

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

**A PHASE 1/2A OPEN-LABEL, DOSE ESCALATION AND EXPANSION  
STUDY TO INVESTIGATE THE SAFETY, PHARMACOKINETICS,  
PHARMACODYNAMICS AND EFFICACY OF MIRDAMETINIB IN  
COMBINATION WITH BGB-3245 IN PATIENTS WITH ADVANCED  
SOLID TUMORS**

Protocol Number: MEKRAF-AST-101

Amendment Number: 2

Study Phase: Phase 1/2a

Short Title: Mirdametinib + BGB-3245 in  
Advanced Solid Tumors

Sponsor Name: SpringWorks Therapeutics, Inc.

Legal Registered Address: 100 Washington Blvd, Stamford, CT  
06902, United States

Regulatory Agency Identifying Number(s):	<b>Registry</b>	<b>ID</b>
	IND-162502	

Approval Date 24 July 2023

**Confidentiality Statement**

The information in this document is confidential information of SpringWorks Therapeutics, Inc. and is not to be disclosed without the prior written consent of SpringWorks. You are allowed to disclose the contents of this document only to your Institutional Review Board or Independent Ethics Committee and study personnel directly involved with conducting this protocol. Persons to whom the information is disclosed must be informed that the information is confidential and proprietary to SpringWorks and that it may not be further disclosed to third parties or used for any other purpose. The disclosure and use of information in this document are subject to a written confidentiality agreement between SpringWorks and your institution.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## INVESTIGATOR'S AGREEMENT

I have read this protocol entitled "A Phase 1/2a Open-Label, Dose Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Efficacy of Mirdametinib in Combination With BGB-3245 in Patients with Advanced Solid Tumors" and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation Guidelines for Good Clinical Practice and applicable Food and Drug Administration regulations/guidelines and any local regulations per country.

I agree to ensure that the confidential information contained in the protocol will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of SpringWorks Therapeutics.

This protocol has been received for information only and must not be implemented before all necessary regulatory agency and Ethics Committee / Institutional Review Board approval documents have been obtained.

---

Printed Name of Investigator

---

Signature of Investigator

---

Date

The contents of this document are confidential and proprietary to SpringWorks Therapeutics. This document is made available for business operations and review by SpringWorks Therapeutics employees, contracting consultants of SpringWorks Therapeutics and regulatory agencies. Distribution to third parties without prior permission is prohibited.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## SPONSOR'S SIGNATORY

DocuSigned by:  
*Wenlin Shao*  
Signer Name: Wenlin Shao  
Signing Reason: I approve this document  
Signing Time: 26-Jul-2023 | 17:28:47 EDT  
358B5741822B404FA85F0FAAE20CA3DF

26-Jul-2023 | 17:29:18 EDT

Wenlin Shao, PhD  
SVP, Head of Early Development Programs

Date

SpringWorks Therapeutics

DocuSigned by:  
*Vincent Amoruccio*  
Signer Name: Vincent Amoruccio  
Signing Reason: I approve this document  
Signing Time: 26-Jul-2023 | 16:00:53 EDT  
6D510249B92444B2A61502CB134C9DD6

26-Jul-2023 | 16:01:22 EDT

Vincent Amoruccio, PhD  
VP of Biometrics

Date

SpringWorks Therapeutics

DocuSigned by:  
*Katie Stabler*  
Signer Name: Katie Stabler  
Signing Reason: I approve this document  
Signing Time: 26-Jul-2023 | 16:19:43 EDT  
26DC0D05D7954057B69E3F5073B56360

26-Jul-2023 | 16:20:10 EDT

Katie Stabler  
Director of Clinical Operations

Date

SpringWorks Therapeutics

DocuSigned by:  
*Eric Sbar*  
Signer Name: Eric Sbar  
Signing Reason: I approve this document  
Signing Time: 26-Jul-2023 | 15:41:10 EDT  
7B224800F85043898AFE94F7B2CD936E

26-Jul-2023 | 15:41:35 EDT

Eric Sbar, DO  
VP, Clinical Development  
SpringWorks Therapeutics

Date

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## 1.            **PROTOCOL SUMMARY**

### 1.1.        **SYNOPSIS**

**Protocol title:** A Phase 1/2a Open-Label, Dose Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Efficacy of Mirdametinib in Combination With BGB-3245 in Patients with Advanced Solid Tumors

**Short title:** Mirdametinib + BGB-3245 in Advanced Solid Tumors

**Rationale:** Multiple therapies targeting the v-RAF murine sarcoma viral oncogene homolog B (BRAF) kinase have been approved by the United States Food and Drug Administration (FDA) as single agents and in combination with mitogen activated protein kinase kinase (MEK) inhibitors for patients with Class I BRAF mutations including those with melanoma and non-small cell lung cancer (NSCLC). Class I BRAF mutations activate the mitogen activated protein kinase (MAPK) pathway via a BRAF monomer. However, this approach provides no benefit for patients with BRAF Class II or Class III mutations, nor those that harbor rat sarcoma virus (RAS) mutations, as each of these activate MAPK pathway via BRAF homodimers or in the case of RAS mutations also heterodimers that form with other members of the RAF family of kinases, Raf-1 proto-oncogene and serine/threonine kinase (RAF1 [also called CRAF]), and A-Raf proto-oncogene serine/threonine kinase (ARAF).

Novel combinations of MEK inhibitors coupled with pan-RAF dimer inhibitors are being investigated to address RAS mutant tumors which occur in ~20% of all human cancers. The therapeutic strategy for this combination focuses on maximizing inhibition of MEK phosphorylation with a MEK inhibitor (to reduce phosphorylated ERK [pERK] and MAPK pathway activation) and with a pan-RAF inhibitor acting to inhibit feedback loops deemed responsible for increasing MAPK signaling, both by directly reactivating the MAPK pathway (e.g., DUSP6), but also by removing negative regulators of RTK signaling (e.g., Sprouty [Spry] proteins) that can activate RAS and associated downstream pathways. The synergy attained by this dual inhibition of RAF and MEK may lead to deeper inhibition of the oncogenic pathway and provide more durable antitumor activity.

Mirdametinib (also known as PD-0325901) is an allosteric inhibitor of MEK1 and MEK2 kinases. As a potent MEK inhibitor, mirdametinib significantly inhibits phosphorylation of the extracellular regulated MAP kinases extracellular signal-regulated kinase [ERK]1 and ERK2, neurofibromatosis type 1 [NF1], mitogen-activated protein kinase kinase 1[MAP2K1], mitogen-activated protein kinase kinase 2 [MAP2K2], and mitogen-activated protein kinase 1 [MAPK1].

Brimarafenib (also known as BGB-3245) is a second-generation RAF kinase dimer inhibitor developed for the treatment of patients with tumors harboring BRAF Class I or V600

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

mutation, the BRAF Class II or non-V600 mutation that is kinase-activated, Class III mutation or non-V600 mutation that is kinase-impaired, or BRAF fusion and splicing variant proteins and other MAPK pathway aberrations that are dependent on RAF monomer or RAF dimer activity. This includes ARAF, RAF1/CRAF, and tumors harboring the mutation of the neuroblastoma RAS viral oncogene homolog (NRAS), Kirsten rat sarcoma viral oncogene homolog (KRAS), or Harvey rat sarcoma viral oncogene homolog (HRAS).

The proposed study MEKRAF-AST-101 sponsored by SpringWorks Therapeutics is a Phase 1/2a study of a pan-RAF inhibitor brimrafenib in combination with a MEK inhibitor mirdametinib in patients with advanced refractory solid cancers harboring MAPK pathway mutation(s) (noted above). This will be the first study to examine brimrafenib in combination with mirdametinib. The main objectives of this study are to evaluate the safety and tolerability of a dose range of each of the combination agents and to assess the clinical anti-tumor activity of the combination agents in participants with advanced, refractory solid tumors that harbor MAPK pathway mutation(s).

### Objectives and Endpoints

#### Primary Objectives:

**Part 1 and Part 2:** To evaluate the safety and tolerability of mirdametinib and brimrafenib administered as a combination in the eligible participant population.

**Part 1 only:** To determine the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) for mirdametinib and brimrafenib administered as a combination in the eligible participant population.

#### Primary Endpoints:

Key safety endpoints will include incidence of treatment emergent Adverse Events (TEAEs), changes in clinical laboratory parameters, vital signs, physical examination findings, Eastern Cooperative Oncology Group (ECOG) status, electrocardiograms (ECGs), ophthalmological examinations, and echocardiogram (ECHO)/Multigated Acquisition (MUGA) scan.

TEAEs severities will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

The MTD, if any, will be based on safety and tolerability during the first 28 days of treatment in Cycle 1.

The RP2D will be determined based on safety, tolerability, PK, preliminary anti-tumor efficacy, and other available data.

Mirdametinib  
Protocol MEKRAF-AST-101SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

<b>Part 2 only:</b> To determine the preliminary anti-tumor efficacy for the RP2D of mirdametinib and brimarafenib administered as a combination in the eligible participant population.	Anti-tumor efficacy as assessed by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI). Objective Response Rate (ORR) defined as the proportion of participants with complete response (CR) + partial response (PR) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1).
<b>Secondary Objectives:</b>	<b>Secondary Endpoints:</b>
<b>Part 1 only:</b> To determine the preliminary anti-tumor efficacy of mirdametinib and brimarafenib administered as a combination in the eligible participant population.	Anti-tumor efficacy as assessed by CT or MRI. Objective Response Rate (ORR) defined as the proportion of participants with complete response (CR) + partial response (PR) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1).
<b>Part 1 and Part 2:</b> To determine duration of response in participants treated with the combination of mirdametinib and brimarafenib.	Duration of response rate, defined as the time from response (CR + PR using RECIST v1.1) to disease progression and/or death.
<b>Part 1 and Part 2:</b> To determine the PK of mirdametinib and brimarafenib administered as a combination in the eligible participant population.	Plasma concentrations of mirdametinib and brimarafenib will be measured to evaluate systemic exposures (AUC, Cmax, Ctrough, and other PK parameters as data allow).
<b>Exploratory Objectives:</b>	<b>Exploratory Endpoints:</b>
<b>Part 2 only:</b> To determine if the combination of mirdametinib and brimarafenib delays disease progression in this participant population.	For each tumor histology in each expansion cohort, estimate of median time-to-progression.
<b>Part 1 and Part 2:</b> To detect tumor mutation/co-mutation status and correlate with anti-tumor activity.	Evaluate Next Generation Sequencing (NGS) in baseline tumor tissue.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

<b><i>Part 1 and Part 2:</i></b> To detect candidate biomarkers of response and to correlate with brimarafenib + mirdametinib exposure.	Evaluate change from Baseline: <ul style="list-style-type: none"><li>• Blood circulating tumor DNA (ctDNA), tumor tissue immunohistochemistry (IHC), immunofluorescence (IF), or similar assay</li></ul>
-----------------------------------------------------------------------------------------------------------------------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

**Overall design:**

This is a Phase 1/2a open-label, multicenter, dose escalation and expansion study of mirdametinib in combination with brimrafenib in adult participants with histologically confirmed, advanced (American Joint Committee on Cancer (AJCC) Stage III or IV) metastatic or unresectable solid cancer that is refractory to or has progressed during or after at least 1 line of appropriate prior systemic anti-cancer therapy including chemotherapy, immunotherapy, or appropriate targeted therapy, or for which there is no treatment available, or prior standard of care therapy was not tolerated.

The study will be conducted in two sequential parts: Part 1 dose escalation (Phase 1) and Part 2 dose expansion (Phase 2a).

Participants will receive mirdametinib and brimrafenib administered by mouth every day on a continuous schedule. Mirdametinib will be dosed twice a day (BID) and brimrafenib will be dosed once a day (QD). One treatment cycle will be 28 days.

**Part 1 (Phase 1 dose escalation)**

Part 1 of the study will assess the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PDx), and preliminary evidence of anti-tumor efficacy. Part 1 will also identify the MTD and the RP2D for the combination of mirdametinib with brimrafenib.

**Part 1 Eligible Population**

Part 1 will include participants with advanced metastatic or unresectable solid tumors harboring an oncogenic mutation or other aberrations of the MAPK pathway. The mutations and aberrations of the MAP pathway include: a known mutation status and tumor harboring an oncogenic mutation of the BRAF gene (including BRAF Class I or V600 mutation, the BRAF Class II or non-V600 mutation that is kinase-activated, Class III mutation or non-V600 mutation that is kinase-impaired, or BRAF fusion), ARAF, and RAF1/CRAF. In addition, participants with tumors harboring the mutation of NRAS, KRAS, HRAS, NF1, MAP2K1, MAP2K2, and MAPK1 are eligible for Part 1. Participants with colorectal cancer (CRC) or pancreatic KRAS mutated tumors together will be limited to no more than one third of the participants enrolled in each cohort in Part 1 to increase participant population diversity.

The tumor mutational status will be determined by the Clinical Laboratory Improvement Amendments (CLIA)-certified next generation sequencing (NGS) assay of the archival tumor sample or the fresh tumor biopsy. This information may be available from historic reports obtained at any time before the start of the study treatments or from the assay at the local laboratory performed during screening.

**Part 1 Dose Escalation Plan**

The planned dose levels of mirdametinib and brimrafenib in Part 1 are shown below:

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

Cohort 1: mirdametinib at 2 mg BID + brimarafenib at 5 mg QD

Cohort 2: mirdametinib at 2 mg BID + brimarafenib at 10 mg QD

Cohort 3: mirdametinib at 2 mg BID + brimarafenib at 20 mg QD

Cohort 4: mirdametinib at 2 mg BID + brimarafenib at 30 mg QD

Cohort 5: mirdametinib at 3 mg BID + brimarafenib at 30 mg QD

Cohort 6: mirdametinib at 4 mg BID + brimarafenib at 30 mg QD

If the highest planned dose level (Cohort 6) is cleared by the Cohort Management Committee (CMC) based on the Bayesian Optimal Interval (BOIN) estimate of the toxicity rate and the review of all available data in the study, then the Sponsor in consultation with the CMC may continue dose escalation. The highest doses of mirdametinib and brimarafenib in Part 1 dose escalation will not exceed 8 mg BID and 40 mg QD, respectively.

If a planned dose level is not tolerated based on the BOIN estimate of the toxicity rate derived from the observed dose-limiting toxicity (DLT) rate and/or the review of all available data in the study, an alternate dose exploration may be implemented to identify the optimal dose ratio for the combination of agents. An alternate dose finding scheme may explore lowering of the brimarafenib dose while escalating the mirdametinib dose. The Sponsor in consultation with the CMC may explore the alternative combination dose ratio based on the review of all available data. During dose escalation or de-escalation, the Sponsor in consultation with the CMC may explore alternative dosing schedules to improve tolerability and facilitate the exploration of the benefit-risk ratio.

### **Part 1 Cohort Management Decisions**

Enrollment will occur in sequential cohorts of between 3 and 6 participants per dose level. In each dose cohort, the incidence of DLTs will be evaluated during the first 28 days of treatment with mirdametinib and brimarafenib in Cycle 1.

Cohort management decisions in Part 1 will be governed by the CMC. The CMC meeting will be scheduled after at least 3 participants in each dose cohort become evaluable for DLT assessment. The CMC will consider the BOIN rules and all available data (safety, toxicity modeling and prediction, PK, tumor response, and PDx) from all participants treated up until the CMC meeting. The CMC will consist of the investigators, the Sponsor representatives, and the Independent Safety Committee (ISC). The ISC composition will be described in a charter and include a minimum of 3 suitably qualified drug development physicians. The ISC will adjudicate the decisions to escalate/de-escalate or expand cohort numbers. In the event of differences of opinion between these 3 groups, the ISC will have the deciding vote.

The dose escalation will employ the BOIN design to determine the MTD. The target toxicity rate used for the MTD identification is  $\phi = 0.3$ . The BOIN design will use the following rules,

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

optimized to minimize the probability of incorrect dose assignment, to guide dose escalation/de-escalation decisions:

1. Participants in the first cohort are treated at dose level 1.
2. To assign a dose to the next cohort of participants, conduct dose escalation/de-escalation according to the rule displayed in [Table 6-2](#). When using [Table 6-2](#), please note the following:
  - a. “Eliminate” means eliminate the current and higher doses from the trial to prevent treating any future participants at these doses because they are overly toxic.
  - b. When a dose is eliminated, this will lead to an automatic de-escalation of the dose to the next lower level or an alternate dose level or schedule depending on observed toxicities. When the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD.
  - c. If none of the actions (i.e., escalation, de-escalation, or elimination) is triggered, treat the new participants at the current dose.
  - d. If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new participants at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point terminate the trial for safety.
  - e. If the current dose is the highest dose and the rule indicates dose escalation, treat the new participants at the highest dose.
3. Repeat step 2 following the BOIN design until the MTD and/or RP2D is determined or stop the dose escalation part if the number of evaluable participants treated at the current dose reaches 6 and the decision according to [Table 6-2](#) is to stay at the current dose.

After the dose escalation is completed, the MTD will be computed using an isotonic regression as specified in ([Liu and Yuan 2015](#)). Specifically, the MTD is selected as the dose for which the isotonic estimate of the toxicity rate is less than or equal to 0.359 and closest to the target toxicity rate.

The non-tolerable dose is defined as the dose of study treatments where the target DLT rate was exceeded.

The dose escalation will be stopped either when the non-tolerable dose is reached or the highest planned dose level of mirdametinib or brimrafenib (8 mg BID or 40 mg QD, respectively) is shown to be tolerated.

### **Part 1 Pharmacodynamic Expansion Cohort**

A minimum of six evaluable participants and a maximum of 20 participants will be enrolled in the Part 1 PDx Expansion Cohort to collect additional biomarker/PDx data. Matched paired biopsies were included to gather relevant pharmacodynamic data to support the RP2D or MTD

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

dose in consultation with the CMC. The PDx Expansion Cohort may be enrolled in parallel with, or before the start of Part 2 dose expansion.

The participants in the PDx Expansion Cohort must meet the eligibility criteria for participants in Part 1 dose escalation; in addition, the participants in the PDx Expansion Cohort must provide paired fresh tumor biopsies at screening and at Cycle 1 Day 22 ( $\pm 2$  days) to be considered evaluable. The participants will undergo all assessments specified in the Schedule of Assessments for Part 1 dose escalation.

### **Part 1 Tumor Biopsy**

Fresh paired tumor biopsies in Part 1 (at screening and at Cycle 1 Day 22 [ $\pm 2$  days]) are mandatory for the participants in the PDx Expansion Cohort.

Fresh paired tumor biopsies (at screening and at Cycle 1 Day 22 [ $\pm 2$  days]) are recommended for participants in the Part 1 dose escalation cohorts.

End of Treatment (EoT) biopsies are optional for participants in Part 1 that discontinue due to disease progression.

### **Part 1 RP2D selection**

Based on the evaluation of all available study data from Part 1, the Sponsor in consultation with the CMC will recommend the dose and dosing schedule to be used as the RP2D for mirdametinib and brimarafenib in Part 2.

### **Part 1 Sample Size**

The planned sample size in Part 1 is up to 56 participants, which includes the following:

- Six dose escalation cohorts (up to 6 evaluable participants per cohort; participant is evaluable, if they complete Cycle 1 or experience DLT)
- PDx Expansion Cohort (up to 20 participants).

The planned number of participants in Part 1 may be increased if deemed necessary by the Sponsor to determine MTD or RP2D.

Participants who are discontinued after the start of treatment in Part 1 (except those discontinued for safety reasons) may be replaced if deemed necessary by the Sponsor to accrue sufficient evaluable participants.

### **Part 2 (Phase 2a dose expansion)**

Part 2 will begin after the RP2D for the combination of mirdametinib and brimarafenib is identified in Part 1. Part 2 may start either in parallel with, or after, the conduct and analysis of the PDx Expansion Cohort in Part 1.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

Part 2 will confirm the safety, tolerability, efficacy, PK, and PDx for the combination of mirdametinib and brimarafenib.

Part 2 will follow a parallel design and include one or more dose expansion cohorts, where each participant would be treated with the combination of mirdametinib and brimarafenib at the RP2D.

Participants who experience a TEAE requiring treatment modification will be managed according to the applicable guidelines in this protocol.

### **Part 2 Eligible Populations**

The populations eligible for Part 2 will include participants with advanced metastatic or unresectable solid tumors harboring the oncogenic mutations specific for each of the expansion cohorts. The tumor mutational status should be determined by CLIA-compliant NGS assay of the archival tumor sample or the fresh tumor biopsy. This information may be available from historic reports obtained at any time before the start of the study treatments or from the assay at the local laboratory performed during screening.

One or more of the following cohorts may be opened in parallel, or sequentially at the Sponsor's discretion:

1. Expansion Cohort A (n=20 evaluable participants): Participants with cutaneous melanoma harboring an NRAS mutation.
  - a. Minimum of 15 (75%) of the 20 participants in Cohort A must have a NRAS Q61x mutation (i.e., Q61R, Q61K, Q61L).
2. Expansion Cohort B (n= 30 evaluable participants): Participants with NSCLC harboring a KRAS mutation
  - a. Minimum of 15 (50%) of the 30 evaluable participants in Cohort B must have a KRAS G12V mutation.
3. Expansion Cohort C (n=30 evaluable participants): Participants with NSCLC or cutaneous melanoma harboring BRAF Class II or Class III mutations or BRAF fusion.
  - a. Cohort C1: Approximately 15 evaluable participants with *NSCLC* harboring BRAF Class II or Class III mutations or BRAF fusion.
  - b. Cohort C2: Approximately 15 evaluable participants with *cutaneous melanoma* harboring BRAF Class II or Class III mutations or BRAF Fusion.

Additional cohorts of up to 30 evaluable participants each with specific tumor histology and/or mutation status may be included in Part 2 expansion phase, if supported by the efficacy signals observed during the dose escalation phase.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

A participant will be evaluable for Part 2 dose expansion cohort if they provide a baseline radiological tumor assessment at the Screening Visit and for at least one time point after the start of study treatment and these assessments allow an evaluation of the tumor response. The first post-treatment tumor assessment after 2 cycles will be used to assess ORR for decision making at the interim analysis. For the final analysis, all post-baseline tumor assessments will be used to assess tumor response status.

### **Part 2 Sample Size**

The planned sample size in Part 2 dose escalation is 80 evaluable participants (20 evaluable participants in Cohort A and 30 evaluable participants each in Cohorts B and C). Up to 100 participants may be treated to achieve the planned number of evaluable participants.

The sample size for the expansion cohorts is based on a Bayesian Optimal Interval Phase 2 design (BOP2) for each of the cohorts ([Zhou, Lee, and Yuan 2017](#)). There will be one interim analysis in each of the 3 cohorts when 50% of the planned total sample size is evaluable for ORR and the stopping criteria at interim and final analysis will be applied as described in [Table 6-3](#). These stopping criteria are non-binding but provide guidance for decision making.

Further details of the BOP2 design will be described in the statistical analysis plan (SAP).

The planned number of participants in Part 2 may be increased if additional dose expansion cohorts are opened.

Participants who are discontinued after the start of treatment in Part 2 (except those discontinued for safety reasons) may be replaced if deemed necessary to accrue enough evaluable participants.

### **Part 2 Interim Analysis**

Once ORR can be assessed in each of the dose expansion cohorts (approximately 10 evaluable participants in cohort A and 15 participants in cohort B and C) the Sponsor will conduct an interim analysis (IA) of all available safety, efficacy, PK and PDx data, and the stopping criteria following the BOP2 design will be assessed. Other efficacy criteria will be considered for the decision at the time of IA. Enrollment may continue in parallel until a decision about the stopping criteria is achieved.

The goal of the IA will be to determine if the anti-tumor efficacy and tolerability of study treatments administered at the RP2D meets the Sponsor's predefined criteria for the clinical proof-of-concept (PoC). If the stopping criteria at the time of the IA are not met additional participants will be enrolled and the final analysis will be repeated after the total planned number of participants become evaluable in each of the dose expansion cohorts. In addition to the stopping criteria following the BOP2 design, other efficacy endpoints such as duration of response (DOR) will be considered for the conclusion at the time of final analysis.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

The expansion cohorts may be expanded if deemed appropriate by the Sponsor based on the analysis of all available safety, efficacy, PK and PDx data from that cohort and the consultation with the Regulatory Authorities (if applicable).

### **Part 2 Tumor Biopsy**

Fresh paired tumor biopsies in Part 2 (at screening and at Cycle 1 Day 22 [ $\pm$  2 days]) are mandatory for at least 6 evaluable participants in Cohort A.

Fresh paired tumor biopsies (at screening and at Cycle 1 Day 22 [ $\pm$  2 days]) are recommended for all other participants in Part 2.

EoT biopsies are optional for all participants in Part 2 that discontinue due to disease progression.

### **Confirmation of Mutational Status (Part 1 and Part 2)**

In both parts of the study, participants must provide a baseline tumor tissue sample for the confirmation of mutational status at the central laboratory and the tumor biomarker analysis. The baseline sample may be obtained at any time before the start of the study treatments, either from the archival tumor tissue or fresh tumor biopsies. If the archival tumor is used for the baseline sample, then it should be available as a formalin-fixed paraffin-embedded (FFPE) block (preferred), or as approximately 20 FFPE unstained slides.

**Disclosure Statement:** Two-part open label dose escalation and expansion study

**Number of participants:** Part 1: 56 participants  
Part 2: 80 participants

### **Intervention groups and duration:**

Part 1:

Cohort 1: mirdametinib at 2 mg BID + brimarafenib (BGB-3245) at 5 mg QD

Cohort 2: mirdametinib at 2 mg BID + brimarafenib (BGB-3245) at 10 mg QD

Cohort 3: mirdametinib at 2 mg BID + brimarafenib (BGB-3245) at 20 mg QD

Cohort 4: mirdametinib at 2 mg BID + brimarafenib (BGB-3245) at 30 mg QD

Cohort 5: mirdametinib at 3 mg BID + brimarafenib (BGB-3245) at 30 mg QD

Cohort 6: mirdametinib at 4 mg BID + brimarafenib (BGB-3245) at 30 mg QD

PDx Expansion Cohort: mirdametinib + brimarafenib (BGB-3245) at MTD or RP2D

One treatment cycle will be 28 days.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

Part 2: Part 2 will follow a parallel design and include one or more dose expansion cohorts, where each participant would be treated with the combination of mirdametinib and brimarafenib (BGB-3245) at the RP2D.
--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

<b>Data Monitoring committee:</b> No
--------------------------------------

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## 1.2. SCHEDULE OF ASSESSMENTS

**Table 1-1: Schedule of Assessments for Dose Escalation (Part 1) and Dose Expansion (Part 2)**

	Screening <sup>1</sup>	Cycle 1				Cycle 2		Cycles 3-12	Cycle 13 & Every 3 Cycles	End of Treatment (EoT) <sup>2</sup>	Safety Follow-up <sup>3</sup>	Long-term Follow-up
Days (window)	Up to 28 days before Day 1	1	8 (±1)	15 (±2)	22 (±2)	1 (+2) <sup>29</sup>	15 (±2)	1 (±2)	1 (±3)	See footnote 2 for visit window	30 (±7) days after last dose <sup>3a</sup>	Every 3 months (±7 days) after last dose
Informed consent <sup>4</sup>	X											
Inclusion/exclusion criteria <sup>5</sup>	X	X										
Demographics/medical history/prior medications <sup>6</sup>	X											
Vital signs <sup>7</sup>	X	X	X	X	X	X	X	X	X	X	X	
Height <sup>8</sup>	X											
Weight <sup>9</sup>	X	X				X		X	X	X	X	
Physical examination <sup>10</sup>	X	X				X		X	X	X	X	
ECOG	X	X				X		X	X	X	X	
12-lead ECG <sup>11</sup>	X	See Table 1-2 and Table 1-3 for details.										
Chemistry <sup>12</sup>	X	X	X	X	X	X	X	X	X	X	X	
Hematology <sup>12</sup>	X	X	X	X	X	X	X	X	X	X	X	
Thyroid function test <sup>13</sup>	X							X	X	X		
Coagulation <sup>14</sup>	X							X	X	X		
Urinalysis <sup>15</sup>	X	X				X		X	X	X	X	
Pregnancy test <sup>16</sup>	X	X				X		X	X	X	X	
Adverse events <sup>17</sup>	X											

Mirdametinib  
Protocol MEKRAF-AST-101SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

	Screening <sup>1</sup>	Cycle 1				Cycle 2		Cycles 3-12	Cycle 13 & Every 3 Cycles	End of Treatment (EoT) <sup>2</sup>	Safety Follow-up <sup>3</sup>	Long-term Follow-up
Days (window)	Up to 28 days before Day 1	1	8 (±1)	15 (±2)	22 (±2)	1 (+2) <sup>29</sup>	15 (±2)	1 (±2)	1 (±3)	See footnote 2 for visit window	30 (±7) days after last dose <sup>3a</sup>	Every 3 months (±7 days) after last dose
Concomitant medications <sup>18</sup>	X											
Ophthalmological examination <sup>19</sup>	X							X	X	X		
LVEF assessment by ECHO or MUGA <sup>20</sup>	X							X	X	X		
Tumor imaging (CT or MRI) & RECIST 1.1 response assessment <sup>21</sup>	X							X	X	X		
Baseline tumor tissue sample (mandatory) <sup>22</sup>	X											
Fresh tumor biopsy <sup>22</sup>	X				X					X		
Biomarkers (blood) <sup>23</sup>		X			X			X <sup>23</sup>	X	X		
Dispensing of study treatments <sup>24</sup>		X				X		X	X			
Study treatment accountability <sup>25</sup>			X	X	X	X	X	X	X	X		
Long-term Follow-up (telephone calls) <sup>26</sup>												X
Administration of study treatments <sup>27</sup>		Daily on the continuous schedule in 28-day cycles (See <a href="#">Section 8.2</a> )										
PK sampling <sup>28</sup>		See <a href="#">Table 1-2</a> and <a href="#">Table 1-3</a> for details.										

Abbreviations: CT = computed tomography; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multigated acquisition; PK = pharmacokinetics; RECIST = response evaluation criteria in solid tumors; X = to be performed at the designated visit.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

**Footnotes:**

1. **Screening** evaluations will be performed within 28 days before the start of the study treatments. Results of the prescribed tests or examinations performed as part of the standard healthcare management within 28 days prior to the first dose of study treatment (if performed before the Informed Consent Form [ICF] was signed) may be used for screening assessments rather than repeating such tests. Participant eligibility will be determined based on a tumor mutation identified by a local assay result obtained in the tumor tissue sample collected at any time prior to screening. If the assessment is performed only once during screening, then the screening result will represent the baseline value. If the assessment is performed more than once during screening, then the most recent result before the start of the study treatments will represent the baseline value. An extension to the Screening Period may be permitted on a case-by-case basis following discussion between the Investigator and the Medical Monitor. The reason(s) for the extension must be clearly documented.
2. **End of Treatment Visit (EoT)** is conducted within 7 days after the investigator determines that study treatment will no longer be used. If the laboratory tests scheduled for the EoT Visit (hematology, chemistry, urinalysis) have been obtained per protocol within 7 days before the treatment discontinuation, the same tests do not need to be repeated. If the tumor assessment and blood tumor biomarkers scheduled for the EoT Visit have been obtained per protocol within 28 days before the treatment discontinuation, the same tests do not need to be repeated.
3. **Safety Follow-Up Visit** should be conducted 30 days ( $\pm 7$  days) after the last dose of study treatment or before the start of the new anti-cancer treatment, whichever comes first. Participants who are discontinued from the study due to an unacceptable study treatment-related adverse event (AE) will be followed until the resolution of the AE to Grade 0-1 or stabilization or until beginning of a new therapy for their cancer, whichever occurs first.
  - a. If participant has been off study treatment  $>30$  days at time of EoT Visit, Safety Follow-Up Visit is not required.
4. **Signed written informed consent** must be obtained at screening before performing any protocol specific procedure. The date of signing the informed consent counts as Day 1 of the 28-day Screening Period.
5. **Inclusion and exclusion criteria** will be assessed at the end of screening and shortly before the start of the study treatments based on the results from the pre-dose assessments on Day 1 of Cycle 1.
6. **Demographics/medical history/prior medications.** See [Section 10.1](#) for details.
7. **Vital signs** will include measurements of temperature, heart rate, pulse oximetry, and blood pressure (systolic and diastolic) after the participant has been resting quietly in sitting position for at least 5 minutes. Vital signs will be obtained at screening, within 2 days before the start of the study treatments, at 1 and 2 hours post-dose ( $\pm 10$  minutes) on Day 1 of Cycle 1, on Days 8, 15 and pre-dose on Day 22 of Cycle 1, pre-dose and at 1 and 2 hours post-dose ( $\pm 10$  minutes) on Day 1 of Cycle 2, on Day 15 of Cycle 2, pre-dose on Day 1 of every cycle (first year), every 12 (-1) weeks (second year, Cycle 13 and beyond), at the EoT Visit (if not done within 7 days of the EoT Visit) and at the Safety Follow-up Visit.
8. **Height** is only required at the Screening Visit.
9. **Weight** should be recorded using the same scale at each time point.
10. **Physical examination** will be performed at screening, within 2 days before the start of the study treatments, pre-dose on Day 1 in every cycle (first year), every 12 (-1) weeks (second year, Cycle 13 and beyond), at the EoT Visit and at the Safety Follow-Up Visit. The physical examination at screening and at the EoT Visit should include an evaluation of 1) head, eyes, ears, nose, throat, 2) cardiovascular, 3)

Mirdametinib  
Protocol MEKRAF-AST-101SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

dermatological, 4) musculoskeletal, 5) respiratory, 6) gastrointestinal, and 7) neurological systems. At other visits (or as clinically indicated), abbreviated physical examinations with ECOG performance status may be performed (to always include cardiovascular, respiratory, gastrointestinal, and dermatological as well as any other symptom-directed organ system).

11. **Electrocardiogram (standard 12-lead ECG) assessments:** See [Table 1-2](#) and [Table 1-3](#) for details.
12. **Hematology and Chemistry assessments** will be conducted in the local laboratory at screening, within 2 days before the start of the study treatments, on Days 8, 15 and pre-dose on Day 22 in Cycle 1, on Days 1 (pre-dose) and 15 in Cycle 2 and thereafter at pre-dose on Day 1 in every cycle, at the EoT Visit (if not done within 7 days of the EoT Visit) and at the Safety Follow-Up Visit. See [Appendix 3](#) for the list of individual tests. Pre-dose samples may be collected any time within the visit window, but the results must be available for review before dosing. For participants experiencing clinically significant laboratory abnormalities, additional hematology and/or chemistry assessment may be performed at the investigator's discretion. For any Grade  $\geq 3$  creatine phosphokinase (CPK) result, see [Section 10.3.6](#) for additional tests needed and [Table 8-4](#) for dose modifications.
13. **Thyroid function testing** (thyroid-stimulating hormone [TSH], free T3, and free T4) will be conducted in the local laboratory at screening, at Week 8 (within 1 week before dosing on Day 1 of Cycle 3), every 8 (-1) weeks thereafter (first year), every 12 (-1) weeks (second year, Cycle 13 and beyond) and at the EoT Visit (if not done within 7 days of the EoT Visit).
14. **Coagulation testing** (aPTT and either INR or PT) will be conducted in the local laboratory at screening, at Week 8 (within 1 week before dosing on Day 1 of Cycle 3), every 8 (-1) weeks thereafter (first year), every 12 (-1) weeks (second year, Cycle 13 and beyond) and at the EoT Visit (if not done within 7 days of the EoT Visit).
15. **Urinalysis** will be conducted in the local laboratory at screening, within 2 days before the start of the study treatments, within 2 days before Day 1 of every cycle (first year), every 12 (-1) weeks (second year, Cycle 13 and beyond), EoT Visit (if not done within 7 days of the EoT Visit) and at the Safety Follow-Up Visit. A standard dipstick urinalysis is sufficient for study purposes; however, sites may perform urinalysis according to their typical site practices. Microscopic analysis of the urine sediment may be performed at the investigator's discretion.
16. **Pregnancy test** (only for women of childbearing potential) A serum pregnancy test must be performed and documented as negative at screening and within 72 hours before the start of the study treatments. Thereafter, serum or urine pregnancy test must be performed and documented as negative within 2 days before Day 1 of every cycle, at the EoT Visit and at the Safety Follow-Up Visit. A serum pregnancy test must be performed if the urine pregnancy test is positive or equivocal.
17. **Adverse events** will be collected from the time of the main study ICF is signed through the Safety Follow-Up Visit or initiation of new anticancer therapy, whichever occurs first. In addition, the treatment-related serious adverse events (SAEs) and the participant's death due to any cause will be collected during the Long-term Follow-up if the site becomes aware of these events.
18. **Concomitant medications.** See [Section 8.6.1](#) for permitted, prohibited, or restricted concomitant medications.
19. **Ophthalmological examination** will include the visual acuity, intraocular pressure (provided as a numerical value), slit lamp examination, cup-to-disc ratio and optical coherence tomography (OCT). Other methods may be performed if indicated by the investigator, an optometrist, or the ophthalmologist (e.g., dilated fundoscopy, fluorescein angiography etc.). Ophthalmological examination will be performed at screening, at Week 8 (within 1 week before dosing on Day 1 of Cycle 3), every 8 (-1) weeks thereafter (first year), every 12 (-1) weeks (second year, Cycle 13 and beyond) and at the EoT Visit (only if the ophthalmological exam has not been done within 4 weeks before the EoT Visit). If a participant experiences an ocular disorder that could be clinically

Mirdametinib  
Protocol MEKRAF-AST-101SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

significant in the investigator's opinion, then an ophthalmological examination should be performed as soon as possible to address the ocular disorder (see also the treatment modification guidelines for ocular toxicities, [Table 8-4](#)). Any clinically significant findings and symptoms, including those confirmed by the ophthalmologist, must be reported as an AE.

20. **LVEF assessment** by ECHO or MUGA will be performed at screening, at Week 8 (within 1 week before dosing on Day 1 of Cycle 3) every 8 (-1) weeks thereafter (first year), every 12 (-1) weeks second year (Cycle 13 and beyond), and at the EoT Visit (only if the LVEF assessment exam has not been done within 4 weeks before the EoT Visit). The same imaging technique should be used in a participant throughout the study.
21. **Tumor imaging** for tumor response assessment by RECIST v1.1 will be performed by CT or MRI. PET-CT is permitted as additional assessment if indicated by the investigator. The same imaging technique should be used in a participant throughout the study. At every scheduled time point, the tumor imaging will include chest, abdomen, and pelvis. The MRI imaging of the brain (and other appropriate central nervous system [CNS] region, if applicable) is required during screening in all participants and during the treatment phase in participants with suspect or known tumor lesions in the CNS.
- Tumor response assessment will be performed within 28 days prior to first dose of study treatment (must include brain MRI to confirm the status of brain metastases, if any), at Week 8 (within 1 week before dosing on Day 1 of Cycle 3), every 8 (-1) weeks thereafter (first year), and every 12 (-1) weeks thereafter second year (Cycle 13 and beyond). In addition, the tumor imaging will be performed at the EoT Visit (only if the tumor scan has not been done within 4 weeks before the EoT Visit). Tumor imaging should continue this calendar schedule regardless of any delays in dosing.
- Tumor response and progression of cancer under study in real time will be evaluated by the investigator at each study site according to the RECIST v1.1 criteria [[Eisenhauer, 2009](#)].
- Sites will submit all CT and/or MRI scans from participants in the PDx Expansion Cohort and Part 2, the dose expansion portion of the study, to the central imaging core laboratory for Central Imaging Review (See [Section 10.2.2](#) for details). The purpose of the Central Imaging Review is to provide an independent, unbiased, and objective review of the CT and MRI data. The Central Imaging Review will begin when deemed appropriate by the Sponsor.
22. **Tumor tissue samples:** Baseline tumor tissue sample is mandatory for mutation status confirmation and the tumor biomarker analysis. The baseline sample may be obtained at any time before the start of the study treatments, either from the archival tumor tissue or fresh tumor biopsies. If the archival tumor is used for the baseline sample, then it should be available as the FFPE block (preferred) or as approximately 20 FFPE unstained slides. The archival sample may have been obtained at any time before the start of the study.
- Paired fresh tumor biopsies are mandatory at screening and Day 22 of Cycle 1 ( $\pm 2$  days) for the PDx Expansion Cohort in Part 1, and at least 6 participants in Cohort A in Part 2. The on-treatment biopsies in Part 1 should be obtained within 3-6 hours after dosing at Day 22 of Cycle 1 ( $\pm 2$  days). The on-treatment biopsies in Part 2 should be obtained pre-dose at Day 22 of Cycle 1 ( $\pm 2$  days). Optional EoT biopsies for participants that discontinue due to disease progression will require additional informed consent and should be obtained within 1 week of stopping study treatment. When permitted by the location of the tumor lesion, all tumor biopsies in one participant should be taken from the same tumor lesion that was used for the baseline tumor biopsy (if applicable). Optional biopsies are allowed for all remaining participants enrolled.
- Tumor biopsies may be taken only if the accessible tumor lesion is available and if the participant consented for this procedure. Tumor biopsies should be limited to readily accessible tumor lesions (i.e., skin; peripheral lymph nodes; lung, liver or internal lymph node

Mirdametinib  
Protocol MEKRAF-AST-101SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

- metastases which can be readily accessed with or without the imaging-guided procedure). Biopsy of a previously irradiated lesion is not permitted. Tumor biopsies should acquire a tissue cylinder that has a proper size for histological examination and biomarker analyses. The fine needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable as fresh tumor biopsies.
23. **Biomarker assessment from blood samples.** Blood samples will be collected from all participants for mutation profiling of the ctDNA by NGS. Additional biomarker analysis from blood samples (as appropriate to the tumor mutation status or histology) may be conducted by other assay types, such as RNA-Seq. Please refer to the Biomarker Analysis Plan and the applicable manual for details. Blood samples for biomarker assessment will be performed at pre-dose on Cycle 1 Day 1, at 3-6 h post-dose (time-matched to biopsy sampling, where applicable) on Cycle 1 Day 22, and at pre-dose on Cycle 3 Day 1 Cycle 6 Day 1 and Cycle 9 Day 1 for the first year and every 12 (-1) weeks, corresponding with the tumor scans, starting Cycle 13 thereafter. In addition, the blood tumor biomarker assessment will be performed at the EoT Visit (only if the assessment has not been done within 4 weeks before the EoT Visit).
24. **Dispensing of study treatments:** Study treatments will be dispensed on Day 1 of every cycle (the first year) and on Day 1 of every 3rd cycle thereafter.
25. **Study treatment accountability:** On all visits to the study center after the initiation of the study treatments and up to the end of the study treatments, participants will be asked to bring their study treatment with them to the clinic so their study treatment compliance may be reviewed with them.
26. **Long-term Follow-up (LTFU)** visits will be performed via phone call every 3 months ( $\pm 7$  days) for 12 months after the last dose of study treatment, except for participants who started new anticancer treatment, died, were lost to follow up, or withdrew consent. The LTFU calls will obtain the information necessary for the DOR and progression-free survival (PFS) endpoints. In addition, the LTFU calls will report the treatment-related SAEs and participant's death due to any cause, if the site becomes aware of these events.
27. **Administration of study treatments:** Mirdametinib and brimrafenib (BGB-3245) will be administered daily on the continuous schedule in 28-day cycles. Of note: all visits are based on Cycle 1 Day 1, not previous cycle. See [Section 8.2](#) for study treatments' dosing instructions.
28. **PK assessments:** See [Table 1-2](#) and [Table 1-3](#) for details.
29. The acceptable window for the visit scheduled on Day 1 of Cycle 2 is "+2 days", i.e., up to 2 days after the nominal Cycle 2 Day 1 date. The window cannot be " $\pm 2$  days" so that the 28-day DLT period could not be inadvertently shortened.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

### 1.3. PART 1 PHARMACOKINETIC AND ECG SAMPLING

**Table 1-2: Part 1 Pharmacokinetic and ECG Sampling**

Visit	Day	Timepoint <sup>1, 2, 4</sup>	PK sampling of brimarafenib	PK sampling of mirdametinib and metabolite	ECG Sampling <sup>5,6</sup>
Screening	Up to 28 days before Day 1	N/A			X <sup>7</sup>
Cycle 1 (28 Days, DLT period) <sup>3</sup>	Day 1 <sup>11</sup>	pre-dose <sup>1</sup>	X	X	X <sup>7</sup>
		1 hour post-dose	X	X	X <sup>7</sup>
		2 hours post-dose	X	X	X <sup>7,9</sup>
		4 hours post-dose	X	X	X <sup>7</sup>
	Day 22 (±2 days)	pre-dose	X	X	
		3-6 hours post-dose <sup>4,10</sup>	X	X	
Cycle 2 (28 Days)	Day 1 <sup>11</sup>	pre-dose	X	X	X <sup>7</sup>
		1 hour post-dose	X	X	X <sup>7</sup>
		2 hours post-dose	X	X	X <sup>7,9</sup>
		4 hours post-dose	X	X	X <sup>7</sup>
Cycle 3 (28 Days)	Day 1 <sup>11</sup>	pre-dose	X	X	X <sup>8,9</sup>
Cycle 5 (28 Days)	Day 1 <sup>11</sup>	pre-dose	X	X	X <sup>8,9</sup>
Cycle 7 (28 Days)	Day 1 <sup>11</sup>	pre-dose	X	X	X <sup>8,9</sup>
Cycle 9 (28 Days)	Day 1 <sup>11</sup>	pre-dose	X	X	X <sup>8,9</sup>
Cycle 11 (28 Days)	Day 1 <sup>11</sup>	pre-dose	X	X	X <sup>8,9</sup>
Cycle ≥13	Day 1	pre-dose			X <sup>8,9</sup>

Mirdametinib  
Protocol MEKRAF-AST-101SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

Visit	Day	Timepoint <sup>1, 2, 4</sup>	PK sampling of brimarafenib	PK sampling of mirdametinib and metabolite	ECG Sampling <sup>5,6</sup>
(Every 12 (-1) weeks)					
EoT Visit					X <sup>8,9</sup>
Safety FU Visit					X <sup>8,9</sup>
Dose reduction or intra- participant dose escalation	4 weeks after the start on new dose	pre-dose	X	X	

Abbreviations: DLT = dose-limiting toxicity; ECG = electrocardiogram; EoT = End of Treatment; FU= follow-up; PK = pharmacokinetic; X = to be performed at the designated visit/timepoint

**Footnotes:**

- It is important that PK sampling occurs as close as possible to the scheduled time. To achieve this, the other assessments scheduled at the same time point need to be initiated prior to or after the PK sampling to allow for the PK sampling to be taken at the scheduled time. Whenever multiple procedures coincide at the same time point, the recommended sequence of procedures at a particular time point is:
  - scheduled ECG;
  - vital sign assessments;
  - PK blood samples and
  - any other scheduled or unscheduled measurements at that time point.

**Note:** on Day 1 of Cycle 1 only, the pre-dose PK sample should be obtained after the pre-dose triplicate ECG and before dosing.
- The exact time of the PK sample collection will be noted on the source document and electronic case report form (eCRF). 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 need not be captured as a protocol deviation. Acceptable time window for PK sampling:
  - Pre-dose time points: within 1 hour prior to dosing
  - Time points between 1.0 to 4.0 hours post-dose:  $\pm 10$  minutes
- The unscheduled pre-dose PK sample is recommended at the earliest possible time after the onset of Grade  $\geq 3$  treatment-emergent AE during Cycle 1.
- Actual clock times of dosing, the biopsy collection, and the PK blood draw must be documented.
- All triplicate ECGs should be obtained as 3 standard 12-lead ECGs obtained in close succession and not more than 2 minutes apart (total of up to 4 minutes for 3 ECGs) after the participant has rested quietly in semi-recumbent or supine position for at least 5 minutes before the first ECG and during the triplicate recording. Please see the footnote '1' for the sequence of multiple assessments scheduled at the same time point. Pre-dose ECG assessment at all time points in Part 1 should be obtained within 45 minutes prior to dosing.
- Single ECG should be performed as one standard 12-lead ECG obtained after the participant has rested quietly in semi-recumbent or supine position for at least 5 minutes before the ECG and during the recording. Please see the footnote '1' for the sequence of multiple assessments scheduled at the same time point.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

7. Triplicate ECG assessments will be performed at the following time points in Part 1:
  - at screening
  - at pre-dose and 1 hr, 2 hr and 4 hr post-dose ( $\pm 10$  minutes) on Day 1 of Cycle 1
  - at pre-dose and 1 hr, 2 hr and 4 hr post-dose ( $\pm 10$  minutes) on Day 1 of Cycle 2 (within two days after the nominal Cycle 2 Day 1 date)
8. Single ECG assessments will be performed at the following time points in Part 1:
  - at pre-dose on Day 1 of Cycle 3 and every 8 (-1) weeks thereafter (first year)
  - at pre-dose on Day 1 of Cycle 13 and every 12 (-1) weeks thereafter (second year)
  - at the EoT Visit (if not done within 7 days of the EoT Visit)
  - at the Safety Follow-Up Visit.
9. Overall safety ECG assessment will be completed by the Investigator at the following time points in Part 1:
  - at 2 hr post-dose on Day 1 of Cycle 1
  - at 2 hr post-dose on Day 1 of Cycle 2
  - at pre-dose on Day 1 of Cycle 3 and every 8 (-1) weeks thereafter (first year)
  - at pre-dose on Day 1 of Cycle 13 and every 12 (-1) weeks thereafter (second year)
  - at the EoT Visit (if not done within 7 days of the EoT Visit)
  - at the Safety Follow-Up Visit.
10. The Cycle 1 Day 22 post-dose PK samples are only required for those participants having a tumor biopsy completed at Cycle 1 Day 22. If possible, PK sample should be collected at the same time (or as close to) as the post-dose biopsy collection to assess PK/pharmacodynamic correlation.
11. If a participant does not receive study treatment on Cycle 1 Day 22 or Cycle 2 Day 1, then continue to collect a single trough PK sample but not additional samples planned for that day. Do not collect additional make up samples during this cycle if Day 1 is missed due to study treatment interruption.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## 1.4. PART 2 PHARMACOKINETIC AND ECG SAMPLING

**Table 1-3: Part 2 Pharmacokinetic and ECG Sampling**

Visit	Day	Timepoint <sup>1, 2, 4</sup>	PK sampling of brimarafenib	PK sampling of mirdametinib and metabolite	ECG Sampling <sup>5,6</sup>
Screening					X <sup>7</sup>
Cycle 1 (28 Days) <sup>3</sup>	Day 1 <sup>11</sup>	pre-dose <sup>1</sup>	X	X	X <sup>7</sup>
		1 hour post-dose	X	X	X <sup>7</sup>
		2 hours post-dose	X	X	X <sup>7,9</sup>
	Day 22 ( $\pm$ 2 days) <sup>4,10</sup>	pre-dose	X	X	
Cycle 2 (28 Days)	Day 1 <sup>11</sup>	pre-dose	X	X	X <sup>7</sup>
		1 hour post-dose	X	X	X <sup>7</sup>
		2 hours post-dose	X	X	X <sup>7,9</sup>
Cycle 4-12 (every 8 (-1) weeks)		pre-dose			X <sup>8,9</sup>
Cycle $\geq$ 13 (every 12 (-1) weeks)		pre-dose			X <sup>8,9</sup>
EoT Visit					X <sup>8,9</sup>
Safety FU Visit					X <sup>8,9</sup>

Abbreviations: ECG = electrocardiogram; EoT = End of Treatment; FU= follow-up; PK = pharmacokinetic; X = to be performed at the designated visit/timepoint

### Footnotes:

1. It is important that PK sampling occurs as close as possible to the scheduled time. To achieve this, the other assessments scheduled at the same time point need to be initiated prior to or after the PK sampling to allow for the PK sampling to be taken at the scheduled time. Whenever multiple procedures coincide at the same time point, the recommended sequence of procedures at a particular time point is:

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

- a. scheduled ECG;
  - b. vital sign assessments;
  - c. PK blood samples and
  - d. any other scheduled or unscheduled measurements at that time point.
- Note:** on Day 1 of Cycle 1 only, the pre-dose PK sample should be obtained after the pre-dose triplicate ECG and before dosing.
2. The exact time of the PK sample collection will be noted on the source document and eCRF. 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 need not be captured as a protocol deviation. Acceptable time window for PK sampling:
  - a. Pre-dose time points: within 1 hour prior to dosing;
  - b. Time points at 1.0 and 2.0 hours post-dose:  $\pm 10$  minutes;
3. The unscheduled pre-dose PK sample is recommended at the earliest possible time after the onset of Grade  $\geq 3$  treatment-emergent AE during Cycle 1.
4. Actual clock times of dosing, the biopsy collection, and the PK blood draw must be documented.
5. Triplicate ECG should be performed as 3 standard 12-lead ECGs obtained in close succession and not more than 2 minutes apart (total of up to 4 minutes for 3 ECGs) after the participant has rested quietly in semi-recumbent or supine position for at least 5 minutes before the first ECG and during the triplicate recording. Please see the footnote '1' for the sequence of multiple assessments scheduled at the same time point.
6. Single ECG should be performed as one standard 12-lead ECG obtained after the participant has rested quietly in semi-recumbent or supine position for at least 5 minutes before the ECG and during the recording. Please see the footnote '1' for the sequence of multiple assessments scheduled at the same time point.
7. Triplicate ECG should be performed at the following time points in Part 2:
  - at screening
  - at pre-dose, 1 hr and 2 hrs post-dose ( $\pm 10$  minutes) on Day 1 of Cycle 1
  - at pre-dose, 1 hr and 2 hrs post-dose ( $\pm 10$  minutes) on Day 1 of Cycle 2
8. Single ECG assessments will be performed at the following time points in Part 2:
  - at pre-dose on Day 1 of Cycle 4 and every 8 (-1) weeks thereafter (first year)
  - at pre-dose on Day 1 of Cycle 13 and every 12 (-1) weeks thereafter (second year)
  - at the EoT Visit (if not done within 7 days of the EoT Visit)
  - at the Safety Follow-Up Visit
9. Overall safety ECG assessment will be completed by the Investigator at the following time points in Part 2:
  - at 2 hr post-dose on Day 1 of Cycle 1
  - at 2 hr post-dose on Day 1 of Cycle 2
  - at pre-dose on Day 1 of Cycle 4 and every 8 (-1) weeks thereafter (first year)
  - at pre-dose on Day 1 of Cycle 13 and every 12 (-1) weeks thereafter (second year)
  - at the EoT Visit (if not done within 7 days of the EoT Visit)
  - at the Safety Follow-Up Visit.
10. The Cycle 1 Day 22 PK samples are only required for those participants having a tumor biopsy completed at Cycle 1 Day 22. If possible, PK sample should be collected at the same time (or as close to) as the biopsy collection to assess PK/pharmacodynamic correlation.
11. If a participant does not receive study treatment on Cycle 1 Day 22 or Cycle 2 Day 1, then continue to collect the trough PK sample but not additional samples planned for that day. Do not collect additional make up samples during this cycle if Day 1 is missed due to study treatment interruption.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## 2. TABLE OF CONTENTS

1.	PROTOCOL SUMMARY .....	4
1.1.	Synopsis .....	4
1.2.	Schedule of Assessments .....	16
1.3.	Part 1 Pharmacokinetic and ECG Sampling .....	22
1.4.	Part 2 Pharmacokinetic and ECG Sampling .....	25
2.	TABLE OF CONTENTS .....	27
3.	LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS .....	33
4.	INTRODUCTION .....	39
4.1.	Background .....	39
4.2.	BRAF Inhibitors .....	40
4.2.1.	Brimarafenib – Pan-RAF Dimer Inhibitor .....	41
4.2.1.1.	Nonclinical Information .....	41
4.2.1.2.	Current Clinical Experience with Brimarafenib as Monotherapy .....	41
4.3.	MEK Inhibitors .....	43
4.3.1.	Mirdametinib (PD-0325901) – MEK inhibitor .....	43
4.3.1.1.	Prior clinical experience with mirdametinib as monotherapy .....	43
4.3.1.2.	Current Clinical trials with Mirdametinib monotherapy .....	43
4.4.	Benefits and risks of combining brimarafenib and mirdametinib .....	44
5.	OBJECTIVES AND ENDPOINTS .....	46
6.	INVESTIGATIONAL PLAN .....	48
6.1.	Overall Study Design .....	48
6.1.1.	Part 1 (Phase 1 dose escalation) .....	49
6.1.1.1.	Starting dose and dose-escalation rules .....	50
6.1.1.2.	Pharmacodynamic Expansion Cohort .....	54
6.1.1.3.	Tumor Biopsy .....	54
6.1.2.	Part 2 (Phase 2 dose expansion) .....	54
6.1.2.1.	Part 2 Design and Sample Size .....	55
6.1.2.2.	Part 2 Interim Analysis .....	56
6.1.2.3.	Tumor Biopsy .....	57

Mirdametinib  
Protocol MEKRAF-AST-101SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

6.2.	Scientific Rationale for Study Design.....	57
6.2.1.	Rationale for Combination of Brimarafenib and Mirdametinib in the Treatment of Human Malignancies .....	57
6.3.	Rationale for Dose Selection.....	58
6.3.1.	Rationale for the Starting Dose of Mirdametinib.....	58
6.3.2.	Rationale for the starting dose of Brimarafenib .....	59
6.4.	Dose-Limiting Toxicity Definition .....	61
6.5.	End of Study Definition .....	62
7.	STUDY POPULATION .....	63
7.1.	Inclusion Criteria.....	63
7.2.	Exclusion Criteria .....	66
7.3.	Lifestyle Considerations .....	68
7.3.1.	Meals and Dietary Restrictions .....	68
7.4.	Screen Failures .....	68
8.	STUDY TREATMENT .....	69
8.1.	Dosage, Formulation, Packaging, and Handling.....	69
8.2.	Administration .....	69
8.3.	Preparation/Handling/Storage/Accountability .....	70
8.4.	Study Treatment Compliance.....	70
8.5.	Overdose .....	71
8.6.	Concomitant Medications and/or Procedures .....	71
8.6.1.	Prohibited or Restricted Concomitant Medications and Therapy .....	71
8.6.2.	Prior and Concurrent Radiotherapy .....	73
8.6.3.	Guideline for COVID-19 Vaccination.....	74
8.7.	Dose Modification.....	74
8.7.1.	Mirdametinib Dose Reduction Guidelines.....	75
8.7.2.	Brimarafenib Dose Reduction Guidelines .....	75
8.7.3.	Requirements for Continuation of the Study Treatments Post Cycle 1 .....	85
8.8.	Intervention After the End of the Study.....	85
9.	DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL .....	86

Mirdametinib  
Protocol MEKRAF-AST-101SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

9.1.	Replacement of Participants in Study .....	86
9.2.	Lost to Follow Up .....	87
10.	STUDY ASSESSMENTS AND PROCEDURES .....	88
10.1	Screening.....	89
10.1.1.	Demographic Data and Medical History .....	89
10.1.2.	Females of Childbearing Potential and Contraception .....	90
10.2.	Tumor Response Evaluation .....	90
10.2.1.	Treatment beyond disease progression .....	90
10.2.2.	Central review of tumor assessment scans.....	90
10.3.	Safety Assessments .....	91
10.3.1.	Vital Signs.....	91
10.3.2.	Physical Examinations and Eastern Cooperative Oncology Group Performance Status.....	91
10.3.3.	Laboratory Safety Tests .....	91
10.3.4.	Electrocardiograms .....	92
10.3.5.	Ophthalmology Examination .....	92
10.3.6.	Creatine Phosphokinase (CPK) Elevation .....	93
10.3.7.	Left Ventricular Ejection Fraction (LVEF) Assessment.....	93
10.4.	Adverse Events and Serious Adverse Events .....	93
10.4.1.	Time Period and Frequency for Collecting AE and SAE Information .....	94
10.4.2.	Method of Detecting AEs, AESIs, Special Situations, and SAEs .....	94
10.4.3.	Follow-up of AEs, AESIs, Special Situations, and SAES .....	94
10.4.4.	Regulatory Reporting Requirements for SAEs .....	94
10.4.5.	Pregnancy.....	95
10.4.6.	Adverse Events of Special Interest .....	96
10.4.6.1.	Adverse Events of Special Interest (AESI) for Brimarafenib.....	96
10.4.6.2.	Adverse Events of Special Interest (AESI) for Mirdametinib .....	97
10.5.	Pharmacokinetic Assessments .....	98
10.6.	Biomarker Assessments .....	98
10.7.	Visit Windows.....	100
10.8.	Unscheduled Visits .....	100

Mirdametinib  
Protocol MEKRAF-AST-101SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

10.9.	Site Closure .....	100
10.10.	Study Termination.....	100
11.	STATISTICAL CONSIDERATIONS.....	102
11.1.	Sample Size Considerations.....	102
11.1.1.	Part 1 .....	102
11.1.2.	Part 2 .....	102
11.2.	Populations for Analyses .....	103
11.3.	Safety Analysis .....	103
11.4.	Efficacy Analysis .....	104
11.5.	Pharmacokinetic and Pharmacodynamic Analyses.....	104
11.6.	Handling Missing Data .....	104
11.7.	Interim Analyses .....	104
12.	STUDY COMMITTEES AND COMMUNICATION.....	105
12.1.	Study Monitoring: Cohort Management Committee .....	105
	SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS .....	106
	APPENDIX 1. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS.....	106
A1-1.	REGULATORY AND ETHICAL CONSIDERATIONS .....	106
A1-2.	FINANCIAL DISCLOSURE .....	107
A1-3.	INFORMED CONSENT PROCESS.....	107
A1-4.	DATA PROTECTION.....	107
A1-5.	DATA QUALITY ASSURANCE.....	108
A1-6.	SOURCE DOCUMENTS .....	108
A1-7.	STUDY AND SITE CLOSURE.....	109
	APPENDIX 2. RECIST CRITERIA V1.1 .....	110
	APPENDIX 3. SAFETY ASSESSMENTS .....	113
A3-1.	CLINICAL LABORATORY TESTS.....	113
A3-2.	EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE .....	116
A3-3.	QT INTERVAL (QTC) PROLONGATION RISK .....	116
A3-4.	CKD-EPI CREATININE EQUATION (2021) NATIONAL KIDNEY FOUNDATION (CKD-EPI CREATININE EQUATION, 2021).....	116

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

APPENDIX 4. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING .....	118
A4-1. DEFINITIONS .....	118
A4-1.1. Adverse Event (AE) .....	118
A4-1.2. Adverse Events of Special Interest (AESI) .....	119
A4-1.3. Serious Adverse Event (SAE) .....	119
A4-1.4. Special Situations .....	120
A4-1.5. Adverse Drug Reaction (ADR), Serious Adverse Reaction (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR) .....	121
A4-2. RECORDING, EVALUATING AND FOLLOW-UP .....	121
A4-2.1. Recording AEs / AESIs / SAEs / Special Situations / Pregnancy .....	121
A4-2.2. Evaluating AEs / AESIs / SAEs / Special Situations .....	122
A4-2.2.1. Severity .....	122
A4-2.2.2. Causality .....	122
A4-2.3. Follow Up .....	123
A4-3. REPORTING .....	124
APPENDIX 5. CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION .....	125
A5-1. WOMEN OF CHILDBEARING POTENTIAL (WOCBP) DEFINITION .....	125
A5-2. CONTRACEPTION GUIDANCE .....	126
A5-3. COLLECTION OF PREGNANCY INFORMATION .....	127
APPENDIX 6. LIST OF CONTACTS FOR STUDY .....	128
A6-1. SPONSOR .....	128
A6-2. CONTRACT RESEARCH ORGANIZATION .....	128
A6-3. MEDICAL MONITORING .....	128
A6-4. SERIOUS ADVERSE EVENT REPORTING .....	128
APPENDIX 7. ADVERSE EVENT MANAGEMENT GUIDELINES .....	129
A7-1. SKIN CARE RECOMMENDATIONS FOR ALL PARTICIPANTS .....	129
A7-2. DIARRHEA CARE RECOMMENDATION FOR ALL PARTICIPANTS .....	132
13. REFERENCES .....	133

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## LIST OF TABLES

Table 1-1: Schedule of Assessments for Dose Escalation (Part 1) and Dose Expansion (Part 2) .....	16
Table 1-2: Part 1 Pharmacokinetic and ECG Sampling.....	22
Table 1-3: Part 2 Pharmacokinetic and ECG Sampling.....	25
Table 3-1: Abbreviations and Specialist Terms .....	33
Table 6-1: Mirdametinib + Brimarafenib Dose Escalation .....	51
Table 6-2: Dose Escalation/De-Escalation Rule for the BOIN Design .....	53
Table 6-3: Stopping Criteria.....	56
Table 6-4: Comparison of Starting Dose with the Respective Maximum Tolerated Dose and Recommended Phase 2 Dose for Each Agent.....	60
Table 8-1: Study Treatments Administered .....	69
Table 8-2: Mirdametinib Dose Reduction.....	75
Table 8-3: Brimarafenib Dose Reduction .....	75
Table 8-4: Guideline for Mirdametinib and Brimarafenib Treatment Modification for Related TEAE .....	76
Table 10-1: AESI for Brimarafenib .....	96
Table 10-2: AESI for Mirdametinib.....	97
Table A3-1: Clinical Laboratory Panels.....	114
Table A7-1: Management Strategies for Skin AEs.....	129
Table A7-2: Guidelines for Treatment Modification for Related Dermatological TEAE.....	130
Table A7-3: CTCAE Scale for Rash Acneiform .....	131
Table A7-4: CTCAE Scale for Rash Maculopapular .....	131

## LIST OF FIGURES

Figure 6-1: Dose Escalation Plan .....	49
Figure 6-2: Alternate Dose Exploration Examples.....	52

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

### 3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

**Table 3-1: Abbreviations and Specialist Terms**

Abbreviation or specialist term	Explanation
ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AR	Adverse Reaction
ARAF	A-Raf proto-oncogene serine/threonine kinase
AST	Aspartate aminotransferase
AUC	Area under the curve
BID	Twice daily
BOIN	Bayesian optimal interval
BOP2	Bayesian Optimal Interval Phase 2
BP	Blood pressure
BRAF	v-Raf murine sarcoma viral oncogene homolog B
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

Abbreviation or specialist term	Explanation
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CLIA	Clinical Laboratory Improvement Amendments
C <sub>max</sub>	Maximum concentration
CMC	Cohort Management Committee
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CR	Complete Response
CRAF	Raf-1 proto-oncogene serine/threonine kinase (see also RAF1)
CRC	Colorectal cancer
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
DLT	Dose-limiting toxicity
DOR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

Abbreviation or specialist term	Explanation
eCRF	Electronic case report form
EDC	Electronic Data Capture
EoT	End of treatment
EPO	Erythropoietin
ERK	Extracellular signal-regulated kinase
FDA	United States Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FU	Follow-up
GCP	Good clinical practice
GCSF	Granulocyte-colony stimulating factor
GGT	Gamma-glutamyl transferase
GMCSF	Granulocyte-macrophage colony-stimulating factor
HDPE	High density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
HRAS	Harvey rat sarcoma viral oncogene homolog
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

Abbreviation or specialist term	Explanation
IF	Immunofluorescence
IHC	Immunohistochemistry
INR	International Normalized Ratio
IRB	Institutional Review Board
ISC	Independent Safety Committee
KRAS	Kirsten rat sarcoma viral oncogene homolog
LD	Longest diameter
LTFU	Long-term follow-up
LVEF	Left ventricular ejection fraction
MAPK	Mitogen-Activated Protein Kinase
MAPK1	Mitogen-Activated Protein Kinase 1
MAP2K1	Mitogen-Activated Protein Kinase Kinase 1
MAP2K2	Mitogen-Activated Protein Kinase Kinase 2
MCV	Mean corpuscular volume
MEK	Mitogen Activated Protein Kinase Kinase
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
MUGA	Multigated Acquisition
NF1	Neurofibromatosis Type I
NGS	Next generation sequencing
NRAS	Neuroblastoma RAS viral oncogene homolog

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

Abbreviation or specialist term	Explanation
NSCLC	Non-small cell lung cancer
OCT	Optical coherence tomography
ORR	Objective Response Rate
PD	Progressive Disease
PD <sub>x</sub>	Pharmacodynamic
pERK	Phosphorylated ERK
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PN	Plexiform neurofibromas
PoC	Proof of Concept
PR	Partial Response
PT	Preferred Term
QD	Once a day
QOD	Every other day
QTcF	corrected QT interval by the Fridericia formula
RAF1	Raf-1 proto-oncogene serine/threonine kinase (see also CRAF)
RAS	Rat sarcoma virus
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors
RP2D	Recommended Phase 2 dose

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

Abbreviation or specialist term	Explanation
RSI	Reference safety information
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SD	Stable disease
SoA	Schedule of Assessments
SOC	System Organ Class
Spry	Sprouty proteins
SUSAR	Suspected unexpected serious adverse reaction
TBIL	Total bilirubin
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Women of Child-Bearing Potential

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## 4. INTRODUCTION

### 4.1. BACKGROUND

Cancer is one of the leading causes of death worldwide. Based on the GLOBOCAN estimates, an estimated 19.3 million new cancer cases (18.1 million excluding nonmelanoma skin cancer) and almost 10.0 million cancer deaths (9.9 million excluding nonmelanoma skin cancer) occurred in 2020 ([Sung et al. 2021](#)). A large percentage of cancer patients are diagnosed with advanced disease and are considered to be incurable by surgery and/or radiation. Despite chemotherapy advances, the development of agents targeted at the molecular level, and most recently the impact of checkpoint inhibitors, the prognosis of patients with advanced cancer remains poor. Consequently, there is a persisting and urgent medical need to develop new therapies to increase survival without causing unacceptable toxicity.

The rat sarcoma virus (RAS)-RAF-mitogen activated protein kinase (MAPK)-extracellular signal-regulated kinase (ERK) kinase signaling cascade is among the most frequently mutated pathways in human cancer ([Dankner et al. 2018](#)). Constitutive activation of the MAPK pathway has been reported in >30% of primary tumor cell lines including cell lines derived from colon, lung, breast, pancreas, ovary, and kidney ([Hoshino et al. 1999](#)). RAS mutations occur in approximately 19% of all cancer patients, with Kirsten rat sarcoma viral oncogene homolog (KRAS) accounting for 75% of Ras mutant cancers, with the neuroblastoma RAS viral oncogene homolog (NRAS) accounting for 17% and Harvey rat sarcoma viral oncogene homolog (HRAS) accounting for 7% of these cancers. ([Prior, Hood, and Hartley 2020](#)). In the United States this implies there are ~200,000 KRAS patients and ~44,000 NRAS patients newly diagnosed per year. The frequency of these mutations varies by organ with KRAS being the most common across most solid tumors, with NRAS being most common in melanoma, thyroid, and hematologic malignancies ([Prior, Hood, and Hartley 2020](#)). Within KRAS, the majority of the mutations occur in the Switch 1 region, at codon 12 or codon 13 (G12x and G13x) with the most common allele mutations being D, V, and C. The Switch 1 region is where the RAF proteins bind to activated RAS. NRAS mutations most commonly occur in the Switch 2 region, at codon 61 (Q61x) with the most common allele mutations being R, L, H, and K ([Li, Balmain, and Counter 2018](#)). The Switch 2 region has been shown to be primarily involved with non-MAPK effector proteins, such as PI3K which ultimately phosphorylates pAKT which can cause oncogenic proliferation in the absence of MAPK activation ([Moodie et al. 1995](#)).

Discovery of covalent inhibitors of the KRAS<sup>G12C</sup> residue that blocks RAS-RAF effector interaction in the KRAS<sup>G12C</sup> mutant cells has led to meaningful clinical benefit of this class of inhibitors and the first United States Food and Drug Administration (FDA) approval of sotorasib (Lumakras<sup>®</sup>) for the treatment of adult patients with non-small cell lung cancer (NSCLC) harboring the KRAS<sup>G12C</sup> genetic mutation who have received at least one prior systemic therapy. However, effective therapies targeting other non-G12C KRAS mutations remain an urgent medical need.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

The proposed study MEKRAF-AST-101 will investigate the novel combination of a pan-RAF inhibitor brimarafenib with a mitogen activated protein kinase kinase (MEK) inhibitor mirdametinib in patients with advanced refractory solid cancers harboring MAPK pathway mutation(s). This therapeutic strategy focuses on maximizing inhibition of MEK phosphorylation with mirdametinib and with brimarafenib acting to inhibit feedback loops deemed responsible for increasing MAPK signaling. Combination activity attained by this dual inhibition of RAF dimers and MEK may lead to deeper inhibition of the oncogenic pathway and provide more durable antitumor activity. The dose escalation portion of the study will seek to explore the safety, tolerability, and preliminary anti-tumor activity of the combination. The dose expansion portion will focus on assessing clinical anti-tumor activity in patients with NRAS mutated melanoma, KRAS mutated NSCLC, and NSCLC or melanoma patients with v-Raf murine sarcoma viral oncogene homolog B (BRAF) class II, III, or fusion mutations.

## 4.2. BRAF INHIBITORS

BRAF is a member of the RAF kinase family of mammalian cytosolic serine/threonine kinases, which transduces signals downstream of RAS via the MAPK pathway. Approximately 50% of melanoma patients possess a druggable hotspot V600E/K mutation in the B-RAF protein kinase. FDA approved combination therapies of BRAF and MEK inhibitors are available that provide survival benefits to patients with a BRAF V600 mutation.

As next generation sequencing becomes increasingly used in clinical practice, oncologists are frequently identifying non-V600 BRAF mutations in their patient's tumors but are uncertain of viable therapeutic options that could be employed for optimal treatment. Non-V600 BRAF mutants are found in many cancers and are more prevalent than V600 mutations in certain tumor types. For example, between 50% to 80% of BRAF mutations in NSCLC and 22% to 30% in colorectal cancer (CRC) encode for non-V600 mutants. From recent studies, a new classification system is emerging for BRAF mutations based on biochemical and signaling mechanisms associated with these mutants ([Dankner et al. 2018](#)). Class I BRAF mutations, as exemplified by V600E, signal as RAS-independent monomers. Class II BRAF mutations function as RAS-independent activated dimers. and Class III BRAF mutations are kinase impaired but increase signaling through the MAPK pathway due to enhanced RAS binding and subsequent CRAF activation. These 3 distinct classes of BRAF mutations predict response to targeted therapies and have important implications for future drug development ([Dankner et al. 2018](#)).

First-generation BRAF inhibitors, including vemurafenib, encorafenib, and dabrafenib, have several limitations including:

1. Development of resistance through secondary mutations in key elements of the MAPK pathway and other mechanisms leading to MAPK reactivation or alternative survival pathways;

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

2. Development of keratoacanthomas or cutaneous squamous cell carcinomas due to increased activation of MAPK signaling through induction of BRAF/CRAF heterodimers; and
3. Not effective toward Class II or Class III BRAF mutations or tumors with other MAPK aberrations in the MAPK pathway including KRAS/NRAS mutations and neurofibromatosis type I (NF1) mutations.

Therefore, a pan-RAF dimer inhibitor that can improve over the first-generation BRAF inhibitors in the above-mentioned aspects would be highly desirable.

#### **4.2.1. Brimarafenib – Pan-RAF Dimer Inhibitor**

Brimarafenib (BGB-3245) is a second-generation BRAF inhibitor that has demonstrated potent inhibitory activity against the RAF family of serine/threonine kinases. It is a molecularly targeted therapeutic agent for the treatment of cancers with aberrations in the MAPK pathway, including BRAF mutations and KRAS/NRAS/HRAS mutations as either monotherapy or in combination with other cancer therapies.

Brimarafenib is differentiated from current registered agents that target RAF kinases in the following aspects:

- Brimarafenib inhibits RAF dimers with nanomolar potency and targets non-V600E BRAF mutations and BRAF/MEK inhibitor-resistant tumors.
- Brimarafenib has reduced paradoxical increase of MAPK signaling that could lead to the development of keratoacanthomas or cutaneous squamous cell carcinomas; therefore, brimarafenib has a lower risk for inducing secondary cancers.

##### **4.2.1.1. Nonclinical Information**

Brimarafenib is an orally administered, selective, and potent small-molecule inhibitor of RAF monomer and dimer kinases. A detailed description of the chemistry, pharmacology, efficacy, and safety of brimarafenib is provided in the brimarafenib (BGB-3245) Investigator's Brochure (IB).

##### **4.2.1.2. Current Clinical Experience with Brimarafenib as Monotherapy**

###### **4.2.1.2.1. BGB-3245-AU-001**

Study BGB-3245-AU-001 is ongoing as a Phase 1a/1b (dose escalation and expansion) study in participants with tumors harboring BRAF or KRAS/NRAS/HRAS mutations that are likely to respond to a RAF dimer inhibitor. As of 11 April 2023, 42 participants received brimarafenib in Study BGB-3245-AU-001 Phase 1a: 4, 12, 7, 7, 8, and 4 participants received brimarafenib at dose levels of 5, 10, 15, 25, 40 and 60 mg orally QD, respectively. In Phase 1b, 8 participants received brimarafenib: 3 and 5 participants at dose level of 40 mg orally QD in Group 1 (patients with tumor types other than CRC that harbor BRAF V600 mutations who have been treated and progressed on prior BRAF and/or MEK inhibition) and Group 2 (patients with advanced solid

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

tumors harboring a BRAF Class II mutation or a BRAF fusion mutation), respectively. Details on the study may be found in the brimarafenib (BGB-3245) IB.

As of the data cutoff date of 11 April 2023, a total of 50 participants contributed serial PK collection from participants in Study BGB-3245-AU-001. The noncompartmental PK of brimarafenib was characterized in 40 participants following single dose and multiple-dose administration of 5 mg to 60 mg QD. The preliminary PK results showed that the C<sub>max</sub> and AUC<sub>0-8h</sub> values increased in a generally dose-proportional manner from 5 mg to 40 mg. The median T<sub>max</sub> occurred at approximately 2 hours at Cycle 1 Day 1. Brimarafenib appeared to have a long terminal half-life and 5.0- and 7.3-fold average accumulation (for C<sub>max</sub> and AUC<sub>0-8h</sub>, respectively) after multiple dosing. For details on the PK, please consult the brimarafenib (BGB-3245) IB.

The maximum tolerated dose of brimarafenib in the Phase 1a portion of the study was noted to be 40 mg QD. The recommended phase 2 dose (RP2D) was not determined and is being evaluated in the Phase 1b portion of the study in patients with BRAF V600 mutations who had disease progression after prior use of BRAF ± MEK inhibitor use.

A total of 47 of 50 participants (94.0%) had at least 1 treatment-emergent adverse event (TEAE). The most common TEAEs (those occurring in > 15% of participants) were dermatitis acneiform (19 participants [38.0%]), maculopapular rash (14 participants [28.0%]), aspartate aminotransferase increased and nausea (13 participants [26.0%] each), alanine aminotransferase increased and pyrexia (12 participants [24.0%] each), dyspnoea and anaemia (11 participants [22.0%] each), abdominal pain and constipation (9 participants [18.0%] each), and fatigue and pneumonia (8 participants [16.0%] each). Details regarding overall severity and relatedness of TEAEs are described in the brimarafenib (BGB-3245) IB.

As of the data cutoff, 29 of the 50 participants (58%) had 76 treatment-emergent serious adverse events (SAEs). Details may be found in the brimarafenib (BGB-3245) IB.

There were no drug-related fatal or life-threatening AEs reported (see brimarafenib (BGB-3245) IB Section 5.2 for detailed clinical safety data).

Based on the currently available data, the main toxicities of brimarafenib include skin and subcutaneous toxicities (a class effect of RAF inhibitors), hypersensitivity described as angioedema, drug rash with eosinophilia and systemic symptoms (DRESS) and urticaria, pyrexia, increased creatine phosphokinase (CPK) levels with one case of rhabdomyolysis, myelosuppression, and changes in the liver and kidney functions. Participants on studies with brimarafenib should have prophylactic skin care management (see [Appendix 7](#)), evaluation of the skin and body temperature at every visit, as well as monitoring of the liver and kidney laboratories. In addition, CPK laboratory tests should be performed to monitor the muscular effect of the study treatment. Participants should be informed about this potential risk and encouraged to promptly report relevant symptoms and signs such as muscle pain, tenderness, and weakness with or without dark urine.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

### 4.3. MEK INHIBITORS

MAPK kinase (MEK) occupies a strategic penultimate position in the intracellular RAS-RAF-MAPK signaling cascade catalyzing the phosphorylation of its substrates, ERK1 and ERK2 (Anderson et al. 1990). No substrates for MEK have been identified other than ERK1 and ERK2 (Roskoski 2010). This constrained substrate specificity in addition to the unique ability to act as a dual specificity kinase is consistent with MEK's central role in the integration of signals into the MAPK pathway.

#### 4.3.1. Mirdametinib (PD-0325901) – MEK inhibitor

Mirdametinib (also known as PD-0325901) is an orally delivered, highly selective, small-molecule inhibitor of the dual specificity kinases, MEK1 and MEK2 (mitogen-activated protein kinase [MAPK]/ ERK). A detailed description of the chemistry, pharmacology, efficacy, and safety of mirdametinib (PD-0325901) is provided in the mirdametinib Investigators Brochure.

##### 4.3.1.1. Prior clinical experience with mirdametinib as monotherapy

Key studies with mirdametinib as monotherapy including A4481001, A4581002, and NF106 are described in detail in the mirdametinib Investigators Brochure.

##### 4.3.1.2. Current Clinical trials with Mirdametinib monotherapy

###### 4.3.1.2.1. Study MEK-NF-201 (ReNeu)

Study MEK-NF-201 (ReNeu) is an ongoing open-label, multi-center, Phase 2b study to determine the efficacy and safety of mirdametinib in adult and pediatric participants with NF1 associated inoperable Plexiform Neurofibromas (PNs). This study completed enrollment of each cohort; 58 adult and 56 pediatric participants with an inoperable PN causing significant morbidity. 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  $\geq 20\%$  as assessed by magnetic resonance imaging (MRI) assessed via independent blinded central radiologic review. Study treatment is administered orally at a dose of 2 mg/m<sup>2</sup> BID, with a maximum dose of 4 mg BID, on a 28-day Cycle (4-week course) with a 3 week on/1 week off schedule. Details on this study may be found in the mirdametinib IB.

As of the data cutoff date of 30 June 2022, 113 participants (99.1%) of the total population experienced at least 1 TEAE. A total of 108 participants (94.7%) had TEAEs that were assessed as related to treatment. Thirty-four participants (29.8%) had a  $\geq$  Grade 3 TEAE, which were considered related to treatment in 21 participants (18.4%). Serious TEAEs occurred in 12 participants (10.5%) overall, from which 1 participant (0.9%) experienced a serious TEAE assessed by investigator as related to treatment with mirdametinib.

Based on the currently available data, the main toxicities of mirdametinib (details noted in the mirdametinib IB) are consistent with its mechanism of action against MEK. Data has been accrued across multiple indications and dose levels up to 30 mg BID. These AEs include skin

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

and subcutaneous toxicities that are manageable with skin prophylaxis (see [Appendix 7](#)), gastrointestinal disorders including diarrhea that are manageable with prophylaxis and supportive care (see [Appendix 7](#)), ophthalmologic disorders including retinal vein obstruction (RVO) with blurred vision, photopsia, and halos in the vision and detached retinal pigment epithelium, cardiac symptoms including electrocardiogram (ECG) changes, congestive heart failure, and decreased left ventricular ejection fraction, nervous system abnormalities like slurred speech and confusion, and general weakness. Participants should be monitored for skin, vision, and musculoskeletal changes as well as liver, kidney, and CPK laboratories.

#### **4.3.1.2.2. Study SJ901**

Study SJ901 is an ongoing open-label Phase 1/2 study of mirdametinib in participants with pediatric low-grade glioma that is being conducted by St. Jude Children's Research Hospital (NCT04923126). This study aims to enroll 132 participants ages 2-25 years with pediatric low-grade glioma. The primary endpoint for Phase 1 is to determine the maximum tolerated dose (MTD) and the RP2D of mirdametinib dosed twice daily on a continuous schedule in this patient population. Additional Phase 1 endpoints include determination of the safety and tolerability, maximum plasma concentration and AUC of mirdametinib. Phase 2 aims to look at ORR, disease stabilization rate, and toxicity profile by cohort. Accrual of the study began in June 2021. As of 4 May 2022, eleven participants have been treated on the study: 5 on dose level 1 (DL1) at 2 mg/m<sup>2</sup> and 6 on dose level 2 (DL2) at 2.5 mg/m<sup>2</sup>. No dose-limiting toxicities (DLTs) or reportable SAEs occurred. Four participants developed grade 3 toxicities with 2 deemed treatment related including one elevated CPK at DL1 and one decreased neutrophil count at DL2. Most common grade 1 and 2 TEAEs observed were: elevated CPK (n=1), elevated aspartate aminotransferase (AST) (n=7), acneiform rash (n=6) and decreased neutrophil count (n=5). This study is currently enrolling participants at dose level 3 (3 mg/m<sup>2</sup> BID) on a continuous schedule ([Vinitsky et al. 2022](#)).

#### **4.4. BENEFITS AND RISKS OF COMBINING BRIMARAFENIB AND MIRDAMETINIB**

Evaluations of the currently available BRAF and MEK inhibitor combinations have shown greater benefit in patients with BRAF V600 mutated tumors over BRAF monotherapy. The National Comprehensive Cancer Network (NCCN) Guidelines for melanoma recommend the combinations of these targeted agents from the improvement in ORR, progression-free survival (PFS), OS, and duration of response seen with vemurafenib/cobimetinib, encorafenib/binimetinib, and dabrafenib/trametinib combination therapy over BRAF monotherapy (NCCN Guidelines V2.2023 Melanoma: Cutaneous, ([Larkin et al. 2014](#); [Dummer et al. 2022](#); [Long et al. 2014](#))). The use of combination BRAF/MEK inhibitors has also been used in other BRAF V600 mutated tumors.

The proposed study will investigate the novel combination of a pan-RAF inhibitor brimrafenib with a MEK inhibitor mirdametinib in patients with advanced refractory solid cancers harboring MAPK pathway mutation(s), including those that harbor non-V600 BRAF mutations or K/NRAS

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

mutations. Combination activity attained by this dual inhibition of RAF dimers and MEK may lead to deeper inhibition of the oncogenic pathway and provide clinical benefit in tumors that remain an unmet medical need.

There are several toxicities that need to be managed and monitored when using combinations of BRAF and MEK inhibitors. The most common include rash, arthralgia, diarrhea, nausea, pyrexia, liver enzyme abnormalities, retinopathy, and blood CPK increase, among others ([Dréno et al. 2017](#); [Dummer et al. 2022](#)). Most of these AEs are low grade and manageable. Recommendations for AE management are included in the protocol, including those related to CPK elevations with symptoms. Both the COLUMBUS and the coBRIM studies ([Dréno et al. 2017](#); [Dummer et al. 2022](#)) showed most CPK elevations were asymptomatic and were carefully monitored without drug interruption. Elevations in CPK observed with the combined administration of brimarafenib and mirdametinib to date have not been clinically significant.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## 5. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Objective	Primary Endpoint
<b>Part 1 and Part 2:</b> To evaluate the safety and tolerability of mirdametinib and brimarafenib administered as a combination in the eligible participant population.	Key safety endpoints will include incidence of treatment emergent Adverse Events (TEAEs), changes in clinical laboratory parameters, vital signs, physician examination findings, Eastern Cooperative Oncology Group (ECOG) status, electrocardiograms (ECGs), ophthalmological examinations, and echocardiogram (ECHO)/Multigated Acquisition (MUGA) scan.  TEAEs severities will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0.
<b>Part 1 only:</b> To determine the MTD and the recommended Phase 2 dose (RP2D) for mirdametinib and brimarafenib administered as a combination in the eligible participant population.	The MTD, if any, will be based on safety and tolerability during the first 28 days of treatment in Cycle 1.  The RP2D will be determined based on safety, tolerability, PK, preliminary anti-tumor efficacy and other available data.
<b>Part 2 only:</b> To determine the preliminary anti-tumor efficacy for the RP2D of mirdametinib and brimarafenib administered as a combination in the eligible participant population.	Anti-tumor efficacy as assessed by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI). Objective Response Rate (ORR) defined as the proportion of participants with complete response (CR) + partial response (PR) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1).
Secondary Objectives	Secondary Endpoints
<b>Part 1 only:</b> To determine the preliminary anti-tumor efficacy of mirdametinib and brimarafenib administered as a combination in the eligible participant population.	Anti-tumor efficacy as assessed by CT or MRI. Objective Response Rate (ORR) defined as the proportion of participants with complete response (CR) + partial response (PR) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1).

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

<b>Part 1 and Part 2:</b> To determine duration of response in participants treated with the combination of mirdametinib and brimrafenib.	Duration of response rate, defined as the time from response (CR + PR using RECIST v1.1) to disease progression and/or death.
<b>Part 1 and Part 2:</b> To determine the PK of mirdametinib and brimrafenib administered as a combination in the eligible participant population.	Plasma concentrations of mirdametinib and brimrafenib will be measured to evaluate systemic exposures (AUC, Cmax, Ctrough, and other PK parameters as data allow).
<b>Exploratory Objectives</b>	<b>Exploratory Endpoints</b>
<b>Part 2 only:</b> To determine if the combination of mirdametinib and brimrafenib delays disease progression in this participant population.	For each tumor histology in each expansion cohort, estimate of median time-to-progression.
<b>Part 1 and Part 2:</b> To detect tumor mutation/co-mutation status and correlate with anti-tumor activity.	Evaluate Next Generation Sequencing (NGS) in baseline tumor tissue.
<b>Part 1 and Part 2:</b> To detect candidate biomarkers of response and to correlate with brimrafenib + mirdametinib exposure.	Evaluate change from Baseline: <ul style="list-style-type: none"> <li>Blood circulating tumor DNA (ctDNA), tumor tissue immunohistochemistry (IHC), immunofluorescence (IF), or similar assay.</li> </ul>

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## **6. INVESTIGATIONAL PLAN**

### **6.1. OVERALL STUDY DESIGN**

This study is a Phase 1/2a open-label, multicenter, dose escalation and expansion study of mirdametinib in combination with brimarafenib in adult patients with histologically confirmed, advanced (American Joint Committee on Cancer (AJCC) Stage III or IV) metastatic or unresectable solid cancer that is refractory to or has progressed during or after at least 1 line of systemic anti-cancer therapy, or for which treatment is not available, not tolerated or refused.

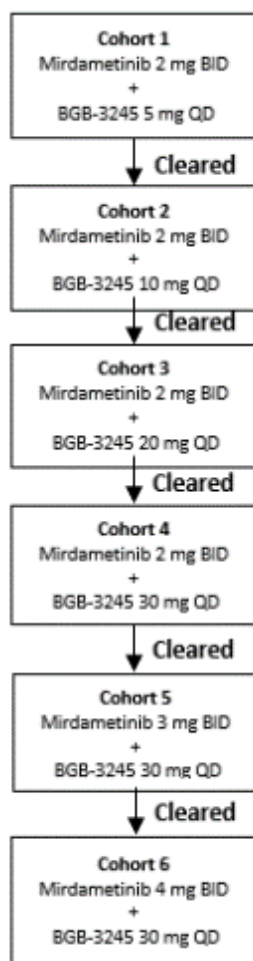
The study will be conducted in two sequential parts: Part 1 dose-escalation (Phase 1) and Part 2 dose expansion (Phase 2a). Part 1 of the study will consist of a dose-escalation and dose-finding component to establish the MTD and RP2D and to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PDx) for the combination of mirdametinib with brimarafenib. The dose of brimarafenib will start at 5 mg QD and the dose of mirdametinib will start at 2 mg BID. Part 2 will consist of a component to further evaluate the PK, safety, and tolerability of the combination of mirdametinib and brimarafenib, and to assess the preliminary antitumor activity of the combination.

Participants will receive mirdametinib and brimarafenib administered by mouth every day on a continuous schedule. Mirdametinib will be dosed twice a day (BID) and brimarafenib will be dosed once a day (QD), as shown in [Figure 6-1](#). One treatment cycle will be 28 days.

Mirdametininib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

**Figure 6-1: Dose Escalation Plan**



BID= twice daily; QD= once daily

In both parts of the study, participants must provide a baseline tumor tissue sample for the confirmation of mutational status at the central laboratory and the tumor biomarker analysis. The baseline sample may be obtained at any time before the start of the study treatments, either from the archival tumor tissue or fresh tumor biopsies. If the archival tumor is used for the baseline sample, then it should be available as a formalin-fixed paraffin-embedded (FFPE) block (preferred), or as approximately 20 FFPE unstained slides.

The tumor mutational status should be determined by the Clinical Laboratory Improvement Amendments (CLIA)-certified NGS assay of the archival tumor sample or the fresh tumor biopsy. This information may be available from historic reports obtained at any time before the start of the study treatments or from the assay at the local laboratory performed during screening.

### **6.1.1. Part 1 (Phase 1 dose escalation)**

Part 1 is a Phase 1, multicenter, open-label, multiple dose, dose-escalation study in participants with advanced metastatic or unresectable solid tumors harboring an oncogenic mutation or other

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

aberrations of the MAPK pathway. The mutations and aberrations of the MAP pathway include: a known mutation status and tumor harboring an oncogenic mutation of the v-RAF murine sarcoma viral oncogene homolog B (BRAF) gene (including BRAF Class I or V600 mutation, the BRAF Class II or non-V600 mutation that is kinase-activated, Class III mutation or non-V600 mutation that is kinase-impaired, or BRAF fusion), A-Raf proto-oncogene serine/threonine kinase [ARAF], and Raf-1 proto-oncogene, serine/threonine kinase [RAF1/CRAF]. In addition, participants with tumors harboring the mutation of NRAS, KRAS, or HRAS, NF1, mitogen-activated protein kinase kinase 1 [MAP2K1], mitogen-activated protein kinase kinase 2 [MAP2K2], and mitogen-activated protein kinase 1 [MAPK1]) are eligible for Part 1.

Participants with CRC or Pancreatic cancer that harbor KRAS mutations will be limited to approximately one third of each cohort (e.g., not to exceed 1 of 3 or 2 of 6 participants per cohort). The Cohort Management Committee (CMC) will evaluate DLTs during the first cycle consisting of the first 28 days of concurrent mirdametinib and brimarafenib treatment.

Cohort management decisions in Part 1 will be governed by the CMC ([Section 12.1](#)). The CMC meeting will be scheduled after at least 3 participants in each dose cohort become evaluable for DLT assessment. If 2 of the first 3 participants have a DLT, the CMC meeting will commence prior to the third participant completing the DLT assessment period as this meets Bayesian Optimal Interval (BOIN) criteria stopping rules. The CMC will consider the BOIN rules and all available data (safety, toxicity modeling and prediction, PK, tumor response and) from all participants treated up until the CMC meeting.

The planned sample size in Part 1 is up to 56 participants, which includes the following:

- Six dose escalation cohorts (minimum of 3 and up to 6 evaluable participants per cohort; participant is evaluable if they complete Cycle 1 or experience DLT)
- PDx Expansion Cohort (minimum of 6 and up to 20 evaluable participants).

The planned number of participants in Part 1 may be increased if deemed necessary by the Sponsor to determine MTD or RP2D.

Participants who are discontinued after the start of treatment in Part 1 (except those discontinued for safety reasons) may be replaced if this is deemed necessary by the Sponsor to accrue enough evaluable participants.

#### **6.1.1.1. Starting dose and dose-escalation rules**

The planned dose levels of mirdametinib and brimarafenib in Part 1 are shown below in [Table 6-1](#).

Mirdametinib  
Protocol MEKRAF-AST-101SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)**Table 6-1: Mirdametinib + Brimarafenib Dose Escalation**

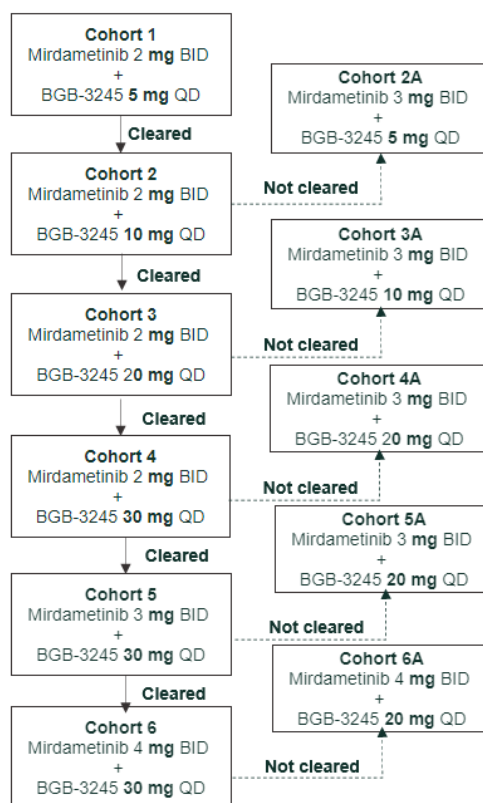
Cohort	Dosing of mirdametinib	Dosing of brimarafenib (BGB-3245)	Number of participants
1	2 mg BID	5 mg QD	3 (up to 6)
2	2 mg BID	10 mg QD	3 (up to 6)
3	2 mg BID	20 mg QD	3 (up to 6)
4	2 mg BID	30 mg QD	3 (up to 6)
5	3 mg BID	30 mg QD	3 (up to 6)
6	4 mg BID	30 mg QD	3 (up to 6)

BID= twice daily; QD= once daily

If the highest planned dose level (Cohort 6) is cleared by the CMC based on the BOIN estimate of the toxicity rate and the review of all available data in the study to that point, then the Sponsor in consultation with the CMC may continue dose escalation. The highest doses of mirdametinib will not exceed 8 mg BID and brimarafenib will not exceed 40 mg QD in Part 1.

If a planned dose level is not tolerated based on the BOIN estimate of the toxicity rate derived from the observed DLT rate, an alternate dose exploration could be implemented to identify the optimal dose ratio for the combination of agents. An alternate dose finding scheme may explore lowering of the brimarafenib dose while escalating the mirdametinib dose. The Sponsor in consultation with the CMC may explore the alternative combination dose ratio based on the review of all available data. A written data summary and interpretation of that data will be prepared by the CMC and the Sponsor to support switching to the alternate dose finding scheme.

In [Figure 6-2](#) below, an alternate dose finding scheme will decrease the dose of brimarafenib while the dose of mirdametinib will be increased. Should this dose level be tolerated based on the BOIN estimate of the toxicity rate described below in the section, doses will be escalated to achieve the MTD and/or RP2D. Should this dose level not be tolerated, the dose of brimarafenib may be further reduced, if necessary, to a minimum brimarafenib dose of 5 mg. Mirdametinib doses may be increased in 50%-100% increments in the alternate dose exploration but will never exceed 8 mg BID. Brimarafenib doses will not increase above the dose where toxicity was observed to cause the switch to the alternate dose exploration.

Mirdametinib  
Protocol MEKRAF-AST-101SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)**Figure 6-2: Alternate Dose Exploration Examples**

BID= twice daily; QD= once daily

During dose escalation, the Sponsor in consultation with the CMC may explore alternative dosing schedules to improve tolerability and facilitate the exploration of the benefit-risk ratio.

The dose escalation will employ the BOIN design to determine the MTD. The target toxicity rate used for the MTD identification is  $\phi = 0.3$ . The BOIN design will use the following rules, optimized to minimize the probability of incorrect dose assignment, to guide dose escalation/de-escalation decisions:

1. Participants in the first cohort are treated at dose level 1.
2. To assign a dose to the next cohort of participants, conduct dose escalation/de-escalation according to the rule displayed in [Table 6-2](#). When using [Table 6-2](#), please note the following:
  - a. “Eliminate” means eliminate the current and higher doses from the trial to prevent treating any future participants at these doses because they are overly toxic.
  - b. When a dose is eliminated, this will lead to an automatic de-escalation of the dose to the next lower level or an alternate dose level or schedule depending on observed toxicities. When the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

- c. If none of the actions (i.e., escalation, de-escalation, or elimination) is triggered, treat the new participants at the current dose.
- d. If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new participants at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point terminate the trial for safety.
- e. If the current dose is the highest dose and the rule indicates dose escalation, treat the new participants at the highest dose.

3. Repeat step 2 following the BOIN design until the MTD and/or RP2D is determined or stop the dose escalation part if the number of evaluable participants treated at the current dose reaches 6 and the decision according to [Table 6-2](#) is to stay at the current dose.

**Table 6-2: Dose Escalation/De-Escalation Rule for the BOIN Design**

Number of evaluable participants treated at current dose	1	2	3	4	5	6
Escalate if # of DLT $\leq$	0	0	0	0	1	1
De-escalate if # of DLT $\geq$	1	1	2	2	2	3
Eliminate if # of DLT $\geq$	NA	NA	3	3	4	4

#= number; DLT= dose-limiting toxicity; NA= not applicable

NOTE: “# of DLT” is the number of participants with at least 1 DLT. When none of the actions (i.e., escalate, de-escalate or eliminate) is triggered, stay at the current dose for treating the next cohort of participants. “NA” means that a dose cannot be eliminated before treating 3 evaluable participants.

The dose escalations rules presented in [Table 6-2](#) correspond to the following rules, optimized to minimize the probability of incorrect dose assignment, to guide dose escalation/de-escalation.

- The escalation (lower) boundary is set at 0.236 and the de-escalation (upper) boundary is set at 0.358.
- If the observed DLT rate at the current dose is  $\leq 0.236$ , escalate the dose to the next higher dose level.
- If the observed DLT rate at the current dose is  $> 0.359$ , deescalate the dose to the next lower dose level.
- If the observed DLT rate at the current dose is  $> 0.236$  and  $\leq 0.359$ , stay at the current dose.

The non-tolerable dose is defined as the dose of study treatments where the target DLT rate was exceeded. The dose escalation will be stopped either when the MTD or the non-tolerable dose is reached or the highest planned dose level of mirdametinib or brimrafenib (8 mg BID and 40 mg QD, respectively) was shown to be tolerated.

After the dose escalation is completed, the MTD will be computed using an isotonic regression as specified in ([Liu and Yuan 2015](#)). Specifically, the MTD is selected as the dose for which the isotonic estimate of the toxicity rate is less than or equal to 0.359 and closest to the target toxicity rate.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

### **6.1.1.2. Pharmacodynamic Expansion Cohort**

When the MTD or RP2D has been determined by the Sponsor in consultation with the CMC, then a PDx Expansion Cohort will be initiated. This cohort will consist of a total of 6 to 20 evaluable participants to collect additional biomarker and PDx data. This additional biomarker and PDx data will support the optimization of the RP2D dose. The PDx Expansion Cohort may be enrolled in parallel with, or before, the start of Part 2 dose expansion as determined by the Sponsor.

The participants in the PDx Expansion Cohort must meet the eligibility criteria for participants in Part 1; in addition, the participants in the PDx Expansion Cohort must provide paired fresh tumor biopsies at screening and at Cycle 1 Day 22 ( $\pm 2$  days). The participants will undergo all assessments specified in the Schedule of Assessments (SoA) ([Section 1.2](#)) for Part 1.

Participants in the PDx Expansion Cohort will be evaluable if they provide the fresh tumor biopsy at baseline (screening) and at Cycle 1 Day 22 ( $\pm 2$  days) as well as the radiological assessment of tumor response at baseline (screening) and for at least one time point after the start of study treatments.

### **6.1.1.3. Tumor Biopsy**

Fresh paired tumor biopsies in Part 1 (at screening and at Cycle 1 Day 22 [ $\pm 2$  days]) are mandatory for the participants in the PDx Expansion Cohort. Tumor biopsies may be taken only if the accessible tumor lesion is available and if the participant consented for this procedure. Tumor biopsies should be limited to readily accessible tumor lesions (i.e., skin; peripheral lymph nodes; lung, liver or internal lymph node metastases which can be readily accessed with or without the imaging-guided procedure). Fresh paired tumor biopsies (at screening and at Cycle 1 Day 22 [ $\pm 2$  days]) are recommended for participants in the Part 1 dose escalation cohorts. End of Treatment (EoT) biopsies are optional for participants in Part 1 that discontinue due to disease progression.

### **6.1.2. Part 2 (Phase 2 dose expansion)**

Part 2 is a Phase 2a multicenter, open-label dose expansion study in participants with advanced metastatic or unresectable solid tumors harboring the oncogenic mutations specific for each of the expansion cohorts. Part 2 will begin after the RP2D for the combination of mirdametinib and brimrafenib is identified in Part 1. Part 2 may start either in parallel with, or after, the conduct and analysis of the PDx Expansion Cohort in Part 1.

Part 2 will confirm the safety, tolerability, efficacy, PK, and PDx for the combination of mirdametinib and brimrafenib.

Part 2 will follow a parallel design and include one or more dose expansion cohorts, where each participant would be treated with the combination of mirdametinib and brimrafenib at the RP2D.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

The tumor mutational status should be determined by CLIA-compliant NGS assay of the archival tumor sample or the fresh tumor biopsy. This information may be available from historic reports obtained at any time before the start of the study treatments or from the assay at the local laboratory performed during screening.

One or more of the following cohorts may be opened in parallel, or sequentially at the Sponsor's discretion:

- Expansion Cohort A (n=20 evaluable participants): Participants with cutaneous melanoma harboring an NRAS mutation.
  - Minimum of 15 (75%) of the 20 participants in Cohort A must have a NRAS Q61x mutation (i.e., Q61R, Q61K, Q61L).
- Expansion Cohort B (n= 30 evaluable participants): Participants with NSCLC harboring a KRAS mutation
  - Minimum of 15 (50%) of the 30 evaluable participants in Cohort B must have a KRAS G12V mutation.
- Expansion Cohort C (n=30 evaluable participants): Participants with NSCLC or cutaneous melanoma harboring BRAF Class II or Class III mutations or BRAF fusion.
  - Cohort C1: Approximately 15 evaluable participants with NSCLC harboring BRAF Class II or Class III mutations or BRAF fusion.
  - Cohort C2: Approximately 15 evaluable participants with cutaneous melanoma harboring BRAF Class II or Class III mutations or BRAF Fusion.

Additional cohorts of up to 30 evaluable participants each with specific tumor histology and/or mutation status may be included in Part 2 expansion phase, if supported by the efficacy signals observed during the dose escalation phase.

A participant will be evaluable for Part 2 dose expansion cohort if they provide a baseline radiological tumor assessment at the Screening Visit and for at least one time point after the start of study treatment and these assessments allow an evaluation of the tumor response. The first post-treatment tumor assessment after 2 cycles will be used to assess ORR for decision making at the interim analysis. For the final analysis all post-baseline tumor assessments will be used to assess tumor response status.

#### **6.1.2.1.      Part 2 Design and Sample Size**

The planned sample size in Part 2 dose escalation is 80 evaluable participants (20 evaluable participants in Cohort A and 30 evaluable participants each in Cohorts B and C). Up to 100 participants may be treated to achieve the planned number of evaluable participants.

The sample size for the expansion cohorts is based on a Bayesian Optimal Interval Phase 2 design (BOP2) for each of the cohorts ([Zhou, Lee, and Yuan 2017](#)). There will be one interim

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

analysis in each of the 3 cohorts when 50% of the planned total sample size is evaluable for ORR and the stopping criteria at interim and final analysis will be applied as described in [Table 6-3](#). These stopping criteria are non-binding but provide guidance for decision making.

**Table 6-3: Stopping Criteria**

Cohort	LRV/TV*	Stopping criteria at interim analysis	Stopping criteria at final analysis	Overall power and 1-sided alpha=0.05
A	15%/40%	$\leq 2/10$	$\leq 5/20$	78%
B	15%/35%	$\leq 3/15$	$\leq 7/30$	78%
C	10%/30%	$\leq 2/15$	$\leq 5/30$	84%

\*LRV = Lower Reference Value; TV = Target Value. LRV is estimated for each of the cohorts from historical data as expected ORR under standard of care in the respective population ([Dummer et al. 2017a, 2017b](#); [Jänne et al. 2017](#); [Menzer et al. 2019](#)).

Further details of the BOP2 design will be described in the statistical analysis plan (SAP).

The planned number of participants in Part 2 may be increased if additional dose expansion cohorts are opened.

Participants who are discontinued after the start of treatment in Part 2 (except those discontinued for safety reasons) may be replaced if deemed necessary to accrue enough evaluable participants.

#### **6.1.2.2. Part 2 Interim Analysis**

Once ORR can be assessed in each of the dose expansion cohorts (approximately 10 evaluable participants in cohort A and 15 participants in cohort B and C the Sponsor will conduct an interim analysis (IA) of all available safety, efficacy, PK and PDx data and the stopping criteria following the BOP2 design will be assessed. Other efficacy criteria will be considered for the decision at the time of IA. Enrollment may continue in parallel until a decision about the stopping criteria is achieved.

The goal of the IA will be to determine if the anti-tumor efficacy and tolerability of study treatments administered at the RP2D meets the Sponsor's predefined criteria for the clinical proof-of-concept (PoC). If the stopping criteria at the time of the IA are not met additional participants will be enrolled and the final analysis will be repeated after the total planned number of participants become evaluable in each of the dose expansion cohorts. In addition to the stopping criteria following the BOP2 design, other efficacy endpoints such as duration of response (DOR) will be considered for the conclusion at the time of final analysis.

Based on the results of any of the interim analyses, the study may be continued, modified, or stopped by the Sponsor. The expansion cohorts may be expanded if deemed appropriate by the

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

Sponsor based on the analysis of all available safety, efficacy, PK and PDx data from that cohort and the consultation with the Regulatory Authorities (if applicable).

### **6.1.2.3. Tumor Biopsy**

Fresh paired tumor biopsies in Part 2 (at screening and at Cycle 1 Day 22 [ $\pm 2$  days]) are mandatory for at least 6 evaluable participants in Cohort A. Tumor biopsies may be taken only if the accessible tumor lesion is available and if the participant consented for this procedure. Tumor biopsies should be limited to readily accessible tumor lesions (i.e., skin; peripheral lymph nodes; lung, liver or internal lymph node metastases which can be readily accessed with or without the imaging-guided procedure). Fresh paired tumor biopsies (at screening and at Cycle 1 Day 22 [ $\pm 2$  days]) are recommended for all other participants in Part 2. EoT biopsies are optional for all participants in Part 2 that discontinue due to disease progression.

## **6.2. SCIENTIFIC RATIONALE FOR STUDY DESIGN**

### **6.2.1. Rationale for Combination of Brimarafenib and Mirdametinib in the Treatment of Human Malignancies**

Within the past decade, therapeutic agents targeting oncogenic BRAF have been developed which demonstrated superior clinical responses over the prior standard of care dacarbazine in patients with BRAF V600 mutated melanoma, thus leading to the US Food and Drug Administration's approval of 4 agents and 2 combinations regimens that target the MAPK pathway ([Larkin et al. 2014](#); [Carvajal et al. 2014](#); [Chapman et al. 2011](#); [Hauschild et al. 2012](#); [Long et al. 2014](#)). While early efforts focused on BRAF inhibitor monotherapy, resistance developed quickly in most patients with a PFS of less than 6 months for these agents ([Chapman et al. 2011](#); [Hauschild et al. 2012](#)). Insights gained from translational research highlighted MAPK reactivation as a major resistance mechanism ([Long et al. 2014](#); [Kwong et al. 2015](#)) and led to therapeutic strategies co-targeting BRAF and MEK, leading to a near doubling in PFS ([Larkin et al. 2014](#); [Long et al. 2014](#)). Resistance still develops in the majority of patients, though a small fraction achieve long-term disease control ([Flaherty, Robert, et al. 2012](#); [Flaherty, Infante, et al. 2012](#); [Reddy, Reuben, and Wargo 2016](#)). Due to the development of resistance with first generation BRAF inhibitors, second generation BRAF inhibitors, including RAF dimer inhibitors, combined with MEK inhibitors, could offer significant potential for improved clinical benefit in participants with refractory advanced cancers driven by MAPK pathway aberrations.

Discovery of covalent inhibitors of the KRAS<sup>G12C</sup> residue has led to the first FDA approval of sotorasib (Lumakras<sup>®</sup>) and investigation of other KRAS<sup>G12C</sup> targeting agents for the treatment of adult patients with NSCLC harboring the KRAS<sup>G12C</sup> genetic mutation ([Amgen 2021](#)). However, effective therapies that could further improve the overall survival of patients harboring KRAS<sup>G12C</sup> tumors and novel therapies targeting other non-G12C KRAS mutations remain an urgent medical need.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

Clinical benefit of a RAF dimer inhibitor in combination with a MEK inhibitor has been evaluated in participants with advanced solid tumors, and emerging data supports clinical activity of the combination in tumors that harbor MAPK pathway mutations. Naproraafenib (also known as LXH254), a type II RAF inhibitor that selectively inhibits both BRAF and CRAF, was used in combination with the MEK inhibitor trametinib for the treatment of participants with KRAS/BRAF-mutated NSCLC and NRAS-mutated melanoma (De Braud et al. 2022). In the dose expansion cohort, an ORR of 30% (9/30) was reported in NRAS-mutated melanoma participants treated with 200 mg BID naproraafenib + 1.0 mg QD trametinib, or 400 mg BID naproraafenib + 0.5 mg QD trametinib, respectively, with a median PFS of 5.03 months (CI 3.42-5.62). Similarly, combination therapy with the pan-RAF inhibitor belvarafenib and the MEK inhibitor cobimetinib also showed clinical benefit at combination doses in participants with RAS- or RAF-mutated solid tumors. Specifically, in NRAS-mutated melanoma participants, an ORR of 26.3% (5/19) was reported with a median PFS of 7.3 months (2.20-NA) at doses of 300 mg BID belvarafenib + 20 mg QOD cobimetinib, or 200 mg BID belvarafenib + 20 mg QD cobimetinib (Kim et al. 2021). Comparable combination activity was also achieved in solid tumors that harbor BRAF Class II and III mutations. Collectively, these studies highlight the potential of combining RAF dimer inhibitors and MEK inhibitors to achieve clinical benefit in participants with MAPK mutated advanced solid tumors.

### 6.3. RATIONALE FOR DOSE SELECTION

While there is considerable evidence for safely combining MEK and RAF inhibitors in clinical trials, this study represents the first instance in which mirdametinib and brimarafenib will be co-administered to patients with advanced cancer. To date, brimarafenib has only been studied in clinical trials as a monotherapy agent. For this reason, the dose rationale for each compound will be primarily based on existing monotherapy data and the consideration for potential enhanced pharmacological activity for each in the combination.

#### 6.3.1. Rationale for the Starting Dose of Mirdametinib

The planned starting dose for mirdametinib in this study is significantly lower than the mirdametinib monotherapy MTD of 15 mg BID on a continuous schedule or its RP2D of 10 mg BID at 5 days on/2 days off schedule (study A4810010) (LoRusso et al. 2010).

The selection of the starting dose of mirdametinib in this study (2 mg BID) is based on the suppression of phosphorylated ERK (pERK) in tumor biopsies of participants with melanoma during the first-in-human study of mirdametinib in advanced cancers (A4581001) (LoRusso et al. 2010). In the Phase 1 study A4581001 in participants with advanced cancer, mirdametinib doses ranging from 1 mg QD to 30 mg BID were explored. Steady-state concentrations of mirdametinib in this study were not maintained above the IC50 for mouse xenograft tumor models at doses below 2 mg BID. In this Phase 1 study, inhibition of pERK  $\geq 60\%$  was observed in melanoma participants receiving 2 mg BID or higher and clinical evidence of objective tumor responses in melanoma participants was observed at doses ranging from 4 mg to 30 mg BID.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

However, it should be noted that the biopsies were mostly obtained around the likely C<sub>max</sub> of mirdametinib in plasma; therefore, it is possible that mirdametinib doses  $\geq 4$  mg BID may be needed for optimal, sustained pERK inhibition during a larger proportion of the 12-hour dosing interval (Section 5.1.2, Mirdametinib IB, October 2021). These data are in agreement with other studies showing that a greater extent of MAPK inhibition (and ERK phosphorylation inhibition) was associated with better responses in advanced cancers with MAPK aberrations ([Bollag Gideon et al. 2010](#)). LoRusso et al. concluded that a clinical effective dose and schedule of mirdametinib at doses between 2 mg and 10 mg BID should be explored to identify a recommended dose for long-term use of mirdametinib in participants with advanced cancer ([LoRusso et al. 2010](#)).

Currently, mirdametinib is being investigated in the ReNeu trial in patients with neurofibromatosis type 1 associated plexiform neurofibromas at a dose level of 2 mg/m<sup>2</sup> up to a maximum of 4 mg BID on a 3 week on/1 week off dosing schedule (NCT03962543). In this study, this dose of mirdametinib has been well tolerated in both pediatric and adult participants with treatment cycles of up to 24 months (see [Section 4.3.1.2.1](#)).

Mirdametinib is also currently being administered to patients ages 2-25 years of age with low grade glioma at doses ranging from 2 mg/m<sup>2</sup> to 3 mg/m<sup>2</sup> BID on a continuous dosing schedule (NCT04923126). Study accrual began in June 2021. As of 4 May 2022, eleven participants have been treated: 5 on dose level 1 (DL1) at 2 mg/m<sup>2</sup> and 6 on dose level 2 (DL2) at 2.5 mg/m<sup>2</sup>. Both dose levels on the continuous dosing schedule were tolerated and the study is currently enrolling participants at dose level 3 (3 mg/m<sup>2</sup> BID) (see [Section 4.3.1.2.2](#)).

### **6.3.2.      Rationale for the starting dose of Brimarafenib**

Brimarafenib is currently being tested as a monotherapy in a first-in-human Phase 1a/1b, open-label dose-escalation and expansion study to investigate the safety, pharmacokinetics, and anti-tumor activity of the RAF dimer inhibitor brimarafenib in patients with advanced or refractory tumors.

The PK data from the monotherapy study with brimarafenib has demonstrated generally proportional increases in exposure at doses ranging from 5 mg to 40 mg QD. The preliminary PK results showed that the C<sub>max</sub> and area under the concentration time curve from time 0 to 8 hours (AUC<sub>0-8h</sub>) values increased in a generally dose-proportional manner from 5 mg to 40 mg at steady state (60 mg cohort only had n=1 participant data at C2D1 thus was excluded from the dose-proportionality assessment). The median T<sub>max</sub> occurred at approximately 2 hours (range of median T<sub>max</sub> of 2 to 8 hours) at Cycle 1 Day 1. Brimarafenib appeared to have a long terminal half-life, but it could not be accurately determined due to insufficient sampling in the terminal elimination phase following single dosing at Cycle 1 Day 1. As a result, AUC<sub>0-∞</sub> following a single dose could not be determined. Significant accumulation was observed after multiple dosing, with the average accumulation of 5.0- and 7.3-fold for C<sub>max</sub> and AUC<sub>0-8h</sub>, respectively. Interpatient variability (coefficient of variation) at steady state was highly variable, ranging from

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

40.0% to 61.4% for C<sub>max</sub> and 37.3% to 65.2% for AUC<sub>0-8h</sub>. The exposures observed in the 5 mg QD dose level of the monotherapy trial with BGB-3245 are also approximately 3.7-fold below the estimated AUC<sub>0-24h</sub> which caused tumor regression in the A375 mouse xenograft model.

Clinical safety data in the ongoing study (BGB-3245-AU-001) participants suggests that brimarafenib is generally well tolerated at doses of 40 mg and below. The most commonly ( $\geq 20\%$ ) reported AEs included acneiform dermatitis, maculopapular rash, nausea, dyspnea, rash, alanine aminotransferase increased, and aspartate aminotransferase increased. Most of the AEs were mild or moderate in severity. There were no drug-related life threatening or fatal events reported. (See brimarafenib (BGB-3245) IB Section 5.2 for detailed clinical safety data). To monitor for any overlapping toxicities with mirdametinib, the 5 mg QD dose was chosen as the starting dose.

In summary, the collection of clinical safety, clinical PK, nonclinical toxicology, and efficacy studies support that the proposed 5 mg starting dose of brimarafenib is safe and will offer a potential benefit to the patients when combined with mirdametinib in which enhanced inhibition of the MAPK pathway is expected. As this is the first study in which brimarafenib has been combined with another agent and the first time these two compounds have been combined, the starting doses for each have been reduced at least 4-fold from their MTD levels to ensure patient safety.

**Table 6-4: Comparison of Starting Dose with the Respective Maximum Tolerated Dose and Recommended Phase 2 Dose for Each Agent**

Compound	Maximum tolerated dose (study number)	Recommended Phase 2 dose (study number)	Starting dose for current study
Mirdametinib	15 mg twice daily (A4581001)	10 mg twice daily continuous with breaks (5 days on/2 days off) (A4581001)	2 mg twice daily
Brimarafenib	$\geq 40$ mg once a day (BGB-3245-AU-001)	TBD	5 mg once a day

TBD= to be determined

Based on nonclinical and clinical safety results for mirdametinib and brimarafenib as monotherapy agents, the combination has the potential risk of overlapping toxicities. The most likely overlapping toxicities could involve the skin (primarily the maculopapular rash and acneiform dermatitis), cardiac function (primarily left ventricular ejection fraction [LVEF] decreased), and skeletal muscle injury (primarily elevated CPK). Safety assessments are described in more detail in the SoA ([Section 1.2](#)).

Guidelines for dose reduction, interruption, or discontinuation as a result of any or all of the above listed potential toxicities, are provided in [Section 8.7](#).

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

In addition to the standard monitoring of participants within this Phase 1 trial, these specific events will be assessed carefully. The Independent Safety Committee will also pay particular attention to these events in deciding dose escalation/ de-escalation steps.

#### **6.4. DOSE-LIMITING TOXICITY DEFINITION**

The incidence of DLTs will be evaluated during the first 28 days of treatment with mirdametinib and brimrafenib in Cycle 1 of Part 1.

Participants evaluable for DLT assessment in Part 1 will have received >80% of the assigned doses of both treatments in Cycle 1 (i.e., at least 23 days on treatment with both study treatments) or have experienced a DLT in Cycle 1.

The severity of DLTs will be graded according to the CTCAE v5.0.

DLT is defined as one or more of the following events occurring during the 28-day DLT assessment period in Cycle 1, with the exclusion of toxicities clearly related to disease progression or intercurrent illness.

##### **Hematologic:**

- Any Grade  $\geq 4$  hematological toxicity.
- Grade 3 neutropenia lasting >7 days.
- Febrile neutropenia (defined as absolute neutrophil count (ANC)  $< 1000/\text{mm}^3$  with a single temperature of  $> 38.3^\circ\text{C}$  ( $101^\circ\text{F}$ ) or a sustained temperature of  $\geq 38.0^\circ\text{C}$  ( $100.4^\circ\text{F}$ ) for >1 hour).
- Grade 3 thrombocytopenia with clinically significant bleeding.

##### **Non-hematologic:**

- Any death not clearly due to the underlying disease or extraneous causes and for any toxicity requiring permanent discontinuation of study treatment(s).
- Grade  $\geq 2$  RVO.
  - The term 'RVO' is not listed in the CTCAE V.5.0. The severity of RVO may be assessed according to the CTCAE grades for 'Eye Disorder, Other.'
- Grade  $\geq 3$  retinopathy (e.g., retinal detachment or serous retinopathy).
- Grade  $\geq 3$  ocular toxicities (other than RVO or retinopathy).
- Decrease in LVEF associated with Grade 2 heart failure (symptoms with moderate activity or exertion)
- Toxicity meeting all three criteria for Hy's law as follows:
  - Participants with AST or alanine aminotransferase (ALT) and total bilirubin (TBIL) baseline values within the normal range who subsequently present with

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

AST or ALT values  $>3 \times$  upper limit of normal (ULN) concurrent with a TBIL value  $>2 \times$  ULN with no evidence of hemolysis and an ALP value  $\leq 2 \times$  ULN or other findings indicating an absence of cholestasis.

- For participants with baseline ALT or AST values above the ULN, AST or ALT value  $>2 \times$  the baseline values should be used in the definition mentioned above. Note that this specific category of DLT uses ULN rather than NCI-CTCAE grade for definition.
- Grade  $\geq 3$  significant neurologic toxicity (e.g., seizure, hallucination, confusion, or delirium).
- Grade  $\geq 3$  generalized muscle weakness.
- Grade  $\geq 3$  CPK elevation associated with renal impairment (an increase of  $\geq 1.5 \times$  the participant's baseline screening creatinine or  $\geq 1.5 \times$  ULN) or associated with Grade  $\geq 2$  rhabdomyolysis.
- Grade  $\geq 3$  skin rash that did not resolve to Grade  $\leq 1$  within 7 days of initiating optimal medical and supportive care.
- Grade  $\geq 3$  non-hematologic toxicity not listed above (except alopecia).

In addition, any clinically important or persistent toxicities that are not included above may also be considered a DLT following review and discussion between the CMC and the Sponsor.

The following toxicities will NOT be considered a DLT:

- Isolated Grade 3 or higher electrolyte abnormalities that lasts up to 72 hours, is not clinically complicated (does not require hospitalization) and resolves spontaneously or responds to conventional medical interventions.
- Grade 3 nausea, vomiting, diarrhea that resolves within 3 days, in the absence of optimal medical therapy.
- Grade 3 fatigue that resolves to Grade  $\leq 1$  within 5 days.
- Grade 3 asymptomatic increases in lipase or amylase without pancreatitis that resolves in within 7 days.

Participants who experience a DLT will be managed according to the guidelines for treatment modification due to TEAEs in this protocol.

## 6.5. END OF STUDY DEFINITION

The End of Study is defined as the date of the last scheduled procedure shown in the SoA ([Section 1.2](#)) has been completed for the last participant in the study.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## 7. STUDY POPULATION

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

### 7.1. INCLUSION CRITERIA

Participants meeting all the following inclusion criteria at screening (and on day of first dosing, where applicable) will be eligible for participation in the study.

1. Able to provide informed consent and can understand and comply with the requirements of the study.
2. Male or female aged  $\geq 18$  years of age at the time of signing the informed consent form (ICF).
3. Have histologically confirmed, advanced (AJCC Stage III or IV), metastatic or unresectable solid cancer that has either not responded to or progressed during or after at least 1 line of appropriate prior systemic anti-cancer therapy including chemotherapy, immunotherapy, or appropriate targeted therapy, or for which there is no treatment available or prior standard of care therapy was not tolerated.
  - a. In Part 1, participants must have an oncogenic mutation or other genomic aberration of the MAPK pathway (e.g., known mutation status and tumor harboring an oncogenic mutation of the BRAF gene (including BRAF Class I or V600 mutation, the BRAF Class II or non-V600 mutation that is kinase-activated, Class III mutation or non-V600 mutation that is kinase-impaired, or BRAF fusion), ARAF, RAF1/CRAF, mutation of NRAS, KRAS, or HRAS, NF1, MAP2K1, MAP2K2, and MAPK1).
    - i. A maximum of 33% (e.g., 1 of 3 or 2 of 6) of the participants with CRC or Pancreatic KRAS mutations together will be enrolled per cohort.
  - b. In Part 2, participant must have the tumor histology and oncogenic mutation or genomic aberration specific to each dose expansion cohort defined below.
    - i. Expansion Cohort A: Participants with cutaneous melanoma harboring NRAS mutations. A minimum of 75% (n=15) of the participants with NRAS mutations must have a Q61x mutation (i.e., Q61R, Q61K, Q61L).
    - ii. Expansion Cohort B: Participants with NSCLC harboring a KRAS mutation. A minimum of 50% (n=15) must have a KRAS G12V mutation
    - iii. Expansion Cohort C: Participants with NSCLC or cutaneous melanoma harboring BRAF Class II or Class III mutations or BRAF Fusion mutation. Approximately 15 participants of each tumor type will be enrolled.
4. Tumor mutational status determined by a CLIA-compliant NGS assay at the local laboratory performed at any time before the start of the study treatments.
5. Able to provide archival tumor tissue or agree to a fresh tumor biopsy at screening for the confirmation of mutational status at the central laboratory and biomarkers analysis.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

- a. The archival tumor tissue sample should be available as an FFPE block (preferred) obtained at any time before the start of the study or as approximately 20 FFPE unstained slides.
  - b. Fresh paired tumor biopsies at screening and Day 22 of Cycle 1 ( $\pm 2$  days) are required for the following participants: Part 1 PDx Expansion Cohort (all participants), Part 2 Expansion Cohort A (at least 6 participants).
6. Have at least one measurable tumor lesion per RECIST 1.1 ([Eisenhauer 2009](#)). A lesion in a previously irradiated area may be considered as measurable if that lesion had a documented progression by RECIST 1.1 (see [Appendix 2](#)) between the prior radiotherapy and the tumor scan at screening. Lesions amenable only to caliper measurements are excluded.
7. Have ECOG performance status of  $\leq 2$  at screening.
8. Have adequate bone marrow function, as determined by:
  - a.  $\text{ANC} \geq 1,500/\text{mm}^3$  (Grade  $\leq 1$ ).
  - b. Platelet count  $\geq 100,000/\text{mm}^3$ .
  - c. Hemoglobin  $\geq 9.0$  mg/dL.

Note: Transfusion or growth factors are prohibited within 14 days before the start of study treatments.

9. Have adequate kidney function, as determined by:
  - a. Estimated glomerular filtration rate (eGFR)  $\geq 60$  mL/min/1.73 m<sup>2</sup> calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Grade  $\leq 1$ ).
10. Have adequate hepatic function, as determined by:
  - a. Total bilirubin  $\leq 1.5 \times \text{ULN}$  (Grade  $\leq 1$ ). Participants with a documented Gilbert's syndrome may have total bilirubin  $\leq 3 \times \text{ULN}$ .
  - b. AST  $\leq 3.0 \times \text{ULN}$  (Grade  $\leq 1$ ). Participants with documented liver metastases may have AST  $\leq 5.0 \times \text{ULN}$ .
  - c. ALT  $\leq 3.0 \times \text{ULN}$  (Grade  $\leq 1$ ). Participants with documented liver metastases may have ALT  $\leq 5.0 \times \text{ULN}$ .
  - d. Albumin level  $\geq 3.0$  g/L (Grade  $\leq 1$ ).
11. Have adequate coagulation function, as determined by:
  - a. International Normalized Ratio (INR)  $\leq 1.5 \times \text{ULN}$  (Grade  $\leq 1$ ). If the participant receives anticoagulant therapy, the INR  $> 1.5 \times \text{ULN}$  is permitted but the dose must be stable for at least 2 weeks before the start of the study treatments.
  - b. PTT  $\leq 1.5 \times \text{ULN}$ .
12. Have adequate cardiac function, as determined by:
  - a. Systolic blood pressure  $< 160$  mmHg and diastolic blood pressure  $< 100$  mmHg (Grade  $\leq 2$ ).

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

- b. LVEF  $\geq 50\%$  by MUGA or ECHO.
  - c. No clinically significant ECG waveform abnormalities.
  - d. QTcF  $\leq 470$  ms, as determined by the mean QTcF values from the ECG assessments at screening (one triplicate).
13. Have adequate glycemic control, as determined by:
- a. Fasting blood glucose level  $< 125$  mg/dL, or
  - b. Random blood glucose level  $< 200$  mg/dL.
14. Have normal serum calcium and phosphate levels (calcium level may be corrected for albumin level).
15. Have intraocular pressure  $\leq 21$  mmHg in both eyes.
16. Female participants are eligible to enroll and participate in the study if:
- a. Participant is of non-childbearing potential (i.e., physiologically incapable of becoming pregnant), including any female who:
    - i. has had a hysterectomy.
    - ii. has had a bilateral oophorectomy (ovariectomy).
    - iii. has had bilateral tubal ligation.
    - iv. is postmenopausal (total cessation of menses for  $\geq 1$  year).
  - b. If participant is not menopausal or surgically sterile, she must be willing to use highly effective birth control methods during the study and for at least 180 days after the last dose of the study treatment. (See [Appendix A5-2](#) for the list of highly effective contraception methods)
  - c. Additionally, the participant agrees not to harvest or donate eggs (ova, oocytes) for the purpose of reproduction during the treatment period and for at least 6 months after the last dose of study treatment. The Investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study treatment.
  - d. If participant is of childbearing potential, she must have a negative serum pregnancy test within 72 hours of the start of the study treatments.
17. Male participants are eligible to enroll and participate in the study if they are vasectomized or agree to use protocol-approved birth control methods (as defined in [Appendix A5-2](#)) from the signing of informed consent until 6 months after the last dose of the study treatments.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## 7.2. EXCLUSION CRITERIA

Participants meeting any of the following exclusion criteria at screening and on the day of first dosing will not be eligible for the study:

1. History (within 3 years before the start of the study treatments) or current evidence of neoplastic disease other than the cancer under study, except cervical carcinoma in situ, superficial noninvasive bladder tumors, curatively treated Stage I-II non-melanoma skin cancer, or any other previous cancer curatively treated >3 years before the start of the study treatments.
2. Current evidence of symptomatic central nervous system (CNS) metastases, leptomeningeal carcinomatosis, or untreated spinal cord compression. Asymptomatic treated brain metastases are allowed if participants are clinically stable in the judgement of the investigator.
  - a. Participants must have MRI scan of the brain or spinal regions (as applicable to the CNS involvement) at screening to confirm the stable status of the above CNS disorders.
  - b. The neurological symptoms of the above CNS disorders must have been stable without the need for steroids at doses above prednisone 5 mg QD or equivalent specifically for metastases-related symptoms  $\geq 14$  days before the start of the study treatments.
  - c. Participants must have no CNS surgery or radiation within 28 days before Cycle 1 Day 1 (except for prophylactic cranial irradiation, where indicated) and no stereotactic radiosurgery within 14 days before Cycle 1 Day 1.
3. Current evidence of Grade >1 toxicities related to prior anti-cancer therapy (excluding alopecia, anorexia, or fatigue); Grade 2 peripheral neuropathy may be allowed at the investigator's discretion.
4. History or current evidence of glaucoma or clinically significant abnormalities on the ophthalmological exam, including but not limited to cataract limiting the ability to examine the retina or any optical coherence tomography (OCT) finding that could be a significant risk factor for RVO, retinopathy or neovascular macular degeneration.
  - a. **Note:** Mild and controlled/stable age-related macular degeneration or non-proliferative diabetic retinopathy may be acceptable at the investigator's discretion after consultation with the ophthalmologist.
5. History or current evidence of an active parathyroid disorder, or of malignancy-associated Grade  $\geq 2$  hypercalcemia despite optimal remedial therapy.
6. History (within 6 months before the start of the study treatments) of clinically significant cardiac disease (New York Heart Association Class III or IV), myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident, clinically significant transient ischemic attack, symptomatic pulmonary embolism, unexplained syncope, or long QT syndrome.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

7. Concurrent neuromuscular disorder that is associated with the potential of elevated CPK (e.g., inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy).
8. History of allergy to mirdametinib or brimarafenib or components thereof, or another type of hypersensitivity that, in the opinion of the investigator, would contraindicate participation in the study.
9. History of significant toxicity related to prior RAF, MEK, or ERK inhibitor requiring discontinuation of treatments with these agents.
10. Current evidence of clinically significant bacterial, fungal, or viral infection that requires systemic therapy at the start of the study treatments.
11. Current evidence of any other severe, uncontrolled systemic disease including but not limited to clinically significant cardiovascular, pulmonary, gastrointestinal, hepatic, or renal disease.
12. Current evidence of a disorder that could reduce the ability to swallow oral dosage forms or alter absorption of orally administered drugs.
13. Current evidence of active infection with HIV, hepatitis B or hepatitis C, defined by a detectable viral load in plasma. Viral serology testing is not required for eligibility.
14. History (within 28 days before the start of the study treatments) of Grade  $\geq 2$  bleeding event.
15. History or current evidence of Immune Thrombocytopenia, Von Willebrand disease and/or other bleeding disorders including congenital or acquired platelet function defects.
16. History (within 6 months before the start of the study treatments) or current evidence of other acute or chronic medical conditions, laboratory abnormality, alcohol or drug abuse or dependence, or suicidal ideation that, in the investigator's opinion, will adversely influence compliance or the interpretation of adverse events (AEs).
17. Participant who is pregnant or breastfeeding.
18. History (within 4 weeks before the start of the study treatments) of major surgery or significant traumatic injury, as determined at the investigator's discretion or if participant is expected to require major surgery during the treatment period.  
**Note:** The 'major' surgery and 'significant' trauma are assessed at the investigator's discretion.
19. History (within 2 weeks or 5 half-lives before the start of the study treatments, whichever is shorter) of prior systemic anti-cancer therapy.  
**Note:** To mitigate the risk of thrombocytopenia, 4 weeks must have elapsed between the last dose of prior bevacizumab and the start of the study treatments.
20. History (within 2 weeks before the start of the study treatments) of systemic or ocular glucocorticoid therapy.
21. History (within 2 weeks or 5 half-lives before the start of the study treatments, whichever is shorter) of therapy with strong inhibitors or inducers of CYP3A4 enzymes, and willing to avoid these agents from the start of study treatments until the EoT Visit.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

22. History (within 4 weeks before the start of the study treatments) of receiving a live vaccine (including the intranasal flu vaccine and the monkeypox vaccine). Initial COVID-19 vaccine procedure must be completed at least 2 weeks before the start of the study treatments. COVID-19 booster shots are permissible during the trial.

**Note:** Injectable flu vaccine is permitted at any time before and during the trial.

### **7.3.            LIFESTYLE CONSIDERATIONS**

#### **7.3.1.        Meals and Dietary Restrictions**

Participants will be required to fast for 8 hours before and 2 hour after the administration of the morning dose of study treatment on serial PK sampling days (i.e., C1D1 and C2D1). Water will be allowed freely. Consumption of grapefruit and grapefruit juice, Seville oranges, pomelos, exotic citrus fruits, or grapefruit hybrids are not allowed throughout the study. No other dietary restrictions will apply.

### **7.4.            SCREEN FAILURES**

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled to study intervention. 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 (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure) for administrative reasons, or who have borderline test results, may be rescreened once. Rescreened participants should repeat all abnormal screening test and procedures

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## 8. STUDY TREATMENT

### 8.1. DOSAGE, FORMULATION, PACKAGING, AND HANDLING

**Table 8-1: Study Treatments Administered**

<b>Treatment Name</b>	Mirdametinib	Brimarafenib
<b>Type</b>	Drug	Drug
<b>Dose Formulation</b>	Capsule	Capsule
<b>Unit Dose Strength (s)</b>	1 mg 2 mg	5 mg 10 mg
<b>Dosage Level (s)</b>	See <a href="#">Table 6-1</a>	
<b>Route of Administration</b>	Oral	Oral
<b>Sourcing</b>	Sponsor will provide sites with study treatment for individual participant distribution	Sponsor will provide sites with study treatment for individual participant distribution
<b>Packaging and Labeling</b>	Study treatment will be provided in high density polyethylene (HDPE) bottles labeled with an expiry date and should be stored at 15°C to 25°C (59°F to 77°F).	Study treatment will be provided in HDPE bottles labeled with an expiry date and should be stored at 15°C to 25°C (59°F to 77°F).
<b>Former name</b>	PD-0325901	BGB-3245
<b>Ingredients</b>	Microcrystalline Cellulose Croscarmellose Sodium Magnesium Stearate Gelatin Capsule Shell Precedented Colorants	Hypromellose Acetate Succinate (HPMCAS) Microcrystalline Cellulose Mannitol Croscarmellose Sodium Talc Magnesium Stearate Gelatin Capsule Shell Precedented Colorants

### 8.2. ADMINISTRATION

Mirdametinib and brimarafenib (BGB-3245) will be administered by mouth on a continuous schedule, where mirdametinib will be dosed BID and brimarafenib will be dosed QD. See [Table 6-1](#) and [Figure 6-1](#) for the planned doses for Part 1. All cycles are based on Cycle 1 Day 1

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

of the study and not on the prior cycle. Based on the evaluation of all available study data, the Sponsor in consultation with the CMC may explore additional doses and dosing schedules to improve tolerability and facilitate the dose exploration. For example, alternative dose ratios of the two compounds or intermittent dosing schedules could be evaluated if the planned doses are not tolerated.

Based on the evaluation of all available study data, the Sponsor in consultation with the CMC will recommend the dose and dosing schedule to be used as the RP2D for mirdametinib and brimarafenib in Part 2 and the Part 1 PDx Expansion Cohort.

In both parts of the study, one treatment cycle will be 28 days. Treatment should be continued if the next visit is delayed.

### **8.3. PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY**

- Study treatments will be dispensed on Day 1 of every cycle for the first year and on Day 1 of every 3rd cycle thereafter during scheduled study visits as described in the SoA ([Section 1.2](#)) or unscheduled visits if study treatment is damaged/lost or a dose modification ([Sections 8.7](#) and [10.8](#)) is necessary.
- Participants will be instructed to keep their study treatment in the bottles provided and not transfer it to any other containers.
- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment shipments received and any discrepancies are reported and resolved before use of the study treatment.
- 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).
- Study treatment returned by the participant will not be re-dispensed.
- Further guidance and information about the handling, storage, and final disposition of unused study treatment (bottles/tablets) are provided in the respective pharmacy manuals.

### **8.4. STUDY TREATMENT COMPLIANCE**

On all visits to the study center, participants will be questioned regarding compliance with study medications. Participants will be instructed to bring the pill bottles with them to every clinic visit, where it will be reviewed for compliance by the study site staff.

The study treatment dispensing logs, and prescription records should contain the following information:

- identification of the participant to whom the study treatment was administered.
- date(s) and quantity of the study treatment administered to the participant.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

- duration, interruptions or discontinuations of each administration and corresponding quantity of the study treatment not administered to the participant.

Actual dose administered (assessed by pill count) vs planned dose will be used to assess compliance.

## **8.5. OVERDOSE**

In a suspected overdose situation, emergency and supportive care should be initiated. Any overdose or incorrect administration of study treatment should be noted on the study treatment administration electronic case report form (eCRF). AEs associated with an overdose or incorrect administration of study treatment will be recorded on the Adverse Event eCRF. If an overdose or incorrect administration of study treatment takes place, the Sponsor is required to be immediately notified (within 24 hours of awareness).

An overdose for mirdametinib would be a single dose greater than 15 mg. For brimarafenib, any dose above the expected MTD (40 mg QD) would be considered an overdose.

## **8.6. 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 informed consent and/or receives during the study through 30 days after the last dose of study treatment must be recorded along with:

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

The medical monitor/Sponsor should be contacted if there are any questions regarding concomitant or prior therapy. Refer to [Appendix A6-3](#) for the medical monitor contact information.

### **8.6.1. Prohibited or Restricted Concomitant Medications and Therapy**

The following medications are prohibited or restricted during the study:

- Prior therapy with mirdametinib or brimarafenib.
- Any systemic antineoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, or other approved or investigational agents for the treatment of cancer) within 14 days or 5 half-lives (whichever is shorter) before the start of study treatments and during the treatment period until the EoT Visit.
- Primary resection of any target lesion is prohibited within 4 weeks of Cycle 1 Day 1 and during the treatment period until the EoT Visit, unless it is necessary for the participant's clinical benefit as determined by the investigator.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

- Bisphosphonate treatment from the start of study treatments and during the treatment period until the EoT Visit. Participants who received bisphosphonate treatment before the start of study treatments may continue at the same dose of bisphosphonate during the study.
- Chronic systemic or ocular glucocorticoid therapy above prednisone 5 mg QD or equivalent corticosteroid within the 14 days before the start of study treatments and during the treatment period until the EoT Visit with the following exceptions:
  - Physiologic or stress doses of steroids, when indicated in participants with endocrine deficiencies.
  - Corticosteroids given as the premedication for blood product transfusions.
  - Corticosteroids given as the pulse treatment for an acute allergic reaction or bronchospasm.
  - Inhaled corticosteroids for asthma, allergies, and reactive airway disease.
  - Oral or intravenous corticosteroids for up to 6 consecutive days, when indicated for the management of AE (e.g., Grade  $\geq 3$  thrombocytopenia) after consultation with the medical monitor and/or ophthalmologist.
- Antibiotic therapy for active infection within 14 days before the start of study treatments.
- Platelet or blood transfusion for the treatment of thrombocytopenia within 14 days before the start of study treatments and during the DLT period (Cycle 1).
- Platelet or blood transfusion for the treatment of thrombocytopenia may be permitted at the investigator's discretion after that particular event of thrombocytopenia has been identified as DLT.
- Red blood cell (RBC) or blood transfusion or erythropoietin (EPO) for the treatment of anemia within 14 days before the start of study treatments and during the DLT assessment period (Cycle 1).
- RBC or blood transfusion for the treatment of anemia may be permitted at the investigator's discretion if the chronic anemia has been persistent within 28 days before the start of study treatments.
- EPO for the treatment of anemia may be permitted at the investigators discretion if the EPO dose has been stable within 28 days before the start of study treatments.
- Granulocyte-colony stimulating factor (GCSF)/ granulocyte-macrophage colony-stimulating factor (GMCSF) for the treatment of leukopenia/neutropenia within 14 days before the start of study treatments and during the DLT assessment period (Cycle 1).

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

- Strong CYP3A4 inhibitors and inducers within 14 days before the start of study treatments and during the treatment period until the EoT Visit.
- Substrates of CYP3A4, CYP2C8 or CYP2C9 with a narrow therapeutic range during the treatment period until the EoT Visit.
- Grapefruit and grapefruit juice, Seville oranges, pomelos, exotic citrus fruits, or grapefruit hybrids within 14 days before the start of study treatments and during the treatment period until the EoT Visit.
- Herbal remedies with a known potential to interfere with liver or other major organ functions (i.e., hypericin) or act as strong CYP3A4 inhibitor within 14 days before the start of study treatments and during the treatment period until the EoT Visit.
- Alcohol or other illicit drugs from the signing of informed consent and during the study.
- Live Vaccines (within 4 weeks before the start of the study treatments), including the intranasal flu vaccine and the monkeypox vaccine are prohibited.
- COVID-19 vaccine procedure must be completed at least 2 weeks before the start of the study treatments ([Section 8.6.3](#)).

**Note:** Injectable flu vaccine is permitted at any time before the start of the study treatments.

### 8.6.2. Prior and Concurrent Radiotherapy

- Prior radiotherapy to tumor lesion(s) that will be chosen as target lesions is prohibited within 28 days before the start of study treatments, unless the lesion(s) exhibited objective progression between the prior radiotherapy and the screening CT or MRI scan.
- Concomitant radiotherapy to tumor lesion(s) chosen as target lesions is prohibited from the start of study treatments and during the treatment period until the EoT Visit.
- CNS surgery or radiation  $\leq 28$  days is prohibited before Cycle 1 Day 1 (except for prophylactic cranial irradiation, where indicated).
- Stereotactic radiosurgery is prohibited  $\leq 14$  days before Cycle 1 Day 1.
- Prior and concomitant palliative radiotherapy to non-target tumor lesions may be allowed at the investigator's discretion at any time before the start of study treatments and during the treatment period until the EoT Visit.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

### 8.6.3.      **Guideline for COVID-19 Vaccination**

COVID-19 vaccination before the start of study treatments is not required but encouraged as oncology participants receiving systemic anticancer treatment are a vulnerable group. The following guidance is provided to facilitate the timing of vaccination and study treatment:

- Participants in screening should schedule their COVID-19 vaccination as follows:
  - If COVID-19 vaccine is administered in 2 doses, then the participant should schedule the 2<sup>nd</sup> dose at least 2 weeks before the planned start of study treatments.
  - If COVID-19 vaccine is administered in a single dose, then the participant should schedule the single dose at least 2 weeks before the planned start of the study treatments.
- COVID-19 vaccination is prohibited during the DLT period (Cycle 1).
- COVID-19 vaccination is permitted from Day 1 of Cycle 2 until the end of the study. A brief treatment hold (1-2 days before and/or after each dose of the vaccine) may be indicated at the investigator's discretion.

Any modification of the above guidelines (e.g., based on the investigator's discretion or the institutional guideline) should be discussed and agreed with the medical monitor.

## 8.7.      **DOSE MODIFICATION**

Every effort should be made to administer the study treatments according to the planned dose and schedule. In the event of significant TEAEs, the investigator may temporarily interrupt, reduce the dose or permanently discontinue one or both study treatments based on the guidelines provided in [Table 8-2](#) and [Table 8-3](#) below. Reasons for dose modification, the supportive measures taken, and the outcome will be documented in the participant's chart and recorded in the eCRF. The tumor assessment schedule will not be altered even if the administration of study treatment is delayed.

The study treatments may be re-started if the TEAE has reached satisfactory resolution per the guidelines in 14 days. The TEAE resolution to Grade 1 or baseline generally within 14 days before resuming therapy at current or reduced dose. Otherwise, treatment should be discontinued.

Dose re-escalation after the TEAE resolution is not permitted. Once a dose of the study treatment has been reduced due to a TEAE, the participant must remain on the reduced dose for the duration of the study. If there is Grade 2 toxicity at mirdametinib 2 mg QD and brimrafenib 5 mg QD, then the combination should be interrupted and resumption with monotherapy of either study treatment must be discussed with the Sponsor and medical monitor, with written approval.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

### 8.7.1. Mirdametinib Dose Reduction Guidelines

In the event a mirdametinib dose reduction is required due to a TEAE, the daily dose will be reduced as shown in [Table 8-2](#).

**Table 8-2: Mirdametinib Dose Reduction**

Dose at the time of the event	Reduced dose
2 mg QD	Discontinue mirdametinib
2 mg BID	2 mg QD
3 mg BID	2 mg BID
4 mg BID	3 mg BID

BID = twice daily; QD=once daily

Participants may undergo dose reductions to mirdametinib 2 mg QD based on their AEs. If 2 mg QD is not tolerated, the participant will be taken off study.

### 8.7.2. Brimarafenib Dose Reduction Guidelines

In the event a brimarafenib dose reduction is required due to a TEAE, the daily dose will be reduced by one dose level as shown in [Table 8-3](#).

**Table 8-3: Brimarafenib Dose Reduction**

Dose at the time of the event	Reduced dose
5 mg QD	Discontinue brimarafenib
10 mg QD	5 mg QD
20 mg QD	10 mg QD
30 mg QD	20 mg QD

QD=once daily

Participants may undergo dose reductions to brimarafenib 5 mg QD based on their AEs. If 5 mg QD is not tolerated, the participant will be taken off study.

Participants who experience a DLT in Part 1 need not be immediately discontinued from study treatments; instead, the treatment modification guideline will be applied as described in, [Table 8-2](#), and [Table 8-3](#). Dosing of other ongoing participants in that dose escalation cohort will continue unless there is reason to suspect that the benefit-risk ratio is unacceptable based on the nature and/or severity of the observed DLT.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

**Table 8-4: Guideline for Mirdametinib and Brimarafenib Treatment Modification for Related TEAE**

<b>RELATED TEAE (Worst Grade by CTCAE V. 5.0)</b>	<b>INTERVENTION</b>
<b>NEUTROPENIA (ANC DECREASE)</b>	
Grade 3 (ANC $<1.0 \times 10^9/L$ )	<p>Interrupt both mirdametinib and brimarafenib until resolution to Grade <math>\leq 1</math>, then</p> <p>If resolved to Grade <math>\leq 1</math> in <math>\leq 7</math> days, re-start mirdametinib and brimarafenib at the same dose at the investigator's discretion.</p> <p>If resolved to Grade <math>\leq 1</math> in <math>&gt;7</math> days, re-start mirdametinib and brimarafenib at the next lower dose (see <a href="#">Table 8-2</a> and <a href="#">Table 8-3</a>).</p> <p>GCSF/GMCSF are permitted at the investigator's discretion. If the GCSF/GMCSF was administered due to medical need in Cycle 1, the DLT must be declared</p>
Grade 4 (ANC $<0.5 \times 10^9/L$ )	<p>Interrupt mirdametinib and brimarafenib until resolution to Grade <math>\leq 1</math>, then</p> <p>If resolved to Grade <math>\leq 1</math> in <math>\leq 7</math> days, re-start mirdametinib and brimarafenib at the next lower dose (see <a href="#">Table 8-2</a> and <a href="#">Table 8-3</a>).</p> <p>If resolved to Grade <math>\leq 1</math> in <math>&gt;7</math> days, permanently discontinue mirdametinib and/or brimarafenib.</p> <p>GCSF/GMCSF are permitted at the investigator's discretion. If the GCSF/GMCSF was administered due to medical need in Cycle 1, the DLT must be declared where applicable.</p>
Grade 3 febrile neutropenia (ANC $<1.0 \times 10^9/L$ with a single temperature of $>38.3^\circ C$ [ $101^\circ F$ ] or a sustained temperature of $\geq 38^\circ C$ [ $100.4^\circ F$ ] for more than one hour)	<p>Interrupt mirdametinib and brimarafenib until resolution of fever and ANC resolution to Grade <math>\leq 1</math>.</p>

Mirdametininib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

	<p>After resolution to Grade <math>\leq 1</math>, re-start mirdametininib and brimarafenib at the next lower dose (see <a href="#">Table 8-2</a> and <a href="#">Table 8-3</a>).</p> <p>GCSF/GMCSF are permitted at the investigator's discretion. If the GCSF/GMCSF was administered due to medical need in Cycle 1, the DLT must be declared where applicable.</p>
Grade 4 febrile neutropenia (ANC and temperature criteria as listed above PLUS life-threatening signs or symptoms including septic shock, hypotension and/or acidosis)	Permanently discontinue mirdametininib and/or brimarafenib.
<b>THROMBOCYTOPENIA (PLATELET COUNT DECREASE)</b>	
Grade 3 thrombocytopenia (platelets $<50 \times 10^9/L$ to $\geq 25 \times 10^9/L$ )	<p>Interrupt mirdametininib and brimarafenib until resolution to Grade <math>\leq 1</math>, then</p> <p>If resolved to Grade <math>\leq 1</math> in <math>\leq 7</math> days, re-start mirdametininib and brimarafenib at the same dose at the investigator's discretion.</p> <p>If resolved to Grade <math>\leq 1</math> in <math>&gt;7</math> days, re-start mirdametininib and brimarafenib at the next lower dose (see <a href="#">Table 8-2</a> and <a href="#">Table 8-3</a>).</p> <p>Platelet transfusion is permitted at the investigator's discretion. If the transfusion was administered due to medical need in Cycle 1, the DLT must be declared where applicable.</p> <p>Concomitant use of other anti-platelet (e.g., acetylsalicylic acid, non-steroidal anti-inflammatory drugs, or other) and anti-coagulant medications (heparin, warfarin, or other) should be used with caution based on the investigator's medical judgment.</p>
Grade 4 thrombocytopenia (platelets $<25 \times 10^9/L$ )	Interrupt mirdametininib and brimarafenib until resolution to Grade $\leq 1$ , then

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

	<p>If resolved to Grade <math>\leq 1</math> in <math>\leq 7</math> days, re-start mirdametinib and brimarafenib at the next lower dose (see <a href="#">Table 8-2</a> and <a href="#">Table 8-3</a>).</p> <p>If resolved to Grade <math>\leq 1</math> in <math>&gt; 7</math> days, permanently discontinue mirdametinib and/or brimarafenib.</p> <p>Platelet transfusion is permitted at the investigator's discretion. If the transfusion was administered due to medical need in Cycle 1, the DLT must be declared where applicable.</p> <p>Concomitant use of other anti-platelet (e.g., acetylsalicylic acid, non-steroidal anti-inflammatory drugs, or other) and anti-coagulant medications (heparin, warfarin, or other) should be used with caution based on the investigator's medical judgment.</p>
<b>OCULAR</b>	
Grade 2 ocular toxicity other than RVO	<p>Either continue mirdametinib and brimarafenib at the same dose without interruption, if supported by the investigator's assessment of the benefit-risk ratio (e.g., if visual acuity impairment is nil or mild).</p> <p>Or temporarily interrupt mirdametinib and brimarafenib until resolution to Grade <math>\leq 1</math> or baseline (e.g., if visual acuity impairment is moderate).</p> <ul style="list-style-type: none"> <li>After resolution to Grade <math>\leq 1</math>, re-start mirdametinib and brimarafenib at the same dose or at the next lower dose (see <a href="#">Table 8-2</a> and <a href="#">Table 8-3</a>), depending on the investigator's assessment of the benefit-risk ratio.</li> </ul> <p>Perform ophthalmological exams at the frequency and duration determined at investigator's discretion until resolution to Grade <math>\leq 1</math> or baseline.</p>

Mirdametininib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

Grade 3 ocular toxicity (other than RVO) with reduced visual acuity limiting basic self-care activities of daily living (ADL)	<p>Temporarily interrupt mirdametininib and brimarafenib until resolution to Grade <math>\leq 1</math> or baseline.</p> <p>After resolution to Grade <math>\leq 1</math> or baseline, re-start mirdametininib and brimarafenib at the next lower dose (see <a href="#">Table 8-2</a> and <a href="#">Table 8-3</a>).</p> <p>Perform ophthalmic examination at the frequency and duration determined at investigator's discretion.</p>
Grade 4 ocular toxicity	Permanently discontinue mirdametininib and brimarafenib.
<p>Grade 2 RVO</p> <p><i>Note: The term 'RVO' is not listed among the Eye Disorders in the CTCAE V.5.0</i></p> <p><i>The severity of RVO may be assessed according to the CTCAE grades for 'Eye Disorder, Other'</i></p>	<p>Temporarily interrupt mirdametininib and brimarafenib.</p> <p>If the RVO is confirmed to be a central retinal vein occlusion (CRVO), permanently discontinue mirdametininib and brimarafenib.</p> <p>If the RVO is confirmed to involve the peripheral part of retinal vasculature, then maintain interruption of mirdametininib and brimarafenib until resolution to Grade <math>\leq 1</math>.</p> <p>After resolution to Grade <math>\leq 1</math>, either re-start mirdametininib and brimarafenib at the next lower dose (see <a href="#">Table 8-2</a> and <a href="#">Table 8-3</a>) or permanently discontinue mirdametininib and brimarafenib, depending on the investigator's assessment of the benefit-risk ratio.</p> <p>Perform ophthalmic examination at the frequency and duration determined at investigator's discretion until resolution to Grade <math>\leq 1</math>.</p>
<p>Grade 3 RVO (leading to reduced visual acuity that limits the basic self-care ADL)</p> <p><i>Note: The severity of RVO is not graded according to the CTCAE V.5.0</i></p>	<p>Permanently discontinue mirdametininib and/or brimarafenib.</p> <p>Perform ophthalmologic exams at the frequency and duration determined at investigator's discretion.</p>

Mirdametinib  
Protocol MEKRAF-AST-101SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

<i>The severity of RVO may be assessed according to the CTCAE grades for 'Eye Disorder'</i>	
<b>NEUROLOGICAL</b>	
Grade $\leq 2$ seizure / convulsion, hallucination, confusion or delirium or similar events lasting $>24$ hours AND after ruling out other possible causes.	Interrupt mirdametinib and brimarafenib until resolution to Grade $\leq 1$ .  After resolution to Grade $\leq 1$ , re-start mirdametinib and/or brimarafenib at the next lower dose (see <a href="#">Table 8-2</a> and <a href="#">Table 8-3</a> ).
Any Grade $\geq 3$ event	Interrupt mirdametinib and brimarafenib until resolution to Grade $\leq 1$ .  After resolution to Grade $\leq 1$ , the investigator may re-start mirdametinib and brimarafenib at the next lower dose (see <a href="#">Table 8-2</a> and <a href="#">Table 8-3</a> ) or permanently discontinue mirdametinib and brimarafenib, depending on the investigator's benefit-risk assessment.
<b>MUSCULOSKELETAL</b>	
Grade $\geq 3$ muscle weakness (symptomatic and interfering with ADL)	Interrupt mirdametinib and brimarafenib until resolution to Grade $\leq 1$ .  After resolution to Grade $\leq 1$ , re-start mirdametinib and brimarafenib at the next lower dose (see <a href="#">Table 8-2</a> and <a href="#">Table 8-3</a> ).
Grade $\geq 3$ CPK elevation <b>with</b> renal impairment (serum creatinine $\geq 1.5\times$ ULN or $1.5\times$ baseline)  OR  Grade $\geq 3$ CPK elevation <b>with</b> Grade $\geq 2$ rhabdomyolysis	Interrupt mirdametinib and brimarafenib until resolution to Grade $\leq 1$ or up to 28 days.  Hydrate either orally or by IV as clinically appropriate. Monitor and measure isoenzymes (CPK1, 2, and 3 fractions) and myoglobin in blood or urine. Monitor closely for myositis, pain, and weakness.  After resolution to Grade $\leq 1$ , re-start mirdametinib and brimarafenib at the next lower dose (see <a href="#">Table 8-2</a> and <a href="#">Table 8-3</a> ).

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

	For a 2 <sup>nd</sup> occurrence, permanently discontinue study treatment.
Grade $\geq 3$ CPK elevation <b>without</b> renal impairment (serum creatinine $\geq 1.5\times$ ULN or $1.5\times$ baseline)  OR Grade $\geq 3$ CPK elevation <b>without</b> Grade $\geq 2$ rhabdomyolysis	Hydrate either orally or by IV as clinically appropriate. Monitor and measure isoenzymes (CPK1, 2, and 3 fractions) and myoglobin in blood or urine. Maintain the current dose of mirdametinib and brimarafenib.  Monitor closely for myositis, pain, and weakness.
<b>DERMATOLOGICAL</b>	
Grade 2 skin rash	Continue mirdametinib and brimarafenib at the same dose without interruption, if supported by the investigator's assessment of the benefit-risk ratio.  <u>Or</u> Temporarily interrupt mirdametinib and brimarafenib until resolution to Grade $\leq 1$ or baseline; thereafter, re-start mirdametinib and brimarafenib at the same dose, if supported by the investigator's assessment of the benefit-risk ratio.  Perform dermatological exams at the frequency determined at investigator's discretion until resolution to Grade $\leq 1$ or baseline.
Grade 3 skin rash	Temporarily interrupt mirdametinib and brimarafenib.  Perform dermatological exams at the frequency determined at investigator's discretion until resolution to Grade $\leq 1$ or baseline.  After resolution to Grade $\leq 1$ or baseline,  Either re-start mirdametinib and brimarafenib at the next lower dose (see <a href="#">Table 8-2</a> and <a href="#">Table 8-3</a> ) if the event did not resolve to Grade $\leq 1$ within 7 days of initiating optimal medical and supportive care  Or re-start mirdametinib and brimarafenib at the same dose if the event has resolved to Grade $\leq 1$

Mirdametinib  
Protocol MEKRAF-AST-101SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

	within 7 days and if supported by the investigator's assessment of the benefit-risk ratio.
Grade 4 skin rash	Permanently discontinue mirdametinib and/or brimarafenib.
<b>Left Ventricular Ejection Fraction (LVEF)</b>	
Grade 2 LVEF decrease that falls below the lower limit of normal (post baseline LVEF of 40-49%)	<p>If asymptomatic, interrupt mirdametinib and brimarafenib until LVEF resolves to <math>\geq 50\%</math>. Perform LVEF exams at least biweekly or more frequently at the investigator's discretion until satisfactory resolution. After resolution to Grade <math>\leq 1</math>, re-start mirdametinib and brimarafenib at the next lower dose (see <a href="#">Table 8-2</a> and <a href="#">Table 8-3</a>).</p> <p>If symptomatic, permanently discontinue mirdametinib and/or brimarafenib.</p>
Grade 3 LVEF decrease (post baseline LVEF of 20-39% or $\geq 20\%$ difference between the post baseline vs. baseline LVEF)	<p>If asymptomatic, interrupt mirdametinib and/or brimarafenib and repeat LVEF exam in one week. If repeat exam shows persistent Grade 3 LVEF decrease, then permanently discontinue mirdametinib and/or brimarafenib.</p> <p>If repeat exam shows <math>\leq</math> Grade 2 LVEF decrease, then apply the guideline listed above for Grade 2 LVEF decrease.</p> <p>If symptomatic, permanently discontinue mirdametinib and/or brimarafenib.</p>
Grade 4 LVEF decrease (postbaseline LVEF $< 20\%$ )	Permanently discontinue study treatment.
<b>QTcF</b>	
Grade 3 QTcF prolongation (absolute QTcF $> 500$ msec or QTcF change from baseline $> 60$ msec)	Repeat ECG in triplicate approximately 1 hour after the initial ECG and consult with a cardiologist. The three ECGs must be recorded in close succession and not more than 2 minutes apart, and after at least 5 minutes of quiet supine rest.

Mirdametininib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

	<p>Calculate the mean QTcF from the three ECGs.</p> <p>If the absolute QTcF is &lt;480 msec or QTcF change from baseline is <math>\leq 30</math> msec on repeat ECG triplicate, and the cardiologist agrees, then mirdametininib and brimarafenib may be re-started immediately at the same dose.</p> <p>If the absolute QTcF is &gt;480 msec to <math>\leq 500</math> msec or QTcF change from baseline is &gt;30 msec to <math>\leq 60</math> msec on repeat ECG triplicate, and the cardiologist confirms that the result is study treatment-related, then mirdametininib and brimarafenib should be temporarily interrupted during the follow up by weekly repeat ECG triplicates. When the absolute QTcF is &lt;480 msec or QTcF change from baseline is <math>\leq 30</math> msec on repeat ECG triplicate, then mirdametininib and brimarafenib should be re-started at the next lower dose (see <a href="#">Table 8-2</a> and <a href="#">Table 8-3</a>).</p> <p>If the absolute QTcF is &gt;500 msec or QTcF change from baseline is &gt;60 msec on repeat ECG triplicate, and the cardiologist confirms that the result is study treatment-related, then mirdametininib and brimarafenib should be permanently discontinued.</p>
<b>TOTAL BILIRUBIN INCREASE</b>	
Grade 2 (total bilirubin >1.5 $\times$ to 3.0 $\times$ ULN if baseline was normal; >1.5 $\times$ to 3.0 $\times$ baseline if baseline was abnormal)	<p>Interrupt mirdametininib and brimarafenib until resolution to baseline, then</p> <p>If resolved in <math>\leq 7</math> days, re-start mirdametininib and brimarafenib at the same dose.</p> <p>If resolved &gt;7 days, re-start mirdametininib and brimarafenib at the next lower dose (see <a href="#">Table 8-2</a> and <a href="#">Table 8-3</a>).</p>
Grade 3 (total bilirubin >3.0 $\times$ to 10.0 $\times$ ULN if baseline was normal; >3.0 $\times$ to 10.0 $\times$ baseline if baseline was abnormal)	<p>Interrupt mirdametininib and brimarafenib until resolution to baseline, then</p> <p>If resolved in <math>\leq 7</math> days, may re-start mirdametininib and brimarafenib at the next lower dose (see</p>

Mirdametininib  
Protocol MEKRAF-AST-101SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

	<p><a href="#">Table 8-2</a> and <a href="#">Table 8-3</a>) at the investigator's discretion.</p> <p>If resolved &gt;7 days, permanently discontinue mirdametininib and/or brimarafenib.</p>
Grade 4 (total bilirubin >10.0× ULN if baseline was normal; >10.0× baseline if baseline was abnormal)	Permanently discontinue mirdametininib and/or brimarafenib.
<b>AST or ALT INCREASE</b>	
Grade 3 AST or ALT increase (>5.0× to 20.0× ULN if baseline was normal; >5.0× to 20.0× baseline if baseline was abnormal)	<p>Interrupt mirdametininib and brimarafenib until resolution to Grade ≤1 (or Grade ≤2 if the participant has liver metastases).</p> <p>After resolution to Grade ≤1, re-start mirdametininib and brimarafenib at the next lower dose (see <a href="#">Table 8-2</a> and <a href="#">Table 8-3</a>).</p>
Grade 4 AST or ALT increase (>20.0× ULN if baseline was normal; >20.0× baseline if baseline was abnormal)	Permanently discontinue mirdametininib and/or brimarafenib.
<b>Potential DILI / Hy's Law (pending clinical adjudication)</b>	
Total bilirubin increase ≥2.0× ULN and ALT or AST increase ≥3.0× ULN	<p>Permanently discontinue mirdametininib and brimarafenib.</p> <p>If clinical adjudication confirms DILI / Hy's Law, then report DILI as SAE.</p>
<b>OTHER</b>	
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, after resolution to Grade ≤ 1, restart mirdametininib and brimarafenib at the next lower dose (see <a href="#">Table 8-2</a> and <a href="#">Table 8-3</a> ).
Grade ≥ 3 nonhematologic toxicity that is not controlled by optimal supportive medication.	Interrupt dosing; after resolution to Grade ≤ 1 or baseline, restart mirdametininib and brimarafenib at the next lower dose (see <a href="#">Table 8-2</a> and <a href="#">Table 8-3</a> ).

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

Other Grade 2 toxicity that is subjectively intolerable (except alopecia) and not controlled by optimal supportive medication.	Interrupt dosing; after resolution to Grade $\leq 1$ or baseline, re-start mirdametinib and brimarafenib 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; after resolution to Grade $\leq 1$ or baseline, restart mirdametinib and brimarafenib at the next lower dose (see <a href="#">Table 8-2</a> and <a href="#">Table 8-3</a> ).  If toxicity is still intolerable, permanently discontinue mirdametinib and brimarafenib (unless otherwise discussed with the Principal Investigator).

### 8.7.3. Requirements for Continuation of the Study Treatments Post Cycle 1

Participants must fulfill the following criteria in order to commence a new cycle of the study treatments:

- All study treatment-related Grade  $\geq 3$  AEs have resolved to baseline or Grade  $\leq 1$ ;
- No clinical evidence of progressive disease (PD);
- No additional therapeutic interventions for the tumor under study.

### 8.8. INTERVENTION AFTER THE END OF THE STUDY

There will be no access to additional study treatment after the study ends.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## **9. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL**

Participants have the right to voluntarily withdraw from the study or discontinue study treatment at any time for any reason. In addition, the investigator has the right to discontinue a participant from the study treatment at any time. Participants who discontinue study treatment early should be followed for assessments of antitumor activity, safety, and survival, if possible. Every effort should be made to obtain information on participants who discontinue the study treatment. The primary reason for discontinuation from the study treatment should be documented on the appropriate eCRF.

Participants must discontinue study treatment for reasons, which may include, but are not limited to the following:

- Participant withdrawal of consent
- Pregnancy in a study participant
- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety, if he or she were to continue the study treatment (i.e., RVO)
- Use of any concurrent antineoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents [including herbal medicine] for the treatment of cancer)
- Participant noncompliance

Stopping study treatment for documented progressive disease or lack of clinical benefit is not considered as premature withdrawal but as study completion.

The participant may be withdrawn from the study at the discretion of the investigator due to safety concerns or non-compliance with study procedures to an extent judged to affect the conclusion of the study.

The Sponsor also has the right to discontinue the study for any reason.

### **9.1. REPLACEMENT OF PARTICIPANTS IN STUDY**

All participant data collected will be analyzed within the analysis set for which the participant is evaluable.

If participants are not evaluable for safety or efficacy, or if the mutation status is not confirmed by the central laboratory, or if insufficient PK or PDx data is available at a given dose level, the participant may be replaced at the Sponsor's decision. The additional participant(s) included to replace non-evaluable participants will be given new, unique participant IDs. If a participant withdraws from the study during the DLT period for reasons other than toxicity, they may be replaced at the Sponsor's decision.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## 9.2. 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 and 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, they will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as whole is handled as part of [Appendix A1-7](#).

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## 10. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA ([Section 1.2](#)).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, 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 7.1](#) and [7.2](#)). The electronic data capture (EDC) will capture all participants who sign the ICF, including all screen-failures.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA ([Section 1.2](#)). Where more than one result is available for the same assessment during the pre-treatment period, the most recent value will be used as the baseline for all on-treatment results for that assessment. Clinical labs may be repeated at the discretion of the Investigator.
- 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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) 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 values entered into the eCRF.
  - ECGs 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 including CT and/or MRI should be performed per the schedule in the SoA at a qualified imaging facility; however, local imaging may be allowed

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

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

- Blood samples will be collected as detailed in the SoA ([Section 1.2](#)). The investigator, in conjunction with the Sponsor, may collect additional blood if necessary for repeat laboratory or safety evaluations, including follow-up to AEs.

## 10.1 SCREENING

Screening evaluations will be performed within 28 days prior to the first administration of study treatment. Patients who agree to participate will sign the ICF prior to undergoing any screening procedure (refer to [Appendix A1-3](#) for details). Screening evaluations may be repeated as needed within the Screening Period; the investigator is to assess participant eligibility according to the latest screening assessment results.

Results of standard of care tests or examinations performed prior to obtaining informed consent and  $\leq 28$  days prior to the first dose of the study treatment(s) may be used for the purposes of screening rather than repeating the standard of care tests, unless otherwise indicated.

Procedures conducted at the Screening Visit only are described in this section. For the description of other assessments that are conducted at Screening as well as throughout the study, refer to Safety Assessment ([Section 10.3](#)), Tumor and Response Evaluation ([Section 10.2](#)), and Biomarker Assessment ([Section 10.6](#)). The PK sampling schedule is shown in [Table 1-2](#) and [Table 1-3](#). Rescreening under limited conditions (e.g., when a participant narrowly misses a laboratory criterion, and it is correctable and not due to rapidly deteriorating condition or disease progression) may be allowed after consultation with medical monitor. Rescreening is allowed only once.

### 10.1.1. Demographic Data and Medical History

Demographic data will include age or year 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., of childbearing potential or no childbearing potential); history of alcohol consumption (i.e., presence or absence); and all medications (i.e., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the participant within 28 days before the first dose of study treatment.

Cancer history will include cancer diagnosis, prior surgery, prior radiotherapy, prior drug therapy including start and stop dates, best response, and reason for discontinuation.

Radiographic studies performed prior to study entry may be collected for review by the investigator.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

### **10.1.2. Females of Childbearing Potential and Contraception**

Refer to [Appendix 5A5-2](#) for contraception guidelines and definitions of “women of childbearing potential” and “no childbearing potential”.

## **10.2. TUMOR RESPONSE EVALUATION**

Tumor response (anti-tumor efficacy) will be assessed by CT or MRI (with oral/intravenous contrast, unless contraindicated); positron emission tomography/CT (PET/CT) is permitted as an additional assessment if indicated by the investigator. The same imaging modality and radiographic procedure used to assess disease sites at screening is required to be used throughout the study (i.e., the same contrast protocol for scans).

Tumor response assessment will be performed within 28 days prior to first dose of study treatment. Results of standard of care tests or examinations performed prior to obtaining informed consent and within 28 days prior to first dose of study treatment may be used for the purposes of screening rather than repeating the standard of care tests. Radiological assessment of tumor response will be performed at the time points listed in the SoA ([Section 1.2](#)).

Tumor response and progression of cancer under study will be assessed using RECIST 1.1 ([Eisenhauer 2009](#)). Participant treatment decisions will be determined by the local investigator based on the tumor response assessment at the site.

Participants who discontinue study treatment early for reasons other than disease progression (e.g., toxicity) will continue to undergo tumor assessments following the tumor response assessment schedule per protocol until the participant begins a subsequent anticancer treatment, experiences disease progression, withdraws consent, dies, or until the study terminates, whichever occurs first.

### **10.2.1. Treatment beyond disease progression**

Participants who are found to have clinical or radiological PD by RECIST 1.1 will discontinue from the study.

### **10.2.2. Central review of tumor assessment scans**

Sites will submit all CT and/or MRI scans from participants in the PDx Expansion Cohort and Part 2, the dose expansion portion of the study, to the central imaging core laboratory for Central Imaging Review. The purpose of the Central Imaging Review is to provide an independent, unbiased, and objective review of the CT and MRI data. The Central Imaging Review will begin when deemed appropriate by the Sponsor. Sites will be provided an Imaging Acquisition Manual and an Imaging Submission Manual, which describe the imaging methods and submission process that must be followed. All image data submitted to the central imaging core laboratory must be de-identified prior to submission. The participant identifiers on the image data must be consistent with all study related documents throughout the study. See imaging manuals for

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

details on the de-identification requirements. Central review will not be done for Part 1 dose escalation of this study.

### **10.3. SAFETY ASSESSMENTS**

#### **10.3.1. Vital Signs**

Body temperature, heart rate, pulse oximetry, and blood pressure (BP) will be assessed as described in the SoA.

Supine BP and heart rate (HR) measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

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

Assessments can be repeated once.

#### **10.3.2. Physical Examinations and Eastern Cooperative Oncology Group Performance Status**

A physical examination, as well as height (screening only) and weight, and assessment of ECOG see [Appendix A3-2](#) performance status will be required throughout the study as described in the SoA.

During the Screening Visit and EoT Visit, the physical examination should include 1) head, eyes, ears, nose, throat, 2) cardiovascular, 3) dermatological, 4) musculoskeletal, 5) respiratory, 6) gastrointestinal, and 7) neurological systems.

At other visits (or as clinically indicated), abbreviated physical examinations with ECOG performance status may be performed (to always include cardiovascular, respiratory, gastrointestinal, and dermatological as well as any other symptom-directed organ system).

Potential dermatological toxicity will be assessed as part of the physical examination with the characteristics and grade of rash. Any abnormality identified at baseline will be recorded on the Medical History eCRF with appropriate disease/condition terms. New or worsening clinically significant abnormalities must be recorded as AEs in the eCRF.

#### **10.3.3. Laboratory Safety Tests**

See [Appendix A3-1](#) for the list of clinical laboratory tests to be performed and to the SoA (see [Section 1.2](#)) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section 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.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in [Section 1.2](#), must be conducted in accordance with the laboratory manual and the SoA.
- 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.

#### 10.3.4. Electrocardiograms

Triplicate or Single 12-lead ECGs will be obtained as outlined in the [Table 1-2](#) and [Table 1-3](#) (see [Section 1.2](#)) using an ECG machine that automatically calculates the HR and measures PR, RR, QRS, QT, and QTcF intervals.

Participants will be rested in supine position for at least 5 minutes prior to the ECG collections and remain in supine rest for the duration of the ECG collection. The site personnel will be instructed to ensure a quiet environment prior to and during the ECG recordings. When ECG assessment coincides with any other study procedures at the same time point, the ECG must be performed first, followed by vital signs, and then blood sample collection, with blood sample collected at the nominal time.

For safety monitoring purposes, the Investigator must review all ECG tracings at all visits with ECG monitoring. At specified time points, the Investigator must review the ECG data and assess any abnormalities for clinical significance, and then sign, and date specified ECG tracings at time points detailed in footnote "9" of [Table 1-2](#) and [Table 1-3](#). Paper or electronic copies of ECG tracings will be kept as part of the source documentation.

Part 1 and 2 triplicate ECGs will be sent to a central laboratory for interpretation.

Refer to [Table 8-4](#) for QTcF withdrawal criteria and any additional QTcF readings that may be necessary.

#### 10.3.5. Ophthalmology Examination

Ophthalmological examination will be conducted as outlined in the SoA (see [Section 1.2](#)) and will include the visual acuity, intraocular pressure (provided as a numerical value), slit lamp examination, cup-to-disc ratio and OCT. Other methods may be performed if indicated by the investigator, an optometrist, or the ophthalmologist (e.g., dilated funduscopy, fluorescein angiography, etc.).

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

If a participant experiences an ocular disorder that could be clinically significant in the investigator's opinion, then an ophthalmological examination should be performed as soon as possible to address the ocular disorder (see also the treatment modification guidelines for ocular toxicities, [Table 8-4](#)). Any clinically significant findings and symptoms, including those confirmed by the ophthalmologist, must be reported as an AE.

### **10.3.6. Creatine Phosphokinase (CPK) Elevation**

CPK evaluation should be conducted as outlined in the Schedule of Assessments (see [Section 1.2](#)). For any Grade  $\geq 3$  CPK result, it is highly recommended that reflex fractionation (CPK1, 2, and 3) be conducted for complete evaluation of the etiology of the CPK increase. The participant should be evaluated for myoglobin in blood or urine. Additionally, the participant should be evaluated for any signs or symptoms of rhabdomyolysis. Any clinically significant findings and symptoms must be reported as an AE. (See also the treatment modification guidelines for CPK elevations, [Table 8-4](#)).

### **10.3.7. Left Ventricular Ejection Fraction (LVEF) Assessment**

LVEF assessment will be conducted as outlined in the SoA (see [Section 1.2](#)) by ECHO or MUGA. The same imaging technique should be used in a participant throughout the study. In addition to the results of ECHO or MUGA, participants will be evaluated for any clinical symptoms of cardiac failure (such as shortness of breath, exercise intolerance, and peripheral edema).

## **10.4. ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS**

The definitions of an AE, Adverse Event of Special Interest (AESI), SAE, adverse reaction (AR), serious adverse reaction (SAR), and a suspected unexpected serious adverse reaction (SUSAR), and Special Situations can be found in [Appendix A4-1](#).

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 on AEs, AESIs, SAEs, Special Situations, or the reason for the participant to discontinue the study treatment ([Section 9](#)).

Study AE management guidelines can be found in [Appendix 7](#). This appendix provides guidance on the management of the common skin-related AEs and diarrhea seen in participants taking mirdametinib and brimrafenib. The goal of the guideline is to provide strategies to reduce the potential for treatment discontinuations or dose reductions by optimizing supportive care for these most common expected events. Study treatment may be continued while supportive care is underway.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

#### **10.4.1. Time Period and Frequency for Collecting AE and SAE Information**

All AEs, AESIs and SAEs will be collected from the signing of the ICF until the Safety Follow Up Visit as specified in the SoA ([Section 1.2](#)).

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in [Appendix 4](#). The investigator will submit any updated SAE and AESI data to the Sponsor within 24 hours of it being available.

Investigators are obligated to report any AE, AESI, or SAE for 30 days after conclusion of the participant's participation in the study. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE, AESI, and SAE and the procedures for completing and transmitting AESI and SAE reports are provided in [Appendix 4](#).

#### **10.4.2. Method of Detecting AEs, AESIs, Special Situations, and SAEs**

The method of recording, evaluating, and assessing causality of AEs, AESIs, Special Situations, and/or SAEs, and the procedures for completing and transmitting reports for each are provided in [Appendix A4-2](#).

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

#### **10.4.3. Follow-up of AEs, AESIs, Special Situations, and SAEs**

After the initial AEs, AESIs, Special Situations, and/or SAEs report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AESIs (as defined in [Section A4-1](#)) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in [Section 9.2](#)).

Within 24 hours of receipt of SAE 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 [Appendix A4-2.3](#).

#### **10.4.4. 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.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

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, IRBs/IECs, and investigators.

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 IB and will notify the IRB/IEC, if appropriate according to local requirements.

#### **10.4.5. 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 the outcome of the pregnancy is known. This may be longer than 30 days after the last dose of study treatment.

If a pregnancy is reported, the investigator must inform the Sponsor within 24 hours of learning of the pregnancy by completing a paper pregnancy form and submitting to Safety (refer to [Appendix A5-3](#) for reporting details).

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

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 from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the Sponsor 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 the Sponsor within 24 hours of learning of a participant's pregnancy.
- 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

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

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 10.4.1](#). 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 or be withdrawn from the study.

#### 10.4.6. Adverse Events of Special Interest

##### 10.4.6.1. Adverse Events of Special Interest (AESI) for Brimarafenib

**Table 10-1: AESI for Brimarafenib**

<b>Musculoskeletal (reported as AESI if Grade <math>\geq</math> 2)</b>
Rhabdomyolysis
Myalgia
Muscular weakness
Muscle spasms
<b>Musculoskeletal (reported as AESI if Grade <math>\geq</math> 3)</b>
Creatine phosphokinase increased
<b>Cardiac Disorders (reported as AESI if Grade <math>\geq</math> 2)</b>
Atrial fibrillation
Cardiac failure
<b>Renal Disorders (reported as AESI if Grade <math>\geq</math> 2)</b>
Acute kidney injury
<b>Skin Disorders (reported as AESI if Grade <math>\geq</math> 3)</b>
Rash

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

Acneiform rash
Maculopapular rash
<b>Hepatic Disorders (reported as AESI if Grade <math>\geq</math> 3)</b>
Aspartate transaminase increase
Alanine transaminase increase
<b>Hematological Disorders (reported as AESI if Grade <math>\geq</math> 2)</b>
Thrombocytopenia/Platelet Count Decreased
<b>Constitutional (reported as AESI if Grade <math>\geq</math> 2)</b>
Pyrexia

#### 10.4.6.2. Adverse Events of Special Interest (AESI) for Mirdametinib

**Table 10-2: AESI for Mirdametinib**

<b>Gastrointestinal (reported as AESI if Grade <math>\geq</math> 3)</b>
Diarrhoea
Nausea
Vomiting
<b>Eye Disorders (reported as AESI if Grade <math>\geq</math> 2)</b>
Retinal vein occlusion (RVO)
Uveitis
Optic neuropathy
Retinopathy
Retinal detachment
<b>Musculoskeletal (reported as AESI if Grade <math>\geq</math> 3)</b>
Creatine phosphokinase increased

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

<b>Cardiac Disorders (reported as AESI if Grade <math>\geq</math> 2)</b>
Ejection fraction decreased
Cardiac failure
Left ventricular dysfunction
<b>Neurologic Disorders (reported as AESI if Grade <math>\geq</math> 2)</b>
Confusion
Hallucination
Delirium
<b>Skin Disorders (reported as AESI if Grade <math>\geq</math> 3)</b>
Rash
Dermatitis Acneiform (Acneiform rash)

## 10.5. PHARMACOKINETIC ASSESSMENTS

Pharmacokinetic sampling will be performed as indicated in [Table 1-2](#) and [Table 1-3](#). PK sampling may change during the study based on emerging data.

PK parameters (e.g., AUC, C<sub>max</sub>, and T<sub>max</sub>) will be calculated for mirdametinib, its active metabolite PD-0315209, and brimarafenib as appropriate using noncompartmental methods.

Shipping, storage, and handling of samples for the assessment of PK assays will be managed through a central laboratory. Instruction manuals and supply kits will be provided for all laboratory assessments.

## 10.6. BIOMARKER ASSESSMENTS

Both tumor tissue and blood biomarkers will be explored in this study. Tumor tissue will be analyzed using immunohistochemical assays (or equivalent) to investigate changes in tumor molecular biology in response to treatment.

Paired fresh tumor biopsies are mandatory at screening and at Day 22 of Cycle 1 ( $\pm$ 2 days) for the following cohorts:

- PDx Expansion Cohort (at least 6 and up to 20 participants)
- At least 6 participants in cohort A in Part 2 (n=6 of the first 10-15 participants)

The on-treatment biopsies in Part 1 and the PDx Expansion Cohort should be obtained within 3-6 hours after dosing at Day 22 of Cycle 1 ( $\pm$ 2 days). The on-treatment biopsies in Part 2 should be obtained pre-dose at Day 22 of Cycle 1 ( $\pm$ 2 days). Optional EoT biopsies for participants that discontinue due to disease progression will require additional informed consent and should be

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

obtained within 1 week of stopping study treatment. When permitted by the location of the tumor lesion, all tumor biopsies in one participant should be taken from the same tumor lesion that was used for the baseline tumor biopsy (if applicable). Optional biopsies are allowed for all remaining participants enrolled.

Tumor biopsies may be taken only if the accessible tumor lesion is available and if the participant consented for this procedure. Tumor biopsies should be limited to readily accessible tumor lesions (i.e., skin; peripheral lymph nodes; lung, liver or internal lymph node metastases which can be readily accessed with or without the imaging-guided procedure). Biopsy of a previously irradiated lesion is not permitted. Tumor biopsies should acquire a tissue cylinder that has a proper size for histological examination and biomarker analyses. The fine needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable as fresh tumor biopsies.

Archival tumor tissues and fresh tumor biopsies will be sent to a central laboratory for analysis by immunohistochemistry, immunofluorescence, or similar assays. Assessment of pERK, phosphorylated MEK, and/or additional markers in the MAP kinase or other pathways associated with secondary mutations of resistance to MAP kinase inhibition will be evaluated.

The mutation status result defining eligibility must be confirmed at the central laboratory once a participant is enrolled. For this reason, the eligible participant must be able to provide a baseline tumor sample at screening (archival tumor tissue or fresh tumor biopsy). Archival tissue should be obtained as an FFPE block with tumor tissue (preferred) obtained at any time before the start of the study. Alternatively, 20 unstained FFPE slides (minimum requirement) may be accepted.

The central laboratory will use a single genomic (NGS) assay with appropriate analytical qualification to confirm the mutation status and explore additional pathogenic co-mutations. Refer to panel mutation testing described in the laboratory manual for a full list of genes to be evaluated.

If the tumor mutation status result by the central laboratory is different from the result used for eligibility, and the participant is on study treatment at the time, the investigator should promptly inform the participant about the non-concordance. At the investigator's discretion, such a participant may continue study treatment if the potential for clinical benefit outweighs the risk. The investigator's decision to continue study treatments for participants with discordant mutational status results from the central laboratory and the participant's verbal informed consent to continue treatment must be confirmed by the medical monitor and documented in the study records at the site.

Blood samples will be collected from all participants for mutation profiling by NGS (ctDNA analysis) for exploratory assessment of molecular residual disease and variant tracking. Samples will be collected at screening and at subsequent visits that align with tumor responses assessments. Additional biomarker analysis from the blood may be conducted by other assay types, such as RNA-Seq.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## **10.7. VISIT WINDOWS**

All visits must occur at the scheduled date, unless otherwise noted (see [Section 10.8 Unscheduled visits](#)). Assessments scheduled on the day of study treatment administration (Day 1) of each cycle should be performed prior to study treatment unless otherwise noted. Laboratory results are required to be reviewed prior to dosing. Visit schedule should be maintained (anchored by Cycle 1 Day 1) regardless of study treatment being interrupted at the time of the scheduled visit.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other events, the Visit should be scheduled on the nearest feasible date.

## **10.8. UNSCHEDULED VISITS**

Unscheduled visits may be performed at any time at the participant's or investigator's request and may include vital signs/focused physical examination; ECOG performance status; AE review; concomitant medications and procedures review; radiographic assessments; eye examination (if clinically indicated); disease-related constitutional symptoms; PK (if clinically indicated); and hematology and chemistry laboratory assessments. The date and reason for the unscheduled visit must be recorded in the source documentation.

If an unscheduled visit is necessary to assess toxicity or for suspected disease progression, then diagnostic tests may be performed based on investigator assessment as appropriate, and the results of these tests should be entered on the unscheduled visit eCRF.

## **10.9. SITE CLOSURE**

The Sponsor has the right to close a site at any time. The decision will be notified to the site in advance. Reasons for closing a site may include but are not limited to the following:

- Excessively slow recruitment,
- Poor protocol adherence,
- Inaccurate or incomplete data recording,
- Good Clinical Practice noncompliance, and
- Study activity is completed (i.e., all participants have completed, and all obligations have been fulfilled).

## **10.10. STUDY TERMINATION**

The Sponsor has the right to terminate this study at any time. Reasons for early termination of the study may include but are not limited to the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to participants.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

- The occurrence of any fatal AEs that are clearly not due to disease under study and are assessed as related to the study agents by the Investigators in consultation with the Sponsor.
- The occurrence of two or more treatment related AEs that are immediately life-threatening (excluding those Grade 4 lab abnormalities that do not necessarily put participants at immediate risk of death).
- Overall participant enrollment is unsatisfactory.

The Sponsor will notify each investigator if a decision is made to terminate the study. In such circumstances, prematurely discontinued participants should be seen as soon as possible for an End of Treatment Visit and end of treatment assessments performed.

The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator will be responsible for informing IRBs and/or IECs of the early termination of the study.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## 11. STATISTICAL CONSIDERATIONS

The study results will be presented by study part and treatment cohort and will be primarily descriptive. The study results may be listed by participant as appropriate.

No statistical hypotheses will be formally evaluated in this study.

A SAP detailing statistical analyses (except for PK/PDx) for this protocol will be prepared. PK and PDx analysis plans will be described in separate SAPs.

### 11.1. SAMPLE SIZE CONSIDERATIONS

The planned sample size in this study is 136 evaluable participants (up to 56 in Part 1 and up to 80 in Part 2); however, the planned number of participants in Part 1 may be increased if deemed necessary by the Sponsor. Approximately 164 participants may be enrolled and treated to achieve the planned number of 136 evaluable participants (estimated replacement rate of approximately 25%).

Participants who are discontinued after the start of treatment (except those discontinued for safety reasons) may be replaced if this is deemed necessary by the Sponsor to accrue enough evaluable participants.

#### 11.1.1. Part 1

The planned sample size in Part 1 is up to 56 evaluable participants, which includes the following:

- 6 dose escalation cohorts (minimum of 3 and up to 6 evaluable participants per cohort; participant is evaluable if they complete Cycle 1 or experience a DLT)
- PDx Expansion Cohort (minimum of 6 and up to 20 evaluable participants; participant is evaluable if they provide the paired fresh tumor biopsy at screening and at Cycle 1 Day 22 ( $\pm 2$  days) and at least one post-baseline tumor assessment).

The planned number of participants in Part 1 may be increased if deemed necessary by the Sponsor.

#### 11.1.2. Part 2

The planned sample size in Part 2 dose escalation is 80 evaluable participants (20 evaluable participants in Cohort A and 30 evaluable participants each in Cohorts B and C). This sample size provides adequate power to demonstrate that the combination of mirdametinib + brimarafenib has potentially beneficial effects in any of the dose expansion cohorts A, B, C.

The sample size for the expansion cohorts is based on a BOP2 design for each of the cohorts (Menzer et al. 2019; Zhou, Lee, and Yuan 2017). There will be one interim analysis in each of the 3 cohorts when 50% of the planned total sample size is evaluable for ORR and the stopping

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

criteria at interim and final analysis will be applied as described in [Section 6.1.2](#). Further details of the BOP2 design are presented in the appendix of the protocol.

Each expansion cohort will be evaluated separately and may be closed due to lack of clinical efficacy based on statistical evaluation or insufficient participant recruitment.

If promising preliminary efficacy results are observed in any dose expansion cohort after treating all planned participants, additional participants could be added to the expansion cohort to further assess the efficacy of the combination and potentially facilitate discussions with Health Authorities.

## 11.2. POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined:

Population	Description
Safety Population	The Safety Population will consist of all participants assigned to study treatment and who take at least 1 dose of study treatment (either brimarafenib or mirdametinib).
DLT Evaluable Population	The DLT evaluable analysis set will include participants who received >80% of the assigned dose of brimarafenib and mirdametinib during Cycle 1 in Part 1 (i.e., at least 25 days on treatment with both study treatments) or who experienced a DLT during Cycle 1 in Part 1.
Efficacy Evaluable Population	The efficacy evaluable population will include all treated participants who have the baseline tumor response assessment (screening) and at least one post treatment tumor response assessment.
Pharmacokinetic (PK) Population	The PK population will include all treated participants for whom valid brimarafenib or mirdametinib PK parameters can be estimated.
Pharmacodynamic (PDx) Population	The PDx population will include all treated participants for whom evaluable biopsy material is provided.

## 11.3. SAFETY ANALYSIS

Safety endpoints will be summarized using the Safety Population. All summaries of safety will be by dose level for Part 1 and by expansion cohort for Part 2.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

AEs will be coded using the current version of MedDRA, and AE data will be summarized by System Organ Class (SOC) and Preferred Term (PT). AEs will also be summarized by worst AE severity/ grade and AE relationship to study treatment. The number of SAEs and AEs which led to discontinuation of study treatment will also be summarized. All AE summaries will be restricted to TEAEs only. The incidence of DLT events and TEAEs will be reported as the number (percentage) of participants with TEAEs by SOC and PT and the worst grade with CTCAE V5.0. In Part 1, DLTs will be summarized for the DLT Evaluable Population.

Descriptive summary statistics (i.e., n, mean, standard deviation, median, minimum, maximum for continuous variables; n [%] for categorical outlier variables) and changes from baseline will be reported for laboratory parameters, vital signs, ECG parameters, LVEF. In addition, the maximum individual outlier QTc values will be summarized by the categories specified in the International Council for Harmonisation (ICH) E14 guideline.

The ECOG score and (if appropriate) the laboratory safety test results will additionally be presented in shift tables.

#### **11.4. EFFICACY ANALYSIS**

The efficacy endpoints will be analyzed using the Efficacy Evaluable Population.

ORR is defined as the proportion of participants who have a disappearance of all target lesions (Complete Response [CR]) or at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum of LD (PR). ORR will be summarized with the two-sided exact (Clopper-Pearson) 95% CI. ORR is derived from the objective tumor response results by RECIST v1.1 and will be summarized by treatment cohort and overall.

DOR will be calculated as the time between the first instance of response until the date of progression or censored date. The DOR will be analyzed using Kaplan Meier method; median duration of response and the 95% CIs on the intervals will be calculated.

All statistical methods, along with any censoring methods will be described in detail in the Statistical Analysis Plan. Exploratory analyses will be described in the SAP.

#### **11.5. PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES**

A separate SAP will be developed to describe the PK and PDx analyses which will be performed on the PK and PDx populations, respectively.

#### **11.6. HANDLING MISSING DATA**

Missing data will not be imputed in this study. If participants have missing or uninterpretable data for PK, the investigator or Sponsor may enroll an additional participant to replace the missing information and maintain the planned sample size for the analysis.

#### **11.7. INTERIM ANALYSES**

For each of the expansion cohorts an interim analysis is planned as described in [Section 6.1.2.2](#).

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## **12.           STUDY COMMITTEES AND COMMUNICATION**

### **12.1.       STUDY MONITORING: COHORT MANAGEMENT COMMITTEE**

The CMC will consist of the investigators, the Sponsor representatives, and the Independent Safety Committee (ISC). The ISC composition will be described in a charter and include a minimum of 3 suitably qualified drug development physicians. The ISC will operate according to an established charter. The ISC will adjudicate the decisions to escalate/ de-escalate or expand cohort numbers. In the event of differences of opinion between these 3 groups the ISC will have the deciding vote.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## **SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS**

### **APPENDIX 1. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS**

#### **A1-1. 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 (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an 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 SAEs 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

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## **A1-2.      FINANCIAL DISCLOSURE**

- Principal 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.

## **A1-3.      INFORMED CONSENT PROCESS**

- The Investigator or his/her 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 will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date/time the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s), as per IRB/IEC guidance, during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

## **A1-4.      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.
- Participants must be informed that their 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.
- Participants must be informed that their medical records may be examined by Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## **A1-5.      DATA QUALITY ASSURANCE**

All participant data relating to the study will be entered into the 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 non-compliance issues and monitoring techniques (central, remote, or onsite 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.

## **A1-6.      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 entered 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 prior to participation in the study. Source documents must completely

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

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.

## **A1-7.        STUDY AND SITE CLOSURE**

The Sponsor (or designee) reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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 Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Conditions that may warrant early study site closure but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to participants participating in the study;
- A negative change in the risk/benefit assessment;
- 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
- The decision on the part of the Sponsor to suspend or discontinue development mirdametinib or brimarafenib for this indication.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## APPENDIX 2. RECIST CRITERIA V1.1

For full guidelines, see RECIST Criteria v1.1 ([Eisenhauer 2009](#))

### Categorizing lesions at Baseline:

- Only participants with measurable disease (i.e., at least one measurable lesion) at screening are included.

**Measurable lesion** – Lesion that can be accurately measured in at least one dimension (longest diameter [LD]) in the plane of measurement is to be recorded) and with longest diameter at least twice the slice thickness and at least 10 mm when assessed by computed tomography (CT) or magnetic resonance imaging (MRI)

- Measurable disease will be assessed by CT or MRI.
- The same method of assessment (CT or MRI) and the same technique will be used to characterize each identified and reported lesion at screening and during follow-up.
- Target Lesions - up to 2 lesions per organ and 5 lesions in total, representative of all involved organs at Baseline.
- Non-target Lesion-All other lesions (or sites of disease) will be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

### Methods of Measurement

CT or MRI must be used to measure target lesions selected for response assessment. Conventional CT and MRI will be performed with cuts of 10 mm or less in slice thickness contiguously.

### Recording Tumor Assessments

All sites of disease must be assessed at screening. Screening assessment must be done within 28 days of starting study treatment. For an adequate screening assessment, all required scans must be done within 28 days prior to first dose of study treatment and all disease must be documented appropriately.

At follow-up, disease site must be assessed using the method (CT or MRI) and same technique as screening, including consistent administration of contrast (CT only) and timing of scanning. If a change needs to be made the case must be discussed with the Sponsor.

Unequivocal new lesions will be recorded at follow-up time points. Measurement of new lesions is not required. If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

### Response Criteria: Evaluation of target lesions

Complete Response (CR):	Disappearance of all target lesions.
Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum of LD.
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum of LD recorded since the treatment started or the appearance of one or more unequivocal new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

LD= longest diameter

### Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the start of study treatment). The participant's best response assignment will depend on the achievement of both measurement and confirmation criteria (defined below).

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD

Mirdametinib  
Protocol MEKRAF-AST-101SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
Any	Any	Yes	PD

CR=Complete Response; NE=Not Evaluable; PD=Progressive Disease; PR=Partial Response; SD=Stable Disease.

Participants with a global deterioration of health status requiring discontinuation of study treatment without objective evidence of disease progression at that time will be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

### Confirmation

- **Confirmation of response:**
  - The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
  - To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that will be performed no less than 4 weeks after the criteria for response are first met.
- **Confirmation of SD:** in the case of SD, follow-up measurements must have met the SD criteria at least once after study entry (signing of ICF) at a minimum interval of 8 weeks.

### Duration of progression free survival ORR and SD

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

### Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## **APPENDIX 3. SAFETY ASSESSMENTS**

### **A3-1. CLINICAL LABORATORY TESTS**

The tests detailed in [Table A3-1](#) will be performed by the local laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in [Section 7](#) of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Pregnancy testing (urine as described in the SoA [Schedule of Assessments]; [Section 1.2](#)) will be conducted at monthly intervals for Women of Child-Bearing Potential (WOCBP).

Serum pregnancy tests may be conducted in place of urine pregnancy tests throughout the study if required by local regulations.

Investigators must document their review of each laboratory report.

Mirdametinib  
Protocol MEKRAF-AST-101SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)**Table A3-1: Clinical Laboratory Panels**

<b>Hematology</b>	<b>Serum Chemistry</b>	<b>Urinalysis (dipstick is acceptable)</b>
<ul style="list-style-type: none"> <li>WBC with 5-part differential #(neutrophils, basophils, eosinophils, lymphocytes, monocytes)</li> <li>hemoglobin</li> <li>hematocrit</li> <li>platelet count</li> <li>MCV</li> <li>Reticulocytes</li> </ul>	<ul style="list-style-type: none"> <li>albumin</li> <li>amylase</li> <li>alkaline phosphatase</li> <li>ALT</li> <li>AST</li> <li>bicarbonate</li> <li>BUN (or equivalent [uric acid, urate])</li> <li>calcium</li> <li>chloride</li> <li>CK/CPK**</li> <li>creatinine</li> <li>eGFR (CKD-EPI calculation)*</li> <li>GGT</li> <li>glucose (fasting or random)</li> <li>glycosylated hemoglobin (HbA1c)*</li> <li>magnesium</li> <li>phosphorous</li> <li>potassium</li> <li>sodium</li> <li>total bilirubin^</li> <li>total protein</li> </ul>	<ul style="list-style-type: none"> <li>appearance</li> <li>color</li> <li>pH</li> <li>specific gravity</li> <li>ketones</li> <li>leukocytes</li> <li>protein</li> <li>glucose</li> <li>bilirubin</li> <li>urobilinogen</li> <li>myoglobin or blood**</li> <li>occult blood (where applicable microscopic examination of sediment will be performed if the results of the urinalysis dipstick evaluation are of positive)</li> </ul>
<b>Coagulation</b>		
<ul style="list-style-type: none"> <li>INR</li> <li>aPTT</li> </ul>		
<b>Lipid panel</b>		
<ul style="list-style-type: none"> <li>total cholesterol*</li> <li>triglycerides*</li> </ul>		
<b>Hormones</b>		
<ul style="list-style-type: none"> <li>βHGC (women of childbearing potential)</li> <li>TSH</li> <li>Free T3 and Free T4</li> </ul>		

ALT = Alanine Aminotransferase; aPTT = Activated Partial Thromboplastin Time; AST = Aspartate Aminotransferase; βHGC = Beta Human Chorionic Gonadotropin; BUN = Blood Urea Nitrogen; CK = Creatine Kinase; CPK = Creatine phosphokinase; eGFR = estimated Glomerular Filtration Rate; GGT = Gamma-glutamyl Transferase; INR = International Normalized Ratio; MCV = Mean Corpuscular Volume; TSH = Thyroid Stimulating Hormone; WBC = White Blood Cells

\* At screening only to establish eligibility and/or baseline and permit full investigation of clinical observations on study.

\*\* See [Section 10.3.6](#). For Grade 3 or higher CK/CPK elevations, it is recommended to monitor and measure isozymes (CPK1,2, and 3). Evaluation for presence of myoglobin with blood test or with urinalysis is also recommended.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

# The absolute number should be reported for the 5-part WBC differential count.

^ If total bilirubin elevated, conduct direct and indirect bilirubin on subsequent samples.

Please refer to the SoA ([Table 1-1](#)) for which samples should be drawn at which visit.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

### **A3-2. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE**

<b>Grade</b>	<b>Description</b>
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: (Oken et al. 1982) Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982; 5:649-655

### **A3-3. QT INTERVAL (QTC) PROLONGATION RISK**

Refer to the Study Reference Manual for a list of substances have been reported to show risk of QTc interval prolongation in published literature or have been demonstrated to have QT effects and risk of effect on cardiac repolarization in clinical studies.

### **A3-4. CKD-EPI CREATININE EQUATION (2021) NATIONAL KIDNEY FOUNDATION (CKD-EPI CREATININE EQUATION, 2021)**

Recommend use of calculator found at:

[https://www.kidney.org/professionals/kdoqi/gfr\\_calculator](https://www.kidney.org/professionals/kdoqi/gfr_calculator), which corresponds to the equation below. Body surface area adjustment is not required. Therefore, select “NO” in the option to adjust for body surface area. Serum Cystatin C is also not required. Therefore, this field should be left blank if using the online calculator.

Expressed as a single equation:

$$eGFR = 142 * \min(\text{standardized } S_{cr}/K, 1)^a * \max(\text{standardized } S_{cr}/K, 1)^{-1.200} * 0.9938^{\text{Age}} * 1.012 \text{ [if female]}$$

#### **Abbreviations / Units:**

eGFR (estimated glomerular filtration rate) = mL/min/ 1.73 m<sup>2</sup>

S<sub>cr</sub> (serum creatinine) = mg/dL

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

$K = 0.7$  (females) or  $0.9$  (males)

$\alpha = -0.241$  (females) or  $-0.302$  (males)

min = indicates the minimum of  $S_{cr}/K$  or 1

max = indicates the maximum of  $S_{cr}/K$  or 1

### **Clinical Use:**

The Recommended method for estimating GFR in adults from the National Kidney Foundation is the 2021 CKD-EPI equations.

Designed for use with laboratory creatinine values that are standardized to IDMS. (See "About GFR" button.)

Estimates GFR from serum creatinine, age, and sex. Corrections for BSA is not needed.

More accurate than the MDRD Study equation, particularly in people with higher levels of GFR.

The CKD-EPI equation is modeled using least squares linear regression to relate log transformed measured GFR to log-transformed filtration markers, age and sex with two slope splines for creatinine.

Some clinical laboratories are still reporting GFR estimates using the MDRD Study equation. The National Kidney Foundation has recommended that clinical laboratories should begin using the 2021 CKD-EPI equation to report estimated GFR.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## **APPENDIX 4. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING**

### **A4-1. DEFINITIONS**

#### **A4-1.1. ADVERSE EVENT (AE)**

An Adverse Event (AE) is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment.

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, hormone levels, or urinalysis) or other safety assessments (e.g., electrocardiograms, 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.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

**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. Any surgeries and/or procedures that were scheduled prior to obtaining the ICF but occurring afterwards will not be treated as an AE or SAE, unless the condition requiring the surgery or procedure worsened.
- 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.

**A4-1.2. ADVERSE EVENTS OF SPECIAL INTEREST (AESI)**

Adverse Events of Special Interest (AESIs) are defined as non-serious or serious AEs that is one of scientific and/or medical concern specific to the Sponsor's product for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate.

**A4-1.3. SERIOUS ADVERSE EVENT (SAE)**

If an event is not an AE per definition in [Appendix A4-1.1](#), then it cannot be a Serious Adverse Event (SAE) even if serious conditions are met.

**An SAE is defined as any untoward medical occurrence that, at any dose:**

- 1. Results in death**
- 2. 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.
- 3. 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

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

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.

#### **4. 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.

#### **5. Is a congenital anomaly/birth defect**

- Congenital anomaly or birth defect identified whether or not the birth has occurred
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered also SAEs

#### **6. 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 intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization.

### **A4-1.4. SPECIAL SITUATIONS**

Special Situations are defined as Abuse, Misuse, Occupational Exposure (inadvertent/accidental), Medication Error study product (with or without participant exposure to the study product e.g., study product name confusion).

- **Abuse:** Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.
- **Misuse:** Situations where a medicinal product is intentionally and inappropriately used not in accordance with the terms of the protocol.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

- **Occupational Exposure:** An exposure to a medicinal product as a result of one's professional or non-professional occupation.
- **Medical Error:** An unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the participant.

#### **A4-1.5.    ADVERSE DRUG REACTION (ADR), SERIOUS ADVERSE REACTION (SAR) AND SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR)**

- **Adverse Drug Reaction (ADR):**

An ADR 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 IB or summary of product characteristics.

#### **A4-2.    RECORDING, EVALUATING AND FOLLOW-UP**

##### **A4-2.1.    RECORDING AEs / AESIs / SAEs / SPECIAL SITUATIONS / PREGNANCY**

- All required information pertaining to the AE/AESI/SAE/Special Situation/Pregnancy will be recorded in the eCRF.
- All AESIs, SAEs, Special Situations, and Pregnancy will require additional information to be reported to Safety utilizing paper forms that must be submitted to Safety. Refer to [Appendix A4-3](#) for 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 AESI/SAE/Special Situation paper forms.
- There may be instances when copies of medical records for certain cases are requested by Safety. In this case, all participant identifiers, with the exception of the participant number, must be redacted on the copies of the medical records before submission to Safety.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

- 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/AESI/SAE/Special Situation.

## **A4-2.2. EVALUATING AEs / AESIs / SAEs / SPECIAL SITUATIONS**

### **A4-2.2.1. Severity**

- The Investigator will make an assessment of severity for each AE/AESI/SAE/Special Situation<sup>1</sup> reported during the study and assign it to one of the following categories:
- Grade refers to the severity of the AE. The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:
  - **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.
  - **Grade 2** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL<sup>2</sup>.
  - **Grade 3** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL<sup>3</sup>.
  - **Grade 4** Life-threatening consequences; urgent intervention indicated.
  - **Grade 5** Death related to AE.
- An event is defined as ‘serious’ when it meets at least 1 of the predefined outcomes as described in the definition of an SAE ([Appendix A4-1.3](#)), **not** when it is rated as severe.

<sup>1</sup>Special Situation reports may not have an applicable CTCAE Grade and may be reported without a CTCAE Grade assigned.

<sup>2</sup>Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

<sup>3</sup>Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

### **A4-2.2.2. Causality**

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of an AE/AESI/SAE/Special Situation.
- 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 causality relationship as related or not related.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

- The Investigator will consider, may investigate, and will report 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.
- The Investigator will also consult the IB when making an assessment.
- For each AE/AESI/SAE/Special Situation, the Investigator **must** document in the medical notes that they have reviewed the AE/AESI/SAE/Special Situation and has provided an assessment of causality.
- There may be situations in which an AESI/SAE/Special Situation has occurred, and the Investigator has minimal information to include in the initial report to SpringWorks. However, **it is very important that the Investigator always makes an assessment of causality for every event with the initial reporting to Safety** (refer to [Appendix A4-3](#) for reporting details)
- The Investigator may change their opinion of causality for an event in light of follow-up information and send a follow-up report with the updated causality assessment of the event.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

#### A4-2.3. FOLLOW UP

- 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 via the data clarification form to elucidate the nature and/or causality of the AE/AESI/SAE/Special Situation 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 provide Safety with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the eCRF.
- The Investigator will submit any new or updated information on the AESI/SAE or Special Situations form to Safety within 24 hours of receipt of the information.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

### **A4-3.        REPORTING**

- The preferred method of submitting AESI/SAE, Pregnancy, or Special Situations information to Safety is to email the scanned paper forms to [PV@springworkstx.com](mailto:PV@springworkstx.com). Facsimile transmission is possible. Please refer to the reporting forms for the fax phone numbers for United States of America and Europe.
- In rare circumstances in the absence of email or facsimile equipment, notification by telephone is acceptable with a copy of the AESI/SAE, Pregnancy, or Special Situations 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 AESI/SAE, Pregnancy, or Special Situations form within the designated reporting time frames.
- The AESI/SAE, Pregnancy, and Special Situation forms can be found in the Study Reference Manual.
- Contacts for AESI/SAE, Pregnancy, or Special Situations reporting can be found in [Appendix A6-4](#).

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## **APPENDIX 5. CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION**

### **A5-1. WOMEN OF CHILDBEARING POTENTIAL (WOCBP) DEFINITION**

Women of Childbearing Potential (WOCBP) are defined as women that are 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 with 1 of the following:
  - a. Documented hysterectomy; or
  - b. Documented bilateral salpingectomy; or
  - c. Documented bilateral oophorectomy.
    - a. 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.
    - b. *Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.*
3. Postmenopausal
  - a. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - i. 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 insufficient.
  - b. Participants on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen containing, 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.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## A5-2. CONTRACEPTION GUIDANCE

### CONTRACEPTIVES<sup>a</sup> ALLOWED DURING THE STUDY INCLUDE:

#### Highly Effective Contraceptive Methods<sup>b</sup> That Have Lower User Dependency

*Note: Failure rate of < 1% per year when used consistently and correctly.*

- Implantable progesterone-only hormone contraception associated with inhibition of ovulation<sup>c</sup>
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner

*Note: 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<sup>b</sup> That Are User Dependent

*Note: Failure rate of < 1% per year when used consistently and correctly.*

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation<sup>c</sup>
  - Oral
  - Intravaginal
  - Transdermal
  - Injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation<sup>c</sup>
  - Oral
  - Injectable
- Sexual abstinence

*Note: 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).*

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

### **A5-3.        COLLECTION OF PREGNANCY INFORMATION**

The Investigator will collect pregnancy information on any participant who becomes pregnant while participating in this study or pregnant partners of a male participant in the study. See [Section 10.4.5](#). Information will be recorded on the eCRF and provided on the appropriate form and submitted to the Sponsor within 24 hours of learning of a pregnancy.

The participant or the pregnant partner of a participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the pregnancy through the outcome of the pregnancy 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 10.4.5](#). While the Investigator is not obligated to actively seek this information in former study participants, they may learn of an SAE through spontaneous reporting.

Any participant who becomes pregnant while participating in the study will discontinue study treatment or be withdrawn from the study.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## **APPENDIX 6. LIST OF CONTACTS FOR STUDY**

### **A6-1. SPONSOR**

SpringWorks Therapeutics  
100 Washington Blvd  
Stamford, CT 06902  
United States  
Telephone: 212-421-8012

### **A6-2. CONTRACT RESEARCH ORGANIZATION**

Refer to the Study Reference Manual.

### **A6-3. MEDICAL MONITORING**

Refer to the Study Reference Manual.

### **A6-4. SERIOUS ADVERSE EVENT REPORTING**

United BioSource Corporation  
920 Harvest Drive, Suite 200  
Blue Bell, PA 19442  
Fax: 866-750-4514  
PV@springworkstx.com

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## APPENDIX 7. ADVERSE EVENT MANAGEMENT GUIDELINES

### A7-1. Skin Care Recommendations for All Participants

Optimizing general skin care may be helpful for preventing and limiting dermatologic reactions. Dry skin often occurs with MEKi and RAFi treatment and preventing dry skin is critical.

All participants should be counseled at treatment initiation to adopt gentle skin care practices that involve daily baths and the use of mild cleansers. Limit soap usage only to "essential areas" (face, axillae, groin, between toes).

High-quality hypoallergenic skin moisturizers should be used at least twice a day. A cream- or ointment-based emollient is preferred because lotions are too thin. Emollients are designed to prevent water loss from skin; therefore, "thicker" emollients (anything in a tub-like container) are recommended.

Proactive skin treatment including skin moisturizer, sunscreen (SPF > 15 UVA and UVB), topical steroid cream (not stronger than 1% hydrocortisone) and an oral antibiotic (e.g., doxycycline) may be useful in the preventative management of skin toxicities. Participants may be advised to apply moisturizer and sunscreen to face, hands, feet, neck, back and chest every morning during treatment, and to apply the topical steroid to face, hands, feet, neck, back and chest every night. Participants should manage sun exposure with caution due to the risks of skin toxicities. Appropriate clothing and a hat covering sun exposed skin and the use of sunscreen may reduce the incidence of skin toxicities.

Treatment of skin reactions should be based on severity and may include a moisturizer, sunscreen, and topical steroid cream applied to affected areas, and/or oral antibiotics, as prescribed by the physician (see below [Table A7-1](#) and [Table A7-2](#) for additional details).

Acneiform dermatitis and maculopapular rashes are common in adult participants who have received mirdametinib and brimarafenib monotherapy treatment. Most reports of acneiform rash and maculopapular rash arise within the first 2 cycles of treatment and may be preventable. Early onset MEKi- and RAFi-associated acneiform dermatitis and maculopapular rash are believed to be associated with disrupted skin barrier and inflammation rather than infection.

**Table A7-1: Management Strategies for Skin AEs**

Event	Management Strategies
Prophylactic strategies at initiation of treatment	<ul style="list-style-type: none"><li>• Prophylactic treatment with topical clindamycin and an oral tetracycline at an anti-inflammatory dose is recommended.</li><li>• Topical clindamycin lotion 1.0% BID should be applied to the face and chest.</li><li>• Begin treatment with a tetracycline (e.g., doxycycline or minocycline) 50mg/day for 3 months.</li></ul>
Mild rash (reactive treatment)	<ul style="list-style-type: none"><li>• If acneiform rash develops and is a bother to the participant, add hydrocortisone cream (2.5%) or</li></ul>

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

	triamcinolone ointment (0.1%) twice a day.
Moderate to severe rash (reactive treatment)	<ul style="list-style-type: none"> <li>• If acneiform rash develops <b>and</b> is a bother to the participant, add hydrocortisone cream (2.5%) or triamcinolone ointment (0.1%) twice a day.</li> <li>• If acneiform rash continues to worsen or if an infection (e.g., pustular) is suspected, refer to dermatology; stronger topical steroids or oral retinoids may be added.</li> </ul>

Do not use agents with the potential to cause dry skin, such as benzoyl peroxide, salicylic acid, acne skin washes, scrubs, exfoliants, anti-aging creams, alcohol (cleansers, wipes) or other agents that can dry skin. Avoid topical retinoids.

Fissured and cracked skin is more likely to lead to a superinfection, which is associated with pain rather than itching. For worsening infectious or noninfectious rash (e.g., rash erythematous), please consult a dermatologist.

The goal is to manage adverse events and keep participants at recommended dose.

**Table A7-2: Guidelines for Treatment Modification for Related Dermatological TEAE**

Related TEAE Worst Grade by CTCAE V5	Intervention
Grade 1 skin rash <i>Includes rash acneiform, rash maculopapular, and skin and subcutaneous tissue disorders—other manifestations might include pruritus, dry skin, etc.</i>	<ul style="list-style-type: none"> <li>• Continue mirdametinib and brimarafenib at the same dose without interruption.</li> <li>• Consider using topical steroids, antihistamines, and antibiotics.</li> <li>• Consider oral antibiotics if topical antibiotics are not improving the rash.</li> </ul>
Grade 2 skin rash	<ul style="list-style-type: none"> <li>• Continue mirdametinib and brimarafenib at the same dose without interruption, if supported by the investigator's assessment of the benefit-risk ratio.</li> </ul> <p>or</p> <ul style="list-style-type: none"> <li>• Temporarily interrupt mirdametinib and brimarafenib until resolution to Grade <math>\leq 1</math> or baseline; thereafter, re-start mirdametinib and brimarafenib at the same dose, if supported by the investigator's assessment of the benefit-risk ratio.</li> <li>• Perform dermatological exams at the frequency determined at investigator's discretion until resolution to Grade <math>\leq 1</math> or baseline.</li> </ul>
Grade 3 skin rash	<ul style="list-style-type: none"> <li>• Temporarily interrupt mirdametinib and brimarafenib.</li> <li>• Perform dermatological exams at the frequency determined at investigator's discretion until resolution to Grade <math>\leq 1</math> or baseline.</li> <li>• After resolution to Grade <math>\leq 1</math> or baseline: <ul style="list-style-type: none"> <li>○ Either re-start mirdametinib and brimarafenib at the next lower dose (see <a href="#">Table 8-2</a> and <a href="#">Table 8-3</a>) if the event did not resolve to Grade <math>\leq 1</math> within 7 days of initiating optimal</li> </ul> </li> </ul>

Mirdametinib  
Protocol MEKRAF-AST-101SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

	<p>medical and supportive care;</p> <ul style="list-style-type: none"> <li>○ Or re-start mirdametinib and brimarafenib at the same dose if the event has resolved to Grade <math>\leq 1</math> within 7 days and if supported by the investigator's assessment of the benefit-risk ratio.</li> </ul>
Grade 4 skin rash	<ul style="list-style-type: none"> <li>• Permanently discontinue mirdametinib and/or brimarafenib.</li> <li>• Provide appropriate supportive care.</li> </ul>

**Table A7-3: CTCAE Scale for Rash Acneiform**

Rash acneiform definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back.	
Grade 1	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness
Grade 2	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering >30% BSA with or without mild symptoms
Grade 3	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated
Grade 4	Life-threatening consequences; papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated
Grade 5	Death

**Table A7-4: CTCAE Scale for Rash Maculopapular**

Rash maculopapular definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritis.	
Grade 1	Macules/papules covering <10% BSA with or without pruritis (e.g., pruritis, burning, tightness)
Grade 2	Macules/papules and/or pustules covering 10-30% BSA with or without symptoms (e.g., pruritis, burning, tightness); limiting instrumental ADS; rash covering >30% BSA with or without mild symptoms
Grade 3	Macules/papules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL

Mirdametininib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

## **A7-2.        Diarrhea Care Recommendation for All Participants**

Diarrhea has been reported with brimarafenib and mirdametininib monotherapy treatment, respectively, with most cases being Grade 1 or Grade 2. For diarrhea, all participants should be counseled at treatment initiation to manage their diet. Initial interventions for Grade 1-2 diarrhea should include avoidance of greasy foods and possible adoption of the BRAT (Bananas, Rice, Apples, Toast) diet. Probiotics can also be added. If this is insufficient, loperamide or similar antidiarrheal agents can be used per institutional practice. Consider if other newly prescribed medications may be contributing to diarrhea.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

### 13. REFERENCES

Lumakras (sotorasib) [package insert]. Amgen; 2021.

Anderson, Neil G., Maller James L., Tonks Nicholas K., and Sturgill Thomas W. 1990.

“Requirement for Integration of Signals from Two Distinct Phosphorylation Pathways for Activation of MAP Kinase.” *Nature* 343 (6259): 651–53.

<https://doi.org/10.1038/343651a0>.

Bollag Gideon, Hirth Peter, Tsai James, Zhang Jiazhong, Ibrahim Prabha N., Cho Hanna, Spevak Wayne, et al. 2010. “Clinical Efficacy of a RAF Inhibitor Needs Broad Target Blockade in BRAF-Mutant Melanoma.” *Nature* 467 (7315): 596–99.

<https://doi.org/10.1038/nature09454>.

Carvajal, Richard D, Jeffrey A Sosman, Jorge Fernando Quevedo, Mohammed M Milhem, Anthony M Joshua, Ragini R Kudchadkar, Gerald P Linette, et al. 2014. “Effect of Selumetinib vs Chemotherapy on Progression-Free Survival in Uveal Melanoma: A Randomized Clinical Trial.” *JAMA : The Journal of the American Medical Association* 311 (23): 2397–2405. <https://doi.org/10.1001/jama.2014.6096>.

Chapman, Paul B., Axel Hauschild, Caroline Robert, John B. Haanen, Paolo Ascierto, James Larkin, Reinhard Dummer, et al. 2011. “Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation.” *New England Journal of Medicine* 364 (26): 2507–16. <https://doi.org/10.1056/NEJMoal103782>.

Dankner, Matthew, April A. N. Rose, Shivshankari Rajkumar, Peter M. Siegel, and Ian R. Watson. 2018. “Classifying BRAF Alterations in Cancer: New Rational Therapeutic Strategies for Actionable Mutations.” *Oncogene* 37 (24): 3183–99. <https://doi.org/10.1038/s41388-018-0171-x>.

De Braud, Filippo, Christophe Doms, Rebecca S. Heist, Celeste Lebbe, Martin Wermke, David Planchard, Dirk Schadendorf, et al. 2022. “Phase Ib Study of LXH254 + Trametinib (TMT) in Patients (Pts) with NRAS-Mutant Melanoma.” *American Association for Cancer Research Meeting*, no. CT 197.

Dréno, Ribas, Larkin, Ascierto, Hauschild, Thomas, Grob, et al. 2017. “Incidence, Course, and Management of Toxicities Associated with Cobimetinib in Combination with Vemurafenib in the CoBRIM Study.” *Annals of Oncology* 28 (5): 1137–44. <https://doi.org/10.1093/annonc/mdx040>.

Dummer, Reinhard, Keith T. Flaherty, Caroline Robert, Ana Arance, Jan Willem B. de Groot, Claus Garbe, Helen J. Gogas, et al. 2022. “COLUMBUS 5-Year Update: A Randomized, Open-Label, Phase III Trial of Encorafenib Plus Binimetinib Versus Vemurafenib or Encorafenib in Patients With BRAF V600–Mutant Melanoma.” *Journal of Clinical Oncology* 40 (36): 4178–88. <https://doi.org/10.1200/JCO.21.02659>.

Dummer, Schadendorf, Ascierto, Arance, Dutriaux, Di Giacomo, Rutkowski, et al. 2017a. “Binimetinib versus Dacarbazine in Patients with Advanced NRAS-Mutant Melanoma (NEMO): A Multicentre, Open-Label, Randomised, Phase 3 Trial.” *Lancet Oncology*, The 18 (4): 435–45. [https://doi.org/10.1016/S1470-2045\(17\)30180-8](https://doi.org/10.1016/S1470-2045(17)30180-8).

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

- Dummer, Schadendorf, Ascierto, Arance, Dutriaux, Di Giacomo, Rutkowski, et al. 2017b. “Binimetinib versus Dacarbazine in Patients with Advanced NRAS-Mutant Melanoma (NEMO): A Multicentre, Open-Label, Randomised, Phase 3 Trial.” *Lancet Oncology, The* 18 (4): 435–45. [https://doi.org/10.1016/S1470-2045\(17\)30180-8](https://doi.org/10.1016/S1470-2045(17)30180-8).
- Eisenhauer, EA. 2009. “New Response Evaluation Criteria in Solid Tumors: RECIST GUIDELINE VERSION 1.1.” *EJC Supplements* 7 (2): 5. [https://doi.org/10.1016/S1359-6349\(09\)70018-7](https://doi.org/10.1016/S1359-6349(09)70018-7).
- Flaherty, Keith T., Jeffery R. Infante, Adil Daud, Rene Gonzalez, Richard F. Kefford, Jeffrey Sosman, Omid Hamid, et al. 2012. “Combined BRAF and MEK Inhibition in Melanoma with BRAF V600 Mutations.” *New England Journal of Medicine* 367 (18): 1694–1703. <https://doi.org/10.1056/NEJMoa1210093>.
- Flaherty, Keith T., Caroline Robert, Peter Hersey, Paul Nathan, Claus Garbe, Mohammed Milhem, Lev V. Demidov, et al. 2012. “Improved Survival with MEK Inhibition in BRAF-Mutated Melanoma.” *New England Journal of Medicine* 367 (2): 107–14. <https://doi.org/10.1056/NEJMoa1203421>.
- Hauschild, A., J.J. Grob, L.V. Demidov, T. Jouary, R. Gutzmer, M. Millward, P. Rutkowski, et al. 2012. “Dabrafenib in BRAF-Mutated Metastatic Melanoma: A Multicentre, Open-Label, Phase 3 Randomised Controlled Trial.” *Lancet, The* 380 (9839): 358–65. [https://doi.org/10.1016/S0140-6736\(12\)60868-X](https://doi.org/10.1016/S0140-6736(12)60868-X).
- Hoshino, Rika, Yuji Chatani, Takao Yamori, Takashi Tsuruo, Hiroya Oka, Osamu Yoshida, Yutaka Shimada, et al. 1999. “Constitutive Activation of the 41-/43-KDa Mitogen-Activated Protein Kinase Signaling Pathway in Human Tumors.” *Oncogene* 18 (3): 813–22. <https://doi.org/10.1038/sj.onc.1202367>.
- Jänne, Pasi A., Michel M. van den Heuvel, Fabrice Barlesi, Manuel Cobo, Julien Mazieres, Lucio Crinò, Sergey Orlov, et al. 2017. “Selumetinib Plus Docetaxel Compared With Docetaxel Alone and Progression-Free Survival in Patients With KRAS-Mutant Advanced Non-Small Cell Lung Cancer: The SELECT-1 Randomized Clinical Trial.” *JAMA : The Journal of the American Medical Association* 317 (18): 1844. <https://doi.org/10.1001/jama.2017.3438>.
- Kim, Lee, Kim, Shin, Han, Kim, Kim, et al. 2021. “529P A Phase Ib Trial of Belvarafenib in Combination with Cobimetinib in Patients (Pts) with RAS- or RAF- Mutated (m) Solid Tumors: Updated Safety Data and Indication-Specific Efficacy Results.” *Annals of Oncology* 32 (September): S595. <https://doi.org/10.1016/j.annonc.2021.08.1051>.
- Kwong, Lawrence N, Genevieve M Boland, Dennie T Frederick, Timothy L Helms, Ahmad T Akid, John P Miller, Shan Jiang, et al. 2015. “Co-Clinical Assessment Identifies Patterns of BRAF Inhibitor Resistance in Melanoma.” *Journal of Clinical Investigation, The* 125 (4): 1459–70. <https://doi.org/10.1172/JCI78954>.
- Larkin, James, Paolo A. Ascierto, Brigitte Dréno, Victoria Atkinson, Gabriella Liskay, Michele Maio, Mario Mandalà, et al. 2014. “Combined Vemurafenib and Cobimetinib in BRAF-Mutated Melanoma.” *New England Journal of Medicine* 371 (20): 1867–76. <https://doi.org/10.1056/NEJMoa1408868>.

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

- Li, Siqi, Allan Balmain, and Christopher Counter. 2018. "A Model for RAS Mutation Patterns in Cancers: Finding the Sweet Spot." *Nature Reviews Cancer* 18 (12). <https://doi.org/10.1038/s41568-018-0076-6>.
- Liu, S, and Y Yuan. 2015. "Bayesian Optimal Interval Designs for Phase I Clinical Trials." *J R Stat Soc Ser C Appl Stat* 64: 507–23.
- Long, Georgina V., Fung Carina, Menzies Alexander M., Pupo Gulietta M., Carlino Matteo S., Hyman Jessica, Shahheydari Hamideh, et al. 2014. "Increased MAPK Reactivation in Early Resistance to Dabrafenib/Trametinib Combination Therapy of BRAF-Mutant Metastatic Melanoma." *Nature Communications*, December, 5694. <https://doi.org/10.1038/ncomms6694>.
- LoRusso, Patricia M., Smitha S. Krishnamurthi, John J. Rinehart, Lisle M. Nabell, Lisa Malburg, Paul B. Chapman, Samuel E. DePrimo, et al. 2010. "Phase I Pharmacokinetic and Pharmacodynamic Study of the Oral MAPK/ERK Kinase Inhibitor PD-0325901 in Patients with Advanced Cancers." *Clinical Cancer Research* 16 (6): 1924–37. <https://doi.org/10.1158/1078-0432.CCR-09-1883>.
- Menzer, Christian, Alexander M. Menzies, Matteo S. Carlino, Irene Reijers, Emma J. Groen, Thomas Eigentler, Jan Willem B. de Groot, et al. 2019. "Targeted Therapy in Advanced Melanoma With Rare BRAF Mutations." *Journal of Clinical Oncology* 37 (33): 3142–51. <https://doi.org/10.1200/JCO.19.00489>.
- Moodie, S A, M Paris, E Villafranca, P Kirshmeier, B M Willumsen, and A Wolfman. 1995. "Different Structural Requirements within the Switch II Region of the Ras Protein for Interactions with Specific Downstream Targets." *Oncogene* 11 (3): 447–54.
- Oken, Martin M., Richard H. Creech, Douglass C. Tormey, John Horton, Thomas E. Davis, Eleanor T. McFadden, and Paul P. Carbone. 1982. "Toxicity and Response Criteria of the Eastern Cooperative Oncology Group." *American Journal of Clinical Oncology* 5 (6): 649–56. <https://doi.org/10.1097/00000421-198212000-00014>.
- Prior, Ian A., Fiona E. Hood, and James L. Hartley. 2020. "The Frequency of Ras Mutations in Cancer." *Cancer Research* 80 (14): 2969–74. <https://doi.org/10.1158/0008-5472.CAN-19-3682>.
- Reddy, Sangeetha, Alexandre Reuben, and Jennifer Wargo. 2016. "Influences of BRAF Inhibitors on the Immune Microenvironment and the Rationale for Combined Molecular and Immune Targeted Therapy." *Current Oncology Reports* 18 (7): 1–9. <https://doi.org/10.1007/s11912-016-0531-z>.
- Roskoski, R. 2010. "RAF Protein-Serine/Threonine Kinases: Structure and Regulation." *Biochemical and Biophysical Research Communications* 399 (3): 313–17. <https://doi.org/10.1016/j.bbrc.2010.07.092>.
- Sung, Hyuna, Jacques Ferlay, Rebecca L. Siegel, Mathieu Laversanne, Isabelle Soerjomataram, Ahmedin Jemal, and Freddie Bray. 2021. "Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries." *CA: A Cancer Journal for Clinicians* 71 (3): 209–49. <https://doi.org/10.3322/caac.21660>.
- Vinitzky, Anna, Jason Chiang, Asim K. Bag, Olivia Campagne, Clinton F. Stewart, Paige Dunphy, Barry Shulkin, et al. 2022. "J901: Phase I/II Evaluation of Single Agent

Mirdametinib  
Protocol MEKRAF-AST-101

SpringWorks Therapeutics, Inc.  
Amendment 2 (24 July 2023)

Mirdametinib (PD-0325901), a Brain-Penetrant MEK1/2 Inhibitor, for the Treatment of Children, Adolescents, and Young Adults with Low-Grade Glioma (LGG).” In .  
Hamburg.

Zhou, H., J. J. Lee, and Y Yuan. 2017. “BOP2: Bayesian Optimal Design for Phase II Clinical Trials with Simple and Complex Endpoints.” *Statistics in Medicine* 36 (21): 3302–14.  
<https://doi.org/10.1002/sim.7338>.