 114 patients enrolled in the ReNeu study had measurable disease at baseline as assessed by BICR. The analysis of tumor response included 56 patients in the pediatric cohort and 58 patients in the adult cohort. In the pediatric cohort, the confirmed ORR was 52% (95% CI: 38, 65) and in the adult cohort, confirmed ORR was 41% (95% CI: 29, 55). All the responses observed in the study were partial responses. The ORR subgroups analysis based on demographic and clinical characteristics were mostly consistent across subgroups in both cohorts.

As of data cutoff date of June 12, 2024 (90-day safety update) the median DOR was not reached in either cohort. The percentage of patients with response who have observed DOR ≥ 12 months and ≥ 24 months were 90% and 48% in the pediatric cohort and 88% and 50% in the adult cohort, respectively.

The median time to onset of response was 7.8 months (range: 4.0 months to 19.0 months) for the adult cohort and 7.9 months (range: 4.1 months to 18.8 months) for the pediatric cohort.

FDA considered the comparisons of efficacy endpoints in the ReNeu study to the placebo control arm of Study 01-C-0222 and the natural history Study 08-C-0079 to be exploratory, due

to potential between-study differences including patient eligibility criteria, assessment frequencies of endpoint, and endpoint definition.

8.1.4. Assessment of Efficacy Across Trials

Primary Endpoints

Data:

Study MEK-NF-201 serves as the primary basis for establishing the efficacy of mirdametinib in the treatment of participants with NF1 PN. In addition, data from Study NF-106 are provided as supportive evidence of efficacy. Data from MEK-NF-201 and NF-106 were not integrated. The rationale for this strategy is provided below.

Both studies evaluated the efficacy of mirdametinib at a dose of 2 mg/m² BID on an intermittent schedule (3 weeks on/1 week off in a 28-day cycle) in participants with NF1 PN, but differences in the study designs do not allow for an integration of results of the two studies. Specifically, participants in Study NF-106 were discontinued from treatment if they did not meet certain tumor volume reduction benchmarks: treatment beyond Cycle 8 was allowed only for participants who had ≥15% reduction from baseline in volume of the target tumor by the end of Cycle 8 and treatment beyond 12 cycles was allowed for participants who achieved ≥20% tumor reduction from baseline by volumetric analysis by the end of Cycle 12. In contrast, there were no requirements for volumetric reduction of the target PN at any cycle to continue receiving mirdametinib in Study MEK-NF-201; participants received study treatment unless they met withdrawal criteria.

TTR results from Study MEK-NF-201 demonstrate that the rule excluding further treatment beyond Cycle 8 in Study NF-106 likely precluded many participants from an opportunity to achieve an objective response with longer durations of mirdametinib administration. Similarly, time to best percentage change in tumor volume results in Study MEK-NF-201 suggest that participants in Study NF-106 who did not achieve the tumor reduction requirements at Cycles 8 and 12 were discontinued from treatment before their tumors could likely reach their greatest reduction in volume, thereby affecting the likelihood of achieving a response. Therefore, efficacy results from these two studies were presented separately with Study NF-106 included as a supportive study of the results in the pivotal Study MEK-NF-201.

The Applicant's Position:

Efficacy Data from Study MEK-NF-201 and NF-106 were not integrated as agreed upon with the Agency.

The FDA's Assessment:

FDA agrees with the description above that efficacy data from the ReNeu study and NF-106 were not integrated. FDA's assessment of efficacy is primarily based on the ReNeu study results. Refer to Section 8.1.3.

Secondary and Other Endpoints

Data:

Not applicable. See results from individual studies above.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

Subpopulations

Data:

Not applicable. See results from individual studies above.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

Additional Efficacy Considerations

The FDA's Assessment:

Not applicable.

8.1.5. Integrated Assessment of Effectiveness

Data:

Not applicable. See results from individual studies above.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

8.2. Review of Safety

8.2.1. Safety Review Approach

Data:

See the Applicant's Position below.

The Applicant's Position:

The pivotal safety data supporting the safety evaluation of mirdametinib is based on Study MEK-NF-201. The studies used to support the integrated summary of safety are described in Table 26. Data from 8 additional non pooled interventional studies and the compassionate use program were used as supportive safety information, for a total of 577 patients exposed to mirdametinib.

As agreed with the agency during the Pre-NDA meeting, the integrated safety data presents 4 clinical studies that were grouped into the following study pools based on the targeted underlying condition (NF1 PN or advanced cancers), dosing regimen (body surface area vs unit dosing), participants, and study design:

- Pool 1: Study MEK-NF-201 and Study NF-106 in adult and pediatric participants with NF1 PN. The data from these studies were analyzed together as a single pool and are the primary safety data used to assess the safety profile of mirdametinib in adult and pediatric participants with NF1 PN.
- Pool 2: Study A4581001 and Study A4581002 in adult participants with advanced cancers. The data from these studies were analyzed together as a single pool and are supportive safety data used to assess the safety profile of mirdametinib.

This Assessment Aid will provide the safety data from Study MEK-NF-201, followed by Pool 1 and Pool 2, and supported by relevant data from healthy volunteers and the Global Pharmacovigilance database. Data will be compared to the MEK-NF-201 data as it serves as the primary basis for establishing the efficacy of mirdametinib in the treatment of participants with NF1 PN.

The FDA's Assessment:

FDA agrees with the Applicant's description of the pivotal and supportive datasets included in the NDA to support the safety evaluation of mirdametinib. FDA independently reviewed exposure and safety data for the pivotal ReNeu study and supportive Study NF-106 in which safety data was analyzed together as Pool 1 to support the safety profile for adult and pediatric patients with NF1 PN treated with mirdametinib 2 mg/m² BID (maximum 4 mg BID); 3 weeks on/1 week off.

A 90-day updated safety analysis with corresponding datasets for Pool 1 (data cut-off date of September 19, 2024) was submitted to supplement the summary of clinical safety. The 90-day safety update included an additional 9 months of safety data. There were no new patients enrolled into Pool 1 since the initial data cut (Primary Analysis). Study NF-106 was completed prior to the primary analysis and there was no additional data in the 90-day safety update. The 90-day safety update did not identify new safety signals not already discussed in this review.

FDA reviewed but did not independently verify the data from Pool 2 which included Study A4581001 and Study A4581002 in adult patients with advanced cancers.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

A total of 577 patients have received at least one dose of mirdametininib across the clinical program.

A total of 56 participants in the pediatric cohort of Study MEK-NF-201 received at least 1 dose of study treatment. The median (min, max) duration of study treatment exposure was 22.0 (1.6, 40.0) months. A total of 58 participants in the adult cohort received at least 1 dose of study treatment. The median (min, max) duration of study treatment exposure was 21.8 (0.4, 45.6) months.

The exposure to mirdametininib in Pool 1 aligns with what was observed in the pivotal study, MEK-NF-201. In Pool 1, a total of 133 participants (58 participants in the pediatric cohort and 75 participants in the adult cohort) received at least one dose of study treatment. As displayed in [Table 48](#), the median (min, max) duration of mirdametininib exposure for the pediatric cohort was 21.87 (1.6, 40.1) months and 18.66 (0.4, 45.6) months in the adult cohort of Pool 1. The median duration of study treatment, median duration to dose reduction and interruption were similar between the pediatric and adult cohorts. The median time to dose modification was slightly longer in the pediatric cohort at 4.2 (range: 0 to 21.6) months compared to the adult cohort at 1.4 (range: 0 to 45) months. In Pool 1, 62% of all participants were on study treatment for 1 year or longer, 38% at 2 years and 12% at 3 years, suggesting that the safety profile of mirdametininib is acceptable over longer term use.

The median duration of exposure in Pool 2 in participants treated with mirdametininib was much lower than what was observed in the adult cohort of Pool 1. Note that Pool 2 participants had advanced cancers and all Pool 2 studies were terminated early.

Table 49: Mirdametinib Exposure for Pool 1

	Pediatric NF1 PN 2 mg/m²BID (N=58)	Adult NF1 PN 2 mg/m²BID (N=75)	Total NF1 PN 2 mg/m²BID (N=133)
Duration of Mirdametinib Exposure (Months)			
N	58	75	133
Mean (StD)	20.86 (10.690)	18.04 (13.002)	19.27 (12.087)
Median	21.87	18.66	21.85
Min, Max	1.6, 40.1	0.4, 45.6	0.4, 45.6
Total Duration of Exposure (years) for all Participants	100.8	112.7	213.5
Number of Participants who Received Study Treatment			
For at least 1 month	58 (100%)	70 (93.3%)	128 (96.2%)
For at least 2 months	57 (98.3%)	68 (90.7%)	125 (94.0%)
For at least 3 months	56 (96.6%)	68 (90.7%)	124 (93.2%)
For at least 6 months	51 (87.9%)	60 (80.0%)	111 (83.5%)
For at least 12 months	42 (72.4%)	41 (54.7%)	83 (62.4%)
For at least 24 months	24 (41.4%)	26 (34.7%)	50 (37.6%)
For at least 36 months	6 (10.3%)	10 (13.3%)	16 (12.0%)
Number of Participants Receiving All Planned Doses	18 (31.0%)	27 (36.0%)	45 (33.8%)
Participants With at least 1 Dose Modification	40 (69.0%)	48 (64.0%)	88 (66.2%)
Time to Dose Modification (Months)			
n	40	48	88
Mean (StD)	7.37 (6.673)	5.96 (8.939)	6.60 (7.977)
Median	4.24	1.37	3.57
Min, Max	0.0, 21.6	0.0, 44.8	0.0, 44.8
Participants With at least 1 Dose Reduction due to a TEAE	7 (12.1%)	15 (20.0%)	22 (16.5%)

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	Pediatric NF1 PN 2 mg/m²BID (N=58)	Adult NF1 PN 2 mg/m²BID (N=75)	Total NF1 PN 2 mg/m²BID (N=133)
Time to Dose Reduction (Months)			
n	7	9	16
Mean (StD)	3.45 (4.734)	5.09 (6.319)	4.37 (5.565)
Median	1.74	1.22	1.48
Min, Max	0.3, 13.9	0.3, 14.4	0.3, 14.4
Participants With at least 1 Dose Interruption	17 (29.3%)	21 (28.0%)	38 (28.6%)
Interruption Due to a TEAE	17 (100%)	21 (100%)	38 (100%)
TEAE Related to Study Treatment	8 (47.1%)	7 (33.3%)	15 (39.5%)
Time to Dose Interruption (Months)			
n	17	21	38
Mean (StD)	9.43 (8.654)	11.65 (12.901)	10.66 (11.118)
Median	7.10	5.65	6.03
Min, Max	0.3, 26.8	0.1, 44.7	0.1, 44.7
Participants With Treatment Discontinuation Due to TEAE	5 (8.6%)	16 (21.3%)	21 (15.8%)
Related to Study Treatment	5 (100%)	15 (93.8%)	20 (95.2%)

AE: adverse event; BID: twice daily; m: meter; Max: Maximum; Min: Minimum; mg: milligram; NF1: Neurofibromatosis Type 1; PN: Plexiform Neurofibromas; QD: once daily; StD: Standard deviation; TEAE: Treatment-Emergent Adverse Event.

Percentages are calculated using the number of participants in the corresponding cohort as the denominator.

Subcategories, shown by an indent, use the number of participants in the category as the denominator.

Participants can have multiple reasons for dose modifications, reductions, or interruptions, and thus can be counted in multiple rows corresponding to reasons.

Source: ADSL, ADEX, ADAE

The Applicant's Position:

The overall exposure to mirdametinib is adequate to support characterization of the safety profile.

The FDA's Assessment:

FDA agrees with the exposure data presented in Table 48 [Mirdametininib Exposure for Pool 1 (n=133)], the pediatric population (n=58) and the adult population (n=75). Among 133 patients who received mirdametininib, 62% were exposed one year or longer, 38% were exposed for 2 years or longer and 12% were exposed for more than 3 years.

For adult patients treated with mirdametininib in the ReNeu study, the median duration of treatment was 22 months (range: 0.4 to 46 months). For pediatric patients treated with mirdametininib in the ReNeu study, the median duration of treatment was 22 months (range: 1.6 to 40 months).

Relevant characteristics of the safety population:

Data:

Table 49 displays the demographics for Pool 1 and Pool 2.

Table 50: Demographics for Participants who Received Mirdametininib for Pool 1 and Pool 2

	Pool 1			Pool 2
	Pediatric NF1 PN 2 mg/m ² BID (N = 58)	Adult NF1 PN 2 mg/m ² BID (N = 75)	Total NF1 PN 2 mg/m ² BID (N = 133)	Total (N = 113)
Age at Informed Consent (years)				
n	58	75	133	113
Mean (StD)	10.3 (4.55)	32.9 (12.48)	23.1 (14.95)	58.8 (12.43)
Median	10	30	21	59
Min, Max	2, 17	18, 69	2, 69	29, 86
Age Groups (years)				
Pediatric				N/A
2 to <12	32 (55.2%)	N/A	N/A	N/A
12 to <18	26 (44.8%)	N/A	N/A	N/A
Adult				
18 to <40	N/A	57 (76.0%)	N/A	8 (7.1%)
40 to <65	N/A	16 (21.3%)	N/A	70 (61.9%)
≥65	N/A	2 (2.7%)	N/A	35 (31.0%)

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	Pool 1			Pool 2
	Pediatric NF1 PN 2 mg/m ² BID (N = 58)	Adult NF1 PN 2 mg/m ² BID (N = 75)	Total NF1 PN 2 mg/m ² BID (N = 133)	Total (N = 113)
Adult				
<65	N/A	73 (97.3%)	N/A	78 (69.0%)
≥65	N/A	2 (2.7%)	N/A	35 (31.0%)
Sex				
Male	27 (46.6%)	27 (36.0%)	54 (40.6%)	58 (51.3%)
Female	31 (53.4%)	48 (64.0%)	79 (59.4%)	55 (48.7%)
Race				
White	38 (65.5%)	56 (74.7%)	94 (70.7%)	100 (88.5%)
Black or African American	11 (19.0%)	10 (13.3%)	21 (15.8%)	9 (8.0%)
Asian	2 (3.4%)	4 (5.3%)	6 (4.5%)	1 (0.9%)
American Indian or Alaska Native	1 (1.7%)	0	1 (0.8%)	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Other	6 (10.3%)	5 (6.7%)	11 (8.3%)	3 (2.7%)
Ethnicity				
Hispanic or Latino	8 (13.8%)	3 (4.0%)	11 (8.3%)	1 (0.9%)
Not Hispanic or Latino	46 (79.3%)	66 (88.0%)	112 (84.2%)	65 (57.5%)
Missing/ Not Reported/ Unknown	4 (6.9%)	6 (8.0%)	10 (7.5%)	47 (41.6%)
Women who are of Child-Bearing Potential at Screening [1]				
Yes	15 (50.0%)	29 (78.4%)	44 (65.7%)	N/A
No	15 (50.0%)	8 (21.6%)	23 (34.3%)	N/A
Height (cm) at Screening				
n	58	75	133	113

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	Pool 1			Pool 2
	Pediatric NF1 PN 2 mg/m ² BID (N = 58)	Adult NF1 PN 2 mg/m ² BID (N = 75)	Total NF1 PN 2 mg/m ² BID (N = 133)	Total (N = 113)
Mean (StD)	137.1 (22.16)	160.0 (9.89)	150.0 (19.93)	169.9 (8.75)
Median	136.5	159	155	170.2
Min, Max	88, 174	137, 193	88, 193	150, 191
Weight (kg) at Screening				
n	58	75	133	112
Mean (StD)	39.5 (20.43)	68.9 (22.29)	56.1 (25.95)	79.3 (19.43)
Median	34.9	61.2	54.7	76.3
Min, Max	11, 92	37, 169	11, 169	48, 183
BSA (m ²) at Screening				
n	56	58	114	N/A
Mean (StD)	1.2 (0.39)	1.7 (0.29)	1.5 (0.43)	N/A
Median	1.1	1.7	1.5	N/A
Min, Max	1, 2	1, 3	1, 3	N/A
BMI (kg/m ²) at Screening				
n	58	75	133	112
Mean (StD)	19.6 (5.54)	26.6 (6.77)	23.6 (7.15)	27.4 (6.13)
Median	18.1	25	21.8	25.7
Min, Max	12, 38	17, 48	12, 48	18, 58

BID: twice daily; BMI: Body Mass Index; BSA: Body Surface Area; Max: Maximum; Min: Minimum; N/A: not applicable; NF1: Neurofibromatosis Type 1; PN: Plexiform Neurofibroma; StD: Standard deviation.

Percentages are calculated using the number of participants in the corresponding cohort as the denominator except for Child-Bearing Potential which uses the number of females in that cohort as the denominator.

[1] Study MEK-NF-201 only

Source: ADSL

The Applicant's Position:

In general, participants in Pool 1 were representative of the NF1 population.

The FDA's Assessment:

FDA agrees that the patients in Pool 1 are representative of the NF1 population. The median age of pediatric participants in Pool 1 is 10 years old (range: 2 to 17 years old), female 53%, White 66%, Black or African American 19%, Other 10%, Asian 3.4% and American Indian or Alaska Native 1.7%. The adult patients in Pool 1 have a median age of 30 years (range: 18 to 69 years old), female 64%, White 75%, Black or African American 13%, Other 7%, and Asian 5%. FDA notes that the Hispanic ethnicity may be under-represented based on the incidence reported for the US patient population; however, ethnicity is not well characterized for patients with NF1.

See Section 8.1.1.1 for a summary of demography and baseline characteristics of patients in the ReNeu study (FAS).

Adequacy of the safety database:

Data:

Refer to [Table 15](#) for the number of participants enrolled in each study used to support the evaluation of safety for mirdametinib.

The Applicant's Position:

The evaluation of safety of mirdametinib for the treatment of participants with NF1 PN is based on data from Study MEK-NF-201 and Pool 1 (Studies MEK-NF-201 and NF-106), which comprises both adult and pediatric cohorts (N=133).

Supportive safety information for mirdametinib as a monotherapy was generated by pooling two studies conducted in adult patients with advanced cancer (A4581001 and A4581002) (N=113). Due to the differences in dosing and patient populations these were pooled separately from the studies in participants with NF1 PN (Pool 2).

Additional supportive safety data from 3 Phase 1 studies in which healthy volunteers received single doses of mirdametinib (88 patients received mirdametinib in these three studies) as well as data from other interventional studies and compassionate use programs were used to support the safety of mirdametinib. A total of 577 patients have received at least one dose of mirdametinib which is considered adequate to define the risks of mirdametinib treatment in this rare disease.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of the adequacy of the safety database to support review of the NDA.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

The quality and integrity of the submitted datasets and individual case narratives are appropriate and adequate to allow for a thorough review of safety.

The FDA's Assessment:

FDA agrees that no issues were identified regarding data integrity or submission quality of the datasets and individual case narratives that had an effect on the safety review.

Categorization of Adverse Events

Data:

The number and proportion of participants reporting at least 1 TEAE in each category is described in Table 50. There were more participants in the adult cohort than in the pediatric cohort that reported TEAEs that led to study discontinuation (12 [16%] participants in the adult cohort vs 4 (7%) participants in the pediatric cohort) and treatment discontinuation (16 [21%] participants in the adult cohort vs 5 [9%] participants in the pediatric cohort).

Table 51: Overall AE Profile for Pool 1 Participants

	Pediatric NF1 PN 2 mg/m² BID (N=58)	Adult NF1 PN 2 mg/m² BID (N=75)	Total NF1 PN 2 mg/m² BID (N=133)
Number of Participants with at least one TEAE	58 (100%)	75 (100%)	133 (100%)
Number of Participants with at least one Treatment-related TEAE	55 (94.8%)	74 (98.7%)	129 (97.0%)
Number of Participants with at least one SAE	8 (13.8%)	12 (16.0%)	20 (15.0%)
Number of Participants with at least one Treatment-related SAE	0	3 (4.0%)	3 (2.3%)
Number of Participants with at least one TEAE in Safety Topic of Interest	57 (98.3%)	75 (100%)	132 (99.2%)
Number of Participants with at least one Treatment-related TEAE in Safety Topic of Interest	51 (87.9%)	73 (97.3%)	124 (93.2%)
Number of Participants with at least one Grade 3 or Above TEAE	23 (39.7%)	26 (34.7%)	49 (36.8%)
Maximum Intensity of TEAE			
Grade 1	8 (13.8%)	9 (12.0%)	17 (12.8%)

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	Pediatric NF1 PN 2 mg/m² BID (N=58)	Adult NF1 PN 2 mg/m² BID (N=75)	Total NF1 PN 2 mg/m² BID (N=133)
Grade 2	27 (46.6%)	40 (53.3%)	67 (50.4%)
Grade 3	21 (36.2%)	23 (30.7%)	44 (33.1%)
Grade 4	2 (3.4%)	2 (2.7%)	4 (3.0%)
Grade 5	0 (0.0%)	1 (1.3%)	1 (0.8%)
Number of Participants with at least one Grade 3 or Above Treatment-related TEAE	14 (24.1%)	11 (14.7%)	25 (18.8%)
Number of Participants with at least one Grade 3 or Above TEAE in Safety Topics of Interest	15 (25.9%)	16 (21.3%)	31 (23.3%)
Number of Participants with at least one TEAE Leading to Study Discontinuation	4 (6.9%)	12 (16.0%)	16 (12.0%)
Number of Participants with at least one TEAE Leading to Mirdametinib Discontinuation	5 (8.6%)	16 (21.3%)	21 (15.8%)

AE: Adverse event; CTCAE: Common Terminology Criteria for Adverse Events; m: meter; MedDRA: Medical Dictionary of Regulatory Activities; mg: milligram; NCI: National Cancer Institute; NF1: Neurofibromatosis Type 1; PN: Plexiform Neurofibromas. SAE: Serious Adverse Event; TEAE: Treatment-Emergent Adverse Event. Percentages are calculated using the number of participants in the corresponding cohort as the denominator (N). Source: ADAE

The Applicant's Position:

The overall TEAE profile in Pool 1 was similar to what was observed in Study MEK-NF-201. Overall, the TEAE profile between the pediatric and adult cohorts of Pool 1 was similar.

Safety analysis included TEAEs, treatment-related TEAEs, Grade ≥3 TEAEs, Grade ≥3 treatment-related TEAEs, SAEs, treatment-related SAEs, TEAEs by maximum severity, deaths, TEAEs that led to treatment discontinuations, dose modifications, dose interruptions, dose reductions, safety topics of special interest (including hypersensitivity, liver function, hematologic disorders, opportunistic infections, effects on cardiac conduction, cardiac effects, gastrointestinal effects, stomatitis, skin disorders, eye disorders, central nervous system (CNS) effects, musculoskeletal effects, upper respiratory infections, and bone effects), clinical laboratory evaluations, ECG parameters, cardiac function (multigated acquisition scan [MUGA] and echocardiogram [ECHO]), and vital signs.

AEs were re-coded for all integrated studies to Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 and displayed in tables and data listings using system organ class (SOC) and preferred term (PT). Analyses of AEs were performed for those events that were considered TEAEs, defined as an AE that starts or worsens on or after the first dose of study

treatment is taken, including those occurring or increasing in severity up to 30 days after the last dose of study treatment for Pool 1. TEAEs for Pool 2 were defined as all AEs reported after initiation of treatment and pre-existing conditions that worsened during the treatment period and up to 30 days after the last dose of study treatment.

TEAE severity was graded by NCI CTCAE (Version 5.0 for Pool 1 and Version 3.0 for Pool 2).

To facilitate a better understanding of specific topics of interest that may have comprised multiple PTs, select TEAEs were evaluated by pre-defined categories.

The FDA's Assessment:

FDA agrees with the Applicant's description of AE categorization; however, FDA does not consider relatedness as part of the safety review of AEs. The FDA review was completed using MedRA preferred terms (PTs) and CTCAE Version 5.0 as well as custom grouped terms (GT) when performing independent analyses of AEs for Pool 1.

Routine Clinical Tests

Data:

See the Applicant's Position below.

The Applicant's Position:

Collection of clinical laboratory assessments were appropriate and adequate to allow for a thorough review of safety.

Laboratory results and toxicities for Pool 1 studies were graded using NCI-CTCAE v5.0. For Pool 2 studies, severity was assessed using NCI-CTCAE v3.0.

The following clinical laboratory safety evaluations endpoints were included for both Pool 1 and Pool 2:

- Hematology parameters:
 - Complete CBC with differential
- Key Serum Chemistry parameters included:
 - Pool 1: Albumin, alkaline phosphatase, ALT, AST, Bicarbonate, Direct Bilirubin, Bilirubin, Calcium, cholesterol, CK, chloride, Creatinine, gamma glutamyl transferase, glucose, potassium, phosphate, total protein, sodium, triglycerides, uric acid, BUN.
 - Pool 2: Albumin, alkaline phosphatase, ALT, AST, Bicarbonate, Bilirubin, BNP, Calcium, CK, chloride, creatinine, glucose, potassium, lactate dehydrogenase,

magnesium, phosphate, protein, parathyroid hormone, sodium, troponin, urea nitrogen.

All summaries are presented by cohort/dose groups within each pool. Unscheduled laboratory assessments (including early termination) were mapped to the nearest planned visit by Day. In the case that multiple assessments mapped to the same visit then the value at the scheduled assessment took precedence over any unscheduled assessments. If there were multiple unscheduled assessments, the assessment closest to the target day was used.

The FDA's Assessment:

FDA agrees that the clinical laboratory assessments for Pool 1 were adequate for safety analysis. Laboratory assessments for hematology and serum chemistry in Pool 1 were performed every cycle and were graded according to CTCAE Version 5.0.

8.2.4. Safety Results

Deaths

Data:

In Study MEK-NF-201, there were no deaths in the pediatric cohort and there was 1 death on study in the adult cohort due to COVID-19 which was considered by the investigator to be unrelated to study treatment. No additional deaths were reported in Pool 1.

In Pool 2, with the exception of 1 death in the ≤ 2 mg BID dose group, the majority (11/12) of deaths were observed in the higher dose groups and none were observed at the 4 mg BID dose group. The TEAEs resulting in deaths included death (7%), hypoxia (1%), respiratory arrest (1%), respiratory failure (1%), cardiac arrest (1%), myocardial infarction (1%), colon cancer metastatic (1%), metastases to the CNS (1%), and cerebrovascular accident (1%). No deaths were attributed to mirdametinib by the investigator.

The Applicant's Position:

Mirdametinib was not considered a cause of death for any reported event.

The increase in number of deaths in Pool 2 compared to Pool 1 was driven by the older population of participants in these early studies who had advanced cancers, including metastatic malignant melanoma and non-small cell lung cancer.

The FDA's Assessment:

The FDA agrees with the Applicant's analysis of 1 death in Pool 1 (adult cohort) due to COVID 19 and not related to study treatment. This patient was a 68-year-old male with NF1 PN who received their first dose of mirdametinib 2 mg/m² at 4 mg twice daily on (b) (6). On Day 70 the patient had Grade 2 ejection fraction decreased that led to a dose interruption from Day 71

to Day 83. On Day 84 the patient resumed treatment at a reduced dose of 3 mg BID and continued this dose until Day 324. On Day 349 the patient had a fatal serious adverse event of Covid-19. There were no additional deaths reported for Pool 1. This death is described in Section 6 of the USPI.

Serious Adverse Events

Data:

In the pediatric cohort of Study MEK-NF-201, SAEs were reported in 8 (14%) participants. No SAEs were reported by >1 participant.

In the adult cohort of Study MEK-NF-201, SAEs were reported in 10 (17%) participants. SAEs reported by >1 participant were COVID-19, abdominal pain, and nephrolithiasis in 2 (3%) participants each. None of these events was assessed as related to mirdametininib.

Overall, the findings regarding SAEs in Pool 1 align with those described in Study MEK-NF-201.

See [Table 51](#) for SAEs that occurred in Pool 1.

Table 52: Incidence of SAEs Occurring in Participants who Received Mirdametininib (In Descending Order of Frequency by the Total Column; Pool 1)

Preferred Term	Pediatric NF1 PN 2 mg/m ² BID (N=58)	Adult NF1 PN 2 mg/m ² BID (N=75)	Total NF1 PN 2 mg/m ² BID (N=133)
Number of Participants with at least one SAE	8 (13.8%)	12 (16.0%)	20 (15.0%)
COVID-19 ^b	0	2 (2.7%)	2 (1.5%)
Abdominal pain ^c	0	2 (2.7%)	2 (1.5%)
Nephrolithiasis ^b	0	2 (2.7%)	2 (1.5%)
Gastrointestinal viral infection ^b	1 (1.7%)	0	1 (0.8%)
Rotavirus infection ^b	1 (1.7%)	0	1 (0.8%)
Urinary tract infection ^b	0	1 (1.3%)	1 (0.8%)
Colitis ischaemic ^b	0	1 (1.3%)	1 (0.8%)
Fall ^b	1 (1.7%)	0	1 (0.8%)
Femoral neck fracture ^b	1 (1.7%)	0	1 (0.8%)
Near drowning ^b	1 (1.7%)	0	1 (0.8%)
Acute kidney injury ^b	0	1 (1.3%)	1 (0.8%)
Diplopia ^b	1 (1.7%)	0	1 (0.8%)

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Preferred Term	Pediatric NF1 PN 2 mg/m ² BID (N=58)	Adult NF1 PN 2 mg/m ² BID (N=75)	Total NF1 PN 2 mg/m ² BID (N=133)
Retinal vein occlusion ^a	0	1 (1.3%)	1 (0.8%)
Back pain ^a	0	1 (1.3%)	1 (0.8%)
Scoliosis ^b	0	1 (1.3%)	1 (0.8%)
Cerebrovascular accident ^b	0	1 (1.3%)	1 (0.8%)
Seizure ^b	1 (1.7%)	0	1 (0.8%)
Non-cardiac chest pain ^b	1 (1.7%)	0	1 (0.8%)
Dehydration ^b	1 (1.7%)	0	1 (0.8%)
Squamous cell carcinoma of skin ^b	0	1 (1.3%)	1 (0.8%)
Device breakage ^b	1 (1.7%)	0	1 (0.8%)
Chronic obstructive pulmonary disease ^b	0	1 (1.3%)	1 (0.8%)
Pregnancy of partner ^a	0	1 (1.3%)	1 (0.8%)
Hypertension ^b	1 (1.7%)	0	1 (0.8%)

^aEvents assessed as related to mirdametinib.

^bEvents assessed as not related to mirdametinib.

^cOne event of abdominal pain assessed as related to mirdametinib, one event of abdominal pain assessed as not related to mirdametinib.

AE: adverse event; BID: twice daily; m: meter; MedDRA: Medical Dictionary of Regulatory Activities; mg: milligram; NF1: Neurofibromatosis Type 1; PN: Plexiform Neurofibroma; SAE: Serious Adverse event.

Each participant is counted only once within each preferred term if they experience an AE with that preferred term more than once.

Percentages are calculated using the number of participants in the corresponding cohort as the denominator.

Source: ADAE

A total of 4 SAEs were reported in participants who received mirdametinib ≤ 4 mg BID in Pool 2. No SAEs were reported by more than one participant in this dose range. The SAEs reported included pyrexia, urinary tract infection, bronchitis, and cardiac failure congestive.

An increased incidence of SAEs can be seen with higher doses of mirdametinib in Pool 2, with 57% of participants in the 8, 10 mg BID dose group and 51% of participants in the 15, 20, 30 mg BID group reporting SAEs. The PT of death was reported most in these dose groups, consistent with the advanced cancer diagnoses and extensive prior treatment in a Phase 1 population in this pool. As described in the deaths section, none of these deaths were considered related to mirdametinib by the investigator.

The Applicant's Position:

For the adult cohort of Pool 1, the most frequently reported SAEs (≥ 2 participants) were COVID-19, abdominal pain, and nephrolithiasis. In the pediatric cohort, all SAE PTs were reported by 1 participant each.

The FDA's Assessment:

FDA performed an independent analysis of the incidence of SAEs in patients included in Pool 1 (e.g., patients from the ReNeu study and Study NF-106) who received mirdametinib at 2 mg/m² twice daily (maximum dose of 4 mg BID) for the first 21 days of each 28-day cycle. SAEs occurred in 20 patients (15%) with the most frequently reported SAEs $\geq 1\%$ being abdominal pain, nephrolithiasis, musculoskeletal pain and Covid-19.

FDA's analysis of the ReNeu study and the incidences of SAEs in the adult and pediatric patient population were used to support Section 6 of the USPI. SAEs occurred in 17% of adult patients who received mirdametinib. SAEs occurring in $\geq 2\%$ of patients were COVID-19 (3.4%) and nephrolithiasis (3.4%), and in 1 patient each: acute kidney injury, abdominal pain, ischemic colitis, urinary tract infection, retinal vein occlusion (RVO), scoliosis, squamous cell carcinoma of skin, cerebrovascular accident, and chronic obstructive pulmonary disease. SAEs occurred in 14% of pediatric patients who received mirdametinib. SAEs in $\geq 2\%$ of pediatric patients included viral gastrointestinal infections (3.6%), and in 1 patient each: diplopia, musculoskeletal pain, seizure, fall, femoral neck fracture, dehydration, and hypertension. Refer to Table 52 for FDA's analysis of SAEs in the ReNeu Study.

Table 53. FDA Analysis of Serious Adverse Events in the ReNeu Study.

	Adult N = 58 N (%)	Pediatric N = 56 N (%)	Total N=114 N (%)
Patients with serious AEs	10 (17)	8 (14)	18 (16)
Renal And Urinary Disorders			
Nephrolithiasis	2 (3.4)	0 (0.0)	2 (1.8)
Acute Kidney Injury (GT)	1 (1.7)	0 (0.0)	1 (0.8)
Gastrointestinal Disorders			
Abdominal Pain (GT)	1 (1.7)	0 (0.0)	1 (0.8)
Ischemic Colitis	1 (1.7)	0 (0.0)	1 (0.8)
Infections And Infestations			

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	Adult N = 58 N (%)	Pediatric N = 56 N (%)	Total N=114 N (%)
Covid-19	2 (3.4)	0 (0.0)	2 (1.8)
Urinary Tract Infection (GT)	1 (1.7)	0 (0.0)	1 (0.8)
Gastrointestinal Viral Infection	0 (0.0)	1 (1.8)	1 (0.8)
Rotavirus Infection	0 (0.0)	1 (1.8)	1 (0.8)
Eye Disorders			
Retinal Vein Occlusion	1 (1.7)	0 (0.0)	1 (0.8)
Diplopia	0 (0.0)	1 (1.8)	1 (0.8)
Musculoskeletal And Connective Tissue Disorders			
Scoliosis	1 (1.7)	0 (0.0)	1 (0.8)
Musculoskeletal Pain (GT)	0 (0.0)	1 (1.8)	1 (0.8)
Neoplasms Benign, Malignant And Unspecified (incl Cysts And Polyps)			
Squamous Cell Carcinoma Of Skin	1 (1.7)	0 (0.0)	1 (0.8)
Nervous System Disorders			
Cerebrovascular Accident	1 (1.7)	0 (0.0)	1 (0.8)
Seizure	0 (0.0)	1 (1.8)	1 (0.8)
Respiratory, Thoracic And Mediastinal Disorders			
Chronic Obstructive Pulmonary Disease	1 (1.7)	0 (0.0)	1 (0.8)
Injury, Poisoning And Procedural Complications			
Fall	0 (0.0)	1 (1.8)	1 (0.8)
Femoral Neck Fracture	0 (0.0)	1 (1.8)	1 (0.8)
Metabolism And Nutrition Disorders			
Dehydration	0 (0.0)	1 (1.8)	1 (0.8)
Vascular Disorders			
Hypertension (GT)	0 (0.0)	1 (1.8)	1 (0.8)

Group Abdominal Pain (GT) includes PT terms ABDOMINAL PAIN,

Group Acute Kidney Injury (GT) includes PT terms ACUTE KIDNEY INJURY,
Group Musculoskeletal Pain (GT) includes PT terms NON-CARDIAC CHEST PAIN,
Group Hypertension (GT) includes PT terms HYPERTENSION,
Group Urinary Tract Infection (GT) includes PT terms URINARY TRACT INFECTION,

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

In the pediatric cohort of Study MEK-NF-201, 5 (9%) participants reported TEAEs that led to treatment discontinuation. All TEAEs that led to treatment discontinuation were Grade 1 or Grade 2. The only TEAE that led to treatment discontinuation in >1 participant in the pediatric cohort was urticaria. Note that individual participants could have reported more than 1 event leading to treatment discontinuation.

In the adult cohort of Study MEK-NF-201, 13 (22%) participants reported TEAEs that led to treatment discontinuation. TEAEs that led to treatment discontinuation in >1 participant in the adult cohort were dermatitis acneiform, diarrhea, and nausea. Most TEAEs that led to treatment discontinuation were Grade 1 or Grade 2; 3 TEAEs were Grade 3 (dermatitis acneiform, rash erythematous, and RVO, no TEAEs were Grade 4, and only 1 TEAE was Grade 5 (COVID-19).

Overall, the findings regarding TEAEs that led to treatment discontinuation in Pool 1 align with those described in Study MEK-NF-201. TEAEs leading to treatment discontinuation in Pool 1 are shown in Table 53. In Pool 1, 5 (9%) pediatric participants and 16 (21%) adult participants reported TEAEs that led to treatment discontinuation. In the pediatric cohort, the only TEAE that led to treatment discontinuation in >1 participant was urticaria which resulted in treatment discontinuation in 2 (3%) pediatric participants. This was the same as what was observed in Study MEK-NF-201 in the pediatric cohort. In the adult cohort, TEAEs that led to discontinuation in >1 participant were dermatitis acneiform [6 (8%) participants], diarrhea and nausea [4 (5%) participants each], and vomiting [2 (3%) participants]; these were the same TEAEs that led to discontinuation in >1 participant in Study MEK-NF-201, with the addition of vomiting.

Table 54: Incidence of TEAEs Leading to Treatment Discontinuation in Participants who Received Mirdametinib (In Descending Order of Frequency by the Total Column; Pool 1)

Preferred Term	Pediatric NF1 PN 2mg/m ² BID	Adult NF1 PN 2mg/m ² BID	Total NF1 PN 2mg/m ² BID
	(N=58)	(N=75)	(N=133)
Number of Participants with at least one TEAE leading to Study Treatment Discontinuation	5 (8.6%)	16 (21.3%)	21 (15.8%)
Dermatitis acneiform	1 (1.7%)	6 (8.0%) ^{a,b,c}	7 (5.3%)
Diarrhoea	1 (1.7%) ^d	4 (5.3%) ^{a,e,f}	5 (3.8%)
Nausea	0	4 (5.3%) ^{a,g,e,f}	4 (3.0%)
Rash	1 (1.7%)	1 (1.3%) ^f	2 (1.5%)
Urticaria	2 (3.4%)	0	2 (1.5%)
Abdominal pain	1 (1.7%) ^d	1 (1.3%) ^f	2 (1.5%)
Vomiting	0	2 (2.7%) ^f	2 (1.5%)
Alopecia	0	1 (1.3%) ^g	1 (0.8%)
Dry skin	0	1 (1.3%) ^h	1 (0.8%)
Rash erythematous	0	1 (1.3%)	1 (0.8%)
Constipation	1 (1.7%) ^d	0	1 (0.8%)
Dizziness	0	1 (1.3%) ^g	1 (0.8%)
Headache	0	1 (1.3%) ^b	1 (0.8%)
Paraesthesia	0	1 (1.3%) ^c	1 (0.8%)
Retinal vein occlusion	0	1 (1.3%)	1 (0.8%)
Peripheral swelling	0	1 (1.3%) ^h	1 (0.8%)
COVID-19	0	1 (1.3%)	1 (0.8%)
Ejection fraction decreased	0	1 (1.3%)	1 (0.8%)
Cough	0	1 (1.3%) ^h	1 (0.8%)
Wheezing	0	1 (1.3%) ^h	1 (0.8%)

AE: Adverse event; BID: twice daily; m: meter; MedDRA: Medical Dictionary of Regulatory Activities; mg: milligram; NF1: Neurofibromatosis Type 1; PN: Plexiform Neurofibroma; TEAE: Treatment-Emergent Adverse Event.

Each participant is counted only once within each preferred term if they experience an AE with that preferred term more than once.

Percentages are calculated using the number of participants in the corresponding cohort as the denominator.

a Participant (b) (6) reported multiple TEAEs that led to treatment discontinuation.

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b Participant (b) (6) reported multiple TEAEs that led to treatment discontinuation.
c Participant (b) (6) reported multiple TEAEs that led to treatment discontinuation.
d Participant (b) (6) reported multiple TEAEs that led to treatment discontinuation.
e Participant (b) (6) reported multiple TEAEs that led to treatment discontinuation.
f Participant (b) (6) reported multiple TEAEs that led to treatment discontinuation.
g Participant (b) (6) reported multiple TEAEs that led to treatment discontinuation.
h Participant (b) (6) reported multiple TEAEs that led to treatment discontinuation.

Source: ADAE

In Pool 2, 4/16 participants (25%) who received mirdametinib ≤ 4 mg BID discontinued study treatment due to TEAEs. The PTs reported included optic neuropathy and retinal hemorrhage (1 participant), vomiting and pyrexia (1 participant), acute kidney injury (1 participant), and metastases to central nervous system and death (1 participant).

The Applicant's Position:

Many TEAEs leading to treatment discontinuation were consistent with the known safety profile of mirdametinib and MEK inhibitors.

The FDA's Assessment:

In FDA's analysis of Pool 1, adverse events leading to treatment discontinuation occurred in 21% of adult patients and in 9% of pediatric patients. Adverse events which resulted in treatment discontinuation of mirdametinib in the adult cohort in $\geq 2\%$ of patients included rash (11%), diarrhea (5%), nausea (5%) and vomiting (2.7%). Adverse events which led to treatment discontinuation of mirdametinib in the pediatric cohort in $\geq 2\%$ of patients included urticaria (3.4%) and rash (3.4%).

FDA's analysis of the ReNeu study showed that adverse events leading to treatment discontinuation occurred in 22% of adult patients and 9% of pediatric patients. Adverse events which led to treatment discontinuation of mirdametinib in $\geq 1\%$ of adult patients included rash, diarrhea, nausea, abdominal pain, alopecia, dry skin, left ventricular dysfunction, cough, wheezing, COVID-19, peripheral swelling, RVO, dizziness and vomiting. See Section 8.2.5.1 for a summary of the RVO event.

Adverse events which led to treatment discontinuation of mirdametinib in $\geq 1\%$ of pediatric patients included rash, urticaria, abdominal pain, constipation and diarrhea.

FDA agrees that the adverse events leading to treatment discontinuations of mirdametinib in the ReNeu study were similar to those observed in Pool 1.

Dose Interruption/Reduction Due to Adverse Effects

Data:

In the pediatric cohort of Study MEK-NF-201, 39 (70%) participants had at least 1 dose modification, including dose interruptions and/or reductions; other than due to changes in BSA, most dose modifications were due to an AE (32%). TEAEs leading to a dose interruption were reported by 17 (30%) participants; the most frequently reported (> 5%) TEAEs leading to dose interruption were SARS-Cov-2 test positive and COVID-19 (3 [5%] participants each). TEAEs leading to a dose reduction were reported by 7 (13%) participants; the most frequently reported (> 5%) TEAE leading to dose reduction was neutrophil count decreased (3 [5%] participants).

In the adult cohort of Study MEK-NF-201, 31 (53%) participants had at least 1 dose modification, including dose interruptions and/or reductions, with most of these being due to an AE (40%). TEAEs leading to a dose interruption were reported by 18 (31%) participants; the TEAEs that most frequently (> 5%) led to dose interruption were ejection fraction decreased (5 [9%] participants) and COVID-19 (3 [5%] participants). TEAEs leading to a dose reduction were reported by 10 (17%) participants; the TEAEs that most frequently (> 5%) led to dose reduction was dermatitis acneiform (6 [10%] participants).

In Pool 1, 50 participants (38%; 20 [35%] in the pediatric cohort, 30 [40%] in the adult cohort) had dose modifications due to TEAEs. TEAEs that led to dose modification of study treatment in >1 participant in the pediatric cohort were COVID-19 (3 participants), neutrophil count decreased (3 participants), SARS CoV-2 test positive (3 participants), blood creatinine phosphokinase increased (2 participants), and weight increased (2 participants). TEAEs that led to dose modification of study treatment in >1 participant in the adult cohort were dermatitis acneiform (8 participants), ejection fraction decreased (6 participants), COVID-19 (3 participants), and fatigue (2 participants).

In Pool 1, 38 participants (29%; 17 [29%] in the pediatric cohort, 21 [28%] in the adult cohort) had dose interruptions due to TEAEs. TEAEs that led to dose interruptions of study treatment in >1 participant in the pediatric cohort were SARS CoV-2 test positive (3 participants), neutrophil count decreased (2 participants), and COVID-19 (3 participants). The median time to dose interruption (min, max) was 7.1 months (0.3, 26.8 months). Ejection fraction decreased (5 participants), COVID-19 (3 participants), and dermatitis acneiform (2 participants) were the only TEAEs that led to dose interruptions of study treatment in >1 participant in the adult cohort. The median time to dose interruption (min, max) was 5.65 months (0.1, 44.7 months).

Pool 2 had a similar incidence of TEAEs that led to dose interruption as compared to the adult cohort in Pool 1. A total of 5 participants reported TEAEs that led to dose interruption in participants who received mirdametinib $\leq$ 4 mg BID in Pool 2. All TEAEs were reported by 1 participant each and included: chills, diarrhea, nausea, vomiting, confusional state, liver function test increased, and cardiac failure congestive. The median duration of exposure in Pool 2 in participants treated with mirdametinib $\leq$ 4 mg BID was much lower than what was observed

in the adult cohort of Pool 1. Pool 2 participants treated at dose levels below the RP2D did not have dose reduction as a pre-specified option.

The Applicant's Position:

The incidence of AEs leading to dose modification (interruption and/or reduction) was similar in Study MEK-NF-201, Pool 1, and Pool 2. The most common AEs leading to dose modification of mirdametinib in patients with NF1 PN were consistent with the known safety profile of mirdametinib or were commonly reported during the global pandemic.

The FDA's Assessment:

In FDA's analysis of Pool 1, dose reductions due to an adverse event occurred in 15 (20%) adult patients, and in 7 (12%) of pediatric patients. Adverse events in $\geq 3\%$ of patients which required dose reduction in the adult population included rash (11%) and in the pediatric population included decreased neutrophil count (5%) and rash (3.4). Dose interruptions occurred in 21 (28%) of adult patients and 17 (29%) of pediatric patients. The most frequently reported adverse events leading to dose interruption in the adult population in $\geq 3\%$ of patients were ejection fraction decreased (7%) and COVID-19 (4%). For the pediatric population, the most frequently reported adverse event leading to dose interruption was Covid-19 (5%).

In the ReNeu study dosage reduction of mirdametinib due to an adverse event occurred in 17% of adults and in 13% of pediatric patients. Adverse events which required dose reduction in $\geq 5\%$ of adult patients included rash (10%). Adverse events which required dose reduction in $\geq 3\%$ of pediatric patients were decreased neutrophil count (5%) and rash (3.6%). Dose interruptions occurred in 31% of adults and in 30% of pediatric patients. Adverse events in $\geq 5\%$ of adult patients that required dosage interruption included left ventricular dysfunction (9%) and COVID-19 (5%). For pediatric patients, the most frequently reported adverse event leading to dose interruption in $\geq 5\%$ of patients was COVID-19 (5%).

FDA agrees that the adverse events leading to dose reductions and dose interruptions of mirdametinib in the ReNeu study were similar to those observed in Pool 1.

Significant Adverse Events

Data:

In the pediatric cohort of Study MEK-NF-201, 43 Grade ≥ 3 events were reported by 22 (39%) participants. Grade ≥ 3 TEAEs reported by > 1 participant were neutrophil count decreased, blood creatine phosphokinase (CPK) increased, diarrhea, weight increased, abdominal pain, and syncope. There were 2 participants who reported maximum Grade 4 events (1 participant with blood CPK increased and 1 participant with near drowning and laryngeal edema).

In the adult cohort of Study MEK-NF-201, 42 Grade ≥ 3 events were reported by 21 (36%) participants. Grade ≥ 3 TEAEs reported by > 1 participant were SARS-COV-2 test positive, dermatitis acneiform, abdominal pain, COVID-19, back pain, and nephrolithiasis. There were 2 participants who reported maximum Grade 4 events (COPD and blood creatine phosphokinase increased) and 1 additional participant experienced a Grade 4 event of pneumonia bacterial secondary to a Grade 5 event of COVID-19.

Grade ≥ 3 TEAEs reported in Pool 1 by ≥ 2 pediatric participants were neutrophil count decreased, blood creatine phosphokinase increased, diarrhea, syncope, weight increased, and abdominal pain. Grade ≥ 3 TEAEs reported in Pool 1 by ≥ 2 adult participants were dermatitis acneiform, abdominal pain, back pain, COVID-19, nephrolithiasis and SARS-CoV-2 test positive.

Grade ≥ 3 TEAEs reported in ≥ 2 participants in either cohort in Pool 1 are displayed in [Table 54](#).

Table 55: Incidence of Grade ≥ 3 TEAEs Occurring in ≥ 2 Participants in Any Cohort who Received Mirdametinib (In Descending Order of Frequency by the Total Column; Pool 1)

Preferred Term	Pediatric NF1 PN 2 mg/m ² BID (N=58)	Adult NF1 PN 2 mg/m ² BID (N=75)	Total NF1 PN 2 mg/m ² BID (N=133)
Number of Participants with at least one TEAE of at Least Grade 3 Severity	23 (39.7%)	26 (34.7%)	49 (36.8%)
Dermatitis acneiform	1 (1.7%)	5 (6.7%)	6 (4.5%)
Blood creatine phosphokinase increased	4 (6.9%)	1 (1.3%)	5 (3.8%)
Neutrophil count decreased	5 (8.6%)	0	5 (3.8%)
Abdominal pain	2 (3.4%)	3 (4.0%)	5 (3.8%)
Syncope	3 (5.2%)	1 (1.3%)	4 (3.0%)
Weight increased	2 (3.4%)	1 (1.3%)	3 (2.3%)
Diarrhoea	3 (5.2%)	0	3 (2.3%)
COVID-19	0	3 (4.0%)	3 (2.3%)

Preferred Term	Pediatric NF1 PN 2 mg/m ² BID (N=58)	Adult NF1 PN 2 mg/m ² BID (N=75)	Total NF1 PN 2 mg/m ² BID (N=133)
Back pain	0	3 (4.0%)	3 (2.3%)
SARS-CoV-2 test positive	0	2 (2.7%)	2 (1.5%)
Headache	1 (1.7%)	1 (1.3%)	2 (1.5%)
Pain in extremity	1 (1.7%)	1 (1.3%)	2 (1.5%)
Nephrolithiasis	0	2 (2.7%)	2 (1.5%)

AE: Adverse event; BID: twice daily; CTCAE: Common Terminology Criteria for Adverse Events; m: meter;

MedDRA: Medical Dictionary of Regulatory Activities; mg: milligram; NCI: National Cancer Institute;

NF1: Neurofibromatosis Type 1; PN: Plexiform Neurofibromas; TEAE: Treatment-Emergent Adverse Event.

Each participant is counted only once within each preferred term if they experience an AE with that preferred term more than once.

Percentages are calculated using the number of participants in the corresponding cohort as the denominator.

Source: ADSL, ADAE

The Applicant's Position:

The most common Grade ≥3 TEAEs reported are consistent with the known safety profile of mirdametinib or MEK inhibition.

The FDA's Assessment:

Significant adverse events ≥ Grade 3 in severity in Pool 1 occurred in 26 (35%) adult patients and 23 (40%) pediatric patients. The most common ≥ Grade 3 adverse events occurring in ≥3% of patients in the adult population included rash (8%), musculoskeletal pain (7%) and abdominal pain (4%). The most common ≥ Grade 3 adverse events occurring in ≥3% of patients in the pediatric population included syncope (5%), rash (3.4%), increased weight (3.4%) and abdominal pain (3.4%).

Treatment Emergent Adverse Events and Adverse Reactions

Data:

In the pediatric cohort of Study MEK-NF-201, 56 (100%) reported at least 1 TEAE.

- SAEs were reported by 8 (14%) participants.
- Grade ≥ 3 TEAEs were reported by 22 (39%) participants.
- Treatment-related TEAEs were reported by 53 (95%) participants.
- TEAEs leading to treatment discontinuation were reported by 5 (9%) participants.
- TEAEs leading to dose modification were reported by 20 (36%) participants.

- No deaths occurred in the pediatric cohort.
- AESIs (AEs of Grade ≥ 3 for the following PTs: diarrhea, nausea, vomiting, rash, and acneiform rash. AEs of Grade ≥ 2 for the following PTs were also considered AESIs: RVO, uveitis, optic neuropathy, retinopathy, retinal detachment, ejection fraction decreased, cardiac failure, left ventricular dysfunction, confusion, hallucinations, and delirium) were reported by 19 (34%) participants.

In the adult cohort in Study MEK-NF-201, 58 (100%) reported at least 1 TEAE.

- SAEs were reported by 10 (17%) participants.
- Grade ≥ 3 TEAEs were reported by 21 (36%) participants.
- Treatment-related TEAEs were reported by 57 (98%) participants.
- TEAEs leading to treatment discontinuation were reported by 13 (22%) participants.
- TEAEs leading to dose modification were reported by 24 (41%) participants.
- One Grade 5 event (death) of COVID-19 occurred.
- AESIs were reported by 18 (31%) participants.

In the pediatric cohort of Study MEK-NF-201, 1016 events were reported by 56 (100%) participants. The most frequently reported PTs ($>35\%$) were diarrhea, dermatitis acneiform, and vomiting.

In the adult cohort of Study MEK-NF-201, 819 events were reported by 58 (100%) participants. The most frequently reported ($>35\%$) PTs were dermatitis acneiform, diarrhea, nausea, and vomiting.

TEAEs occurred in all (100%) participants in the pediatric and adult cohorts of Pool 1. In the pediatric cohort, the most frequently reported PTs ($>35\%$) were diarrhea, dermatitis acneiform, vomiting and headache. In the adult cohort, the most frequently reported PTs ($>35\%$) were dermatitis acneiform, diarrhea, nausea, vomiting, and fatigue.

TEAEs reported in $\geq 15\%$ of all participants or in either cohort in Pool 1 are displayed in [Table 55](#).

Table 56: Incidence of Frequently ($\geq 15\%$ of Participants in Any Cohort) Occurring TEAEs in Participants who Received Mirdametinib (In Descending Order of Frequency by the Total Column; Pool 1)

Preferred Term	Pediatric NF1 PN 2 mg/m ² BID (N=58)	Adult NF1 PN 2 mg/m ² BID (N=75)	Total NF1 PN 2 mg/m ² BID (N=133)
Number of Participants with at least one TEAE	58 (100%)	75 (100%)	133 (100%)

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Preferred Term	Pediatric NF1 PN 2 mg/m ² BID (N=58)	Adult NF1 PN 2 mg/m ² BID (N=75)	Total NF1 PN 2 mg/m ² BID (N=133)
Dermatitis acneiform	25 (43.1%)	62 (82.7%)	87 (65.4%)
Diarrhoea	31 (53.4%)	41 (54.7%)	72 (54.1%)
Nausea	17 (29.3%)	41 (54.7%)	58 (43.6%)
Vomiting	23 (39.7%)	28 (37.3%)	51 (38.3%)
Fatigue	7 (12.1%)	27 (36.0%)	34 (25.6%)
Headache	21 (36.2%)	12 (16.0%)	33 (24.8%)
Abdominal pain	16 (27.6%)	12 (16.0%)	28 (21.1%)
COVID-19	14 (24.1%)	13 (17.3%)	27 (20.3%)
Blood creatine phosphokinase increased	14 (24.1%)	11 (14.7%)	25 (18.8%)
Ejection fraction decreased	15 (25.9%)	9 (12.0%)	24 (18.0%)
Pain in extremity	12 (20.7%)	12 (16.0%)	24 (18.0%)
SARS-CoV-2 test positive	11 (19.0%)	12 (16.0%)	23 (17.3%)
Paronychia	19 (32.8%)	2 (2.7%)	21 (15.8%)
Dizziness	5 (8.6%)	16 (21.3%)	21 (15.8%)
Arthralgia	9 (15.5%)	12 (16.0%)	21 (15.8%)
Dry skin	10 (17.2%)	10 (13.3%)	20 (15.0%)
Constipation	6 (10.3%)	14 (18.7%)	20 (15.0%)
Cough	13 (22.4%)	6 (8.0%)	19 (14.3%)
Upper respiratory tract infection	15 (25.9%)	1 (1.3%)	16 (12.0%)
Weight increased	9 (15.5%)	7 (9.3%)	16 (12.0%)
Rash	11 (19.0%)	4 (5.3%)	15 (11.3%)
Pyrexia	11 (19.0%)	4 (5.3%)	15 (11.3%)
Abdominal pain upper	9 (15.5%)	3 (4.0%)	12 (9.0%)

AE: Adverse Event; BID: twice daily; m: meter; MedDRA: Medical Dictionary of Regulatory Activities; mg: milligram; NF1: Neurofibromatosis Type 1; PN: Plexiform Neurofibroma; TEAE: Treatment-Emergent Adverse Event.

Each participant is counted only once within each system organ class and preferred term if they experience an AE with that system organ class and preferred term more than once.

Percentages are calculated using the number of participants in the corresponding cohort as the denominator.

Source: ADSL, ADAE

Adverse Drug Reactions

Adverse drug reactions (ADRs) for mirdametinib are defined as those AEs considered related to mirdametinib based on the assessment of numerical frequency data and review of individual case details such as temporal association of the event with administration of mirdametinib, dechallenge and rechallenge information, and confounding factors such as intercurrent illnesses and administration of concomitant medications which could be plausible alternative causes for the reported events. The presence of a description of a plausible mechanism by which MEK inhibition could lead to the reported event in the literature was also taken into account when considering if a reported event was an adverse reaction for mirdametinib.

Based on the totality of the data, AEs that are considered ADRs for mirdametinib in Study MEK-NF-201 and Pool 1 are presented in [Table 56](#) and [Table 57](#), respectively, which forms the basis for the ADR information included in the prescribing information.

The data described below reflect exposure to mirdametinib in participants with NF1 PN in Study MEK-NF-201 (N=114) or pooled across studies MEK-NF-201 and NF-106 in Pool 1 (N=133). Serious ADRs, permanent discontinuation of mirdametinib due to an ADR, dose interruptions due to ADRs and dose reductions due to ADRs are described below. Note that individual participants could have reported more than 1 event leading to a dose modification or dose modifications, or as reasons for treatment discontinuation.

Study MEK-NF-201

No serious ADRs occurred in pediatric participants who received mirdametinib. Serious ADRs occurred in 2 (3%) adult participants who received mirdametinib. Serious ADRs occurring in adult participants were RVO (1 [2%] participant) and abdominal pain (1 [2%] participant).

Permanent discontinuation of mirdametinib due to an ADR occurred in 3 (5%) pediatric participants. ADRs which resulted in permanent discontinuation of mirdametinib in pediatric participants were abdominal pain, constipation, dermatitis acneiform, diarrhea, and rash in 1 (2%) participant each. Permanent discontinuation of mirdametinib due to an ADR occurred in 12 (21%) adult participants. ADRs which resulted in permanent discontinuation of mirdametinib in adult participants were dermatitis acneiform (4 [7%] participants), diarrhea (4 [7%] participants), nausea (4 [7%] participants), and abdominal pain, alopecia, dry skin, ejection fraction decreased, rash, rash erythematous, RVO, and vomiting in 1 (2%) participant each.

Dose interruptions of mirdametinib due to an ADR occurred in 5 (9%) pediatric participants. ADRs which required dose interruption in pediatric participants included neutrophil count decreased (2 [4%] participants), and abdominal pain, blood CPK increased, diarrhea, and ejection fraction decreased in 1 (2%) participant each. Dose interruptions of mirdametinib due to an ADR occurred in 7 (12%) adult participants. ADRs which required dose interruption in adult participants included ejection fraction decreased (5 [9%] participants), and stomatitis and vomiting in 1 (2%) participant each.

Dose reductions of mirdametinib due to an ADR occurred in 7 (13%) pediatric participants. ADRs which required dose reduction in pediatric participants included neutrophil count decreased (3 [5%] participants), and abdominal pain upper, blood CPK increased, dermatitis acneiform, diarrhea, and rash in 1 (2%) participant each. Dose reductions of mirdametinib due to an ADR occurred in 10 (17%) adult participants. ADRs which required dose reduction in adult participants included dermatitis acneiform (6 [10%] participants), and blood CPK increased, constipation, ejection fraction decreased, and fatigue in 1 (2%) participant each.

Pool 1

No serious ADRs occurred in pediatric participants who received mirdametinib. Serious ADRs occurred in 3 (4%) adult participants who received mirdametinib. Serious ADRs occurring in adult participants were abdominal pain (2 [3%] participants) and RVO (1 [1%] participant).

Permanent discontinuation of mirdametinib due to an ADR occurred in 3 (5%) pediatric participants. ADRs which resulted in permanent discontinuation of mirdametinib in pediatric participants were abdominal pain, constipation, dermatitis acneiform, diarrhea, and rash in 1 (2%) participant each. Permanent discontinuation of mirdametinib due to an ADR occurred in 15 (20%) adult participants. ADRs which resulted in permanent discontinuation of mirdametinib in adult participants were dermatitis acneiform (6 [8%] participants), diarrhea (4 [5%] participants), nausea (4 [5%] participants), vomiting (2 [3%] participants), and abdominal pain, alopecia, dry skin, ejection fraction decreased, rash, rash erythematous, and RVO in 1 (1%) participant each.

Dose interruptions of mirdametinib due to an ADR occurred in 5 (9%) pediatric participants. ADRs which required dose interruption in pediatric participants included neutrophil count decreased (2 [3%] participants), and abdominal pain, blood CPK increased, diarrhea, and ejection fraction decreased in 1 (2%) participant each. Dose interruptions of mirdametinib due to an ADR occurred in 9 (12%) adult participants. ADRs which required dose interruption in adult participants included ejection fraction decreased (5 [7%] participants), dermatitis acneiform (2 [3%] participants), and rash pustular, stomatitis, and vomiting in 1 (1%) participant each.

Dose reductions of mirdametinib due to an ADR occurred in 7 (12%) pediatric participants. ADRs which required dose reduction in pediatric participants included neutrophil count decreased (3 [5%] participants), and abdominal pain upper, blood CPK increased, dermatitis acneiform, diarrhea, and rash in 1 (2%) participant each. Dose reductions of mirdametinib due to an ADR occurred in 15 (20%) adult participants. ADRs which required dose reduction in adult participants included dermatitis acneiform (8 [11%] participants), fatigue (2 [3%] participants), and abdominal pain, blood CPK increased, constipation, ejection fraction decreased, and nausea in 1 (1%) participant each.

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Table 57: Adverse Reactions Reported for Mirdametinib in Study MEK-NF-201 (N=114)

System Organ Class Preferred Term	Pediatric N=56		Adult N=58		Total N=114	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Skin and Subcutaneous Tissue Disorders						
Dermatitis acneiform	24 (42.9%)	1 (1.8%)	45 (77.6%)	5 (8.6%)	69 (60.5%)	6 (5.3%)
Rash ^a	19 (33.9%)	1 (1.8%)	10 (17.2%)	1 (1.7%)	29 (25.4%)	2 (1.8%)
Dry Skin	10 (17.9%)	0	9 (15.5%)	0	19 (16.7%)	0
Alopecia	8 (14.3%)	0	7 (12.1%)	0	15 (13.2%)	0
Pruritus	7 (12.5%)	0	7 (12.1%)	0	14 (12.3%)	0
Eczema	8 (14.3%)	0	2 (3.4%)	0	10 (8.8%)	0
Hair colour changes	7 (12.5%)	0	1 (1.7%)	0	8 (7.0%)	0
Hair texture abnormal	3 (5.4%)	0	1 (1.7%)	0	4 (3.5%)	0
Gastrointestinal Disorders						
Diarrhoea	31 (55.4%)	3 (5.4%)	34 (58.6%)	0	65 (57.0%)	3 (2.6%)
Nausea	15 (26.8%)	0	30 (51.7%)	0	45 (39.5%)	0
Vomiting	22 (39.3%)	0	22 (37.9%)	0	44 (38.6%)	0
Abdominal pain ^b	22 (39.3%)	2 (3.6%)	13 (22.4%)	2 (3.4%)	35 (30.7%)	4 (3.5%)
Constipation	6 (10.7%)	0	9 (15.5%)	0	15 (13.2%)	0
Stomatitis ^c	11 (19.6%)	0	3 (5.2%)	0	14 (12.3%)	0
General Disorders and Administration Site Conditions						
Fatigue	7 (12.5%)	0	17 (29.3%)	1 (1.7%)	24 (21.1%)	1 (0.9%)

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System Organ Class Preferred Term	Pediatric N=56		Adult N=58		Total N=114	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Infections and Infestations						
Paronychia	18 (32.1%)	0	1 (1.7%)	0	19 (16.7%)	0
Eye Disorders						
Retinal vein occlusion	0	0	2 (3.4%)	1 (1.7%)	2 (1.8%)	1 (0.9%)

a Rash includes Rash, Rash maculo-papular, Rash pustular, Rash erythematous, Rash papular, Exfoliative rash, Papule, Rash macular, Rash pruritic

b Abdominal pain includes abdominal pain and abdominal pain upper

c Stomatitis includes stomatitis, mouth ulceration, aphthous ulcer

Source: ADSL, ADAE

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Mirdametinib (GOMEKLI)

Table 58: Adverse Reactions Reported for Mirdametinib in Pool 1 (N=133)

System Organ Class Preferred Term	Pediatric NF1 PN 2 mg/m ² BID N=58		Adult NF1 PN 2 mg/m ² BID N=75		Total NF1 PN 2 mg/m ² BID N=133	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Skin and Subcutaneous Tissue Disorders						
Dermatitis acneiform	25 (43.1%)	1 (1.7%)	62 (82.7%)	5 (6.7%)	87 (65.4%)	6 (4.5%)
Rash ^a	19 (32.8%)	1 (1.7%)	13 (17.3%)	1 (1.3%)	32 (24.1%)	2 (1.5%)
Dry Skin	10 (17.2%)	0	10 (13.3%)	0	20 (15.0%)	0
Alopecia	8 (13.8%)	0	9 (12.0%)	0	17 (12.8%)	0
Pruritus	7 (12.1%)	0	10 (13.3%)	0	17 (12.8%)	0
Eczema	8 (13.8%)	0	2 (2.7%)	0	10 (7.5%)	0
Hair colour changes	7 (12.1%)	0	1 (1.3%)	0	8 (6.0%)	0
Hair texture abnormal	3 (5.2%)	0	1 (1.3%)	0	4 (3.0%)	0
Gastrointestinal Disorders						
Diarrhoea	31 (53.4%)	3 (5.2%)	41 (54.7%)	0	72 (54.1%)	3 (2.3%)
Nausea	17 (29.3%)	0	41 (54.7%)	0	58 (43.6%)	0
Vomiting	23 (39.7%)	0	28 (37.3%)	0	51 (38.3%)	0
Abdominal pain ^b	23 (39.7%)	2 (3.4%)	15 (20.0%)	3 (4.0%)	38 (28.6%)	5 (3.8%)
Constipation	6 (10.3%)	0	14 (18.7%)	0	20 (15.0%)	0

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System Organ Class Preferred Term	Pediatric NF1 PN 2 mg/m ² BID N=58		Adult NF1 PN 2 mg/m ² BID N=75		Total NF1 PN 2 mg/m ² BID N=133	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Stomatitis ^c	11 (19.0%)	0	4 (5.3%)	0	15 (11.3%)	0
General Disorders and Administration Site Conditions						
Fatigue	7 (12.1%)	0	27 (36.0%)	1 (1.3%)	34 (25.6%)	1 (0.8%)
Infections and Infestations						
Paronychia	19 (32.8%)	0	2 (2.7%)	0	21 (15.8%)	0
Eye Disorders						
Retinal vein occlusion	0	0	2 (2.7%)	1 (1.3%)	2 (1.5%)	1 (0.8%)

AE: Adverse event; MedDRA: Medical Dictionary of Regulatory Activities; PT: Preferred Term; TEAE: Treatment-Emergent Adverse Event.

Each participant is counted only once within each preferred term if they experience an AE with that preferred term more than once.

Percentages are calculated using the number of participants in the corresponding cohort as the denominator.

a Rash includes Rash, Rash maculo-papular, Rash pustular, Rash erythematous, Rash papular, Exfoliative rash, Papule, Rash macular, Rash pruritic PTs

b Abdominal pain includes abdominal pain and abdominal pain upper PTs

c Stomatitis includes stomatitis, mouth ulceration, aphthous ulcer PTs.

Source: ADSL, ADAE

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Mirdametinib (GOMEKLI)

Table 59: Select Laboratory Abnormalities Worsening from Baseline in Study MEK-NF-201

System Organ Class Preferred Term	Pediatric N=56		Adult N=58		Total N=114	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Chemistry						
Increased blood creatinine phosphokinase	33 (58.9%)	3 (5.4%)	31 (53.4%)	2 (3.4%)	64 (56.1%)	5 (4.4%)
Increased AST	5 (8.9%)	0	10 (17.2%)	0	15 (13.2%)	0
Increased ALT	12 (21.4%)	0	5 (8.6%)	0	17 (14.9%)	0
Increased blood alkaline phosphatase	16 (28.6%)	0	7 (12.1%)	0	23 (20.2%)	0
Hematology						
Decreased neutrophils	17 (30.4%)	6 (10.7%)	4 (6.9%)	0	21 (18.4%)	6 (5.3%)
Echocardiography						
Decreased ejection fraction	15 (26.8%)	1 (1.8%)	10 (17.2%)	0	25 (21.9%)	1 (0.9%)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; NCI-CTCAE: National Cancer Institute – Common Terminology Criteria for Adverse Events.
Source: ADSL, ADLB, ADCV

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Table 60: Select Laboratory Abnormalities Worsening from Baseline in Pool 1

System Organ Class Preferred Term	Pediatric NF1 PN 2 mg/m ² BID N=58		Adult NF1 PN 2 mg/m ² BID N=75		Total NF1 PN 2 mg/m ² BID N=133	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Chemistry						
Increased blood creatinine phosphokinase	34 (58.6%)	3 (5.2%)	34 (45.3%)	2 (2.7%)	68 (51.1%)	5 (3.8%)
Increased AST	5 (8.6%)	0	12 (16.0%)	0	17 (12.8%)	0
Increased ALT	12 (20.7%)	0	5 (6.7%)	0	17 (12.8%)	0
Increased blood alkaline phosphatase	16 (27.6%)	0	10 (13.3%)	0	26 (19.5%)	0
Hematology						
Decreased neutrophils	17 (29.3%)	6 (10.3%)	6 (8.0%)	1 (1.3%)	23 (17.3%)	7 (5.3%)
Echocardiography						
Decreased ejection fraction	15 (25.9%)	1 (1.7%)	10 (13.3%)	0	25 (18.8%)	1 (0.8%)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; NCI-CTCAE: National Cancer Institute – Common Terminology Criteria for Adverse Events.

Source: ADSL, ADLB, ADCV

The Applicant's Position:

The overall TEAE profile in Pool 1 was similar to what was observed in Study MEK-NF-201. Overall, the TEAE profile between the pediatric and adult cohorts of Pool 1 was similar. There were more participants in the adult cohort that reported TEAEs that led to study discontinuation (12 [16%] participants in the adult cohort vs 4 (7%) participants in the pediatric cohort) and treatment discontinuation (16 [21%] participants in the adult cohort vs 5 [9%] participants in the pediatric cohort).

Overall, the incidence of TEAEs in Pool 1 was similar to what was seen in the pivotal study, MEK-NF-201. The most frequently (>35%) reported TEAEs for the total population from Study MEK-NF-201 and Pool 1 were dermatitis acneiform, diarrhea, nausea, and vomiting. The most frequently reported PTs were expected with MEK inhibition ([Subbiah 2020](#), [Solares 2021](#)).

The following events are recognized as risks for patients with NF1 PN treated with mirdametininib 2 mg/m² BID:

- The following events were recognized as identified risks because of the frequency of their reports, temporal relationship to the start of treatment with mirdametininib, and presence of a plausible biologic mechanism, and were deemed important due to their potential impact on patients: ejection fraction decreased and retinal vein occlusion. Given their importance, these risks are recommended for inclusion in Warnings and Precautions.
- The following events were reported at an increased incidence relative to that anticipated for the patient population with NF1 PN and are recognized as non-important identified risks as these events were generally Grade 1 or 2 and did not frequently result in the discontinuation of study treatment: diarrhea, nausea, vomiting, abdominal pain, constipation, skin events (including dermatitis acneiform, rash, pruritus, dry skin, alopecia, hair color changes, and hair texture), blood CPK increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, and fatigue.
 - While dermatitis acneiform and rash are considered non-important identified risks, they are proposed for inclusion in the Warnings and Precautions due to recommended dose modifications for severe events.
- The data presented support recognizing stomatitis as a non-important identified risk for mirdametininib in the pediatric population and as a non-important potential risk in the adult population.
- The data presented support recognizing paronychia, eczema, and neutrophil count decreased, as non-important identified risks for mirdametininib in the pediatric population.
- Given the low frequency and severity of events, the data support vision blurred and detachment of retinal pigment epithelium being recognized as important potential risks. Given their importance, these risks are recommended for inclusion in Warnings and

Precautions.

The FDA's Assessment:

The safety databases for Pool 1 and the ReNeu study were analyzed at each level of the MedDRA hierarchy for TEAEs. TEAEs are defined as AEs that occurred from the time of the first dose up to 30 days after the last dose of mirdametininb or the data cutoff date if that date was earlier. All patients in the adult and pediatric population that were exposed to mirdametininb had at least one AE during treatment. FDA's analysis of adverse events in Pool 1 and the ReNeu study did not consider relatedness as part of the safety review.

Table 60 represents the most frequent AEs ($\geq 20\%$) observed in the ReNeu study. The most common adverse reactions ($>25\%$) in the adult population were rash, diarrhea, nausea, musculoskeletal pain, vomiting, and fatigue. The most common adverse reactions ($>25\%$) in the pediatric population were rash, diarrhea, musculoskeletal pain, abdominal pain, vomiting, headache, paronychia, left ventricular dysfunction, and nausea.

Table 61: Adverse Events ($\geq 20\%$) in Adult and Pediatric Patients with NF1-Associated PN Who Received Mirdametininb in ReNeu.

	Adult N=58		Pediatric N=56		Total N=114	
	All Grades (%)	Grade 3 or 4 ^a (%)	All Grades (%)	Grade 3 or 4 ^a (%)	All Grades (%)	Grade 3 or 4 ^a (%)
Skin and Subcutaneous Tissue Disorders						
Rash ^b	90	10	73	3.6	82	7
Gastrointestinal Disorders						
Diarrhea ^c	59	0	55	5	57	2.6
Nausea	52	0	27	0	40	0
Vomiting	38	0	39	0	39	0
Abdominal Pain ^d	24	3.4	39	3.6	32	3.5
Stomatitis ^e	5	0	20	0	12	0
Musculoskeletal and Connective Tissue Disorders						
Musculoskeletal Pain ^f	41	5	41	1.8	41	3.5

	Adult N=58		Pediatric N=56		Total N=114	
	All Grades (%)	Grade 3 or 4 ^a (%)	All Grades (%)	Grade 3 or 4 ^a (%)	All Grades (%)	Grade 3 or 4 ^a (%)
Infections and Infestations						
COVID-19 ^a	22	5	25	0	24	2.6
Paronychia	1.7	0	32	0	17	0
Upper Respiratory Tract Infection	0	0	23	0	11	0
Nervous System Disorders						
Headache ^g	14	1.7	34	1.8	24	1.8
Peripheral Neuropathy ^h	21	0	3.6	0	12	0
General Disorders and Administration Site Conditions						
Fatigue	29	1.7	13	0	21	0.9
Pyrexia	7	0	20	0	13	0
Cardiac Disorders						
Left Ventricular Dysfunction	16	0	27	1.8	21	0.9
Respiratory, Thoracic and Mediastinal Disorders						
Cough ⁱ	9	0	21	0	15	0

^aAll reactions were Grade 3 except one fatal case of Covid-19 in an adult.

^bRash includes dermatitis acneiform, eczema, maculo-papular rash, pustular rash, dermatitis, erythematous rash, palmar-plantar erythrodysesthesia syndrome, exfoliative rash, skin exfoliation, pruritic rash, papule, papular rash and macular rash.

^cDiarrhea includes frequent bowel movements.

^dAbdominal pain includes upper abdominal pain, gastrointestinal pain and abdominal discomfort

^eStomatitis includes mouth ulceration, aphthous ulcer.

^fMusculoskeletal pain includes non-cardiac chest pain, back pain, pain in extremity, neck pain, musculoskeletal chest pain, myalgia, arthralgia, and bone pain

^gHeadache includes migraine.

^hPeripheral neuropathy includes paresthesia, hypoesthesia, neuralgia, peripheral sensory neuropathy.

ⁱCough includes upper-airway cough syndrome.

Laboratory Findings

Data:

Refer to [Table 58](#) and [Table 59](#).

The Applicant's Position:

The data supports recognizing blood CPK increased, AST increased, ALT increased, and blood alkaline phosphatase increased as non-important identified risks for mirdametinib, neutrophil count decreased as a non-important identified risk for pediatric patients receiving mirdametinib, and ejection fraction decreased as an important identified risk for mirdametinib. Of these identified risks, only ejection fraction decreased is assessed as being an important identified risk and is therefore proposed for inclusion in Warnings and Precautions. While the measured decreases in ejection fraction were asymptomatic in study participants, the potential clinical impact of an undetected decrease in ejection fraction is not known, hence this risk is considered important. Blood CPK increased is considered a non-important identified risk in view of the lack of reports of serious events, including no reports of rhabdomyolysis. AST and ALT increased are considered non-important identified risks due to the infrequency of Grade 3 shifts and dose modifications. Blood alkaline phosphatase is considered a non-important identified risk due to the absence of correlation with other markers of liver injury in Pool 1. Neutrophil count decreased is recognized as a non-important identified risk for mirdametinib in pediatric participants only given the infrequent reporting of the event in the adult cohort, and the absence of risks of opportunistic infections to participants reporting or observed to have decreased neutrophils.

The FDA's Assessment:

Laboratory tests to assess hematology and chemistries parameters were measured at baseline, followed by Day 15 during every Cycle. The reported percentages were calculated using the number of patients with baseline and post-baseline results for each respective parameter. Table 50 summarizes the common laboratory abnormalities for adult and pediatric patients with NF1-associated PN receiving mirdametinib in the ReNeu study. The most common Grade 3 or 4 laboratory abnormality (>2%) in the adult population was increased creatine phosphokinase. The most common Grade 3 or 4 laboratory abnormalities (>2%) in the pediatric population were decreased neutrophil count and increased creatine phosphokinase.

Table 62: Select Laboratory Abnormalities (≥15%) that Worsened from Baseline in Adult and Pediatric Patients with NF1-Associated PN Who Received Mirdametinib in ReNeu.

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	Adult ^a		Pediatric ^b		Total ^c	
Laboratory Abnormality ^{d,e}	All Grades (%)	Grade 3 or 4 ^d (%)	All Grades (%)	Grade 3 or 4 ^d (%)	All Grades (%)	Grade 3 or 4 ^d (%)
Chemistry						
Increased Creatine Phosphokinase	55	3.6	59	5	57	4.5
Increased Triglycerides	29	0	45	0	37	0
Decreased Glucose	5	0	36	1.8	21	0.9
Decreased Calcium ^f	23	0	20	0	21	0
Increased Creatinine	13	0	30	0	21	0
Increased Cholesterol	23	0	16	0	20	0
Increased Alkaline Phosphatase	13	0	29	0	21	0
Decreased Bicarbonate	11	0	21	0	16	0
Increased Alanine Aminotransferase (ALT)	9	0	21	0	15	0
Increased Aspartate Aminotransferase (AST)	18	0	9	0	13	0
Hematology						
Decreased Hemoglobin	21	0	29	0	25	0
Decreased Leukocytes	7	0	40	0	23	0
Decreased Neutrophils	7	0	31	11	19	5

	Adult ^a		Pediatric ^b		Total ^c	
Laboratory Abnormality ^{d,e}	All Grades (%)	Grade 3 or 4 ^d (%)	All Grades (%)	Grade 3 or 4 ^d (%)	All Grades (%)	Grade 3 or 4 ^d (%)
Increased Lymphocytes	7	0	27	0	17	0
Decreased Lymphocytes	16	0	1.8	0	9	0

^a The denominator used to calculate the rate was 56 based on the number of patients with a baseline value and at least one post-treatment value.

^b The denominator used to calculate the rate varied from 55 to 56 based on the number of patients with a baseline value and at least one post-treatment value.

^c The denominator used to calculate the rate varied from 111 to 112 based on the number of patients with a baseline value and at least one post-treatment value.

^d Graded per NCI-CTCAE version 5.0.

^e No Grade 5 laboratory abnormalities were reported in the ReNeu study.

^f Calcium corrected for albumin (mmol/L).

Vital Signs and Physical Examinations

Data:

Clinically significant findings from physical examinations were reported as TEAEs.

Clinically significant changes in vital sign findings in Pool 1, excluding those associated with the 6-min walk test, are presented in [Table 45](#) below. Qualifying vital signs in this table were based on an assessment taken at any timepoint throughout the duration of the study, and not necessarily a change from baseline at the end of study.

Table 63: Clinically Significant Changes in Vital Signs for Participants who Received Mirdametinib in Pool 1 Excluding Values Flagged as Taken with 6-min Walk Test

	Pediatric NF1 PN 2 mg/m ² BID Age 2-<12 years (N=32)	Pediatric NF1 PN 2 mg/m ² BID Age 12-<18 years (N=26)	Adult NF1 PN 2 mg/m ² BID Age ≥18 (N=75)
Systolic Blood Pressure			
Increase of ≥20 mmHg	0	10 (38.5%)	18 (24.0%)

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	Pediatric NF1 PN 2 mg/m² BID Age 2-<12 years (N=32)	Pediatric NF1 PN 2 mg/m² BID Age 12-<18 years (N=26)	Adult NF1 PN 2 mg/m² BID Age ≥18 (N=75)
Post-Baseline Value >150 mmHg	0	1 (3.8%)	6 (8.0%)
Increase of ≥20 mmHg and a Post-Baseline Value >150 mmHg	0	1 (3.8%)	5 (6.7%)
Decrease of ≥20 mmHg	0	3 (11.5%)	21 (28.0%)
Post-Baseline Value <90 mmHg	0	0	1 (1.3%)
Decrease of ≥20 mmHg and a Post-Baseline Value <90 mmHg	0	0	1 (1.3%)
Post-Baseline Value >130 mmHg	4 (12.5%)	0	0
Decrease of ≥20 mmHg	4 (12.5%)	0	0
Diastolic Blood Pressure			
Increase of ≥10 mmHg	0	17 (65.4%)	42 (56.0%)
Post-Baseline Value >95 mmHg	0	0	11 (14.7%)
Increase ≥10 mmHg and a Post-Baseline Value >95 mmHg	0	0	9 (12.0%)
Decrease ≥10 mmHg	0	10 (38.5%)	26 (34.7%)
Post-Baseline Value <60 mmHg	0	15 (57.7%)	19 (25.3%)
Decrease ≥10 mmHg or greater and a Post-Baseline Value <60 mmHg	0	7 (26.9%)	13 (17.3%)
Post-Baseline Value >80 mmHg	8 (25.0%)	0	0
Decrease of ≥10 mmHg	18 (56.3%)	0	0
Heart Rate			
Increase ≥20 bpm	0	10 (38.5%)	22 (29.3%)
Post-Baseline Value ≥110 bpm	0	3 (11.5%)	11 (14.7%)
Increase of ≥20 bpm and Post-Baseline Value ≥110 bpm or more	0	2 (7.7%)	6 (8.0%)
Decrease ≥20 bpm or more	0	6 (23.1%)	15 (20.0%)
Post-Baseline Value ≤50 bpm	0	0	1 (1.3%)
Decrease of ≥20 bpm and Post-Baseline Value ≤50 bpm	0	0	0
Heart Rate >120 bpm	11 (34.4%)	0	0

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BID: Twice Daily; bpm: beats per minute; mmHg: millimeters of mercury; NF1: Neurofibromatosis Type 1;
PN: Plexiform Neurofibromas.

Percentages are calculated using the number of participants in each cohort as the denominator.

Source: ADSL, ADVS

The Applicant's Position:

The overall data suggests that changes in vital signs during treatment with mirdametininib is likely attributable to normal variability and fluctuations and does not support recognizing any changes in vital signs as an identified risk for mirdametininib.

The FDA's Assessment:

Vital signs were collected at baseline and then once every Cycle until Cycle 7 followed by every other cycle. In Pool 1, the adult cohort had 7 (9%) patients with Grades 1 and 2 hypertension and 1 (1.3%) patient with Grade 3 hypertension. Four patients (7%) in the pediatric cohort had Grade 2 hypertension; one event was captured as a serious adverse event and is included in the USPI. The event of hypertension occurred ≥ 1 year from the first study treatment administration and was assessed as not related to mirdametininib. FDA agrees that that changes in vital sign were likely consistent with normal variability and generally not a safety concern.

Electrocardiograms (ECGs)

Data:

ECG parameters were not collected in Study NF-106 and therefore observations concerning ECGs came from Study MEK-NF-201 only.

In Study MEK-NF-201, in the pediatric cohort, there were no major changes observed in ECG parameters. In the adult cohort, several participants had QTcF between 450 and 480 msec throughout the study and 1 participant had a QTcF >480 msec on Cycle 5 Day 15. One TEAE of Grade 1 electrocardiogram QT prolonged was reported; this participant did not report a QTcF >450 msec. There were no major changes observed in other ECG parameters.

There were no major changes observed in ECG parameters in Pool 2.

The Applicant's Position:

Mirdametininib did not appear to have clinically meaningful adverse effects on ECG values during any study.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

QT

Data:

A thorough QT/QTc study to evaluate the effect of mirdametinib and metabolite exposures on cardiac repolarization in healthy participants (MEK-NF-102) was conducted. In that study, the relationship between mirdametinib concentration and QTcF was successfully characterized using a pre-specified linear mixed-effects model. No clinically significant effects of both mirdametinib 6 and 14mg doses (approximately 2x and 6x the therapeutic exposure of mirdametinib, respectively) were observed on the ECG.

Additionally, a search of the MedDRA Standardized MedDRA Queries “Torsades de pointes/QT prolongation” plus the PT of seizure in the pooled clinical safety data was conducted. Five pediatric and 5 adult participants with NF1 PN in Pool 1 were identified. All participants were receiving mirdametinib 2 mg/m² BID, with a maximum total daily dose of 4 mg BID. In Pool 1, 1 adult participant reported a non-serious TEAE of ECG QT prolonged. This participant had an average baseline QTcF of 367.1 msec. On C1D15, their average QTcF was 404.92 msec, representing an increase of 37.82 msec, when the event of electrocardiogram QT prolonged was reported. The event resolved with the next triplicate ECG during the C2D15 visit (Day 42), when the average QTcF was 369.17 msec. No events of torsades de pointes were reported.

In Pool 1, 2 pediatric and 2 adult participants reported TEAEs of seizure, including 1 serious event in a pediatric participant. All 4 participants experiencing seizure had confounding medical history, including seizure, epilepsy, complex partial seizures, or ongoing long-term use of levetiracetam and clonazepam.

All other TEAEs from Pool 1 were non-serious; these included: 3 pediatric participants and 1 adult participant reporting events of syncope and 1 adult participant reporting an event of electrocardiogram repolarization abnormality. All events of syncope were assessed as not related to study treatment. One participant interrupted study treatment due to syncope; no other participants modified study treatment as a result of syncope events. One participant reported a related event of electrocardiogram repolarization abnormality on Day 15. The event resolved with the next triplicate ECG on Day 42 with no change to study treatment.

In Pool 2, 10 adult participants with advanced cancers were identified with MedDRA PTs under the Standardized MedDRA Queries for “Torsades de pointes/QT prolongation” plus the PT of seizure. All events in Pool 2 occurred in participants receiving doses of mirdametinib ≥8mg BID, which is twice the upper limit evaluated in participants with NF1 PN in Pool 1. However, this may have occurred because of the small number of participants in Pool 2 receiving mirdametinib doses ≤4mg BID (n = 16 versus n = 97), combined with the participants’ advanced, often metastatic, cancers.

In Pool 2, 1 participant reported a non-serious TEAE of electrocardiogram QT prolonged. This participant’s triplicate QTcF readings at screening were 427, 422, and 431 msec. On Day 1, their triplicate QTcF readings were 424, 423, and 431 msec. On Day 8, when the event was reported, the triplicate QTcF readings were 420, 427, and 423 msec. The event was assessed as related

and not resolved as of the end of study treatment. No other ECG reports are available for this participant. No events of torsades de pointes were reported.

Four participants reported TEAEs of syncope, including 1 participant who also reported cardiac arrest, loss of consciousness, ventricular fibrillation, and ventricular tachycardia. This participant died, with the cause of death noted as myocardial infarction, cerebrovascular accident, and cerebral disorder. This participant's event of syncope which occurred and resolved on Day 41 resulted in dose interruption. The event of myocardial infarction resulted in study drug discontinuation. All other events (cardiac arrest, loss of consciousness, ventricular fibrillation, and ventricular tachycardia) occurred following discontinuation of study treatment and in the context of the participant's myocardial infarction. Importantly, this participant was found to have a total occlusion of the left anterior descending artery, which was assessed as not related to study treatment.

One additional participant reported cardiac arrest assessed as not related to study treatment. This participant's cause of death was listed as cancer and cardio-respiratory arrest due to disease progression from their metastatic breast cancer.

One additional participant reported loss of consciousness on Day 4, 1 day after the TEAE of renal failure and 3 days after the TEAE of hypoxia, both of which resulted in study drug discontinuation. The participant died on Day 5 with cause of death cited as hypoxia, disease progression, and renal failure. None of these events were assessed as related to study treatment.

Two participants reported serious TEAEs of seizure. Both events were assessed as not related to study treatment. One participant interrupted study treatment as a result of the event. The second participant did not modify study treatment as a result of the event; this participant subsequently died, with cause of death listed as disease progression due to malignant melanoma.

One participant reported a TEAE of electrocardiogram repolarization abnormality resulting in discontinuation from the study. Of note, this participant was found to have a T-wave abnormality noted on the first of their triplicate baseline ECGs. This finding was then noted on their triplicate ECGs on Day 1, along with non-specific ST-T changes, when the event was reported. It was assessed as related to study treatment and study treatment was discontinued.

The Applicant's Position:

In the thorough QT/QTc study, mirdametinib had no effect on QTc at doses of 6 and 14mg, which resulted in approximately 2x and 6x the therapeutic exposures, respectively.

An analysis of the pooled clinical safety data demonstrated that mirdametinib has not been shown to cause QT prolongation or Torsade de pointes. In addition, no death or discontinuations were reported due to QT prolongation events.

The FDA's Assessment:

FDA agrees with the Applicant's assessment that mirdametinib had no effect on QTc interval.

Immunogenicity

The Applicant's Position:

Mirdametinib is a small molecule and not expected to elicit an immune response.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

8.2.5. Analysis of Submission-Specific Safety Issues

The adverse events of special interest (AESIs) defined in the pivotal Study MEK-NF-201 included AEs of Grade ≥ 3 for the following PTs: diarrhea, nausea, vomiting, rash, and acneiform rash. AEs of Grade ≥ 2 for the following PTs were also considered AESIs: RVO, uveitis, optic neuropathy, retinopathy, retinal detachment, ejection fraction decreased, cardiac failure, left ventricular dysfunction, confusion, hallucinations, and delirium.

To account for legacy studies in which no AESIs were prospectively identified per the protocol, safety topics of interest, which include the AESIs for MEK-NF-201 and other events that emerged upon review of the data across studies including events from Pool 2 and the Global Pharmacovigilance database were analyzed. Important identified risks for mirdametinib included the following topics: Ocular effects: retinal vein occlusion and Cardiac effects: ejection fraction decreased.

8.2.5.1. Retinal Vein Occlusion

Data:

In Pool 1, RVO occurred in 2 (3%) adult participants, both from Study MEK-NF-201. One participant reported a SAE of RVO while the other participant was observed to have 2 non-serious asymptomatic Grade 1 RVO events, 1 in each eye occurring approximately 1 year apart. These non-serious events were identified via routine monitoring. No events of RVO have been observed in pediatric participants in Pool 1.

In Pool 2, RVO occurred in 3 (3%) participants, all of which were serious. Of the 3 participants, 2 (9%) were in the 8, 10 mg BID dose group, while 1 (1%) participant was treated with mirdametinib 15 mg BID.

An analysis of all participants with RVO in Pools 1 and 2 showed that all participants reported at least 1 predisposing factor for RVO, including hypertension, diabetes, hypercholesterolemia, COVID-19 vaccination, and advanced cancer, as well as concomitant medications. However, the role of mirdametinib cannot be excluded (Li 2023).

The microvascular abnormalities associated with NF1 may make this patient population susceptible to RVO (Moadel 1994; Mori 2001). RVO has been described in clinical trials of MEK inhibitors (Méndez-Martínez 2019). MEK inhibitors may block antiapoptotic proteins, block natural retinal reactions to stress or oxidative injury, and prevent the repair of damaged retinal pigment epithelial cells, ultimately leading to the accumulation of damage and the degeneration of cells (van der Noll 2013). It has been shown that asymptomatic retinal changes may be present in a large percentage of MEK inhibitor treated patients (van Dijk 2018) and ocular toxicities with MEK inhibitors appear to be a class effect that is generally transient in nature (Leijen 2012; LoRusso 201; van der Noll 2013; van Dijk 2018). Dose and dosing schedules may be important factors for the risk of RVO in patients treated with MEK inhibitors (van derNoll 2013). Individual characteristics that have not been fully characterized likely also contribute to the risk for RVO.

The Applicant's Position:

The available data, along with a plausible mechanism associated with MEK inhibition, support recognizing RVO as an important identified risk for mirdametinib, and therefore proposed for inclusion in the Warnings and Precautions of the label, though it should be noted that events in patients with NF1 PN may be confounded by the microvascular abnormalities associated with NF1 (Moadel 1994, Mori 2001).

The FDA's Assessment:

The FDA agrees with the Applicant's incidence rates for retinal and visual AEs in Pool 1. In the pooled safety population, ocular toxicity occurred in 25% of patients treated with mirdametinib; of these 20% were Grade 1, 3.8% were Grade 2, and 0.8% were Grade 3. In the adult pooled safety population, ocular toxicity occurred in 28% of patients treated with mirdametinib, of these 21% were Grade 1, 5% were Grade 2, and 1.3% were Grade 3. RVO occurred in 2.7% of adult patients including one Grade 3 case which required permanent discontinuation; a narrative is provided below. Retinal pigment epithelium detachment (RPED) occurred in one adult (1.3%) and blurred vision occurred in 9% of adult patients.

Patient narrative for the SAE of RVO: 26-year-old female with Grade 3 RVO on Day 130. Posterior segment/fundus imaging showed 360-degree Grade 2 edema of the right optic nerve with blurring of disc margins, tortuous temporal artery occlusion that extended from the optic nerve head (ONH) until the superior region of the macula, and nasal branch retinal vein occlusion; scattered hemorrhages throughout the posterior pole of the eye and midperiphery of the right retina due to the event of RVO. Treatment was discontinued on Day 129 in

response to the event. The event of RVO resolved with sequelae reported as “fuzzy vision.”

In the pediatric pooled safety population, ocular toxicity occurred in 19% of patients treated with mirdametinib. Of these, 17% were Grade 1 and 1.7% were Grade 2. Blurred vision occurred in 7% of patients.

While serious toxicities such as RVO and RPED occurred in the adult population, there is no evidence that pediatric patients have a lower risk for MEK-associated retinal AEs than adult patients.

Ocular toxicity will be included in the Warnings and Precautions section of the USPI.

8.2.5.2. Ejection Fraction Decreased

Data:

In Study MEK-NF-201, 20 events of ejection fraction decreased were observed in 15 (27%) pediatric participants. One participant had a Grade 3 event, and all other participants had Grade 2 events. Of note, there is no Grade 1 ejection fraction decreased per CTCAE v5.0 criteria. One pediatric participant (2%) had one event of ejection fraction decreased that led to dose interruption of mirdametinib. No pediatric participants had events of ejection fraction decreased that led to dose reduction or discontinuation of mirdametinib. Fourteen (25%) participants had resolution of events; 5 (9%) of these participants had recurrence of events which were not resolved as of the data cut.

In Study MEK-NF-201, 13 events of ejection fraction decreased were observed in 9 (16%) adult participants. No adult participants had Grade ≥ 3 events. Five (9%) participants had events of ejection fraction decreased that led to treatment interruption. One (2%) participant each had an event of ejection fraction decreased that led to dose reduction or treatment discontinuation.

In Pool 2, while baseline values are available from all participants receiving doses of mirdametinib ranging from 1 mg QD to 10 mg BID, there are no subsequent on-treatment ejection fraction values reported in these participants. Five (22%) participants receiving mirdametinib at 8, 10 mg BID had an event of ejection fraction decreased. Five (7%) participants receiving mirdametinib at 15, 20, 30 mg BID had events of ejection fraction decreased. In total, events of ejection fraction decreased were less frequently reported in Pool 2 (10 [8%]) than in Pool 1 (24 [18%]), suggesting that there is not a dose response observed with mirdametinib and ejection fraction decreased. While the events were only reported in mirdametinib doses ≥ 8 mg BID in Pool 2, this may have occurred due to the limited numbers of participants receiving mirdametinib doses ≤ 4 mg BID coupled with a lack of on-treatment evaluations. Ejection fraction data is limited from Pool 2; the infrequent reporting of clinically meaningful ejection fraction decreases, the lack of serious events, and infrequent dose

interruption or discontinuation suggest that these events in Pool 2 are similar to those observed in Pool 1.

The Applicant's Position:

Ejection fraction decreased is recognized as an identified risk for mirdametinib and therefore proposed for inclusion in the Warnings and Precautions section of the label. While the measured decreases in ejection fraction were asymptomatic in the study participants, the potential clinical impact of an undetected decrease in ejection fraction is not known, hence this risk is considered important.

The FDA's Assessment:

The FDA agrees with the Applicant's summary of data for events of decreased ejection fraction in Pool 1; all events observed were from the ReNeu study as echocardiograms were not routinely obtained in Study NF-106. In the ReNeu study, decreased LVEF of 10 to <20% occurred in 20% of patients and decreased LVEF of $\geq 20\%$ occurred in 0.9% of patients treated with mirdametinib. All patients with events of decreased LVEF were identified during routine echocardiography and these events resolved in 75% of these patients. Per NCI CTCAE Version 5, severity grading for "decreased LVEF" begins with Grade 2, defined as a reduction of 10 to <20% from baseline.

In adult patients in the ReNeu study, decreased LVEF of 10 to <20% occurred in 16% of adult patients. Of the adult patients with decreased LVEF, five patients (9%) required dose interruption, one patient (1.7%) required a dose reduction and one patient required permanent discontinuation of mirdametinib. All 7 patients who required dose interruption, dose reduction and discontinuation of mirdametinib, recovered from event of decreased LVEF. The median time to first onset of decreased LVEF in adult patients was 70 days.

In pediatric patients in the ReNeu study, decreased LVEF of 10 to <20% occurred in 25% of patients, and decreased LVEF of $\geq 20\%$ occurred in 1.8% of patients treated with mirdametinib. Of the pediatric patients with decreased LVEF, one patient (1.8%) required dose interruption of mirdametinib, after which the event resolved. The median time to first onset of decreased LVEF in pediatric patients was 132 days.

Left ventricular dysfunction will be included in Warnings and Precautions of the USPI.

8.2.5.3. Skin Events (dermatitis acneiform, rash, pruritus, dry skin, alopecia, hair color changes, and hair texture)

Data:

Collectively, dermatitis acneiform and a composite of other rash terms including rash, rash maculo-papular, rash pustular, rash erythematous, rash papular, exfoliative rash, papule, rash macular, and rash pruritic were reported by 39 (70%) pediatric participants and 52 (90%) adult participants in Study MEK-NF-201. Similar to Study MEK-NF-201, dermatitis acneiform and a composite of other rash terms were reported by 40 (69%) pediatric participants and 69 (92%) adult participants in Pool 1.

In Pool 1, dermatitis acneiform and non-acneiform rashes occurred in 69% of pediatric patients. Dermatitis acneiform occurred with a higher frequency in patients aged 12 to 17 years, while non-acneiform rashes occurred with a higher frequency in patients aged 2 to 11 years. Grade 3 dermatitis acneiform occurred in 1.7% of pediatric patients, and Grade 3 non-acneiform rashes occurred in 1.7% of pediatric patients. These rashes resulted in discontinuations in 3.4% of pediatric patients and dose reductions in 3.4% of pediatric patients, but no dose interruptions were reported in pediatric patients.

In Pool 1, dermatitis acneiform and non-acneiform rashes occurred in 92% of adults. Grade 3 dermatitis acneiform and non-acneiform rashes occurred in 7% and 1.3% of adults, respectively. These rashes resulted in discontinuations in 11%, dose interruptions in 2.7%, and dose reductions in 11% of adult patients.

In Pool 1, 20 (15%) participants reported dry skin. No significant difference was observed across age cohorts. Of the 20 participants who reported the event of dry skin, 16 (12%) were assessed as related to the study treatment with none being Grade ≥ 3 severity. One (1%) participant reported a TEAE of dry skin that led to study treatment discontinuation. No participants reported SAEs and no participants reported TEAEs of dry skin that led to death. The data from the Study MEK-NF-201 were aligned with the data in Pool 1.

Pruritus was reported in Pool 1 by 17 (13%) participants. Among the 17 participants who reported the TEAE, 10 (13%) were in the adult cohort and 7 (12%) were in the pediatric cohort. A total of 11 (8%) participants reported a TEAE of pruritus that was considered related to the study treatment by the investigator. No occurrences of Grade ≥ 3 events or SAEs, and no treatment discontinuations, were reported in Pool 1.

Collectively, hair changes, including alopecia and hair texture abnormal, were reported by 11 (19%) pediatric and 10 (13%) adult participants in Pool 1. Among the events classified as hair changes, alopecia was the most frequently reported TEAE with an incidence of 13% (17 participants) in Pool 1. Alopecia was reported in 8 (14%) pediatric participants and 9 (12%) adult participants. A total of 16 (12%) participants who reported alopecia were assessed as related to the study treatment by the investigators. One (1%) participant discontinued treatment due to alopecia. A higher incidence of hair color changes and hair texture abnormality were reported in the pediatric cohort compared to the adult cohort. In Pool 1, 7 (12%) out of the 8 participants who reported hair color changes were pediatric.

Additionally, 4 (3%) participants in Pool 1 reported hair texture abnormality, including 3 (5%) participants who were in the pediatric cohort. Of note, hair texture abnormal was reported less frequently compared to alopecia. None of the reports of hair changes in Pool 1 were Grade ≥ 3 .

The Applicant's Position:

Skin events, including dermatitis acneiform, a composite of non-acneiform rashes (including rash, rash maculo-papular, rash pustular, rash erythematous, rash papular, exfoliative rash, papule, rash macular, and rash pruritis), alopecia, hair texture changes, hair color changes, dry skin, and pruritus, were reported at an increased incidence relative to that anticipated for the patient population with NF1 PN. They are recognized as non-important identified risks as these events were generally Grade 1 or 2 and did not frequently result in the discontinuation of study treatment. However, dose modifications may be beneficial for patients; as such, skin toxicity is proposed for inclusion in the Warnings and Precautions section of labeling.

The FDA's Assessment:

FDA agrees with the Applicant's summary of data for dermatologic adverse events for patients in Pool 1. In the pooled safety population, rash occurred in 84% of patients; of these, 31% were Grade 2 and 6% were Grade 3. FDA's assessment of the grouped term for rash included the following preferred terms (PTs): dermatitis acneiform, eczema, maculo-papular rash, pustular rash, dermatitis, erythematous rash, palmar-plantar erythrodysesthesia syndrome, exfoliative rash, skin exfoliation, pruritic rash, papule, papular rash and macular rash. The most frequent PTs included in the grouped term for rash that occurred in $\geq 2\%$ of patients were dermatitis acneiform (65%), rash (11%), eczema (8%), maculo-papular rash (4.5%) and pustular rash (3.8%).

In the pooled adult safety population, an event of rash occurred in 92% of patients: 37% were Grade 2 and 8% were Grade 3 in severity. An event of rash requiring permanent discontinuation of mirdametininib occurred in 11% of adult patients.

In the pooled pediatric safety population, rash occurred in 72% of patients: 22% were Grade 2 and 3.4% were Grade 3 reactions. An event of rash resulting in permanent discontinuation of mirdametininib occurred in 3.4% of pediatric patients.

Dermatitis acneiform occurred with a higher frequency in patients aged 12 to 17 years (77%) than those aged 2 to 11 years (16%), while non-acneiform rashes occurred with a higher frequency in patients aged 2 to 11 years (53%) than those aged 12 to 17 years (15%). This observation is consistent with the known safety profile of MEK inhibitors in adolescent patients for whom dermatitis acneiform-related events occur at a relatively high incidence.

An instance of discrepant data was noted in the dataset for Study NF-106 in which one patient with an AE of "rash acneiform" was included with an AE outcome of death. However, the AE end date was missing, and the event was graded as "Mild" (Grade 1). FDA sent an

information request (IR) for clarification and the Applicant confirmed that the fatal outcome on the AE CRF represented an error in data reporting and was not a fatal event or SAE.

Dermatologic adverse reactions will be included in the Warning and Precautions of the USPI.

Other Noteworthy Adverse Events

The Applicant's Position:

In addition to the skin events mentioned in Section 8.2.5.3, the following events are considered non-important identified risks: diarrhea, nausea, vomiting, abdominal pain, constipation, fatigue, blood CPK increased, alanine aminotransferase increased, aspartate aminotransferase increased, and blood alkaline phosphatase increased. While these were reported at an increased incidence relative to that anticipated for the patient population with NF1 PN, and so are recognized as identified risks for mirdametinib, these events were generally Grade 1 or 2 and did not frequently result in the discontinuation of study treatment, hence they are considered non-important.

Stomatitis was recognized as a non-important identified risk for the pediatric population and as a potential risk in the adult population. In addition, the following risks were recognized as non-important identified risks in the pediatric population only: paronychia, eczema, and neutrophil count decreased.

The FDA's Assessment:

GI toxicity is a known MEK inhibitor class effect. FDA's analysis of events of gastrointestinal disorders in Pool 1 revealed that most adverse events of diarrhea, nausea, vomiting, abdominal pain, constipation, and stomatitis were Grades 1 and 2 in severity. Grade 3 adverse events of abdominal pain occurred in 4% of adult patients; Grade 3 diarrhea and abdominal pain occurred in 5% and 3.4% of pediatric patients, respectively. There were no Grade 4 adverse events.

Based on FDA's analysis of the safety data describing the observed GI toxicity in Pool 1, it was not included in the Warnings and Precautions section of the mirdametinib USPI due to the very low incidence of severe (Grade 3) events and the low incidence of events requiring discontinuation of therapy.

Increased CPK is a class effect reported with other MEK inhibitors. In Pool 1, increased CPK occurred in 52% of patients and $\geq$ Grade 3 events of increased CPK occurred in 3.8% of patients. Most of the events were Grade 1 or 2 in severity, with Grade 3 events occurring in 3 (5%) pediatric patients and a Grade 4 event occurring in 1 (2%) pediatric patient. One (1%) Grade 4 event was observed in an adult patient.

Among the 34 (59%) pediatric and 34 (47%) adult patients in Pool 1 with events of increased CPK, coincident events of “pain in extremity” occurred in 2 pediatric and 2 adult patients. Coincident events of “arthralgia” occurred in 1 adult and 1 pediatric patient while coincident event of “musculoskeletal chest pain” occurred in 1 adult patient. No events of rhabdomyolysis were reported.

In Pool 1, musculoskeletal pain occurred in 41% of adult and pediatric patients. There were 5 (7%) Grade 3 events in adult patients and 1 (1.7%) Grade 3 event in a pediatric patient. Myalgia occurred in 3 (4%) adult patients and 3 (5%) pediatric patients, and all events were Grade 1.

Based on FDA’s analysis of the safety data describing increased CPK in Pool 1, it was not included in the Warnings and Precautions section of the USPI given the high proportion of Grade 1 and 2 adverse events and the low incidence of severe consequences of increased CPK (including no observed rhabdomyolysis events).

Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant’s Position:

PROs are discussed in [Section 8.1.1](#) and [Section 8.1.2](#).

The FDA’s Assessment:

Refer to [Section 8.1.1](#) and [Section 8.1.2](#).

8.2.6. Safety Analyses by Demographic Subgroups

Data:

Intrinsic factors

The safety of mirdametininib was analyzed by the following subgroups: age, sex, race, ethnicity, BMI, and organ dysfunction.

For Pool 1, TEAEs were described according to age subgroup (2 to <12 years, 12 to <18 years, 18 to <40 years, 40 to <65 years, and ≥65 years). A total of 2 participants ≥65 years of age in Pool 1 were exposed to mirdametininib at doses of 2mg/m². The small sample size limits the ability to identify differences in the safety of mirdametininib in this age group. In Pool 1, there were some differences in the incidence of TEAEs between the pediatric and adult cohorts. A summary of PTs with an apparent age-associated trend in incidence in Pool 1 is presented in [Table 63](#). Trends were identified using the following criteria: incidence of ≥10% in either cohort and a >1.5x incidence in the adults versus the pediatric participants or the pediatric versus the adult participants. TEAEs of abdominal pain upper, cough, eczema, hair color changes, headache, nasal congestion, neutrophil count decreased, and WBC count decreased, oropharyngeal pain, paronychia, pharyngitis streptococcal, pyrexia, rash, rhinitis allergic and URTI occurred at a higher frequency in the pediatric cohort. An evaluation of TEAEs where

incidence increases with decreasing age in the pediatric cohort suggested that there were some differences between prepubertal participants (2 to 11 years of age) and post-pubertal participants (12 to 18 years of age). TEAEs of eczema, hair color changes, pharyngitis streptococcal, pyrexia, rash, rhinitis allergic, stomatitis, and upper respiratory tract infection occurred at a higher frequency in the prepubertal participant. On review of TEAEs where incidence increases with increasing age, the data suggested that dermatitis acneiform mostly occurred at a higher frequency in the post-pubertal participants.

In Pool 2, TEAEs were described according to age subgroup (18 to <40 years, 40 to <65 years, and ≥65 years). A total of 35 (31%) participants were ≥65 years of age. Participants reported at least one SAE in the age groups: 65 years and above (n=21/35, 60%), 40 to <65 years (n=30/70, 43%), and 18 to <40 years (n=4/8, 50%). There were no differences in SAEs reported in these age groups in Pool 2.

It is difficult to draw conclusions regarding TEAEs by sex in Pool 1, based on the disproportionate impact of the difference in the number of females (n=79) to males (n=54), and the limited number of participants reporting each event.

The majority of participants were White (71% in Pool 1 and 89% in Pool 2), limiting the ability to draw conclusions about the effect of race on the safety of mirdametininib.

The majority of participants in either pool were 'Not Hispanic or Latino' (84% in Pool 1 and 58% in Pool 2), limiting the ability to draw conclusions about the effect of ethnicity on the safety of mirdametininib.

Due to the small sample sizes in the pediatric BMI subgroups in Pool 1, no apparent trends in TEAEs by BMI could be determined. There were no apparent trends in TEAEs by BMI in the adult cohort. Due to the small sample sizes in the BMI subgroups in Pool 2, no trends could be determined.

Urinary excretion of unchanged mirdametininib or its primary metabolite is a minor route of elimination. The major route of elimination is renal excretion of the glucuronide metabolite (67.7%), which is substantially less biologically active than the parent mirdametininib. Hence, the potential impact of renal impairment on the PK of mirdametininib is considered to be low.

No studies with mirdametininib were conducted in participants with altered hepatic function. PopPK analyses suggest that mirdametininib PK is not expected to be altered in patients with mild hepatic impairment. Mirdametininib is extensively metabolized, but to what extent this occurs in the liver is unknown, and it is not a narrow therapeutic index drug.

At the maximum recommended dose of 4 mg BID, clinically significant QTc interval prolongation was not observed, and the overall safety data do not support recognizing an effect on cardiac

conduction as a risk for mirdametinib. This data demonstrates that asymptomatic ejection fraction decreased is an important identified risk for mirdametinib, but other cardiac effects, including cardiomyopathy or cardiac failure, are not identified risks for mirdametinib. Given that clinical data in this population is currently limited, there is not sufficient information to draw conclusions on the use of mirdametinib in patients with pre-existing cardiovascular impairment.

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Table 64: Age Subgroup, TEAEs with Age-associated Trends in Participants who Received Mirdametinib in Pool 1

	Pediatric NF1 PN 2 mg/m² BID Age 2-<12 years (N=32)	Pediatric NF1 PN 2 mg/m² BID Age 12-<18 years (N=26)	Pediatric NF1 PN 2 mg/m² BID Total (N=58)	Adult NF1 PN 2 mg/m² BID Age 18-<40 (N=57)	Adult NF1 PN 2 mg/m² BID Age 40-<65 (N=16)	Adult NF1 PN 2 mg/m² BID Age ≥65 (N=2)	Adult NF1 PN 2 mg/m² BID Total (N=75)
TEAEs where incidence increases with decreasing age							
Abdominal pain	10 (31.3%)	6 (23.1%)	16 (27.6%)	8 (14.0%)	3 (18.8%)	1 (50.0%)	12 (16.0%)
Abdominal pain upper	6 (18.8%)	3 (11.5%)	9 (15.5%)	0	3 (18.8%)	0	3 (4.0%)
Blood creatine phosphokinase increased	8 (25.0%)	6 (23.1%)	14 (24.1%)	9 (15.8%)	1 (6.3%)	1 (50.0%)	11 (14.7%)
Cough	10 (31.3%)	3 (11.5%)	13 (22.4%)	4 (7.0%)	1 (6.3%)	1 (50.0%)	6 (8.0%)
Eczema	7 (21.9%)	1 (3.8%)	8 (13.8%)	2 (3.5%)	0	0	2 (2.7%)
Ejection fraction decreased	9 (28.1%)	6 (23.1%)	15 (25.9%)	4 (7.0%)	4 (25.0%)	1 (50.0%)	9 (12.0%)
Hair colour changes	6 (18.8%)	1 (3.8%)	7 (12.1%)	1 (1.8%)	0	0	1 (1.3%)
Headache	13 (40.6%)	8 (30.8%)	21 (36.2%)	9 (15.8%)	2 (12.5%)	1 (50.0%)	12 (16.0%)
Nasal congestion	5 (15.6%)	3 (11.5%)	8 (13.8%)	4 (7.0%)	0	0	4 (5.3%)
Neutrophil count decreased	4 (12.5%)	3 (11.5%)	7 (12.1%)	0	0	0	0

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Mirdametinib (GOMEKLI)

	Pediatric NF1 PN 2 mg/m² BID Age 2-<12 years (N=32)	Pediatric NF1 PN 2 mg/m² BID Age 12-<18 years (N=26)	Pediatric NF1 PN 2 mg/m² BID Total (N=58)	Adult NF1 PN 2 mg/m² BID Age 18-<40 (N=57)	Adult NF1 PN 2 mg/m² BID Age 40-<65 (N=16)	Adult NF1 PN 2 mg/m² BID Age ≥65 (N=2)	Adult NF1 PN 2 mg/m² BID Total (N=75)
Oropharyngeal pain	4 (12.5%)	2 (7.7%)	6 (10.3%)	1 (1.8%)	0	0	1 (1.3%)
Paronychia	11 (34.4%)	8 (30.8%)	19 (32.8%)	2 (3.5%)	0	0	2 (2.7%)
Pharyngitis streptococcal	6 (18.8%)	0	6 (10.3%)	0	0	0	0
Pyrexia	10 (31.3%)	1 (3.8%)	11 (19.0%)	2 (3.5%)	2 (12.5%)	0	4 (5.3%)
Rash	9 (28.1%)	2 (7.7%)	11 (19.0%)	3 (5.3%)	1 (6.3%)	0	4 (5.3%)
Rhinitis allergic	6 (18.8%)	0	6 (10.3%)	0	0	0	0
Stomatitis	7 (21.9%)	1 (3.8%)	8 (13.8%)	3 (5.3%)	0	0	3 (4.0%)
Upper respiratory tract infection	10 (31.3%)	5 (19.2%)	15 (25.9%)	1 (1.8%)	0	0	1 (1.3%)
Weight increased	4 (12.5%)	5 (19.2%)	9 (15.5%)	6 (10.5%)	1 (6.3%)	0	7 (9.3%)
White blood cell count decreased	3 (9.4%)	3 (11.5%)	6 (10.3%)	1 (1.8%)	0	0	1 (1.3%)

NDA/IND Multi-disciplinary Review and Evaluation NDA 219379/219389
Mirdametinib (GOMEKLI)

	Pediatric NF1 PN 2 mg/m² BID Age 2-<12 years (N=32)	Pediatric NF1 PN 2 mg/m² BID Age 12-<18 years (N=26)	Pediatric NF1 PN 2 mg/m² BID Total (N=58)	Adult NF1 PN 2 mg/m² BID Age 18-<40 (N=57)	Adult NF1 PN 2 mg/m² BID Age 40-<65 (N=16)	Adult NF1 PN 2 mg/m² BID Age ≥65 (N=2)	Adult NF1 PN 2 mg/m² BID Total (N=75)
TEAE where incidence increases with increasing age							
Dermatitis acneiform	5 (15.6%)	20 (76.9%)	25 (43.1%)	49 (86.0%)	11 (68.8%)	2 (100%)	62 (82.7%)
Nausea	9 (28.1%)	8 (30.8%)	17 (29.3%)	34 (59.6%)	6 (37.5%)	1 (50.0%)	41 (54.7%)
Constipation	5 (15.6%)	1 (3.8%)	6 (10.3%)	11 (19.3%)	2 (12.5%)	1 (50.0%)	14 (18.7%)
Fatigue	5 (15.6%)	2 (7.7%)	7 (12.1%)	22 (38.6%)	4 (25.0%)	1 (50.0%)	27 (36.0%)
Oedema peripheral	0	2 (7.7%)	2 (3.4%)	4 (7.0%)	3 (18.8%)	1 (50.0%)	8 (10.7%)
Dizziness	4 (12.5%)	1 (3.8%)	5 (8.6%)	13 (22.8%)	3 (18.8%)	0	16 (21.3%)
Paraesthesia	2 (6.3%)	0	2 (3.4%)	5 (8.8%)	4 (25.0%)	0	9 (12.0%)

AE: Adverse Event; BID: twice daily; m: meter; MedDRA: Medical Dictionary of Regulatory Activities; mg: milligram; NF1: Neurofibromatosis Type 1; PN: Plexiform Neurofibromas; TEAE: Treatment-Emergent Adverse Event.

Each participant is counted only once within each system organ class and preferred term if they experience an AE with that system organ class and preferred term more than once.

Percentages are calculated using the number of participants in the corresponding cohort as the denominator.

Source: ADSL, ADAE

Extrinsic factors

The safety of mirdametinib was analyzed by geographic location, food intake, or use of tobacco and alcohol. Although studies were conducted in the US in accordance with the principles of ICH E5 R1 guidance, the results can be extrapolated to the European Union (EU) population as NF1 PN is an orphan condition and there are no ethnic differences. There are no intrinsic or extrinsic ethnic factors that will preclude the extrapolation of the results. Moreover, the diagnosis and treatment of NF1 PN are similar in the US and EU.

No overall differences in safety were observed among participants as a result of food intake or use of tobacco and alcohol.

The Applicant's Position:

Overall, the observed differences among subgroups by age are not considered to have a clinical impact on the safety profile of mirdametinib as they were most likely attributable to the age difference between the groups and age-related development. As hepatic metabolism of mirdametinib has not been studied, its use in patients with moderate and severe hepatic impairment should be considered to have significant effects on the pharmacokinetics of mirdametinib. Please see [Section 6.2.1](#) for additional discussion of the effect of hepatic impairment on mirdametinib PK.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment of safety subgroup analyses for age, sex, race, ethnicity, BMI, and organ dysfunction in the adult and pediatric cohorts of Pool 1. Please refer to [Section 6.2.1](#) for a discussion on the effect of hepatic impairment on mirdametinib PK.

8.2.7. Specific Safety Studies/Clinical Trials

The Applicant's Position:

No studies have been conducted with mirdametinib specifically to address safety concerns. Safety monitoring continues in the ongoing long-term follow-up phase of Study MEK-NF-201.

The FDA's Assessment:

The FDA agrees and notes that the ReNeu study includes an optional Long-Term Follow-up (LTFU) Phase with continued safety monitoring that is currently ongoing. Patients who completed Cycle 24 of the Treatment Phase and did not meet withdrawal criteria were eligible to participate in the LTFU.

Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

No human carcinogenicity studies have been conducted with mirdametinib.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

Human Reproduction and Pregnancy

Data:

Studies with mirdametinib have not been conducted in women who are pregnant or lactating. Reproductive animal toxicology studies have been completed with mirdametinib and confirm the reproductive toxicity of mirdametinib, consistent with effects observed in nonclinical studies with other MEK inhibitors. In embryo-fetal developmental toxicity studies in pregnant rats and rabbits, oral dosing of mirdametinib induced early resorptions, post-implantation loss and decreased fetal body weights in rats at dosages ≥ 3 mg/kg/day and in rabbits at dosages ≥ 0.3 mg/kg/day; these exposures were equivalent to the human exposure or approximately 0.4 times the human exposures at the recommended dose, respectively. In the rat study, at 3 mg/kg/day, a single fetus had extremity malformations.

There are no data on the presence of mirdametinib in human milk or the effects of mirdametinib on a breastfed child or milk production.

The Applicant's Position:

Mirdametinib should not be used during pregnancy. If a patient becomes pregnant while receiving this drug, treatment with mirdametinib should be stopped and the patient should be apprised of the potential hazard to the fetus.

Since drugs are commonly excreted in human milk and because of the potential for serious adverse reactions in nursing infants, women should not breastfeed during treatment with mirdametinib and for at least 1 week after the last dose of mirdametinib. Given a terminal elimination half-life of approximately 28 hours, it is expected that mirdametinib would no longer be present 1 week after the last dose.

The FDA's Assessment:

FDA agrees with the Applicant's statement. There were no patients who discontinued from the study due to pregnancy, and birth control measures during treatment and ongoing pregnancy screening were enforced to ensure that no fetus was exposed to study drug.

On the ReNeu study, one case of pregnancy that occurred 31 days after the patient received her last dose of treatment with mirdametinib was reported. Seventy days after the patient

discontinued mirdametinib, she had a dilation and curettage of uterus due to a spontaneous abortion.

Pediatrics and Assessment of Effects on Growth

Data:

Fifty-six pediatric participants aged 2 to 17 years were enrolled in the pivotal Phase 2b Study MEK-NF-201. For all participants 2 to 17 years of age, radiographs of the distal femur and proximal tibia were obtained at baseline. If the investigator determined that the physes were open, these participants underwent a radiograph in accordance with the Treatment Phase Schedule of Activities to monitor for changes in physal growth plates.

Relevant bone events from 4 pediatric participants in Study MEK-NF-201 were identified, as shown in Table 64. All 4 events were assessed as not related to mirdametinib treatment. The femoral neck fracture was reported as serious, and Grade 3, while the other events were Grade 1 or Grade 2 and non-serious. The femoral neck fracture was reported by a 12-year old female with a relevant medical history of protrusion acetabuli, leg length discrepancy, and levoscoliosis, on Day 269. The verbatim term was reported as right pathologic femoral neck fracture due to fall. The participant's target tumor was located in the hip affected by the fracture and was noted to be 426.60 mL at baseline (SW-000421). The location and size of the participant's tumor are confounding factors in this event.

A Grade 2 radius fracture was reported by a 6-year-old female on Day 735. No relevant medical history was noted, though the participant's target tumor was noted to be located in the upper limb. Additional details concerning the event are not available, though forearm fractures are the most common fracture in children under 16 years old, and account for approximately 40% of all pediatric long bone fractures (Oh 2022). The location of the participant's target tumor and epidemiology do not suggest this event was caused by mirdametinib.

Grade 1 osteopenia was reported by a 5-year-old female (Study MEK NF 201) on Day 664. The participant had a relevant medical history of bowing tibia, dextroscoliosis, and spinal fusion rods, and reported a fall resulting in a fractured spinal fusion rod and requiring surgery from Day 40 to Day 308. The participant's target tumor is noted as occurring in the mediastinum with intrathoracic involvement to the right upper extremity and cervical spine, with a tumor volume at baseline of 140.59 mL. The clinical effect of the participant's tumor, as evidenced by their medical history, is considered a confounder to the event of osteopenia.

A Grade 1 spinal deformity, described as a mild dextroconvex curvature of the thoracolumbar spine, with apex approximately at T11, and measuring 5 degrees, was reported in a 7-year-old male (Study MEK-NF-201) on Day 636. The participant's target tumor was located in the paraspinal region. The location of the participant's tumor is a confounder for this event.

All 4 events identified in the search of data from Study MEK-NF-201 are thus confounded, most frequently by the location of the participant's target tumor.

Table 65: TEAEs of Standardized MedDRA Queries Osteoporosis/Osteopenia from Study MEK-NF-201

	Pediatric NF1 PN 2 mg/m² BID (N=56)	Adult NF1 PN 2 mg/m² BID (N=58)	Total NF1 PN 2 mg/m² BID (N=114)
Total	4 (7.1%)	0	4 (3.5%)
Femoral neck fracture	1 (1.8%)	0	1 (0.9%)
Osteopenia	1 (1.8%)	0	1 (0.9%)
Radius fracture	1 (1.8%)	0	1 (0.9%)
Spinal deformity	1 (1.8%)	0	1 (0.9%)

BID: twice daily; m: meter; mg: milligram; NF1: Neurofibromatosis Type 1; PN: Plexiform Neurofibromas
N represents the number of participants in the corresponding cohort.

Source: ADSL, ADAE

The Applicant's Position:

The safety and effectiveness of mirdametininib have been established in pediatric patients aged ≥ 2 years. The clinical data is not suggestive of an effect on bone as a result of mirdametininib treatment. All the relevant events identified in Study MEK-NF-201 were confounded by a variety of factors which are expected to have contributed to their events. The available clinical data do not support recognizing bone effects, including fracture, as a risk for mirdametininib.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. However, given the relevant bone toxicities identified in the non-clinical data and the limitations associated with a small safety database, a further assessment of growth and development parameters in pediatric patients will be included as a PMR. Refer to Section 13.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:

Overdose:

The MEK-NF-201 protocol defined overdose as any dose greater than 150% of the BSA assigned maximum total daily dose within a 24-hour period. The largest treatment dose administered in Study MEK-NF-201 was 4 mg BID. No overdoses, accidental or otherwise, were reported in Study MEK-NF-201.

The largest treatment dose of mirdametinib administered to advanced cancer participants in Pool 2 was in adults at 30 mg BID. Twenty-three participants in Pool 2 received mirdametinib doses of 8, 10 mg BID, in addition to 74 participants who received doses of mirdametinib of 15, 20, or 30 mg BID. Treatment emergent SAEs were reported by 13 (57%) participants in the 8, 10 mg BID dose group and by 37 (50%) participants in the 15, 20, 30 mg BID dose group, respectively. Grade ≥ 3 TEAEs were reported by 11 (48%) and 49 (66%) participants in the 2 dose groups, respectively. Grade 5 TEAEs were reported by 3 (13%) and 9 (12%) participants in each dose group, respectively, and all were due to disease progression.

Table 65 summarizes the incidence of TEAEs that were reported in at least 15% of participants in either of the two highest dose groups in Pool 2, in comparison to the same TEAEs in both Pool 1 cohorts. Given that mirdametinib generally has a dose-proportional increases in exposure in the dose range of 1 mg QD/BID to 30 mg BID, mirdametinib exposure in these two Pool 2 dose groups represent approximately 2 to 8 times the maximum recommended NF1 PN dose for mirdametinib of 4mg BID. Thus, data from the highest dose groups in Pool 2 may represent possible outcomes for mirdametinib overdoses. However, dosing of mirdametinib in participants in Pool 2 was sustained so the events observed may not necessarily represent events that may occur in the setting of a single excessive dose of mirdametinib in a patient receiving treatment with mirdametinib 4 mg BID or in the setting of accidental ingestion of mirdametinib.

Events with an incidence in Pool 2 of at least double or >20% higher than the incidence in either of the Pool 1 cohorts included fatigue, edema peripheral, edema, pyrexia, face edema, rash, pruritis, erythema, dyspnea, visual impairment, vision blurred, muscular weakness, ALT increased, hypoalbuminemia, decreased appetite, dehydration, confusional state, and anemia. Hypoalbuminemia and anemia are unlikely to occur acutely following an acute overdose of mirdametinib since changes in these laboratory parameters typically occur gradually (with the exception of acute anemia due to blood loss).

Thirteen of these events are considered identified risks for mirdametinib at doses studied in MEK-NF-201, and thus are not specific toxicities of an overdose. These events are diarrhea, nausea, vomiting, constipation, abdominal pain, fatigue, rash, pruritis, dermatitis acneiform, dry skin, ALT increased, AST increased, and ejection fraction decreased.

Table 66: Incidence of TEAEs That Were Reported in at Least 15% of Participants in Either of the Two Highest Dose Groups in Pool 2, In Comparison to the Same TEAEs in Both Pool 1 Cohorts

System Organ Class Preferred Term	Pool 1: Pediatric 2 mg/m ² BID (N=58)	Pool 1: Adult 2 mg/m ² BID (N=75)	Pool 2: 8, 10 mg BID (N=23)	Pool 2: 15, 20, 30 mg BID (N=74)
Gastrointestinal disorders				
Diarrhea	31 (53.4%)	41 (54.7%)	10 (43.5%)	54 (73.0%)
Nausea	17 (29.3%)	41 (54.7%)	8 (34.8%)	31 (41.9%)
Vomiting	23 (39.7%)	28 (37.3%)	7 (30.4%)	27 (36.5%)
Constipation	6 (10.3%)	14 (18.7%)	6 (26.1%)	10 (13.5%)
Abdominal pain	16 (27.6%)	12 (16.0%)	1 (4.3%)	12 (16.2%)
General disorders and administration site conditions				
Fatigue	7 (12.1%)	27 (36.0%)	13 (56.5%)	38 (51.4%)
Oedema peripheral	2 (3.4%)	8 (10.7%)	7 (30.4%)	25 (33.8%)
Oedema	0	0	6 (26.1%)	11 (14.9%)
Pyrexia	11 (19.0%)	4 (5.3%)	4 (17.4%)	11 (14.9%)
Face edema	1 (1.7%)	3 (4.0%)	2 (8.7%)	11 (14.9%)
Skin and subcutaneous tissue disorders				
Rash	11 (19.0%)	4 (5.3%)	18 (78.3%)	51 (68.9%)
Pruritis	7 (12.1%)	10 (13.3%)	6 (26.1%)	13 (17.6%)
Dermatitis acneiform	25 (43.1%)	62 (82.7%)	3 (13.0%)	17 (23.0%)
Dry skin	10 (17.2%)	10 (13.3%)	3 (13.0%)	12 (16.2%)
Erythema	1 (1.7%)	3 (4.0%)	6 (26.1%)	7 (9.5%)
Respiratory, thoracic and mediastinal disorders				
Dyspnea	3 (5.2%)	6 (8.0%)	6 (26.1%)	20 (27.0%)
Eye disorders				
Visual impairment	0	0	3 (13.0%)	17 (23.0%)
Vision blurred	4 (6.9%)	7 (9.3%)	0	15 (20.3%)
Musculoskeletal and connective tissue disorders				
Pain in extremity	12 (20.7%)	12 (16.0%)	1 (4.3%)	12 (16.2%)
Muscular weakness	1 (1.7%)	1 (1.3%)	0	12 (16.2%)

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System Organ Class Preferred Term	Pool 1: Pediatric 2 mg/m ² BID (N=58)	Pool 1: Adult 2 mg/m ² BID (N=75)	Pool 2: 8, 10 mg BID (N=23)	Pool 2: 15, 20, 30 mg BID (N=74)
Investigations				
ALT increased	2 (3.4%)	4 (5.3%)	4 (17.4%)	9 (12.2%)
AST increased	1 (1.7%)	6 (8.0%)	2 (8.7%)	11 (14.9%)
Ejection fraction decreased	15 (25.9%)	9 (12.0%)	5 (21.7%)	5 (6.8%)
Nervous system disorders				
Dizziness	5 (8.6%)	16 (21.3%)	3 (13.0%)	15 (20.3%)
Headache	21 (36.2%)	12 (16.0%)	5 (21.7%)	8 (10.8%)
Metabolism and nutrition disorders				
Hypoalbuminemia	1 (1.7%)	5 (6.7%)	6 (26.1%)	14 (18.9%)
Decreased appetite	2 (3.4%)	2 (2.7%)	5 (21.7%)	11 (14.9%)
Dehydration	4 (6.9%)	0	1 (4.3%)	11 (14.9%)
Psychiatric disorders				
Confusional state	0	2 (2.7%)	2 (8.7%)	14 (18.9%)
Blood and lymphatic disorders				
Anemia	1 (1.7%)	6 (8.0%)	3 (13.0%)	13 (17.6%)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BID: twice daily; TEAE: treatment-emergent adverse event.

Each participant is counted only once within each system organ class and preferred term if they experience an AE with that system

organ class and preferred term more than once.

Percentages are calculated using the number of participants in the corresponding cohort as the denominator.

Source: ADSL, ADAE

Drug abuse:

The potential for abuse was assessed by reviewing the psychiatric disorders SOC for TEAEs that might suggest a psychoactive effect that could lead to drug abuse. In both Pool 1 and Pool 2, there were no psychiatric TEAEs for euphoria, disinhibition, dissociation, or any other PTs that might suggest a psychoactive effect that could lead to drug abuse.

Withdrawal and rebound:

Dependence was assessed by reviewing TEAE tables from Pool 1 and Pool 2. There were no TEAEs for drug dependence, drug withdrawal, or other terms that might suggest mirdametininib could cause physical dependence or symptoms of withdrawal.

The Applicant's Position:

In general, the adverse reactions associated with a mirdametinib overdose are likely to be consistent with the known adverse reactions at recommended doses of ≤ 4 mg BID, albeit potentially more severe. Clinical data above 30 mg BID in adults and above 4 mg BID in pediatrics are not available. No specific antidotes exist for the treatment of mirdametinib overdose. Hemodialysis is unlikely to result in additional elimination as the estimated fraction unbound for mirdametinib is 0.3%. Consequently, in the case of overdose, general supportive and symptomatic care is recommended.

No potential for abuse or dependence has been identified for mirdametinib.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment.

8.2.8. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

The safety population included in Study MEK-NF-201 and Pool 1 is representative of the intended real-world population of patients with NF1 PN. The observed safety profile represents a manageable safety profile for mirdametinib 2mg/mg2 BID for the treatment of adult and pediatric patients 2 years of age and older with NF1 PN, and can be reasonably expected to reflect the safety profile to be observed when used as indicated following marketing authorization.

The FDA's Assessment:

The FDA agrees with the description of the safety profile of mirdametinib provided by the Applicant and refers to product labeling and FDA's analysis of adverse events. See Section 13 for additional clinical postmarketing requirements (PMRs).

8.2.9. Integrated Assessment of Safety

Data:

Mirdametininib has been studied in 133 participants with NF1 PN, including 58 pediatric and 75 adult participants (Pool 1). In Pool 1, 83 (62%) participants have been treated for at least 12 months, 50 (38%) for at least 24 months, and 16 (12%) for at least 36 months. The most frequently (>35%) reported TEAEs for the total population from Study MEK-NF-201 and Pool 1 were dermatitis acneiform, diarrhea, nausea, and vomiting which are expected with MEK inhibition (Solares 2021, Subbiah 2020).

For the total population of Pool 1, the most frequently reported Grade ≥ 3 TEAEs ($\geq 4\%$) were dermatitis acneiform (5%), blood creatine phosphokinase increased (4%), neutrophil count decreased (4%), and abdominal pain (4%). Grade ≥ 3 TEAEs reported by ≥ 2 pediatric participants were neutrophil count decreased, blood creatine phosphokinase increased, diarrhea, syncope, weight increased, and abdominal pain. Grade ≥ 3 TEAEs reported by ≥ 2 adult participants were dermatitis acneiform, abdominal pain, back pain, COVID-19, nephrolithiasis and SARS-CoV-2 test positive.

In Pool 1, there were 2 participants in the pediatric cohort of Study MEK-NF-201 who reported Grade 4 events (blood creatine phosphokinase increased by 1 participant, and near drowning and laryngeal edema by the second participant). In the adult cohort of Pool 1, there were 2 participants from Study MEK-NF-201 who reported Grade 4 events (COPD and pneumonia bacterial, by 1 participant each).

There were no deaths on study in the pediatric cohort of Pool 1 or in the healthy volunteer studies. The 1 death in an adult participant in Pool 1 due to COVID-19 was assessed by the investigator as due to the infection and not to mirdametininib.

For the total population and adult cohort of Pool 1, the most frequently reported SAEs (≥ 2 participants) were COVID-19, abdominal pain, and nephrolithiasis. In the pediatric cohort, all SAE PTs were reported by 1 participant each.

In Pool 1, 21 (16%; 5 [9%] pediatric, 16 [21%] adult) participants discontinued study treatment due to TEAEs. The PTs reported in the pediatric cohort were: urticaria (2 participants [3%]), dermatitis acneiform, rash, diarrhea, abdominal pain, and constipation (1 participant each [2%]). TEAEs that led to the discontinuation of study treatment in >1 participant in the adult cohort were dermatitis acneiform, diarrhea, nausea, and vomiting.

The following events were recognized as risks for patients with NF1 PN treated with mirdametininib 2 mg/m² BID:

- The following events were recognized as identified risks because of the frequency of their reports, temporal relationship to the start of treatment with mirdametininib, and presence of a plausible biologic mechanism, and were deemed important due to their potential impact on patients: ejection fraction decreased and retinal vein occlusion.
- The following events were reported at an increased incidence relative to that

anticipated for the patient population with NF1 PN and are recognized as identified risks as these events were generally Grade 1 or 2 and did not frequently result in the discontinuation of study treatment: diarrhea, nausea, vomiting, abdominal pain, constipation, skin events (including dermatitis acneiform, rash, pruritus, dry skin, alopecia, hair color changes, and hair texture), blood CPK increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, and fatigue.

- The data presented support recognizing stomatitis as an identified risk for mirdametinib in the pediatric population and as a potential risk in the adult population.
- The data presented support recognizing paronychia, eczema, and neutrophil count decreased, as identified risks for mirdametinib in the pediatric population only.
- Given the low frequency and severity of events, the data support vision blurred and detachment of retinal pigment epithelium being recognized as important potential risks.

Nonclinical data support embryo-fetal toxicity being recognized as an important potential risk for mirdametinib, and mirdametinib should not be used during pregnancy. Mirdametinib had no adverse effects on male and female rat fertility.

The following relevant observations were made, but they do not represent adverse clinical findings: decreased hemoglobin, decreased leukocytes, lymphocyte count increased, increased cholesterol, increased creatinine, decreased bicarbonate, hypo calcium corrected for albumin, and increased glucose.

No clinically significant changes in urinalysis, vital signs, or ECG data were observed.

The most clinically impactful identified risks associated with the use of mirdametinib 2 mg/m² BID in the treatment of NF1 PN and included in the Warnings and Precautions of the label are retinal vein occlusion, ejection fraction decreased, dermatitis acneiform, and rash. Impactful potential risks associated with the use of mirdametinib 2 mg/m² BID in the treatment of NF1 PN and included in the Warnings and Precautions of the label are vision blurred, detachment of retinal pigment epithelium, and embryo-fetal toxicity. None of these events, nor any of the other risks associated with the use of mirdametinib, in isolation or in aggregate, would preclude the use of mirdametinib 2 mg/m² BID for the treatment of patients with NF1 PN.

The Applicant's Position:

The observed safety profile described in the integrated summary of safety represents a manageable safety profile for mirdametinib 2 mg/m² BID for the treatment of adult and pediatric patients 2 years of age and older with NF1 PN. No aspects of the observed safety profile would preclude the use of mirdametinib 2 mg/m² BID for treating adult or pediatric patients aged ≥2 years with NF1 PN and the benefit: risk profile is favorable.

The FDA's Assessment:

FDA generally agrees with the Applicant's integrated assessment of safety.

The pooled safety data from the ReNeu study and Study NF-106 (Pool 1) and the additional safety analysis (90-day-update) allowed for an informed risk assessment of mirdametinib in the intended NF1 PN populations. Among 133 patients who received mirdametinib, 62% were exposed for one year or longer, 38% were exposed for 2 years or longer, and 12% were exposed for 3 years or longer, allowing for a reasonable evaluation of risk for cumulative toxicities with chronic dosing.

In Pool 1, serious adverse events occurred in 16% of adult patients and 14% of pediatric patients. There was one fatal adverse event due to Covid-19. AEs leading to permanent discontinuation occurred in 21% of adults and 9% of pediatric patients and AEs leading to dose reduction occurred in 20% of adult and 12% of pediatric patients. The most common AEs (>25%) in the adult population included rash, diarrhea, nausea, musculoskeletal pain, vomiting, and fatigue. The most common AEs (>25%) in the pediatric population included rash, diarrhea, musculoskeletal pain, abdominal pain, vomiting, fatigue, upper respiratory tract infection, paronychia, headache, left ventricular dysfunction and nausea. Grade 3-4 AEs occurred in 33% of adult patients and 40% of pediatric patients. Given the relatively low discontinuation and reduction rate, it appears that AEs were tolerable and manageable with dose modifications and supportive care in patients treated with mirdametinib.

Important risks of mirdametinib are similar to those of other MEK inhibitors including ocular, cardiac and dermatologic toxicities. Some rare, but serious, class related safety signals (e.g., rhabdomyolysis) were not identified in the Pool 1 population. RVO and RPED were not observed in the pediatric population. No new safety signals were identified for mirdametinib compared to commercially approved MEK inhibitors. The identified toxicities can be managed through labeling, including relevant warnings, precautions, and dose modification guidelines.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

The ReNeu study is an open-label, single arm, multi-center trial which served as the primary basis for establishing the efficacy of mirdametinib for the treatment of pediatric and adult patients with NF1-PN. The primary endpoint of the trial was confirmed ORR per BICR using modified REiNS criteria, supported by the secondary endpoint of DOR. Since the ReNeu study is a single-arm trial, there was no control for multiplicity in any of the hypothesis tests included in this report. Therefore, the p-values reported by the Applicant should be interpreted with caution.

The Applicant also provided results from a second study, NF-106, which were evaluated solely as supportive evidence given significant study design differences whereby one-third of patients were discontinued from treatment unless they had at least a 15% or 20% reduction in target tumor volume at Cycle 8 and 12, respectively, precluding a full evaluation of ORR and DOR. In addition, external control data from NCI trials 01-C-022 and 08-C-0079 were presented. While these descriptive data were considered supportive, the primary review of mirdametinib relied on a benefit:risk assessment of the data from Study MEK-NF-201 (ReNeu).

During the review it was noted that the Applicant used a modified REiNS criteria for disease assessments, confirming response within 2-6 months as opposed to 3-6 months per the criteria. Results using strict adherence to the criteria were consistent with the pre-specified analysis (50% and 52% in pediatric cohorts, respectively; 35% and 41% in adult cohorts, respectively). See Section 8.1 for more detail. Additional sensitivity analyses of ORR across BICR readers and in the Per Protocol Set population confirm the observed ORR benefit is robust.

Median estimates of DOR per Kaplan-Meier methods were not met in either cohort even at the time of the 90-day safety update, due to only a small number of events occurring after a response. A total of 90% of pediatric and 88% of adult responders had a DOR of ≥ 12 months and 48% of pediatric and 50% of adult responders had DOR ≥ 24 months indicating that the observed responses are durable.

In summary, the primary efficacy data of confirmed ORR and DOR from the ReNeu study demonstrate clinically meaningful durable anti-tumor activity of mirdametinib in the treatment of pediatric and adult patients with NF1 PN.

8.4. Conclusions and Recommendations

The FDA's Assessment:

Study MEK-NF-201 (ReNeu) is a multicenter, single-arm trial investigating mirdametinib in adult and pediatric patients with NF1 and progressive or symptomatic plexiform neurofibromas not amenable to complete surgical resection. Eligible patients were at least 2 years of age with PN causing significant morbidity, and a target PN that was evaluable by volumetric analysis. Patients were enrolled by age group into pediatric and adult cohorts. Treatment consisted of mirdametinib at a dosage of 2 mg/m² orally twice daily for the first 21 days of each 28-day cycle. The study included a treatment phase lasting 24 cycles and an optional long-term follow-up phase. The primary endpoint to demonstrate the efficacy of mirdametinib for this population was confirmed ORR, defined as PN decrease $\geq 20\%$ compared to baseline in consecutive scans within 2-6 months, using independent central review of MRI volumetric analysis. DOR was a key secondary endpoint. The primary efficacy population consisted of 114 patients, including 56

pediatric and 58 adult patients.

The confirmed BICR-assessed ORR in the primary efficacy population of pediatric patients was 52% (95% CI: 38, 65); the median DOR was not reached. A total of 90% of responders had a DOR of ≥ 12 months and 48% of responders had a DOR of ≥ 24 months. The confirmed ORR as assessed by BICR in the primary efficacy population of adult patients was 41% (95% CI: 29, 55); the median DOR was not reached. A total of 88% of responders had a DOR of ≥ 12 months and 50% of responders had a DOR of ≥ 24 months. While NF1-PNs are benign tumors, they carry potential for severe associated morbidity including profound impact on quality of life, as described by participants at FDA's listening session for patients and caregivers with NF in June 2019 (see Section 2). In this context, FDA considered it critical that the ReNeu study demonstrate unequivocal evidence of a treatment effect supported by data showing improvement in physical function or an improvement in specific symptoms related to NF1-PN disease that correlates with radiographic tumor shrinkage. Despite the limitations of interpretation of the formal COA data, there was a general trend toward improvement in symptoms associated with radiographic responses. FDA's detailed review of patient-level narratives for each responder, which included assessments of physical function, use of pain or other symptom-ameliorating medications, as well as patient reported outcomes, provided clear supportive evidence of the clinical benefit of tumor shrinkage. It is noted, however, that narratives were not available for non-responders. FDA considers the totality of efficacy data to represent a clinically meaningful treatment effect in patients with symptomatic, unresectable NF1-PN and to constitute substantial evidence of effectiveness in this setting.

The safety profile of mirdametinib is acceptable for the intended population when considered in the context of a serious and life-threatening disease. Important toxicities of mirdametinib that were noted in this review include ocular toxicity, left ventricular dysfunction, dermatologic adverse reactions, and embryo-fetal toxicity. These toxicities are addressed in the Warnings and Precautions in the product label. Instructions for monitoring and dose modifications are provided in the USPI.

Based on the evaluation of clinical data from the ReNeu study, the review team recommends regular approval for mirdametinib for adult and pediatric patients 2 years of age and older with neurofibromatosis type 1 (NF1) who have progressive or symptomatic plexiform neurofibromas not amenable to complete surgical resection. In this study, mirdametinib demonstrated a robust and clinically meaningful effect on ORR that is durable and associated with improvements in disease-related morbidities. These factors represent direct clinical benefit to patients and support regular approval of the drug.

X

X

Primary Statistical Reviewer
Shabnam Ford

Statistical Team Leader
Flora Mulkey

X

X

Primary Clinical Reviewer
Kristin Wessel

Clinical Team Leader
Amy Barone

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

FDA did not refer this application to an advisory committee or seek input from other external consultants because this application did not raise significant public health questions regarding the role of mirdametininib for the proposed indication.

10 Pediatrics

The Applicant's Position:

This NDA is for a pediatric and adult indication. Data supporting the pediatric indication are described throughout the application.

The FDA's Assessment:

FDA agrees with the Applicant's position. This NDA is exempt from the requirements under Section 505B of the FD&C Act as amended by Title V of the FDA Reauthorization Act of 2017 (FDARA) because the marketing application is not intended for the treatment of an adult cancer. Additionally, because the product has an orphan drug designation for this indication, this NDA is exempt from the requirements to conduct pediatric assessments under the Pediatric Research Equity Act (PREA). Therefore, an Initial Pediatric Study Plan (iPSP) is not required for mirdametinib for the treatment of NF1-PN.

Given that there is limited long-term safety data for mirdametinib and a signal of growth delay has been identified, the review team recommends a PMR to further characterize the potential serious risk of long-term adverse effects of mirdametinib on growth and development in pediatric patients (See Section 13).

11 Labeling Recommendations

The Applicant's Position:

This is an original application. The proposed label is included in the NDA.

The FDA's Assessment:

The proposed labeling submitted by the Applicant required extensive revision by FDA. The format, language, and content of the proposed labeling was evaluated and revised for consistency with 21 CFR, labeling guidances and current labeling practices of the Office of Oncologic Diseases. The following table summarizes key changes.

Table 67 Key Labeling Revisions

Label Section	FDA Revised Text
1. INDICATIONS AND USAGE	FDA revised the indication statement to include the qualifiers "not amenable to complete resection" for consistency with the studied population.
2.1 Recommended Evaluation and Testing Before Initiating GOMEKLI	FDA added a new labeling section to ensure proper patient evaluation prior to administration of GOMEKLI.
2.2 GOMEKLI Dosage Form Overview	FDA added a new labeling section to highlight the 2 dosage forms for prescribers.
2.3 Recommended Dosage	FDA added text regarding missed dose and vomiting to ensure safe use.
2.4 GOMEKLI Preparation and Administration Instructions	FDA added a new labeling section to provide instructions for preparation of GOMEKLI as an oral suspension.
Table 3: Recommended Dosage Modifications and Management of Adverse Reactions for GOMEKLI	FDA revised the proposed 2-column table to a 3-column format for consistency across oncology labeling. Dosage modifications and management of adverse reactions advice was revised for safety and adherence to protocol specifications.
5.1 Ocular Toxicity	FDA revised the ocular toxicity warning to provide the incidences of toxicity for each safety population: total pool, adults and pediatric patients.
5.2 Left Ventricular Dysfunction	FDA revised the left ventricular dysfunction warning to provide the incidences of toxicity for adults and pediatric patients in the ReNeu study. Data on left ventricular dysfunction was not collected for the rest of the safety pool.
5.3 Dermatologic Adverse	FDA revised "skin toxicity" to dermatologic adverse

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Reactions	reactions for consistency across oncology labeling. Text was revised for clarity and brevity.
5.4. Embryo-Fetal Toxicity	FDA revised text to include human data of a pregnancy reported 31 days after the last dose of GOMEKLI that resulted in a first trimester spontaneous abortion and to provide data from studies of rats and rabbits demonstrating embryo-fetal mortality, structural abnormalities and alterations to growth.
6.1 Clinical Trials Experience	FDA revised this section for consistency across oncology labeling.
7 Drug Interactions	FDA removed this section as non-actionable, consistent with 21 CFR 201.56(d)(4).
8.1. Pregnancy	FDA revised this section for consistency with the Guidance Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format (July 2020). FDA added data from studies of rats and rabbits demonstrating embryo-fetal mortality, structural abnormalities and alterations to growth. FDA added the subsection, <i>Human Data</i> to include human data of first trimester spontaneous abortion where a pregnancy was reported 31 days after the last dose of GOMEKLI. Additional details from the rat and rabbit studies were provided that demonstrate nonclinical embryo-fetal toxicity.
Contraception Females	FDA revised the Applicant's proposed requirement of female contraception for 1 week to 6 weeks, based on human and animal demonstration of embryo-fetal toxicity.
Contraception Males	FDA revised the Applicant's proposed requirement of male contraception to 3 months, based on nonclinical studies.
8.4. Pediatric Use	FDA provided information on the data supporting the pediatric indication and included nonclinical toxicity findings that were not demonstrated in the clinical studies.
8.5 Geriatric Use	FDA revised text for consistency with 21 CFR 201.57(c)(9)(v)(B)(1).
8.6 Renal Impairment	FDA revised text for clarity and brevity.
8.7 Hepatic Impairment	FDA revised text for clarity and brevity.

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10 OVERDOSAGE	FDA removed this section as non-actionable, consistent with 21 CFR 201.56(d)(4).
11 DESCRIPTION	FDA provided minor revisions for consistency with 21 CFR 201.57(c)(12).
12.1 Mechanism of Action	FDA revised the text to be specific to the indication statement.
12.2 Pharmacodynamics	FDA revised this section for consistency with 21 CFR 201.57(c)(13)(i)(B) requirements and specified that the metabolism pathway via UGT [uridine diphosphate (UDP)-glycosyltransferase] is primarily UGT1A6 and UGT2B7.
14.1 Neurofibromatosis Type 1 Associated Plexiform Neurofibromas	FDA revised the text for clarity, brevity and consistency across oncology labeling. Duration of response >12 months and >24 months was added.
17 PATIENT COUNSELING INFORMATION	FDA revised this section for consistency with Section 5.

The agreed upon labeling conveys adequate information for the safe and effective use of GOMEKLI.

The Patient Information document and Instructions for Use were reviewed and revised by the Patient Labeling Team, Office of Prescription Drug Promotion and the Division of Medication Error Prevention and Analysis.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

There were no significant safety concerns identified during the NDA review requiring risk management beyond labeling or warranting consideration for a Risk Evaluation and Mitigation Strategy (REMS). Safety concerns are adequately addressed by information in the Warnings and Precautions and Dosage and Administration sections of product labeling.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The review team recommends the following PMRs/PMCs which were described in the 6-week PMR/PMC Communication Letter to the Applicant:

PMR 1: Complete a carcinogenicity study in rats to evaluate the potential serious risk of carcinogenicity.

Trial Completion: 10/2027

Final Report Submission: 04/2028

PMR 2: Conduct an integrated safety analysis of data from clinical trials to characterize and evaluate the potential serious risk of long-term adverse effects of mirdametinib on growth and development in pediatric patients. Include long-term follow-up data from pediatric patients enrolled on the MEK-NF-201 (ReNeu) trial (NCT03962543) and from ongoing and completed clinical trials of mirdametinib. Pediatric patients must be evaluated for growth and sexual development milestones annually for at least 7 years from initiation of mirdametinib or until a patient has achieved sexual maturity. Evaluations must include growth as measured by weight, height, height velocity, and height standard deviation scores (SDS); if available, include, age at thelarche (females), age at adrenarche (males), age at menarche (females), and Tanner Stage progression.

Trial Completion: 12/2028

Final Report Submission: 06/2029

PMR 3: Conduct an integrated safety analysis of data from clinical trials to further characterize the long-term incidence, severity, and outcomes of the known serious risks of ocular toxicity, left ventricular dysfunction, and dermatologic adverse reactions. Include the long-term follow-up safety data (minimum of 7 years) from adult and pediatric patients enrolled on the MEK-NF-201 (ReNeu) trial (NCT03962543) and all other ongoing and completed trials of mirdametinib to include an analysis of the following toxicities: ocular toxicity (including but not limited to retinal pigment epithelial detachment and retinal vein occlusion), cardiac toxicity (including but not limited to left ventricular dysfunction), and serious dermatologic toxicity.

Trial Completion: 12/2028

Final Report Submission: 06/2029

PMR 4: Conduct a clinical pharmacokinetic trial to evaluate the potential serious risk of increased drug toxicity, and to determine an appropriate, safe dose of mirdametinib, in patients

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with moderate (total bilirubin > 1.5 – 3.0 x ULN, any AST) and severe (total bilirubin > 3 – 10 x ULN, any AST) hepatic impairment. Design and conduct the trial in accordance with the FDA Guidance for Industry titled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

Draft Protocol Submission: 11/2024 (complete)
Final Protocol Submission: 02/2025
Trial Completion: 07/2026
Final Report Submission: 01/2027

PMC 1: Complete the MEK-NF-201 (ReNeu) trial (NCT03962543) to further characterize the clinical benefit of mirdametinib in adult and pediatric patients with neurofibromatosis type 1 (NF1) who have symptomatic plexiform neurofibromas (PN) not amenable to complete resection. To characterize response rate and duration, patients will be followed for at least 24 months from the onset of response.

Trial Completion: 12/2028
Final Report Submission: 06/2029

PMC 2: Conduct a clinical pharmacokinetic trial with a strong CYP3A4 inducer (that also induces UGTs, P-gp, and CES enzymes) with mirdametinib to evaluate the effect of strong CYP3A4 induction on decreasing the systemic exposure of mirdametinib and to provide dosage recommendations for mirdametinib when used concomitantly with strong CYP3A4 inducers. Design and conduct the trial in accordance with the FDA Guidance for Industry titled “M12 Drug Interaction Studies.”

Draft Protocol Submission: 06/2025
Final Protocol Submission: 10/2025
Trial Completion: 10/2026
Final Report Submission: 04/2027

FDA PMC/PMR Checklist for U.S. Population Representativeness

The following were evaluated and considered as part of FDA’s review:		Is a PMC/PMR needed?
x	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age group of the U.S. population for the proposed indication.	☐ Yes ☒ No
x	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	☐ Yes ☒ No

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☐	Other considerations (e.g.: PK/PD), if applicable:	☐ Yes ☐ No
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14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Deputy Division Director (Clinical)

X

Nicole Drezner, MD

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

Paul Kluetz, MD

19 Appendices

19.1. References

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19.2. Financial Disclosure

The Applicant's Position:

See [Sections 8.1.1.1](#) through [Section 8.1.2.1](#) for financial disclosure information.

The FDA's Assessment:

FDA has reviewed the financial disclosure information and agrees with the table below.

Covered Clinical Study (Name and/or Number):* MEK-NF-201 (ReNeu)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>417</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>N/A</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3. Nonclinical Pharmacology/Toxicology

Data:

Not applicable.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

Not applicable.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Summary of Bioanalytical Method Validation and Performance

Bioanalytical methods using liquid chromatography with liquid chromatography with tandem mass spectrometry (LC-MS/MS) were developed and validated to measure mirdametinib and PD-0315209 concentrations in human plasma and urine samples. An overview of PK assays used in mirdametinib clinical studies is shown in **Table 50**. Summaries of individual bioanalytical method validation and performance are provided below (**Table 51 to Table 60**).

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Table 68. Overview of PK assays used in mirdametinib clinical studies.

Study No.	Analytical Lab	Bioanalytical Report No.	Analyte	Matrix	Method Validated/Qualified (V/Q)	Validation/Qualification Report
A4581001	(b) (4)	Unable to obtain report	Mirdametinib and PD-0315209	Plasma	V	764-04368
		Unable to obtain report	Mirdametinib and PD-0315209	Urine	V	764-04369
		05046AKLN_PLC	Mirdametinib and PD-0315209	Plasma	V	05479VDAC_PLC
A4581002		05435AKLN_PLC	Mirdametinib and PD-0315209	Plasma	V	05479VDAC_PLC
A4581004		05394AKLN_PLC	Mirdametinib (b) (4) and PD-0315209	Plasma	V	230372VCWB_SPSC
NF-106		131495ASMB_SPSC	Mirdametinib and PD-0315209	Plasma	V	05479VDAC_PLC
MEK-NF-101		200519AHTVL_SPSC	Mirdametinib and PD-0315209	Plasma	V	05479VDAC_PLC Addendum 1 and Addendum 3
		200520AHTVL_SPSC	Mirdametinib and PD-0315209	Urine	V	200555VHTVL_SPSC
MEK-NF-102		211438AKLNC_SPSC	Mirdametinib and PD-0315209	Plasma	V	05479VDAC_PLC Addendum 1 and Addendum 3
		211436AKLNC_SPSC	Moxifloxacin	Plasma	V	06568VGPH_AIN_R3 and 140916PVCPM_QIN
MEK-NF-201		191627AKLNC_SPSC	Mirdametinib and PD-0315209	Plasma	V	05479VDAC_PLC Addendum 1, Addendum 3, and Addendum 4

Source: Applicant's 2.7.1 Summary of Biopharmaceutic Studies / Associated Analytical Methods (Table 3).

Table 69. Bioanalytical method to determine mirdametinib and PD-0315209 concentrations in human plasma (Study A4581001 Phase 1).

Bioanalytical method validation report name	Method Validation Report: A Modified LC/MS/MS Analysis of PD 0325901, (b) (4) and PD 0315209 in EDTA Human Plasma (Report 764-04368)		
Method description	A liquid chromatographic method with tandem mass spectrometry detection was validated to quantitate PD 0325901, (b) (4) and 0315209 in human plasma with EDTA as an anticoagulant.		
Standard calibration curve concentrations	0.100, 0.200, 1.20, 2.40, 12.0, 30.0, 90.0, 100 ng/mL		
Validated assay range	0.100-100 ng/mL		
Quality control concentrations	0.400, 20.0, 80.0 ng/mL		
Regression model and weighting	1/concentration ² weighted quadratic regression analysis		
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	
	Cumulative accuracy (%bias)	-1.7 to 2.5 (mirdametinib), (b) (4)	-2.5 to 3.3 (PD-0315209)
	Cumulative precision (%CV)	0.5 to 3.1 (mirdametinib), (b) (4)	1.0 to 5.5 (PD-0315209)
Performance of QCs during accuracy and precision runs (Mirdametinib)		Accuracy (% bias)	Precision (% CV)
	Intra Assay	-3.0 to 1.9	≤3.5
	Inter Assay	-1.3 to -0.5	≤3.0
(b) (4)			
Performance of QCs during accuracy and precision runs (PD-0315209)		Accuracy (% bias)	Precision (% CV)
	Intra Assay	-2.5 to 5.1	≤8.5
	Inter Assay	-1.8 to 2.4	≤6.4
Selectivity	Selectivity: Six of 6 sources of EDTA human plasma tested were found to be free of any interfering endogenous materials.		
Hemolysis effect	Not required per guidance at time of validation		
Lipemic effect	Not required per guidance at time of validation		
Benchtop/process matrix stability	Refer to 764-04406		
Dilution Linearity			
Freeze-thaw matrix stability			
Long-term matrix storage			
Matrix Effect			
Recovery			
Reinjection Reproducibility			
Carry-over	Carryover was not reported during validation		
Method Performance in Study A4581001 - Unable to obtain report			

Source: Applicant's 2.7.1 Summary of Biopharmaceutic Studies / Associated Analytical Methods (Appendix 1).

Table 70. Bioanalytical method to determine mirdametinib and PD-0315209 concentrations in human urine (Study A4581001 Phase 1).

Bioanalytical method validation report name	Method Validation Report: LC/MS/MS Analysis of PD 0325901 (b) (4) and PD 0315209 in Human Urine (Report 764-04369)		
Method description	An LC/MS/MS method to quantify PD 0325901, (b) (4) and 0315209 in human urine was validated over the concentration range of 1.00 to 1000 ng/mL.		
Standard calibration curve concentrations	1.00, 2.00, 12.0, 24.0, 120, 300, 900, 1000		
Validated assay range	1.00 to 1000 ng/mL		
Quality control concentrations	4.00, 200, 800		
Regression model and weighting	1/concentration ² weighted linear regression		
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	
	Cumulative accuracy (%bias)	-7.5 to 6.0 (mirdametinib)	(b) (4) -5.8 to 3.0 (PD-0315209)
	Cumulative precision (%CV)	0.7 to 8.9 (mirdametinib),	(b) (4) 0.6 to 3.9 (PD-0315209)
Performance of QCs during accuracy and precision runs (Mirdametinib)		Accuracy (% bias)	Precision (% CV)
	Intra Assay	2.9 to 9.4	≤7.1
	Inter Assay	5.8 to 6.5	≤6.1
(b) (4)			
Performance of QCs during accuracy and precision runs (PD-0315209)		Accuracy (% bias)	Precision (% CV)
	Intra Assay	0.8 to 7.0	≤5.0
	Inter Assay	3.5 to 4.0	≤4.7
Selectivity and matrix effect	Six of 6 sources tested were free of any interfering endogenous materials. No matrix effect that would affect the quantitation of samples was observed.		
Hemolysis effect	Not applicable		
Lipemic effect	Not applicable		
Dilution Linearity	Above the calibration range, 2000 ng/mL diluted 100-fold		
Benchtop/process matrix stability	Stable for at least 6 hours in ambient conditions. Processed extracts for 88 hours in ambient conditions.		
Freeze-thaw matrix stability	Stable for 3 cycles at -20°C		
Long-term matrix storage	Stable at -20°C for at least 99 days		
Carry-over	No carryover was not reported during validation		
Recovery	Recovery of PD 0325901 from human urine was determined to be 93.6(±5.7%) and 110 (±4.4%) at the LQC and HQC, respectively. (b) (4). Recovery of PD 0315209 from human urine was determined to be 88.4 (±3.7%) and 107 (±3.6%) at the LQC and HQC, respectively. Recovery of PD 0319039 from human urine was determined to be 90.0 (±4.7%).		
Reinjection Reproducibility	Not applicable		
Method Performance in Study A4581001 – Unable to obtain report			

Source: Applicant's 2.7.1 Summary of Biopharmaceutical Studies / Associated Analytical Methods (Appendix 2).

Table 71. Bioanalytical method to determine mirdametinib and PD-0315209 concentrations in human plasma (Study A4581001 Phase 2).

Bioanalytical method validation report name	Validation of an LC/MS/MS Assay Method for the Determination of PD-0325901 and Its Metabolite PD-0315209 in K2EDTA Human Plasma (Report 05479VDAC_PLC)		
Method description	This method is applicable for the determination of PD-0325901, PD-0315209 and internal standards ([2H3]PD-0325901 and [2H3]PD-0315209) in potassium EDTA human plasma. Samples are extracted by liquid-liquid (95:5 MTBE/ethanol) and analyzed by LC/MS/MS		
Standard calibration curve concentrations	1.00, 2.00, 5.00, 10.0, 50.0, 100, 500, 900, 1000 ng/mL		
Validated assay range	1 to 1000 ng/mL		
Quality control concentrations	1, 3, 400, and 800 ng/mL		
Regression model and weighting	Calibration curves were fitted by linear least squares regression analysis (weighted as 1/x ²)		
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	9	
	Cumulative accuracy (%bias)	-2.9 to 2.8 (mirdametinib), -2.0 to 1.2 (PD-0315209)	
	Cumulative precision (%CV)	0.7 to 2.5 (mirdametinib), 1.0 to 7.1 (PD-0315209)	
Performance of QCs during accuracy and precision runs (Mirdametinib)		Accuracy (% bias)	Precision (% CV)
	Intra Assay	-15.7 to 3.0	≤3.3
	Inter Assay	-10.0 to -0.3	≤5.4
Performance of QCs during accuracy and precision runs (PD-0315209)		Accuracy (% bias)	Precision (% CV)
	Intra Assay	-14.3 to 3.5	≤6.3
	Inter Assay	-5.8 to -0.5	≤8.5
Selectivity and matrix effect	No chromatographic interferences were observed at the retention times of the analytes or IS in any of the human control samples analyzed		
Hemolysis effect	Not applicable		
Lipemic effect	Not applicable		
Dilution Linearity	Above the calibration range, 4000 ng/mL diluted 10-fold		
Benchtop/process matrix stability	Stable for at least 29 hours in ambient conditions. Processed extracts for 104 hours in ambient conditions.		
Freeze-thaw matrix stability	Stable for 3 cycles at -20°C and -70°C		
Long-term matrix storage	Stable at -20°C and -70°C for at least 421 days		
Carry-over	For PD-0315209, >20% of the LLOQ (only observed in one analytical run and due to high baseline signal), Not detected for mirdametinib nor internal standards.		
Recovery	53.5% (mirdametinib) and 32.9% (PD-0315209) at QC levels 3, 400, and 800 ng/mL; 47.2% ([2H3]PD-0325901) and 14.6% ([2H3]PD-0315209) at 125 ng/mL		
Reinjection Reproducibility	97 hours at ambient conditions		
Method Performance in Study A4581001 Phase 2			
Assay passing rate	7 out of 8 runs (87.5%) were acceptable.		
Number of calibration standards (LLOQ to ULOQ)	9		
Standard curve performance		mirdametinib	PD-0315209
	Cumulative accuracy (%bias)	-6.4 to 4.0	-1.6 to 3.5
	Cumulative precision (%CV)	3.0 to 5.6	1.6 to 5.0
QC performance		mirdametinib	PD-0315209
	Cumulative accuracy (%bias)	-3.3 to 6.9	-2.7 to 1.0
	Cumulative precision (%CV)	0.8 to 8.0	0.7 to 3.8
Study sample analysis/stability	Stable at -20°C for at least 421 days. The longest period between collection and analysis was 590 days and occurred for Subject (b) (6)		

Source: Applicant's 2.7.1 Summary of Biopharmaceutical Studies / Associated Analytical Methods (Appendix 3).

Table 72. Bioanalytical method to determine mirdametinib and PD-0315209 concentrations in human plasma (Study A4581002).

Method Performance in Study A4581002			
Assay passing rate	8 out of 8 runs (100%) were acceptable.		
Number of calibration standards (LLOQ to ULOQ)	9		
Standard curve performance		mirdametinib	PD-0315209
	Cumulative accuracy (%bias)	-4.2 to 3.0	-2.0 to 2.0
	Cumulative precision (%CV)	2.1 to 3.5	3.3 to 5.7
QC performance		mirdametinib	PD-0315209
	Cumulative accuracy (%bias)	-1.1 to 2.0	-2.7 to 1.0
	Cumulative precision (%CV)	≤6.2	≤5.2
Study sample analysis/stability	Stable at -20°C for at least 421 days. The longest period between collection and analysis was 662 days.		

Source: Applicant's 2.7.1 Summary of Biopharmaceutic Studies / Associated Analytical Methods (Appendix 4).

Table 73. Bioanalytical method to determine mirdametinib and PD-0315209 concentrations in human plasma (Study A4581004).

Bioanalytical method validation report name	Method Validation for the Quantitation of PD-0325901, (b) (4) and PD-0315209 in Human Plasma by Turbo Ion Spray Chiral LC/MS/MS (Report 230372VCWB_SPSC)		
Method description	This method is applicable for the determination of PD-0325901, (b) (4), PD-0315209 and internal standards (b) (4) and [³ H]PD-0315209 in potassium EDTA human plasma. Samples are extracted by liquid-liquid (95:5 MTBE/ethanol) and analyzed by LC/MS/MS.		
Standard calibration curve concentrations	0.1, 0.2, 1.2, 2.4, 12, 30, 90, and 100 ng/mL		
Validated assay range	0.1 to 100 ng/mL		
Quality control concentrations	0.1, 0.3, 40.0, and 80.0 ng/mL		
Regression model and weighting	Calibration curves were fitted by quadratic regression analysis (weighted as 1/concentration ²)		
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	8	
	Cumulative accuracy (%bias)	-1.7 to 1.3 (mirdametinib)	(b) (4) -3.3 to 1.5 (PD-0315209)
	Cumulative precision (%CV)	2.21 to 4.4 (mirdametinib)	(b) (4) 1.5 to 9.6 (PD-0315209)
Performance of QCs during accuracy and precision runs (Mirdametinib)		Accuracy (% bias)	Precision (% CV)
	Intra Assay	-4.7 to 5.3	≤6.5
	Inter Assay	-2.4 to 2.3	≤5.1
(b) (4)			
Performance of QCs during accuracy and precision runs (PD-0315,209)		Accuracy (% bias)	Precision (% CV)
	Intra Assay	-5.3 to 6.0	≤18.9 (value at LLOQ, all other concentrations at ≤9.9)
	Inter Assay	-1.3 to 1.6	≤14.8

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Selectivity and matrix effect	No chromatographic interferences were observed at the retention times of analytes and internal standards		
Hemolysis effect	Not applicable		
Lipemic effect	Not applicable		
Dilution Linearity	Above the calibration range, 200 ng/mL diluted 10-fold		
Benchmark/process matrix stability	24 hours benchmark/39 hours process matrix		
Freeze-thaw matrix stability	5 cycles at -20°C and -70°C		
Long-term matrix storage	Stable at -20°C and -70°C for at least 147 days.		
Carry-over	Not detected for mirdametinib and (b) (4). PD-0315209 was >20% of LLOQ response for the blank sample after the ULOQ, but <20% in the second blank sample.		
Recovery	For QC low, medium, high: 64.9% (mirdametinib); (b) (4) 33.8% (PD-0315209); (b) (4) 28.1% ([³ H]PD-0315209)		
Reinjection Reproducibility	165 hours		
Method Performance in Study A4581004			
Assay passing rate	Mirdametinib: 10 out of 12 runs (83.3%) were acceptable. (b) (4) PD-0315209: 12 out of 13 runs (92.3%) were acceptable.		
Number of calibration standards (LLOQ to ULOQ)	8		
Standard curve performance		mirdametinib	(b) (4) PD-0315209
	Cumulative accuracy (%bias)	-0.6 to 1.0	-1.7 to 2.7
	Cumulative precision (%CV)	2.9 to 7.3	2.0 to 7.1
QC performance		mirdametinib	PD-0315209
	Cumulative accuracy (%bias)	-5.4 to 2.7	-1.9 to 4.0
	Cumulative precision (%CV)	≤9.0	≤8.5
Study sample analysis/stability	Stable at -20°C and -70°C for at least 147 days. The longest period between collection and analysis was 94 days.		

Source: Applicant's 2.7.1 Summary of Biopharmaceutical Studies / Associated Analytical Methods (Appendix 5).

Table 74. Bioanalytical method to determine mirdametinib and PD-0315209 concentrations in human plasma (Study NF-106).

Method Performance in Study NF106			
Assay passing rate	2 out of 2 (100%) were acceptable		
Number of calibration standards (LLOQ to ULOQ)	9		
Standard curve performance		mirdametinib	PD-0315209
	Cumulative accuracy (%bias)	-2.0 to 2.4	-4.3 to 2.6
	Cumulative precision (%CV)	≤11.9	≤8.1
QC performance		mirdametinib	PD-0315209
	Cumulative accuracy (%bias)	-1.9 to 0.0	2.1 to 6.7
	Cumulative precision (%CV)	≤4.7	≤6.8
Study sample analysis/stability	All samples were analyzed within 931 days within the established stability of 1136 days at -20°C		

Source: Applicant's 2.7.1 Summary of Biopharmaceutical Studies / Associated Analytical Methods (Appendix 6).

Table 75. Bioanalytical method to determine mirdametininb and PD-0315209 concentrations in human plasma (Study MEK-NF-101).

Bioanalytical method validation report name	The Partial Validation of an HPLC-MS/MS Method for the Determination of PD-0325901 and PD-0315209 in Human K2EDTA Plasma on an API-4000 (Report 05479VDAC_PLC_Addendum 1)		
Method description	This method is applicable for the determination of PD-0325901, PD-0315209 and internal standards (PD-0325901-d3 and PD-0315209-d3) in potassium EDTA human plasma. Samples are extracted by liquid-liquid (95:5 MTBE/ethanol) and analyzed by LC/MS/MS		
Standard calibration curve concentrations	1.0, 2.0, 5.0, 10.0, 50.0, 100, 500, 900, 1000 ng/mL		
Validated assay range	1.0 to 1000 ng/mL		
Quality control concentrations	3.00, 400 and 800 ng/mL		
Regression model and weighting	Calibration curves were fitted by linear least squares regression analysis (weighted as 1/x ²)		
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	9	
	Cumulative accuracy (%bias)	-2.4 to 2.7 (mirdametininb); -2.0 to 1.3 (PD-0315209)	
	Cumulative precision (%CV)	1.5 to 5.8 (mirdametininb); 2.2 to 8.4 (PD-0315209)	
Performance of QCs during accuracy and precision runs (Mirdametininb)		Accuracy (% bias)	Precision (% CV)
	Intra Assay	-0.6 to 4.0	≤10.0
	Inter Assay	-1.2 to 4.3	≤9.9
Performance of QCs during accuracy and precision runs (PD-0315209)		Accuracy (% bias)	Precision (% CV)
	Intra Assay	-4.7 to 2.8	≤6.9
	Inter Assay	-4.2 to -0.5	≤6.9
Selectivity Matrix effect Recovery Reinjection Reproducibility	Reported in 05479VDAC_PLC		
Hemolysis effect	No hemolysis effect on assay performance		
Lipemic effect	No lipolysis effect on assay performance		

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Dilution Linearity	Above the calibration range, 4000 ng/mL diluted 10-fold		
Benchmark/process matrix stability	Not applicable		
Freeze-thaw matrix stability	Stable for 5 cycles at -20°C and -70°C		
Long-term matrix storage	Stable at -20°C and -70°C for at least 421 days as reported in 05479VDAC_PLC		
Carry-over	≤20% for all validation runs except 2, 6, and 9. Carryover was mitigated, and no QC samples were adversely affected.		
Bioanalytical method validation report name	Partial Validation for the Quantitation of PD-0325901 and PD-0315209 in Human Plasma by Turbo Ion Spray LC/MS/MS (Report 05479VDAC_PLC_Addendum 3)		
Method description	This method is applicable for the determination of PD-0325901, PD-0315209 and internal standards (PD-0325901-d3 and PD-0315209-d3) in potassium EDTA human plasma. Samples are extracted by liquid-liquid (95:5 MTBE/ethanol) and analyzed by LC/MS/MS		
Standard calibration curve concentrations	1.0, 2.0, 5.0, 10.0, 50.0, 100, 500, 900, 1000 ng/mL		
Validated assay range	1.0 to 1000 ng/mL		
Quality control concentrations	3.00, 40.0, 400, 800 and 4000 ng/mL		
Regression model and weighting	Calibration curves were fitted by linear least squares regression analysis (weighted as 1/x ²)		
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	9	
	Cumulative accuracy (%bias)	-3.3 to 3.0 (mirdametinib); -4.4 to 4.0 (PD-0315209)	
	Cumulative precision (%CV)	1.5 to 9.6 (mirdametinib); 1.7 to 7.6 (PD-0315209)	
Performance of QCs during accuracy and precision runs (Mirdametinib)		Accuracy (% bias)	Precision (% CV)
	Intra Assay	-1.7 to 0.8	≤6.8
	Inter Assay	-6.0 to -0.5	≤6.5
Performance of QCs during accuracy and precision runs (PD-0315209)		Accuracy (% bias)	Precision (% CV)
	Intra Assay	-1.6 to 2.5	≤3.6
	Inter Assay	-6.9 to 3.0	≤7.2
Selectivity	Reported in 05479VDAC_PLC		
Matrix effect			
Process matrix stability			
Recovery			
Reinjection Reproducibility			
Hemolysis/Lipemic effect	Reported in 05479VDAC_PLC_Addendum 1		
Dilution Linearity	Above the calibration range, 4000 ng/mL diluted 10-fold		
Benchmark matrix stability	Stable for at least 24 hours at ambient conditions.		
Freeze-thaw matrix stability	Stable for 5 cycles at -20°C and 4 cycles at -70°C		
Long-term matrix storage	Stable at -20°C for at least 516 days		
Carry-over	≤20% for all validation runs except 2, 6, and 9. Carryover was mitigated, and no QC samples were adversely affected.		
Method Performance in Study MEK-NF-101 (Plasma)			
Assay passing rate	3 out of 4 runs (75.0%) were acceptable.		
Number of calibration standards (LLOQ to ULOQ)	9		
Standard curve performance		mirdametinib	PD-0315209
	Cumulative accuracy (%bias)	-2.6 to 4.5	-3.1 to 3.0
	Cumulative precision (%CV)	2.5 to 4.7	2.2 to 6.2
QC performance		mirdametinib	PD-0315209
	Cumulative accuracy (%bias)	-7.0 to -2.0	-7.8 to 1.0
	Cumulative precision (%CV)	2.5 to 8.4	2.6 to 7.3

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ISR Performance	Mirdametininib: 41 samples. 100% of the repeated samples had a relative percent difference of within $\pm 20.0\%$ PD-0315209: 41 samples. 100% of the repeated samples had a relative percent difference of within $\pm 20.0\%$
Study sample analysis/stability	Stable at -20°C for at least 113 days (at time of study). The longest period between collection and analysis was 23 days.

Source: Applicant's 2.7.1 Summary of Biopharmaceutic Studies / Associated Analytical Methods (Appendix 7).

Table 76. Bioanalytical method to determine mirdametininib and PD-0315209 concentrations in human urine (Study MEK-NF-101).

Bioanalytical method validation report name	Method Validation for the Quantitation of PD-0325901 and PD-0315209 in Treated Human Urine by Turbo Ion Spray LC/MS/MS (200555VHTVL_SPSC)		
Method description	An LC/MS/MS method for the quantitation of PD-0325901 and PD-0315209 in 50 mL of human urine treated to contain 0.2% Triton X-100 has been validated over the concentration range of 1.00 to 200 ng/mL.		
Standard calibration curve concentrations	1.00, 2.00, 5.00, 20.0, 100, 160, 200		
Validated assay range	1.00 to 200 ng/mL		
Quality control concentrations	1.00, 3.00, 60.0, 150 ng/mL		
Regression model and weighting	Calibration curves were fitted by linear least squares regression analysis (weighted as 1/x ²)		
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	7	
	Cumulative accuracy (%bias)	-3.1 to 2.5	
	Cumulative precision (%CV)	3.7 to 7.2	
Performance of QCs during accuracy and precision runs (Mirdametininib)		Accuracy (% bias)	Precision (% CV)
	Intra Assay	-4.8 to 5.3	≤ 18.1
	Inter Assay	-1.2 to 3.0	≤ 12.5
Performance of QCs during accuracy and precision runs (PD-0315209)		Accuracy (% bias)	Precision (% CV)
	Intra Assay	-6.2 to 4.3	≤ 9.3
	Inter Assay	-2.3 to 2.3	≤ 7.3
Selectivity and matrix effect	No chromatographic interferences were observed at the retention times of analytes and internal standards		
Hemolysis effect	Not applicable		
Lipemic effect	Not applicable		
Dilution Linearity	Above the calibration range, 200 ng/mL diluted 10-fold		

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Benchtop/process matrix stability	24 hours benchtop/94 hours at 4°C		
Freeze-thaw matrix stability	5 cycles at -20°C and -70°C		
Long-term matrix storage	Stable at -20°C and -70°C for at least 40 days.		
Carry-over	No response >20% of the mean response ratio of the LLOQ standards in the carryover blank, or by the last mitigation blank.		
Recovery	Not applicable		
Reinjection Reproducibility	99 hours		
Method Performance in Study MEK-NF-101 (Urine)			
Assay passing rate	2 out of 2 runs (100%) were acceptable.		
Number of calibration standards (LLOQ to ULOQ)	7		
Standard curve performance		mirdametinib	PD-0315209
	Cumulative accuracy (%bias)	-2.0 to 2.0	-0.6 to 0.5
	Cumulative precision (%CV)	≤3.8	≤5.3
QC performance		mirdametinib	PD-0315209
	Cumulative accuracy (%bias)	-2.2 to 0.0	-0.7 to 5.0
	Cumulative precision (%CV)	≤5.1	≤2.7
Study sample analysis/stability	All samples were analyzed in 35 days within the established stability of 40 days at the time of the study.		

Source: Applicant's 2.7.1 Summary of Biopharmaceutic Studies / Associated Analytical Methods (Appendix 8).

Table 77. Bioanalytical method to determine mirdametinib and PD-0315209 concentrations in human plasma (Study MEK-NF-102).

Method Performance in Study MEK-NF-102			
Assay passing rate	16 out of 16 runs (100%) were acceptable.		
Number of calibration standards (LLOQ to ULOQ)	7		
Standard curve performance		mirdametinib	PD-0315209
	Cumulative accuracy (%bias)	-3.7 to 1.6	-4.4 to 2.2
	Cumulative precision (%CV)	≤4.7	≤5.2
QC performance		mirdametinib	PD-0315209
	Cumulative accuracy (%bias)	-1.5 to 3.7	-4.5 to 3.0
	Cumulative precision (%CV)	≤3.9	≤4.5
ISR Performance	Mirdametinib: 140 samples. 100% of the repeated samples had a relative percent difference of within ±20.0% PD-0315209: 140 samples. 99.3% of the repeated samples had a relative percent difference of within ±20.0%		
Study sample analysis/stability	All samples were analyzed within 97 days within the established stability of 516 days at -20°C		

Source: Applicant's 2.7.1 Summary of Biopharmaceutic Studies / Associated Analytical Methods (Appendix 9).

Table 78. Bioanalytical method to determine mirdametinib and PD-0315209 concentrations in human plasma (Study MEK-NF-201).

Method Performance in Study MEK-NF-201			
Assay passing rate	22 out of 24 runs (91.7%) were acceptable.		
Number of calibration standards (LLOQ to ULOQ)	9		
Standard curve performance		mirdametinib	PD-0315209
	Cumulative accuracy (%bias)	-2.6 to 1.6	-3.2 to 1.8
	Cumulative precision (%CV)	≤6.5	≤5.1
QC performance		mirdametinib	PD-0315209
	Cumulative accuracy (%bias)	-1.9 to 3.0	-2.4 to 3.8
	Cumulative precision (%CV)	≤5.1	≤4.5
ISR Performance	Mirdametinib: 170 samples. 100% of the repeated samples had a relative percent difference of within ±20.0% PD-0315209: 170 samples. 99.4% of the repeated samples had a relative percent difference of within ±20.0%		
Study sample analysis/stability	All samples were analyzed within 798 days within the established stability of 1136 days at -20°C		

Source: Applicant's 2.7.1 Summary of Biopharmaceutical Studies / Associated Analytical Methods (Appendix 10).

19.4.2. Population PK Analysis

19.4.2.1. Executive Summary

A PopPK model was developed to support the dose rationale for mirdametinib and is included in this NDA. This activity included the following objectives:

- Develop fit-for-purpose PopPK models to characterize the PK of mirdametinib and its active metabolite, PD-0315209, in healthy participants and participants with NF1 PN;
- Evaluate the effect of covariates on the variability of mirdametinib and PD-0315209 PK;
- Evaluate the magnitude and clinical relevance, when possible, of the statistically significant findings from the analysis;
- Predict mirdametinib and PD-0315209 exposures following doses of mirdametinib under scenarios of clinical importance.

Methods: Fit-for-purpose PopPK models were developed separately for mirdametinib and PD-0315209. The PD-0315209 model was developed sequentially, using empirical Bayes estimates (EBE) from the mirdametinib model. PD-0315209 PK was driven by fraction of parent drug converted to metabolite (Fm) from the mass balance study (MEK-NF-101). Nonlinear mixed effects modeling was employed to evaluate additional effects on model parameters and improve the ability of the model to describe all available data. Covariate-parameter relationships of interest were explored graphically and formally tested in each model if substantial trends were evident. Numerical checks of parameter precision and model robustness, goodness of fit (GOF) model diagnostics, and visual predictive checks (VPCs) were used to qualify the models for use in simulations.

Results: Apparent clearance (CL/F) of mirdametininib was 4.17 L/h for a typical 75 kg participant. At the median weight in pediatric participants (34.8 kg), CL/F of mirdametininib was 2.57 L/h. At the median weight in adult participants (72.8 kg), CL/F of mirdametininib was 4.09 L/h. Apparent clearance (CL/F) of mirdametininib was 4.17 L/h for a typical 75 kg participant. No difference in mirdametininib CL/F was observed between healthy participants and patient populations. Estimates for V_c/F , apparent peripheral volume of distribution – shallow compartment (V_{p1}/F) and apparent peripheral volume of distribution - deep compartment (V_{p2}/F) were 16.0, 22.4 and 54.3 L, respectively. The PopPK model included allometric scaling of time-varying weight on clearances and volumes of distribution. The estimated allometric coefficient for clearances was 0.631 and the estimate for volumes of distribution was 0.586.

The rapid absorption of mirdametininib following oral administration was described using a transit compartment absorption model (TCAM) model, driven by a mean transit time (MTT) of 0.542 h and 2.46 transit compartments. No statistically significant differences in absorption were found between fasted and unknown food status. However, administration of mirdametininib with a high-fat meal resulted in increased variability in TCAM model parameters, delayed absorption (MTT = 3.08 h), and an 8.80% decrease in relative bioavailability (F_{rel}). No statistically significant differences were observed between the tablet and capsule formulations.

For PD-0315209, apparent clearance (CL_m/F) was 0.583 L/h. At the median weight in pediatric participants (34.85 kg), CL_m/F of PD-0315209 was 0.328 L/h. At the median weight in adult participants (72.8 kg), CL_m/F of mirdametininib was 0.570 L/h. No statistically significant difference in CL_m/F was identified between healthy participants and patient populations. In addition to allometric effects of weight on PD-0315209 clearances and volumes, the final PD-0315209 PopPK model includes effects of CL_{cr} on CL_m/F and concomitant UGT2B7 inducer use and age on F_m . While these effects were statistically significant when tested individually in the model, the impact of each effect is limited relative to the overall variability of PD-0315209 exposures.

The applicant tested the effect of concomitant use of several inhibitors or inducers (e.g. CES1, UGT1A6 and UGT2B7) through popPK analysis. The comedication analysis included the use of multiple comedications and multiple classifications for the comedications used. The design of the studies, in which multiple concomitant medications were allowed, along with the lack of specificity of these medicines for a single enzyme, limits the precise characterization of enzyme modulator interactions on the PK of mirdametininib using the PopPK analysis. Therefore, the review team does not think popPK results alone can support the proposed DDI statement in the label.

The sponsor also proposed unified dosing table to simplify the dosing regimen. The exposures at steady state of unified dose are comparable to the previously tested tablets in the trial in each BSA band based on the simulation. Therefore, the review team thinks the proposed unified dosage is acceptable.

Overall Conclusions:

- Mirdametinib PK was adequately characterized by a three-compartment model with absorption described by a TCAM.
- PD-0315209 PK was adequately characterized by a three-compartment model driven by Fm with IIV on CLm/F, Vmc/F, Fm, Qm1/F, and Vmc/F.
- Mirdametinib and PD-0315209 exposure is linear with dose over the range of doses evaluated (up to 20 mg).
- While a statistically significant effect for CLcr on CLm/F was identified, CL/F was not impacted by CLcr and mild and moderate impairment were not associated with clinically meaningful changes in exposure for mirdametinib and PD-0315209.
- Fm in participants using concomitant UGT2B7 inducers was 19% higher than without concomitant UGT2B7 inducers. In MEK-NF-201 participants, the median Fm with and without UGT2B7 inducers was 16.7% and 11.7%, respectively; however, steady-state observed and model-predicted exposures following nominal BID mirdametinib dosing were similar.
- Model qualifications show that the PopPK models describe the PK of mirdametinib and PD-0315209 adequately. VPCs support use of the models for exposure predictions and for simulations in support of predictive applications.
- Due to use of multiple comedications and multiple classifications for the comedications used, and the limitation of the study design, PopPK results alone can not support the proposed DDI statement in the label.
- The proposed unified dosage is acceptable as the exposures at steady state of unified dose are comparable to the previously tested tablets in the trial in each BSA band based on the simulation.

19.4.2.2. PPK Assessment Summary

The Applicant's Position:

The PK of mirdametinib was well described by a three-compartment model with central clearance and a transit compartment absorption model. Covariates with significant but minor impact included fed status on mean transit time and bioavailability, and body weight on clearance and central volume. A three-compartment model was also used to describe the PK of the metabolite PD-0315209. Covariates with significant but minor impact for the metabolite included time-varying weight on clearance and central volume, creatinine clearance on clearance, age on fraction metabolized, and concomitant use of UGT2B7 inducers on fraction metabolized. All covariate effects were minor and none considered clinically relevant. There was no relevant difference in PK between patients and healthy volunteers.

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Mirdametinib (GOMEKLI)

General Information		
Objectives of PPK Analysis		- Develop fit-for-purpose PopPK models to characterize the PK of mirdametinib and PD-0315209 in healthy participants and participants with NF1 PN - Evaluate the effect of covariates on the variability of mirdametinib and PD-0315209 PK - Evaluate the magnitude and clinical relevance, when possible, of the statistically significant findings from the analysis - Predict mirdametinib and PD-0315209 exposures following doses of mirdametinib under scenarios of clinical importance.
Studies Included		A4581001, A4581002, A4581004, NF106, and MEK-NF-201
Dose(s) Included		Non-NF1 PN studies: ranged from 1 mg QD to 30 mg BID, including 20 mg single dose NF1 PN studies: 2 mg/m² BID (maximum dose of 4 mg BID intermittent 3 weeks on/1-week off dosing). Actual administered doses ranged from 1 to 4 mg BID.
Population Included		Non-NF1 PN participants: advanced cancers, advanced non-small cell lung cancer (NSCLC), healthy Asian participants NF1 PN participants: adult and pediatric participants
Population Characteristics	General	Age median (range): 36.0 yrs (2 – 86.0) Weight median (range): 68 kg (11.4 – 181) Male: 131 (50.4%) Female: 129 (49.6%) Asian: 30 (11.5%) Black/African American: 29 (11.2%) Native American: 1 (0.385%) Other: 14 (5.38%) White/Caucasian: 186 (71.5%)
	Organ Impairment	Hepatic impairment based on NCI-ODWG: Group B2 (Mild, Bilirubin >1 to 1.5x ULN) – 19 (7.3%); Group C (Moderate, Bilirubin >1.5x to 3x ULN) – 6 (2.3%) Renal impairment: 60 (23.1%) participants w/ mild renal impairment (CRCL 60 to < 90 ml/min), and 10 (3.85%) participants w/ moderate renal impairment (CRCL 30 to <60 ml/min)
	Pediatrics (if any)	Age 2 to 11 – 32 (12.3%); Age 12 to 17 – 26 (10%)
No. of Patients, PK Samples, and BLQ		202 adult participants (77.7%) 58 pediatric participants (22.3%) 4871 PK samples 477 (9.79%) and 455 (9.34%) of samples were BLQ for mirdametinib and PD-0315209, respectively. 230 (5.05%) and 206 (4.53%) of post-dose samples were BLQ for mirdametinib and PD0315209, respectively.
Sampling Schedule		A4581001: QD cohort – pre-dose, 0, 1, 2, 3, 4, 6, 8, 12, 24h BID cohort – pre-dose, 0, 1, 2, 3, 4, 6, 8, 12h Terminal elimination sampling – 30, 36, 48, and 54h (after last AM dose Cycle 1/Day 21 of RP2D cohort RP2D: Cycle 1/Day 15 – pre-dose, 1, 2, 3, 4, 6, and 10h A4581002:

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		Cycles 1, 2, 3, 5, 7/Days 1 and 19 – pre-dose, 2-8h A4581004: Day 1 – pre-dose, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 36, 72, 168, 264, 336h NF106: Cycle 1/Day 1 – pre-dose, 0.5, 1, 2, 3, 4, 6, 8, and 10-12h MEK-NF-101: Pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, and 312h MEK-NF-201: Cycle 1/Day 1 – pre-dose, 1h and 2h Cycle 1/Day 15 – pre-dose, 0.5, 1, 2, 3, and 4h Cycles 2-7, 9, 11, 13, 15, 17, 19, 21, and 23/Day15 – pre-dose Cycle 24/Day 21 – 0
Covariates Evaluated	Static	Disease type/patient population, dose, sex, race, formulation, fed status, bilirubin, AST, ALT, ALP, albumin, creatinine clearance,
	Time-varying	Body-weight, dose, BMI, age, BSA, concomitant medications (UGT1A6, UGT2B7, CES1 inhibitors/inducers, and P-gp inhibitors)
Final Model		Summary Acceptability [FDA's comments]
Software and Version		NONMEM (Version 7.4) Acceptable
Model Structure		Mirdametininib: Three-compartment model with drug absorption characterized by a TCAM PD-0315209: Three-compartment model driving by Fm. Acceptable
Model Parameter Estimates		Mirdametininib, Table 49 PD-0315209, Table 50 Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)		In the final mirdametininib model, η-shrinkage for CL/F, Vc/F, Q2/F, Vp1/F, NTR, MTT and Frel was 21.8%, 38.8%, 58.1%, 29.0%, 56.5%, 23.8% and 45.0%, respectively. Shrinkage was acceptable, except for Vc/F, Q2/F, NTR and Frel, which may mask, falsely induce, or distort the shape of the covariate-parameter relationship. IIV was included on CL/F, Vc/F, Q2/F, Vp2/F, NTR, MTT and Frel with estimates of 26.7% CV, 41.5% CV, 21.8% CV, 80.4% CV, 88.3% CV, 75.8% CV and 15.3% CV, respectively. Residual variability was described by a proportional error model, with estimates of 39.7% CV for studies A4581001, A4581002 and MEK-NF-201, 14.5% for NF106 and 20.8% for A4581004. Generally, RUV increased with the study size and the proportion of samples with unknown food status. Large inter- and intra-study variability was observed in mirdametininib exposures, Acceptable

	mainly due to the administration of mirdametinib with different food status (fasted, unknown food status, and fed high-fat meal). PK samples obtained after a high-fat meal showed larger variability and a complex absorption profile. A TCAM resulted in an adequate characterization of the data –except for participants showing a biphasic absorption profile– and an estimate for MTT after a high-fat meal (3.08 h) consistent with gastrointestinal transit. (b) (4) In the final PD-0315209 model, η-shrinkage for CLm/F, Vmc/F, Fm, Qm1/F, and Vmp1/F were 21.6%, 31.0%, 18.1%, 34.2%, and 28.2%, respectively. Shrinkage was low for CLm/F and Fm and moderate for the remaining parameters. IIV was included on CLm/F, Vmc/F, Fm, Qm1/F, and Vmp1/F with estimates of 47.4% CV, 163% CV, 49.7% CV, 65.7% CV, and 51.9% CV. IIV on all modeled parameters was high (at or above 50%), reflecting the substantial variability observed in PD-0315209 plasma exposures. Residual unexplained variability was described by a proportional plus additive error with estimates of 27.3% for the proportional error and 7.4% for the additive error.	
BLQ for Parameter Accuracy	The LLOQ for all methods was 0.1 ng/mL [A4581001 (Phase 1) and A4581004] or 1 ng/mL [A4581001 (Phase 2), A4581002, MEK-NF-101, NF106 and MEK-NF-201]. Since BLQ frequency was relatively low, missing values were unlikely to unduly influence model development. As such, likelihood-based approaches for handling BQL data were not considered.	Acceptable

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GOF, VPC	The final mirdametininib and PD-315209 models were considered adequate based on evaluation of diagnostic goodness-of-fit (GOF) plots, individual PK predictions over time, and visual predictive checks (VPC).	Acceptable
Significant Covariates and Clinical Relevance	Effects of intrinsic and extrinsic factors, including sex, race, age, baseline creatinine clearance (CLcr), baseline liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin (BILI)), baseline albumin, and baseline alkaline phosphatase (ALP) were evaluated graphically. Concomitant medications, including CES1 inducers, P-glycoprotein (P-gp) inhibitors, and UGT1A6 and UGT2B7 inducers and inhibitors were also evaluated graphically. No relationships with mirdametininib PK parameters were observed. Statistically significant effects were found for CLcr on apparent clearance of PD-0315209 (CLm/F), UGT2B7 use on fraction metabolized (Fm), and age on Fm; however, the impacts were limited relative to overall variability of PD-0315209 exposures. Thus, the limited changes to predicted exposures matched with the low concentrations relative to in vitro IC50s suggest that these effects are not clinically relevant.	Acceptable except assessment of concomitant medications((CES1 inducers, P-gp inhibitors, UGT1A6 and UGT2B7 inducers and inhibitors)
Analysis Based on Simulation (optional)	Steady-state concentrations of mirdametininib and PD-0315209 were simulated for NF1 PN participants and are presented in Table 51 and Table 52 . Analysis was conducted to predict the clinical impact of renal function, resulting in predicted exposure changes that are not clinically relevant for patients with mild or moderate renal impairment (Figure 14). Analysis was conducted to predict the clinical impact of notable covariate relationships including dose form, demographic characteristics, and baseline lab values. The relationship with bilirubin is presented in (Figure 15).	Acceptable
Labeling Language	Description	Acceptability [FDA's comments]
12.3 PK	General mirdametininib PK parameters are summarized in the USPI. General PD-0315209 PK parameters were not	In general acceptable.

	summarized based on the lack of clinical relevance to safety and efficacy. <u>Specific Populations</u> (b) (4)	We do not agree that DDI assessment based on popPK analysis alone is sufficient to support the proposed statement in the label.
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	<u>Drug Interaction Studies</u> (b) (4) (b) (4) (b) (4) (b) (4) <i>In Vitro Studies</i> <i>CYP Enzymes:</i> Mirdametinib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. Mirdametinib does not induce CYP1A2, CYP2B6, CYP2C8, CYP2C9, or CYP2C19. (b) (4) <i>Transporter Systems:</i> Mirdametinib does not inhibit (b) (4) (BCRP), (b) (4) (P-gp), OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1, or MATE2K transporters. Mirdametinib is a substrate of BCRP and P-gp transporters.	
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Table 79: Parameter Estimates of the Final Mirdametinib PopPK Model

Parameter	Descriptor	Estimate	CI95
θ_1	Apparent Clearance (L/h)	4.17	(3.88 - 4.49)
θ_2	Apparent Central Volume of Distribution (L)	16.0	(13.9 - 18.3)
θ_3	Apparent Intercompartmental Clearance - Shallow Compartment (L/h)	0.520	(0.469 - 0.577)
θ_4	Apparent Peripheral Volume of Distribution - Shallow Compartment (L)	22.4	(20.6 - 24.3)
θ_5	Apparent Intercompartmental Clearance - Deep Compartment (L/h)	8.16	(7.23 - 9.22)
θ_6	Apparent Peripheral Volume of Distribution - Deep Compartment (L)	54.3	(43.3 - 68.0)
θ_7	Number of Transit Compartments (n)	2.46	(1.84 - 3.30)
θ_8	Mean Transit Time - High-fat meal (h)	3.08	(2.30 - 4.13)
θ_9	Proportional Error	0.397	(0.368 - 0.426)
θ_{11}	Mean Transit Time - Fasted or Unknown food (ratio)	0.176	(0.0771 - 0.274)
θ_{12}	Relative Bioavailability - High-fat meal (ratio)	0.912	(0.872 - 0.953)
θ_{13}	Proportional Error - Study NF106	0.145	(0.108 - 0.181)
θ_{14}	Proportional Error - Study A4581004	0.208	(0.188 - 0.228)
θ_{16}	Apparent Intercompartmental Clearance Deep Compartment - Healthy Volunteers (ratio)	0.430	(0.354 - 0.506)
θ_{17}	Allometric Coefficient - Body Weight on Clearances	0.631	(0.429 - 0.832)
θ_{18}	Allometric Coefficient - Body Weight on Volumes of Distribution	0.586	(0.0938 - 1.08)
$\omega_{1.1}$	$\omega_{\text{Apparent Clearance}}^2$	0.0714	(0.0500 - 0.0928)
$\omega_{2.2}$	$\omega_{\text{Apparent Central Volume of Distribution}}^2$	0.172	(0.0753 - 0.268)
$\omega_{5.5}$	$\omega_{\text{Apparent Intercompartmental Clearance - Deep Compartment}}^2$	0.0476	(0.0102 - 0.0850)
$\omega_{6.6}$	$\omega_{\text{Apparent Peripheral Volume of Distribution - Deep Compartment}}^2$	0.647	(0.0809 - 1.21)
$\omega_{7.7}$	$\omega_{\text{Number of Transit Compartments}}^2$	0.779	(0.327 - 1.23)
$\omega_{8.8}$	$\omega_{\text{Mean Transit Time}}^2$	0.574	(0.331 - 0.817)
$\omega_{9.9}$	$\omega_{\text{Relative Bioavailability}}^2$	0.0235	(0.00363 - 0.0434)

Abbreviations: CI95, 95% Confidence Interval; ω_X^2 , variance of inter-individual variability of parameter X.

Table 80: Parameter Estimates of the PD-0315209 PopPK Model

Parameter	Descriptor	Estimate	CI95
θ_1	CL _m /F, Apparent Clearance PD-0315209 (L/h)	0.583	(0.536 - 0.635)
θ_2	Apparent Central Volume of Distribution (L)	0.700	(0.231 - 2.12)
θ_4	Apparent Intercompartmental Clearance - Deep Compartment (L/h)	4.77	(3.01 - 7.54)
θ_5	Apparent Peripheral Volume of Distribution - Deep Compartment (L)	3.90	(3.51 - 4.34)
θ_6	Apparent Intercompartmental Clearance - Shallow Compartment (L/h)	0.446	(0.382 - 0.520)
θ_7	Apparent Peripheral Volume of Distribution - Shallow Compartment (L)	5.48	(4.65 - 6.46)
θ_8	Proportional Error	0.273	(0.244 - 0.302)
θ_9	Additive Error	0.0742	(0.00550 - 0.143)
θ_{10}	Allometric Coefficient - Time-Varying Weight on Clearances	0.750	NC
θ_{11}	Allometric Coefficient - Time-Varying Weight on Volumes of Distribution	0.652	(0.652 - 0.652)
θ_{12}	Creatinine Clearance on CL _m /F (power)	0.225	(0.225 - 0.225)
θ_{14}	UGT2B7 Inducer on logit of F _m (ratio)	0.854	(0.635 - 1.07)
θ_{15}	Age on F _m (power)	-0.148	(-0.148 - -0.148)
$\omega_{1.1}$	$\omega_{\text{Apparent Clearance of the Metabolite}}^2$	0.351	(0.155 - 0.547)
$\omega_{2.1}$	$\omega_{\text{Covariance CL}_m - V_5}^2$	-0.198	(-0.643 - 0.247)
$\omega_{2.2}$	$\omega_{\text{Apparent Central Volume of Distribution of the Metabolite}}^2$	2.65	(-0.0313 - 5.32)
$\omega_{3.1}$	$\omega_{\text{Covariance CL}_m - F_m}^2$	-0.237	(-0.394 - -0.0789)
$\omega_{3.2}$	$\omega_{\text{Covariance V}_5 - F_m}^2$	0.151	(-0.207 - 0.509)
$\omega_{3.3}$	$\omega_{F_m}^2$	0.247	(0.133 - 0.361)
$\omega_{4.1}$	$\omega_{\text{Covariance CL}_m - Q_{56}}^2$	0.306	(0.0535 - 0.559)
$\omega_{4.2}$	$\omega_{\text{Covariance V}_5 - Q_{56}}^2$	-0.452	(-1.01 - 0.102)
$\omega_{4.3}$	$\omega_{\text{Covariance F}_m - Q_{56}}^2$	-0.213	(-0.391 - -0.0355)
$\omega_{4.4}$	$\omega_{\text{Apparent Intercompartmental Clearance - Deep}}^2$	0.432	(0.126 - 0.738)
$\omega_{5.1}$	$\omega_{\text{Covariance CL}_m - V_6}^2$	0.264	(0.0104 - 0.518)
$\omega_{5.2}$	$\omega_{\text{Covariance V}_5 - V_6}^2$	-0.409	(-1.15 - 0.336)
$\omega_{5.3}$	$\omega_{\text{Covariance F}_m - V_6}^2$	-0.178	(-0.403 - 0.0475)
$\omega_{5.4}$	$\omega_{\text{Covariance Q}_{56} - V_6}^2$	0.313	(0.104 - 0.521)
$\omega_{5.5}$	$\omega_{\text{Apparent Peripheral Volume of Distribution - Deep}}^2$	0.269	(0.0673 - 0.470)

Abbreviations: CI95, 95% Confidence Interval; ω_X^2 , variance of inter-individual variability of parameter X.

Table 81: Predicted Steady-State Mirdametinib Exposures in NF1 PN Participants

	AUC0-12, ng.hr/mL	Cavg, ng/mL	Cmax, ng/mL	Trough, ng/mL	Observed Trough, ng/mL
All Participants					
Mean (CV%)	973 (31%)	81.1 (31%)	202 (32.3%)	50.8 (42.5%)	42.5 (49.7%)
Median [Min, Max]	924 [323, 2260]	77 [26.9, 188]	201 [69.6, 356]	45.4 [14.6, 154]	42.1 [0.5, 139]
Geo. Mean (Geo. CV%)	931 (30.2%)	77.6 (30.2%)	190 (36.2%)	47.2 (38.9%)	35.6 (85.3%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	29 (21.8%)
Adult Participants					
Mean (CV%)	990 (35.7%)	82.5 (35.7%)	203 (32.8%)	52.5 (48.1%)	42.7 (50.1%)
Median [Min, Max]	948 [323, 2260]	79 [26.9, 188]	202 [69.6, 348]	45.4 [14.6, 154]	43.4 [0.5, 98.4]
Geo. Mean (Geo. CV%)	934 (35.8%)	77.8 (35.8%)	191 (37.4%)	47.7 (46.2%)	34.6 (102%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	23 (30.7%)
Pediatric Participants					
Mean (CV%)	950 (22.8%)	79.1 (22.8%)	200 (31.9%)	48.6 (32.1%)	42.3 (49.8%)
Median [Min, Max]	907 [570, 1640]	75.6 [47.5, 137]	189 [73.2, 356]	45.1 [27.3, 122]	40.8 [3.27, 139]
Geo. Mean (Geo. CV%)	928 (21.7%)	77.3 (21.7%)	189 (35%)	46.7 (27.9%)	36.6 (69%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (10.3%)

Abbreviations: AUC, area under the concentration vs. time curve; Cavg, average concentration; Cmax maximum concentrations; CV, coefficient of variation; Geo, geometric; Min, minimum; Max, maximum; SD, standard deviation; SS, steady-state

For Observed Trough, the N=133 participants includes the 19 participants from NF106 for whom trough observations were not collected. An additional 10 participants from MEK-NF-201 had no trough observations collected within the first 7 cycles within 15 hours after the dose.

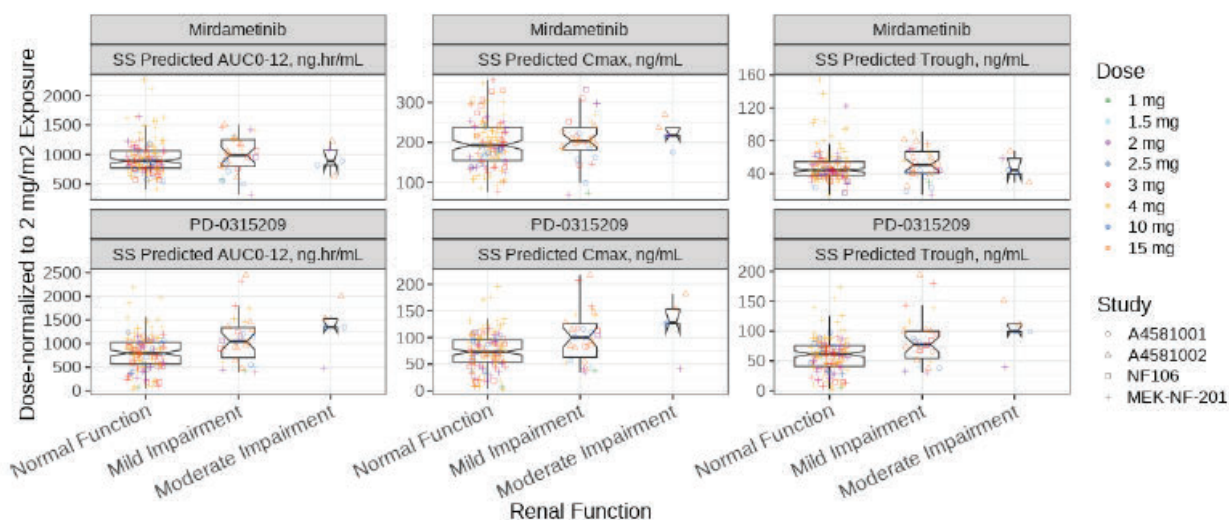
Table 82: Predicted Steady-State PD-0315209 Exposures in NF1 PN Participants

	AUC0-12, ng.hr/mL	Cavg, ng/mL	Cmax, ng/mL	Trough, ng/mL	Observed Trough, ng/mL
All Participants					
Mean (CV%)	817 (52.5%)	68.1 (52.5%)	75.7 (52%)	61.8 (53.5%)	54.7 (64.6%)
Median [Min, Max]	797 [34.6, 2320]	66.4 [2.88, 194]	72.1 [3.21, 207]	61.4 [2.66, 180]	45.7 [0.5, 170]
Geo. Mean (Geo. CV%)	681 (79.2%)	56.7 (79.2%)	63 (79.7%)	51.5 (78.7%)	42.3 (105%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	29 (21.8%)
Adult Participants					
Mean (CV%)	901 (53.1%)	75.1 (53.1%)	83.3 (52%)	68.3 (54.5%)	62.5 (65.6%)
Median [Min, Max]	859 [86.5, 2320]	71.6 [7.21, 194]	77.6 [7.88, 207]	65.1 [6.69, 180]	53.2 [0.5, 170]
Geo. Mean (Geo. CV%)	750 (78.2%)	62.5 (78.2%)	69.6 (77.5%)	56.7 (78.5%)	46.4 (127%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	23 (30.7%)
Pediatric Participants					
Mean (CV%)	707 (46.3%)	58.9 (46.3%)	65.8 (47.6%)	53.4 (46%)	46.9 (57%)
Median [Min, Max]	754 [34.6, 1560]	62.8 [2.88, 130]	67.2 [3.21, 135]	56.2 [2.66, 126]	43.5 [1.78, 115]
Geo. Mean (Geo. CV%)	600 (78.4%)	50 (78.4%)	55.4 (80.3%)	45.5 (77%)	38.6 (82.9%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (10.3%)

Abbreviations: AUC, area under the concentration vs. time curve; Cavg, average concentration; Cmax maximum concentrations; CV, coefficient of variation; Geo, geometric; Min, minimum; Max, maximum; SD, standard deviation; SS, steady-state

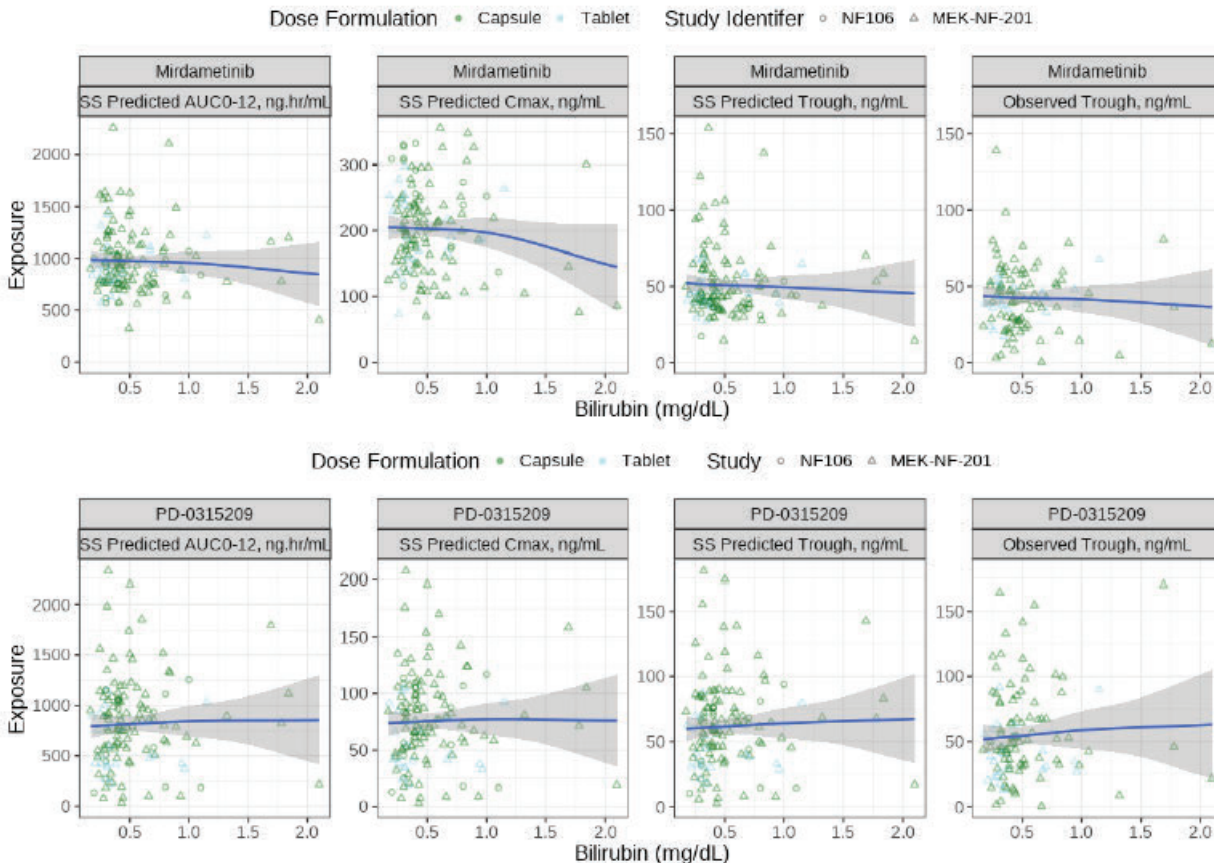
For Observed Trough, the N=133 participants includes the 19 participants from NF106 for whom trough observations were not collected. An additional 10 participants from MEK-NF-201 had no trough observations collected within the first 7 cycles within 15 hours after the dose.

Figure 16: Predicted Steady-State Exposures in All PopPK Studies, Stratified by Renal Function



Abbreviations: AUC, area under the concentration vs. time curve; Cmax maximum concentrations. Individual model-predicted exposure predictions are at steady-state following BID dosing at the participants nominal dose and are dose-normalized to 2 mg/m². Renal function is assigned as follows: Normal, CRCL ≥ 90 mL/min; Mild Impairment, CRCL ≥ 60 and < 90 mL/min; Moderate Impairment, CRCL ≥ 30 and < 90 mL/min.

Figure 17: Predicted and Observed Steady-State Exposures versus Bilirubin in All Participants



Abbreviations: AUC, area under the concentration vs. time curve; Cmax maximum concentrations. Individual model-predicted exposure predictions are at steady-state following BID dosing at the participant's nominal dose.

The FDA's Assessment:

- Mirdametinib PK was adequately characterized by a three-compartment model with absorption described by a TCAM.
- PD-0315209 PK was adequately characterized by a three-compartment model driven by Fm with IIV on CLm/F, Vmc/F, Fm, Qm1/F, and Vmc/F.
- Mirdametinib and PD-0315209 exposure is linear with dose over the range of doses evaluated (up to 20 mg).
- While a statistically significant effect for CLcr on CLm/F was identified, CL/F was not impacted by CLcr and mild and moderate impairment were not associated with clinically meaningful changes in exposure for mirdametinib and PD-0315209.
- Fm in participants using concomitant UGT2B7 inducers was 19% higher than without concomitant UGT2B7 inducers. In MEK-NF-201 participants, the median Fm with and

without UGT2B7 inducers was 16.7% and 11.7%, respectively; however, steady-state observed and model-predicted exposures following nominal BID mirdametinib dosing were similar.

- Model qualifications show that the PopPK models describe the PK of mirdametinib and PD-0315209 adequately. VPCs support use of the models for exposure predictions and for simulations in support of predictive applications.
- Due to use of multiple comedications and multiple classifications for the comedications used, and the limitation of the study design, PopPK results alone can not support the proposed DDI statement in the label.
- The proposed unified dosage is acceptable as the exposures at steady state of unified dose are comparable to the previously tested tablets in the trial in each BSA band based on the simulation.

19.4.2.3. PPK Review Issues

None

19.4.2.4. Reviewer's Independent Analysis

None

19.4.3. Exposure-Response Analysis

19.4.3.1. FDA's ER (efficacy) Executive Summary

PKPDx models were developed to identify exposure-response relationships with TGI, best overall response (BOR), duration of response (DOR), and time-to-progression (TTP). This activity included the following objectives:

- Characterize the PKPDx relationships between mirdametinib dose/exposure and change in tumor volume.
- Conduct population and trial simulations in support of dose justification and dose optimization.

Methods: The TGI model was developed sequentially, beginning with a natural history model to describe PN tumor growth in untreated participants from historical studies (01-C-022 and 08-C-0079). Tumor volume measurements and PopPK-model predicted exposure parameters for participants receiving mirdametinib in Studies NF-106 and MEK-NF-201 were included to characterize the drug effect attributable to mirdametinib treatment. Covariate-parameter relationships of interest were explored and structurally tested using stepwise covariate

modeling (SCM) and final models were qualified by visual predictive checks (VPCs) and numerical checks of parameter precision and model robustness.

Bayesian post hoc pharmacokinetics (PK) parameter estimates were used to estimate mirdametinib for subsequent exposure-response analysis. To assess the impact of changes in exposure for DOR, BOR, and TTP exposure-response relationships were graphically evaluated in all patients in MEK-NF-201 and NF-106. Covariate relationships were explored when the ER relationship was found to be significant. BOR, DOR, and TTP were evaluated by logistic regression or Cox regression analyses.

Results: Disease progression was best described by a Gompertz growth model with natural decay. The natural history data (NHD) model showed effects of age and tumor volume baseline on natural growth parameters. Participants aged 2-17 years old had higher natural growth rates (K_G) combined with lower tumor decay rates (K_D) but a higher drug effect (K_{Drug}). Adults (>17 years) were found to have a lower K_G and higher K_D but a lower K_{Drug} . These factors led to a similar change in tumor volume over time between the two age groups. A higher tumor baseline was also linked to a higher maximum tumor volume (TS_{max}).

The NHD model was used as a basis for the TGI model to describe tumor growth in the absence of treatment. When mirdametinib treated participants were included in the model, a linear drug effect of mirdametinib on tumor growth with a slope of 0.189 week⁻¹/(ng/mL) described the data best. The effect was estimated to diminish exponentially over time and this decay was 82.8% lower in the pediatric population (2-17 years old) compared to adults, changing from 0.172 month⁻¹ in adults to 0.0292 month⁻¹ in the pediatric population. The half-life of the decay of the drug effect in adults was estimated to be 4.03 months, compared to 23.7 months in the pediatric population.

BOR was analyzed as a function of nominal mirdametinib maximum concentration at steady state ($C_{max,ss}$), mirdametinib minimum concentration at steady state ($C_{min,ss}$), mirdametinib area under the concentration vs. time curve at steady state within a dosing interval ($AUC_{0-12,ss}$). $AUC_{0-12,ss}$ and $C_{min,ss}$ were statistically significant predictors of BOR; $C_{max,ss}$ was not a significant predictor of BOR. No statistically significant covariates were identified with the relationship to $AUC_{0-12,ss}$. No significant relationships were found between exposure parameters and DOR or TTP.

Comparison of efficacy showed that probability of response and reduction in tumor growth both increase with target dose and mirdametinib exposure. Longitudinal simulations suggest an increasing and earlier rate of response as dose increases and a greater rate of response in adult and adolescent subjects compared to children. All responses were associated with substantial, overlapping prediction intervals (PIs). Based on a utility analysis of evaluating a smaller cohort at a target dose of 1.5 mg/m², the probabilities of achieving 50, 60, or 70% response rates were substantially higher for the 2 mg/m² cohort than the 1.5 mg/m² cohort in the full population.

Overall Conclusions:

- Mirdametinib was predicted to have a concentration-dependent impact on tumor growth, with an exponential decay of this effect over time. This decay was higher in adults, possibly due to the differences in disease presentation between the pediatric population and adults. Given this difference in decay, the half-life of effect in adults was estimated to be 4.03 months, compared to 23.7 months in the pediatric population.
- Of the mirdametinib exposure metrics, AUC_{0-12,ss} was found to be the best predictor of BOR, with an increasing probability of BOR as AUC_{0-12,ss} increased. No exposure-response relationships were identified for DOR or TTP.
- Simulations suggested an increasing magnitude of %CFB and increasing response rate with increasing dose in the full population, and in children (2-12), adolescents (12-17), and adults. However, this trend should be taken with caution as it has not been verified in the clinical trial.

19.4.3.2. ER (efficacy) Assessment Summary

The Applicant's Position:

PKPDx and exposure-response analyses established clear relationships between exposure and both tumor growth inhibition and overall response in participants with NF1 PN. Mirdametinib has a concentration-dependent effect on tumor growth, with increasing steady-state exposure being predictive of greater reduction in tumor volume, increased probability of response, and shorter time to response. The models are sufficiently robust to predict tumor response at target dose levels below 3 mg/m². Simulations at target dose levels of 1.0, 1.5, 2.0, 2.2, and 3.0 mg/m² provide support for efficacy against PN in this range, with expectation of substantially improved probability of efficacy with increasing target dose. Further evaluation of a lower target dose in clinical studies is unlikely to alter the selection of 2 mg/m² BID as optimal for the treatment of NF1 PN.

General Information	
Goal of ER analysis	PKPDx models were developed to evaluate the PKPDx and ERR for mirdametinib in adult and pediatric participants with NF1 PN, which included the following objectives: • Characterize the PKPDx relationships between mirdametinib dose/exposure and change in tumor volume; • Characterize the relationships between mirdametinib exposure and efficacy in NF1 PN participants; • Conduct population and trial simulations in support of dose justification and dose optimization.

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Study Included		01-C-022 and 08-C-0079 included adult and pediatric participants with NF1 PN receiving no treatment and were used to develop a natural history tumor growth model. MEK-NF-201 and NF-106 included adult and pediatric participants with NF1 PN receiving a target dose of 2 mg/m ² BID mirdametininib for 3 weeks on and 1 week off with a maximum dose of 4 mg BID.
Endpoint		Tumor Volume (MRI); DOR (MEK-NF-201 and NF-106 only); BOR (MEK-NF-201 and NF-106 only); TTP (MEK-NF-201 only)
No. of Patients (total, and with individual PK)		99 total participants in natural history model (29 from 01-C-022, 70 from 08-C-0079). 133 total participants from mirdametininib clinical studies (19 from NF-106, 114 from MEK-NF-201). 277 participants included in individual PK.
Population Characteristics	General	Age median (range): 21.0 yrs (2.00 – 69.0), 75 (56.4)% participants > 17 yr, 26 (19.5)% participants 12-17 yr, < 12 yr, 32 (24.1%) Weight median (range): 54.7 kg (11.4-169) Male: 54 (40.6%) Female: 79 (59.4%) Asian: 6 (4.5%) Black/African American: 21 (15.8%) Other: 11 (8.3%) White/Caucasian: 94 (70.7%)
	Organ impairment	Hepatic impairment – NCI Hepatic Organ Dysfunction definition. Normal 125 (93.98%), Mild B2 4 (3.01%), Moderate 4 (3.01%) Renal impairment- Renal Function Normal 118 (88.72%), Mild 14 (10.53%), Moderate 1 (0.752 %)
	Pediatrics (if any)	Described in General Population Characteristics
	Geriatrics (if any)	Described in General Population Characteristics
Dose(s) Included		NF-106 and MEK-NF-201: multiple oral doses of 2 mg/m ² BID (max dose, 4 mg) 3 weeks on/ 1 week off in 28-day cycles treatment phase of 24 cycles. Actual doses administered are visualized in Figure 4 .
Exposure Metrics Explored (range)		TGI Model: Mirdametininib Cavg BOR, DOR, TTP: Mirdametininib Cmax,ss; Mirdametininib AUC0-12,ss, Mirdametininib Cmin,ss
Covariates Evaluated		TGI Model: Categorical Age (2-9 years, 9-17 years, >17 years), Baseline Age, Weight, Height, BSA, Dose, Study, Race, Sex, Tumor Status (progressive or non-progressive), Lansky/Karnofsky performance status BOR, DOR, TTP: Continuous age, Categorical age (2-12 years, 12-17 years, >17 years), Lansky/Karnofsky performance status, Sex, Tumor status (progressive or non-progressive), baseline tumor volume.
Final Model Parameters		Summary Acceptability [FDA's comments]

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Model Structure	The relationships between mirdametinib exposure and efficacy endpoints were evaluated as PKPDx or ERR models. The PKPDx model development for tumor size used individual parameter estimates from the final PopPK model added to the PKPDx datasets. For the ERR analyses of DOR, BOR, and TTP the final PopPK model was used to calculate individual estimates of exposure at nominal steady state. For the TGI model, a disease progression model was first developed based on data from 01-C-0222 and 08-C-0079. The model was based on a Gompertz growth model and was expanded with a natural tumor decay rate (KD), an age-effect on tumor growth rate (KG) and KD, and an effect of baseline tumor volume on maximum tumor volume (T_{max}). A drug effect for mirdametinib (KDrug) was then estimated for treated participants in MEK-NF-201 and NF-106 with disease progression model parameters fixed. KDrug is modeled as a decaying linear effect as a function of C_{avg,ss} with a categorical age effect on the decay rate for KDrug (λ). Proportional error is included for Study 80079, Study 10222, and for each reader in MEK-NF-201. IIV is included for KG, T_{MAX}, KD, KDrug, and λ. Exposure-response relationship with BOR was evaluated by logistic regression with participants reaching stable disease, progressive disease, and with missing evaluations categorized as non-responders. AUC_{0-12,ss} was the best predictor of response and no statistically significant covariates were identified.	Acceptable
Model Parameter Estimates	TGI model (Table 53)	Acceptable

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Model Evaluation	Final safety PKPDx models were determined based on model fit improvement using AIC: Akaike's Information Criterion, Chi-square test statistic statistical significance, physiological plausibility of parameter values, successful numerical convergence.	Acceptable
Covariates and Clinical Relevance	TGI: The natural history model showed effects of age and baseline tumor volume on natural growth parameters. Pediatric participants had higher natural growth rates (K_G) combined with lower tumor decay rates (K_D) and higher drug effect. Adult participants had lower K_G and higher K_D but with lower drug effect. These factors lead to a similar change in tumor volume over time between the age groups. No other covariate effects were supported by the data. BOR: No statistically significant covariates were identified for the relationship between BOR and mirdametinib exposure. A longer time-to-tumor growth (TTG), a predicted parameter from the TGI model was associated with higher probability of BOR. Age group (2 to <12, 12 to 17, and >17) and baseline tumor volume were significant covariates in the relationship with BOR, suggesting that a better response is correlated with younger age and smaller baseline tumor volume. However, correlation with baseline tumor volume is not considered clinically relevant because a single tumor lesion is not reflective of the overall disease burden.	Acceptable
Simulation for Specific Population	Population simulations of tumor volume response to varying dose levels of mirdametinib treatment were conducted using virtual participants with weight, BSA, and age sampled from NHANES demographic distributions. Simulations were conducted for no treatment and at 1, 1.5, 2, 2.2, and 3 mg/m ² BID administered 3 weeks on and 1 week	Acceptable

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	off for 24 cycles. Percent response, defined as a reduction in volume of at least 20%, is plotted by dose along with safety event predictions and exposure distributions in Figure 16. Population simulations were conducted to evaluate the impact of using a unified nomogram for dosing guidance regardless of dose form. Simulations were conducted using virtual participants with weight, BSA, and age sampled from NHANES demographic distributions and predicted efficacy and safety responses were summarized by age group.	
Visualization of E-R relationships	For the population simulations, percent response, defined as a reduction in volume of at least 20%, is plotted by dose along with safety event predictions and exposure distributions in Figure 16. The relationship between exposure and overall response was characterized by logistic regression and is presented in Figure 17. For the trial simulations of various dose levels, tumor volume over time and percent change from baseline over time are plotted by dose in Figure 18.	Acceptable
Overall Clinical Relevance for ER	• Mirdametinib is predicted to have a concentration-dependent impact on tumor growth. Due to the interplay between disease presentation, drug effect, and age-related influences, the relationship between exposure and efficacy is anticipated to be similar in adult and pediatric populations. • Probability of response increases with increasing exposure to mirdametinib. AUC_{tau,ss} is the best predictor of response. • Simulations of response at various target doses of mirdametinib from 1 to 3 mg/m² BID (3 weeks on/1week off) predict an increasing magnitude of	Acceptable

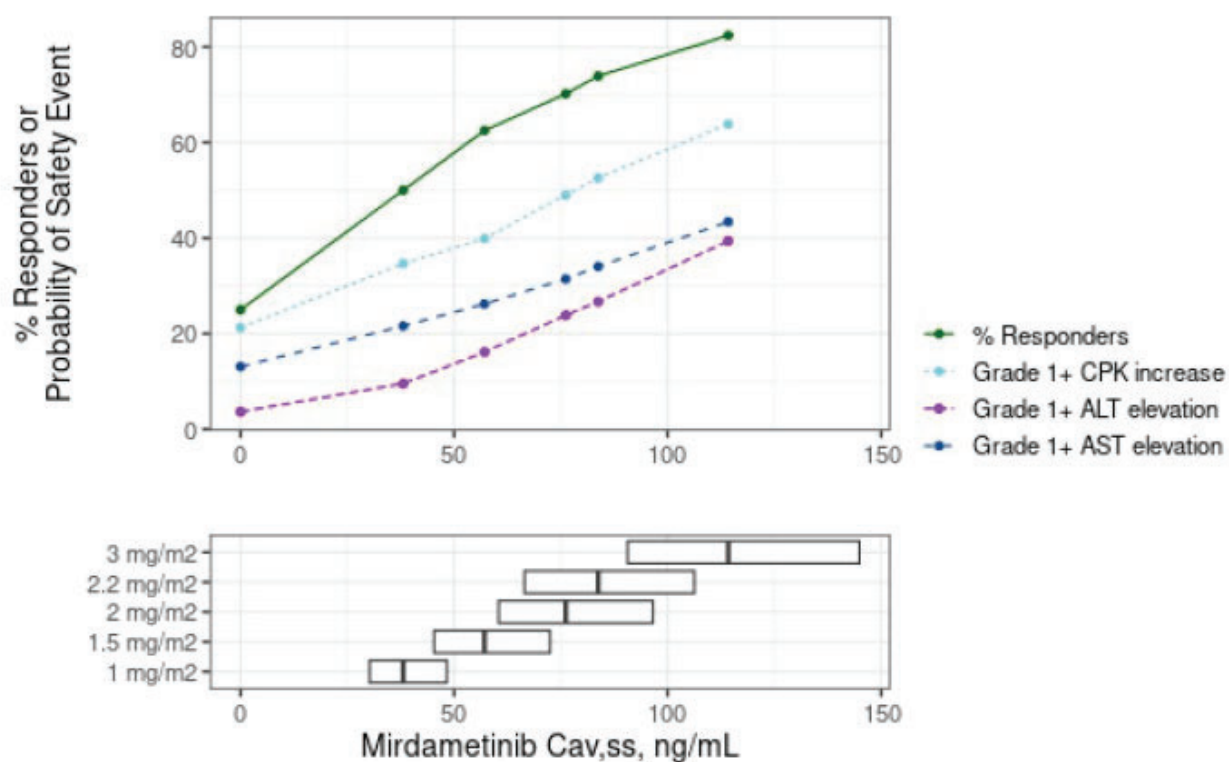
	%CFB, increasing response rate, and earlier time to response with increasing dose. • Trial simulations predict that evaluation of a small cohort (n=10) of NF1 PN participants at a dose of 1.5 mg/m² may result in decreased efficacy and is unlikely to change the determination that 2 mg/m² BID is an optimal dose for NF1 PN patients. • Use of a single nomogram for the tablet and capsule dose forms is unlikely to result in clinically meaningful differences in exposure or efficacy.	
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	No statements related to Exposure-Efficacy models are made in the proposed label.	Acceptable

Table 83: Parameter Estimates for the Final Drug Effect Model

Parameter	Descriptor	Estimate	Relative SE (%)	CI95
θ_1	$K_{G,max}$ (1/week)	0.00157	30.3	(0.000638 - 0.00250)
θ_2	TS_{max} (mL)	1070	33	(378 - 1.76e+03)
θ_3	Proportional Error Study 106	0.0415	22.7	(0.0231 - 0.0599)
θ_4	$K_{D,11y}$ (1/week)	0.000392	44.3	(5.14e-05 - 0.000732)
θ_6	DEC50 AGE on K_G (years)	20.4	7	(17.6 - 23.2)
θ_7	Power BASE on TS_{max} (-)	0.611	15.8	(0.421 - 0.800)
θ_8	$K_{G,min}$ (1/week)	0.00083	39.5	(0.000187 - 0.00147)
θ_9	Power AGE on K_D (-)	1.44	21.2	(0.844 - 2.05)
θ_{10}	K_{Drug} , 1/week/mg/L	0.189	18	(0.122 - 0.255)
θ_{11}	λ , 1/month	0.172	43.6	(0.0249 - 0.320)
θ_{12}	Proportional Error Study 201, reader A	0.239	7.4	(0.205 - 0.274)
θ_{13}	Proportional Error Study 201, reader B	0.295	16.7	(0.198 - 0.391)
θ_{14}	Proportional Error Study 80079	0.0668	13.5	(0.0491 - 0.0844)
θ_{15}	Proportional Error Study 10222	0.0411	10.4	(0.0327 - 0.0495)
θ_{16}	Change in λ , children, %	-0.83	4.8	(-0.909 - -0.752)
$\omega_{1.1}$	$\omega^2 IIV_{KG}$	0.542	35.8	(0.161 - 0.923)
$\omega_{2.2}$	$\omega^2 IIV_{TS_{max}}$	0.301	47.9	(0.0186 - 0.583)
$\omega_{4.4}$	$\omega^2 IIV_{KD}$	1.28	45.2	(0.147 - 2.41)
$\omega_{5.5}$	$\omega^2 IIV_{KDrug}$	0.24	26.4	(0.116 - 0.365)
$\omega_{6.6}$	$\omega^2 IIV_{\lambda}$	0.339	86.2	(-0.234 - 0.912)

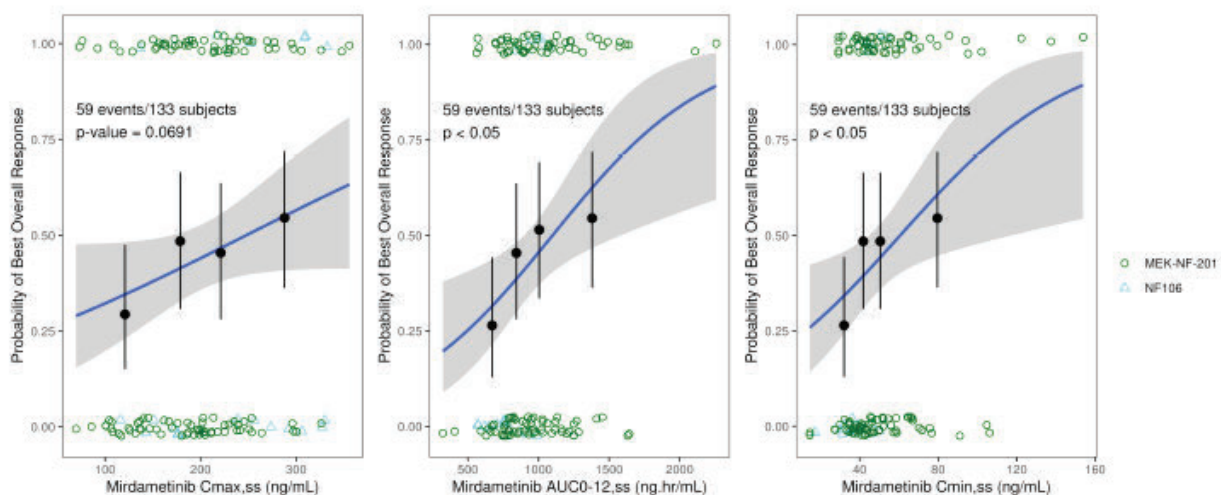
Abbreviations: CI95, 95% Confidence Interval; CV, coefficient of variation; DEC50, time-varying age of the half-maximal reduction in K_G ; IIV, inter-individual variability; K_D , tumor shrinkage rate constant; K_{Drug} , linear drug effect; K_G , growth rate constant; SE, standard error; TS_{max} , maximum tumor volume; λ , decay rate; ω_X^2 , variance of inter-individual variability of parameter X.

Figure 18: Percent Responders and Safety Events as a Function of Mirdametinib Exposure



Abbreviations: Cav,ss, average concentration at steady-state; CPK, creatine phosphokinase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

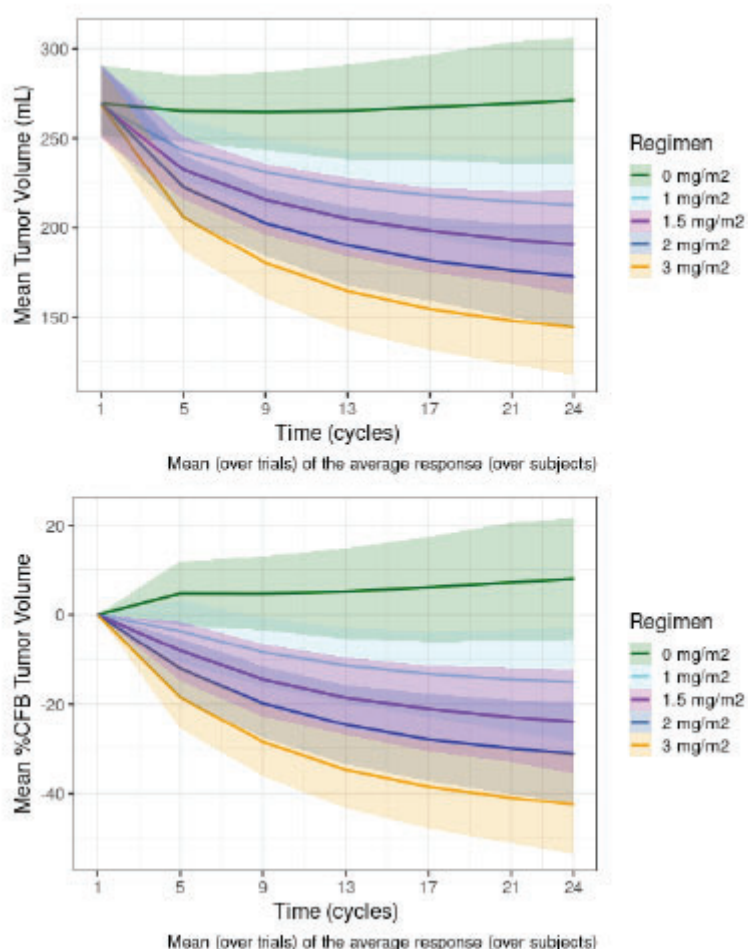
Figure 19: Logistic Regression Relationship for Overall Response vs Exposure Metrics



Abbreviations: C_{max} , nominal maximum concentration at steady-state; AUC_{0-12} , nominal area under the concentration-time curve at steady-state within a dosing interval; $C_{min,ss}$, nominal minimum concentration at steady-state, CI, confidence interval.

Solid black points represent mean exposure and response rates stratified by mirdametininb exposure quartile. Vertical black bars represent the 5th and 95th %CI on the response rate. Solid blue line indicates the logistic regression model fit. The shaded gray region represents the 95% CI on the modeled response rate.

Figure 20: Trial Simulation of Tumor Volume and %Change from Baseline vs Time



Abbreviations: CFB, change from baseline.

Simulated responses shown at Day 1 of Cycle 1, Day 15 of Cycles 5, 9, 13, 17, and 21, Day 21 of cycle 24. Solid lines are the mean of the average response across 500 virtual trials. Shaded areas represent the 95% CI of the mean response across 500 virtual trials.

19.4.3.3. FDA's ER (safety) Executive Summary

PKPDx models were developed to identify exposure-response relationships with TEAEs. This activity included the following objectives:

- Characterize the relationships between mirdametinib and PD-0315209 exposure and safety response in NF1 PN participants.
- Conduct population and trial simulations in support of dose justification and dose optimization.

Methods: Bayesian post hoc PK parameter estimates were used to estimate mirdametinib and PD-0315209 exposures for subsequent exposure-safety analysis. To assess the impact of changes in exposure for safety endpoints, exposure-response relationships were graphically evaluated in all patients in MEK-NF-201 and NF-106. Covariate relationships were explored when the ER relationship was found to be significant. TEAEs and time to first dose reduction were evaluated by logistic regression or Cox regression analyses.

Results: Mirdametinib and/or PD-0315209 AUC_{0-12,ss} were found to be the best exposure predictors for all significant TEAEs. Of the grade 1+ binary endpoints, the probability of an ALT elevation, AST elevation, or CPK increase event were found to have statistically significant relationships with mirdametinib exposure. The probability of acneiform rash, ALT elevation, and AST elevation were found to have statistically significant relationships with PD-0315209 exposure. The similarity in TEAE ER relationships was driven by the strong correlation between mirdametinib and PD-0315209 as PD-0315209 exposure is a function of mirdametinib exposure.

Age group (2-12, 12-17, >17) was a significant covariate for the probability of grade 1+ AST elevation (mirdametinib and PD-0315209 models), grade 1+ CPK increase (mirdametinib model), and grade 1+ acneiform rash (PD-0315209 model only). For grade 1+ AST elevation as a function of either mirdametinib or PD-0315209 AUC_{0-12,ss}, the probability of events was greater in adults, but lower in adolescent participants compared to the reference group of children less than 12 years of age. The probability of grade 1+ CPK increase was shown to increase with mirdametinib AUC_{0-12,ss} and decreased with increasing age group. The probability of grade 1+ acneiform rash increased with PD-0315209 AUC_{0-12,ss} and increasing age. Baseline tumor volume was the only significant covariate for grade 1+ ALT elevation with both mirdametinib and PD-0315209 AUC_{0-12,ss}. While this significantly improved the model, baseline tumor volume was not found to be statistically different from zero and there is no clinical reason to support this covariate selection in the model.

No ER relationships for grade 2+ events were significant with mirdametinib or PD-0315209 exposure. No mirdametinib exposure-response relationships were found for dose reductions or time to first dose reduction.

Comparison of safety events showed that probability of incidence increases with target dose and mirdametinib exposure; however, statistically significant ER relationships were only observed for grade 1+ events. The predicted increase in probability of grade 1+ events is unlikely to be clinically impactful.

Overall Conclusions:

- Mirdametinib and PD-0315209 AUC_{0-12,ss} were found to be the best exposure predictor for significant safety events. For grade 1+ events, the probability of ALT elevation, AST elevation, and CPK increase was found to increase with mirdametinib

exposure. The probability of grade 1+ acneiform rash, grade 1+ ALT elevation, and grade 1+ AST elevation was found to increase with PD-0315209 exposure.

- Age group (2-12, 12-17, >17) was shown to be a significant covariate for the occurrence of grade 1+ AST elevation (mirdametinib and PD-0315209 models), grade 1+ CPK increase (mirdametinib model), and grade 1+ acneiform rash (PD-0315209 model).
- Baseline tumor volume was found to be a significant covariate for the occurrence of grade 1+ ALT elevation with both mirdametinib and PD-0315209 AUC0–12,ss. While this significantly improved the model, baseline tumor volume was not found to be statistically different from zero and no clinical rationale was identified to support this covariate selection in the model.
- No exposure-response relationships were observed for the occurrence of other binary grade 1+ safety events. No grade 2+ events were significant with mirdametinib or PD-0315209 exposure.
- No mirdametinib exposure-response relationships were found for the occurrence of dose reductions or the time to first dose reduction.

19.4.3.4. ER (safety) Assessment Summary

The Applicant's Position:

Exposure-response analyses were conducted using both the mirdametinib and PD-0315209 PopPK model to assess relationships with selected safety endpoints obtained from patient Studies NF-106 and MEK-NF-201. Mirdametinib and/or PD-0315209 AUC0–12,ss were found to be the best exposure predictors for all significant TEAEs. Of the Grade 1+ binary endpoints, the probability of an ALT elevation, AST elevation, or CPK increase event were found to have statistically significant relationships with mirdametinib exposure. The probability of acneiform rash, ALT elevation, and AST elevation were found to have statistically significant relationships with PD-0315209 exposure. The similarity in TEAE ER relationships was driven by the strong correlation between mirdametinib and PD-0315209 as PD-0315209 exposure is a function of mirdametinib exposure.

No ER relationships for Grade 2+ events were significant with mirdametinib or PD-0315209 exposure. No mirdametinib exposure-response relationships were found for dose reductions or time to first dose reduction.

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Mirdametinib (GOMEKLI)

General Information		
Goal of ER analysis		PKPDx models were developed to evaluate the ERR for mirdametinib and PD-0315209 in participants with NF1 PN, which included the following objectives: Characterize the ERR between mirdametinib and PD-0315209 exposure and the incidence events of Grade 2 or higher with at least 5% incidence and at least 10 events, the ER relationship was evaluated using logistic regression models or ordered categorical regression models.
Study Included		MEK-NF-201 and NF-106 included adult and pediatric participants with NF1 PN receiving a target dose of 2 mg/m ² BID mirdametinib for 3 weeks on and 1 week off with a maximum dose of 4 mg (Mirdametinib E-R Report Table 1).
Population Included		133 participants were included in safety analyses.
Endpoint		Thirteen selected TEAEs were evaluated for grade 1+ occurrence and grade 2+ occurrence: Acneiform rash, Rash, left ventricular ejection fraction (LVEF) decrease, Paronychia (in pediatric cohort only), Fatigue & Malaise, Headache & Migraine, Leukopenic events, Eye disorders, Gastrointestinal disorders, alkaline phosphatase (ALP) elevation, alanine aminotransferase (ALT) elevation, aspartate aminotransferase (AST) elevation, and creatine phosphokinase (CPK) increase. Exposure response of dose reduction (binary) and time to first dose reduction were also explored.
No. of Patients (total, and with individual PK)		133 total participants (277 participants included individual PK)
Population Characteristics	General	- Age median (range): 21.0 yrs (2.00 – 69.0), 75 (56.4)% participants > 17 yr, 26 (19.5)% participants 12-17 yr, < 12 yr, 32 (24.1%) Weight median (range): 54.7 kg (11.4-169) Male: 54 (40.6%) Female: 79 (59.4%) Asian: 6 (4.5%) Black/African American: 21 (15.8%) Other: 11 (8.3%) White/Caucasian: 94 (70.7%)
	Organ impairment	Hepatic impairment – NCI Hepatic Organ Dysfunction definition. Normal 125 (93.98%), Mild b2 4 (3.01%), Moderate 4 (3.01%) Renal impairment- Renal Function Normal 118 (88.72%), Mild 14 (10.53%), Moderate 1 (0.752 %)
	Pediatrics (if any)	Described in General Population Characteristics
	Geriatrics (if any)	Described in General Population Characteristics
Dose(s) Included		NF-106 and MEK-NF-201: multiple oral doses of 2 mg/m ² BID (max dose, 4 mg) 3 weeks on/ 1 week off in 28-day cycles treatment phase of 24 cycles.

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	Actual doses administered are visualized in Figure 4 .	
Exposure Metrics Explored (range)	AUC ₀₋₁₂ , Cavg, Cmin (trough) and Cmax	
Covariates Evaluated	Age (continuous), Age group (<12, 12-17, adult), Lansky/Karnofsky performance status, Sex, Baseline progression, Baseline tumor volume, Baseline laboratory values, as appropriate for each endpoint.	
Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	The relationships between (mirdametinib and PD-0315209) exposure and safety endpoints were evaluated as PKPDx or ERR models. For the ERR analyses of safety endpoints evaluated by logistic regression, the final PopPK model was used to calculate individual estimates of exposure on the day of onset, as available. For each safety endpoint, nominal steady state exposure was used for participants with no event. Exposure-response relationships with safety events were evaluated by logistic regression. For significant relationships, covariates were tested in a stepwise forward search at a $p < 0.05$ level of significance. Only covariates that were significant in a univariate search were included in multivariate testing. Mirdametinib and/or PD-0315209 AUC_{0-12,ss} were found to be the best exposure predictors for all significant TEAEs. Of the grade 1+ binary endpoints, the probability of a ALT elevation, AST elevation, or CPK increase event were found to have statistically significant relationships with mirdametinib exposure. The probability of acneiform rash, ALT elevation, and AST elevation were found to have statistically significant relationships with PD-0315209 exposure.	Acceptable

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Model Evaluation	Final safety PKPDx models were determined based on model fit improvement using AIC: Akaike's Information Criterion, Chi-square test statistic statistical significance, physiological plausibility of parameter values, successful numerical convergence.	Acceptable
Covariates and Clinical Relevance	Age group (2-12, 12-17, >17) was a significant covariate for the probability of grade 1+ AST elevation (mirdametinib and PD-0315209 models), grade 1+ CPK increase (mirdametinib model), and grade 1+ acneiform rash (PD-0315209 model only).	Acceptable
Simulation for Specific Population	Population simulations of tumor volume response to varying dose levels of mirdametinib treatment were conducted using virtual participants with weight, BSA, and age sampled from NHANES demographic distributions. Simulations were conducted for no treatment and at 1, 1.5, 2, 2.2, and 3 mg/m ² BID administered 3 weeks on and 1 week off for 24 cycles. Percent response, defined as a reduction in volume of at least 20%, is plotted by dose along with safety event predictions and exposure distributions in Figure 16 .	Acceptable
Visualization of E-R relationships	For the population simulations, percent response, defined as a reduction in volume of at least 20%, is plotted by dose along with safety event predictions and exposure distributions in Figure 16 .	Acceptable
Overall Clinical Relevance for ER	Mirdametinib and PD-0315209 AUC_{0-12,ss} were found to be the best exposure predictor for significant safety events. For grade 1+ events, the probability of ALT elevation, AST elevation, and CPK increase was found to increase with mirdametinib exposure. The probability of	Acceptable

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	grade 1+ acneiform rash, grade 1+ ALT elevation, and grade 1+ AST elevation was found to increase with PD-0315209 exposure. • Age group (2-12, 12-17, >17) was shown to be a significant covariate for the occurrence of grade 1+ AST elevation (mirdametinib and PD-0315209 models), grade 1+ CPK increase (mirdametinib model), and grade 1+ acneiform rash (PD-0315209 model). • Baseline tumor volume was found to be a significant covariate for the occurrence of grade 1+ ALT elevation with both mirdametinib and PD-0315209 AUC0–12,ss. While this significantly improved the model, baseline tumor volume was not found to be statistically different from zero and no clinical rationale was identified to support this covariate selection in the model. • No exposure-response relationships were observed for the occurrence of other binary grade 1+ safety events: Rash, LVEF decrease, Paronychia (in pediatric cohort only due to low incidence in adults), Fatigue & Malaise, Headache & Migraine, Leukopenic events, Eye disorders, Gastrointestinal disorders, or ALP elevation. No grade 2+ events were significant with mirdametinib or PD-0315209 exposure. • No mirdametinib exposure-response relationships were found for the occurrence of dose reductions or the time to first dose reduction.	
Labeling Language	Description	Acceptability [FDA's comments]

12.2 Pharmacodynamics	No statements related to Exposure-Efficacy models are made in the proposed label.	Acceptable
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19.4.3.5. ER Review Issues

None

19.4.3.6. Reviewer's Independent Analysis

None

19.4.3.7. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

Mirdametinib has a clear exposure-response relationship with tumor volume, with increasing exposure being predictive of greater reductions in tumor response, increased probability of response, and shorter time to response. Exposure-response relationships were identified for both mirdametinib and PD-0315209 with some Grade 1+ TEAEs, however these relationships were not apparent when severity was limited to Grade 2+. Additionally, the events for which significant relationships are identified have not been correlated to observations of clinical intolerability. The models were sufficiently qualified to provide predictive application and simulations of various target dose levels support the conclusion that 2 mg/m² BID is an optimal dose level for treatment of NF1.

The FDA's Assessment:

Positive trend between mirdametinib exposure and efficacy endpoints were observed. However, the prediction of efficacy for untested dosing regimen should be interpreted with caution as it has not been verified in the clinical trial.

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

N A

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORE D/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Kristin Wessel, M.D.	CDER/OOD/DO2	Sections: 1, 2, 3, 4, 7, 8.1, 8.4, 9, 10, 12, 13, 19.2	Select one: ☐ _x_ Authored ☒ _x_ Approved
	Signature: Kristin M. Wessel -S Digitally signed by Kristin M. Wessel -S Date: 2025.02.04 12:38:04 -05'00'			
Clinical Reviewer	Jeannette Nashed, C.R.N.P.	CDER/OOD/DO2	Sections: 1, 8.1, 8.2, 13	Select one: ☒ _x_ Authored ☐ _ Approved
	Signature: JEANNETTE C. NASHED -S Digitally signed by JEANNETTE C. NASHED -S Date: 2025.02.04 13:29:28 -05'00'			
Statistical Reviewer	Shabnam Ford, Ph.D.	CDER/OTS/DBV	Sections: 1,7, 8.1, 8.3	Select one: ☐ _X_ Authored ☒ _ Approved
	Signature: SHABNAM A. FORD -S Digitally signed by SHABNAM A. FORD -S Date: 2025.02.04 12:01:19 -05'00'			
Statistical Team Leader	Flora Mulkey M.S.	CDER/OTS/DBV	Sections: 1,7, 8.1, 8.3	Select one: ☒ _X_ Authored ☐ _ Approved
	Signature: Flora M. Mulkey -S Digitally signed by Flora M. Mulkey -S Date: 2025.02.04 12:10:41 -05'00'			
Division Director (OB/DBV)	Shenghui Tang, Ph.D.	CDER/OTS/DBV	Sections: 1,7, 8.1, 8.3	Select one: ☐ _ Authored ☒ _X_ Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S Date: 2025.02.04 12:14:23 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORE D/ APPROVE	AUTHORED/ APPROVED
Nonclinical Reviewer	Sachia Khasar, Ph.D.	CDER/OND/OOD/D HOT	Sections: 5, 19.1	Select one: ☒ X Authored ☐ X Approved
Signature: Gabriel S. Khasar -S Digitally signed by Gabriel S. Khasar -S Date: 2025.02.03 20:35:51 -05'00'				
Nonclinical Reviewer	Melissa Pegues, Ph.D.	CDER/OND/OOD/D HOT	Sections: 5, 19.1	Select one: ☐ X Authored ☒ X Approved
Signature: Melissa A. Pegues -S Digitally signed by Melissa A. Pegues -S Date: 2025.02.03 17:52:34 -05'00'				
Nonclinical Team Leader	Claudia Miller, Ph.D.	CDER/OND/OOD/D HOT	Sections: 5, 19.1	Select one: ☒ X Authored ☐ X Approved
Signature: Claudia Miller -S Digitally signed by Claudia Miller -S Date: 2025.02.03 20:50:55 -05'00'				
Nonclinical Acting Deputy Division Director	Tiffany Ricks, Ph.D.	CDER/OND/OOD/D HOT	Sections: 5, 19.1	Select one: ☐ Authored ☒ X Approved
Signature: Tiffany K. Ricks -S Digitally signed by Tiffany K. Ricks -S Date: 2025.02.04 08:35:10 -05'00'				
Clinical Pharmacology Reviewer	Vicky Hsu, Ph.D.	CDER/OTS/OCP/DC PI	Sections: 6, 19.4	Select one: ☒ X Authored ☐ Approved
Signature: WENCHI HSU -S Digitally signed by WENCHI HSU -S Date: 2025.02.04 10:58:08 -05'00'				
Pharmacometrics Reviewer	Hezhen Wang, Ph.D.,	CDER/OTS/OCP/DP M	Sections: 6, 19.4	Select one: ☒ X Authored ☐ Approved
Signature: Hezhen Wang -S Digitally signed by Hezhen Wang -S Date: 2025.02.04 11:06:33 -05'00'				

Pharmacometrics Team Leader	Youwei Bi, Ph.D.,	CDER/OTS/OCP/DP M	Sections: 6, 19.4	Select one: ☐ Authored ☒ Approved
	Signature: Youwei Bi -S Digitally signed by Youwei Bi -S Date: 2025.02.04 11:14:06 -05'00'			
Genomics Reviewer	Javier Blanco, Ph.D	CDER/OTS/OCP/DT PM	Sections: 6	Select one: ☒ Authored ☐ Approved
	Signature: Javier G. Blanco -S Digitally signed by Javier G. Blanco -S Date: 2025.02.04 11:17:31 -05'00'			
Master Pharmacokineticist (Genomics)	Sarah Dorff, Ph.D	CDER/OTS/OCP/DT PM	Sections: 6	Select one: ☐ Authored ☒ Approved
	Signature: Sarah E. Dorff -S Digitally signed by Sarah E. Dorff -S Date: 2025.02.04 11:21:58 -05'00'			
Master Pharmacokineticist (Clinical Pharmacology)	Jeanne Fourie Zirkelbach, Ph.D.	CDER/OTS/OCP/DC PII	Sections: 6, 19.4	Select one: ☐ Authored ☒ Approved
	Signature: Jeanne Fourie Zirkelbach -S Digitally signed by Jeanne Fourie Zirkelbach -S Date: 2025.02.04 11:39:26 -05'00'			
Clinical Pharmacology Division Director	Nam Atiqur Rahman, Ph. D.	CDER/OTS/OCP/DCP II	Sections: 6, 19.4	Select one: ☐ Authored ☒ Approved
	Signature: NAM A. RAHMAN -S Digitally signed by NAM A. RAHMAN -S Date: 2025.02.04 11:45:39 -05'00'			
Associate Director for Labeling (ADL)	Barbara Scepura, M.S.N., C.R.N.P.	CDER/OND/OOD/DOI I	Sections: 11	Select one: ☒ Authored ☐ Approved

	Signature: Barbara A. Scepura -S Digitally signed by Barbara A. Scepura -S Date: 2025.02.04 12:42:32 -05'00'			
Cross-Disciplinary Team Leader (CDTL)	Amy Barone, M.D.	CDER/OOD/DO2	Sections: All	Select one: ☐ Authored ☒ Approved
	Signature: See Signature Page			
Deputy Division Director (Signatory)	Nicole Drezner, M.D.	CDER/OOD/DO2	Sections: All	Select one: ☒ Authored ☐ Approved
	Signature: See Signature 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/

AMY K BARONE
02/10/2025 03:55:59 PM

NICOLE L DREZNER
02/10/2025 03:58:03 PM

PAUL G KLUETZ
02/10/2025 06:23:46 PM