MEK-NF-201: A Phase 2b Trial of the MEK 1/2 Inhibitor (MEKi) PD-0325901 in Adult and Pediatric Patients with Neurofibromatosis Type 1 (NF1)-Associated Inoperable Plexiform Neurofibromas (PNs) that are Causing Significant Morbidity

Protocol Amendment 4: 17 May 2022

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Title Page

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Compound Number: PD-0325901

Compound Name: Mirdametinib

Study Phase: Phase 2b

Short Title: A Phase 2b Trial of the MEK Inhibitor PD-0325901 in Patients with Neurofibromatosis Type 1 (NF1)-Associated Plexiform Neurofibromas

Sponsor Name: SpringWorks Therapeutics

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Regulatory Agency Identifier Number(s)

Registry	ID
IND	139883

Approval Date: 17 May 2022

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Sponsor Signatory:

Medical Monitor Contact Information can be found in Section 10.10.3

Protocol History

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Document	**Date**
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Original Protocol	06 March 2019

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 2b Trial of the MEK 1/2 Inhibitor (MEKi) PD-0325901 in Adult and Pediatric Patients with Neurofibromatosis Type 1 (NF1)-Associated Inoperable Plexiform Neurofibromas (PNs) that are Causing Significant Morbidity

Short Title: A Phase 2b Trial of the MEK Inhibitor PD-0325901 in Patients with Neurofibromatosis Type 1 (NF1)-Associated Plexiform Neurofibromas

Rationale:

MEK-NF-201 is an open-label, multi-center, Phase 2b study being conducted to determine the efficacy and safety of mirdametinib (PD-0325901) in participants ≥ 2 years old with symptomatic inoperable NF1-associated plexiform neurofibromas (PNs). A Phase 2 study with PD-0325901 was previously conducted in NF1-associated plexiform neurofibromas (Weiss, 2017). Based on preliminary results, this Phase 2, open-label study evaluated 19 participants (range 16-39 years) with symptomatic or growing PNs. Quantitative radiographic response in a target lesion after administration of PD-0325901 at a dose 2 mg/m^2 twice daily (maximum dose of 4 mg twice daily) on a 3 weeks on/1 week off schedule was assessed. Eight participants (42.1%; 95% CI: 20%, 67%) had a response to PD-0325901 as defined by a ≥ 20% reduction by volumetric analysis of the target lesion by Cycle 12. PD-0325901 was well tolerated with the most common adverse event (AE) resulting in a dose reduction being acneiform rash in 2/19 participants (10.5%). Five participants (26.3%) developed Grade 3 toxicities, with four of those participants (21%) reporting Grade 3 pain. No participants developed Grade 4 or higher toxicities.

Objectives and Endpoints

Primary Objectives	Primary Endpoints
To evaluate the confirmed complete and partial response (PR) rate of mirdametinib (PD-0325901) using volumetric magnetic resonance imaging (MRI) analysis in participants with an inoperable NF1-associated PN that is causing significant morbidity.	Objective response rate at the end of the Treatment Phase (PR defined as PN decrease ≥ 20% compared to Baseline) using centrally read MRI volumetric analysis.

Overall Design:

MEK-NF-201 is a multi-center, open-label, longitudinal, uncontrolled, Phase 2b study to evaluate the efficacy, safety, and tolerability of mirdametinib (PD-0325901) in participants ≥ 2 years of age with an inoperable NF1-associated PN that is causing significant morbidity. All participants will have their primary efficacy measure analysis conducted by a blinded central review. A Data Monitoring Committee (Section 9.5) will monitor the progress of the study.

Participants will be screened up to 45 days prior to the first dose of study treatment (PD-0325901) and eligibility will be based on the inclusion and exclusion criteria (Sections 5.1 and 5.2). Eligible participants will take their first dose of study treatment following all pre-dose assessments at Cycle 1 Day 1. All participants will remain in the Treatment Phase of the study until disease progression (confirmed by central review), they discontinue study treatment for any other reason, the study is stopped by the Sponsor for any reason, or the participant has completed the study through Cycle 24. Refer to the Treatment Phase schedule of activities (SoA [Section 1.3]) for the required assessments and Table 7 for additional details regarding each scheduled study visit.

At the completion of the Treatment Phase (Cycle 24), participants who did not meet withdrawal criteria will have the option to continue study treatment in the Long-Term Follow-up (LTFU) Phase. Refer to the LTFU Phase SoA (Section 1.4) for the required assessments and for additional details regarding each scheduled study visit.

Disclosure Statement: This is a Parallel Treatment study with 1 Arm, 2 Cohorts and No masking.

Number of Participants:

Approximately 150 participants will be screened (assessed for eligibility) to achieve approximately 100 participants assigned to study treatment. Of these participants, approximately 50 will be ≥ 18 years of age and approximately 50 will be 2 to 17 years of age.

Treatment Groups and Duration:

Treatment Phase:

Participants will be screened for up to 45 days prior to the first dose of study treatment (PD-0325901). Study treatment will be administered orally at a dose of 2 mg/m^2 twice daily (BID) with a maximum dose of 4 mg, BID throughout the study. Dosing will be on a 28-day Cycle (4-week course) with a 3 week on/1 week off schedule. The Treatment Phase will last for up to 24 Cycles followed by a 30-day Safety Follow-Up period (the Safety Follow-Up visit is only required after Cycle 24 for participants who are not continuing in the LTFU Phase).

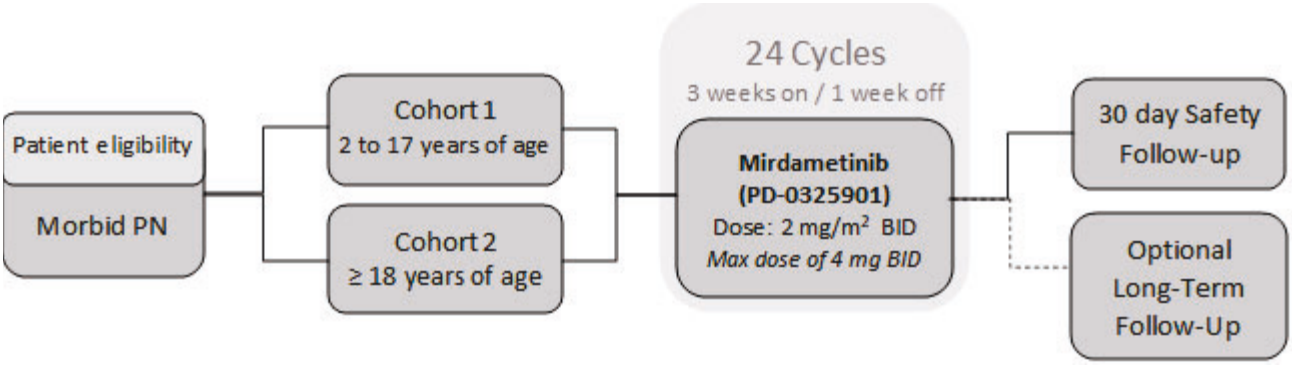
Long-Term Follow-Up (LTFU) Phase:

Participants who complete Cycle 24 of the Treatment Phase and did not meet withdrawal criteria (Section 7) are eligible to participate in the LTFU Phase. Eligible participants will continue

taking the last dose assigned in the Treatment Phase (approximately 2 mg/m^2 BID [maximum dose of 4 mg BID]) of PD-0325901 (mirdametinib; open-label study treatment), on an intermittent (3 weeks on/1 week off) dosing schedule in 28-day cycles. Participants will remain in the LTFU Phase until a withdrawal criterion is met as described in Section 7 or mirdametinib is commercially available.

Data Monitoring Committee: Yes

1.2. Schema



1.3. Treatment Phase Schedule of Activities (SoA)

Cycle (Treatment Phase)	**Screening[1]**	**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)[27]**	**Safety Follow-Up (SFU)[28]**
Visit		**Baseline[3] 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[2]	X								
Inclusion/exclusion review	X	X							
Demographics	X								
Medical history	X								
Karnofsky/Lansky performance status criteria[4]	X	X		X		X	X	X	X
Weight/height[5]	X	X			X *(C3, C7, C11, C15, C19 and C23 only*	X	X	X	X
Physical examination[6]	X	X	X	X	X	X	X	X	X
Vital signs[7]	X	X	X	X	X	X	X	X	X
Post 6-minute walk test blood pressure & heart rate[19]		X				X	X	X	
Laboratory									
Blood for serology[8]	X								
Blood for serum pregnancy test[9] (WOCBP only)	X								
Monthly urine pregnancy test[9] (WOCBP only)		X	X	X	→ *(monthly)*	→ *(monthly)*	→X *(monthly)*	X	X
Blood for hematology and serum chemistry[10]	X	X	X	X	X	X	X	X	X
Urinalysis[10]	X	X	X	X		X	X	X	X

Cycle (Treatment Phase)	**Screening[1]**	**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)[27]**	**Safety Follow-Up (SFU)[28]**
Visit		**Baseline[3] 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**
Blood for PK sampling[11]		X[11a] *(pre-dose, 1- and 2-hours post dose)*	X[11b] *(serial sampling)*	X[11c] *(pre-dose)*	X[11c] *(pre-dose)*	X[11c] *(pre-dose)*	X[11c]		
Tumor Assessment									
MRI for tumor volume[12]	X[12a]					X	X	X[12b]	
Target tumor biopsy[13]		X[13]					X	X	
Other Clinical Assessments									
Ophthalmic assessments[14]	X			X		X	X	X	X
12-Lead ECG[15]	X	X[15a] *(pre-and post-dose)*	X[15b] *(post dose)*	X[15c]		X[15c]	X[15c]	X[15c]	X[15c]
Echocardiogram[16]	X[16a]			X		X	X	X[16b]	X
Strength assessment[17]		X				X	X	X	
Range of motion assessment[18]		X				X	X	X	
6-minute walk test[19]	X	X				X	X	X	
Photography of PN[20]		X				X	X	X	
Bone plate radiographs[21]		X				X *(C13 only)*	X	X[21a]	
Patient Reported Outcomes (PROs)[22]									
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)*

Cycle (Treatment Phase)	**Screening[1]**	**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)[27]**	**Safety Follow-Up (SFU)[28]**
Visit		**Baseline[3] 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**
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[22a]	X[22a]	X[22a]	X[22a]	
Study Treatment[23]									
Assign study treatment using IRT and first dose[23a]		X							
Study treatment dispensing (every 2 Cycles)[23b]		X			X *(C3, C7, C11, C15, C19 and C23 only)*	X	X[23b]		
Study treatment administration[23c]		X→	→	→	→	→			
Study treatment accountability[23d]					X *(C3, C7, C11, C15, C19 and C23 only)*	X	X	X	
Study treatment diary[23d]		X→	→	→	→	→	→X		
Ongoing Monitoring									
Monthly wellness checks[24]					X→	→	→X		
Concomitant medication review[25]	X→	→	→	→	→	→	→	→	→X
AE / SAE review[26]	X→	→	→	→	→	→	→	→	→X

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

1. **Screening visit** assessments may occur up to 45 days prior to first dose of study treatment with a minimum Screening period of 7 days to allow for the Baseline PRO assessments to be done 6 days prior to the Baseline visit and for central imaging confirmation of an analyzable target PN. The first 5 participants enrolled in the pediatric cohort **must be** 9 to 17 years of age at the time of signing informed consent. Enrollment may commence in younger participants (aged 2 to 8 years) after Data Monitoring Committee (DMC) safety review of this run-in cohort (Section 9.5).
2. **Informed consent/assent process** (Section 10.1.3), signing of the informed consent/assent form must be conducted prior to any study procedures being performed. The date the participant signs the ICF will be Day 1 of the Screening period.
3. **Baseline visit** assessments can be performed up to 48 hours prior to first dose of study treatment (defined as Cycle 1 Day 1). For adult participants requiring a tumor biopsy, this assessment may occur during the Screening period, but must be performed after the Screening MRI volumetric assessment has been confirmed evaluable by central radiologic review. All Baseline assessments are to be conducted prior to first dose of study treatment except for the following assessments: post dose 12-Lead ECGs and post dose blood draws for PK sampling.
4. **Karnofsky/Lansky performance status** scale can be found in Section 10.6. Participants ≥ 16 years of age at Screening will be assessed using the Karnofsky scale and participants < 16 years of age at Screening will be assessed using the Lansky scale. Must be done prior to first dose of study treatment at the Baseline visit. Participants who are assessed with the Lansky scale at Screening will continue to be assessed using this scale throughout the study, regardless of age at time of administration.
5. **Height/weight** will be assessed to monitor body surface area (BSA) at applicable study visits to coincide with study treatment dispensing visits.
6. **Physical examinations** (Section 8.2.2) must be done prior to first dose of study treatment at the Baseline visit.
7. **Vital signs** (Section 8.2.3) are to include blood pressure, respiratory rate, pulse rate, and body temperature following at least 5 minutes of rest. Must be done prior to first dose of study treatment at the Baseline visit. Must always be collected prior to the 6-minute walk test, as applicable.
8. **Serology** (Section 10.2) includes testing for HBV (hepatitis B surface antigen [HBsAg]), and HCV (hepatitis C antibody [HCV PCR if hepatitis C antibody positive]). Refer to central laboratory manual for sample processing details.
9. **Pregnancy testing** (Section 8.2.6) only required for women of childbearing potential (WOCBP). If applicable, a serum pregnancy test will be conducted at Screening to confirm eligibility. Urine dipstick pregnancy tests will be conducted at the Baseline visit (prior to first dose of study treatment) to reconfirm eligibility, and monthly during the treatment period. During the month when there is not a scheduled study visit, participants will be required to return to the Site for a urine pregnancy test, or if more convenient for the participant, they may visit a Sponsor approved local laboratory.
10. **Hematology**, **serum chemistry and urinalysis:** Refer to Section 10.2 for a complete list of analytes and central laboratory manual for sample processing details. Must be done prior to first dose of study treatment at the Baseline visit. Microscopy is to be performed only as needed based on positive dipstick test results.
11. **PK sampling** will be collected throughout the study, in parallel according to the sampling schedule found in Section 10.8. The evening before each study visit (as described in the SoA), participants will record the exact time study treatment was taken in the home ePRO device. Refer to Section 8.5, Section 8.6 and central laboratory manual for more details.
    - **11a.** At Cycle 1 Day 1, PK sampling is required prior to the first dose of study treatment and 1-hour post dose with an additional PK sample 2-hours post dose. Refer to Section 10.8 for sampling window requirements.
    - **11b.** At Cycle 1 Day 15, serial PK sampling is required at the following timepoints: pre-dose and 0.5, 1, 2, 3 and 4-hours post dose. Refer to Section 10.8 for sampling window requirements.
    - **11c.** Pre-dose PK sampling is required at select visits throughout the study as described in the SoA and Section 10.8. These blood draws will be collected prior to the morning dose of study treatment. Participants will **not** take their planned morning dose the day of the study visit. The morning dose will be taken following the pre-dose blood draw.
12. **Tumor volume** of target PN will be measured by MRI (no contrast required) and all scans will be submitted for independent, blinded central radiologic review throughout the study. If sedation is used for the MRI assessment, sedation must be administered after the strength, range of motion, and 6-minute walk assessments if assessments are to be completed on the same day.

12a. MRI at Screening is required for all participants to confirm that PN is analyzable to volumetrics (determined by central radiologic review to confirm Inclusion Criterion 5) using the REiNS criteria and will serve as the participant's Baseline scan throughout the study. If applicable, scans acquired prior to the participant signing ICF may be used as Screening time point scans if they were obtained within 45 days of the first study treatment administration and the participant meets study requirements.

12b. MRI at early termination (ET) visit only required if not performed within the past 3 months.

13. **Tumor (core needle) biopsy** (Section 8.1.6) This assessment may occur during the Screening period, but must be performed after the Screening MRI volumetric assessment has been confirmed evaluable by central radiologic review and prior to first dose of study treatment. Tumor biopsy will be utilized for PD tumor response in participants ≥ 18 years of age. Participants 2 to 17 years of age should not undergo biopsy unless there is a clinical indication to obtain fresh tumor tissue. If a study biopsy was collected and the participant did not initiate study treatment, this biopsy may be utilized as the baseline biopsy if the participant subsequently re-screens for enrollment.
14. **Ophthalmic assessments** (Section 8.2.7) will include slit lamp with binocular indirect ophthalmoscopy and intraocular pressure measurements. Assessments **must** be performed by an ophthalmologist. Participants in the pediatric cohort **must** be evaluated by a pediatric ophthalmologist.
15. **12-Lead Electrocardiograms (ECGs)** (Section 8.2.4) should be administered in triplicate (approximately 2-3 minutes apart and averaged) and read locally at the Site. Participants should rest in semi-recumbent supine position for at least 5 minutes prior to ECG collection.

    15a. At Cycle 1 Day 1, triplicate ECGs are required prior to the first dose of study treatment and approximately 1-hour post dose.

    15b. At Cycle 1 Day 15, triplicate ECGs are required 1-hour post dose of study treatment with a ±10-minute allowed window.

    15c. Triplicate ECG may be conducted at any time during the visit after completion of applicable PROs.
16. **Echocardiogram** (Section 8.2.8): Left ventricular ejection fraction (LVEF) will be assessed via echocardiogram.

    16a. Echocardiogram required at Screening to confirm or re-confirm Exclusion Criterion 11 and will serve as the Baseline echocardiogram throughout the study.

    16b. Echocardiogram at the ET visit only required if not performed within the past 1 month.
17. **Strength assessment** (Section 8.1.3) will be measured utilizing a dynamometer and Medical Research Council (MRC) Muscle Scale for participants with a target plexiform neurofibroma (PN) that causes motor dysfunction or weakness. The MRC grading assessment should be conducted prior to the dynamometer assessment. Must be done prior to first dose of study treatment at the Baseline visit. Strength assessment at the early termination (ET) visit only required if not performed within the past 1 month.
18. **Range of motion assessment** (Section 8.1.5) will be assessed for participants with a target PN that causes motor dysfunction or weakness. Must be done prior to first dose of study treatment at the Baseline visit. Range of motion assessment at the early termination (ET) visit only required if not performed within the past 1 month.
19. **6-minute walk test** (Section 8.1.7) will be conducted if a target PN causes airway dysfunction or lower extremity motor dysfunction. A practice 6-minute walk test must be conducted during Screening. Must be done prior to first dose of study treatment at the Baseline visit. The 6-minute walk assessment at the early termination (ET) visit is only required if not performed within the past 1 month. Heart rate and blood pressure will be collected after completion of the 6-minute walk test in accordance with the study reference manual.
20. **Photography of PN** (Section 8.1.4) will be performed if target PN and/or its effects are visible and amenable to photography. Baseline photographs should be present at the time of follow-up photography to allow for the most accurate positioning and setting replication. Photography assessment at the early termination (ET) visit only required if not performed within the past 1 month. Refer to study reference manual for details.
21. **Bone plate radiographs:** (Section 8.2.9) For all participants 2 to 17 years of age, radiographs of the distal femur and proximal tibia will be obtained at Baseline. If the Investigator determines that the physes are open, these participants will undergo radiographs at the schedule specified in the SoA.

    21a. Bone plate radiograph at ET visit only required if not performed within the past 6 months.
22. **Patient reported outcomes (PROs)** (Section 8.1.2): Refer to Table 9 for the PROs and Age Range Scale. Participants will complete the questionnaires using an electronic PRO device (ePRO) for all questionnaires except for the PedsQL and P-OMAQ, which will be paper questionnaires. The paper PedsQL should always be the first PRO administered at the visit. During study visits, the PROs should be the first assessment to minimize participant bias.

    22a. Pediatric Oral Medicines Acceptability Questionnaire (P-OMAQ) (Section 8.1.2.7)**:** All participants that are utilizing the dispersible tablet (pediatric formulation) dosage form will complete the P-OMAQ (paper) self-report and caregivers will complete an observer report, as applicable. This assessment will only be completed once during the study.

23. **Study treatment** (Section 6):

    23a. Study treatment assignment and first dose: After all study entry criteria (Sections 5.1 and 5.2) have been met and all Baseline pre-dose assessments have been conducted (SoA footnote 3), study treatment will be assigned using the interactive response technology (IRT) and first dose of study treatment will be administered followed by a 2-hour observation period.

    23b. Dispensing: Study treatment will be dispensed to participants using the IRT every 2 Cycles at scheduled study visits (as described in the SoA). Cycle 24 Day 21 dispensing for 4 cycles will only occur if participant is continuing to LTFU Phase.

    23c. Administration: Following the first dose (Cycle 1 Day 1), participants will self-administer study treatment orally on a twice daily (BID) dosing schedule of 2 mg/m^2 dose with a maximum dose of 4 mg BID. Dosing will be on a 28-day Cycle (4-week course) with a 3 week on/1 week off schedule.

    23d. Diary/Accountability: Participants will record their daily dosing administration of each study treatment dose in the home ePRO device (provided by the Sponsor). Accountability will be performed by the Site personnel coinciding with each dispensing visit and recorded in the electronic case report form (eCRF).

24. **Monthly wellness check-in** (Section 8.2.10): Monthly telephone or email contact is required throughout the study (may be replaced by a face-to-face interaction when study visits occur, and the information can be obtained during the visit).

25. **Concomitant medications** will be collected starting at the time of informed consent/assent to 30 days after the last dose of study treatment. Refer to Section 6.5.2 for prohibited or restricted medications.

26. **Adverse events (AEs) and Serious Adverse Events (SAEs)**, which may include clinical laboratory test variables, will be monitored and documented from the time of informed consent/assent to 30 days after the last dose of study treatment. Refer to Section 8.3 for more detail.

27. **Early Termination (ET) visit** is applicable if a participant discontinues study treatment early for any reason during the study and participant should be encouraged to return to the Site to complete this visit as soon as possible. The ET visit should be conducted as close to the last dose of study treatment as possible and every effort should be made to complete all procedures.

28. **Safety Follow-Up (SFU) visit** is required to be conducted 30 days (+5 days) after the last dose of study treatment. This visit is not required for participants who are continuing study treatment in the Long-Term Follow-up Phase at Cycle 24 (End of Treatment Phase).

1.4. Long-Term Follow-up Phase Schedule of Activities (SoA)

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→ *(monthly)*	→X *(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 Treatment[12]			
Study treatment dispensing[13a]	X		
Study treatment administration[13b]	X	X	
Study treatment accountability[13c]	X	X	
Ongoing Monitoring			
Monthly wellness checks[14]	X→	→X	

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**
Concomitant medication review[15]	X→	→	→X
AE / SAE review[16]	X→	→	→X

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

1. **Karnofsky/Lansky performance status** scale can be found in Section 10.6. Participants will be assessed using the same scale utilized in the Treatment Phase.
2. **Height/weight** will be assessed to monitor body surface area (BSA) at applicable study visits to coincide with study treatment dispensing visits.
3. **Vital signs** (Section 8.2.3) are to include blood pressure, respiratory rate, pulse rate, and body temperature following at least 5 minutes of rest.
4. **Pregnancy testing** (Section 8.2.6) only required for women of childbearing potential (WOCBP). *Urine dipstick pregnancy tests will be conducted monthly during the LTFU Phase.* During the months when there is not a scheduled study visit, participants will be required to return to the Site for a urine pregnancy test, or if more convenient for the participant, they may visit a Sponsor approved local laboratory.
5. **Hematology, serum chemistry and urinalysis:** Refer to Section 10.2 for a complete list of analytes and central laboratory manual for sample processing details. Microscopy is to be performed only as needed based on positive dipstick test results.
6. **Tumor volume** of target PN will be measured by MRI (no contrast required) and all scans will be submitted for independent, blinded central radiologic review throughout the study.

   6a. MRI at End of Treatment (EOT) visit only required if not performed within the past 3 months.
7. **Ophthalmic assessments** (Section 8.2.7) will include slit lamp with binocular indirect ophthalmoscopy and intraocular pressure measurements. Assessments **must** be performed by an ophthalmologist. Pediatric participants **must** be evaluated by a pediatric ophthalmologist.

   7a. Ophthalmic assessment at End of Treatment (EOT) visit only required if not performed within the past 3 months.
8. **12-Lead Electrocardiograms (ECGs)** (Section 8.2.4) should be administered in triplicate (approximately 2-3 minutes apart and averaged) and read locally at the Site. Participants should rest in semi-recumbent supine position for at least 5 minutes prior to ECG collection.
9. **Echocardiogram** (Section 8.2.8): Left ventricular ejection fraction (LVEF) will be assessed via echocardiogram.

   9a. Echocardiogram at the End of Treatment visit only required if not performed within the past 3 months.
10. **Photography of PN** (Section 8.1.4) will be performed if target PN and/or its effects are visible and amenable to photography. Baseline photographs from the Treatment Phase should be present at the time of follow-up photography to allow for the most accurate positioning and setting replication. Photography assessment at the end of treatment (EOT) visit is only required if not performed within the past 3 months. Refer to study reference manual for details.
11. **PedsQL** (Section 8.1.2): Refer to Table 9 for the Age Range Scale. The study participant (and proxy, as applicable) will continue to complete the same form that was used in the Treatment Phase.
12. **Pediatric Oral Medicines Acceptability Questionnaire (P-OMAQ)** (Section 8.1.2.7)**:** All participants that are utilizing the dispersible tablet (pediatric formulation) dosage form will complete the P-OMAQ (paper) self-report and caregivers will complete an observer report, as applicable. This assessment will only be conducted once

for each participant and caregiver during the study. If this assessment was completed during the Treatment Phase, the assessment is not required to be completed in the LTFU phase.

13. **Study treatment** (Section 6):

    13a. Dispensing: Study treatment will be dispensed to participants using the IRT every 4 Cycles at scheduled study visits (as described in the SoA).

    13b. Administration: Participants will self-administer study treatment orally on a twice daily (BID) dosing schedule of 2 mg/m^2 dose with a maximum dose of 4 mg BID. Dosing will be on a 28-day Cycle (4-week course) with a 3 week on/1 week off schedule.

    13c. Accountability: Accountability will be performed by the Site personnel coinciding with each dispensing visit and recorded in the electronic case report form (eCRF).

14. **Monthly wellness check-in** (Section 8.2.10): Monthly telephone or email contact is required throughout the study (may be replaced by a face-to-face interaction when study visits occur, and the information can be obtained during the visit).

15. **Concomitant medications** Refer to Section 6.5.2 for prohibited or restricted medications.

16. **Adverse events (AEs) and Serious Adverse Events (SAEs)**, which may include clinical laboratory test variables, will be monitored and documented from the time of informed consent/assent to 30 days after the last dose of study treatment. Refer to Section 8.3 for more detail.

17. **End of Treatment visit** will be conducted when a participant permanently discontinues study treatment for any reason and the participant should be encouraged to return to the Site to complete this visit as soon as possible. The EOT visit should be conducted as close to the last dose of study treatment as possible and every effort should be made to complete all procedures.

18. **Safety Follow-Up (SFU) visit** is required to be conducted 30 days (+5 days) after the last dose of study treatment. However, this visit is not required for participants who are transitioning directly to commercial mirdametinib at time of discontinuation (End of Treatment visit).

2. Introduction

Mirdametinib (PD-0325901) is an orally delivered, highly selective, small-molecule inhibitor of the dual specificity kinases, MEK1 and MEK2 (mitogen-activated protein kinase [MAPK]/ extracellular signal-regulated kinase [ERK]) that is being developed for the treatment of neurofibromatosis type 1.

Neurofibromatosis is classified into three major clinically and genetically distinct forms: neurofibromatosis types 1 and 2 (NF1 and NF2) and schwannomatosis. NF1, also known as von Recklinghausen disease, is the most common form of neurofibromatosis. NF1 is an autosomal dominant genetic disorder with an incidence of approximately 1 in 1900 to 2700 individuals (Uusitalo 2015, Evans 2010). 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 (GAPs) 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 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 gene product.

NF1 is characterized by diverse, progressive cutaneous, neurological, skeletal and neoplastic manifestations with no standard drug treatment options available. 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). Neurofibromas are the most common type of benign tumor that develops in patients with NF1 and occur in 20-50% of patients with NF1.

Neurofibromas are benign peripheral nerve sheath tumors that are comprised of a mixture of Schwann cells, fibroblasts, perineurial 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). Plexiform neurofibromas rarely regress spontaneously, and in many patients their growth is relentless. Plexiform neurofibromas represent a major cause of morbidity and disfigurement in individuals with NF1, and when symptomatic, are associated

with increased mortality (Rasmussen 2001, Prada 2012). As tumor growth progresses, such lesions produce dysfunction, pain, and cosmetic disfigurement and can compress the airway or spinal cord. Furthermore, PNs have the potential to undergo malignant transformation producing malignant peripheral nerve sheath tumors (MPNSTs).

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. Plexiform neurofibroma usually involve multiple nerve fascicles, with serpiginous growth and significant vascularity. These lesions can be 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 is unclear. In several series, 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 ten years of age, with head and neck tumors that could not be completely resected (Needle 1997). Surgical resection often is 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. While no specific medical treatment for PNs exists, several therapies have been evaluated.

Clinical trials in patients with NF1 and associated PNs with the farnesyl transferase inhibitor tipifarnib (Widemann 2014), the mammalian target of rapamycin (mTOR) inhibitor sirolimus (Weiss 2014, Weiss 2015), and the fibroblast inhibitor pirfenidone (Widemann 2014b) have not demonstrated sufficient benefit to warrant clinical use. However, the placebo control arm of the tipifarnib study by Wideman et al (2014) reported a plexiform neurofibroma mean time-to-progression of 10.6 months and can serve as historical control group for phase 2 single-arm trials evaluating therapies in this population. Imatinib has resulted in shrinkage of PNs in a limited number of patients with NF1 and PNs (Robertson 2012, Jakacki 2011, Jakacki 2017). The most promising results have been obtained with selumetinib, an oral selective MAPK (MEK) inhibitor that was approved on April 13, 2020 for the treatment of pediatric patients ≥ 2 years with neurofibromatosis type 1 (NF1) who have symptomatic, inoperable PNs (Koselugo, 2020). Selumetinib was studied in a Phase 1 trial that enrolled 24 children with inoperable PNs (Dombi 2016). Children were treated for up to 56 months with selumetinib 20 to 30 mg/m^2 orally twice daily. All patients showed a decrease from baseline in the PN volume (median decrease 31%), and no patients had disease progression. A partial response, defined as a ≥ 20% decrease in tumor volume from baseline for at least four weeks, was confirmed in 17 of 24 patients and was maintained for the duration of the study in 15 of 17 patients. Dose-limiting toxic effects included cellulitis, mucositis, urticaria, acneiform rash, elevated creatine kinase, and decreased left ventricular ejection fraction.

Additionally, a Phase 2 study (SPRINT) conducted by the same group of investigators, enrolled 50 patients aged 3-18 with inoperable morbid PNs. Using the same volumetric endpoint as the Phase 1 study, an independent centralized review of the final tumor response per REiNS criteria resulted in an objective response rate of 44% (95% CI: 30, 59) (Koselugo, 2020). Similar safety results were observed compared to the Phase 1 study. This trial also included individualized

functional assessments based on PN location. Between baseline and end of year 1 evaluations, parent and child-reported pain intensity and pain interference scores significantly improved ($p < 0.01$), as did strength (0-5 scale) and range of motion (degrees) of affected muscle groups/joints ($p < 0.01$) (Gross, 2018). Based on these data, selumetinib (Koselugo™) was FDA-approved for the treatment of pediatric patients (2 years and older) with neurofibromatosis type 1 who have symptomatic inoperable plexiform neurofibromas in April of 2020.

2.1. Study Rationale

Protocol MEK-NF-201 is an open-label, multi-center, Phase 2b study being conducted to determine the efficacy and safety of mirdametinib (PD-0325901) in participants ≥ 2 years old with symptomatic inoperable NF1-associated PNs. A Phase 2 study with PD-0325901 was previously conducted in NF1-associated plexiform neurofibromas (Weiss, 2017). This Phase 2, open-label study evaluated 19 participants (range 16 to 39 years) with symptomatic or progressing plexiform neurofibromas. Quantitative radiographic response in a target PN after administration of PD-0325901 at a dose 2 mg/m^2 BID (maximum dose of 4 mg BID) on a 3 weeks on/1 week off schedule was assessed. Overall, PD-0325901 was well tolerated; five subjects (26.3%) developed Grade 3 toxicities, with four of those subjects (21%) reporting a Grade 3 toxicity of pain. No subjects developed Grade 4 or higher toxicities and 1 subject experienced a SAE. This study demonstrated activity of PD-0325901 in subjects with a PN with eight participants (42.1%; 95% confidence interval [CI]: 20%, 67%) responding to PD-0325901 as defined by a ≥ 20% reduction of the target PN after 1 year of therapy.

2.2. Background

To determine whether sustained Ras/Raf/MEK/ERK signaling contributes to neurofibroma growth, Jessen et al. conducted a study in a neurofibromatosis mouse model ($Nf1_{fl/fl}$; *Dhh-Cre*) with PD-0325901 (Jessen 2013). In this study, tumor bearing mice were randomly assigned to receive 10 mg/kg, 5 mg/kg or 1.5 mg/kg of either PD-0325901 or vehicle by oral gavage. All doses tested resulted in significant tumor volume reductions. A striking reduction in neurofibroma volumes was achieved after 60 days of PD-0325901 treatment. In all doses tested, PD-0325901 was well-tolerated with no apparent toxicity. Reduced tumor volume indicated that cell proliferation or cell death may be altered in neurofibromas. There was decreased cell proliferation observed at the end of treatment (60 days) as measured by reduction in the percentage of Ki67+ cells compared to controls.

A follow-up study utilizing the same $Nf1_{fl/fl}$; *Dhh-Cre* mouse model by Jousma and colleagues (Jousma, 2015) demonstrated that PD-0325901 at a dose of 0.5 mg/kg/day resulted in neurofibroma shrinkage and sustained inhibition of pERK equivalent to the 1.5 mg/kg/day dose. In this study, mice were exposed at the age of 1 month in some experiments with no apparent toxicities. The dose of 0.5 mg/kg/day used in this murine study is approximately equivalent to a dose of 2.5 mg twice daily (BID) in humans. These data are supportive of the use of low dose treatment with PD-0325901 for volume reduction of neurofibromas and are congruous with the

clinical dosing strategy used in the Weiss et al. (Section 2.1) study and the proposed Phase 2b study.

A detailed description of the chemistry, pharmacology, efficacy, and safety of mirdametinib (PD-0325901) is provided in the Investigator's Brochure.

2.3. Benefit/Risk Assessment

To date, the safety profile of single-agent mirdametinib (PD-0325901) in patients with advanced cancer (doses < 10 mg BID, intermittent schedule) has been characterized by mostly manageable and reversible toxicities. The most frequently reported adverse events have been rash, nausea, vomiting, diarrhea, and fatigue. The majority of the events were mild-to-moderate intensity. Other events that have been reported in lesser frequency include ocular disorders (visual disturbances, blurred vision, retinal vein occlusion), nervous system disorders (including confusion, slowed ideation, slurred speech, and hallucinations), musculoskeletal and connective tissue disorders (general weakness as well as neck muscle weakness associated with mild and moderate elevations in creatine kinase [CK]), and cardiac disorders (decreased left ventricular ejection fraction [LVEF], congestive heart failure). These events primarily occurred in patients receiving doses ≥ 10 mg (up to 30 mg) BID.

In order to minimize potential risk during study participation, participants will be carefully monitored for the development of toxicities throughout the study and guidelines for dose modification/discontinuation for selected adverse events are provided.

Based on the available nonclinical and clinical trial data, the benefit-risk balance is considered favorable for further development in patients with NF.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of mirdametinib (PD-0325901) may be found in the Investigator's Brochure.

3. Objectives and Endpoints

Table 1 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the confirmed complete and partial response (PR) rate of mirdametinib (PD-0325901) using volumetric magnetic resonance imaging (MRI) analysis in participants with an inoperable NF1-associated PN that is causing significant morbidity.	Objective response rate at the end of the Treatment Phase (defined as PN decrease ≥ 20% compared to Baseline) using centrally read MRI volumetric analysis.
Secondary	
To evaluate the safety and tolerability of mirdametinib (PD-0325901) in participants with NF1 and symptomatic inoperable PN as measured by the incidence of adverse events (AEs);	Safety endpoints will include incidence of treatment-emergent adverse events, changes in laboratory parameters, vital signs, physical examination findings, and electrocardiograms (ECGs); Tolerability will be assessed according to toxicities graded by National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version (v) 5.0;
To determine the duration of response;	Duration of response for participants whose best response is complete response (CR) or PR using centrally read MRI volumetric analysis;
To evaluate the effect of mirdametinib (PD-0325901) on quality of life as measured by patient-reported outcomes (PROs); and	Change from Baseline in quality of life (QoL) assessed by the age specific Pediatric Quality of Life Inventory (PedsQL); and
To evaluate the effect of mirdametinib (PD-0325901) on pain as measured by patient-reported outcomes.	Change from Baseline in pain (assessed using the Numeric Rating Scale-11 [NRS-11] and Pain Interference Index [PII]) in the Treatment Phase.

Tertiary/Exploratory	
To evaluate the effect of mirdametinib (PD-0325901) on physical functioning as measured by PROs;	Change from Baseline in physical function status (Patient-Reported Outcomes Measurement Information System [PROMIS] – Physical Function/Mobility/Upper Extremity Scale) in the Treatment Phase;
To determine Baseline functional impairments secondary to PN, and the effect of mirdametinib (PD-0325901) on functional outcomes depending on PN location;	Change 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;
To determine time to progression (TTP) and progression free survival (PFS) in progressive PN;	TTP and PFS in progressive PN ($\geq$ 20% increase in PN volume within 12 months prior to first dose of study treatment) using centrally read MRI volumetric analysis;
To assess TTP of mirdametinib (PD-0325901) versus historical controls;	Time until Progressive Disease (defined as PN increase $\geq$ 20% compared to Baseline) using centrally read MRI volumetric analysis;
To evaluate the effect of mirdametinib (PD-0325901) on PN associated disfigurement;	Change from Baseline in PN-associated disfigurement using standardized photography;
To correlate MRI responses with Pharmacodynamic (PD) biomarkers in PN biopsies obtained pre- and post-treatment with mirdametinib (PD-0325901);	Change in levels of pERK and other applicable biomarkers in tumor biopsies at Baseline and Cycle 24 / Early Termination (ET) visit; and
To evaluate the acceptability of the dispersible tablet formulation of mirdametinib (PD-0325901).	Summarize separately by self-report and the caregiver.

4. Study Design

4.1. Overall Design

MEK-NF-201 is a multi-center, open-label, single-arm, longitudinal, uncontrolled, Phase 2b study to evaluate the efficacy, safety, and tolerability of mirdametinib (PD-0325901) in participants ≥ 2 years of age with an inoperable NF1-associated PN that is causing significant morbidity. This study will consist of two phases: the Treatment Phase and the optional Long-Term Follow-Up (LTFU) Phase. Approximately 100 participants will be enrolled and stratified by age (approximately 50 participants 2 to 17 years of age and 50 participants ≥ 18 years of age). The first 5 participants enrolled in the pediatric cohort must be 9 to 17 years of age at the time of signing informed consent. After the first 5 participants have enrolled in the pediatric cohort, enrollment into this cohort will be paused, and only after Data Monitoring Committee (DMC) evaluation of at least 2 cycles of cumulative safety data for these 5 participants will the pediatric cohort be re-opened and potentially expand down to 2 years of age. The primary efficacy endpoint for each cohort is objective response rate (ORR), which is defined as the proportion of participants who have a reduction of target PN volume ≥ 20% as assessed by MRI. All participants will have their primary efficacy measure analysis conducted by an independent, blinded, central radiologic review. Key secondary endpoints include duration of response, and Health-Related Quality of Life (HRQOL) questionnaires and safety and tolerability of PD-0325901. Additionally, change in functional outcome assessments (e.g., strength, range of motion, endurance) will be conducted throughout the course of the study, optimized for tumor location and morbidity effect. Participants will also be monitored for change in pain over the course of study, with tracking of change in concomitant analgesic medications. Participants will be screened for up to 45 days prior to the first dose of study treatment (PD-0325901) and eligibility will be based on the inclusion and exclusion criteria (Sections 5.1 and 5.2). Study treatment will then be administered orally at a dose of 2 mg/m^2 BID with a maximum dose of 4 mg BID. Dosing will be on a 28-day Cycle (4-week course) with a 3 week on/1 week off schedule for up to 24 Cycles. Refer to the schedule of activities ([SoA] Section 1.3) for the required assessments for the Treatment Phase.

Participants who complete Cycle 24 of the Treatment Phase and did not meet withdrawal criteria (Section 7) are eligible to participate in the LTFU Phase. Eligible participants will continue taking the last dose assigned in the Treatment Phase (approximately 2 mg/m^2 BID [maximum dose of 4mg BID]) of PD-0325901 (mirdametinib; open-label study treatment), on an intermittent (3 weeks on/1 week off) dosing schedule in 28-day cycles. Participants will remain in the LTFU Phase until a withdrawal criterion is met as described in Section 7 or mirdametinib is commercially available. Refer to the schedule of activities ([SoA] Section 1.4) for the required assessments for the LTFU Phase.

4.2. Scientific Rationale for Study Design

The tumor response criterion used for evaluation cancers are based on one-dimensional (1-D) and two-dimensional (2-D) tumor measurements (James 1999, Therasse 2000, Eisenhauer 2009).

These methods have limited value in the assessment of treatment outcome for plexiform neurofibromas, which are frequently large, have a complex (non-spherical) shape, and have a slow, erratic growth pattern. To evaluate these different methodologies of measuring change in PNs, Widemann et al compared the use of Response Evaluation Criteria In Solid Tumors (RECIST), World Health Organization (WHO), and volumetric MRI to determine disease progression in a double-blind, placebo-controlled study of tipifarnib (Widemann 2014). Volumetric analysis detected tumor progression (PN volume increase ≥ 20%) much earlier than 1-D and 2-D measurements. The median observed TTP was 14.3 vs 52.2 months utilizing volumetric analysis and WHO criteria, respectively. The median TTP could not be determined by RECIST criteria. This finding accentuates the limitations in using RECIST criteria to describe longitudinal change in PNs. As increasing numbers of clinical trials for NF-related tumor manifestations are ongoing, the need for the development of standardized trial endpoints specifically for NF has emerged. Volumetric MRI analysis accounts for every part of the tumor and thus reflects the actual size of the lesion more closely than 1-D or 2-D measurements. Critical to use and effectiveness in clinical trials, volumetric analysis is less sensitive to differences in body position between scans and can reproducibly detect small changes over time. To allow for meaningful comparisons of trial results and to accelerate the development of active and beneficial agents, the Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) International Collaboration has developed standardized endpoints in numerous domains (e.g., imaging, PROs, functional outcomes) for NF clinical trials (Widemann 2013, Widemann 2016). The REiNS working group recommends MRI and volumetric analysis to measure benign NF-related tumors, inclusive of PNs, to assess response in clinical trials (Dombi 2013). Therefore, this study will incorporate and utilize the findings of the REiNS working group to implement MRI volumetric analysis of participants plexiform neurofibromas to assess the primary endpoint.

While this is a single-arm study by design, the study will consist of two population cohorts, an adult and pediatric cohort. A difference in statistical assumptions for each cohort is needed for this study spanning the adult and pediatric populations due to the observed age-dependent differences in tumor growth rate which is further described below. Each cohort will be analyzed independently for efficacy.

The assumptions for the response rate in the adult population used for the basis of sample size justification are based on the study conducted by Weiss et al (Weiss, 2017). The preliminary results from this study describe an ORR (as defined by a 20% reduction by of the target lesion) of 42% in response to one year of mirdametinib (PD-0325901) therapy. This finding is consistent with the preliminary data of cabozantinib by Shih et al (ORR of 42%; Shih, 2018). In a similar design and population to Weiss et al, Shih et al investigated cabozantinib in a Phase 2 study of patients ≥ 16 years of age with a morbid or progressing PN, with 8 of 19 patients achieving an objective response (42%).

Sample size assumptions for the pediatric population are based on the interim objective response rate of 66% from the SPRINT study conducted by Gross et al. The SPRINT study enrolled 50 patients aged 3-18 years with inoperable morbid PNs (Gross, 2018). These findings are

consistent with the preliminary data of another PN study with trametinib. Twenty-six patients aged 1 to 17 years of age (median 5.5 years) with a measurable PN were treated with trametinib for a median of 61 weeks (range 3 to 124 weeks). In this study, 12 patients (46%) achieved an objective response (Moertel, 2018).

Previous longitudinal retrospective review studies have demonstrated age dependent differences in plexiform neurofibromas, with high inverse correlation of PN growth to patient age (Dombi 2007, Nguyen 2012, Tucker 2008). In a retrospective review, Tucker et al. analyzed serial MRIs of 34 patients (median 10 years of age, range 1 to 47 years) with a measurable PN for a median follow-up length of 6 years (range 1 to 15 years). This study observed that the difference between the initial and final two-dimensional estimated tumor size was significantly greater in younger individuals compared to older individuals; 3.2 cm^2 vs 0.2 cm^2, respectively ($p = 0.031$). In addition, the growth rate of tumors in patients < 10 years of age (0.7 cm^2/year) was significantly greater than that of tumors in patients > 10 years of age at initial examination (0.03 cm^2/year, $p = 0.014$).

Similarly, in an observational study of 49 patients age 3 to 25 years of age (median 8.3 years), Dombi et al. observed that PN volume increased more rapidly than body weight over time ($p = 0.026$). Furthermore, there was a tendency for patients younger than the median age of 8.3 years to have a greater increase in PN volume per year vs older children; 21.1% vs 8.4% volume change per year, respectively ($p = 0.001$). This trend holds true when PN growth rate is expressed relative to the rate of increase in body size.

Based on the findings of Tucker and Dombi, Nguyen et al. conducted a retrospective cohort study of 71 patients with an evaluable internal PNs for a median follow-up of 2.2 years (range 1.1 to 4.9 years). The rate of growth of the individual tumors was inversely correlated with age at initial examination (Spearman's rho = -0.33, $p < 0.001$), but not with the tumor volume on initial MRI examination. Also, tumors that grew more than 20% per year were significantly more frequent among children than among adults ($p < 0.001$). In summation, findings from three independent retrospective reviews of PN volume clearly show that the growth rate of PNs in NF1 patients is inversely correlated with age, indicating discrete age dependent tumor differences.

In addition to tumor volume changes, this study is seeking to assess change in clinical status while on study treatment. NF1 is highly variable in its expression with the severity and specificity of specific manifestations varying among affected individuals even within the same family (Easton 1993). Therefore, a broad understanding of the complete effect of the disease on the patient's life is critical. Even PNs can have drastically different impacts on morbidity and mortality, primarily dependent on location and growth rate of the PN. Plexiform neurofibromas may be located superficially and associated with overgrowth of skin and soft tissues, may be located deep inside the body, or may have both superficial and deep components. PNs represent a major cause of morbidity and disfigurement in individuals with NF1, and when symptomatic, are associated with increased mortality (Rasmussen 2001, Prada 2012). As tumor growth progresses, such lesions produce dysfunction, pain, cosmetic disfigurement, and can compress the airway or spinal cord. Participants in NF1 clinical studies are followed longitudinally with

periodic radiographic imaging. However, due to the irregular and fibrotic nature of neurofibromas, assessing tumor mass accurately and consistently is an arduous process. Some NF1 studies have also reported improvement of clinically significant symptoms without a correlating significant decrease in tumor size (Jakaki 2011). Patients with little tumor shrinkage have anecdotally reported large improvements in functioning and well-being that could be measured with a HRQOL instrument.

The PedsQL 4.0 Generic Core Scales are multidimensional self-report and parent proxy-report scales to assess HRQOL in children, adolescents, young adults and adults. It is a brief standardized HRQOL scale with good reliability and validity. The PedsQL has four subscales: physical functioning, emotional functioning, social functioning, and school/work functioning. In addition to the PedsQL, other HRQOL questionnaires will be critical in capturing changes in clinical status including change in pain (NRS-11 and PII) and change in physical function (PROMIS-Physical Function/Mobility/Upper Extremity). This study will utilize questionnaires applicable for both adults and participants 2 to 17 years. Most HRQOL will also have an associated parent-proxy questionnaire. While monitoring the change in patient perceived change in clinical status via HRQOL questionnaires, participants entering the study due to a functional impairment will also be evaluated for localized strength and range of motion of the impaired physiological location. Paramount to the majority of patients with a highly morbid PN, patient perceived pain as well as tracking of all concomitant analgesic regimens will also be monitored throughout the study.

Lastly, an epidemiologic study conducted by Kallionpaa et al analyzed the estimated prevalence of NF1 by age in the Finnish population (Kallionpaa, 2017). These data show an estimated prevalence of approximately 1 in 1745 for ages 10 to 19 and a prevalence decreasing with age ranging from 1 in 1807 to 1 in 3380 for age groups 20 to 24 and 70 to 74, respectively. Based on the inclusion of participants ≥ 16 years in the previously conducted Phase 2 study by Weiss et al., the juvenile age of animals used in previous toxicology studies, and the lack of any age specific safety signals for the adolescent population, this study will enroll participants ≥ 2 years of age.

4.3. Justification for Dose

The rationale for exploring doses of mirdametinib (PD-0325901) as low as 2 mg is based on the observation that PD-0325901 ≥ 2 mg BID consistently caused ≥ 60% suppression of phosphorylated ERK in tumor biopsies of patients with melanoma during the First-In-Patient study of PD-0325901. In addition, plasma concentrations achieved in adults at the doses proposed for this trial were similar to the plasma concentrations in mice which resulted in tumor volume reductions in 85% of mice. Further exploration of low-doses of PD-0325901 is supported by the Phase 1 data, which concluded that an intermittent dose scheduling between 2 and 10 mg BID should be explored to identify a recommended dose for long-term use of PD-0325901 (LoRusso, 2010).

As described in Section 2.1, the Phase 2 study conducted by Weiss et al. utilized a dose of 2 mg/m^2 (intermittent schedule) which was well tolerated and resulted in response rates > 40% at

12 months (Weiss, 2017). Based on this study and information that doses as low as 2 mg BID consistently caused ≥ 60% suppression of phosphorylated ERK; the following dosing nomogram was selected for this Phase 2b study. Notably, the dispersible tablet formulation (pediatric formulation) is available in 0.5 mg increments whereas the capsule formulation is only available in 1 mg increments. Therefore, while the approximate total dose per BSA is the same regardless of formulation, the unit dose per BSA may vary between formulations.

Table 2 Study Treatment Dosing

Capsule dosage form[1]

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

Dispersible tablet dosage form (pediatric formulation)[1]

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

[1] The dispersible tablet formulation (pediatric formulation) is available in 0.5 mg increments whereas the capsule formulation is only available in 1 mg increments. Therefore, while the approximate total dose per BSA (2 mg/m^2) is the same regardless of formulation, the unit dose per BSA may vary between formulations.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed the Cycle 24 visit (End of Treatment Phase) and the Safety Follow-Up visit shown in the schedule of activities (Section 1.3) or has entered into the Long-Term Follow-Up Phase (Section 1.4).

The end of the study is defined as the date of the last scheduled procedure shown in the SoA (Section 1.3, Section 1.4) (including telephone contact) for the last participant in the study.

5. Study Population

The estimated number of participants assigned to study treatment is 100 participants between two cohorts, approximately 50 participants ≥ 18 years of age and 50 participants 2 to 17 years of age. The first 5 participants enrolled in the pediatric cohort must be 9 to 17 years of age at the time of signing informed consent. Only after DMC evaluation of at least 2 cycles of cumulative safety data for these 5 participants will the pediatric cohort be expanded down to 2 years of age.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participant must be ≥ 2 years of age inclusive, at the time of signing the informed consent/assent;

Type of Participant and Disease Characteristics

2. Participants must have EITHER the clinical diagnosis of NF1 using the National Institute of Health (NIH) Consensus Conference criteria of at least 1 other diagnostic criterion (Inclusion 2.1 – 2.6, see below) in addition to the presence of PN, OR have a constitutional NF1 mutation documented in a Clinical Laboratory Improvement Amendments / College of American Pathologists certified lab; additional criteria are as follows:

    2.1. Six or more café-au-lait macules with a diameter > 5 mm in prepubertal and > 15 mm in post-pubertal individuals, respectively

    2.2. Freckling in axilla or inguinal regions;

    2.3. Optic glioma;

    2.4. Two or more Lisch nodules;

    2.5. A distinctive bony lesion (dysplasia of the sphenoid bone or dysplasia of thinning of long bone cortex);

    2.6. A first degree relative with NF1;

3. 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 (Inclusion 3.1), lesions of the extremity that cause limb hypertrophy or loss of function, and painful lesions. Participants with paraspinal PNs will be eligible for this study. Histologic confirmation of tumor is not necessary in the presence of consistent clinical and radiographic findings but should be considered if malignant degeneration of a PN is clinically suspected;

3.1. For participants enrolled exclusively for a “major deformity” or “significantly disfiguring” tumor, eligible tumors will be limited to tumors of the head & neck or those on other areas of the body that are unable to be concealed by standard garments. In order to enroll a PN for these indications, the Medical Monitor **must** be contacted to review participant eligibility prior to first dose of study treatment.

4. 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 who previously underwent surgery for a PN will be eligible to enter the study after the surgery, provided the PN was incompletely resected and is evaluable by volumetric analysis;

5. 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. As determined by central radiologic review, a target PN must be analyzable by volumetrics using the REiNS criteria, at least 5 mL in volume, and will be classified as “typical PN”, “nodular PN”, or "solitary nodular PN" prior to first dose of study treatment;

6. Participants ≥ 18 years of age must have a PN amenable to a percutaneous biopsy and must be willing to undergo pre-, and end of treatment tumor biopsies providing fresh tumor tissue; there should be no contraindication for serial biopsy; Participants 2 to 17 years of age should not undergo biopsy unless there is a clinical indication to obtain fresh tumor tissue;

7. Participants ≥ 16 years of age must have a Karnofsky performance level of ≥ 50%, and participants < 16 years must have a Lansky performance of ≥ 50%. Note: Participants who are unable to walk because of paralysis, but who are upright in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score;

8. Participant has adequate organ and bone marrow function as defined by the following Screening laboratory values:

   8.1. Absolute neutrophil count ≥ 1500 cells/μL;

   8.2. Platelets ≥ 100 x 10^3/μL;

   8.3. Hemoglobin ≥ 9.5 g/dL;

   8.4. Serum albumin ≥ 2.8 g/dL;

8.5. Calculated creatinine clearance at Screening ≥ 60 mL/min (by Cockcroft-Gault formula) OR a normal serum creatinine based on age described in the table below;

Age (years)	Maximum Serum Creatinine (mg/dL)
≤ 5	0.8
> 5 and ≤ 10	1.0
> 10 and ≤ 15	1.2
> 15	1.5

9. Participant has the ability to swallow capsules whole if the capsule dosage form is being utilized. This criterion does not apply if participant is utilizing the dispersible tablet (Pediatric Dosage formulation; Section 6.1) dosage form of study treatment;

10. Participant is willing and able to comply with all aspects of the protocol;

Weight

11. Participant must weigh at least 10 kg, inclusive, at the time of signing the informed consent/assent;

12. Participant must have a body surface area (BSA) of at least 0.4 m^2 (inclusive) calculated using the Du Bois formula ($BSA = 0.007184 \times W^{0.425} \times H^{0.725}$);

Contraception

13. Male or Female

Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male participants:

Male participants are eligible to participate if they agree to the following during the Treatment Phase (and LTFU Phase, as applicable) and **for at least 90 days** after the last dose of study treatment:

- Refrain from donating sperm

  PLUS either:

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

  OR

- Must agree to use a male condom when having sexual intercourse with a woman of childbearing potential (WOCBP). An additional form of contraception as described in Section 10.4 should also be used by the female partner, if she is of childbearing potential. Refer to Section 10.4 for definition of a WOCPB.

b. Female participants:

Female participants are eligible to participate if they are not pregnant or breastfeeding, and at least one of the following conditions applies:

- Is not a woman of childbearing potential (refer to Section 10.4 for definition of WOCBP)

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), preferably with low user dependency, as described in Section 10.4 during the Treatment Phase (and LTFU Phase, as applicable) and for at least 90 days after the last dose of study treatment and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during the study and for a period of 90 days after last dose of study treatment. The Investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.
  - A WOCBP must have a negative serum pregnancy test result at Screening and a negative urine pregnancy test result at the Baseline visit prior to the first dose of study treatment.
- The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy;

Informed Consent/Assent

14. The Investigator, or a person designated by the Investigator, will obtain written informed consent from each study participant or the participant's legally acceptable representative, parent(s), or legal guardian and the participant's assent, when applicable, before any study-specific activity is performed. The Investigator will retain the original copy of each participant's signed consent/assent document.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Participant has a Screening alanine transaminase (ALT) value of > 2.0 x upper limit of normal (ULN);

2. Participant has 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%);
3. Participant has a history of malignancy associated hypercalcemia;
4. Participant has an active parathyroid disorder, hyperphosphatemia at Screening (serum phosphorus > 1 x ULN), or serum calcium (mg/dL) x serum phosphorus (mg/dL) product > 70 at Screening;
5. 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);
    5.1. Hepatitis serology and viral load will be tested at Screening. Patients who are hepatitis B surface antigen (HBsAg) positive or hepatitis C virus (HCV) antibody positive at Screening must not be enrolled until further definite testing with hepatitis B virus (HBV) deoxyribonucleic acid (DNA) titers is < 500 IU/mL or HCV ribonucleic acid (RNA) polymerase chain reaction test is negative;
6. Lymphoma, leukemia, or any malignancy (including malignant glioma or MPNST) within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years;
7. Breast cancer within the past 10 years;
8. Participants with evidence of an active optic glioma or other low-grade glioma, requiring treatment with chemotherapy or radiation therapy. Participants not requiring treatment are 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;
9. Participant has abnormal QT interval corrected by Fridericia’s formula (> 450 msec for male participants, > 470 msec for female participants, or > 480 msec for participants with bundle branch block) (triplicate ECG readings taken approximately 2 to 3 minutes apart and averaged) at Screening;
10. Participant has experienced any of the following within 6 months (24 weeks) of signing informed consent/assent: clinically significant cardiac disease, myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism;
11. Participant has recorded a LVEF < 55% at Screening or within 3 years of signing informed consent/assent, OR has a history of congestive heart failure;
12. Participant has 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 will be excluded from study participation if they have any of the following risk factors for RVO at Screening:

12.1. Intraocular pressure > 21 mmHg;

12.2. Serum cholesterol > 300 mg/dL;

12.3. Serum triglycerides > 300 mg/dL;

12.4. Hyperglycemia (fasting blood glucose > 125 mg/dL or random blood glucose > 200 mg/dL);

12.5. Age specific hypertension

12.5.1. Participants ≥ 13 years of age with a blood pressure ≥ 140/90 mm Hg

12.5.2. Participants ≤ 12 years of age with a blood pressure ≥ 95th percentile for age +12 mmHg (Section 10.11);

13. Participant has a history of glaucoma;

14. Participant has a history of a positive human immunodeficiency virus (HIV) antibody test;

15. Participant has a known malabsorption syndrome or preexisting gastrointestinal conditions that may impair absorption of PD-0325901 (e.g., gastric bypass, lap band, or other gastric procedures). Delivery of PD-0325901 via nasogastric tube or gastrostomy tube is not allowed;

Prior/Concomitant Therapy

16. Participant has 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;

17. Participant previously received or is currently receiving therapy with PD-0325901 or any other MEK1/2 inhibitor (e.g., selumetinib, trametinib, cobimetinib, binimetinib, etc.);

18. Participant is receiving systemic, inhaled, or ocular glucocorticoid therapy (with the exception of participants with endocrine deficiencies who are allowed to receive physiologic or stress doses of steroids, if necessary) within 14 days prior to first dose of study treatment;

19. Participant has received radiation therapy within the 6 months prior to signing of informed consent/assent. Participants who have received radiation to the orbit at any time are excluded;

Prior/Concurrent Clinical Study Experience

20. Current enrollment or past participation in any other clinical study (excluding observational studies) within 28 days of signing of informed consent/assent;

Other Exclusions

21. Participant is unable to tolerate MRI or for whom MRI is contraindicated;

22. Tumor is not able to be reliably evaluated by MRI volumetric analysis;

23. Sensitivity to the study treatment, or components thereof, or drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates participation in the study;
24. Participant with active bacterial, fungal, or viral infection including but not limited to the use of antibiotics, antifungals, or antiviral agents at the time of Screening;
25. Underlying medical conditions, laboratory abnormality, or alcohol or drug abuse or dependence that, in the Investigator's opinion, will be unfavorable for the administration of study treatment or affect the explanation of drug toxicity or adverse events; or insufficient compliance during the study according to Investigator's judgement; or
26. Participant has experienced other severe acute or chronic medical or psychiatric conditions, including recent (within 1 year of signing informed consent/assent) or active suicidal ideation or behavior, or a laboratory abnormality that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the participant inappropriate for entry into this study.

5.3. Lifestyle Considerations

1. There are no lifestyle restrictions in this study.
2. Study treatment may be taken without regard to food.
3. Refer to Section 6.5 for more detail on concomitant therapy including exclusions and restrictions.

5.4. Screen Failures

Screen failures are defined as participants who consent/assent to participate in the clinical study but are not subsequently assigned to study treatment (PD-0325901) at Cycle 1 Day 1 of the Treatment Phase. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened at any time and do not need to wait the full 45 days of the Screening period. These cases must be discussed with the Medical Monitor prior to rescreening. The participant must be re-consented/assented if approved for rescreening. In addition, all Screening assessments must be repeated with the exception of imaging, echocardiogram, and the ophthalmic assessment, which would only be repeated if the assessments were obtained > 45 days prior to the first dose of study treatment. There is no set limit to how many times a participant may be rescreened if the Investigator considers the rescreening medically and scientifically appropriate. Rescreened participants will be assigned a new participant number at the time of rescreening using interactive response technology (IRT).

6. Study Treatment

Study treatment for this study is defined as investigational product and intended to be administered to a study participant according to the study protocol. For this protocol, study treatment refers to capsules or dispersible tablets (pediatric formulation) of mirdametinib (PD-0325901).

6.1. Study Treatment Administered

- Participants utilizing the **capsule** dosage form of study treatment:
    - Participants will be instructed to swallow capsules whole and not to open or chew them prior to swallowing.
    - No capsule should be ingested if it is broken, cracked, or otherwise not intact.
- Participants utilizing the **dispersible tablet** (pediatric formulation) dosage form of study treatment:
    - Additional dosage preparation instructions must be provided to the participant and/or primary caregiver.
    - Participants will be instructed to disperse the tablet(s) in water in a provided oral dosing syringe immediately prior to administration. Tablet(s) should never be crushed, chewed, or swallowed whole.
- Participants should be encouraged to take their dose approximately every 12 hours and can be taken without regard to food.
- Delivery of any dosage form of mirdametinib (PD-0325901) via nasogastric tube or gastrostomy tube is not allowed.
- During the Treatment Phase, participants will be instructed to record daily administration of study treatment dose in a home electronic patient reported outcome (ePRO) device, which will be provided by the Sponsor. Missed doses will also be recorded in the home ePRO device. For participants < 12 years of age, the primary caregiver will be asked to complete the electronic dosing diary.
- If a participant misses a scheduled dose of study treatment, and it is within 6 hours of the scheduled dose, the participant should immediately administer the missed dose and resume study treatment in accordance with the normal administration schedule. If more than 6 hours has elapsed since the time of scheduled administration, the participant will **not** be instructed to administer the missed dose and to resume study treatment as prescribed.
- Participants should not take 2 doses together to “make-up” for a missed dose.

- If a participant vomits any time after taking a dose, then they must be instructed not to take another dose to "make up" for vomiting, but rather, to resume subsequent doses as prescribed.
- If a participant inadvertently takes 1 extra dose, then the participant should not take the next scheduled dose of study treatment.
- If applicable, instructions related to dosing should be provided to parent(s)/legal guardians as well as study participants.

Table 3 Study Treatment Administration

ARM Name	Treatment	
Treatment Name	Mirdametinib (PD-0325901)	
Type	Drug	
Dose Formulation	Capsule	Dispersible tablets
Unit Dose Strength(s)	1 mg and 2 mg	0.5 mg and 1 mg
Drug Product Components	mirdametinib, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, hard gelatin capsule shell	mirdametinib, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, sucralose, grape flavor
Dosage Level(s)	2 mg/m^2 (maximum single dose of 4 mg, BID)	
Route of Administration	Oral	
Sourcing	Sponsor will provide Sites with study treatment for individual participant distribution. Oral syringes will also be provided for participants utilizing the dispersible tablet formulation.	
Packaging and Labeling	Study treatment will be provided in 75 count bottles. Each bottle will be labeled as required per country requirement.	
Former Names	PD-0325901-00, PD-0325901-0000, PF-00192513-00	

6.1.1. Study Treatment Dosing and Administration

Once the informed consent/assent process (Section 10.1.3) has been conducted and all entry criteria have been met, study treatment will be assigned and dispensed using the IRT. The default formulation of study treatment will be the capsule. If a participant requires the use of the dispersible tablet (pediatric formulation) dosage form, this must be specifically requested in the IRT. The first dose of study treatment will then be administered orally at the Site followed by a ≥ 2-hour observation period.

Throughout the Treatment Phase, participants will self-administer study treatment BID (twice daily [approximately every 12 hours without regard to food]), utilizing an intermittent (3 weeks on/1 week off) dosing schedule in 28-day Cycles. If the participant is receiving the dispersible tablet (pediatric formulation) dosage form of study treatment, dosing instructions must be provided to detail dose preparation and administration utilizing provided oral dosing syringes.

Participants will be instructed to **not** take their planned morning dose prior to each study visit during the Treatment Phase. Instead, the morning dose will be taken following the pre-dose PK blood draw. To accommodate site scheduling, modifications to holding the morning dose for the purposes of PK sample collection may be made on a case-by-case basis with prior approval from the Sponsor.

Study treatment (and oral syringes if the dispersible tablets [pediatric formulation] are utilized) will be dispensed to participants every 2 Cycles during scheduled study visits in the Treatment Phase and every 4 Cycles in the LTFU Phase as described in the SoA (Section 1.3, Section 1.4) or unscheduled visits if study treatment is damaged/lost or dose modification (Section 6.6) is necessary.

Participants enrolled in the LTFU Phase of the study will continue taking the last dose assigned in the Treatment Phase (approximately 2 mg/m^2 BID [maximum dose of 4mg BID]) of PD-0325901 (mirdametinib; open-label study treatment), on an intermittent (3 weeks on/1 week off) dosing schedule in 28-day cycles unless a dose modification is required (e.g., BSA change).

6.1.2. Study Treatment Errors

Study treatment errors may result in this study from the administration or consumption of the study treatment by the wrong participant or at the wrong dosage strength. Such study treatment errors occurring to a study participant are to be captured in the electronic case report form (eCRF) when appropriate. Missed doses are not considered dosing errors. In the event of a dosing error, the Medical Monitor should be notified immediately.

Study treatment errors are reportable irrespective of the presence of an associated AE/SAE, including errors involving participant exposure to the product.

If the study treatment error is accompanied by an AE (as determined by the Investigator), the study treatment error (if applicable), and any AE(s), must be captured on an AE eCRF page.

6.2. Preparation/Handling/Storage/Accountability

Only participants enrolled in the study, who meet study entry criteria (Sections 5.1 and 5.2) may receive study treatment, as assigned by the IRT. Only authorized Site personnel may supply or administer study treatment (PD-0325901, mirdametinib). Only in extenuating circumstances and with written permission from the Sponsor, direct to participant shipment of study treatment may be accommodated via site request.

Preparation:

- Study treatment does not require special preparation by Site personnel prior to dispensing to participants. If the dispersible tablet (pediatric formulation) is being utilized, oral dosing syringes will be supplied with study treatment for participant/primary caregiver preparation and administration.

- Study treatment will be supplied as hard gelatin capsules (1- and 2-mg) or rapidly dispersible tablets (0.5- and 1-mg) for oral administration.
- Study treatment will be packaged in high-density polyethylene bottles.
- Participants will be instructed to keep their study treatment in the original bottles provided by the Sponsor and not transfer it to any secondary containers.

Handling:

- Study treatment must be handled by authorized/delegated Site personnel only.
- No special handling of study treatment is required.

Storage:

- Capsules must be stored at 15°C to 30°C (59°F to 86°F). Dispersible Tablets must be stored at 15°C to 25°C (59°F to 77°F).
- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- All study treatment must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized Site staff.

Accountability:

- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Participants will be instructed not to dispose of any study treatment bottles, and to bring all bottles (used and unused) back to the Site at every visit.
- Accountability will be performed by Site personnel at each dispensing visit as described in the SoA (Section 1.3, Section 1.4), and participants will be re-educated about the importance of following the prescribed dosing regimen (if compliance is low).
- Returned study treatment will not be re-dispensed to the participants.
- Further guidance and information for the final disposition of unused study treatments are provided in the pharmacy manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

This study is an open-label, single arm/intervention study; potential bias will be reduced by the utilization of an independent, blinded, central radiologic review for the primary endpoint adjudication and analysis.

Study treatment blinding and randomization are not applicable in this study.

6.4. Study Treatment Compliance

Participant compliance with study treatment will be assessed at each visit where study treatment is dispensed. Compliance will be assessed by counting returned capsules/dispersible tablets in addition to reviewing the dosing diary entries from the home ePRO device used in the Treatment Phase (participants will be trained on the home ePRO device at the Screening visit). At each study visit, any discrepancies or deviations will be discussed with the participant and will be recorded in the source documentation. The number of capsules/dispersible tablets dispensed, and the number of capsules/dispersible tablets returned will be recorded in the eCRF, as well as any deviations. In the case of an overdose, refer to Section 8.4 for instructions.

6.5. Concomitant Therapy

6.5.1. Prior/Concomitant Medications and/or Procedures

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of signing informed consent/assent or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy. Refer to Section 10.10.3 for the Medical Monitor contact details.

6.5.2. Prohibited or Restricted Concomitant Medications/Treatments

- Prior use of mirdametinib (PD-0325901) or any other MEK1/2 inhibitor is prohibited.
- Alternative therapy for the treatment of PNs (e.g., farnesyltransferase inhibitors, kinase inhibitors, etc.) within 45 days (or 5.5 half-lives, whichever is longer) of first dose of study treatment and throughout the Treatment Phase or LTFU Phase is prohibited.
- Medical treatment (e.g., chemotherapy, biologic therapy, radiation therapy) directed towards any NF1-related tumor such as optic pathway glioma is prohibited throughout the Treatment Phase or LTFU Phase.
- The use of chronic systemic, inhaled, or ocular glucocorticoid therapy is prohibited within the 14 days prior to first dose of study treatment and throughout the Treatment Phase or LTFU Phase with the following exceptions:
    - Physiologic or stress doses of steroids, when indicated in participants with endocrine deficiencies
    - Glucocorticosteroids given as the premedication for blood product transfusions

- Glucocorticosteroids given as the pulse treatment for an acute allergic reaction or bronchospasm
- Oral or intravenous glucocorticosteroids for up to 6 consecutive days, when indicated for the management of an adverse event only after consultation with the Medical Monitor and/or ophthalmologist
- Topical steroids for dermatological purposes are permitted at the discretion of the Investigator

6.5.3. Supportive Care

Refer to Section 10.12.

6.6. Dose Modification

Every effort should be made to administer study treatment at 2 mg/m^2 BID; however, in the event of significant toxicity, dosing must be interrupted and/or dose reduced as described in Table 4 and Table 5.

Interruption of study treatment should continue until the toxicity is resolved to ≤ Grade 1 or Baseline. An interruption of study treatment for more than 14 days due to any toxicity may require permanent discontinuation. After 14 days of interruption, study treatment may be resumed only after discussion with the Medical Monitor and approval by the Sponsor. Refer to Section 10.10.3 for the Medical Monitor contact details.

After interruption, study treatment may be resumed at a reduced dose as described in Table 4 and Table 5. Should the same Grade toxicity recur at the reduced dose and the AE is considered related to the study treatment, the participant may be discontinued at the discretion of the Investigator, pursuant to discussion with the Medical Monitor and Sponsor. Following a dose reduction, an increase in the study treatment dose due to a BSA change is permitted at the discretion of the Investigator with approval from the Medical Monitor and Sponsor.

An unscheduled visit may be performed at any time during the study. Assessments to be performed at the visit will be determined by the Investigator.

Table 4 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 Table 5. Consider ophthalmologic exams every 2 to 4 weeks.
Grade ≥ 3 retinal vein occlusion (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 Table 5.
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 ADL).	Interrupt dosing; if resolution to Grade ≤ 1 or baseline occurs within 14 days, re-start study treatment at the next lower dose following Table 5.
DERMATOLOGICAL	
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 Table 5.
CARDIAC	
Asymptomatic, absolute decrease in left ventricular ejection fraction (LVEF) of ≤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 ≤ 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 Section 7.1.1)	
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 Table 5.
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 Table 5.
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 Table 5. If toxicity is still intolerable, permanently discontinue study treatment (unless otherwise discussed with the Medical Monitor or Sponsor).

ADL=activities of daily living; CHF=congestive heart failure; LLN=lower limit of normal; LVEF=left ventricular ejection fraction

In the event a dose reduction is required, the study treatment total daily dose will be reduced as follows in Table 5:

Table 5 Dose Reduction

Capsule dosage form

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

Capsule dosage form Dose Modification Nomogram

BSA (m^2)	0.4 to 0.69	0.7 to 1.04	1.05 to 1.49	≥ 1.5
Modified Dose	1 mg AM	2 mg AM, 1 mg PM	2 mg BID	3 mg BID

BID = twice daily; BSA = body surface area; mg = milligrams

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

Dispersible tablet dosage form (pediatric formulation)

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

Dispersible tablet dosage form (pediatric formulation) Dose Modification Nomogram

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
Modified Dose	1 mg AM, 0.5 mg PM	1 mg BID	1.5 mg BID	2 mg AM, 1.5 mg PM	2.5 mg AM, 2 mg PM	2.5 mg BID	3 mg AM, 2.5 mg PM

BID = twice daily; BSA = body surface area; mg = milligrams

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

6.7. Treatment after the End of the Study

Long-Term Follow-up Phase:

Participants who complete Cycle 24 of the Treatment Phase and did not meet withdrawal criteria (Section 7) are eligible to participate in the LTFU Phase. Eligible participants will continue taking the last dose assigned in the Treatment Phase (approximately 2 mg/m^2 BID [maximum dose of 4mg BID]) of PD-0325901 (mirdametinib; open-label study treatment), on an intermittent (3 weeks on/1 week off) dosing schedule in 28-day cycles. Participants will remain in the LTFU Phase until a withdrawal criterion is met as described in Section 7 or mirdametinib is commercially available.

7. Discontinuation of Study Treatment and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Treatment

It may be necessary for a participant to permanently discontinue study treatment prematurely or for the Sponsor to suspend study enrollment.

Participants who permanently discontinue from the Treatment Phase prior to the Cycle 24 visit will be required to return to the clinic for an early termination (ET) visit as close as possible to the last dose of study treatment (PD-0325901, mirdametinib). Participant will also be required to return for a Safety Follow-Up visit (30 days [+5 days] after the last dose of study drug) (refer to the SoA in Section 1.3 for timing and a complete list of required assessments to be conducted).

Conditions upon which the Sponsor will suspend additional enrollment in the study are described in the specified stopping criteria in Section 10.1.7.

Reasons for discontinuation of study treatment early may include:

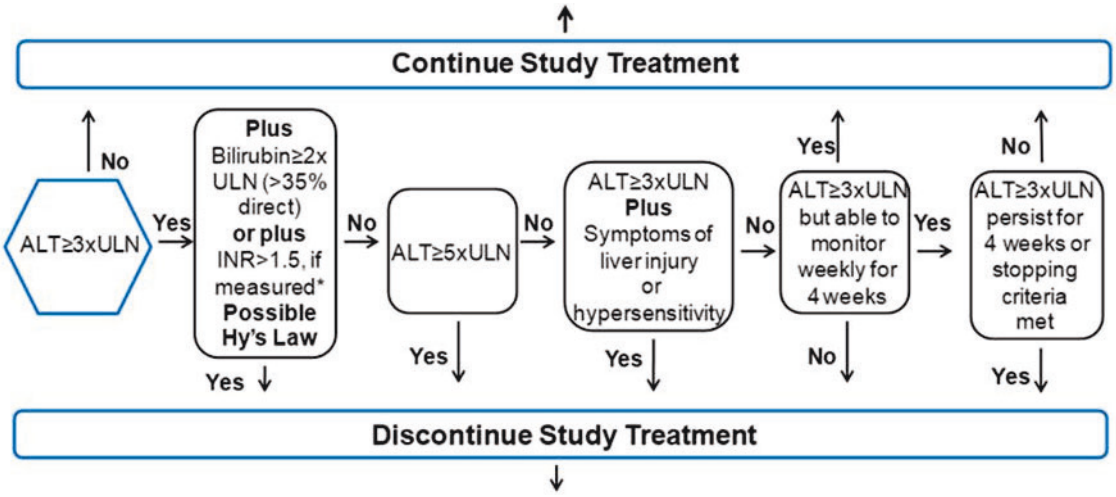
- Participants who meet the definition of progressive disease (a ≥ 20% increase in the volume of the target PN as compared to the Treatment Phase Baseline [Section 10.7], confirmed by central radiologic review);
- Occurrence of any medical condition or circumstance that exposes the participant to substantial risk and/or does not allow the participant to adhere to the requirements of the protocol.
- Any SAE (refer to Section 10.3.2 for SAE criteria), clinically significant AE (refer to QTc stopping criteria below; Section 7.1.2), severe laboratory abnormality (refer to liver chemistry stopping criteria below; Section 7.1.1), intercurrent illness, RVO, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the participant;
- Pregnancy (refer to Sections 8.3.6 and 10.4 for additional details);
- Requirement of prohibited concomitant medication (Section 6.5.2);
- Participant failure to comply with protocol requirements or study-related procedures; or
- Termination of the study by the Sponsor as described in Section 10.1.7, the IRB or the regulatory authority.

7.1.1. Liver Chemistry Stopping Criteria

Discontinuation of study treatment for abnormal liver function should be considered by the Investigator when a participant meets one of the conditions outlined in Figure 1 or if the Investigator believes that it is in the best interest of the participant.

Figure 1 Liver Chemistry Stopping Criteria and Increased Monitoring Algorithm

- **If participant is to be monitored weekly, must refer to Liver Safety: Suggested Actions and Follow-up Assessments (Section 10.5)**



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

- **Must refer to Liver Safety: Suggested Actions and Follow-up Assessments (Section 10.5)**
- **Report as an SAE if possible Hy's Law case:** ALT ≥ 3xULN and Bilirubin ≥ 2xULN (> 35% direct) or INR > 1.5, if measured*

  *INR value not applicable to participants on anticoagulants

7.1.2. QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to changes from Baseline in QT interval corrected using Fridericia's formula [QTcF]) after first dose of study treatment, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

A participant who meets either bulleted criterion based on the average of triplicate ECG readings will be withdrawn from study treatment:

- QTcF > 500 msec OR Uncorrected QT > 600 msec
- Change from Baseline of QTcF > 60 msec

Table 6 describes the discontinuation criteria for participants with underlying bundle branch block.

Table 6 Bundle Branch Block Discontinuation Criteria

Baseline QTcF with Bundle Branch Block	Discontinuation QTcF Threshold with Bundle Branch Block
< 450 msec	> 500 msec
450 to 480 msec	≥ 530 msec

See the SoA (Section 1.3, Section 1.4) for data to be collected at the time of discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.3. Pregnancy

A female participant who becomes pregnant will be withdrawn from study treatment. See Section 8.3.6 for additional details.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the Treatment Phase early, the ET visit should be conducted as close to the last dose of study treatment as possible. See SoA (Section 1.3) for specific data to be collected at the time of premature study treatment discontinuation, as well as follow-up for any further evaluations that need to be completed.
- If the participant withdraws consent/assent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent/assent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the Site study records.

7.3. Lost to Follow up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and is unable to be contacted by the study Site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The Site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific Sites or of the study as a whole are handled as part of Section 10.1.7.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Sections 1.3 and 1.4). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor and/or Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment (PD-0325901, mirdametinib).
- Adherence to the study design requirements, including those specified in the SoAs, is essential and required for study conduct.
- All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria (Sections 5.1 and 5.2). The electronic data capture (EDC) will capture all participants who sign the informed consent/assent, including all screen failures.
- The amount of blood collected from each participant over the duration of the Treatment Phase of the study (24 months) will be less than 200 mL. The amount of blood collected from each participant in the LTFU Phase is approximately 30 mL per year. This does not include any extra assessments that may be required for unscheduled assessments. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with samples.
- In the event that a study site or participant is unable to complete a study visit or procedure due to restrictions caused by a public health emergency such as COVID-19, the following accommodations may be allowed temporarily with prior approval from the Medical Monitor / Sponsor. Any deviations from the study protocol due to a public health emergency should be documented in the source data and eCRF and reported to the IRB/EC in accordance with their reporting requirements.
    - If a study participant cannot attend a study visit onsite due to a public health emergency, they may be able to attend a local hospital/clinic or arrange for a telehealth or home healthcare visit.
    - Clinical laboratory assessments may be performed locally with results and local laboratory normal ranges entered into the eCRF.
    - Electrocardiograms may be performed locally. If ECGs are performed locally, ECG tracings should be collected and the Investigator (or designee) assessment should be documented. Every effort should be made to perform ECGs in triplicate; however, a single ECG will be allowed if necessary due to a public health emergency.
    - Study imaging (MRI) should be performed per the schedule in the SoAs at a qualified imaging facility; however, local imaging may be allowed if able to meet study imaging requirements (inclusive of required STIR sequence) and

with prior Sponsor approval. Local imaging will need to be uploaded for Central Imaging Review.

Table 7 Treatment Phase Key Study Visit Reminders

This table supplements the Treatment Phase SoA and highlights key study reminders. Refer to the SoA (Section 1.3) for a complete list of study assessments, and the study reference manual for study visit checklists which will include the recommended sequence of assessments for each study visit.

Screening Visit
The Screening visit may occur up to 45 days prior to the first dose of study treatment. However, to allow for the complete collection of the Baseline PRO assessments (Table 9) (which will begin 6 days prior to the Baseline visit), the minimum Screening period is 7 days. Screening period begins the day a participant signs the informed consent form. The first 5 participants enrolled in the pediatric cohort must be 9 to 17 years of age at the time of signing informed consent. After the first 5 participants have enrolled in the pediatric cohort, enrollment into this cohort will be paused, and only after Data Monitoring Committee (DMC) evaluation of at least 2 cycles of cumulative safety data for these 5 participants will the pediatric cohort be re-opened and potentially expand down to 2 years of age. During the Screening period, participants will receive training on how to use the home ePRO device (provided by the Sponsor), which will include a practice questionnaire to be completed prior to the participant leaving the Site. A MRI (Section 8.1.1.1) scan is required at Screening for all participants and will be submitted to central radiologic review to confirm that the target PN is analyzable by volumetrics (required to confirm Inclusion Criterion 5) using the REiNS criteria (Dombi, 2013). This Screening scan will serve as a participant's Baseline scan throughout the study. If applicable, scans acquired prior to the participant signing informed consent/assent may be used as the Screening time point scan if obtained within 45 days of the first dose of study treatment administration and the participant meets study requirements. No other pre-enrollment images will be collected for the study. For participants enrolling exclusively for a "major deformity" or "significantly disfiguring" tumor, the Medical Monitor **must** be contacted to review participant eligibility prior to study treatment assignment using the IRT. As noted in the SoA, urine and blood will be collected/processed for central laboratory analysis. Central lab results must be received and reviewed prior to the Cycle 1 Day 1 visit to ensure participant meets eligibility criteria. Screening tests with results considered by the Investigator to be transient and inconsistent with the participant's clinical condition may be repeated once during the Screening period for confirmation of eligibility.

Consideration of re-screening of a participant who did not meet eligibility criteria must be discussed with the Medical Monitor. The participant must be re-consented/assented if approved for rescreening. In addition, all Screening assessments must be repeated with the exception of imaging, echocardiogram, and the ophthalmic assessment, which would only be repeated if the assessments were obtained > 45 days from the first dose of study treatment.

Ophthalmic assessments (Section 8.2.7) must be performed by an ophthalmologist throughout the study. Participants in the pediatric cohort must be evaluated by a pediatric ophthalmologist. The Screening ophthalmic exam will reconfirm Exclusion Criterion 12.

For WOCBP, a serum pregnancy test will be conducted at Screening to confirm eligibility (Inclusion Criterion 13).

An echocardiogram (Section 8.2.8) is performed to confirm Exclusion Criterion 11.

Triplicate 12-Lead ECGs (Section 8.2.4) are performed to confirm Exclusion Criterion 9.

A practice 6-minute walk test (Section 8.1.7) must be conducted during Screening, if applicable for the participant.

Baseline and Cycle 1 Day 1

The Baseline visit may occur up to 48 hours prior to first dose of study treatment. However, the PRO assessments will begin 6 days prior to the first day of the Baseline visit. The PII and NRS-11 questionnaires will be completed using the home ePRO device daily for 6 consecutive days prior to the scheduled Baseline visit. At the Baseline visit, the following PRO assessments will be completed prior to all other study assessments to minimize participant bias in the clinic: (PedsQL [paper], PII, NRS-11, PROMIS and PGIS [Table 9]). The paper PedsQL should always be the first PRO administered at the visit.

Because the Baseline visit may occur over 48 hours, Cycle 1 Day 1 will be defined as the date of administration of the first dose of study treatment. The following Baseline assessments are to be conducted prior to the first dose of study treatment:

- PROs (to be completed prior to all other study assessments to minimize participant bias) (Section 8.1.2)
- Concomitant medication and AE/SAE review (Section 8.3);
- Urinalysis / urine pregnancy for WOCBP;
- Blood draw for hematology and serum chemistry (Section 8.2.5);
- Pre-dose PK blood draw (should be within 1 hour prior to dosing when possible) (Section 10.8);
- Vital signs (including height and weight) (Section 8.2.3);
- Pre-dose triplicate 12-Lead ECGs (Section 8.2.4);

- Physical examination and Karnofsky/Lansky performance status (Section 8.2.2)
- Range of motion assessment and strength assessment utilizing a dynamometer and Medical Research Council (MRC) Muscle Scale (for participants with a target PN that causes motor dysfunction or weakness) (Section 8.1.3 and 8.1.5), and should be conducted prior to lab draws if the range of motion or strength assessment may be affected by the lab draw;
- 6-minute walk test (for participants with a target PN that causes airway or lower extremity motor dysfunction) (Section 8.1.7);
- Target tumor biopsy (if applicable) (Section 8.1.6). For adult participants requiring a tumor biopsy, this assessment may occur during the screening period, but must be performed after the screening MRI volumetric assessment has been confirmed evaluable by central radiologic review and prior to first dose of study treatment. If a study biopsy was collected and the participant did not initiate study treatment, this biopsy may be utilized as the baseline biopsy if the participant subsequently re-screens for enrollment;
- Bone plate radiograph for participants 2 to 17 years of age (Section 8.2.9); and

Photography of PN (if target PN and/or its effects are visible and amenable to photography) (Section 8.1.4) can be done before or after first dose of study treatment.

After the pre-dose Baseline assessments (as noted above) have been completed and the participant meets all entry criteria (Sections 5.1 and 5.2) they will be assigned study treatment using the IRT and the first dose will be administered at the Site.

The following Baseline assessments are to be conducted after the first dose of study treatment:

- Triplicate 12-Lead ECGs to be conducted approximately 1-hour post-dose;
- PK sampling (Sections 8.5 and 10.8) to be conducted 1- and 2-hours post-dose (± 10-minute allowed window);
- Record first dose of study treatment in the ePRO device at Site;
- ≥ 2-hour observation period following the first dose of study treatment; and
- Concomitant medication and AE/SAE review (Section 8.3).

Participants should be reminded to complete their dosing diary daily and return all study treatment at every visit.

Cycle 1 Day 15

Participants will not take their planned morning dose the day of the study visit. Instead they will take their morning dose of study treatment following the pre-dose PK blood draw in the clinic (Section 10.8).

Additional PK sampling to be conducted at 0.5, 1, 2, 3- and 4-hours post-dose (± 10-minute allowed window) (Sections 8.5 and 10.8). Triplicate 12-Lead ECGs to be conducted 1-hour post-dose (± 10-minute allowed window) (Section 8.2.4). Participants will not be dispensed new study treatment at this visit; therefore, they should continue dosing with the same study treatment that was dispensed at Cycle 1 Day 1. Refer to the SoA (Section 1.3) for all additional procedures required at this visit.
Cycle 2 Day 15
Participants will not take their planned morning dose the day of the study visit. Instead they will take their morning dose of study treatment following the pre-dose PK blood draw (Section 10.8). Participants will not be dispensed new study treatment at this visit; therefore, they should continue dosing with the same study treatment that was dispensed at Cycle 1 Day 1. Refer to the SoA (Section 1.3) for all additional procedures required at Cycle 2 Day 15.
Cycle 3 Day 15
Participants will not take their planned morning dose the day of the study visit. Instead they will take their morning dose of study treatment following the pre-dose PK blood draw (Section 10.8). The PII and NRS-11 questionnaires will be completed using the home ePRO device daily for 6 consecutive days prior to the scheduled Cycle 3 Day 15 visit. At the Cycle 3 Day 15 visit, all PRO assessments (PedsQL [paper], PII, NRS-11, PROMIS, PGIS and PGIC [Table 9]) will be completed prior to all other study assessments to minimize participant bias in the clinic. If the participant is utilizing the dispersible tablet (pediatric formulation) dosage form and has not yet completed the P-OMAQ (paper), they should complete the assessment at this visit. This assessment should only be completed once during the study. All previously dispensed study treatment will be collected for accountability, and participants will be dispensed new study treatment using the IRT at this study visit. Refer to the SoA (Section 1.3) for all additional procedures required at Cycle 3 Day 15.
Cycle 4 Day 15
Participants will not take their planned morning dose the day of the study visit. Instead they will take their morning dose of study treatment following the pre-dose PK blood draw. Participants will not be dispensed new study treatment at this visit; therefore, they should continue dosing with the same study treatment that was dispensed at Cycle 3 Day 15.

If the participant is utilizing the dispersible tablet (pediatric formulation) dosage form and has not yet completed the P-OMAQ (paper), they should complete the assessment at this visit. This assessment should only be completed once during the study. Refer to the SoA (Section 1.3) for all additional procedures required at Cycle 4 Day 15.
Cycle 5 Day 15
Participants will not take their planned morning dose the day of the study visit. Instead they will take their morning dose of study treatment following the pre-dose PK blood draw. The PII and NRS-11 questionnaires will be completed using the home ePRO device daily for 6 consecutive days prior to the scheduled Cycle 5 Day 15 visit. At the Cycle 5 Day 15 visit, all PRO assessments (PedsQL [paper], PII, NRS-11, PROMIS, PGIS and PGIC [Table 9]) will be completed prior to all other study assessments to minimize participant bias in the clinic. If the participant is utilizing the dispersible tablet (pediatric formulation) dosage form and has not yet completed the P-OMAQ (paper), they should complete the assessment at this visit. This assessment should only be completed once during the study. Tumor volume will be measured by MRI (no contrast required) and scans will be submitted for central radiologic review (Section 8.1.1). If sedation is used for the MRI assessment, sedation must be administered after the strength, range of motion and 6-minute walk assessments if assessments are to be completed in the same day. All previously dispensed study treatment will be collected for accountability, and participants will be dispensed new study treatment using the IRT at this study visit. Refer to the SoA (Section 1.3) for additional procedures at Cycle 5 Day 15.
Cycle 6 Day 15
Participants will not take their planned morning dose the day of the study visit. Instead they will take their morning dose of study treatment following the pre-dose PK blood draw (Section 10.8). Participants will not be dispensed new study treatment at this visit; therefore, they should continue dosing with the same study treatment that was dispensed at Cycle 5 Day 15. If the participant is utilizing the dispersible tablet (pediatric formulation) dosage form and has not yet completed the P-OMAQ (paper), they should complete the assessment at this visit. This assessment should only be completed once during the study. Refer to the SoA (Section 1.3) for all additional procedures required at Cycle 6 Day 15.

Cycle 7 Day 15
Participants will not take their planned morning dose the day of the study visit. Instead they will take their morning dose of study treatment following the pre-dose PK blood draw (Section 10.8). The PII and NRS-11 questionnaires will be completed using the home ePRO device daily for 6 consecutive days prior to the scheduled Cycle 7 Day 15 visit. At the Cycle 7 Day 15 visit, all PRO assessments (PedsQL [paper], PII, NRS-11, PROMIS, PGIS and PGIC [Table 9]) will be completed prior to all other study assessments to minimize participant bias in the clinic. If the participant is utilizing the dispersible tablet (pediatric formulation) dosage form and has not yet completed the P-OMAQ (paper), they should complete the assessment at this visit. This assessment should only be completed once during the study. All previously dispensed study treatment will be collected for accountability, and participants will be dispensed new study treatment using the IRT at this study visit. Refer to the SoA (Section 1.3) for all additional procedures required at Cycle 7 Day 15.
Cycle 9 Day 15
Participants will not take their planned morning dose the day of the study visit. Instead they will take their morning dose of study treatment following the pre-dose PK blood draw (Section 10.8). The PII and NRS-11 questionnaires will be completed using the home ePRO device daily for 6 consecutive days prior to the scheduled Cycle 9 Day 15 visit. At the Cycle 9 Day 15 visit, all PRO assessments (PedsQL [paper], PII, NRS-11, PROMIS, PGIS and PGIC [Table 9]) will be completed prior to all other study assessments to minimize participant bias in the clinic. If the participant is utilizing the dispersible tablet (pediatric formulation) dosage form and has not yet completed the P-OMAQ (paper), they should complete the assessment at this visit. This assessment should only be completed once during the study. Tumor volume will be measured by MRI (no contrast required) and scans to be submitted for central radiologic review (Section 8.1.1). If sedation is used for the MRI assessment, sedation must be administered after the strength, range of motion, and 6-minute walk assessments if assessments are to be completed in the same day. All previously dispensed study treatment will be collected for accountability, and participants will be dispensed new study treatment using the IRT at this study visit. Refer to the SoA (Section 1.3) for all additional procedures required at Cycle 9 Day 15.

Cycle 11 Day 15
Participants will not take their planned morning dose the day of the study visit. Instead they will take their morning dose of study treatment following the pre-dose PK blood draw (Section 10.8). All previously dispensed study treatment will be collected for accountability, and participants will be dispensed new study treatment using the IRT during this study visit. If the participant is utilizing the dispersible tablet (pediatric formulation) dosage form and has not yet completed the P-OMAQ (paper), they should complete the assessment at this visit. This assessment should only be completed once during the study. Refer to the SoA (Section 1.3) for all additional procedures required at Cycle 11 Day 15.
Cycle 13 Day 15
Participants will not take their planned morning dose the day of the study visit. Instead they will take their morning dose of study treatment following the pre-dose PK blood draw (Section 10.8). The PII and NRS-11 questionnaires will be completed using the home ePRO device daily for 6 consecutive days prior to the scheduled Cycle 13 Day 15 visit. At the Cycle 13 Day 15 visit, all PRO assessments (PedsQL [paper], PII, NRS-11, PROMIS, PGIS and PGIC [Table 9]) will be completed prior to all other study assessments to minimize participant bias in the clinic. If the participant is utilizing the dispersible tablet (pediatric formulation) dosage form and has not yet completed the P-OMAQ (paper), they should complete the assessment at this visit. This assessment should only be completed once during the study. Tumor volume will be measured by MRI (no contrast required) and scans to be submitted for central radiologic review (Section 8.1.1). If sedation is used for the MRI assessment, sedation must be administered after the strength, range of motion, and 6-minute walk assessments if assessments are to be completed in the same day. Bone plate radiographs for participants 2 to 17 years of age, if applicable (Section 8.2.9). All previously dispensed study treatment will be collected for accountability, and participants will be dispensed new study treatment using the IRT at this study visit. Refer to the SoA (Section 1.3) for additional procedures at Cycle 13 Day 15.
Cycle 15 Day 15
Participants will not take their planned morning dose the day of the study visit. Instead they will take their morning dose of study treatment following the pre-dose PK blood draw (Section 10.8).

All previously dispensed study treatment will be collected for accountability, and participants will be dispensed new study treatment using the IRT during this study visit. If the participant is utilizing the dispersible tablet (pediatric formulation) dosage form and has not yet completed the P-OMAQ (paper), they should complete the assessment at this visit. This assessment should only be completed once during the study. Refer to the SoA (Section 1.3) for additional procedures at Cycle 15 Day 15.
Cycle 17 Day 15
Participants will not take their planned morning dose the day of the study visit. Instead they will take their morning dose of study treatment following the pre-dose PK blood draw (Section 10.8). The PII and NRS-11 questionnaires will be completed using the home ePRO device daily for 6 consecutive days prior to the scheduled Cycle 17 Day 15 visit. At the Cycle 17 Day 15, visit all PRO assessments (PedsQL [paper], PII, NRS-11, PROMIS, PGIS and PGIC [Table 9]) will be completed prior to all other study assessments to minimize participant bias in the clinic. If the participant is utilizing the dispersible tablet (pediatric formulation) dosage form and has not yet completed the P-OMAQ (paper), they should complete the assessment at this visit. This assessment should only be completed once during the study. Tumor volume will be measured by MRI (no contrast required) and scans to be submitted for central radiologic review (Section 8.1.1). If sedation is used for the MRI assessment, sedation must be administered after the strength, range of motion, and 6-minute walk assessments if assessments are to be completed on the same day. All previously dispensed study treatment will be collected for accountability, and participants will be dispensed new study treatment using the IRT during this study visit. Refer to the SoA (Section 1.3) for all additional procedures required at Cycle 17 Day 15.
Cycle 19 Day 15
Participants will not take their planned morning dose the day of the study visit. Instead they will take their morning dose of study treatment following the pre-dose PK blood draw (Section 10.8). All previously dispensed study treatment will be collected for accountability, and participants will be dispensed new study treatment using the IRT during this study visit. If the participant is utilizing the dispersible tablet (pediatric formulation) dosage form and has not yet completed the P-OMAQ (paper), they should complete the assessment at this visit. This assessment should only be completed once during the study. Refer to the SoA (Section 1.3) for additional procedures at Cycle 19 Day 15.

Cycle 21 Day 15
Participants will not take their planned morning dose the day of the study visit. Instead they will take their morning dose of study treatment following the pre-dose PK blood draw (Section 10.8). The PII and NRS-11 questionnaires will be completed using the home ePRO device daily for 6 consecutive days prior to the scheduled Cycle 21 Day 15 visit. At the Cycle 21 Day 15 visit, all PRO assessments (PedsQL [paper], PII, NRS-11, PROMIS, PGIS and PGIC [Table 9]) will be completed prior to all other study assessments to minimize participant bias in the clinic. If the participant is utilizing the dispersible tablet (pediatric formulation) dosage form and has not yet completed the P-OMAQ (paper), they should complete the assessment at this visit. This assessment should only be completed once during the study. Tumor volume will be measured by MRI (no contrast required) and scans to be submitted for central radiologic review (Section 8.1.1). If sedation is used for the MRI assessment, sedation must be administered after the strength, range of motion, and 6-minute walk assessments if assessments are to be completed on the same day. All previously dispensed study treatment will be collected for accountability, and participants will be dispensed new study treatment using the IRT during this study visit. Refer to the SoA (Section 1.3) for additional procedures at Cycle 21 Day 15.
Cycle 23 Day 15
Participants will not take their planned morning dose the day of the study visit. Instead they will take their morning dose of study treatment following the pre-dose PK blood draw (Section 10.8). All previously dispensed study treatment will be collected for accountability, and participants will be dispensed new study treatment using the IRT during this study visit. If the participant is utilizing the dispersible tablet (pediatric formulation) dosage form and has not yet completed the P-OMAQ (paper), they should complete the assessment at this visit. This assessment should only be completed once during the study. Refer to the SoA (Section 1.3) for additional procedures at Cycle 23 Day 15.
Cycle 24 Day 21 (End of Treatment Phase Visit)
Participants will not take their planned morning dose the day of the study visit. Instead they will take their morning dose of study treatment following the pre-dose PK blood draw (Section 10.8). The PII and NRS-11 questionnaires will be completed using the home ePRO device daily for 6 consecutive days prior to the scheduled Cycle 24 Day 21 visit. At the Cycle 24 Day 21 visit, all PRO assessments (PedsQL [paper], PII, NRS-11, PROMIS, PGIS and PGIC [Table 9]) will

be completed prior to all other study assessments to minimize participant bias in the clinic. If the participant is utilizing the dispersible tablet (pediatric formulation) dosage form and has not yet completed the P-OMAQ (paper), they should complete the assessment at this visit. This assessment should only be completed once during the study.

Tumor volume will be measured by MRI (no contrast required) and scans to be submitted for central radiologic review (Section 8.1.1). Scan must precede the target PN biopsy. If sedation is used, sedation must be administered after the strength, range of motion, and 6-minute walk assessments if assessments are to be completed on the same day.

Tumor biopsy will be collected from the target PN (Section 8.1.6), if applicable.

Bone plate radiographs for participants 2 to 17 years of age, if applicable. (Section 8.2.9)

All previously dispensed study treatment will be collected for accountability.

LTFU Participants Only: Dispense 4 cycles of study treatment

Refer to the SoA (Section 1.3) for all additional procedures required at Cycle 24 Day 21.

Early Termination (ET) Visit
Participants that permanently discontinue study treatment early will be required to return to the clinic for an ET visit as close to the last dose of study treatment as possible. At the ET visit, all PRO assessments (PedsQL [paper], PII, NRS-11, PROMIS, PGIS and PGIC [Table 9]) will be completed prior to all other study assessments to minimize participant bias in the clinic. If the participant is utilizing the dispersible tablet (pediatric formulation) dosage form and has not yet completed the P-OMAQ (paper), they should complete the assessment at this visit. This assessment should only be completed once during the study. A MRI scan (Section 8.1.1) is only required if not performed within the last 3 months. MRI scan must precede the target PN biopsy. If sedation is used, sedation must be administered after the strength, range of motion, and 6-minute walk assessments if assessments are to be completed on the same day. Tumor biopsy will be collected from the target PN, if applicable (Section 8.1.6). Bone plate radiographs (Section 8.2.9) for participants 2 to 17 years of age (if applicable) only required if not performed within the last 6 months. Range of motion, strength, photography, and 6-minute walk assessments are only required if not performed within the past month. Echocardiogram (Section 8.2.8) only required if not performed within the past 1 month. All previously dispensed study treatment will be collected for accountability. Refer to the SoA (Section 1.3) for all additional procedures required at the ET visit. Every effort should be made to complete all procedures at the ET visit.
Safety Follow-Up Visit
Visit is only applicable if participant is not continuing onto the LTFU Phase. Participants will return to the Site for the Safety Follow-Up visit 30 days (+ 5-day window) after the last dose of study treatment. The PII and NRS-11 questionnaires will be completed using the home ePRO device daily for 6 consecutive days prior to the scheduled Safety Follow-Up visit. At the Safety Follow-Up visit all PRO assessments (PedsQL [paper], PII, NRS-11, PROMIS, PGIS and PGIC [Table 9]) will be completed prior to all other study assessments to minimize participant bias in the clinic. Refer to the SoA (Section 1.3) for all additional procedures required at the Safety Follow-Up visit.
Monthly Wellness Checks
Monthly telephone or email contact is required throughout the study.

May be replaced by a face-to-face interaction when study visits occur if the information can be obtained during the visit. Refer to Section 8.2.10.
Monthly Urine Pregnancy Tests
Applicable to woman of child bearing potential (WOCBP) only. In between study visits, participants will be required to return to the Site for a monthly urine pregnancy test. If it is more convenient for the participant, they may alternatively visit a Sponsor-approved local laboratory for this assessment. Refer to Section 8.2.6
Unscheduled Visits
Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 8 Long-Term Follow-up Phase Key Study Visit Reminders

This table supplements the SoA and highlights key study reminders. Refer to the LTFU SoA (Section 1.4) for a complete list of study assessments, and the study reference manual for study visit checklists which will include the recommended sequence of assessments for each study visit. The Cycle 24 Day 21 (End of Treatment) visit in the Treatment Phase will serve as the Baseline Visit for the Long-Term Follow-up (LTFU) Phase.

Cycle 28 Day 15 & Every 4 Cycles
At each visit, the PedsQL [paper] [Table 9] should be completed prior to all other study assessments to minimize participant bias in the clinic. If the participant is utilizing the dispersible tablet (pediatric formulation) dosage form and has not yet completed the P-OMAQ (paper), they should complete the assessment at this visit. This assessment should only be completed once during the study. Tumor volume will be measured by MRI (no contrast required) and scans will be submitted for central radiologic review (Section 8.1.1). All previously dispensed study treatment will be collected for accountability, and participants will be dispensed new study treatment using the IRT at this study visit. Refer to the SoA (Section 1.4) for additional procedures.
End of Treatment (EOT) Visit
Participants who permanently discontinue study treatment will be required to return to the clinic for an EOT visit as close to the last dose of study treatment as possible. A MRI scan (Section 8.1.1) is only required if not performed within the last 3 months. Echocardiogram (Section 8.2.8) is only required if not performed within the past 3 months. Ophthalmic assessment (Section 8.2.7) is only required if not performed within the past 3 months. All previously dispensed study treatment will be collected for accountability. If the participant is utilizing the dispersible tablet (pediatric formulation) dosage form and has not yet completed the P-OMAQ (paper), they should complete the assessment at this visit. This assessment should only be completed once during the study. Refer to the SoA (Section 1.4) for all additional procedures required at the EOT visit. Every effort should be made to complete all procedures at the EOT visit.
Safety Follow-Up Visit
Visit is applicable only if participant is **not** transitioning directly to commercial mirdametinib at the time of discontinuation (End of Treatment visit). Participant will return to the Site for the follow-up visit 30 days (+5 days) after the last dose of study treatment.
Monthly Wellness Checks
Monthly telephone or email contact is required throughout the study. May be replaced by a face-to-face interaction when study visits occur if the information can be obtained during the visit.

Refer to Section 8.2.10.
Monthly Urine Pregnancy Tests
Applicable to woman of child-bearing potential (WOCBP) only. In between study visits, participants will be required to return to the Site for a monthly urine pregnancy test. If it is more convenient for the participant, they may alternatively visit a Sponsor-approved local laboratory for this assessment. Refer to Section 8.2.6
Unscheduled Visits
Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

8.1. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Section 1.3)

8.1.1. Tumor Imaging

8.1.1.1. MRI Assessment

Target PN volume will be measured by MRI (no contrast required, sedation permitted per institutional policy) at the Screening visit and throughout the Treatment Phase and Long-Term Follow-Up (LTFU) Phase as described in the SoA (Section 1.3, Section 1.4). Sites will submit all MRI scans for independent, blinded centralized radiologic review of tumor volume throughout the study.

MRI at Screening is required for all participants to confirm that PN is analyzable to volumetrics (determined by central radiologic review to confirm Inclusion Criterion 5) using the REiNS criteria and will serve as the participant's Baseline scan throughout the study. If applicable, scans acquired prior to the participant signing ICF may be used as Screening time point scans if they were obtained within 45 days of the first study treatment administration, central radiologic review confirms that the target PN scan is analyzable by volumetrics using the REiNS criteria, and the participant meets study requirements. These scans will then be collected, stored, and documented as the Screening scan, and will be required to be submitted to the central radiologic review. No other pre-enrollment images will be collected or stored for the study.

Before the study is initiated at each Site, Sites will be trained on imaging requirements and guidance on how to submit scans for central radiologic review. Refer to the imaging acquisition manual and the imaging submission manual, which describe the imaging methods and submission process that Sites must follow.

The imaging protocol outlined in the imaging manual will be used each time MRI examinations are performed to assess progression or response. In participants with clinical suspicion of disease progression, MRI volumetric analysis should be performed earlier than specified in the protocol. If because of unforeseen reasons, a MRI time window is passed, but not yet at the time of the opening of the subsequent window, the MRI should be performed, and the protocol deviation noted.

8.1.2. Patient Reported Outcomes

- PRO questionnaires (except the PedsQL and P-OMAQ, which will be administered on paper) will be completed by each participant (or parent proxy, as required) using a home ePRO device (supplied by the Sponsor) throughout the Treatment Phase of the study.
- The ePRO devices will be provided to the Sites prior to study initiation and to the participant at the Screening visit. All devices will be collected at the end of the Treatment Phase.
- The ePRO devices will be programmed to always administer the PROs in a particular order and at specific timepoints throughout the study (refer to Table 9). The paper PedsQL should always be the first PRO administered at the visit.
- It is important that data from the PROs be collected in a uniform manner so that study participants' responses to items on the questionnaires are not influenced by the actions or words of the data collector.
- The Site should make every effort to have the participant complete all PROs prior to all other study assessments at the visit to minimize participant bias.
- The age specific PRO will be determined at Screening, and the participant must be administered the same age-specific PRO at every visit, regardless of age at time of administration.
- Refer to the study reference manual for more information on the PROs and user guides for administration.
- The only PROs that will be completed during the LTFU Phase will be the paper P-OMAQ, if not previously completed during the Treatment Phase, and the PedsQL with associated proxy, as applicable.

Table 9 Patient Reported Outcomes (PROs) and Age Range Scale

PROs	PII		NRS-11	PROMIS		PedsQL[1]		P-OMAQ[3]		PGIS	PGIC
Age of Patient (years)	Self-Report	Parent Proxy	Self-Report	Self-Report	Parent Proxy	Self-Report	Parent Proxy	Self-Report	Parent Proxy	Self-Report	Self-Report
2							X		X		
3							X		X		
4							X		X		
5					X	X	X		X		
6	X	X			X	X	X		X	X	X
7	X	X			X	X	X		X	X	X
8-17	X	X	X	X	X	X	X	X	X	X	X
≥ 18	X		X	X		X	X[2]	X	X[2]	X	X

PGIC = patient global impression of change; PGIS = patient global impression of severity; PedsQL = Pediatric Quality of Life Inventory; PII = Pain Interference Index; P-OMAQ = Pediatric Oral Medicines Acceptability Questionnaire; PRO = patient-reported outcome; PROMIS = Patient-Reported Outcomes Measurement Information System; NRS-11 = Numerical Rating Scale-11

[1] Administered as a paper assessment. The paper PedsQL should always be the first PRO administered at the visit.

[2] If a participant is ≥ 18 years of age, but in the opinion of the investigator has cognitive deficiencies that would inhibit accurate collection of PRO data, a parent or legal guardian must also complete the appropriate parent-proxy PRO

[3] Administered as a paper assessment. This assessment will only be completed once during the study for participants utilizing the dispersible tablet dosage form.

8.1.2.1. Pain Interference Index

The Pain Interference Index (PII) assesses self-reported consequences of pain on relevant aspects of one's life over the past 24 hours. The PII will be administered over 7 consecutive days, inclusive of the study visit day, as described in the SoA (Section 1.3). For the ET visit, the assessment will only be conducted once at the Site and not for the preceding 6 days. Pain interference refers to the degree to which pain interferes with or limits an individual's daily activities. The PII also incorporates items probing sleep and mood. The PII is universal rather than disease-specific. All participants ≥ 6 years of age will complete the PII as a self-report during the Treatment Phase. In this study, parents or legal guardians of children from 6 to 17 years of age will complete the parent proxy PII in parallel. The same parent or legal guardian should be administered the PII throughout the study. The Pain Interference Index is recommended as a core outcome measure of pain interference for clinical trials in children and adults with NF1 (Wolters, 2016).

8.1.2.2. Numerical Rating Scale-11

The Numerical Rating Scale-11 (NRS-11) is a self-report segmented 11-point numeric scale that assesses pain severity over the past 24 hours. The NRS-11 will be administered over 7 consecutive days, inclusive of the study visit day, as described in the SoA (Section 1.3) during the Treatment Phase. For the ET visit, the assessment will only be conducted once at the Site and not for the preceding 6 days. Participants ≥ 8 years of age will be administered the NRS-11 as a

self-report. Participants are asked to select the one number from 0 to 10 that best describes their worst pain over the past 24 hours for target tumor pain with 0 representing “no pain” and 10 representing “worst pain you can imagine”. It takes less than 1 minute to complete. The NRS-11 is recommended as a core outcome measure of pain intensity for clinical trials in children and adults with NF1 (Wolters, 2016).

8.1.2.3. PROMIS-Physical Function/Mobility/Upper Extremity

The PROMIS Physical Function instruments measure self-reported capability rather than actual performance of physical activities. This includes the functioning of one’s upper extremities (dexterity), lower extremities (walking or mobility), and central regions (neck, back), as well as instrumental activities of daily living, such as running errands. A single Physical Function capability score is obtained from each short form. This PRO is only completed during the Treatment Phase. All adult participants ≥ 18 years of age with a target PN causing significant physical functioning impairment will complete the PROMIS Short Form v2.0 – Physical Function 8b. For all participants 2 to17 years of age, the questionnaire will be specific to the location of the target PN. For participants 2 to 17 years of age with upper extremity morbid target PNs, participants ≥ 8 years of age will self-report utilizing the PROMIS Pediatric Short Form v2.0 – Upper Extremity 8a and the primary care giver of children ≥ 5 to 17 years of age will complete the PROMIS Parent Proxy Short Form v2.0 – Upper Extremity 8a. The Upper Extremity short form will assess activities that require use of the upper extremity including shoulder, arm, and hand activities. Examples include writing, using buttons, or opening containers. Participants ≥ 8 and ≤ 17 years of age with lower extremity morbid target PNs will self-report utilizing the PROMIS Pediatric Short Form v2.0 – Mobility 8a in parallel with completion of the PROMIS Parent Proxy Short Form v2.0 – Mobility 8a by the primary care giver for participants ≥ 5 to ≤ 17 years of age. The Mobility short form will assess activities of physical mobility such as getting out of bed or a chair to activities such as running. As applicable, the same parent or legal guardian should be administered the PROMIS short form throughout the study. The PROMIS Physical Functioning questionnaires are recommended as core outcome measures of physical functioning for clinical trials in children and adults with NF1 (Wolters, 2016).

8.1.2.4. Pediatric Quality of Life Inventory

The Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales are multidimensional self-report and parent proxy-report scales to assess HRQOL in children, adolescents, young adults and adults over the past 7 days. It is a brief standardized HRQOL scale with good reliability and validity. It consists of a 23-item core measure of global QOL and can be completed in approximately 5 minutes. The PedsQL has four subscales: physical functioning, emotional functioning, social functioning, and school/work functioning. In this study, participants ≥ 5 years of age will complete a self-report and parents or legal guardians of children from 2 to 17 years of age will complete the parent proxy measures of the age specific PedsQL. The same parent or legal guardian should be administered the PedsQL throughout the study. If a participant is ≥ 18 years of age, but in the opinion of the investigator has cognitive deficiencies

that would inhibit accurate collection of PRO data, a parent or legal guardian must also complete the appropriate parent-proxy PedsQL. The PedsQL will be administered on paper and should always be the first PRO administered at the visit. The paper PedsQL and associated proxy will also be completed during the LTFU Phase, as applicable.

8.1.2.5. Patient Global Impression of Severity

The patient global impression of severity (PGIS) is a single item scale that evaluates the participant's perception of the overall severity of their NF1-related symptoms over the past week on a 4-point scale ranging from "none" to "severe." The PGIS will have a 7-day recall period and will be completed by participants ≥ 6 years of age during the Treatment Phase.

8.1.2.6. Patient Global Impression of Change

The patient global impression of change (PGIC) is a single item scale that evaluates the participant's perception of the overall change in their overall status since the start of the study treatment on a 7-point scale ranging from "very much better" to "very much worse." The PGIC will be completed by participants ≥ 6 years of age during the Treatment Phase.

8.1.2.7. Pediatric Oral Medicine Acceptability Questionnaire

The Pediatric Oral Medicine Acceptability Questionnaire (P-OMAQ) is the first empirically derived, content-valid clinical outcome assessment questionnaire designed to measure and quantify acceptability of targeted pediatric oral medicines (Turner-Bowker, 2020). The P-OMAQ is 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 dispersible tablet (pediatric) dosage formulation. The pediatric self-report (P-OMAQ-P) is a 12-item PRO for pediatric respondents of ≥8 years of age. The caregiver observer report (P-OMAQ-C) is a 19-item PRO for adult caregivers (aged ≥18 years) overseeing study drug dosing of pediatric patients aged 6 months to 17 years. Each questionnaire is provided with a "past 7 days" recall with all items using a 5-point Numerical Rate Scale (NRS) with higher item-scores reflecting greater oral treatment acceptability.

8.1.3. Strength Assessment

All participants with a target PN that causes motor dysfunction or weakness will undergo a focused evaluation of strength of the affected muscle groups in accordance with the SoA (Section 1.3) during the Treatment Phase. The contralateral side will be tested for comparison. This evaluation should be performed by Rehabilitation Medicine, Physiatry, or Physical Therapy, if possible, and should ideally be completed by the same examiner at each visit, if feasible.

Strength should be assessed utilizing a Sponsor provided dynamometer and Medical Research Council (MRC) Muscle Scale. The MRC grading assessment should be conducted prior to the dynamometer assessment. Dynamometer assessment and MRC grading (0-5/5) must be conducted in accordance with the study reference manual.

8.1.4. Photography of Tumor

Photography will be performed if target PN and/or its effects are visible and amenable to photography. Photography will be performed in accordance with the SoA (Section 1.3, Section 1.4) during both the Treatment and LTFU Phases. All photographs at each timepoint should be taken from the same distance, using similar lighting and camera settings, if possible. Baseline photographs from the Treatment Phase should be present at the time of follow-up photography to allow for the most accurate positioning and setting replication. All photographs will be submitted and analyzed at study completion by an independent central review. Refer to the photography manual for additional details and photograph submission guidelines.

8.1.5. Range of Motion Assessment

All participants with a target PN that causes motor dysfunction or weakness will undergo a focused evaluation of range of motion of the affected joints during the Treatment Phase. The contralateral side will be tested for comparison. This evaluation should be performed by Rehabilitation Medicine, Physiatry, or Physical Therapy, and should ideally be completed by the same examiner at each visit, if feasible. Testing will be performed in accordance with the SoA (Section 1.3).

Refer to the study reference manual for additional instructions.

8.1.6. Target Tumor Biopsy

For participants ≥ 18 years of age, a core needle or Tru-Cut needle biopsy of the target tumor will be performed at Baseline in the Treatment Phase prior to receiving any study treatment and after the MRI volumetric assessment has been confirmed evaluable by central radiologic review. This is a percutaneous biopsy method using a hollow-bored needle to obtain a volume of tissue in order to assess both cellular and architectural information. A 16-gauge needle or larger must be used. Fine needle aspirates are not acceptable. Participants 2 to 17 years of age should not undergo biopsy unless there is a clinical indication to obtain fresh tumor tissue. If a pediatric participant turns 18 years old during study participation, a biopsy is not required at the Cycle 24/Early Termination visit of the Treatment Phase. If a study biopsy was collected and the participant did not initiate study treatment, this biopsy may be utilized as the baseline biopsy if the participant subsequently re-screens for enrollment. If the participant did not have evaluable biopsy tissue at Baseline, they are not required to provide an End of Treatment biopsy of the target tumor.

Refer to Section 10.8 for the sampling schedule and the central laboratory manual for instructions for handling, processing and shipment of tumor biopsies.

8.1.7. 6-Minute Walk Test

Participants with a target PN that causes airway or lower extremity motor dysfunction will undergo a 6-Minute Walk Test in accordance with the SoA (Section 1.3) during the Treatment Phase. This assessment must always be completed after the Strength (Section 8.1.3) and Range

of Motion (Section 8.1.5) assessments. This evaluation should be performed by Rehabilitation Medicine, Physiatry, or Physical Therapy, if possible, and should ideally be completed by the same examiner at each visit, if feasible. Refer to the study reference manual for additional instructions.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3, Section 1.4).

8.2.1. Demographics Data and Medical History

Demographic data will include age or date of birth, sex, and self-reported race/ethnicity.

Medical history includes any history of clinically significant disease, surgery, or cancer history; reproductive status (i.e., WOCBP or no WOCBP); history of alcohol consumption (i.e., presence or absence); and review of concomitant medications.

Cancer history will include an assessment of prior surgery, prior radiotherapy, prior drug therapy, including start and stop dates, best response and reason for discontinuation. Participant's NF1 mutational status will also be recorded, if known. Radiographic studies performed prior to study entry may be collected for review by the Investigator.

8.2.2. Physical Examination and Performance status

Complete physical examinations, as well as height/weight, and assessment of Karnofsky or Lansky performance status, as applicable (Section 10.6), will be required throughout the study as described in the SoA (Section 1.3, Section 1.4).

A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems.

Investigators should pay special attention to clinical signs related to previous serious illnesses, and changes from Baseline of the Treatment Phase will be recorded in the source documentation. New or worsened clinically significant abnormalities are to be recorded as AEs on the eCRF page.

Refer to Section 8.3 regarding AE definitions and reporting and follow-up requirements.

8.2.3. Vital Signs

Body temperature, pulse rate, respiratory rate, and blood pressure will be assessed throughout the study as described in the SoA (Section 1.3, Section 1.4).

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

8.2.4. Electrocardiograms

Triplicate 12-Lead ECGs readings (done approximately 2-3 minutes apart and averaged) will be obtained using an ECG machine that automatically calculates the heart rate and measures RR, PR, QRS, QT, and QTc intervals, at the timepoints described in the SoA (Section 1.3, Section 1.4). Prior to the ECG assessments, participants should rest in a semi-recumbent supine position for at least 5 minutes.

For safety monitoring purposes, the Investigator must review, sign, and date all ECG tracings. Paper or electronic copies of ECG tracings will be kept as part of the source documentation at the Site.

All ECGs of participants 2 to 17 years of age at the time of ECG acquisition must be reviewed by a pediatric cardiologist, and this review must be documented. Participants ≥ 18 years of age must have ECGs reviewed by a physician on the delegation of authority log.

Refer to Section 7.1.2 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

8.2.5. Clinical Safety Laboratory Assessments

All protocol-required laboratory assessments as defined in Section 10.2, must be conducted in accordance with the central laboratory manual and the SoA (Section 1.3, Section 1.4). The use of intravascular catheters should be considered when multiple blood draws will occur on the same visit.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study on the AE page of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with abnormal values considered to be clinically significant during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or Baseline of the Treatment Phase or are no longer considered clinically significant by the Investigator or Medical Monitor. If such values do not return to normal/Baseline of the Treatment Phase within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Medical Monitor notified.

If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF. Additionally, local laboratory results are only to be used in extenuating circumstances to make a study treatment decision with approval from the Medical Monitor.

8.2.6. Pregnancy Testing

Pregnancy testing will only be required for women of childbearing potential (WOCBP) (refer to Section 10.4 for definition of WOCBP and additional details on contraceptive guidelines and collection of pregnancy information).

A negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline (prior to first dose of study treatment) will be required to meet study entry criteria.

Monthly urine pregnancy tests will be required for WOCBP throughout the duration of the study. Serum pregnancy testing is allowed per local regulations. In between study visits, participants will be required to return to the Site for a monthly urine pregnancy test. If it is more convenient to the participant, they may visit a Sponsor approved local laboratory for this assessment.

8.2.7. Ophthalmic Assessments

These assessments must be performed by an ophthalmologist. Participants in the pediatric cohort must be evaluated by a pediatric ophthalmologist throughout the study. Participants will have a standard of care ocular evaluation inclusive of a targeted retinal exam consisting of slit lamp examination with binocular indirect ophthalmoscopy in addition to intraocular pressure measurements in accordance with the SoA (Section 1.3, Section 1.4) while on study treatment. Participants with evidence of disease (e.g., retinal vein occlusion) will undergo a full evaluation (such as fluorescein angiography and/or optical coherence tomography). Refer to the study reference manual for additional information regarding these required assessments.

8.2.8. Echocardiogram

Left ventricular ejection fraction will be assessed via echocardiogram in accordance with the SoA (Section 1.3, Section 1.4). Echocardiogram is a noninvasive and well-established technique for assessment of LVEF. All measurements will be made in accordance with the American Society of Echocardiography guidelines. Sites should utilize routine hospital protocol for echocardiogram methodologies and measures.

8.2.9. Radiography

For all participants 2 to 17 years of age, radiographs of the distal femur and proximal tibia will be obtained at Baseline. If the Investigator determines that the physes are open, these participants will undergo a radiograph in accordance with the Treatment Phase SoA (Section 1.3) to monitor for changes in physeal growth plates.

8.2.10. Monthly Wellness Checks

Monthly telephone or email contact is required throughout the study and may be replaced by a face-to-face interaction when study visits occur if the information can be obtained during the visit.

A copy of the telephone report or email must be documented in the source documentation. Email must not replace direct follow-up by phone or in clinic for clinically significant AEs or

other emergent issues. Adverse events and concomitant medications changes will be captured in the associated eCRFs.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Sections 10.3.1 and 10.3.2, respectively.

An AE will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study treatment (Section 7).

8.3.1. Adverse Events of Special Interest

Table 10 Adverse Events of Special Interest (AESI)

Gastrointestinal (reported as AESI if Grade ≥ 3)		
Diarrhea	Nausea	Vomiting
Eye Disorders (reported as AESI if Grade ≥ 2)		
Retinal Vein Occlusion (RVO)	Uveitis	Optic neuropathy
Retinopathy	Retinal detachment	
Cardiac Disorders (reported as AESI if Grade ≥ 2)		
Ejection fraction decreased	Cardiac failure	Left ventricular dysfunction
Neurologic Disorders (reported as AESI if Grade ≥ 2)		
Confusion	Hallucinations	Delirium
Skin Disorders (reported as AESI if Grade ≥ 3)		
Rash	Acneiform rash	

These are selected, non-serious AEs and SAEs that **must be reported within 24 hours** regardless of relationship to study treatment. For participants who experience signs or symptoms that may be consistent with an AESI, sites are strongly encouraged to immediately notify the Medical Monitor of the event via email and/or phone. Documentation of potential AESIs should occur after discussion between the investigator and the Medical Monitor. Many of these events may also qualify as SAEs. Any event that meets the criteria described in Table 10 must be reported regardless of investigator-determined relationship to study treatment (unless otherwise

specified). Investigators/study coordinators/designated site personnel are required to record these experiences in the eCRF (as described in the eCRF completion guidance document) and to provide supplemental information (such as medical history, concomitant medications, investigations, etc.) about the event. Please note this table lists known AESI, and additional events may be identified during the course of the study.

8.3.2. Time Period and Frequency for Collecting AE and SAE Information

All SAEs and AEs will be collected from the time of signing informed consent/assent until 30 days after the last dose of study treatment at the time points specified in the SoA (Section 1.3, Section 1.4).

Medical occurrences that begin before the start of study treatment but after obtaining informed consent/assent will be recorded as AEs.

All SAEs will be recorded and reported to the Sponsor's safety group (Safety) immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3.3 and Section 10.3.4. The Investigator will submit any updated SAE data to Safety within 24 hours of it being available.

To report the SAE, a paper SAE form must be completed, scanned, and emailed Safety at PV@springworkstx.com. The paper SAE form can be found in the Site reference manual. Refer to Section 10.3.4 for more details on reporting SAEs to Safety.

Investigators are not obligated to actively seek AEs and/or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study and considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

8.3.3. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.4. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Within 24 hours of receipt of follow-up information, the Investigator must complete a paper follow-up SAE form and submit any supporting documentation if requested to Safety. Further information on follow-up procedures is given in Section 10.3.3.

8.3.5. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

Investigator safety reports must be prepared for Suspected Unexpected Serious Adverse Reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.6. Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment and until 30 days after the last dose of study treatment.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy by completing a paper pregnancy form and submitting to Safety (refer to Section 10.4 for reporting details).

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4. Treatment of Overdose

For this study, any administration of study treatment greater than 150% of the BSA assigned maximum total daily dose within a 24-hour period will be considered an overdose. Noncompliance with the intermittent dosing schedule does not in itself constitute a study treatment overdose.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately (refer to Section 10.10.3 for contact information).
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities for at least 4 days.

3. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Sparse PK samples will be collected during the Treatment Phase of the study to inform development of a population PK model of mirdametinib (PD-0325901) and its active metabolite (PD-0315209). See Section 10.8 for the study sampling schedule.

- Whole blood samples of approximately 3 mL will be collected for measurement of plasma concentrations of PD-0325901 and PD-0315209. Refer to the SoA (Section 1.3) and Section 10.8 for details on PK sampling time points. Each plasma sample will be divided into 2 aliquots (1 each for PK and a back-up). Samples may be stored for a maximum of 10 years (or according to local regulations) following the last participant's last study visit at a facility selected by the Sponsor to enable further analysis of kinetic responses to PD-0325901.
- All efforts will be made to obtain the pharmacokinetic samples at the exact nominal time relative to dosing. However, samples obtained within 10 minutes of the nominal time (± 10 minutes) from dosing will not be captured as a protocol deviation if the exact time of the sample collection is noted on the source document and eCRF. The actual date and time (24-hour clock time) of each sample will be recorded.
- Instructions for the collection, handling, and shipment of pharmacokinetic samples will be in the central laboratory manual.
- Genetic analyses will not be performed on these samples. Participant confidentiality will be maintained.
- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the Sponsor or Medical Monitor and then archived in the Sponsor and Site study files but will not constitute a protocol amendment.

8.6. Pharmacodynamics

As a marker of effects of PD-0325901, biomarkers indicative of inhibition of downstream targets of MEK (e.g., ERK phosphorylation) will be measured in PNs as described in Section 8.8.

Percutaneous core needle biopsies from participants ≥ 18 years of age will be collected as described in the Treatment Phase SoA (Section 1.3) and Section 10.8. These samples are required for pharmacodynamic biomarker analysis, but they will not be processed for DNA (tumor mutagenesis evaluation).

Instructions on the collection, processing, storage and shipment will be provided in the laboratory manual.

Samples may be stored for a maximum of 10 years (or according to local regulations) following the last participant's last study visit at a facility selected by the Sponsor to enable further analysis of PD responses to PD-0325901.

8.7. Genetics

Genetics will not be assessed in this study.

8.8. Biomarkers

As discussed in Section 8.6, PD biomarkers will be evaluated in this study.

Two (2) percutaneous core needle biopsies from participants ≥ 18 years of age will be collected as described in the Treatment Phase SoA (Section 1.3) and Section 10.8. These samples are required for pharmacodynamic biomarker analysis, but they will not be processed for DNA (tumor mutagenesis evaluation)

- Samples will be tested for biomarkers indicative of inhibition of downstream targets of MEK (e.g., ERK phosphorylation) to evaluate their association with the observed clinical responses (e.g., tumor volume reduction) to PD-0325901 and its metabolite(s).
- Details on processes for collection, processing, shipment, and destruction of these samples can be found in laboratory manual.

Samples may be stored for a maximum of 10 years (or according to local regulations) following the last participant's last study visit at a facility selected by the Sponsor to enable further analysis of biomarker responses to PD-0325901.

8.9. Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

The null hypothesis for the participants ≥ 18 years of age at Baseline (the adult population) is that the objective response rate (ORR) is less than or equal to 23%. The alternative hypothesis is that the ORR is greater than 23%. The null hypothesis for participants 2 to 17 years of age at Baseline (the pediatric population) is that the ORR is less than or equal to 42%. The alternative hypothesis is that the ORR is greater than 42%.

9.2. Sample Size Determination

MEK-NF-201 is a single-stage, single-arm, open-label, potentially registrational study to evaluate the efficacy, safety, and tolerability of mirdametinib (PD-0325901) in participants ≥ 2 years of age with an inoperable NF1-associated PN that is causing significant morbidity.

Approximately 150 participants will be screened in this study to assure approximately 100 participants are assigned to the open-label treatment with mirdametinib. These 100 participants will be stratified by age, with 50 participants ages 2 to 17 years for the pediatric cohort and 50 participants ≥ 18 years of age for the adult cohort.

Sample size assumptions for the pediatric population are based on the interim ORR of 66% from the SPRINT study conducted by Gross et al. The SPRINT study enrolled 50 patients aged 3-18 years with inoperable morbid PNs (Gross, 2018). For the pediatric cohort, an ORR of at least 66%, as mentioned above, will result in a lower bound of 55% for a one-sided 95% CI. Under these assumptions, the Type II error of a one-sided Z-test is under 20% for any null hypothesis of ORR ≤ 49%.

Sample size assumptions for the adult population are based on an ORR of at least 42%, as determined from a previous SpringWorks interim analysis of phase 2 mirdametinib study in adult participants. With 50 participants in this cohort, the response rate of 42% will result in a lower bound of the one-sided 95% CI that excludes 30%. Under these assumptions, the Type II error of a one-sided Z-test (using normal approximation to the binomial distribution) at a 95% statistical significance level is below 20% for any null hypothesis of ORR ≤ 24%.

For the safety analysis, there is a 95% chance of observing at least one adverse event that occurs at an underlying rate of 3.0 % in a sample size of 100 participants.

The primary and secondary endpoints in the pediatric and adult cohorts will be analyzed separately since each cohort is age-dependent, as shown by the difference in tumor growth rates between pediatric patients and adult patients (Dombi 2007, Nguyen 2012, Tucker 2008). Other secondary endpoints may be pooled, if appropriate to the endpoint.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled Set	All participants who signed the ICF and passed Screening.
Full Analysis Set	The primary statistical analysis will be based on the Full Analysis Set, which is defined as all participants who received at least one dose of PD-0325901 (mirdametinib).
Per-Protocol Set	A Per-Protocol population, defined as a subset of the Full Analysis Set who have completed a minimum of disease evaluations and who do not have any major deviations, including but not limited to efficacy assessments or compliance, will be used to analyze a set of analysis considered supportive to the primary efficacy analyses.
Safety Set	All participants assigned to study treatment and who took at least one dose of study treatment.

9.4. Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. As stated in Section 9.2 above, the primary and secondary endpoints in the pediatric and adult cohorts will be analyzed separately since each cohort is age-dependent. Other secondary endpoints may be pooled, if appropriate to the endpoint.

9.4.1. Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary endpoint is objective response rate (ORR) at the end of the Treatment Phase, defined as the proportion of participants who have a ≥ 20% reduction in target tumor volume as compared to Baseline. Exact 1-sided binomial 95% confidence intervals will be calculated on the response rate. Participants who are missing all response data will be treated as non-responders. Participants who discontinue early from the study without responding will be treated as non-responders. Objective response rate will be calculated separately by age cohort.
Secondary	Duration of response (DOR) in participants who meet the criteria for ORR will be calculated as the time between the first instance of response until the date of progression or censored date (censorship rules will be specified in the analysis plan). The DOR will be analyzed using Kaplan Meier method; median duration of response and the 95% CIs on the intervals will be calculated. Kaplan Meier will be used for the overall population, and also on cohort groups. Details of censoring methods and sensitivity analyses will be described in the statistical analysis plan. Time-to-Response will also be calculated as the time between first dose and the first date of objective response. Univariate statistics will be reported. Change from baseline in overall clinical status: All participants and/or parents/legal representatives will complete a HRQOL (PedsQL) to assess overall change in clinical status. Change from baseline in pain: Pain will be measured using an 11-point numeric rating scale (NRS-11) and the Pain Interference Index. For the NRS-11, participants will report overall pain in the location of the primary target tumor. The Pain Interference Index questionnaire will assess self-reported and parent/legal representative reported consequences of pain on relevant aspects of one's life over the previous 7-day period.
Exploratory	Progression Free Survival is defined as the time in months from the first dose to the date of a ≥ 20% increase in tumor volume or death. Participants who do not meet the criteria for progression will be censored (censorship rules will be specified in the analysis plan). The PFS will be analyzed using Kaplan Meier methods; median PFS and the 95% CIs on the intervals will be calculated. Details of censoring methods and sensitivity analyses will be described in the statistical analysis plan. Change from baseline in functional assessments: In participants who have tumors that affect functional status at Baseline, the change from Baseline in

	muscle strength and range-of-motion in the PN affected areas will be measured. Participants with a target PN causing airway or lower extremity motor dysfunction at Baseline will be assessed for change in 6-minute walk test distance. Participants and/or parents/legal representatives-reported questionnaires (e.g., PROMIS) will be assessed for change in functionality and mobility. Self-reported overall severity of symptoms and status (e.g., PGIS, PGIC) will also be assessed. Self-reported and observer-reported acceptability (e.g., P-OMAQ) of the dispersible tablet (pediatric formulation) will be assessed. Additional exploratory endpoints will be described in the statistical analysis plan finalized before database lock.

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Safety Endpoints	The safety and tolerability of mirdametinib (PD-0325901) will be evaluated by means of study drug-related adverse event reports, physical examinations, and laboratory safety evaluations. National Cancer Institute CTCAE Version 5.0 will be used for grading of adverse events. Investigators will provide their assessment as related to treatment (definite, probable, or possible relationship). The incidence of treatment-emergent adverse events, SAEs, adverse events of at least Grade 3 in severity, study drug-related adverse events, and adverse events leading to withdrawal of study drug will be summarized. Treatment-emergent adverse events will be those that start or worsen on or after the first day of study drug through 30 days after the last dose of study drug; related adverse events will be those with an Investigator determination of related to treatment. Laboratory data will be analyzed by summary statistics over time, as well as by shift tables based on NCI CTCAE Version 5.0 grades of severity. In addition, ECG intervals will be summarized by visit. The number and percentage of participants who have a post-Baseline QTcF between 450 and 480, > 480, and > 500, as well as the number and percentage of participants who have a change from Baseline in QTcF of < 30, 30 to 60, and > 60 will be summarized.

9.4.3. Other Analyses

Pharmacokinetic, pharmacodynamic, and biomarker exploratory analyses will be described in the statistical analysis plan finalized before database lock. The population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report.

9.5. Data Monitoring Committee (DMC)

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

Following each data review, the DMC may recommend 1) no changes to the study are needed, 2) changes to the protocol or informed consent/assent based on clinical safety findings, or 3) early termination of the study based on safety analyses. The recommendations made by the DMC to alter the conduct of the study will be forwarded to the Sponsor for final decision. Additionally, the DMC may be asked to assist the Sponsor in evaluating the impact of data from other company-sponsored studies or other published studies.

The DMC charter will outline the frequency of meetings and detail all aspects of DMC's scope of review and procedures.

In addition to routine scheduled meetings as described in the DMC charter, the DMC will also convene after the first 5 participants aged 9 to 17 years in the pediatric cohort have completed at least 2 cycles of study treatment. The DMC will evaluate cumulative safety data for these 5 participants and based on these data, will determine further enrollment requirements for the pediatric cohort, potentially expanding enrollment of the pediatric cohort to include participants aged 2 to 17 years of age.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines;
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines; and
- Applicable laws and regulations.

The protocol, protocol amendments, informed consent/assent form (ICF), Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an institutional review board/independent ethics committee (IRB/IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC;
- Notifying the IRB/IEC of serious adverse event or other significant safety findings as required by IRB/IEC procedures; and
- Providing oversight of the conduct of the study at the Site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.
- The Investigator will be responsible for reporting cases of suspected child abuse and/or neglect according to local medical association (e.g., AAP) or health department guidelines.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are

responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent/Assent Process

- The Investigator or their representative will explain the nature of the study to the participant or their legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative (parent/guardian) will be required to sign a statement of informed consent/assent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that legally authorized representative (parent/guardian) consent and child/adolescent assent (if deemed appropriate by local ethics review) was obtained before the participant was enrolled in the study and the date the written consent/assent was obtained. The medical record should also describe how the clinical Investigator determined that the person signing the ICF was the participant's legally authorized representative (parent/guardian). The authorized person obtaining the informed consent/assent must also sign the ICF.
- Participants and their legally authorized representative (parent/guardian) must be re-consented/assented to the most current version of the ICF(s) during their participation in the study.
- Minor participants must be re-consented if they reach the age of majority during the course of the study, in order to continue participating.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Consideration of rescreening of a participant who did not meet eligibility criteria must be discussed with the Medical Monitor. The participant must be re-consented/assented if approved for rescreening. In addition, all Screening assessments must be repeated with the exception of imaging, which would only be repeated if the imaging assessment was obtained > 45 days from the first dose of study treatment.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Data Quality Assurance

- All participant data relating to the study will be entered into the electronic case report forms (eCRFs) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide 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) will be indicated in the monitoring plan to ensure the protocol and GCP is followed.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized Site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the clinical trial agreement, whichever is longer. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.6. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's Site.
- Data reported in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Investigators will maintain records separate from the eCRFs in the form of clinical charts, medical records, original laboratory, radiology and pathology reports, pharmacy records, etc. The Investigator will document in the clinic chart or medical record the date on which the participant signed informed consent/assent prior to participation in the study. Source documents must completely reflect the nature and extent of the participant's medical care and must be available for source document verification against entries in the eCRFs when the Sponsor's monitor visits the Site. In order to meet data integrity requirements, source documentation should be attributable, legible, contemporaneous, accurate, available/accessible, original, complete and credible. All information obtained from these documents will be kept in strict confidentiality. Definition of what constitutes source data can be found in the study reference manual.

10.1.7. Study and Site Closure

The Sponsor reserves the right to suspend or terminate the study at any time for any reason at the sole discretion of the Sponsor. Reasons which would cause the Sponsor to suspend/terminate enrollment include, but are not limited to, the occurrence of any of the following:

- One Grade 5 AE;
- Two Grade 4 AEs;
- One occurrence of any of the following ocular toxicities: retinal vein occlusion, unexplained Grade 3+ Optic Neuropathy, Grade 3+ retinal vein detachment, or unexplained Grade 3+ retinopathy;
- Two absolute decreases in LVEF > 20% from Baseline of the Treatment Phase or symptomatic congestive heart failure not explained by any other cause; or
- One participant meeting QTc stopping criteria as described in Section 7.1.2.

Study Sites will be closed upon study completion. A study Site is considered closed when all required documents and study supplies have been collected, a study Site closure visit has been performed, and the IRB has been notified of closure.

Study Site closure prior to completion of the study should be avoided. The Investigator and Sponsor will agree to the circumstances that could cause early study Site closure.

The Sponsor reserves the right to close the study Site at any time for any reason at the sole discretion of the Sponsor. Reasons for the early closure of a study Site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the Investigator; or
- Discontinuation of further study treatment development.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 11 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, local laboratory results are only to be used in extenuating circumstances to make either a study treatment decision with approval from the Medical Monitor, and the results must be entered into the electronic case report form.
- Protocol-specific requirements for inclusion and exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests, as part of unscheduled visits, may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Urine pregnancy testing will be conducted at monthly intervals for women of child bearing potential (WOCBP). Refer to Section 8.2.6 and 10.4 for more details on the monthly pregnancy testing requirements. Results of pregnancy testing should be shared with the parent(s)/legal guardian(s) of female participants ≤ 17 years of age.
- Urine pregnancy testing will also be conducted 30 days after the last dose of study treatment to correspond with the end of relevant systemic exposure and correspond with the time frame for female participant contraception described in Inclusion 13.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.
- Investigators must document their review of each laboratory report.

Table 11 Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry[2]	Urinalysis	Serology[5]

• HGB
• HCT
• PLT count
• RBC count
• RBC Indices:
  ○ MCV
  ○ MCH
  ○ %Reticulocytes
• WBCC with Differential[1]:
  ○ neutrophils
  ○ lymphocytes
  ○ monocytes
  ○ eosinophils
  ○ basophils
	• AST/SGOT
	• ALT/SGPT
	• Total and Direct BIL
	• GGT
	• Sodium
	• Chloride
	• Potassium
	• Calcium
	• Bicarbonate
	• Inorganic phosphorus
	• Alkaline phosphatase
	• Creatinine[3]
	• Creatine Kinase
	• BUN
	• Glucose (non-fasting)
	• Uric acid
	• Albumin
	• Total protein
	• Triglycerides
	• Total Cholesterol
		• Specific gravity
		• Bilirubin
		• Glucose
		• Leukocyte esterase
		• Nitrite
		• Protein
		• Urobilinogen
		• Blood
		• Ketones
		• pH
		• Microscopy[4]
			• HBV
			  ○ HBsAg
			• HCV
			  ○ hepatitis C antibody (HCV PCR if hepatitis C antibody positive)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BIL = bilirubin; BUN = blood urea nitrogen; GGT = gamma-glutamyl transferase; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCT = hematocrit; HCV = hepatitis C virus; HGB = hemoglobin; MCH = mean cell hemoglobin; MCV = mean cell volume; PCR = polymerase chain reaction; PLT = platelet; RBC = red blood cell; SGOT = serum glutamic-oxaloacetic transaminase; SGPT =serum glutamic-pyruvic transaminase; WBCC = white blood cell count

1. Manual microscopic review is performed only if white blood cell count and/or differential values are out of reference range.
2. Details of liver stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Sections 7.1.1 and 10.5.
3. Creatinine < the maximum age specific serum creatinine seen below, or calculated creatinine clearance ≥ 60 mL/min (using the Cockcroft-Gault formula).

Age (years)	Maximum Serum Creatinine (mg/dL)
≤ 5	0.8
> 5 and ≤ 10	1.0
> 10 and ≤ 15	1.2
> 15	1.5

4. Microscopy examination is performed only if blood or protein is abnormal.
5. Serology only required at Screening.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.
Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:
c. **Results in death**
d. **Is life-threatening** The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
e. **Requires inpatient hospitalization or prolongation of existing hospitalization** In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.
f. **Results in persistent disability/incapacity** • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
g. **Is a congenital anomaly/birth defect**

h. **Other situations:**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical treatment to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- All required information will be recorded in the electronic case report form (eCRF). SAEs will require additional information to be reported to Safety utilizing a paper SAE form that must be scanned and emailed or faxed to Safety immediately, without undue delay, under no circumstances later than 24 hours after becoming aware of the event. Refer to Section 10.3.4 for further SAE reporting details.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Safety in lieu of completion of the SAE eCRF page/paper SAE form.
- There may be instances when copies of medical records for certain cases are requested by Safety for reported SAEs. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Safety.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The intensity of all SAEs/AEs should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. For those SAEs/AEs not listed in the CTCAE, the following grading system should be used:

- CTCAE **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.

- CTCAE **Grade 2** Moderate; minimal, local or noninvasive treatment indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
- CTCAE **Grade 3** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
- CTCAE **Grade 4** Life-threatening consequences; urgent treatment indicated.
- CTCAE **Grade 5** Death related to AE.

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE (Section 10.3.2), **not** when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to Safety. However, **it is very important that the Investigator always make an assessment of causality for every event with the initial SAE reporting to Safety via paper SAE form.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Safety to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will make all attempts to provide Safety with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF. In addition, Sites must email or fax a follow-up SAE form to Safety.
- The Investigator will submit any updated SAE data to Safety within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Safety

- The primary mechanism for reporting an SAE to Safety will be emailing (preferred method) to [redacted] or faxing the paper SAE form.
- A copy of the paper SAE form can be found in the Investigator Site file.
- All SAEs must be reported to Safety immediately, without undue delay, under no circumstances later than24 hours after awareness. This initial reporting can be done by emailing/faxing the SAE form to Safety, or by entering the SAE term into the electronic case report form (eCRF) which will alert Safety of the event. However, a paper SAE form must still be completed and submitted to Safety as soon as possible.
- In rare circumstances and in the absence of email or facsimile equipment, notification by telephone is acceptable with a copy of the SAE form sent by overnight mail or courier service. However, initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE form within the designated reporting time frames.
- After the study is completed at a given Site, the eCRFs will be locked to prevent the entry of new data or changes to existing data.
- If a Site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the eCRFs have been locked, then the Site can report this information on a paper SAE form to Safety by telephone/email/fax.
- Contacts for SAE reporting can be found in Section 10.10.4.

10.3.5. Definition of AR, SAR and SUSAR

Adverse Reaction (AR):
An AR is any noxious and unintended response to a medical product or procedure, for which a causal relationship with the product or procedure is at least a reasonable possibility (i.e., the relationship cannot be ruled out).
Serious Adverse Reaction (SAR):
A SAR is an SAE for which a causal relationship with the product or procedure is at least a reasonable possibility (i.e., the relationship cannot be ruled out).
Suspected Unexpected Serious Adverse Reaction (SUSAR):
A SUSAR is a SAR that is judged as unexpected. An event is considered "unexpected" if it is not listed as expected in the reference safety information (RSI) section of the investigator brochure (IB) or summary of product characteristics.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP) is defined as a woman that is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study treatment, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy; or
   - Documented bilateral salpingectomy; or
   - Documented bilateral oophorectomy.

   For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry. Bilateral tubal occlusion is not considered to be a permanent form of infertility.

   Note: Documentation can come from the Site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of < 1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
• Intrauterine device
• Intrauterine hormone-releasing system
• Bilateral tubal occlusion
• Vasectomized partner *(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)*
Highly Effective Methods[b] That Are User Dependent *Failure rate of < 1% per year when used consistently and correctly.*
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] o Oral o Intravaginal o Transdermal o Injectable • Progestogen-only hormone contraception associated with inhibition of ovulation[c] o oral o injectable
• Sexual abstinence *(Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*
a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b) Failure rate of < 1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c) Barrier methods such as condoms (male or female) or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream or vaginal suppository must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction)

Collection of Pregnancy Information:

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study treatment.
- After obtaining the necessary signed informed consent/assent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit the form to Safety by email/fax within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female Participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to Safety by email/fax within 24 hours of learning of a participant's pregnancy.
- For a female participant who becomes pregnant, this information will be shared with the study participant's parent/guardian if the participant is ≤ 17 years of age.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 10.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study treatment and be withdrawn from the study.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Liver Chemistry Stopping Criteria and Follow-Up Assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥ 5 x ULN
ALT Increase	ALT ≥ 3 x ULN persists for ≥ 4 weeks
Bilirubin[1, 2]	ALT ≥ 3 x ULN **and** bilirubin ≥ 2 x ULN (> 35% direct bilirubin)
INR[2]	ALT ≥ 3 x ULN **and** INR > 1.5, if INR measured
Cannot Monitor	ALT ≥ 3 x ULN and cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3 x ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Suggested Actions and Follow-up Assessments	
Actions	**Follow-Up Assessments**
• **Immediately** discontinue study treatment • Report the event to the Sponsor **within 24 hours** • Complete the liver event in the eCRF and complete the SAE eCRF form if the event also met the criteria for an SAE[2] • Perform liver chemistry follow-up assessments • Monitor the participant until liver chemistry test abnormalities resolve, stabilize, or return to baseline (see **Monitoring below**) • Restart/rechallenge is **not allowed per protocol and not granted**, permanently discontinue study treatment and continue participant in the study for any protocol specified follow up assessments	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Serum CPK and LDH • Fractionate bilirubin, if total bilirubin ≥ 2 x ULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE eCRF page • Record use of concomitant medications (including acetaminophen, herbal remedies, and other over-the-counter medications) on the concomitant medications eCRF page.

Monitoring	
If ALT ≥ 3 x ULN AND bilirubin ≥ 2 x ULN or INR > 1.5: • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver event follow-up assessments within **24 hours.** • Monitor participant twice weekly until liver chemistry test abnormalities resolve, stabilize, or return to baseline. • A specialist or hepatology consultation is recommended. **If ALT ≥ 3 x ULN AND bilirubin < 2 x ULN and INR ≤ 1.5:** • Repeat liver chemistry tests (include ALT, AST, alkaline phosphatase, bilirubin and INR) and perform liver chemistry follow-up assessments within **24 to 72 hours.** • Monitor participants weekly until liver chemistry abnormalities resolve, stabilize, or return to baseline.	**If ALT ≥ 3 x ULN AND bilirubin ≥ 2 x ULN or INR > 1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total IgG or gamma globulins. • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). • Liver imaging (ultrasound, magnetic resonance, or computerized tomography) and/or liver biopsy to evaluate liver disease; complete liver.

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; eCRF = electronic case report form; HPLC = high performance liquid chromatography; IgG = immunoglobulin G; INR = international normalized ratio; LDH = lactate dehydrogenase; SAE = serious adverse event; ULN = upper limit of normal

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment if ALT ≥ 3 x ULN **and** bilirubin ≥ 2 x ULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record the absence/presence of detectable urinary bilirubin on dipstick** which is indicative of direct bilirubin elevations suggesting liver injury.
2. All events of ALT ≥ 3 x ULN **and** bilirubin ≥ 2 x ULN (> 35% direct bilirubin) or ALT ≥ 3 x ULN **and** INR > 1.5 may indicate severe liver injury **(possible 'Hy's Law') and must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**. The INR stated threshold value will not apply to participants receiving anticoagulants.
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or hypersensitivity (such as fever, rash or eosinophilia).
4. Includes: Hepatitis A immunoglobulin M (IgM) antibody; hepatitis B surface antigen and hepatitis B core antibody; hepatitis C RNA; cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and hepatitis E IgM antibody.

Liver Chemistry Increased Monitoring Criteria with Continued Study Treatment

Liver Chemistry Increased Monitoring Criterion and Follow-Up	
Criterion	**Actions**
ALT ≥ 3 x ULN and < 5 x ULN **and** bilirubin < 2 x ULN, **without** symptoms believed to be related to liver injury or hypersensitivity, **and** participant can be monitored weekly for 4 weeks	• Notify the Medical Monitor within **24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant must return weekly for repeat liver chemistry tests (ALT, AST, alkaline phosphatase, bilirubin) until the abnormalities resolve, stabilize or return to baseline. • If at any time, the participant meets liver chemistry stopping criteria, proceed as described in Section 7.1.1. • If, after 4 weeks of monitoring, ALT < 3 x ULN and bilirubin < 2 x ULN, monitor participant twice monthly until liver chemistry tests resolve, stabilize, or return to baseline.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

10.6. Appendix 6: Karnofsky/Lansky Performance Status Criteria

Performance Status Criteria Karnofsky and Lansky performance scores are intended to be multiples of 10			
Karnofsky (≥ 16 years of age)		**Lansky (< 16 years of age)**	
Score	**Description**	**Score**	**Description**
100	Normal, no complaints, no evidence of disease.	100	Fully active, normal
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of, and less time spent in, active play
60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.
0	Dead	0	Unresponsive

Note: Participants who are unable to walk because of paralysis, but who are upright in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

10.7. Appendix 7: Response Criteria

For the purpose of determining the level of response (complete, partial, etc.) measurements from the follow-up scans are compared to the target PN size in the pretreatment MRI scan using volumetric data analysis.

Complete Response (CR):	A complete resolution of the target PN
Partial Response (PR):	A ≥ 20% reduction in the volume of the target PN
Stable Disease (SD):	A < 20% increase or < 20% decrease in the volume of the target PN
Progressive Disease:	A ≥ 20% increase in the volume of the target PN

10.8. Appendix 8: Pharmacokinetic and Pharmacodynamic Sampling Schedule

		Day	Timepoint (hours post-dose)	PK sampling of PD-0325901 and metabolite (PD-0315209)	PD biopsy of target PN[b]
Treatment Phase	Cycle 1	1	0 (Pre-dose)	X[a]	X
			1	X[a]	
			2	X[a]	
	Cycle 1	15	0 (Pre-dose)	X[a]	
			0.5	X[a]	
			1	X[a]	
			2	X[a]	
			3	X[a]	
			4	X[a]	
	Cycle 2	15	0 (Pre-dose)	X	
	Cycle 3	15	0 (Pre-dose)	X	
	Cycle 4	15	0 (Pre-dose)	X	
	Cycle 5	15	0 (Pre-dose)	X	
	Cycle 6	15	0 (Pre-dose)	X	
	Cycle 7	15	0 (Pre-dose)	X	
	Cycle 9	15	0 (Pre-dose)	X	
	Cycle 11	15	0 (Pre-dose)	X	
	Cycle 13	15	0 (Pre-dose)	X	
	Cycle 15	15	0 (Pre-dose)	X	
	Cycle 17	15	0 (Pre-dose)	X	
	Cycle 19	15	0 (Pre-dose)	X	
	Cycle 21	15	0 (Pre-dose)	X	
	Cycle 23	15	0 (Pre-dose)	X	
	Cycle 24	21	0	X	X[c]
	Early Termination Visit				X[c]

Abbreviations: PD = pharmacodynamic; PK = pharmacokinetic;

Note: Actual drug dosing and PK sampling times must be documented by the Sites and will be captured in the database. It is important that PK sampling occurs as close as possible to the scheduled time. In order to achieve this, some of the other assessments scheduled at the same time need to be initiated prior to or after the time point to allow for completion of these measurements in enough time for the PK sampling to be taken at the designated time point. Thus, the sequence at a particular time point is: 1) vital sign measurements; 2) scheduled ECG 3); PK blood samples and 4) any other scheduled or unscheduled measurements at that time point.

[a] Sampling window: Pre-dose collections should occur approximately within 1 hour prior to dosing. All post-dose timepoints have a ± 10 minute window. All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. However, samples obtained within the sampling window will not be captured as a protocol deviation if the exact time of the sample collection is noted on the source document and eCRF

[b] Percutaneous target PN core needle biopsies will be collected only from participants ≥ 18 years of age. When completed on the same visit, MRI must always precede a target PN biopsy.

[c] End of Treatment Phase target PN biopsy will not be collected if the participant did not have a pre-dose target PN biopsy.

10.9. Appendix 9: Abbreviations

Abbreviation	Definition
1-D	one dimensional
2-D	two dimensional
ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
ASCO	American Society of Clinical Oncology
BID	twice daily
BSA	body surface area
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CK	creatine kinase
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
ePRO	electronic patient reported outcome
ERK	extracellular signal-regulated kinase
ET	early termination
FSH	follicle stimulating hormone
GAPs	GTPase activating proteins
GCP	Good Clinical Practice
GTPase	guanosine triphosphate hydrolase
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQOL	Health-Related Quality of Life
HRT	hormone replacement therapy
IB	Investigator Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Independent Research Board/Institutional Review Board
IRT	interactive response technology

ITT	intent-to-treat
LLN	lower limit of normal
LTFU	Long-Term Follow-Up
LVEF	left ventricular ejection fraction
MAPK	mitogen-activated protein kinase
MRC	Medical Research Council
MPNST	malignant peripheral nerve sheath tumor
MRI	magnetic resonance imaging
mTOR	mammalian target of rapamycin
NCI	National Cancer Institute
NF1	neurofibromatosis type 1
NF2	neurofibromatosis type 2
NIH	National Institute of Health
NRS	Numeric Rating Scale
ORR	objective response rate
PD	pharmacodynamic
PedsQL	Pediatric Quality of Life Inventory
PF	physical functioning
PFS	progression free survival
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
PR	partial response
PROs	patient reported outcomes
PROMIS	Patient-Reported Outcomes Measurement Information System
QoL	quality of life
RECIST	Response Evaluation Criteria In Solid Tumors
REiNs	Response Evaluation in Neurofibromatosis and Schwannomatosis
RNA	ribonucleic acid
RVO	retinal vein occlusion
SAE	serious adverse event
SD	stable disease
SFU	Safety Follow-Up
SoA	schedule of activities
TTP	time to progression
ULN	upper limit of normal
v	version
vs	versus
WHO	World Health Organization
WOCBP	woman of child bearing potential

10.10. Appendix 10: List of Contacts for Study

10.10.1. Sponsor

SpringWorks Therapeutics
100 Washington Blvd
Stamford, CT 06902
United States

[redacted]

10.11. Appendix 11: Pediatric Blood Pressure Charts

Table 12 Blood Pressure for Girls Aged 2 to 12 Years of Age

Age (y)	BP Percentile	SBP (mm Hg)							DBP (mm Hg)						
2	Height (cm)	84.9	86.3	88.6	91.1	93.7	96	97.4	84.9	86.3	88.6	91.1	93.7	96	97.4
	95th	104	105	106	106	107	108	109	62	63	63	64	65	66	66
	95th + 12 mm Hg	116	117	118	118	119	120	121	74	75	75	76	77	78	78
3	Height (cm)	91	92.4	94.9	97.6	100.5	103.1	104.6	91	92.4	94.9	97.6	100.5	103.1	104.6
	95th	106	106	107	108	109	110	110	64	65	65	66	67	68	69
	95th + 12 mm Hg	118	118	119	120	121	122	122	76	77	77	78	79	80	81
4	Height (cm)	97.2	98.8	101.4	104.5	107.6	110.5	112.2	97.2	98.8	101.4	104.5	107.6	110.5	112.2
	95th	107	108	109	109	110	111	112	66	67	68	69	70	70	71
	95th + 12 mm Hg	119	120	121	121	122	123	124	78	79	80	81	82	82	83
5	Height (cm)	103.6	105.3	108.2	111.5	114.9	118.1	120	103.6	105.3	108.2	111.5	114.9	118.1	120
	95th	108	109	109	110	111	112	113	68	69	70	71	72	73	73
	95th + 12 mm Hg	120	121	121	122	123	124	125	80	81	82	83	84	85	85
6	Height (cm)	110	111.8	114.9	118.4	122.1	125.6	127.7	110	111.8	114.9	118.4	122.1	125.6	127.7
	95th	109	109	110	111	112	113	114	70	71	72	72	73	74	74
	95th + 12 mm Hg	121	121	122	123	124	125	126	82	83	84	84	85	86	86
7	Height (cm)	115.9	117.8	121.1	124.9	128.8	132.5	134.7	115.9	117.8	121.1	124.9	128.8	132.5	134.7
	95th	109	110	111	112	113	114	115	72	72	73	73	74	74	75
	95th + 12 mm Hg	121	122	123	124	125	126	127	84	84	85	85	86	86	87
8	Height (cm)	121	123	126.5	130.6	134.7	138.5	140.9	121	123	126.5	130.6	134.7	138.5	140.9
	95th	110	111	112	113	115	116	117	72	73	74	74	75	75	75
	95th + 12 mm Hg	122	123	124	125	127	128	129	84	85	86	86	87	87	87
9	Height (cm)	125.3	127.6	131.3	135.6	140.1	144.1	146.6	125.3	127.6	131.3	135.6	140.1	144.1	146.6
	95th	112	112	113	114	116	117	118	74	74	75	75	75	75	75
	95th + 12 mm Hg	124	124	125	126	128	129	130	86	86	87	87	87	87	87
10	Height (cm)	129.7	132.2	136.3	141	145.8	150.2	152.8	129.7	132.2	136.3	141	145.8	150.2	152.8
	95th	113	114	114	116	117	119	120	75	75	76	76	76	76	76
	95th + 12 mm Hg	125	126	126	128	129	131	132	87	87	88	88	88	88	88
11	Height (cm)	135.6	138.3	142.8	147.8	152.8	157.3	160	135.6	138.3	142.8	147.8	152.8	157.3	160
	95th	115	116	117	118	120	123	124	76	77	77	77	77	77	77
	95th + 12 mm Hg	127	128	129	130	132	135	136	88	89	89	89	89	89	89
12	Height (cm)	142.8	145.5	149.9	154.8	159.6	163.8	166.4	142.8	145.5	149.9	154.8	159.6	163.8	166.4
	95th	118	119	120	122	124	125	126	78	78	78	78	79	79	79
	95th + 12 mm Hg	130	131	132	134	136	137	138	90	90	90	90	91	91	91

BP = blood pressure; cm = centimeter; DBP = diastolic blood pressure; SBP = systolic blood pressure; y = years

Table 13 Blood Pressure for Boys Aged 2 to 12 Years of Age

Age (y)	BP Percentile	SBP (mm Hg)							DBP (mm Hg)						
2	Height (cm)	86.1	87.4	89.6	92.1	94.7	97.1	98.5	86.1	87.4	89.6	92.1	94.7	97.1	98.5
	95th	104	105	105	106	107	107	108	57	58	58	59	60	61	61
	95th + 12 mm Hg	116	117	117	118	119	119	120	69	70	70	71	72	73	73
3	Height (cm)	92.5	93.9	96.3	99	101.8	104.3	105.8	92.5	93.9	96.3	99	101.8	104.3	105.8
	95th	106	106	107	107	108	109	109	60	61	61	62	63	64	64
	95th + 12 mm Hg	118	118	119	119	120	121	121	72	73	73	74	75	76	76
4	Height (cm)	98.5	100.2	102.9	105.9	108.9	111.5	113.2	98.5	100.2	102.9	105.9	108.9	111.5	113.2
	95th	107	107	108	108	109	110	110	63	64	65	66	67	67	68
	95th + 12 mm Hg	119	119	120	120	121	122	122	75	76	77	78	79	79	80
5	Height (cm)	104.4	106.2	109.1	112.4	115.7	118.6	120.3	104.4	106.2	109.1	112.4	115.7	118.6	120.3
	95th	107	108	109	109	110	111	112	66	67	68	69	70	70	71
	95th + 12 mm Hg	119	120	121	121	122	123	124	78	79	80	81	82	82	83
6	Height (cm)	110.3	112.2	115.3	118.9	122.4	125.6	127.5	110.3	112.2	115.3	118.9	122.4	125.6	127.5
	95th	108	109	110	111	112	113	114	69	70	70	71	72	72	73
	95th + 12 mm Hg	120	121	122	123	124	125	126	81	82	82	83	84	84	85
7	Height (cm)	116.1	118	121.4	125.1	128.9	132.4	134.5	116.1	118	121.4	125.1	128.9	132.4	134.5
	95th	110	110	111	112	114	115	116	71	71	72	73	73	74	74
	95th + 12 mm Hg	122	122	123	124	126	127	128	83	83	84	85	85	86	86
8	Height (cm)	121.4	123.5	127	131	135.1	138.8	141	121.4	123.5	127	131	135.1	138.8	141
	95th	111	112	112	114	115	116	117	72	73	73	74	75	75	75
	95th + 12 mm Hg	123	124	124	126	127	128	129	84	85	85	86	87	87	87
9	Height (cm)	126	128.3	132.1	136.3	140.7	144.7	147.1	126	128.3	132.1	136.3	140.7	144.7	147.1
	95th	112	112	113	115	116	118	119	74	74	75	76	76	77	77
	95th + 12 mm Hg	124	124	125	127	128	130	131	86	86	87	88	88	89	89
10	Height (cm)	130.2	132.7	136.7	141.3	145.9	150.1	152.7	130.2	132.7	136.7	141.3	145.9	150.1	152.7
	95th	112	113	114	116	118	120	121	76	76	77	77	78	78	78
	95th + 12 mm Hg	124	125	126	128	130	132	133	88	88	89	89	90	90	90
11	Height (cm)	134.7	137.3	141.5	146.4	151.3	155.8	158.6	134.7	137.3	141.5	146.4	151.3	155.8	158.6
	95th	114	114	116	118	120	123	124	77	78	78	78	78	78	78
	95th + 12 mm Hg	126	126	128	130	132	135	136	89	90	90	90	90	90	90
12	Height (cm)	140.3	143	147.5	152.7	157.9	162.6	165.5	140.3	143	147.5	152.7	157.9	162.6	165.5
	95th	116	117	118	121	124	126	128	78	78	78	78	78	79	79
	95th + 12 mm Hg	128	129	130	133	136	138	140	90	90	90	90	90	91	91

BP = blood pressure; cm = centimeter; DBP = diastolic blood pressure; SBP = systolic blood pressure; y = years

10.12. Appendix 12: Supportive Care

Appropriate antibiotics, blood product support, anti-emetics, and general supportive care may be used as indicated at the discretion of the caring physician/healthcare provider and consistent with local standard of care and Section 6.5.

Dermatologic adverse events:

The use of medications for the supportive care of rash is permitted, provided that compliance with Section 6.5 regarding concomitant medications is observed. Early initiation of treatment for rashes is strongly recommended to minimize the duration and severity of the adverse event.

Acneiform rash: Experience with acneiform rash suggests that topical clindamycin gel or lotion applied BID, rather than steroids, is the most helpful for pustular rash. In severe cases, semisynthetic oral tetracyclines such as doxycycline or minocycline may also be useful for older children, adolescents, and adults, but should be avoided in children younger than 8 years old because of risk to tooth development.

Eczematous rash/xerosis: Eczematous/dry skin rash and other macular (non-acneiform) rash should be treated with a moisturizer such as CeraVe or Eucerin or another equivalent product. A low potency topical steroid such as betamethasone valerate lotion (0.05%), desonide cream (0.05%), fluocinolone acetonide solution (0.01%), dexamethasone sodium phosphate cream (0.1%), hydrocortisone acetate cream (1%), methylprednisolone acetate cream (0.25%) or equivalent may also be used if symptomatic.

Ketoconazole shampoo should be used for any rash involving the scalp.

Paronychia: Paronychia if acute and non-surgical (i.e., no fluctuance suggesting an abscess) can resolve with warm soaks only applied 3 to 4 times daily. If there is extensive redness suggesting cellulitis, OR if there is non-surgical paronychia but the participant is a diabetic or is immuno-compromised, then an oral antibiotic that covers *staphylococcus aureus* should be started. The choice of antibiotics includes a *staphylococcus aureus* covering penicillin/clindamycin/first generation cephalosporin/augmentin.

If an abscess develops, surgical treatment with incision and drainage with or without debridement should be done. Any infectious organisms identified should be treated accordingly. If the participant has diabetes or is immune compromised, oral antibiotics ensuring coverage for staphylococcal aureus (see above) should be started prior to a culture and sensitivity report. Once culture report is obtained, the antibiotic therapy should be adjusted as appropriate.

Visual adverse events:

All participants will have a detailed ophthalmologic evaluation at Screening. In participants who develop visual symptoms, a repeat ophthalmologic evaluation will be performed to include: best corrected visual acuity, intraocular pressure, slit lamp fundoscopy (photograph if abnormal).

If a diagnosis of retinal pigment epithelial detachment or central serous retinopathy is made, treatment with PD-0325901 will be held and repeat ophthalmologic evaluations will be performed until resolution. Treatment may be restarted after complete resolution of symptoms to baseline.

If a diagnosis of retinal vein occlusion (RVO) is made, PD-0325901 will be discontinued permanently.

Gastrointestinal adverse events:

Diarrhea: Non-infectious diarrhea should be treated with loperamide. Additional agents may be used concurrently if loperamide is not adequate to control diarrhea as a single agent. In addition, the following dietary advice should be considered: BRAT diet (bananas, rice, apple sauce, toast, plain pasta), readily digestible food, avoidance of lactose-containing products and fried, fatty or spicy foods, increased fluid intake (8-10 glasses of clear fluids/day (including water, clear broth, fluids containing salt and sugar). Participants should be encouraged to seek advice early from their physician or study nurse if they have persistent diarrhea, diarrhea complicated by vomiting, or inability to take oral liquids.

Oral mucositis: Participants should be encouraged to follow a daily oral health care regime during treatment with PD-0325901. Use of a mouthwash immediately after PD-0325901 intake is recommended. Participants with a healthy mouth may use nonalcoholic mouthwash 4 to 6 times daily (e.g., after each meal), or according to the instructions, during the study. Participants with, or at risk of, stomatitis should not use commercial/over-the-counter mouthwashes because of the alcohol content and astringency. Saline mouthwashes (Sodium chloride 0.9%) are preferred in cases of stomatitis and should be used at a different time than toothbrushing (e.g., after tea). Chlorhexidine mouthwashes are not recommended for the treatment of established stomatitis. Teeth should be brushed twice daily with a fluoride toothpaste and soft toothbrush, in the morning before breakfast and last thing in the evening before bed, about 30 minutes after eating. The tongue can be gently brushed (if not sore) with a soft toothbrush. The toothbrush should be replaced regularly (at least every 3 months). Participants with stomatitis should change their toothbrush every 4 to 6 weeks.

Consider treating stomatitis at an early stage (CTCAE grade 1) or as soon as the participant complains of a sore mouth. Consider using an oral topical analgesic, with or without topical steroids, depending on the participant's clinical condition and the local standard medical practice.

The mouth should be regularly inspected by the participant and healthcare professionals.

Consider culture to rule out herpes simplex.

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