A TWO-PART, PHASE 1A/B, OPEN-LABEL, MULTICENTER TRIAL EVALUATING PHARMACOKINETICS, SAFETY AND EFFICACY OF PF-07284890 (ARRY-461) IN PARTICIPANTS WITH BRAF V600-MUTANT SOLID TUMORS WITH AND WITHOUT BRAIN INVOLVEMENT

Study Intervention Number:	PF-07284890 (ARRY-461)
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Protocol Number:	C4471001
Phase:	1a/b

Short Title: *A First-In-Human Study of PF-07284890 in Participants With BRAF V600 Mutant Solid Tumors With and Without Brain Involvement*

Document History

Document	Version Date
Amendment 3	20 July 2022
Amendment 2	14 January 2021
Amendment 1	03 August 2020
Original protocol	12 June 2020

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative change letter(s).

Protocol Amendment Summary of Changes Table

Amendment 3 (20 July 2022)

Overall Rationale for the Amendment: The protocol was amended to modify the required number of patients per expansion cohort, to allow for an optional food effect substudy, and to clarify aspects of the protocol.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Addition of intracranial extracranial response evaluation to endpoints related to objective of anti-tumor efficacy	Extracranial and intracranial will be evaluated separately and collectively as overall response.
1.1 Synopsis	Revised sample size for Phase 1b expansion cohorts	Removal of NSCLC population from cohorts 1-4 to evaluate efficacy in patients with melanoma; sample size was reduced to reflect the removal of NSCLC with no impact to statistical design. Addition of patients to cohort 5 to better estimate treatment effect in diverse population including NSCLC.
1.1 Synopsis	Evaluation of repeated administration of PF-07284890 in combination with binimetinib on single dose PK of midazolam (Cohort 6 only)	This substudy is now optional.

Section # and Name	Description of Change	Brief Rationale
	moved from secondary to tertiary objective	
1.1 Synopsis	Addition of optional food-effect substudy	If the effect of food on exposures, based on results from C4471002 is positive and large (2-fold or more), the tolerability of repeat dosing with food will be studied in a substudy of patients.
1.1 Synopsis	Modification of DDI substudy to optional	A DDI substudy may be performed optionally now.
1.1 Synopsis	Added information regarding the communication of results from the ongoing food-effect study, C4471002	To address how fasting requirements may be changed.
1.2 Schema	Updated with substudies, changes to eligibility and sample sizes.	For consistency.
1.3 Schedule of Activities	Clarifications and addition of testing and evaluation	To assess maturity and trigger requirement for contraceptive measures.
2.2.3 Nonclinical Safeety	Updated genotoxicity risk	Due to new data from in vitro mouse lymphoma, comet assay, and in vivo micronucleus.
2.3 Benefit/Risk	Added facial paresis to list of risks for BRAF inhibitors	For completeness and consistency with package inserts of other approved BRAFis.
2.2.4.1 PF-07284890	Instruction to reference IB for information regarding clinical experience	To clarify that the accumulated clinical data are summarized there.
3 Objectives and Endpoints	Addition of intracranial and extracranial response evaluation to endpoints related to objective of anti-tumor efficacy	Extracranial and intracranial will be evaluated separately and collectively as overall response.
3 Objectives and Endpoints	Evaluation of repeated administration of PF-07284890 in combination with binimetinib on single dose PK of midazolam (Cohort 6 only)	This substudy is now optional.

Section # and Name	Description of Change	Brief Rationale
	moved from secondary to tertiary objective	
4.1 Overall Design	Revised sample size for Phase 1b expansion cohorts	Removal of NSCLC population from cohorts 1-4 to evaluate efficacy in patients with melanoma; sample size was reduced to reflect the removal of NSCLC with no impact to statistical design. Addition of patients to cohort 5 to better estimate treatment effect in diverse population including NSCLC.
4.1 Overall Design	Addition of optional food-effect substudy and modification of DDI substudy to optional	If the effect of food on exposures, based on results from C4471002 is positive and large (2-fold or more), the tolerability of repeat dosing with food will be studied in a substudy of patients. A DDI substudy may be performed optionally now.
4.1 Overall Design	Added information regarding the communication of results from the ongoing food-effect study, C4471002	To address how fasting requirements may be changed.
4.2.6 Rationale for Food-effect	Added Rationale for Food-effect Substudy	To clarify the rationale for the substudy.
4.3.5 Stopping Criteria in Phase 1b Dose Expansion	Added Stopping Criteria in Phase 1b Dose Expansion	For patient safety.
5.1 Inclusion Criteria	Addition of adolescents aged 16 and over with body weight 40 kg and over and added clarification on consenting adolescent participants	Based on guidance from the regulatory authorities, adolescent patients may be considered for inclusion in trials including adult patients under certain circumstances. Adolescents with certain BRAF V600-mutant cancers (eg, primary brain tumros) have unmet need and therefore are appropriate for this study.

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Adding requirement for measurable disease in Cohort 5	To aid in the assessment of anti-tumor response.
6.1.1.1 Food Requirements	Added information regarding the communication of results from the ongoing food-effect study, C4471002	To address how fasting requirements may be changed.
6.4 Study Intervention compliance	Clarify requirements for study intervention compliance	For clarity.
6.6.3 Dose Delays	Removal of separate hematologic requirements for cycle start; clarification to refer to the Dose Modification table and clarification on treatment resumption	To eliminate contradictory guidance.
6.6.4 Dose Reductions	Clarify dose reductions for patients receiving PF-07284890 BID	Based on observed data within the trial, BID dosing was implemented, and dose reduction guidance has been clarified therefore.
7.2 Participant Discontinuation/With drawal from Study	Clarification criteria for withdrawal from study	For clarification.
8.1 Efficacy Assessments	Clarify tumor response assessments for patients with primary brain tumors	For clarity.
8.2.1 Physical Examinations	Add Tanner Stage assessment to Physical Exam for adolescents	To assess maturity and trigger requirement for contraceptive measures.
8.2.8 Clinical Safety Laboratory Assessments	Remove requirement for repeat laboratory assessments at C1D1 if collected in 7 days prior during screening	To reduce patient burden without impact to study objectives.
8.2.11 Additional Asssessments for Adolescent Participants	Added assessments for adolescent participants	To assess maturity and trigger requirement for contraceptive measures.
8.3.8 Adverse Events of Speical Interest	Added clarification on AESI review	For clarity.

Section # and Name	Description of Change	Brief Rationale
8.5 Pharmacokinetics	Change to sample volume of CSF sample	To facilitate the required testing.
9.2 Sample Size Determination	Update sample size for cohorts 1-4, addition of optional food-effect substudy and modification of DDI substudy to optional	Removal of NSCLC population from cohorts 1-4 to evaluate efficacy in patients with melanoma; sample size was reduced to reflect the removal of NSCLC with no impact to statistical design. Addition of patients to cohort 5 to better estimate treatment effect in diverse population in NSCLC.
9.5 Data Monitoring Committee or Other Independent Oversight Committee	Addition of safety review committee for review of safety during dose expansion phase	To ensure patient safety.
10 Apppendices	Addition of list of prohibited concomitant medications that may result in DDI; clarifications of alternative measures to take during public emergencies	For patient safety and to allow for adequate monitoring of patients during the trial.
10 Appendices	Addition of assent requirements for adolescents; addition of food-effect substudy appendix; further specification of response assessment by mRECIST 1.1; further specification of response assessment by RANO (HGG vs. LGG);	To facilitate other changes as previously referenced.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1a/b Study of PF-07284890 in Participants With BRAF V600-Mutant Solid Tumors With and Without Brain Involvement

Rationale: The purpose of this first-in-human study is to assess the PK, safety and preliminary clinical activity of PF-07284890 (also known as ARRY-461) as a single agent and in combination with the MEK inhibitor, MEKTOVI (binimetinib), in participants with BRAF V600-mutated advanced solid tumor malignancies with and without brain involvement.

Objectives and Endpoints

Objectives	Endpoints
Phase 1a Primary:	**Phase 1a Primary:**
• To assess the safety and tolerability of PF-07284890 at increasing dose levels, to estimate the MTD, and to select the recommended dose for further study, as both a single agent and in combination with binimetinib, in participants with BRAF V600-mutated advanced solid tumor malignancies with and without brain involvement.	• Incidence of Cycle 1 DLTs. • MTD/recommended dose for further study. • AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to study therapy. • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing. • Incidence of dose interruptions, dose modifications and discontinuations due to AEs.
Phase 1a Secondary:	**Phase 1a Secondary:**
• To characterize the single- and multiple-dose PK of PF-07284890 as a single agent and in combination with binimetinib and of binimetinib in combination with PF-07284890.	• PK parameters of PF-07284890 and binimetinib: • Single dose: C_{max}, T_{max}, AUC_{last}, and as data permit, $t_{½}$, AUC_{inf}, CL/F and V_z/F. • Multiple dose (assuming steady state is achieved): $C_{ss,max}$, $T_{ss,max}$, $AUC_{ss,\tau}$, $C_{ss,min}$, and as data permit, CL_{ss}/F, V_{ss}/F, $t_{½}$ and R_{ac} ($AUC_{ss,\tau}$/$AUC_{sd,\tau}$).
• To evaluate preliminary clinical activity of PF-07284890 as a single agent and in combination with binimetinib.	• Extracranial response by RECIST version 1.1. • Intracranial response by mRECIST version 1.1. • Overall response (combined extracranial and intracranial) by mRECIST version 1.1. • RANO for primary brain tumors.
Phase 1a Tertiary/Exploratory:	**Phase 1a Tertiary/Exploratory:**
• To explore the effect of CCI on PF-07284890 exposures in participants treated with PF-07284890 as a single agent and in combination with binimetinib.	• PF-07284890 PK parameters (single dose C_{max} and AUC_{last}; multiple dose $C_{ss,max}$, $AUC_{ss,\tau}$) in participants CCI.
• To explore the brain penetration of PF-07284890 as a single agent and in combination with binimetinib.	• CSF concentrations of PF-07284890 (in participants in whom CSF is obtained as SOC).
• To evaluate tumor and blood-based biomarkers of response and resistance to PF-07284890 as a single agent and in combination with binimetinib.	CCI

Objectives	Endpoints
• To assess the relationship between PF-07284890 concentrations and changes in QTcF.	• Maximal changes in QTcF estimated using a linear mixed effect model.
Phase 1b Primary:	**Phase 1b Primary:**
• To evaluate anti-tumor efficacy of PF-07284890 at the recommended dose for further study in combination with binimetinib in participants with BRAF V600mutated advanced solid tumor malignancies with and without brain involvement.	• Extracranial response by RECIST version 1.1. • Intracranial response by mRECIST version 1.1. • Overall response (combined extracranial and intracranial) by mRECIST version 1.1. • RANO for primary brain tumors.
Phase 1b Secondary:	**Phase 1b Secondary:**
• To confirm the safety and tolerability of PF-07284890 at the recommended dose for further study in combination with binimetinib.	• AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to study therapy. • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing. • Incidence of dose interruptions, dose modifications and discontinuations due to AEs.
• To evaluate single- and multiple-dose PK profiles of PF-07284890 at the recommended dose for further study in combination with binimetinib and of binimetinib in combination with PF-07284890.	PK parameters of PF-07284890 and binimetinib: • Single dose - C_{max}, T_{max}, AUC_{last}, and as data permit, $t_{½}$, AUC_{inf}, CL/F and V_z/F. • Multiple dose (assuming steady state is achieved) - $C_{ss,max}$, $T_{ss,max}$, $AUC_{ss,\tau}$, $C_{ss,min}$, and as data permit, CL_{ss}/F, V_{ss}/F, $t_{½}$ and R_{ac} ($AUC_{ss,\tau}/AUC_{sd,\tau}$).
• To assess additional measures of anti-tumor efficacy of PF-07284890 at the recommended dose for further study in combination with binimetinib.	• DCR (overall and intracranial). • PFS (overall and intracranial), OS, DoR (overall and intracranial) and TTR (overall and intracranial).
Phase 1b Tertiary/Exploratory:	**Phase 1b Tertiary/Exploratory:**
• To explore the effect of CCI on PF-07284890 exposures in participants treated with PF-07284890 in combination with binimetinib.	CCI
• To explore the brain penetration of PF-07284890 in combination with binimetinib.	• CSF concentrations of PF07284890 (in participants in whom CSF is obtained as SOC).
• To evaluate tumor and blood-based biomarkers of response and resistance to PF-07284890 in combination with binimetinib.	CCI
• To evaluate the effect of repeated administration of PF-07284890 in combination with binimetinib on single dose PK of midazolam (Cohort 6 only).	PK parameters of CYP3A4 probe substrate midazolam: • C_{max}, T_{max}, AUC_{last}, and as data permit, $t_{½}$, AUC_{inf}, CL/F and V_z/F.

Overall Design

This is a Phase 1a/b, open-label, multicenter, dose-finding study of the safety, PK and preliminary clinical activity of PF-07284890 in adult or adolescent participants with selected BRAF V600-mutant advanced or metastatic solid tumor malignancies and primary brain tumors. The study will be conducted in 2 parts, ie, Phase 1a (Dose Escalation) and Phase 1b (Dose Expansion, an optional DDI substudy, and optional food-effect substudy).

Participants will have experienced disease progression after prior treatment and have no acceptable alternative treatment options.

Participants must provide documented evidence of a BRAF V600 mutation in tumor tissue or blood (ie, CCI) as previously determined by PCR or NGS-based laboratory assay in a CLIA or similarly certified laboratory at any time prior to Screening. Local testing is permitted (see Section 4.2.4). Participants are required to submit either archival or newly collected tissue sample (the latter if a biopsy is safe to perform; if not, participants may be eligible as long as they meet other eligibility criteria) and a blood sample prior to enrollment, which may be used for retrospective analysis of BRAF V600 mutation status but not to determine eligibility/enrollment.

Enrolled participants may be with or without brain involvement at baseline, with the allowed extent of and symptoms from intracranial disease determined by the degree of calculated BRAF V600E target coverage during dose escalation, and the specific cohort during dose expansion (see Section 5).

Phase 1a Dose Escalation

Approximately 35 participants will be enrolled to determine the MTD and/or recommended dose for further study of PF-07284890 alone and in combination with binimetinib 45 mg BID. Monotherapy dose escalation will initiate first.

A participant is classified as DLT evaluable if he/she experiences a DLT (Section 4.3.3) or if he/she otherwise in the absence of a DLT receives at least 75% of the planned PF-07284890 doses (and at least 75% of the planned binimetinib doses if the participant is receiving combination treatment) and has received all scheduled safety assessments during the DLT observation window (first cycle of treatment, a 21-day cycle).

A BLRM will be used to model the DLT relationship of PF-07284890. This model, along with the EWOC, will guide the dose escalation of PF-07284890 after the completion of the DLT observation period of each cohort, until adequate DLT data has accumulated throughout the monotherapy dose escalation to inform then combination BLRM or until the determination of MTD/recommended dose for PF-07284890 monotherapy.

Cohorts of 2-4 evaluable participants will be treated at each dose level of PF-07284890 on an outpatient basis starting from 50 mg QD until the determination of MTD/recommended dose for further study. A minimum of 6 participants are expected to be treated at MTD/recommended dose for further study (ie, 6 participants each for both monotherapy and combination therapy) in order to evaluate safety, tolerability, PK as well as preliminary activity of PF-07284890 when given at the MTD/recommended dose for further study (both alone and in combination with binimetinib). The actual dose increases between dose levels will be determined by safety and observed PK as described in Section 4.3.2. In addition, an alternative schedule (eg, BID, dosing holiday) may be evaluated depending on safety and observed PK.

BLRM and EWOC will be used to model the DLT relationship of PF-07284890 in combination with binimetinib at the approved dose of 45 mg BID (monotherapy dose escalation will continue simultaneously). Based on preliminary PK and safety, the combination dose escalation phase of PF-07284890 with binimetinib may be started prior to the determination of the monotherapy PF-07284890 MTD/recommended dose for further study. The starting dose level for PF-07284890 in the combination dose therapy escalation will not be higher than previously studied doses in the monotherapy escalation and will satisfy EWOC criteria. The parameters will be derived from the combination BLRM by incorporating DLT data obtained from the PF-07284890 monotherapy escalation and historical data for binimetinib (see Section 9.3.1.1).

For both monotherapy and combination therapy dose escalations, toxicities will only be considered DLTs if they occur within the DLT window of the first cycle (21 days). However, overall safety, including later cycles, and PK data will be evaluated for the recommended dose for further study determination.

Phase 1b Dose Expansion, optional DDI Substudy, and optional Food-Effect Substudy

After identification of the combination MTD/recommended dose for further study, approximately 20 participants will be enrolled to each of the Cohorts 1-4 and 40 participants to Cohort 5 of Phase 1b dose expansion based on tumor type, whether brain involvement is asymptomatic or symptomatic and measurable or non-measurable, prior treatment history and a history of or current leptomeningeal metastases. The participants intended for each cohort are described in Section 1.2 and Section 5. The dose expansion phase (Cohorts 1-5) will evaluate efficacy, safety and PK at the recommended dose for further study in combination with binimetinib.

The effect of food (low fat and high fat meal versus fasted state) on PF-07284890 PK is being assessed in study C4471002 in healthy participants. Once the results of this food-effect study are available, it may trigger the opening of an optional Cohort 7 and/or the instructions for administration of C4471001 may be changed as appropriate so that patients can take PF-07284890 without regard to food at the MTD/RDE, or should take PF-07284890 in the fed state, with adjustment of dose based on C4471002 data (ie, the dose equivalent to the fasted state MTD/RDE adjusted based on the difference in exposure observed in C4471002 in the fasted state compared to the fed state). However, if the effect of food is found to be substantial, positive and clinically significant (ie, ≥2-fold increase in AUC for either the low-fat or high-fat meal), an additional cohort of patients will be enrolled in the current study before changing administration instructions for the current study. This cohort (optional Cohort 7) of approximately 6-8 patients will be enrolled to assess the safety and PK of a recommended dose for further study (ie, the dose equivalent to the fasted state MTD/RDE adjusted based observed on C4471002 PK) to be given with food. If the recommended dose in combination with food is tolerated, patients accrued into Cohorts 1-6 will receive instruction to administer drug with food. To mitigate burden to patients, change(s) in dose and dosing instructions regarding administration with food may initially be communicated by PACL followed by subsequent protocol amendment.

In addition, approximately 10 participants may be enrolled to an optional substudy (Cohort 6) to evaluate the effect of PF-07284890 in combination with binimetinib on CYP3A activity using midazolam as a probe CYP3A4 substrate.

Treatment with study intervention will continue until either disease progression, participant refusal, unacceptable toxicity occurs, or up to 2 years, whichever occurs first. Participants who have disease progression but are deriving clinical benefit may continue if criteria are met and the participant consents/assents to continue treatment (see Section 7.1.1). Participants who complete 2 years on study intervention and demonstrate clinical benefit with manageable toxicity and are willing to continue receiving the study intervention will be given the opportunity to continue treatment upon agreement between investigator and sponsor, using the same safety assessments as were being performed most recently, but with efficacy monitored at intervals consistent with clinical practice.

Number of Participants

An expected number of approximately 120-138 participants will be enrolled to study intervention. Refer to Section 9.2 for sample size determination.

Note: "Enrolled" means a participant's, or his or her legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent/assent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration

The total duration of the study from the beginning of screening to the safety follow-up visit is approximately 2 years.

Dose Level Review Meeting

This study will utilize a DLRM for dose escalation decisions (see Section 9.5). The members of the DLRM includes a mix of internal Pfizer study team members and external investigators and/or medically qualified designee.

Statistical Methods

Adaptive Bayesian approach: The dose escalation in the Phase 1a of the study will be guided by a BLRM analysis of the first 21 days (Cycle 1) of DLT data for PF-07284890. Toxicity is modelled using a logistic regression for the probability of a participant experiencing a DLT at the given dose. A similar approach will be used to guide the combination dose escalation for the PF-07284890 with binimetinib.

Assessment of participant risk: After each cohort of participants, the posterior distribution for the risk of DLT for new participants at different doses of interest for PF-07284890 will be evaluated. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the following intervals:

Under-dosing:	[0, 0.16]
Target dosing:	[0.16, 0.33]
Overdosing:	[0.33, 1]

The EWOC principle: Dosing decisions are guided by the EWOC principal. A dose may only be used for newly enrolled participants if the risk of over-dosing at that dose is less than 25%.

Prior distributions: MAP prior distribution based on clinical/expert opinion information will be chosen for the logistic parameters.

For Phase 1b, the expansion arms will be conducted to assess efficacy as well as safety and tolerability of PF-07284890 in combination therapy with binimetinib.

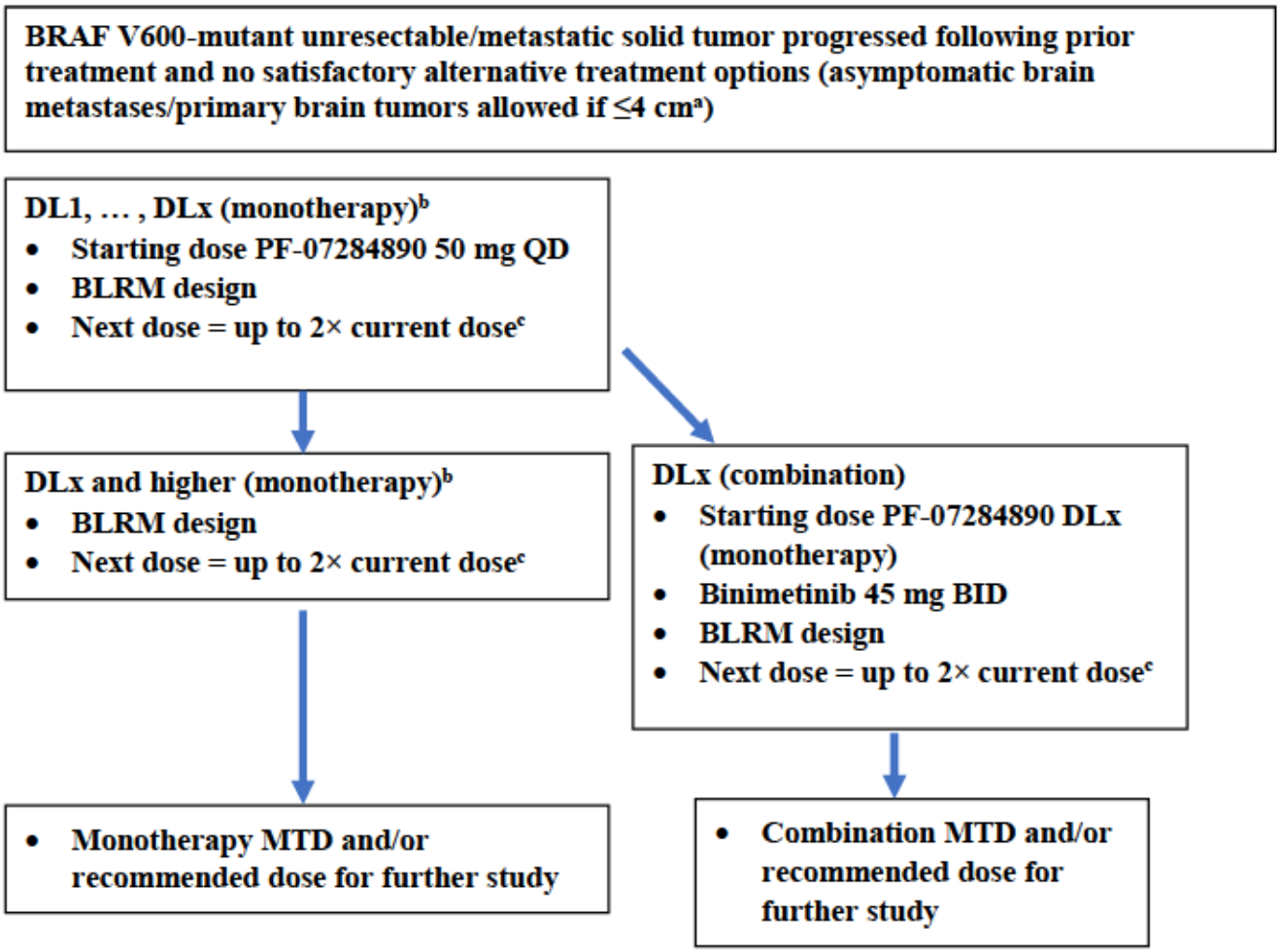
In Phase 1b, the primary endpoint of overall response by RECIST version 1.1 and intracranial response by mRECIST version 1.1 (RANO for primary brain tumors) will be summarized and listed by expansion cohort and disease type. The secondary endpoints of DCR (overall and intracranial), PFS (overall and intrcranial), OS, DoR (overall and intracranial) and TTR (overall and intracranial) will be summarized (graphically where appropriate) and listed by expansion cohort and disease type.

AEs will be graded by the investigator according to the NCI CTCAE version 5.0 and coded using the MedDRA. The number and percentage of participants who experienced any AE, SAE, treatment-related AE, and treatment-related SAE will be summarized according to worst toxicity grades. The summaries will present Aes both on the entire study period and by cycle (Cycle 1 and beyond).

1.2. Schema

A diagram of the study design is displayed in Figure 1 and Figure 2.

Figure 1. Study Schema for Phase 1a Dose Escalation (Approximately 35 Participants)



a. Once the trough concentration of PF-07284890 at steady state is ≥0.168 µg/mL (equal to the fu-adjusted IC_{70} for inhibition of BRAF V600E) in at least two-thirds of participants at the same dose level (a level at which anti-tumor activity in the brain and systemically may be expected), subsequent participants entering the study during dose escalation may have a lesion(s) >4 cm and/or be symptomatic in the brain as defined in Section 5.1.

b. Intrapatient dose escalation and/or addition of binimetinib may be allowed after 12 weeks of monotherapy or disease progression. See Section 4.3.2.3.

c. If no DLTs at the current and all prior dose levels, and if the observed trough concentration at steady state with the current dose is < the calculated IC_{50} of PF-07284890 in at least two-thirds of participants, the next dose will not exceed 3× the current dose level. See Section 4.3.2.

Figure 2. Study Schema for Phase 1b Dose Expansion with Optional Food-Effect and DDI Substudy (Approximately 20 Participants Per Cohort for Cohorts 1-4, 40 Participants for Cohort 5 and 10 Participants for Optional Cohort 6 and 6-8 Participants for Cohort 7)

BRAF V600-mutant unresectable/metastatic solid tumor

PF-07284890 at the recommended dose for further study + binimetinib at 45 mg BID

Cohort 1:
melanoma, no prior BRAF or MEK inhibitor in metastatic setting (or in the adjuvant setting within 6 months of study treatment), asymptomatic[a] in the brain, with measurable disease[b] in the brain.

Cohort 2:
melanoma, no prior BRAF or MEK inhibitor in metastatic setting (or in the adjuvant setting within 6 months of study treatment), symptomatic[a] in the brain, with measurable disease[b] in the brain.

Cohort 3:
melanoma, prior BRAF inhibitor in the metastatic (or adjuvant setting within 6 months of study treatment) required, asymptomatic[a] in the brain, with measurable[b] disease in the brain.

Cohort 4:
melanoma, prior BRAF inhibitor in the metastatic (or adjuvant setting within 6 months of study treatment) required, symptomatic[a] in the brain, with measurable[b] disease in the brain.

Cohort 5:
any solid tumor; history of or current leptomeningeal metastases is permitted; with or without disease in the brain as long as it is measurable and does not meet criteria for Cohorts 1-4; with or without prior BRAF and/or MEK inhibitor; asymptomatic[a] or symptomatic[a] in the brain.

Optional Cohort 6:
DDI (midazolam) substudy

Optional Cohort 7:
Food-effect substudy

a. Asymptomatic in the brain is defined as, within 14 days of the start of study: no neurological symptoms due to brain metastases/primary brain tumor; not requiring initiation of or an increase in steroid dosing to control neurological symptoms due to brain metastases/primary brain tumor; and not requiring initiation of or an increase in anti-epileptic dosing to control seizure activity due to brain metastases/primary brain tumor. Symptomatic in the brain is defined as any of the above within 14 days of the start of study treatment.

b. For Cohorts 1-4: a measurable lesion must be at least 0.5 cm and ≤4 cm in long axis and evaluable by mRECIST v1.1; if all disease in the brain was previously irradiated, at least 1 lesion must demonstrate progression by RECIST v1.1 since irradiation. For Cohort 5, patients must have at least 1 measurable lesion (per RANO for primary brain tumor, for non-glioma, and if extracranial per RECIST 1.1, if intracranial per mRECIST 1.1).

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

		Study Treatment (cycle duration = 21 days)									Notes/Protocol Section
		Cycle 1			Cycle 2		Subsequent Cycles				
Visit Identifier[a]	Screening[1]	Day 1	Day 8	Day 15	Day 1	Day 15	Day 1	EOT	30-Day Follow-Up[2]	Survival Follow-Up[3]	
Visit Window	Day -28 to Day -1	-3 days[b]	±3 days	±3 days	±3 days	±3 days	±3 days	±7 days	±7 days	Q12W±7 days	
Informed consent/assent[4]	X										Section 10.1.3
Inclusion/exclusion criteria	X	X									Sections 5.1 and 5.2 and 5.2
Demography and baseline characteristics	X										
Documentation of BRAF V600 mutation[5]	X										Section 8.7.1
Archived tumor sample[6]	X										Section 8.7.2
Fresh tumor sample (optional and only if consent provided, for pharmacodynamic analysis)[7]	X		X (window: +28 days)					X (as close to date of radiographic disease progression as possible if feasible)			Section 8.8.1
Whole blood (matched normal)[8]	X										
Blood sample for CDx[9]	X										Section 8.7.2

		Study Treatment (cycle duration = 21 days)									Notes/Protocol Section
		Cycle 1			Cycle 2		Subsequent Cycles				
Visit Identifier[a]	**Screening[1]**	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**EOT**	**30-Day Follow-Up[2]**	**Survival Follow-Up[3]**	
Visit Window	**Day -28 to Day -1**	**-3 days[b]**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±7 days**	**±7 days**	**Q12W±7 days**	
Blood sample for CCI (Specified Genetics)[10]	X	X		X	X		X (every other cycle starting with Cycle 3)	X			Section 8.7.3
HBV and HCV serology testing and HIV where applicable	X										
LH, FSH, and Estradiol for female adolescents or LH, FSH, and Testosterone for male adolescents (Phase 1b)	X						Every 4 cycles (±1 week)	X			For participants <18 years of age and Tanner Stage <4 at the time of informed consent/assent only. See Section 8.2.11.
Oncology history	X										
Medical history, prior systemic cancer therapies, radiation and surgeries	X										
Physical examination (Including height at Screening only)[11,35]	X	X	X		X	X	X		X		Section 8.2.1

		Study Treatment (cycle duration = 21 days)									Notes/Protocol Section
		Cycle 1			Cycle 2		Subsequent Cycles				
Visit Identifier[a]	**Screening**[1]	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**EOT**	**30-Day Follow-Up**[2]	**Survival Follow-Up**[3]	
Visit Window	**Day -28 to Day -1**	**-3 days**[b]	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±7 days**	**±7 days**	**Q12W±7 days**	
Tanner Stage (Phase 1b)	X						Every 4 cycles (±1 week)				For participants <18 years of age at the time of informed consent/assent only. See Section 8.2.11
Full ophthalmic examination[12,35]	X	If clinically indicated (note: visual acuity should be tested by the treating physician on Day 1 of every cycle).									Section 8.2.3
Dermatologic examination[13,35]	X	X			X		C3D1 then every other cycle/Q6W	X	X		Section 8.2.2
Neurologic examination[14]		X		X	X	X	Day 1 of Cycles 3-8, then if clinically indicated				Section 8.2.4
Vital signs and weight[15]	X	X	X	X	X	X	X	X	X		Section 8.2.6
ECOG PS[16,35]	X	X			X		X		X		Section 8.2.5
Contact IWRS	X	X			X		X	X			
Laboratory											
Hematology[17]	X	X	X	X	X		X	X	X		Appendix 2
Blood chemistry (troponin measured only for participants receiving binimetinib)[18]	X	X	X	X	X		X	X	X		Appendix 2

		Study Treatment (cycle duration = 21 days)									Notes/Protocol Section
		Cycle 1			Cycle 2		Subsequent Cycles				
Visit Identifier[a]	Screening[1]	Day 1	Day 8	Day 15	Day 1	Day 15	Day 1	EOT	30-Day Follow-Up[2]	Survival Follow-Up[3]	
Visit Window	Day -28 to Day -1	-3 days[b]	±3 days	±3 days	±3 days	±3 days	±3 days	±7 days	±7 days	Q12W±7 days	
Coagulation (aPTT, INR/PT)[19]	X	X	X	X	X	X	Day 1 of Cycles 3-8, then if clinically indicated				Appendix 2
Urinalysis[20]	X				X		If clinically indicated	X			Appendix 2
Serum FSH[21]	X										
Serum pregnancy test[22]	X							X			Section 8.2.10
Serum or urine pregnancy test					X		X				Section 8.2.10
Contraception check[23]	X	X			X		X	X			Section 5.3.3
Single 12-lead ECG[24]	X										Section 8.2.7
Triplicate 12-lead ECG[25]		X		X	X		Day 1 of Cycles 3-6				Section 8.2.7
ECHO[26]	X				X		C6D1 then every 4 cycles/Q12W	X	X		Section 8.2.9
Treatment[27]											Section 6
Administer AM dose of PF-07284890 and binimetinib in the clinic		X		X	X		Day 1 Cycles 3-6 on PK sampling/ECG days				
Dispense PF-07284890 and binimetinib		X			X		X				

		Study Treatment (cycle duration = 21 days)									Notes/Protocol Section
		Cycle 1			Cycle 2		Subsequent Cycles				
Visit Identifier[a]	**Screening**[1]	**Day 1**	**Day 8**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**EOT**	**30-Day Follow-Up**[2]	**Survival Follow-Up**[3]	
Visit Window	**Day -28 to Day -1**	**-3 days**[b]	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±7 days**	**±7 days**	**Q12W±7 days**	
Administer PF-07284890 and binimetinib		Continuously in 21-day cycles (QD for PF-07284890; BID for binimetinib)									
Review dosing diary			X	X	X	X	X	X			
Tumor assessments[28]											
CT or MRI imaging	X		every 6 weeks (2 cycles) ±1 week for 1 year (through Cycle 17) then every 12 weeks ±1 week thereafter								Section 8.1.1
Other clinical assessments											
Prior and concomitant medication[29]	X	→	→	→	→	→	→	→			
Serious and nonserious AE monitoring[30]	X	→	→	→	→	→	→	→	→		
Document subsequent anticancer therapies									X	X	Section 7.1
Survival status									X	X	Section 7.1
PK blood sampling[31]		X		X	X		X	X			Windows for PK blood samples provided in tables below; Section 8.5
PK and genetic biomarker CSF sampling[32]	Any time CSF is sampled as part of SOC										Section 8.5
Pharmacogenetics sampling[33]	X										Section 8.7.4

		Study Treatment (cycle duration = 21 days)									Notes/Protocol Section
		Cycle 1			Cycle 2		Subsequent Cycles				
Visit Identifier[a]	Screening[1]	Day 1	Day 8	Day 15	Day 1	Day 15	Day 1	EOT	30-Day Follow-Up[2]	Survival Follow-Up[3]	
Visit Window	Day -28 to Day -1	-3 days[b]	±3 days	±3 days	±3 days	±3 days	±3 days	±7 days	±7 days	Q12W±7 days	
Pfizer Prep D1 Banked Biospecimen(s)[3,4]	X										Section 8.7.5

a. Day relative to start of study intervention (Day 1).

b. -3 day window is to allow assessments and examinations to occur up to 3 days before initiation of study drug (C1D1) unless otherwise stated (eg, triplicate pre-dose ECG should occur per PK SOA).

Abbreviations used in this table are in Appendix 21.

1. **Screening:** To be obtained within 28 days prior to study entry.
2. **30-Day Follow-up:** At least 23 calendar days and no more than 37 calendar days after discontinuation from study intervention, participants will return to undergo review of concomitant treatments, vital signs, and assessment for resolution of any treatment-related Aes. Participants continuing to experience Aes at this point following discontinuation of treatment will continue to be followed at least every 4 weeks until resolution or determination, in the clinical judgment of the investigator, that no further improvement is expected.
3. **Survival Follow-Up**: The survival follow-up occurs approximately Q12W.
4. **Informed Consent/assent:** Must be obtained prior to undergoing any study-specific procedures. The duration of obtaining ICD should be changed if the screening window is revised.
5. **Documentation of BRAF V600 Mutation**: tissue or blood (eg, CCI) results performed during normal course of clinical care in CLIA or similarly certified laboratory (ie, local testing). Redacted molecular report(s) must be provided during Screening.
6. **Tissue Sample:** Confirmation of availability of adequate tumor tissue for submission to the sponsor. If multiple specimens are available, the most recently obtained is preferred. If participants do not have sufficient archival tissue, a fresh biopsy should be obtained if it can be performed safely in the opinion of the investigator. If adequate archive tissue is not available and a fresh biopsy cannot be performed safely, participants may still be eligible if all other eligibility criteria are met. See Section 8.7.2 for tissue requirements.
7. **Fresh Tumor Sample (Optional):** For participants who provide informed consent/assent for optional biopsy; may be obtained prior to starting treatment, between C1D8 and C2D15, and at EOT (as close to the date of radiographic disease progression as possible if feasible). If feasible, on-treatment and EOT biopsies should be obtained within 2-4 hours after dosing. See Section 8.8.1.
8. **Whole Blood:** as control for tumor molecular analysis.
9. **Blood Sample for CDx:** See Section 8.7.2.

10. **Blood Sample for** [redacted] **(Specified Geneticss):** Blood sample ([redacted]) should also be collected at radiographic progression. See Section 8.7.3.
11. **Physical Examination**: Height will be measured at Screening only. Complete physical examination will be performed at initial examination only. Brief, symptom-directed physical examinations will be performed subsequently. See Section 8.2.1.
12. **Full Ophthalmic Examination**: Repeat ophthalmic examination will be performed only if clinically indicated. Visual acuity should be tested by the treating physician on Day 1 of every cycle. See Section 8.2.3.
13. **Dermatologic Examination**: Performed Q6W after C3D1 and then Q9W after EOT until 6 months after the last dose of PF-07284890. See Section 8.2.2.
14. **Neurologic Examination**: Neurologic examination will be performed on Day 1 and Day 15 of Cycles 1-2 and on Day 1 of Cycles 3-8. Additional examination will be conducted if clinically indicated. See Section 8.2.4.
15. **Vital Signs:** BP and pulse rate to be recorded in sitting position. See Section 8.2.6.
16. **ECOG PS:** see Appendix 14 for ECOG classification of performance status. See Section 8.2.5.
17. **Hematology**: No need to repeat on C1D1 if Screening assessment performed within 7 days. See Appendix 2 Clinical Laboratory Tests.
18. **Blood Chemistry**: No need to repeat on C1D1 if Screening assessment performed within 7 days prior to that date. See Appendix 2 Clinical Laboratory Tests.
19. **Coagulation**: No need to repeat on C1D1 if Screening assessment performed within 7 days prior to that date. See Appendix 2 Clinical Laboratory Tests. Participants on anticoagulation treatment should have parameters monitored throughout the study as clinically indicated.
20. **Urinalysis:** Dipstick is acceptable at minimum at Screening, C2D1 and EOT visit. See Appendix 2 Clinical Laboratory Tests.
21. **Serum FSH:** High FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.
22. **Pregnancy Test**: Serum pregnancy test will be performed at Screening, and if more than 7 days prior to C1D1 at Screening, again at C1D1, and at EOT. Details are described in Section 8.2.10.
23. **Contraception Check:** See Section 5.3.3.
24. **Single 12-Lead ECG:** Single ECG will be performed during Screening to determine eligibility. May be repeated twice (performed approximately 2 minutes apart) if the initial QTcF value is >470 msec; if 3 ECGs are performed, the average QTcF should be ≤470 msec to be eligible.
25. **Triplicate 12-Lead ECG**: For eligibility, the QTcF interval at C1D1 pre-dose must be ≤470 msec. Additional ECGs will be performed as clinically indicated. The timing of ECG collection may be adjusted based on emerging data. During Phase 1b Dose Expansion, ECG collection may be simplified. Details of ECG guidance, including obtaining additional ECGs to confirm specific abnormalities, are provided in Section 8.2.7. Details provided in table below when ECGs are obtained at the same time as the PK sample.
26. **ECHO**: ECHO scans will be performed at Screening, Day 1 of Cycle 2, then Q12W until EOT, and at EOT and 30-Day follow-up. For participants who have been on treatment for ≥24 months, ECHO scans should be every 24 weeks (or more frequently if clinical indicated) if the LVEF is within 10% of baseline and >LLN at any time while on study. Evaluation of the heart valves should be included and any baseline and treatment-emergent findings should be clearly documented and evaluated for consideration of AE (including grade according to NCI CTCAE version 5.0 and relation to study interventions). See Section 8.2.9.
27. **Study Intervention**: PF-07284890 and binimetinib (for participants receiving combination treatment) will be dispensed with dosing diary. PF-07284890 and binimetinib (for participants receiving combination treatment) will be administered orally QD and BID, respectively, continuously in a 21-day cycle.

AM doses of PF-07284890 and binimetinib will be administered in the clinic on PK sampling days through Cycle 6. Study intervention will be described in Section 6.

28. **Tumor Assessments**: Tumor assessments will include all known or suspected disease sites. MRI of brain and contrast enhanced-CT or MRI of chest, abdomen and pelvis will be performed at Screening, C3D1, then every other cycle/Q6W ±1 week through Cycle 17 (ie, for 1 year), and every 4 cycles/Q12W ±1 week after Cycle 17 until progressive disease, withdrawal of consent, initiation of subsequent anticancer therapy, participant is lost to follow-up, death, or defined end of study. MRI of spinal cord will only occur at Screening for participants with known spinal cord disease at baseline. CR or PR confirmation assessments must take place at least 4 weeks after the initial response and may be performed a minimum of 4 weeks (28 days) after the initial scan showing a CR or PR at the discretion of the investigator, with the next scan performed according to the original schedule. Scan at EOT is not required if a scan was done within 8 weeks of treatment discontinuation and progressive disease has been documented. See Section 8.1.1.
29. **Prior and Concomitant Medication**: all concomitant medications and NonDrug Supportive Interventions should be recorded on the CRF.
30. **AE Assessments**: Aes should be documented and recorded at each visit using the NCI CTCAE version 5.0. Assessment of Aes should include questions pertaining to the incidence, severity, and timing of visual changes (eg, flashes or color changes), palpitions, and bruising or bleeding. The time period for actively eliciting and collecting Aes and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent through and including a minimum of 28 calendar days after the last study intervention administration. If the participant begins a new anticancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment. See Section 8.3.
31. **PK Blood Sampling:** Details provided in the table below. Also, see Section 8.5.
32. **PK CSF Sampling**: Details provided in the table below. Also, see Section 8.5.
33. **Pharmacogenomics sampling**: Pharmacogenomic samples will be obtained during Screening. See Section 8.7.4.
34. **Pfizer Prep D1 Banked Biospecimen(s):** See Section 8.7.5.
35. Assessment does not need to be repeated if performed within 72 hours prior to Cycle 1 Day 1 (ie, first day of dosing) unless otherwise explicitly stated (eg, pregnancy test).

Pharmacokinetic Sampling and ECGs Schedule for Phase 1a

		Study Treatment (cycle duration = 21 days)																
		Cycle 1												Cycle 2 -6		Cycles 7-12		
Visit Identifier	**Screening**	**Day 1**						**Day 2**	**Day 15**						**Day 1**		**Day 1**		**EOT**
	Day -28 to Day -1	**No window**						**No window**	**(±3 days)**						**(±3 days)**		**(±3 days)**		**(±7 days)**
Hours Before/After Dose		**0[a]**	**1**	**2**	**4**	**6**	**8**	**0[a]**	**0[a]**	**1**	**2**	**4**	**6**	**8**	**0[a]**	**2**	**0[a]**	**2**	
Study intervention administration (PF-07284890 or PF-07284890 and binimetinib), AM dose in clinic		X						X	X						X		X		
PK blood plasma sampling[1]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
PK and genetic biomarker CSF sampling[2]	Any time CSF is sampled as part of SOC																		
Singlet 12-lead ECG[3]	X																		
Triplicate 12-lead ECG[3]		X		X				X	X		X					X			

a. Pre-dose sample collection.

1. **PK Sampling:** Blood will be collected for determining the concentration of PF-07284890 (and binimetinib for patients receiving the combination) on C1D1 and C1D15 at pre-dose (within 30 min before the dose), 1 hour (±5 min), 2 hour (within 15 minutes after the last of the triplicate ECGs scheduled at that time point), 4 hour (±10 min), 6 hour (±15 min), and 8 hour (±20 min) postdose, and for QD administration only at 24 hours (±2 hours) postdose on C1D1 (ie, pre-dose on C1D2 within 30 minutes prior to dose; participants will need to return to clinic on C1D2 for the 24-hour postdose sample). On Day 1 of C2-C6, PK samples will also be obtained pre-dose (within 30 min) and at 2 hours (within 15 minutes following the last of the triplicate ECGs scheduled at that time point) postdose. A PK sample will also be obtained during the EOT visit and at the time of CSF sampling (when CSF sampling is not done on a PK day) if possible. Additional PK samples may be obtained at other timepoints if clinically indicated. Detailed instruction of sample collection, processing and shipment will be provided in the Lab Manual. See Section 8.5.
2. **PK and genetic biomarker CSF Sampling**: PK and genetic biomarker CSF samples will be collected for participants in whom CSF sampling is being performed as part of SOC. If possible, samples should be collected during screening, on any PK day, ideally 2 to 4 hours after dosing on any PK day, with the time collected relative to dosing clearly indicated on the requisition and/or eCRF. If the CSF sample is collected but not on a PK day, an additional PK sample should be collected soon after if possible. See Section 8.5.
3. **12-Lead ECG:** A singlet ECG will be collected at Screening. Triplicate ECGs will be collected at pre-dose (within approximately 15 minutes before the pre-dose PK sample) and at 2 hours (±10 min) after dosing on C1D1 and C1D15; when PF-07284890 is administered QD and PK sampling necessitates a pre-dose visit on C1D2 at 24 hours after the C1D1 dose on C1D2 (ie, within 30 minutes prior to the dose on C1D2) the ECG will be collected pre-dose (within approximately 15 minutes before the pre-dose PK sample); and at 2 hours (±30 min) postdose on Day 1 of Cycles 2-6 (intended to approximate the T_{max} of PF-07284890), with 3 consecutive 12 lead ECGs performed approximately 2 minutes apart to determine mean QTcF interval. When ECGs are obtained at the same time as a PK sample, the ECGs must be completed before the PK sample is taken. Additional ECGs will be performed as clinically indicated. The

timing of ECG collection may be adjusted based on emerging data. Details of ECG guidance, including obtaining additional ECGs to confirm specific abnormalities, are provided in Section 8.2.7.

Pharmacokinetic Sampling and ECGs Schedule for Cohorts 1-5[a] in Phase 1b

		Study Treatment (cycle duration = 21 days)										
		Cycle 1								Cycle 2-6		
Visit Identifier	**Screening**	**Day 1**				**Day 15**				**Day 1**		**EOT**
	Day -28 to Day -1	**No window**				**(±3 days)**				**(±3 days)**		**(±7 days)**
Hours Before/After Dose		**0[b]**	**1**	**2**	**4**	**0[b]**	**1**	**2**	**4**	**0[b]**	**2**	
Study intervention administration (PF-07284890 and binimetinib), AM dose in clinic		X				X				X		
PK blood plasma sampling[1]		X	X	X	X	X	X	X	X	X	X	X
PK CSF sampling[2]		Any time CSF is sampled as part of SOC										
Singlet 12-lead ECG[3]	X											
Triplicate 12-lead ECG[3]		X		X		X		X			X	

a. Table for PK sampling and ECGs for Cohort 6 in Phase 1b is found in Appendix 15.

b. Predose sample collection.

1. **PK Sampling:** Blood will be collected for determining the concentration of PF-07284890 and binimetinib on C1D1 and C1D15 at pre-dose (within 30 min before the dose), 1 hour (±5 min), 2 hour (within 15 minutes after the last of the triplicate ECGs scheduled at that time point) and 4 hour (±10 min) postdose. On Day 1 of C2-C6, PK samples will also be obtained pre-dose (within 30 min) and at 2 hours (within 15 minutes following the last of the triplicate ECGs scheduled at that time point) postdose. A PK sample will also be obtained during the EOT visit and at the time of CSF sampling (when CSF sampling is not done on a PK day) if possible. Additional PK samples may be obtained at other timepoints if clinically indicated. Detailed instruction of sample collection, processing and shipment will be provided in the Lab Manual. See Section 8.5.
2. **PK CSF Sampling**: PK CSF samples will be collected for participants in whom CSF sampling is being performed as part of SOC. If possible, samples should be collected on any PK day, ideally 2 to 4 hours after dosing on any PK day, with the time collected relative to dosing clearly indicated on the requisition and/or eCRF. If the CSF sample is collected but not on a PK day, an additional PK sample should be collected soon after if possible. See Section 8.5.
3. **12-Lead ECG:** A singlet ECG will be collected at Screening. Triplicate ECGs will be collected at pre-dose (within approximately 15 minutes before the pre-dose PK sample) and at 2 hours (±10 min) after dosing on C1D1 and C1D15, and at 2 hours (±30 min) postdose on Day 1 of Cycles 2-6 (intended to approximate the T_{max} of PF-07284890), with 3 consecutive 12 lead ECGs performed approximately 2 minutes apart to determine mean QTcF interval. When ECGs are obtained at the same time as a PK sample, the ECGs must be completed before the PK sample is taken. Additional ECGs will be performed as clinically indicated. The timing of ECG collection may be adjusted based on emerging data. Details of ECG guidance, including obtaining additional ECGs to confirm specific abnormalities, are provided in Section 8.2.7.

2. INTRODUCTION

PF-07284890 (also known as ARRY-461) is a potent, selective, highly brain-penetrant small -molecule inhibitor of BRAF V600 mutations that is being investigated in participants with BRAF V600-mutant solid tumors with or without brain involvement. PF-07284890 is being developed to address the limited overall efficacy of approved BRAF inhibitors resulting from disease progression in the brain. By inhibiting BRAF V600-mutant enzyme in tumor cells both extracranially and intracranially, PF-07284890 has the potential to prolong the duration of overall disease control compared to approved BRAF inhibitors.

2.1. Study Rationale

The purpose of the study is to assess the PK, safety and preliminary clinical activity of PF-07284890, as monotherapy and in combination with the MEK inhibitor, MEKTOVI® (binimetinib), in participants with BRAF V600-mutated advanced solid tumor malignancies with and without brain metastases. Although approved BRAF inhibitors have transformed the treatment of patients with certain BRAF V600-mutant cancers, their long term efficacy is thought to be limited by poor brain penetration.[1] As a result, disease progression in the brain is a significant cause of morbidity and mortality. PF-07284890 is fully brain penetrant, with the potential to address this key unmet medical need and thereby define a new class of brain-penetrant, potent and selective BRAF inhibitor.

2.2. Background

Metastatic spread to the CNS is a particularly poor prognostic factor for many solid cancers, with average survival typically <6 months.[2] Among solid tumors, metastatic melanoma and NSCLC have the highest risks of spread to the CNS, with lifetime prevalence's of 40-60% and 20-40%, respectively.[3,4,5]

BRAF V600 mutations occur in approximately 50% of melanoma and PTC, 45% of ATC, 15% of CRC, 2% of NSCLC and less commonly in several other tumor types (Table 1). BRAF mutations drive constitutive MAPK pathway activation and in turn proliferation with enhanced cellular survival. Small molecule BRAF inhibitors block mutant BRAF, MAPK signaling, proliferation and survival in some BRAF V600-mutant tumor cells, effects that are enhanced by combination with MEK inhibitors. To date, there are 3 BRAF inhibitor/MEK inhibitor combinations approved for select BRAF V600-mutant cancers: dabrafenib/trametinib (melanoma, NSCLC and ATC), vemurafenib/cobimetinib (melanoma) and encorafenib/binimetinib (melanoma). Although BRAF inhibitors have limited activity in BRAF V600-mutant CRC as monotherapy due to endogenous EGFR -mediated signaling, this can be overcome by concomitant treatment with EGFR inhibitors; consistent with this, encorafenib in combination with the EGFR antibody cetuximab was recently approved for BRAF V600-mutant CRC.[6]

Table 1. Prevalence of BRAF V600 Mutations in Different Tumor Types

Tumor Type	Frequency	Estimated US prevalence[a]
Melanoma	0.5	3500
ATC	0.45	500
PTC	0.5	1000
CRC	0.15	7500
Biliary cancer	0.05	350
NSCLC	0.02	2000
Low grade glioma	0.6-0.8 PXA, 0.1-0.2 PA	NE[b]
High grade glioma	0.03	NE[b]
Other[c]	Varies	NE[b]

a. With advanced, standard treatment-refractory disease; calculated from SEER database (seer.cancer.gov) using overall mortality from each cancer type as surrogate for advanced, treatment-refractory cancer.
b. Not estimated; overall number is expected to be low.
c. Other examples include breast cancer and ovarian cancer.

Due to poor brain penetration and limited intracranial activity in early clinical trials, randomized studies of approved BRAF/MEK inhibitors in patients with melanoma and NSCLC (the frequency of brain metastases in CRC and ATC is low) excluded patients with untreated (ie, with local brain therapy), symptomatic (including a requirement for steroids and anti-epileptic therapy to control symptoms) and/or progressing brain metastases.[7,8,9] In a recent Phase 2 trial (COMBI-MB), dabrafenib plus trametinib treatment of BRAF V600-mutant melanoma patients with brain metastases achieved overall and intracranial tumor response rates of 41-75% and 44-59%, respectively, depending on whether brain metastases were asymptomatic or symptomatic and untreated or previously treated with local brain therapy.[7] However, the median DoR for patients with asymptomatic, untreated brain metastases was shorter (6.5 months overall) than for patients without brain metastases treated on the COMBI-d trial (12 months),[10,11] and even shorter (4.5 months) for patients with symptomatic brain metastases. A similar trend has been observed for vemurafenib and encorafenib.[8,9,12,13] Although randomized trials of ICIs also excluded patients with untreated, symptomatic and/or progressive brain metastases at baseline, in the Phase 2 Keynote-204 trial, ipilumimab plus nivolumab treatment of metastatic melanoma patients with asymptomatic, untreated brain metastases achieved overall and intracranial response rates of 54 and 59% (including 29% intracranial CR), with median intracranial and overall DoR not reached (12 month landmark global PFS was 56.6%).[14] However, treatment with ICIs is toxic, with high rates of severe AEs; as a result, only a minority of patients receive all prescribed doses. Furthermore, the efficacy of ICIs in patients with symptomatic and/or progressive brain metastases is not known.

For these reasons, patients with BRAF V600-mutant melanoma and NSCLC with metastases to the brain usually receive local brain therapy (eg, SRS, surgical resection, WBRT) at some point during their disease course. SRS and surgery are generally limited to 3 or fewer lesions (SRS) or a single large (>3 cm) or posterior fossa lesion (surgery) and do not control disease at untreated sites. WBRT causes accelerated cognitive decline and was no better than supportive care in NSCLC patients.[15] A multicenter retrospective review reported that 37% of the patients with brain metastases treated with stereotactic radiosurgery alone underwent salvage therapy at a median 5.7 months after treatment compared to 7% after a

median 8 months when SRS was followed by WBRT.[16] The optimal number of lesions and fractionation schedules appropriate for SRS, the feasibility of repeat SRS and the role of WBRT given neurological toxicity remain topics of investigation.

BRAF V600 mutations occur in several other cancers with brain involvement, including primary brain tumors. Their occurrence in pediatric gliomas is predictive of poor response to conventional radiation and chemotherapy.[17] BRAF inhibitors alone or in combination with MEK inhibitors have limited activity in patients with BRAF V600-mutant primary gliomas, especially for patients with higher grade tumors (ie, glioblastoma).[18,19,20]

Therefore, there is an urgent need to identify new treatment approaches that target BRAF V600-mutant cancers both systemically and in the brain.

2.2.1. Nonclinical Pharmacology of PF-07284890

PF-07284890 is an ATP-competitive inhibitor of the BRAF kinase family that demonstrates distribution to the brain. Its biological activity has been evaluated in numerous non-GLP in vitro, cell culture, and in vivo studies. In cell-free systems, PF-07284890 inhibits BRAF and CRAF with CCI [redacted]. Additionally, PF-07284890 inhibits the clinically relevant kinase domain BRAF V600 mutants (V600E and V600K) at similar concentrations. In cell-based systems, PF-07284890 CCI [redacted]

In vivo, PF-07284890 has been evaluated for its ability to inhibit phosphorylation of ERK signal transduction pathway protein in tumors and to control BRAF V600E cell line and patient-derived xenograft tumor growth in nude mice when implanted either subcutaneously or intracranially. CCI [redacted] In all models, regardless of tumor location, maximal efficacy was observed in dose ranges of CCI [redacted]. The addition of the MEK inhibitor, binimetinib, improved activity in some models which supports combination therapy of PF-07284890 and binimetinib. Further, activity in intracranial models was superior in durability to approved BRAF/MEK inhibitors that do not effectively partition to the brain, supporting the hypothesis that a brain penetrant BRAF V600 inhibitor may provide additional therapeutic benefit in patients with BRAF V600 mutant brain metastases.

PF-07284890 was evaluated at concentrations up CCI [redacted] In addition, secondary pharmacodynamic evaluations showed that PF-07284890 demonstrated high selectivity for CCI [redacted] Based on these results, off-target kinase, receptor, and transporter activity at relevant free-therapeutic concentrations in vivo is not anticipated. CCI [redacted]

2.2.2. Nonclinical Pharmacokinetics and Metabolism of PF-07284890

Plasma PK of PF-07284890 has been investigated following single oral and IV doses in mouse, rat, dog and monkey. After IV administration across preclinical species, PF-07284890 PK parameters consistently demonstrated low total systemic plasma clearance, low hepatic extraction (<10%), and low volume of distribution at steady state (V_{ss} <1.0 L/kg). The mean CCI [redacted] The low clearance and low volume of distribution of PF-07284890 correlated with the high observed in vitro plasma protein binding across species (99.2% in humans). After oral administration, plasma exposures of PF-07284890 (AUC and C_{max}) increased with dose in all species and the absolute oral bioavailability was moderate to complete. GLP TK studies in the rat (doses of 10, 30 and 60 mg/kg) and monkey (doses of 10, 30 and 100 mg/kg) showed less than dose-proportional exposures, as might be expected based on relatively low aqueous solubility (ie, in simulated gastric fluid at 37°C at a pH of 1.2, 131.6 µg/mL, and in fasted state simulated intestinal fluid at a pH of 6.5, 7.6 µg/mL).

PF-07284890 was designed to distribute to the brain by good cellular membrane permeability and minimal efflux through transporters expressed in the blood-brain barrier including P-gp and BCRP. As such, in vitro experiments indicated that PF-07284890 had high permeability and was not a substrate for human P-gp. Although PF-07284890 was a substrate for human BCRP, its combination of high intrinsic permeability and modest efflux ratio of 3.7 in an overexpressed system was thought to be acceptable as minimal efflux, which was further explored in vivo. After oral administration of PF-07284890 to mice and rats, PF-07284890 distributed to brain where the free fraction adjusted exposure in brain was approximately proportional to the free fraction adjusted exposure in plasma (ie, the unbound concentration in the brain divided by the unbound concentration in the plasma approached 1.0).

The routes of PF-07284890 metabolism were generally conserved across nonclinical species. However, the efficiency of PF-07284890 metabolism to specific metabolites varied across species. In vitro and in vivo metabolite identification suggested that PF-07284890 was metabolized through multiple oxidative and/or glucuronosyltransferase enzymes. Comparisons across species suggested that direct N-glucuronidation is predicted to be the predominant metabolic route in humans. PF-07284890 glucuronidation is the primary route of metabolism in human hepatocytes with minor contribution from glucose conjugation and oxidation mediated by CYP3A4 and aldehyde oxidase. CCI [redacted] Renal clearance was a minor elimination route of unchanged PF-07284890 in rats (<1% of an IV dose) and is predicted to be a minor route across all species, including humans.

The PK DDI potential of PF-07284890 for enzymes was assessed in various in vitro systems. PF-07284890 inhibited CYP2C9 (K_i = 8.0 µM) and CYP3A4 (K_i = 6.8 µM). The K_i values for PF-07284890 for all the other CYPs evaluated were greater than 10 µM. PF-07284890 was a weak time-dependent inhibitor of CYP3A4 (K_I = 20.8 µM and k_{inact} = 0.149 min^{-1}) and a weak concentration-dependent inducer of CYP3A4. CCI [redacted]

The DDI potential of PF-07284890 for transporters was also assessed in vitro. As mentioned earlier, PF-07284890 was a substrate for BCRP, which is also expressed in the GI tract and therefore presents the potential for a DDI in terms of rate of absorption. PF-07284890 was an inhibitor of P-gp in MDR1 LLC-PK1 cell monolayers (IC_{50} = 2.9 µM). The inhibition of various transporters by PF-07284890 was studied in transfected cells or vesicles. The IC_{50} for PF-07284890 inhibition of OATP1B1 and OATP1B3 were 5.7 and 8.0 µM, respectively. PF-07284890 was not a potent inhibitor of other transporters tested (BCRP, BSEP, MATE1, MATE2-K, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2 and P-gp, IC_{50} approximately 10 µM or higher).

The ability of binimetinib to impact PF-07284890 PK or PF-07284890 to impact binimetinib PK appears to be minimal. Binimetinib is a substrate of P-gp, but no clinically important drug interactions have been observed with binimetinib either as a victim or perpetrator of interactions.

2.2.3. Nonclinical Safety of PF-07284890

The acute, 28-day studies in Sprague Dawley rats and cynomolgus monkeys were conducted in accordance with international regulatory guidelines for nonclinical toxicity studies and in adherence to current GLP regulations, and were intended to support administration of PF-07284890 in humans. These studies were supplemented with GLP genotoxicity assays (bacterial mutagenicity, in vitro mouse lymphoma, comet assay, and in vivo micronucleus) and a GLP phototoxicity study, and 4 GLP safety pharmacology studies (in vitro hERG, in vivo cardiovascular telemetry in monkey, and Irwin FOB and GI motility in rats).

Following 28 days of QD oral administration of PF-07284890 (CCI [redacted] mg/kg) to Sprague Dawley rats, the toxicological response was characterized primarily by clinical observations of hind limb swelling requiring euthanasia of 6 (out of 150) PF-07284890-treated rats, mild clinical pathology changes (decreased ALP, decreased red cell parameters, increased reticulocytes, increased white cell parameters, increased APTT and increased urine volumes); all of which resolved in recovery animals. It is important to note that many PF-07284890-treated animals were noted to have blistering, swelling or scabbing on the hindlimbs and, in all but the 6 animals that were euthanized, the findings resolved or were of reduced severity and incidence with continued dosing. Organ weight decreases in epididymides and increases in heart at CCI [redacted] mg/kg CCI [redacted] in males and/or females and increases in liver, ovaries, and spleen in males and/or females were noted at all dose levels. Myxomatous degeneration of the heart valves at CCI [redacted] mg/kg, degeneration of seminiferous tubules in the testes and debris in the lumen and decreased cellularity of

sperm in the epididymides at CCI mg/kg were considered adverse histopathology changes from terminal necropsy. Progression of the heart valve finding over time possibly could lead to incomplete closure of the valves. The effects seen in male reproductive organs would impact fertility. All PF-07284890-related changes from terminal necropsy exhibited significant recovery, except for those in the testes and epididymides at CCI mg/kg. Based on the requirement for euthanasia due to impairment of mobility and pain at the lower dose level and adverse pathology findings at CCI mg/kg, the NOAEL could not be determined. In light of the intended therapeutic usage of this compound in patients with advanced cancer, the ICH S9 guidance would apply. The STD_{10} was determined from test article-related lethality or irreversible and life-threatening findings. Thus, the CCI mg/kg based on the early euthanasia of 4 animals at that dose level, due to impaired mobility and clinical signs consistent with pain (4 out of 32). This corresponds to CCI males and females, respectively. And a human equivalent dose of CCI mg/m^2.

Following 28 days of QD oral administration of PF-07284890 (CCI mg/kg) in cynomolgus monkeys, no adverse toxicological findings were seen and the only histopathologic finding was minimal stomach ulceration at the high dose. Decreases in the weights of male reproductive organs could portend effects on fertility in longer term studies in more mature animals. Given the lack of adverse findings at any dose level, the NOAEL and HNSTD for daily oral dosing of PF-07284890 in male and female cynomolgus monkeys for 28 days was CCI mg/kg. This corresponds to an CCI

The testicular and epididymal toxicity observed in rats with findings of atrophy, degeneration, epididymal debris and hypospermia were observed at human equivalent doses approximately 6 times greater than the planned initial dose in humans. However, based on predicted human PK, the exposure window is predicted to be the CCI. These effects on male reproductive organs are known, on-target effects of BRAF inhibition and have been reported for dabrafenib[21] and encorafenib.[22]

Given that PF-07284890 was designed to be brain-penetrant in order to address the unmet need in patients with BRAF V600E brain metastases, neurological safety is of paramount importance. There were no pathological findings in the brains of rats or monkeys receiving PF-07284890 for 28 consecutive days. Most importantly, detailed neurological assessments performed during the course of both repeat-dose toxicology studies revealed no effect on motor activity, reactions to environmental stimuli, oculomotor, pupillary assessments or body temperature.

In addition to the nonclinical investigations summarized above, the weight of evidence from the genotoxicity battery of assays shows low genotoxic risk and no adverse effects on GI mucosa in the rat GI irritation assay.

Safety pharmacology studies were conducted in rats and monkeys to assess the effects of PF-07284890 on key organ systems (cardiovascular, respiratory, neurobehavioral and gastrointestinal function). All safety pharmacology studies were conducted in accordance with GLP (21CFR§58). Rats received single oral doses of CCI [redacted] of PF-07284890. There were no significant in vivo safety pharmacology findings at doses up to CCI [redacted] in monkeys.

PF-07284890 was determined to have phototoxic potential in the in vitro neutral red assay. Thus, it is recommended that patients receiving PF-07284890 should avoid excessive direct sun exposure and take appropriate precautions (eg, sunscreen, UV-protective clothing, etc.)

The overall conclusion from these studies is that PF-07284890 has an acceptable safety profile for human administration at the doses selected for treating patients with BRAF V600E-driven malignancies.

2.2.4. Clinical Overview

2.2.4.1. PF-07284890

During the conduct of this study, please refer to the PF-07284890 Investigator Brochure for updated information regarding clinical experience.

2.2.4.2. Binimetinib

Binimetinib is a potent and selective allosteric, ATP-uncompetitive inhibitor of MEK1/2. Binimetinib 45 mg orally BID in combination with the potent and selective ATP-competitive inhibitor of BRAF V600-mutant kinase encorafenib 450 mg orally QD have been approved by the US FDA, the EMA and other global health authorities for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation. Detailed information regarding nonclinical studies and clinical pharmacokinetics of binimetinib are presented in the binimetinib Investigator's Brochure.

Clinical Safety of Binimetinib as a Single Agent

The maximum well-tolerated dose of binimetinib when given as a single agent is 60 mg BID.[23] An observed incidence of reversible retinal events and rash led to the selection of 45 mg BID as the RP2D. Among 44 patients receiving binimetinib at the RP2D in the Phase 1 trial, the most common AEs (≥20%, all grades) were rash (77%), nausea (61%), vomiting (52%), diarrhea (39%), peripheral edema (45%) and fatigue (46%). Combination of binimetinib at this dose with encorafenib at 450 mg QD resulted in a significantly lower frequency of rash with similar frequencies of gastrointestinal AEs.

Detailed information regarding clinical safety of binimetinib is presented in the binimetinib Investigator's Brochure.

Clinical Safety of Binimetinib in Combination With a BRAF Inhibitor

As described above, binimetinib in combination with encorafenib have been approved for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation.

This is consistent with a body of literature that suggests the combination of a MEK inhibitor and a BRAF inhibitor results in improved tolerability compared with either agent alone, due to the amelioration of paradoxical activation of wild-type BRAF in normal tissues when a BRAF inhibitor is utilized as monotherapy.[8,10,24,25,26]

Among patients receiving encorafenib and binimetinib combination therapy in the randomized clinical trial of encorafenib and binimetinib (COLUMBUS trial)[9,27] the most common adverse reactions (≥20%, all grades) were fatigue (43%), nausea (41%), diarrhea (36%), vomiting (30%), abdominal pain (28%), arthralgia (26%), myopathy (23%), hyperkeratosis (23%), rash (22%), headache (22%), constipation (22%), visual impairment (20%) and serous retinopathy (20%). Most of these toxicities were generally reversible and manageable by supportive medical care, dose modifications or treatment discontinuation. Other clinically important adverse reactions occurring in <10% of patients were facial paresis, pancreatitis, panniculitis, drug hypersensitivity and colitis. The most common laboratory abnormalities (≥2%, Grade 3 or 4) were increased GGT (11%), increased ALT (6%), increased creatine phosphokinase (5%), increased fasting glucose (5%), increased creatinine (4%), anemia (4%), hyponatremia (4%), increased AST (3%), neutropenia (3%) and lymphopenia (2%). Detailed information regarding clinical safety is presented in the respective investigator's brochures for encorafenib and binimetinib.

Important potential adverse effects associated with the administration of the combination of encorafenib and binimetinib established primarily from safety data from the COLUMBUS study and, where indicated, from other studies of the combination, include:

- **New primary malignancies:** Based on its mechanism of action, encorafenib may promote malignancies associated with activation of *RAS* through mutation or other mechanisms. Cutaneous and non-cutaneous malignancies occurred in patients, including cutaneous squamous carcinoma/keratoacanthoma (2.6%) and basal cell carcinoma (1.6%).

- **Left ventricular dysfunction:** Symptomatic or asymptomatic decreases in ejection fraction occurred in 7% of patients, with Grade 3 left ventricular dysfunction occurring in 1.6% of patients.

- **Hemorrhage:** Hemorrhage occurred in 19% of patients, with events ≥Grade 3 occurring in 3.2% of patients. Fatal intracranial hemorrhage in the setting of new or progressive brain metastases occurred in 1.6% of patients. The most frequent hemorrhagic events were gastrointestinal, including rectal hemorrhage (4.2%), hematochezia (3.1%), and hemorrhoidal hemorrhage (1%).

- **Venous thromboembolism:** Occurred in 6% of patients, including 3.1% of patients who developed pulmonary embolism.

- **Ocular toxicities:** Serous retinopathy is a class effect of MEK inhibitors. It is generally asymptomatic or mildly symptomatic and reversible.[28] Serous retinopathy occurred in 20% of patients. Symptomatic serous retinopathy occurred in 8% of patients with no cases of blindness. The median time to onset of the first event of serous retinopathy (all grades) was 1.2 months. RVO is a known class-related adverse reaction of MEK inhibitors and may occur in patients treated with binimetinib in combination with encorafenib. In patients with BRAF mutation-positive melanoma across multiple clinical trials, 0.1% of patients experienced RVO.

- **Pneumonitis/Interstitial Lung Disease**: Pneumonitis occurred in 0.3% of patients with BRAF mutation-positive melanoma across multiple clinical trials.

- **Hepatotoxicity:** The incidence of Grade 3 or 4 increases in liver function laboratory tests was 6% for ALT, 2.6% for AST, and 0.5% for alkaline phosphatase. No patient experienced Grade 3 or 4 serum bilirubin elevation.

- **CK Elevation/Rhabdomyolysis**: Asymptomatic elevations of laboratory values of serum CK occurred in 58% of patients. Rhabdomyolysis was reported in 0.1% of patients with BRAF mutation-positive melanoma across multiple clinical trials.

- **QTc Prolongation:** QT prolongation has been observed in patients treated with BRAF inhibitors. Encorafenib is associated with dose-dependent QTc interval prolongation in some patients. In the COLUMBUS study, an increase in QTcF to >500 msec was measured in 0.5% of patients.

- **Embryo-Fetal Toxicity:** Encorafenib or binimetinib can cause fetal harm when administered to pregnant women (based on animal studies).

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of PF-07284890 may be found in the Investigator's Brochure, which is the SRSD for this study. The SRSD for the combination agent binimetinib is the binimetinib Investigator's Brochure.

Potential risks of PF-07284890 based on nonclinical studies include: GI irritation, skin toxicity (hyperkeratosis), phototoxicity, heart valve ultrastructural changes, hyperplasia of several tissues including the GI tract, increased urine volume, decreased testitcular size and oligospermia, mild decrease in red blood cell count, mild increase in white blood cell count, increased heart rate and vascular inflammation. All findings are reversible except for effects on male reproductive organs. Several are known class effects of BRAF inhibitors (ie, encorafenib, dabrafenib, vemurafenib).

Additional potential risks of PF-07284890 alone or in combination with binimetinib are based on the well characterized risks of approved BRAF inhibitors and binimetinib from product labeling for these agents. These include:

- BRAF inhibitors: fatigue, uveitis, rash, nausea, vomiting, arthralgias, new primary malignancies, tumor promotion in BRAF wild-type tumors, embryo-fetal toxicity (only observed in animals to date), arrhythmia, bleeding including in the GI tract and brain, skin reaction (which could be severe), hepatotoxicity, cardiomyopathy, and facial paresis.

- Binimetinib: fatigue, serous retinopathy, retinal vein occlusion, left ventricular dysfunction, interstitial lung disease, nausea, vomiting, diarrhea, abdominal pain, venous thromboembolism, hemorrhage, hepatotoxicity, CK elevation/rhabdomyolysis and embryo-fetal toxicitiy (only observed in animals to date).

However, it is unknown whether these events will be associated with administration of PF-07284890. These toxicities are generally manageable by dose modification, temporary interruption or discontinuation in conjunction with established medical management.

Investigators selected to participate in this study are experienced in managing toxicities associated with combination BRAF and MEK inhibitor therapy. This, together with regular monitoring for these potential toxicities (see SoA and Section 8.2) and appropriate patient counseling regarding potential toxicities, minimizes the potential risks associated with treatment with PF-07284890 alone and in combination with binimetinib. The level of risk compared to the potential benefit to participants with advanced/metastatic BRAF V600-mutant solid tumors is acceptable.

The study design, including initial PF-07284890 monotherapy dose escalation and safety and PK-guided dose increases for both the monotherapy and binimetinib combination dose escalations will mitigate these safety risks. Results will identify a safe dose of PF-07284890 alone and in combination with binimetinib, and may provide initial signs of clinical activity for participants with BRAF V600-mutant solid tumors with and without brain metastasis. The results from this study will contribute to establishing a new, potentially effective treatment alternative for participants with BRAF V600-mutant solid tumors with and without brain involvement.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention PF-07284890		
Potential risks associated with PF-07284890 include the following: GI irritation, skin toxicity, phototoxicity, heart valve ultrastructural changes, hyperplasia of several tissues including the GI tract, increased urine volume, decreased testicular size and oligospermia, mild decrease in red blood cell count, mild increase in white blood cell count, increased heart rate and vascular inflammation.	*The potential risks are based on nonclinical toxicology studies in the rat and monkey. GI irritation (minimal stomach ulcerations) occurred in the 28-day monkey study and it was reversible. Structural changes in the heart valves (resulting in thickening of the valve leaflets) was seen in the 28-day rat study with near complete resolution after a non-dosing recovery period. Skin toxicity (swelling, blisters, scabs) was seen in rat hind paws and was reversible. Adverse effects on male rat reproductive organs (testicular atrophy/degeneration and hypospermia) of up to marked severity were seen and these were not completely reversible after a 28-day non-dosing recovery period. Also, in the rat only: minimal to mild decreases in RBC, Hgb and Hct; minimal increases in WBC, neutrophils and eosinophils and mild increases in APTT were observed and were reversible.*	*Eligibility criteria have been selected to ensure that only appropriate participants are included in the study (see Section 5).* *Adverse events and clinical laboratory results will be monitored on an ongoing basis. Instructions for managing potential cases of GI, cardiac or skin abnormalities or significant changes in clinical pathology parameters are provided (see Section 6.6).*
Study Interventions PF-07284890 + Binimetinib		
Potential risks associated with PF-07284890 (alone or in combination with binimetinib) may include the following: • *BRAF inhibitors: fatigue, uveitis, rash, nausea, vomiting, arthralgias, new primary malignancies, tumor promotion in BRAF wild-type tumors, embryo-fetal toxicity (only observed in animals to date), arrhythmia, bleeding including in the GI tract and brain, skin reaction (which could be severe),*	*The potential risks are based on product labeling for binimetinib and approved BRAF inhibitors.*	*Eligibility criteria have been selected to ensure that only appropriate participants are included in the study (see Section 5).* *Adverse events and clinical laboratory results will be monitored on an ongoing basis. Instructions for managing these potential risks are provided (see Section 6.6 and Appendix 6).*

hepatotoxicity, cardiomyopathy, and facial paresis. • *Binimetinib: fatigue, serous retinopathy, retinal vein occlusion, left ventricular dysfunction, interstitial lung disease, nausea, vomiting, diarrhea, abdominal pain, venous thromboembolism, hemorrhage, hepatotoxicity, CK elevation/rhabdomyolysis and embryo-fetal toxicity (only observed in animals to date).*		
Study Procedures		
Up to 3 optional tumor tissue biopsies will be performed during the study (before initiating study treatment, on treatment and at EOT/disease progression on/after treatment).	*There is a risk of pain, bleeding or infection from biopsy.*	*All biopsies are optional, only to be performed if they can be performed safely (as assessed by the investigator) and informed consent/assent is required.*
Other		
BRAF testing	*Participants will be eligible for the study based on identification of a BRAF V600 mutation. Inaccurate BRAF testing (ie, false positive or false negative) may lead to inappropriate enrollment to or exclusion from this study. A participant with a false negative result may be excluded from receiving potentially beneficial study intervention. Alternatively, a false positive result may lead a participant to receive study intervention, which may be inappropriate given the tumor mutation status.*	*Participants must provide documented evidence (eg, redacted molecular report(s)) of a BRAF V600 mutation in tumor tissue or blood (ie, CCI) as previously determined by PCR or NGS-based local laboratory assay in a CLIA or similarly certified laboratory. There are data to support the conclusion that BRAF V600 mutational testing is generally of good quality within certified laboratories within the United States and globally, with high levels (>97%) of interlaboratory concordance of results.[29] Eligible participants are required to be refractory to previous treatment and have no acceptable alternative treatment options (see Section 5.1 Inclusion Criteria 6 for specific requirements related to prior treatment with a BRAF inhibitor). Therefore, the risk of some participants foregoing or delaying a treatment that is known to be effective is minimal.*

2.3.2. Benefit Assessment

Participants with BRAF V600-mutant solid tumors with or without brain involvement, particularly when symptomatic and/or progressive in the brain after standard local and systemic treatments, have high unmet clinical need. Treatment with PF-07284890 (alone and in combination with binimetinib) has the potential to alleviate morbidity and mortality from intracranial disease involvement, control disease in the brain and extend overall disease control as a result.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with PF-07284890 are justified by the anticipated benefits that may be afforded to participants with BRAF V600-mutant solid tumors.

3. OBJECTIVES AND ENDPOINTS

The study will be conducted in 2 parts (Phase 1a and Phase 1b). The study objectives and endpoints are presented in the table below.

Objectives	Endpoints
Phase 1a Primary:	**Phase 1a Primary:**
• To assess the safety and tolerability of PF07284890 at increasing dose levels, to estimate the MTD, and to select the recommended dose for further study, both as a single agent and in combination with binimetinib, in participants with BRAF V600mutated advanced solid tumor malignancies with and without brain involvement.	• Incidence of Cycle 1 DLTs. • MTD/recommended dose for further study. • AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to study therapy. • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing. • Incidence of dose interruptions, dose modifications and discontinuations due to AEs.
Phase 1a Secondary:	**Phase 1a Secondary:**
• To characterize the single- and multiple-dose PK of PF07284890 as a single agent and in combination with binimetinib and of binimetinib in combination with PF07284890.	• PK parameters of PF-07284890 and binimetinib: • Single dose: C_{max}, T_{max}, AUC_{last}, and as data permit, $t_{½}$, AUC_{inf}, CL/F and V_z/F. • Multiple dose (assuming steady state is achieved): $C_{ss,max}$, $T_{ss,max}$, $AUC_{ss,\tau}$, $C_{ss,min}$, and as data permit, CL_{ss}/F, V_{ss}/F, $t_{½}$ and R_{ac} ($AUC_{ss,\tau}/AUC_{sd,\tau}$).
• To evaluate preliminary clinical activity of PF07284890 as a single agent and in combination with binimetinib.	• Extracranial response by RECIST version 1.1. • Intracranial response by mRECIST version 1.1. • Overall response (combined extracranial and intracranial) by mRECIST version 1.1. • RANO for primary brain tumors.
Phase 1a Tertiary/Exploratory:	**Phase 1a Tertiary/Exploratory:**
• To explore the effect of CCI [redacted] on PF07284890 exposures in participants treated with	• PF-07284890 PK parameters (single dose C_{max} and AUC_{last}; multiple dose $C_{ss,max}$, $AUC_{ss,\tau}$) in participants CCI [redacted].

Objectives	Endpoints
PF07284890 as a single agent and in combination with binimetinib.	
• To explore the brain penetration of PF07284890 as a single agent and in combination with binimetinib.	• CSF concentrations of PF07284890 (in participants in whom CSF is obtained as SOC).
• To evaluate tumor and blood-based biomarkers of response and resistance to PF07284890 as a single agent and in combination with binimetinib.	CCI [redacted]
• To assess the relationship between PF07284890 concentrations and changes in QTcF.	• Maximal changes in QTcF estimated using a linear mixed effect model.
Phase 1b Primary:	**Phase 1b Primary:**
• To evaluate anti-tumor efficacy of PF07284890 at the recommended dose for further study in combination with binimetinib in participants with BRAF V600mutated advanced solid tumor malignancies with and without brain involvement.	• Extracranial response by RECIST version 1.1. • Intracranial response by mRECIST version 1.1. • Overall response (combined extracranial and intracranial) by mRECIST version 1.1. • RANO for primary brain tumors.
Phase 1b Secondary:	**Phase 1b Secondary:**
• To confirm the safety and tolerability of PF07284890 at the recommended dose for further study in combination with binimetinib.	• AEs as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relationship to study therapy. • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE version 5.0), and timing. • Incidence of dose interruptions, dose modifications and discontinuations due to AEs.
• To evaluate single- and multiple-dose PK profiles of PF07284890 at the recommended dose for further study in combination with binimetinib and of binimetinib in combination with PF07284890.	PK parameters of PF-07284890 and binimetinib: • Single dose - C_{max}, T_{max}, AUC_{last}, and as data permit, $t_{½}$, AUC_{inf}, CL/F and V_z/F. • Multiple dose (assuming steady state is achieved) - $C_{ss,max}$, $T_{ss,max}$, $AUC_{ss,\tau}$, $C_{ss,min}$, and as data permit, CL_{ss}/F, V_{ss}/F, $t_{½}$ and R_{ac} ($AUC_{ss,\tau}$ /$AUC_{sd,\tau}$).
• To assess additional measures of anti-tumor efficacy of PF07284890 at the recommended dose for further study in combination with binimetinib.	• DCR (overall and intracranial). • PFS (overall and intracranial), OS, DoR (overall and intracranial) and TTR (overall and intracranial).
Phase 1b Tertiary/Exploratory:	**Phase 1b Tertiary/Exploratory:**
• To explore the effect of CCI [redacted] on PF07284890 exposures in participants treated with PF07284890 in combination with binimetinib.	CCI [redacted]
• To explore the brain penetration of PF07284890 in combination with binimetinib.	• CSF concentrations of PF07284890 (in participants in whom CSF is obtained as SOC).
• To evaluate tumor and blood-based biomarkers of response and resistance to PF07284890 in combination with binimetinib.	CCI [redacted]
• To evaluate the effect of repeated administration of PF-07284890 in combination with binimetinib on single dose PK of midazolam (Cohort 6 only).	PK parameters of CYP3A4 probe substrate midazolam: • C_{max}, T_{max}, AUC_{last}, and as data permit, $t_{½}$, AUC_{inf}, CL/F and V_z/F.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1a/b, open-label, multicenter, dose-finding study of the PK, safety and preliminary clinical activity of PF-07284890 in adult and adolescent participants with selected BRAF V600-mutant advanced or metastatic solid tumor malignancies and primary brain tumors. The study will be conducted in 2 parts. Phase 1a will be a Dose Escalation study, which will be divided into monotherapy (PF-07284890 alone) and combination therapy (PF-07284890 plus binimetinib); Phase 1b will be a Dose Expansion, an optional food-effect substudy, and an optional DDI substudy (both PF-07284890 plus binimetinib).

Participants will have experienced disease progression after prior treatment and have no acceptable alternative treatment options. See Section 5.1 Inclusion Criteria 6 for specific requirement related to prior treatment with a BRAF inhibitor.

Phase 1a Dose Escalation

Approximately 35 participants will be enrolled to determine the MTD and/or recommended dose for further study of PF-07284890 alone and in combination with binimetinib 45 mg BID. Monotherapy and combination dose escalation cohorts may overlap, with monotherapy dose escalation initiating first.

Cohorts of 2-4 evaluable participants will be treated at each dose level of PF-07284890 on an outpatient basis starting from 50 mg QD until the determination of MTD/recommended dose for further study. A minimum of 6 participants are expected to be treated at MTD/recommended dose for further study (ie, 6 participants each for both monotherapy and combination therapy) in order to characterize safety, tolerability, PK as well as preliminary activity of PF-07284890 when given at the MTD/recommended dose for further study (both alone and in combination with binimetinib). The actual dose increases between dose levels will be determined by safety and observed PK as described below. In addition, an alternative schedule (eg, BID, dosing holiday) may be evaluated depending on safety and observed PK.

For the monotherapy dose escalation part, a participant is classified as DLT evaluable if he/she experiences a DLT (Section 4.3.3) or if he/she otherwise in the absence of a DLT receives at least 75% of the planned PF-07284890 doses and has received all scheduled safety assessments during the DLT observation window (first cycle of treatment, a 21-day cycle). For the combination therapy dose escalation part, a participant is classified as DLT evaluable if he/she experiences a DLT (Section 4.3.3) or if he/she otherwise in the absence of a DLT receives at least 75% of the planned PF-07284890 and 75% of the planned binimetinib doses and has received all scheduled safety assessments during the DLT observation window (first cycle of treatment, a 21-day cycle).

A BLRM will be used to model the DLT relationship of PF-07284890. This model, along with the EWOC, will guide the dose escalation of PF-07284890 after the completion of the DLT observation period of each cohort, until adequate DLT data have accumulated throughout the monotherapy dose escalation to inform the combination BLRM or until the determination of MTD/recommended dose for PF-07284890 monotherapy.

Once initial doses of PF-07284890 monotherapy are determined to be safe and meet the EWOC criteria, BLRM and EWOC will be used to model the DLT relationship of PF-07284890 in combination with binimetinib at the approved dose of 45 mg BID (monotherapy dose escalation will continue simultaneously). Based on preliminary PK and safety, the combination dose escalation phase of PF-07284890 with binimetinib may be started prior to the determination of the monotherapy PF-07284890 MTD/recommended dose for further study. The starting dose level for PF-07284890 in the combination dose therapy escalation will not be higher than previously studied doses in the monotherapy escalation and will satisfy EWOC criteria. The parameters will be derived for the combination BLRM by incorporating DLT data obtained from the PF-07284890 monotherapy escalation and historical data for binimetinib (see Section 9.3.1.1).

For both monotherapy and combination therapy dose escalations, toxicities will only be considered DLTs if they occur within the DLT window of the first cycle (21 days); however, overall safety, including later cycles, and PK data will be evaluated for the recommended dose for further study determination.

Phase 1b Dose Expansion, optional DDI Substudy, and optional Food-effect Substudy

After identification of the combination MTD/recommended dose for further study, approximately 20 participants will be enrolled to each of Cohorts 1-4 and 40 participants to Cohort 5 of Phase 1b dose expansion based on tumor type, whether brain involvement is asymptomatic or symptomatic and measurable or non-measurable, prior treatment history and a history of or current leptomeningeal metastases. The participants intended for each cohort are described in Section 1.2 and Section 5. The dose expansion phase (Cohorts 1-5) will evaluate efficacy, safety and PK at the recommended dose for further study in combination with binimetinib.

The effect of food (low fat and high fat meal versus fasted state) on PF-07284890 PK is being assessed in study C4471002 in healthy participants. Once the results of this food-effect study are available, it may trigger the opening of an optional Cohort 7 and/or the instructions for administration of C4471001 may be changed. See Appendix 16. To mitigate burden to patients, change(s) in dose and dosing instructions regarding administration with food may initially be communicated by PACL followed by subsequent protocol amendment.

The results of C4471002 and/or Cohort 7 may not be available prior to initiation of Cohorts 1- 6. If the effect of food on PF-07284890 PK based on the results of C4471002 is found to be positive and the instructions for PF-07284890 administration are changed, the patients in those cohorts administered PF-07284890 following the previous instructions may be replaced with participants from Cohort 7 or newly enrolled participants.

In addition, approximately 10 participants may be enrolled to a substudy (Cohort 6) to evaluate the effect of PF-07284890 in combination with binimetinib on CYP3A activity using midazolam as a probe CYP3A4 substrate. A synopsis including SoA for the substudy is provided in Appendix 15.

For both Phase 1a and Phase 1b, treatment with study intervention will continue until either disease progression, participant refusal, unacceptable toxicity occurs, or up to 2 years, whichever occurs first. Participants who have disease progression but are deriving clinical benefit may continue if criteria are met and the participant consents to continue treatment (see Section 7.1.1). Participants who complete 2 years on study intervention and demonstrate clinical benefit with manageable toxicity and are willing to continue receiving the study intervention will be given the opportunity to continue treatment upon agreement between investigator and sponsor, using the *same safety assessments as were being performed most recently, but with efficacy monitored at intervals consistent with clinical practice*.

Please see SoA for the schedule of administration. The proposed doses, schedule(s), and PK sampling time points may be reconsidered during the study based on the emerging safety and PK data.

One of the elements of this study is the possibility to evaluate potential molecular targets that could be modified in vivo by the drug PF-07284890 as a single agent or in combination with binimetinib used in this study. Planned biomarker studies include analysis of changes in CCI [redacted] during treatment (all participants), and analysis of fresh tumor biopsies for changes in tumor cell levels of CCI [redacted] during treatment (only if fresh biopsy can be performed safely, and only for participants who provide informed consent/assent for biopsy).

The biomarker studies will be used to help understand the in vivo mechanism of action of the agent(s). The studies may help in the future development of PF-07284890 as a single agent, or in combination with other compounds, and may provide information on tumor sub-types that may respond to the study intervention. Details of biomarker studies are provided in Section 8.8.

4.2. Scientific Rationale for Study Design

The purpose of the first-in-human, open-label study is to determine the MTD and/or recommended dose for further study of PF-07284890 as a single agent and in combination with binimetinib and evaluate the PK, safety and preliminary clinical activity overall and in the brain.

The effect of PF-07284890 on embryo-fetal development is unknown. Binimetinib is known to cause risk for severe manifestations of developmental toxicity in humans or suspected on the basis of the intended pharmacology. Therefore, the use of a highly effective method of contraception is required, including at least 1 form of non-hormonal contraception, given the potential for CYP3A induction by PF-07284890 (see Appendix 4).

Banked Biospecimens will be collected and stored for further analyses which may, for example, provide greater understanding of the study intervention.

4.2.1. Rationale for Dose Escalation Approach

PK and safety from prior dose levels will be used to guide dose escalation (see Section 4.3.2). No dose increase will exceed approximately 2-fold over the current dose level ("approximately" to take into account available tablet dose sizes and to minimize pill burden for participants). However, if exposures at the current dose level are much lower than expected, and no DLTs are observed at the current and all prior dose levels, the dose increase may be up to approximately 3-fold the current dose level. "Lower than expected" is defined in Section 4.3.2 as: observed trough PF-07284890 concentration at steady-state ($C_{ss,min}$), is less than the calculated fu-adjusted IC_{50} for inhibiting ERK phosphorylation in a BRAF V600E cell-based assay in at least two-thirds (eg, 2 out of 2, 2 out of 3, or 3 out of 4) of the participants treated at that dose level. After a dose level of 300 mg, the next dose will not exceed 1.5 times the current dose level.

This approach is justified by safety considerations. Thus, the level of PF-07284890 that is equivalent to the calculated IC_{50} for BRAF V600E is approximately 30-160 times lower than the level achieved at the NOAEL in monkeys and STD_{10} in rats, respectively, in the GLP toxicology studies.

In addition, this approach is justified by ethical considerations. By utilizing both observed safety and observed PK to determine the actual dose interval increase, the number of participants exposed to a potentially sub-efficacious dose of PF-07284890 may be decreased, which minimizes the chance that a significant number of participants will not benefit from treatment.

4.2.2. Rationale for Combination with Binimetinib

Early clinical trials of BRAF inhibitors in BRAF V600-mutant melanoma indicated improved efficacy when the BRAF inhibitor was combined with a MEK inhibitor, due to more robust inhibition of the MAPK pathway.[24] In addition, certain toxicities (eg, rash, cutaneous squamous cell carcinoma), which result in part from paradoxical activation of the MAPK pathway that occurs in the absence of mutant BRAF, could be ameliorated by the addition of a MEK inhibitor.[27,30] These results have been validated in multiple clinical trials; thus, combining a BRAF inhibitor with a MEK inhibitor is the standard targeted therapy treatment approach for BRAF V600-mutant cancers. The approved dose of encorafenib when coadministered with binimetinib is 450 mg QD, but when administered as a single agent is 300 mg QD, due to improved tolerability with binimetinib coadministration.[27,31] This approach has been validated preclinically with PF-07284890: the addition of the MEK inhibitor binimetinib to PF-07284890 led to more rapid and sustained tumor response in an intracranial mouse model of BRAF V600-mutant melanoma than either PF-07284890 monotherapy or combined encorafenib (a poorly brain penetrant BRAF inhibitor)-binimetinib treatment (data on file, Pfizer, Inc), with tolerability maintained. Finally, binimetinib has a well-characterized safety profile and excellent pharmacology (eg, tolerated exposures consistent with target inhibition and minimal drug interactions),

permitting it to be combined with multiple other agents in clinical trials, including small molecule BRAF inhibitors (ie, encorafenib) and therapeutic antibodies (ie, cetuximab). Therefore, as described in Section 4.3, during dose escalation, PF-07284890 will be combined with binimetinib at the approved dose of 45 mg BID, which is 1 dose level lower than the MTD of 60 mg BID established in the first-in-human clinical trial.[23] Since combined treatment with a MEK inhibitor may be critical for maximizing efficacy and minimizing toxicity, the protocol is flexible to the timing of introducing binimetinib co-treatment during monotherapy dose escalation of PF-07284890 (see Section 4.3.2).

4.2.3. Rationale for Unmet Medical Need for Participants with Symptomatic Brain Involvement

As discussed in Section 2.2, randomized/registrational studies of approved BRAF inhibitors in BRAF V600-mutant melanoma and NSCLC excluded patients with untreated (ie, with local brain therapy), symptomatic (including a requirement for steroid or anti-epileptic therapy to control symptoms) and/or progressive brain metastases at baseline. Recent single-arm, noncomparative trials indicated the potential for anti-tumor activity in the brain for the BRAF inhibitor dabrafenib (in combination with trametinib) and the ICIs ipilumimab plus nivolumab in patients with asymptomatic brain metastases not requiring local brain therapy, steroids or anti-epileptic therapy. In the former, the median overall DoR and PFS for patients with untreated, asymptomatic brain metastases was shorter than for patients without brain metastases in the registrational studies, and shorter still for patients with symptomatic brain involvement. In the latter, treatment was limited to patients with asymptomatic, untreated brain metastasis and was toxic, and only a minority of patients received all planned treatments. Local brain therapy with SRS or surgery provides modest disease control to treated lesions but may only be used for a limited number and size of lesions and has no effect on untreated lesions. WBRT is associated with long-term neurocognitive effects and is normally used only once.

For these reasons, patients with BRAF V600-mutant solid tumors for whom BRAF inhibitors are approved and considered standard systemic treatment in the absence of active brain metastases (ie, melanoma, NSCLC, ATC and CRC, though the frequency of brain metastases in ATC and CRC is low), and who have symptomatic brain lesions, have high unmet medical need: the long-term efficacy of available BRAF inhibitors remains unproven in this patient population. Therefore, during monotherapy dose escalation, once the levels of PF-07284890 achieved in participants are consistent with significant calculated BRAF V600-mutant target coverage (ie, steady-state concentration is $\geq$ the IC_{70} for inhibition of BRAF V600E in the brain; see Section 5.1), subsequently enrolled participants (to both the monotherapy and combination dose escalation) with these tumor types who are suffering from symptomatic brain metastases may be eligible without prior treatment with a BRAF inhibitor. These participants require prior treatment with other available standard therapy prior to enrollment (eg, ICI treatment for melanoma, platinum-based chemotherapy and/or ICI treatment for NSCLC, local brain therapy for both if consistent with institutional/country standard of care) (see Section 5 for specific Inclusion Criteria). Such participants who are without brain metastases or with asymptomatic brain metastases at baseline require previous treatment with a BRAF inhibitor to be eligible. In all cases, close follow-up surveillance with brain MRI

every 6 weeks is required by the protocol, consistent with current guidelines for patients with (active) brain involvement treated with systemic therapy.[32]

4.2.4. Rationale for BRAF V600 Mutation Testing Paradigm

In the current study, participants may be eligible for enrollment based on BRAF V600 mutation status determined locally by PCR or NGS in a CLIA (or similarly certified) laboratory (see Section 5.1 Inclusion Criteria 3). The use of local BRAF V600 mutation testing as planned in this study allows efficient enrollment of and access for participants with a valid BRAF V600 mutation test result who are suffering from advanced, treatment-refractory cancers, and has been previously demonstrated to be highly accurate when performed in a certified laboratory.[29] Specific questions about whether a local testing results is eligible should be discussed with the sponsor.

4.2.5. Rationale for CCI Assessment

The primary mechanism of PF-07284890 clearance is thought to be through CCI (Section 2.2.2). CCI with the potential for clinical relevance.[33,34] Therefore, the relationship between PF-07284890 exposures and CCI will be assessed.

4.2.6. Rationale for Food-effect SubStudy

Food can have a significant impact on drug pharmacokinetics, and therefore on drug safety and efficacy. The effect of food on PF-07284890 PK is being assessed in clinical Study C4471002. This open-label, randomized, single dose, 2-sequence, 3-period crossover study will evaluate the effect of a low-fat and high-fat meal on the relative bioavailability of PF-07284890 in approximately 12 healthy participants. If the low-fat and high-fat meal have less than a 2-fold increase on PF-07284890 exposures, the results of this study may be used to modify administration instructions for PF-07284890 in Phase 1b of the current study, including the potential use of this data to determine the dose in the fed state that is equivalent to the fasted state MTD/RDE. However, in the case of a positive food effect, as the effect of food on relative bioavailability of PF-07284890 increases, the width of the confidence interval around the estimated effect of food is also expected to increase, and therefore the precise effect of food is known with less certainty. Therefore, if food increases the relative bioavailability by more than 2-fold for either the low-fat or high-fat meal, more data are needed to determine whether the equivalent dose for the fed state achieves the proper exposure and is safe with repeat administration. For this reason, the effect of food on PF-07284890 PK and safety will be characterized in a substudy (Appendix 16) if data from C4471002 indicate more than a 2-fold increase from taking PF-07284890 with food. Until the effect of food on its pharmacokinetics is understood, either based on C4471002 or in the case of a more substantial food effect also based on the food-effect substudy, PF-07284890 must be taken on an empty stomach (except for food-effect substudy participants).

4.2.7. Rationale for CYP3A4 Drug-Drug Interaction Substudy

PF-07284890 showed competitive and time-dependent inhibition as well as induction of CYP3A4 in vitro. As a result, there is a potential that PF-07284890 may alter PK in concomitantly administered medicines metabolized by CYP3A, possibly increasing or decreasing their exposures. For this reason, coadministration of PF-07284890 with CYP3A substrates with narrow therapeutic indices is prohibited (Section 6.5.1.1). For this reason, 1 of the dose expansion groups will be included as a substudy to evaluate the effect of PF-07284890 in combination with binimetinib on CYP3A probe midazolam at the MTD/recommended dose for further study and schedule (Appendix 15). Although binimetinib will be coadministered, it is not expected to impact the DDI results due to its limited ability to cause DDIs.[35]

4.3. Justification for Dose

Doses presented are projected based on nonclinical data and may be modified based on emerging safety, tolerability, and PK data.

4.3.1. Starting Dose

The starting dose for PF-07284890 will be 50 mg QD in 21-day cycles. The starting dose of PF-07284890 is based on CCI [redacted] (the more sensitive of the 2 species tested) from the 28-day GLP nonclinical toxicology studies. The STD_{10} is CCI [redacted] (based on a 1.62 m^2 human). Based on available tablet configurations (10, 25 and 100 mg) and the rat data, a starting dose of 50 mg/day was chosen.

The starting dose of binimetinib is 45 mg BID, which is the approved dose in combination with the BRAF inhibitor encorafenib, and is one dose level lower than the MTD identified in the Phase 1 clinical trial.[23]

4.3.2. Criteria for Dose Escalation

Dose Escalation will be guided by safety and observed PK, with overlapping monotherapy dose escalation and combination dose escalation with binimetinib (see Section 1.2 Schema).

BLRM guided by the EWOC principle will be used in dose escalation. See Section 9 and Appendix 9 for more details on the model.

4.3.2.1. PF-07284890 Monotherapy Dose Escalation

Dose escalation of PF-07284890 will initiate as monotherapy. The DLT evaluation period will be the first 21 days (Cycle 1). The decision to enroll participants to the next and subsequent dose levels will depend on the rate of DLTs according to the BLRM design. The dose for the next and subsequent dose levels will depend on the observed PK at the preceding dose level(s), the PF-07284890 exposure predicted at the next dose level and the occurrence of DLTs in the current dose level.

During each dose escalation decision, the next dose will normally not exceed 2 times the current dose level. However, in the absence of DLTs at the current and all prior dose levels, and if the observed trough concentration at steady state ($C_{ss,min}$ estimated as the predose plasma concentration on Cycle 1 Day 15) with the current dose is < the calculated IC_{50} (adjusted for the unbound fraction, fu, in plasma protein and in the in vitro assay) of PF-07284890 for inhibiting ERK phosphorylation in a BRAF V600E cell-based assay in at least two-thirds of patients (eg, 2 out of 2, 2 out of 3, or 3 out of 4), the next dose will not exceed 3 times the current dose level. After a dose level of 300 mg, the next dose will not exceed 1.5 times the current dose level. The actual total daily dose may be slightly higher or lower than the calculated dose based on safety, available tablet dose sizes and pill burden.

The concentration of PF-07284890 required to achieve CCI [redacted]

Steady-state levels of PF-07284890 in plasma are estimated to be achieved by pre-dose on Cycle 1 Day 15, although this timing may be adjusted based on emerging PK data.

Determination of the actual dose levels will be made by the SRC, which will meet by teleconference for each dose escalation decision and consider the PK, the occurrence of DLTs/DLT probability, and the cumulative safety profile to date. Based on available tablet dose sizes and the parameters indicated above, potential dose levels for PF-07284890 (as monotherapy and in combination with binimetinib) are outlined in Table 2:

Table 2. Example Dose Levels for PF-07284890

Dose Level	PF-07284890 Dose[a]	Scenario
Dose level -2	10 mg QD	DLT probability at Dose level -1 exceeds threshold by BLRM.
Dose level -1	25 mg QD	DLT probability at Dose level 1 exceeds threshold by BLRM.
Starting Dose level 1	50 mg QD	
Dose level 2 alternate 1[b]	100 mg QD (50 mg BID)	No DLTs at Dose level 1, SRC has no safety concerns, calculated $C_{ss,min}$ ≥0.072 µg/mL in 2/3 participants.
Dose level 2 alternate 2[b]	150 mg QD (75 mg BID)	No DLTs at Dose level 1, SRC has no safety concerns, calculated $C_{ss,min}$ <0.072 µg/mL in 2/3 participants.

a. PF-07284890 tablet dose sizes are 10, 25 and 100 mg. QD dosing will be utilized initially; dosing frequency may be changed (eg, BID) by SRC based on available safety and PK data.
b. Dose level 2, alternates 1 and 2 are maximum doses given the scenarios depicted; the SRC may choose a lower dose than shown based on available PK and safety.

Dose Modification for PF-07284890 is described in Section 6.6.

4.3.2.2. PF-07284890 Dose Escalation in Combination with Binimetinib

The starting dose of binimetinib in combination with PF-07284890 will be the approved dose of 45 mg BID. Dose escalation of PF-07284890 in combination with binimetinib at a dose of 45 mg BID will follow the BLRM design, using the prior distribution of the safety data

determined in the monotherapy cohorts that have been observed at that time and PK- and safety-guided dose escalation as indicated for PF-07284890 monotherapy.

Initiation of combination dose escalation will only begin at a monotherapy dose of PF-07284890 previously determined to be safe according to BLRM/EWOC. The actual dose of PF-07284890 at which combination dose escalation is initiated will be determined by the sponsor and investigators after consideration of PK, safety and efficacy data (the latter if available) from previous monotherapy dose levels, but will not be higher than the highest monotherapy dose determined to be safe based on BLRM/EWOC.

Dose Modification for binimetinib is described in Section 6.6.

During Phase 1a, dose escalation will proceed until the identification of the MTD/recommended dose for further study for PF-07284890 for each of monotherapy and in combination with binimetinib (monotherapy and combination dose escalation may overlap; see Section 4.3.2).

During monotherapy and combination dose escalation, a change to a different dosing frequency (eg, BID dosing, different number of days of dosing per cycle) of PF-07284890 may be explored based on emerging PK, safety and efficacy data. The actual dose and frequency of PF-07284890 (and binimetinib) to be used for each dose level (and the recommended dose for further study) will be clearly communicated to the study sites but will not require an immediate protocol amendment.

4.3.2.3. Intrapatient Dose Escalation

To minimize the risk that an individual participant may be exposed to a subtherapeutic dose, intrapatient dose escalation of PF-07284890 to a higher dose(s) previously determined to be safe (based on BLRM/EWOC) may be allowed, after a minimum of 12 weeks of treatment at the current dose (eg, 4 cycles including scheduled disease assessments) or disease progression, whichever occurs first. Binimetinib may also be added to patients initially receiving PF-07284890 monotherapy after the above criteria are met (eg, after 12 weeks of treatment or PD, and the combination dose was determined to be safe). See Section 7.1.1 for request to continue study intervention.

4.3.3. Dose Limiting Toxicity Definition

A participant is classified as DLT-evaluable if he/she experiences a DLT or if he/she otherwise in the absence of a DLT receives at least 75% of the planned doses of the study intervention (ie, ≥16/21 doses if QD dosing; ≥32/42 doses if BID dosing; a participant treated with the combination must meet this threshold for each agent) and has received all scheduled safety assessments during the DLT window. If a participant fails to meet these criteria, he/she may be replaced.

For the purpose of dose escalation, the DLT observation period will be during the first cycle of treatment or within 21 days after the start of the study treatment in each participant.

Any AE resulting in a participant receiving less than 75% of the planned doses of the study intervention during the first 21 days of treatment will be evaluated by the SRC and may be considered a DLT if it is considered related to study treatment (ie, cannot be reasonably attributed to the participant's underlying disease, concomitant medications or preexisting conditions).

Significant adverse events considered to be related to the study intervention or treatment under investigation that occur after the DLT observation period will be reviewed in context of all safety data available. That review may result in re-evaluation of the dosing level or regimen.

Severity of AEs will be graded according to CTCAE version 5.0. For the purpose of dose escalation, any AE greater than or equal to CTCAE Grade 3 occurring in the first cycle of study treatment or within 21 days after the start of study treatment is considered a DLT unless it can clearly be shown to be unrelated to the drug (eg, due to disease progression). DLT exceptions and clarification are indicated below.

Exceptions/clarifications:

Hematological:

- Isolated Grade 3 or 4 neutropenia (eg, without associated infection and not meeting CTCAE version 5.0 criteria for febrile neutropenia) lasting >7 days is a DLT;
- Grade 3 or 4 neutropenia associated with infection or meeting CTCAE version 5.0 criteria for febrile neutropenia is a DLT;
- Grade 3 thrombocytopenia associated with clinically significant (eg, requiring hospitalization/prolongation of hospitalization, disabling, limiting self-care ADLs, or invasive medical intervention) bleeding or Grade 4 thrombocytopenia is a DLT;
- Lymphocyte count decreased Grade ≥3 that is clinically significant (eg, requiring hospitalization/prolongation of hospitalization, disabling, or limiting self-care ADLs) is a DLT.

Non-Hematologic:

- Grade 3 toxicities that are clinically significant (eg, requiring hospitalization/prolongation of hospitalization, disabling, or limiting self-care ADLs), except those that have not been maximally treated (eg, nausea, vomiting, diarrhea) or can be easily treated (eg, electrolyte abnormalities) and any Grade 4 non-hematologic adverse events are DLTs;
- For participants with Grade 2 hepatic transaminase or alkaline phosphatase levels at baseline as a result of liver metastasis or bone metastasis: a hepatic transaminase or alkaline phosphatase level >10× ULN is a DLT;

- Confirmed DILI meeting Hy's law criteria (ALT/AST >3× the ULN with bilirubin >2× ULN without another explanation [eg, cholestasis]) is a DLT;
- CK elevation ≥ Grade 3 associated with an increase in serum creatinine ≥1.5× the participant's screening serum creatinine is a DLT;
- Grade 3 fatigue persisting >5 days is a DLT;
- Grade 3 diarrhea persisting >48 hours despite optimal use of antidiarrheal therapy is a DLT;
- Grade 3 nausea persisting >48 hours despite optimal use of antiemetic therapy is a DLT;
- Grade 3 skin toxicity (eg, rash, dermatitis, hand foot skin reaction) persisting >14 consecutive days despite maximal skin toxicity treatment (as per local practice), is a DLT;
- Grade 2 eye disorders assessed to be irreversible or unresponsive to local therapy within 21 days and confirmed by ophthalmic evaluation, Grade ≥3 eye disorders confirmed by ophthalmic evaluation, or retinal vascular disorder (including RVO) and confirmed by ophthalmic examination, are DLTs;
- In an asymptomatic participant, Grade 3 QTcF prolongation will first require repeat testing, reevaluation by a qualified person, and correction of reversible causes such as electrolyte abnormalities or hypoxia for confirmation. If, after correction of any reversible causes, the Grade 3 QTcF prolongation persists, then the event is a DLT;
- Absolute decrease of LVEF >10% compared to baseline and the LVEF is below the institution's LLN is a DLT;
- Grade 3 hypertension persisting >14 consecutive days is a DLT;
- Any death not clearly due to the underlying disease or extraneous cause is a DLT;
- CNS effects (eg, changes in speech, memory, sleep, congnition, or vision) that are severe or clinically significant (eg, requiring hospitalization/prolongation of hospitalization, disabling, or limiting self-care ADLs) are DLTs.

The following AEs will not be adjudicated as DLTs:

- Isolated Grade 3 or 4 laboratory abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.

4.3.4. Recommended Dose For Further Study

The recommended dose for further study (RDE) is the dose chosen for further investigation based on Phase 1 dose escalation study results. If the MTD proves to be clinically feasible for long-term administration in a reasonable number of participants, then this dose usually becomes the recommended dose for further study. Further experience with the MTD may result in a recommended dose for further study lower than the MTD. During escalation prior to an MTD being reached, the sponsor may choose to advance a lower dose into expansion, particularly (but not exclusively) when considering combination cohorts. This decision must be made based on safety, PK, PD, and/or efficacy.

4.3.5. Stopping Criteria in Phase 1b Dose Expansion

The criteria for placing the study on temporary hold for safety reasons are based on Bayesian posterior probabilities using a non-informative Beta (0.5, 0.5) prior distribution.

If either of the following criteria listed below are met in any of the cohorts in the Phase 1b dose expansion, further enrollment into that cohort will be placed on hold:

- The posterior probability that the true incidence of Grade 5 treatment-related AEs exceeding 10% is ≥0.90.
- The posterior probability that the true incidence of Grade 4-5 treatment-related AEs in a particular cohort exceeding 30% is ≥0.80.

If a cohort is placed on temporary hold, Pfizer will review all safety information with the SRC and subsequently decide whether the cohort will be permanently terminated or resume enrollment with any potential modifications.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last scheduled visit/procedure shown in the SoA.

The end of the study is defined as 2 years after treatment initiation of the last participant enrolled or the point at which all participants have died or withdrawn consent/assent or have been lost to follow-up, whichever occurs first. At the end of the study, if feasible, access to study treatment may be provided in accordance with applicable regulations and requirements to all participants who are continuing to benefit from study treatment upon agreement between investigator and sponsor (see Section 6.7).

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

Pfizer will review eligibility criteria verified by the investigator or qualified designee to confirm that participants meet study eligibility criteria before they are enrolled into the study. The enrollment approval process will be initiated for a participant after an informed consent/assent document has been signed and the investigator or qualified designee has assessed the participant as eligible. The enrollment approval will be based on review of CRF/system data.

5.1. Inclusion Criteria

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

Unless otherwise indicated, criteria apply to both Phase 1a (dose escalation) and Phase 1b (dose expansion).

1. Female and/or male participants age ≥18 years at the time of informed consent are eligible for all parts of the study. Adolescent participants aged 16 years and older (at the time of informed consent/assent) with body weight ≥40 kg may be enrolled in the Phase 1b dose expansion only. Admission of adolescents to the study will be as appropriate according to institutional approvals and will require the additional screening/monitoring procedures as described in Section 8.2.1 and 8.2.11.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

    - Female participants of childbearing potential, as described must: (1) have a negative serum β-HCG test result obtained within 24 hours of C1D1; (2) use protocol-approved methods of contraception (including at least 1 form of non-hormonal contraception due to potential CYP3A4 induction by PF-07284890); and (3) not donate ova from Screening until 28 days after the last dose of study intervention.

    - Male participants must agree to: (1) use methods of contraception that are highly effective or acceptable (including at least 1 form of non-hormonal contraception due to potential CYP3A4 induction by PF-07284890); and (2) not donate sperm from Screening until 28 days after the last dose of study intervention.

2. Histologically confirmed diagnosis of advanced/metastatic solid tumor including primary brain tumor.

3. Documented evidence of a BRAF V600 mutation in tumor tissue or blood (eg, CCI) as previously determined by either PCR or NGS-based local laboratory assay obtained during the course of normal clinical care in a CLIA or similarly certified laboratory at any time prior to Screening. A molecular report clearly documenting the presence of the BRAF V600 mutation (and other molecular findings

from samples as performed during the normal course of clinical care) must be provided for confirmation that testing meets eligibility during Screening.

4. Confirmation of availability of adequate tumor tissue for submission to the sponsor/central laboratory.

   - *Note:* FFPE block, or a minimum of 15 unstained slides must be provided, ideally with ≥20% tumor nuclei. Participants with fewer than 15 slides of analyzable tissue may be considered eligible if the sponsor determines that the slides are sufficient for BRAF V600 mutation testing. A fresh tumor tissue biopsy may be provided for participants unable to provide archival tumor tissue. If a fresh biopsy is taken, the biopsy should be taken from a nontarget lesion when possible. Participants who do not have sufficient/adequate archival tissue and in whom a fresh biopsy to obtain sufficient tissue cannot be performed safely in the opinion of the investigator may be eligible if they meet all other eligibility criteria.

   - *Note*: Whenever possible, the archival sample should be from the same tumor block that was used for local BRAF V600 mutation testing. If that sample is different than the most recent, previously obtained sample, the most recent sample should also be provided if feasible.

5. Presence or absence of brain involvement.

   - Participants entering the study in dose escalation:

     - Brain involvement is not required. Initially during dose escalation, all brain lesions must be ≤4 cm in longest dimension, and participants with brain involvement must be asymptomatic in the brain for at least 14 days prior to the start of study treatment, defined as: (1) be neurologically asymptomatic from brain metastases/primary brain tumor; (2) not require initiation of or an increase in steroid dosing to control neurological symptoms due to brain metastases/primary brain tumor; and (3) not require initiation of or an increase in anti-epileptic dosing to control seizure activity due to brain metastases/primary brain tumor. Exception: anti-epileptic therapy to prevent neurological symptoms caused by a preexisting condition and not related to brain involvement is allowed provided there are no concerning drug-drug interactions (see Section 6.5 and Appendix 10 for allowed/prohibited concomitant medications, including anti-epileptic therapy).

     - Once the trough concentration of PF-07284890 at steady state is ≥0.168 µg/mL (equal to the fu-adjusted IC_{70} for inhibition of BRAF V600E) in at least two-thirds of participants at the same dose level, a level at which anti-tumor activity in the brain and systemically may be expected, subsequent participants entering the study during dose escalation may have a lesion(s) larger than 4 cm, and/or be symptomatic in the brain, defined as: any of the above within 14 days of the start of study treatment.

- Participants entering the study in dose expansion:
  - Cohorts 1, 2, 3 and 4: melanoma, with at least 1 parenchymal brain lesion at least 0.5 cm and ≤4 cm in longest diameter and measurable (by mRECIST v1.1). If all disease in the brain was previously irradiated, at least 1 measurable lesion must demonstrate progression since irradiation or a new measurable lesion(s) must be present.
  - Cohorts 1, 3: asymptomatic in the brain for at least 14 days prior to the start of study treatment as defined above.
  - Cohorts 2, 4: symptomatic in the brain within 14 days prior to the start of study treatment as defined above.
  - Cohort 5: any solid tumor with at least 1 measurable lesion (refer to RECIST, mRECIST, or RANO criteria); history of or current leptomeningeal metastases is permitted; with or without disease in the brain as long as it does not meet requirements for Cohorts 1-4; with or without prior BRAF and/or MEK inhibitor; asymptomatic or symptomatic in the brain as defined above. For patients with primary brain tumors, RANO should be used to determine baseline brain lesion status and response assessment during the study. Patients without measurable disease may be allowed if a compelling clinical rationale is provided by the investigator and approved by the sponsor.
  - Cohort 6, 7 (DDI and food-effect substudy): if brain involvement is present, lesion(s) must be ≤4 cm in longest diameter and it must be asymptomatic in the brain for at least 14 days prior to the start of study treatment as defined above.

6. Disease progression despite prior treatment and no acceptable alternative treatment options available.
   - *Note:* participants for whom the risk:benefit ratio of a specific available alternative therapy is unfavorable in the opinion of the investigator may be eligible if the reason is clearly documented and approved by the sponsor.
   - Participants entering the study in dose escalation:
     - Once the concentration of PF-07284890 at steady state is ≥0.168 µg/mL (equal to the IC_{70} for inhibition of BRAF V600E) in at least two-thirds of participants at the same dose level, a level at which anti-tumor activity in the brain and systemically may be expected, participants with BRAF V600-mutant melanoma, NSCLC, CRC or ATC do not require prior treatment with a BRAF inhibitor if brain involvement is present and symptomatic as defined above. These participants still require other prior standard systemic

therapy as well as prior local brain therapy, the latter if consistent with institutional/country standard of care.

- Participants entering the study in dose expansion:
  - Cohorts 1, 2: Prior BRAF or MEK inhibitor in the metastatic setting (or in the adjuvant setting within 6 months of study treatment) is not allowed.
  - Cohorts 3, 4: Prior BRAF inhibitor in the metastatic setting (or in the adjuvant setting within 6 months of study treatment) is required.
  - Cohort 5: Prior BRAF inhibitor in the metastatic or adjuvant setting is allowed but not required.
  - Cohort 6 and 7: Prior BRAF inhibitor is allowed but not required.

7. ECOG PS 0 or 1.
   - Participants entering the study in dose escalation: ECOG PS 2 due to underlying cancer is allowed once the concentration of PF-07284890 at steady state is ≥0.168 µg/mL (equal to the IC_{70} for inhibition of BRAF V600E) in at least two-thirds of participants at the same dose level, a level at which anti-tumor activity in the brain and systemically may be expected.
   - Participants entering the study in dose expansion: ECOG PS 2 due to underlying cancer is allowed for Cohorts 1-5.
8. Adequate Bone Marrow Function, including:
   - ANC ≥1,250/mm^3 or ≥1.25 × 10^9/L;
   - Platelets ≥75,000/mm^3 or ≥75 × 10^9/L;
   - Hemoglobin ≥9 g/dL. Transfusion support is permitted if completed 14 days prior to the start of study treatment and hemoglobin remains ≥9 g/dL at the start of study treatment.
9. Adequate Renal Function, including:
   - Estimated creatinine clearance ≥60 mL/min (≥50 mL/min for dose expansion) as calculated using the method standard for the institution. In equivocal cases, a 24-hour urine collection test can be used to estimate the creatinine clearance more accurately.

10. Adequate Liver Function, including:

    - Total serum bilirubin ≤1.5 × ULN; ≤3.0 × ULN if the participant has documented Gilbert syndrome; ≤2.5 × ULN for HCC;
    - AST and ALT ≤2.5 × ULN; ≤5.0 × ULN if there is liver involvement by the tumor; ≤5 × ULN for HCC;
    - Alkaline phosphatase ≤2.5 × ULN; ≤5 × ULN in case of bone/liver metastasis.

11. Resolved acute effects of any prior therapy to baseline severity or CTCAE Grade ≤1 except for AEs not constituting a safety risk by investigator judgment and discussion with the sponsor. *Note*: Stable chronic conditions (≤ Grade 2) that are not expected to resolve (eg, neuropathy, myalgia, alopecia, prior therapy-related endocrinopathies) are also exceptions and participants with these conditions may enroll.

12. Participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

13. Capable of giving signed informed consent/assent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

14. For adolescent participants: The investigator, or a person designated by the investigator, will obtain written informed consent from each study participant's legal guardian (as defined in Appendix 1 [and the participant's assent, when applicable,]) before any study-specific activity is performed (unless a waiver of informed consent/assent has been granted by an IRB/EC). All legal guardians should be fully informed, and participants should be informed to the fullest extent possible, about the study in language and terms they are able to understand. The investigator will retain the original copy of each participant's signed consent/assent document.

5.2. Exclusion Criteria

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

Unless otherwise indicated, criteria apply to both Phase 1a (dose escalation) and Phase 1b (dose expansion).

1. Brain metastasis/primary brain tumor requiring immediate local intervention (surgery, radiosurgery) in the opinion of the investigator.

2. During dose escalation (initially) and during dose expansion Cohorts 1-4, 6 and 7: history of or current leptomeningeal metastases. Such participants may be eligible during dose escalation once the concentration of PF-07284890 at steady state is ≥0.168 µg/mL (equal to the IC_{70} for inhibition of BRAF V600E, a level at which

anti-tumor activity in the brain and systemically may be expected) in at least two-thirds of participants at the same dose level.

3. Participants with any other active malignancy within 2 years prior to enrollment, except for adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix, Bowen's disease, prostate intraepithelial neoplasm and ≤6 prostate cancer. Participants with a history of other curatively treated cancers must be reviewed by the sponsor prior to entering the study.

4. Major surgery (eg, inpatient procedure with general anesthesia) within 28 days prior to study entry, within 14 days for craniotomy. If craniotomy performed, neurological sequelae must have fully resolved. For minor surgical procedures within 28 days prior to start of study treatment, consult the sponsor.

5. Radiation therapy to visceral metastases (including SRS to the brain) within 14 days prior to the start of study treatment or WBRT within 28 days prior to the start of study treatment. If SRS or WBRT performed, neurological sequelae must have fully resolved and steroid dosing must meet Inclusion/Exclusion Criteria.

6. Systemic anti-cancer therapy or small-molecular therapeutic(s) (approved or investigational) within 1 week (2 weeks for cytotoxic chemotherapy, 6 weeks for mitomycin C or nitrosoureas) or 5 half-lives (whichever is shorter) of the agent(s) prior to the start of study treatment; antibody based agent(s) (approved or investigational), within 4 weeks of the start of study treatment or 5 half-lives (whichever is shorter) of the agent(s) prior to the start of study treatment. Antihormonal therapy(ies) for concurrent breast or prostate cancer, if consistent with inclusion/exclusion criteria, concomitant therapy and supportive care guidelines, (see Sections 6.5.2 and 6.5.3) may be allowed if approved by the sponsor.

7. Participants with active, uncontrolled bacterial, fungal, or viral infection, including HBV, HCV, known HIV or AIDS related illness. In equivocal cases, participants whose viral load is negative, may be eligible. HIV seropositive participants who are healthy and low risk for AIDS related outcomes could be considered eligible. Eligibility criteria for HIV positive participants should be evaluated and discussed with sponsor's medical monitor and will be based on current and past CD4 and T cell counts, history (if any) of AIDS defining conditions (eg, opportunistic infections), and status of HIV treatment. The potential for drug-drug interactions will also be taken into consideration.

   Note regarding COVID-19/SARS-CoV2: this protocol excludes participants with active infections, as noted above. While SARS-CoV2 testing is not mandated for entry into this protocol, testing should follow local clinical practice standards. If a participant has a positive test result for SARS-CoV2 infection, is known to have asymptomatic infection or is suspected of having SARS-CoV2, he/she is excluded but may be rescreened according to protocol requirements for rescreening if the participant subsequently tests negative.

8. Impaired cardiovascular function or clinically significant cardiovascular disease including, but not limited to, the following:

   - Baseline triplicate 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results. Examples include: screening or baseline (ie, C1D1 pre-dose) QTcF interval >470 msec, baseline QRS >120 msec, complete LBBB, signs of an acute or indeterminate age myocardial infarction, ST-T interval changes suggestive of active myocardial ischemia, second- or third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias. The QT interval should be rate corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting. If QTcF exceeds 470 msec or QRS exceeds 120 msec, the ECG should be repeated 2 more times and the average of the 3 QTcF or QRS values should be used to determine the participant's eligibility (in addition, the QTcF should be <470 msec on at least 2 individual ECGs). If more than 3 ECGs are performed, this should be reviewed with the sponsor's medical monitor to confirm eligibility. Computer interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding participants. Such cases must be discussed in detail with sponsor's medical monitor to judge eligibility. If a participant has a cardiac rhythm device/pacemaker placed and QTcF >470 msec or cannot be accurately determined, the participant must be discussed in detail with sponsor's medical monitor to judge eligibility.

   - Any of the following in the previous 6 months: myocardial infarction, unstable angina, coronary/peripheral artery bypass graft or coronary angioplasty/stenting.

   - Ongoing cardiac dysrhythmias of NCI CTCAE ≥ Grade 2 (participants with atrial fibrillation controlled for >30 days prior to the start of study treatment are eligible provided medications for rate control are not subject to potential DDI with study medications).

   - Blood pressure that cannot be controlled by medications (eg, >140/90 mmHg) despite optimal medical therapy.

   - Congestive heart failure requiring treatment (New York Heart Association Grade ≥2) and/or LVEF <50% as determined by ECHO.

9. Known or suspected hypersensitivity to active ingredient/excipients.

10. Active inflammatory gastrointestinal disease, chronic diarrhea, known diverticular disease, previous gastric resection or lap band surgery or inability to swallow and retain study treatment. Gastroesophageal reflux disease under treatment with H2 blockers or antacids is allowed provided dosing instructions in the protocol are followed. Use of PPIs are not allowed within 7 days of study start (C1D1) and during study treatment.

11. Known history of acute or chronic pancreatitis.

12. Concurrent neuromuscular disorder that is associated with elevated CK (eg, inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy).

13. History or current evidence of RVO or current risk factors for RVO (eg, uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes); history of retinal degenerative disease.

14. History of a thromboembolic event <12 weeks prior to starting study treatment. Examples of thromboembolic events include transient ischemia attack, cerebrovascular accident, deep vein thrombosis or pulmonary embolism.

    Note: Participants with a deep vein thrombosis or pulmonary emboli that do not result in hemodynamic instability are exceptions and may participate as long as they are stable, asymptomatic, and on a stable dose of anticoagulants for at least 4 weeks prior to starting study treatment (C1D1).

    Note: Catheter-related venous thrombosis is not considered a thromboembolic event for this trial even if <12 weeks prior to starting study treatment.

15. Current use or anticipated need for drugs that are known CCI [redacted], including the administration within 10 days or 5 half-lives, whichever is longer, or CCI [redacted], including the administration within 5 half-lives plus 10 days, prior to first dose of PF-07284890. Refer to Section 6.5 for further details.

16. Serum or urine pregnancy test (for females of childbearing potential) positive at Screening.

17. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

18. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

19. Participants in dose escalation: history of pneumonitis that required steroids or active pneumonitis.

5.3. Lifestyle Considerations

5.3.1. Photosensitivity

Given the potential for phototoxicity from nonclinical toxicology studies with PF-07284890, participants will be advised to report any reaction to sun exposed skin. In addition, special precautions will be taken to limit any potential photoirritation effect, by minimizing the participants' exposure to light including sunlight, and high intensity UVB light sources such

as tanning beds, tanning booths and sunlamps. Participants should be encouraged to apply sunscreen/sunblock daily and to wear clothing that covers areas of exposed skin when outdoors during daylight hours.

5.3.2. Activity

Strenuous physical activities, such as competitive sports, may result in significant increases in CK levels while on binimetinib treatment. Participants should be cautioned to avoid new strenuous exercise after first dose of study treatment.

5.3.3. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4 and Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Tests with results that fail eligibility requirements may be repeated during Screening if the investigator believes the result to be in error. Additionally, a participant who fails Screening may repeat the Screening process 1 time if the investigator believes that there has been a change in eligibility status.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

For the purposes of this protocol, study interventions refer to PF-07284890 and binimetinib (and midazolam, for participants enrolled into Phase 1b DDI substudy, Cohort 6).

6.1. Study Intervention(s) Administered

Intervention Name	PF-07284890	Binimetinib	Midazolam
ARM Name (group of participants receiving a specific treatment	Phase 1a dose escalation (monotherapy and combination) Phase 1b dose expansion (combination)	Phase 1a dose escalation (combination) Phase 1b dose expansion (combination)	Phase 1b DDI substudy
Type	Drug	Drug	Drug
Dose Formulation	Tablet	Tablet	Syrup
Unit Dose Strength(s)	10 mg, 25 mg, 100 mg	15 mg	2 mg/mL
Dosage Level(s)	Starting dose 50 mg QD; see Schema	45 mg BID	2 mg, 3 single doses
Route of Administration	Oral	Oral	Oral
Use	Experimental	Experimental	Probe
IMP or NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor. *Please see IP Manual.*	Provided centrally by the sponsor. *Please see IP Manual.*	Provided centrally by the sponsor.
Packaging and Labeling	Study intervention will be provided in high-density polyethylene bottles. Each bottle will be labeled as required per country requirement. *Please see IP Manual.*	Study intervention will be provided in high-density polyethylene bottles. Each bottle will be labeled as required per country requirement. *Please see IP Manual.*	Commercial drug will be provided. Each bottle will be labeled as required per country requirement. *Please see IP Manual.*
Current/Former Name(s) or Alias(es)	PF-07284890 ARRY-461 AR00504461	Binimetinib PF-06811462 ARRY-438162 MEK162 ONO-7703 MEKTOVI	Midazolam

PF-07284890 will be provided as tablets for oral administration. The 10 mg, 25 mg and 100 mg tablets will be supplied in separate bottles and labeled according to local regulatory requirements.

Binimetinib will be provided as tablets for oral administration. The 15 mg tablets will be supplied in bottles and labeled according to local regulatory requirements.

Midazolam will be provided as syrup for oral administration.

6.1.1. Administration

Participants will swallow the study intervention whole, and will not manipulate or chew the study intervention prior to swallowing.

PF-07284890 will be administered QD (initially; the dosing frequency may be changed, eg, BID) on a continuous basis.

In participants administered the combination, binimetinib will be administered BID on a continuous basis.

A cycle is defined as 21 days, regardless of missed doses or dose delays.

PF-07284890 will be administered orally on an empty stomach without adjustment for body size at every cycle.

When binimetinib is administered together with PF-07284890, it will be administered orally on an empty stomach without adjustment for body size at every cycle.

When a dose of binimetinib is administered without a dose of PF-07284890 (eg, the second dose of binimetinib, when PF-07284890 dosing is QD and binimetinib dosing is BID), it may be administered orally without regard to food and without adjustment for body size at every cycle.

See Section 6.1.1.1 for additional details on food requirements and timing of dosing.

Participants should be instructed to take their medication at the same time each day and to not take more than the prescribed dose at any time.

If a participant misses a dose of treatment, he/she must be instructed not to "make it up" but to resume with the subsequent dose as prescribed. A missed dose of treatment is defined as more than 2 hours past the planned/scheduled dosing time for BID dosing, or more than 4 hours past the planned/scheduled dosing time for QD dosing.

If less than or equal to 2 hours (for BID dosing) or less than or equal to 4 hours (for QD dosing) has passed, then the participant should be instructed to take the dose, and continue the normal dosing schedule.

If more than 2 hours (for BID dosing) or more than 4 hours (for QD dosing) has passed, then the participant should be instructed to skip the missed dose, and resume the normal dosing scheduled/time for the next dose.

If a participant vomits any time after taking a dose, he/she must be instructed not to "make it up" but to resume with the subsequent dose as prescribed.

If a participant inadvertently takes 1 extra dose during a day, the participant should not take the next planned dose.

6.1.1.1. Food Requirements for All Cohorts and Substudies Excluding the Food-effect Cohort/Substudy

PF-07284890 will be administered with at least 8-oz (240 mL) of water on an empty stomach at the same time each day. No food or liquids other than water will be consumed for 2 hours before and 1 hour following each dose throughout the study.

- PF-07284890 administered QD (monotherapy or combination): PF-07284890 will be administered QD in the morning.

- PF-07284890 administered BID (monotherapy or combination): PF-07284890 will be administered BID, 12 ± 2 hours apart, in the morning and in the evening.

Binimetinib will be taken with at least 8-oz (240 mL) of water in the morning and in the evening at approximately the same time every day.

- Binimetinib in combination with QD PF-07284890: The morning dose of binimetinib should be taken with PF-07284890 following the PF-07284890 food instructions. When taken without PF-07284890 in the evening, binimetinib may be taken without regard to food. The morning and evening doses of binimetinib should be taken 12 ± 2 hours apart.

- Binimetinib in combination with BID PF-07284890: The morning and evening dose of binimetinib should be taken with the morning and evening dose of PF-07284890 and should be taken 12 ±2 hours apart following the PF-07284890 food instructions.

Note: On PK sampling days, participants must be in fasted state, ie, no food within 2 hours before or 2 hours after dosing (this requirement may result in no food until more than 2 hours after dosing because they cannot eat until after their 2-hour postdose ECGs and PK sample). The sites should record in the source documents if participants did or did not eat within this time frame.

These fasting requirements for PF-07284890 may be removed or modified (via a PACL to the investigators) if the data from a separate food-effect study indicate that there is no effect of food or a positive effect of food on PF-07284890 PK.

The effect of food (low fat and high fat meal versus fasted state) on PF-07284890 PK is being assessed in C4471002 in a study of healthy participants. Once the results of this food-effect study are available, the instructions for administration of PF-07284890 in C4471001 may be changed as appropriate so that patients can take PF-07284890 without regard to food at the MTD/RDE, or should take PF-07284890 in the fed state, with adjustment of dose based on C4471002 data (ie, the dose equivalent to the fasted state MTD/RDE adjusted based on the difference in exposure observed in C4471002 in the fasted state compared to the fed state). However, if the effect of food is found to be substantial, positive and clinically significant (ie, ≥2-fold increase in AUC for either the low-fat or high-fat meal), an additional cohort of patients will be enrolled before changing administration instructions in the current study. This cohort of approximately 6-8 patients will be enrolled to assess the safety and PK of a recommended dose for further study (ie, the dose equivalent to the fasted state MTD/RDE adjusted based on observed C4471002 PK) to be given with food. If the recommended dose in combination with food is tolerated, patients accrued into cohorts 1-6 will receive instruction to administer drug with food.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.

3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.

4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

5. Study interventions should be stored in their original containers.

6. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record. All PF-07284890 (and binimetinib if combination treatment) that is taken home by the participant, both used and unused, must be returned to the investigator by the participant. Returned study intervention must not be redispensed to the participants.

8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with

applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP Manual.

6.2.1. Preparation and Dispensing

A qualified staff member will dispense PF-07284890 (and binimetinib if combination treatment) in the bottles provided, in quantities appropriate for the participants' dosing cohort. The IRT Manual should be referenced for technical instructions. A second staff member will verify the dispensing. *The participant/caregiver should be instructed to maintain the product in the bottle provided throughout the course of dosing, keep the study intervention away from children, and* return *the bottle to the site at the next study visit.*

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Eligible participants will be enrolled to receive PF-07284890 alone or in combination with binimetinib in an open-label, unblinded manner. Dose level allocation will be performed by the sponsor after participants have given their written informed consent/assent and have completed the necessary baseline assessments. The site staff will complete a Registration Form and return it to the designated sponsor study team member or designee. The sponsor will assign a participant identification number and supply this number to the site. The participant identification number will be used on all study-related documentation at the site.

No participant will receive study intervention until the investigator or designee has received the following information in writing from the sponsor:

- Confirmation of the participant's eligibility;
- Specification of the dose level for that participant and;
- Permission to proceed with dosing the participant.

Study intervention will be dispensed at the study visits summarized in the SoA.

Returned study intervention must not be redispensed to the participant.

Allocation of participants to treatment groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to have an active or valid account and password with the IRT system, enter or select information including but not limited to the users ID and password, protocol number, specific protocol entrance criteria indicated in the system and the participant number. The site personnel will then be provided with, at a minimum, a treatment assignment, randomization number, and DU or container number when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Participant fasting compliance will be confirmed and documented at each visit.

When participants self-administer study intervention at home, compliance with study intervention will be discussed at each visit to the study site. During both phases of the study, compliance will be assessed at the end of the cycle by direct questioning, diary review and counting of returned tablets. During the phase 1a, compliance will be assessed at each visit in Cycle 1 by direct questioning and diary review. Compliance will be documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

A record of the number of PF-07284890 tablets (and binimetinib, if combination treatment) dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. It is important for participants to be fully informed and provided with detailed instructions to avoid overdosing (see Section 8.4). Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the CRF.

A diary will be provided to the participants to aid in compliance with the dosing instructions. The diary will be maintained by the participant to include missed or changed PF-07284890 (and binimetinib if combination treatment) doses. Participants will be required to return all bottles of PF-07284890 (and binimetinib) at every cycle. The number of PF-07284890 (and binimetinib) tablets remaining will be documented and recorded at each cycle. The participant diary may also be used to support this part of the PF-07284890 (and binimetinib) accountability process.

6.5. Concomitant Therapy

Concomitant treatment considered necessary for the participant's well-being may be given at discretion of the treating physician.

All concomitant treatments, blood products, as well as nondrug interventions (eg, paracentesis) received by participants from screening until the end of treatment visit will be recorded on the CRF.

Sites are encouraged to contact the sponsor should there be questions as to whether a medication is permitted or prohibited.

CYP3A4/5:
Concomitant use of PF-07284890 and a CYP3A4/5 substrate may increase or decrease the exposure of the CYP3A4/5 substrate. Coadministration of PF-07284890 with CYP3A4/5 substrates with narrow therapeutic indices, such as astemizole, terfenadine, cisapride, pimozide, quinidine, tacrolimus, cyclosporine, sirolimus, alfentanil and fentanyl (excluding transdermal patch), or ergot alkaloids (ergotamine, dihydroergotamine)[37,38] is not permitted. Coadministration with other CYP3A4/5 substrates is permitted but caution is warranted. Due to potential CYP3A4 induction, the use of at least 1 form of non-hormonal contraception will be needed during participation in this study.

CYP2B6:
Concomitant use of PF-07284890 and a CYP2B6 substrate may decrease the exposure of the CYP2B6 substrate. PF-07284890 coadministration with CYP2B6 substrates (eg, a sensitive substrate like bupropion and narrow therapeutic index substrates like efavirenz, also a sensitive substrate, and cyclophosphamide)[37,39] is permitted but caution is warranted.

CYP2C9:
Concomitant use of PF-07284890 and a CYP2C9 substrate may increase the exposure of the CYP2C9 substrate. CYP2C9 substrates of a narrow therapeutic index, may include warfarin, phenytoin, glimepiride, glipizide, glyburide, ibuprofen, diclofenac, indomethacin, naproxen, rosiglitazone, sulfamethoxazole, tolbutamide, candesartan, irbesartan, losartan and valsartan.[37,40] PF-07284890 coadministration with these and other CYP2C9 substrates is permitted but caution is warranted.

BCRP:
Concomitant use of PF-07284890 and a BCRP inhibitor or inducer may alter the rate and/or extent of PF-07284890 absorption, which could potentially increase (inhibitor) or decrease (inducer) PF-07284890 exposures. PF-07284890 coadministration with BCRP inhibitors or inducers is permitted but caution is warranted.

P-glycoprotein:
Concomitant use of PF-07284890 and a P-glycoprotein substrate may increase the exposure of the P-glycoprotein substrate. PF-07284890 coadministration with P-glycoprotein substrates is permitted but caution is warranted.

Acid Reducing Agents:
Concomitant use of PF-07284890 and an acid reducing agent (eg, PPIs) may cause reduced exposures to PF-07284890. PPIs are not allowed within 7 days of study start (C1D1) and during study treatment, but other acid reducing agents (eg, H2 blockers, antacids) may be used, but only between 2 and 3 hours after administration of each dose of PF-07284890.

6.5.1.2. Binimetinib

UGT1A1:
In vitro, binimetinib has been identified to be primarily metabolized by glucuronidation. It is advised that inhibitors and inducers of UGT1A1 should be taken with caution when co-administered with binimetinib.

P-glycoprotein:
Binimetinib has been shown to be a substrate of P-gp and BCRP. It is advised that inhibitors and inducers of P-gp and BCRP transporters should be taken with caution when co-administered with binimetinib.

6.5.2. Other Anti-tumor/Anti-cancer or Experimental Drugs

No additional anti-tumor treatment will be permitted while participants are receiving study treatment. Additionally, the initiation of new concurrent vitamins or herbal supplements is not permitted unless discussed and agreed with the sponsor.

Potential exception: participants currently being treated with anti-hormonal therapy for concurrent breast or prostate cancer may continue treatment while on clinical study as long as the treatment has been well tolerated for at least 3 months prior to study entry and treatment, is not subject to drug-drug interactions and continued treatment is discussed with the

sponsor's medical monitor. Tamoxifen and exemestane should be used with caution due to the concern of PF-07284890 causing CYP3A induction. For drugs such as anastrazole, letrozole, fulvestrant, leuprolide, and goselerin, no interaction is expected.

6.5.3. Supportive Care

Palliative and supportive care for disease related symptoms may be administered at the investigator's discretion and according to the specific supportive care product Prescribing Information or the current ASCO guidelines.

6.5.4. Anti-epileptic Medications

Certain anti-epileptic medications may be administered if clinically indicated, consistent with Inclusion/Exclusion Criteria (see Section 5) and not subject to drug-drug interactions with study medication(s). Guidance for anti-epileptic medications that can be used on study are provided in Appendix 10.

6.5.5. Hematopoietic Growth Factors

Primary prophylactic use of colony stimulating factors is not permitted during Cycle 1 (the first 21 days) for participants in Phase 1a, but they may be used to treat treatment emergent neutropenia as indicated by the current ASCO guidelines.[37] During the screening window (ie, 14 days prior to Day 1), granulocyte colony stimulating factors are not permitted to qualify a participant with low WBC counts.

Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia.

6.5.6. Anti-Diarrheal, Anti-Emetic Therapy

Primary prophylaxis beyond the first cycle is at the investigator's discretion. The choice of the prophylactic drug as well as the duration of treatment is up to the investigator with sponsor approval assuming there is no known or expected drug-drug interaction and assuming the drug is not included in the Concomitant Therapy section.

6.5.7. Anti-Inflammatory Therapy

Anti-inflammatory or narcotic analgesic may be offered as needed assuming there is no known or expected drug-drug interaction and assuming the drug is not included in the Concomitant Therapy section.

6.5.8. Corticosteroids

Systemic corticosteroid use to control/treat symptoms from brain metastases/primary brain tumor is allowed, up to 8 mg/day dexamethasone or equivalent, provided use is consistent with Inclusion/Exclusion Criteria (see Section 5) and not subject to drug-drug interactions with study medications. The minimum dose required to control symptoms should be used if feasible. For other palliative or supportive purposes, chronic systemic corticosteroid use (eg, prednisone >10 mg/day or equivalents) is not permitted. Steroid use for short duration

(eg, 5 mg QD of prednisone, for 2 weeks) as symptomatic treatment on individual basis and upon discussion with the sponsor is allowed. Acute emergency administration, topical applications, inhaled sprays, eye drops, or local injections of corticosteroids are allowed.

6.5.9. Surgery

While participants are on study treatment, palliative surgery is permitted for non-target lesions that are either new or present at baseline. Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and PF-07284890 (and binimetinib) required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping PF-07284890 (and binimetinib) is recommended at least 2 days prior to surgery. Postoperatively, the decision to reinitiate PF-07284890 (and binimetinib) treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery. For participants obtaining a tumor biopsy, PF-07284890 administration may be held or continued, at the discretion of the investigator, prior the procedure. These participants should still stop dosing binimetinib at least 2 days prior to the procedure, if applicable. These time intervals may be altered based on emerging PK data.

6.5.10. Radiation Therapy

While participants are on study treatment, palliative radiation therapy is permitted for non-target lesions that are either new or present at baseline. Caution is advised on theoretical grounds for any radiation during the study. The appropriate interval of time between radiation and PF-07284890 (and binimetinib) required to minimize the risk of impaired wound healing and radiation skin injury has not been determined. Stopping PF-07284890 (and binimetinib) is recommended at least 2 days prior to radiation. Postoperatively, the decision to reinitiate PF-07284890 (and binimetinib) treatment should be based on a clinical assessment of satisfactory wound healing and recovery from radiation. These time intervals may be altered based on emerging PK data.

6.6. Dose Modification

Every effort should be made to administer study intervention on the planned dose and schedule. In the event of significant toxicity, dosing may be delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed (and attribution for the combination treatment – use if a combination is to be tested). Participants are to be instructed to notify investigators at the first occurrence of any adverse symptom.

Dose modifications may occur in 1 of 3 ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;

- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

Individual guidance for dose modifications and interruptions are outlined in Table 5 (PF-07284890) and Table 6 (binimetinib). These tables incorporate guidance from the FDA labels for the BRAF inhibitor encorafenib (for PF-07284890) and binimetinib, and include guidance based on nonclinical toxicology findings for PF-07284890. Individual decisions regarding dose interruptions and modifications should be made using appropriate clinical judgment in consultation with the sponsor medical monitor, considering relatedness of the AE to the study treatment and the participant's underlying condition. AEs that have a clear alternative explanation, or transient (≤72hours) abnormal laboratory values without associated clinically significant signs or symptoms may be exempt from dose-reduction rules as clinically appropriate. Dose interruptions are permitted in the case of medical or surgical events or logistical reasons not related to study treatment (eg, elective surgery, unrelated medical events, participant vacation, holidays). The reason for interruption will be documented in the participant's study record. All dose modifications are based on the worst preceding toxicity.

During Cycle 1 of Phase 1a dose escalation, dose modifications (eg, interruptions/decreases) that result in treatment with <75% of the prescribed dose(s) may be considered DLTs, provided that the AE that led to the dose modification in the opinion of the investigator cannot be reasonably attributed to the participant's underlying disease, concomitant medications or preexisting conditions.

6.6.1. Dosing Interruptions

With respect to study intervention, participants experiencing the following AEs should have their treatment interrupted: participants experiencing Grade 3 or 4 potentially treatment related toxicity or intolerable Grade 2 toxicity despite supportive care. Criteria for treatment resumption and the need for a dose reduction are described in Section 6.6.3 and Section 6.6.4. Doses may be held up to 4 weeks until toxicity resolution. In the event of a treatment interruption for reasons other than treatment-related toxicity lasting >4 weeks, treatment resumption will be decided in consultation with the sponsor.

6.6.2. Rescue Medicine

There is no rescue therapy to reverse the AEs observed with PF-07284890 (and binimetinib); standard medical supportive care must be provided to manage the AEs.

6.6.3. Dose Delays

Re-treatment following treatment interruption for treatment-related toxicity or at the start of any new cycle may not occur until the parameters outlined for each study intervention in Table 5 and Table 6 have been met.

If participants require discontinuation of treatment(s) for more than 4 weeks at any time during the study, then study treatment should be permanently discontinued, unless the investigator's benefit/risk assessment suggests otherwise after discussion with the sponsor's medical monitor.

The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in the Dose Reductions section (Section 6.5.1), unless expressly agreed otherwise following discussion between the investigator and the sponsor.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, elective surgery) lasting more than 4 weeks, treatment resumption will be decided in consultation with the sponsor.

If a participant receiving combination treatment permanently discontinues binimetinib (ie, no dose for more than 4 weeks), the participant may continue single-agent PF-07284890 if, in the opinion of the investigator, the participant is deriving clinical benefit.

If a participant receiving combination treatment permanently discontinues PF-07284890, he or she must ALSO discontinue treatment with binimetinib.

6.6.4. Dose Reductions

Dose reduction of study treatment(s) by 1 and, if needed, 2 dose levels will be allowed depending on the type and severity of toxicity encountered. Participants requiring more than 2 dose reductions will be discontinued from the treatment and enter the follow-up phase, unless otherwise agreed between the investigator and the sponsor. Once a dose has been reduced and the participant has tolerated treatment at the reduced dose for a minimum of 1 full cycle, intraparticipant dose re-escalation by 1 dose level at a time may be allowed after discussion between the investigator and the sponsor.

Table 3. Available Dose Levels (PF-07284890 Monotherapy)

Dose Level	PF-07284890 (at starting doses not noted to the right)		Monotherapy Starting Doses				
Current	Current dose level	Starting Dose	300 mg BID	200 mg BID	200 mg QD	100 mg QD	50 mg QD
-1	1 dose level lower (BID)	-1	200 mg BID	100 mg BID	50 mg BID	25 mg BID	10 mg BID
-2	2 dose levels lower[a] (BID)	-2	100 mg BID	50 mg BID	25 mg BID	10 mg BID	Discontinue

a. PF-07284890 tablet dose sizes are 10, 25 and 100 mg; dose decrease below 10 mg QD is not allowed.

Table 4. Available Dose Levels (PF-07284890 Plus Binimetinib Combination Therapy)

Dose Level	PF-07284890 (at starting doses not noted to the right)	-	Combination Therapy PF-07284890 Starting Doses				Binimetinib
Starting	Current dose level	Starting Dose	225 mg BID	150 mg BID	100 mg BID	100 mg QD	45 mg BID
-1	1 dose level lower	-1	150 mg BID	100 mg BID	50 mg BID	25 mg BID	30 mg BID
-2	2 dose levels lower[a]	-2	100 mg BID	50 mg BID	25 mg BID	10 mg BID	15 mg BID[b]

a. PF-07284890 tablet dose sizes are 10, 25 and 100 mg; dose decrease below 10 mg BID is not allowed.

b. Binimetinib tablet dose size is 15 mg; dose decrease below 15 mg BID is not allowed.

Participants experiencing a DLT may resume dosing at the next lower dose level once adequate recovery is achieved, and in the opinion of the investigator and the sponsor, the participant is benefitting from therapy.

For combination treatment with binimetinib, dose modifications, delays or interruptions should be assigned to each product based on attribution to each component (ie, when PF-07284890 and binimetinib are combined and toxicity occurs and is attributed to PF-07284890, a dose lowering, delay, or interruption of PF-07284890 may be applicable but not necessarily to binimetinib).

Recommended dose reductions for study intervention are described in Table 5 (PF-07284890) and Table 6 (binimetinib).

Table 5. Recommended Dose Modifications for PF-07284890-related[a] Adverse Events

Severity of Adverse Event	Dose Modifications
New Primary Malignancies	
Non-cutaneous *RAS* mutation-positive malignancies	Permanently discontinue PF-07284890 (and binimetinib).
Uveitis	
Grade 1-3	If Grade 1 or 2 does not respond to specific ocular therapy, or for Grade 3 uveitis, withhold PF-07284890 (and binimetinib) for up to 4 weeks. • If improved, resume at same or reduced dose. • If not improved, permanently discontinue PF-07284890 (and binimetinib).
Grade 4	Permanently discontinue PF-07284890 (and binimetinib).
Other Eye Disorders (ie, non-Uveitis Events)	
Grade 1–2	Maintain dose level of PF-07284890 (and binimetinib) and increase frequency of ophthalmic monitoring to at least every 14 days until stabilization or resolution.
Grade 3	Interrupt dosing of PF-07284890 (and binimetinib) and refer participants to ophthalmologist within 7 days. • If resolved to Grade ≤1 in ≤21 days, resume treatment at 1 reduced dose level of PF-07284890 (and binimetinib). • If not resolved to Grade ≤1 in ≤21 days, permanently discontinue PF-07284890 (and binimetinib) and close follow-up with ophthalmic monitoring until stabilization or resolution.
Grade 4	Permanently discontinue PF-07284890 (and binimetinib) and immediate follow-up with ophthalmic monitoring until stabilization or resolution.
QTc Prolongation	
QTcF >500 msec and ≤60 msec increase from baseline	First occurrence: • Temporarily interrupt dosing of PF-07284890 treatment until QTcF ≤470 msec. Then resume treatment at 1 reduced dose level of PF-07284890. Second occurrence: • Temporarily interrupt dosing of PF-07284890 treatment until QTcF ≤470 msec. Then resume treatment at 1 reduced dose level of PF-07284890. Third occurrence: • Permanently discontinue PF-07284890 (and binimetinib).
QTcF >500 msec and >60 msec increase from baseline	Permanently discontinue PF-07284890 (and binimetinib).
Hepatotoxicity	
Grade 2 AST or ALT increased	Maintain PF-07284890 (and binimetinib) dose. • If no improvement within 4 weeks, withhold PF-07284890 (and binimetinib) until improved to Grade 0-1 or to pretreatment/baseline levels and then resume at the same dose.
Grade 3 or 4 AST or ALT increased	See Other Adverse Reactions.

Dermatologic (Except Hand-foot Skin Reactions)	
Grade 2	If no improvement within 2 weeks (supportive measures, such as topical therapy, for symptomatic relief, are permitted), withhold PF-07284890 until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent (supportive measures may be continued).
Grade 3	Withhold PF-07284890 until Grade 0-1 (supportive measures, such as topical therapy, for symptomatic relief, are permitted). Resume at same dose if first occurrence or reduce dose if recurrent (supportive measures may be continued).
Grade 4	Permanently discontinue PF-07284890 (and binimetinib).
Hand-foot Skin Reaction (HFSR)/Palmar-plantar Erythrodysesthesia Syndrome (Dose Adjustment for PF-07284890 ONLY)	
Grade 1	Maintain dose of PF-07284890. Promptly institute supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications.
Grade 2	First occurrence: • Maintain dose of PF-07284890 and HFSR should be closely monitored. Promptly institute supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. • If no improvement ≤14 days, interrupt dosing of PF-07284890 until resolved to Grade ≤1. Resume treatment with PF-07284890 at current dose level. Continue supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. Additional occurrence: • Treatment with PF-07284890 may be maintained or interrupted based upon the investigator's discretion. Continue supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. If interrupted dosing of PF-07284890 per investigator's judgment, interrupt until resolved to Grade ≤1. Resume treatment with PF-07284890 at the same dose level or 1 reduced dose level based upon the investigator's discretion.
Grade 3	First or second occurrence: • Interrupt dosing of PF-07284890 until resolved to Grade ≤1. Promptly initiate supportive measures, such as topical therapy, for symptomatic relief. Give instruction on life-style modifications. Reassess the participant weekly. Then resume treatment at 1 reduced dose level of PF-07284890. • Consider referral to dermatologist and manage HFSR per dermatologist's recommendation. Third occurrence: • Interrupt dosing of PF-07284890 until resolved to Grade ≤1, decision to resume treatment with PF-07284890 at 1 reduced dose level or permanently discontinue PF-07284890 (and binimetinib) should be based upon the investigator's discretion.

Nausea/Vomiting	
Grade 1-2	Maintain dose level of PF-07284890 (and binimetinib). Promptly institute antiemetic measure.
Grade 3	Interrupt dosing of PF-07284890 (and binimetinib) until resolved to Grade ≤1. Then resume treatment at 1 reduced dose level of PF-07284890. Resume treatment with binimetinib at the current dose if, in the judgment of the investigator, the toxicity is considered to be unrelated to binimetinib, or at 1 reduced dose level. Note: Interrupt dosing of PF-07284890 (and binimetinib) for Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetics (as per local practice).
Grade 4	Permanently discontinue PF-07284890 (and binimetinib).
CNS effects (eg, changes in speech, memory, sleep, cognition or vision)	
Grade 1	Maintain dose level of PF-07284890 or withhold dose until recovery to baseline and then continue at the same dose.
Grade 2	Maintain dose level of PF-07284890 or withhold dose until recovery to Grade ≤1. Consider dose reduction or resume at same dose.
Grade 3	Interrupt dosing of PF-07284890 until resolved to Grade ≤1. Then resume treatment at 1 reduced dose level of PF-07284890.
Grade 4	Permanently discontinue PF-07284890 (and binimetinib).
Other Adverse Reactions (including hemorrhage)	
Recurrent Grade 2 or First occurrence of any Grade 3	Withhold PF-07284890 for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, resume at reduced dose of PF-07284890. • If no improvement, permanently discontinue PF07284890 (and binimetinib).
First occurrence of any Grade 4	Permanently discontinue PF-07284890 or withhold for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, then resume at a reduced dose of PF-07284890. • If no improvement, permanently discontinue PF07284890 (and binimetinib).
Recurrent Grade 3	Consider permanently discontinuing PF-07284890 (and binimetinib).
Recurrent Grade 4	Permanently discontinue PF-07284890 (and binimetinib).

a. For AEs that may be related to both PF-07284890 and binimetinib, guidance is provided for the other agent also, for participants receiving the combination. If PF-07284890 is permanently discontinued, binimetinib must be discontinued as well.

Table 6. Recommended Dose Modifications for Binimetinib-related[a] Adverse Events

Severity of Adverse Event	Dose Modifications
Cardiomyopathy	
Asymptomatic, absolute decrease in LVEF of >10% from baseline that is also below the LLN	Withhold binimetinib for up to 4 weeks, evaluate LVEF every 2 weeks. Resume binimetinib at a reduced dose if the following are present: • LVEF is at or above the LLN; and • Absolute decrease from baseline is 10% or less; and • The participant is asymptomatic. If LVEF does not recover within 4 weeks permanently discontinue binimetinib.
Grade 3-4 (Symptomatic congestive heart failure or absolute decrease in LVEF of >20% from baseline that is also below LLN)	Permanently discontinue binimetinib. Closely monitor LVEF until resolution or up to 16 weeks.
Venous Thromboembolism	
Uncomplicated DVT or PE	Withhold binimetinib. • If improves to Grade 0-1, resume at a reduced dose. • If no improvement, permanently discontinue binimetinib.
Life threatening PE	Permanently discontinue binimetinib.
Serous Retinopathy	
Symptomatic serous retinopathy/Retinal pigment epithelial detachments	Withhold binimetinib for up to 10 days. • If improves and becomes asymptomatic, resume at the same dose. • If not improved, resume at a lower dose level or permanently discontinue binimetinib.
RVO	
Any Grade	Permanently discontinue binimetinib.
Uveitis	
Grade 1-3	If Grade 1 or 2 does not respond to specific ocular therapy, or for Grade 3 uveitis, withhold binimetinib and PF-07284890 for up to 4 weeks. • If improved, resume at same or reduced dose. • If not improved, permanently discontinue binimetinib and PF-07284890.
Grade 4	Permanently discontinue binimetinib and PF-07284890.
Other Eye Disorders (ie, Non-retinal Events, non-Uveitis Events)	
Grade 1-2	Maintain dose level of binimetinib and PF-07284890 and increase frequency of ophthalmic monitoring to at least every 14 days until stabilization or resolution.
Grade 3	Interrupt dosing of binimetinib and PF-07284890 and refer participants to ophthalmologist within 7 days. • If resolved to Grade ≤1 in ≤21 days, resume treatment at 1 reduced dose level of binimetinib and PF-07284890. • If not resolved to Grade ≤1 in ≤21 days, permanently discontinue binimetinib and PF-07284890 and close follow-up with ophthalmic monitoring until stabilization or resolution.

Grade 4	Permanently discontinue binimetinib and PF-07284890 and immediate follow-up with ophthalmic monitoring until stabilization or resolution.
Interstitial Lung Disease	
Grade 2	Withhold binimetinib for up to 4 weeks. • If improved to Grade 0-1, resume at a reduced dose. • If not resolved within 4 weeks, permanently discontinue.
Grade 3 or Grade 4	Permanently discontinue binimetinib.
Hepatotoxicity	
Grade 2 AST or ALT increased	Maintain binimetinib and PF-07284890 dose. • If no improvement within 2 weeks, withhold binimetinib and PF-07284890 until improved to Grade 0-1 or to pretreatment/baseline levels and then resume at the same dose.
Grade 3 or 4 AST or ALT increased	See Other Adverse Reactions.
Rhabdomyolysis or CPK elevations	
Grade 4 asymptomatic CPK elevation or any Grade CPK elevation with symptoms or with renal impairment	Withhold binimetinib dose for up to 4 weeks. • If improved to Grade 0-1 resume at a reduced dose. • If not resolved within 4 weeks, permanently discontinue binimetinib.
Dermatologic	
Grade 2	If no improvement within 2 weeks, withhold binimetinib until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
Grade 3	Withhold binimetinib until Grade 0-1. Resume at same dose if first occurrence or reduce dose if recurrent.
Grade 4	Permanently discontinue binimetinib.
Nausea/Vomiting	
Grade 1-2	Maintain dose level of binimetinib and PF-07284890. Promptly institute antiemetic measure.
Grade 3	Interrupt dosing of binimetinib and PF-07284890 until resolved to Grade ≤1. Then resume treatment at 1 reduced dose level of PF-07284890. Resume treatment with binimetinib at the current dose if, in the judgment of the investigator, the toxicity is considered to be unrelated to binimetinib, or at 1 reduced dose level. Note: Interrupt dosing of binimetinib and PF-07284890 for ≥Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetics (as per local practice).
Grade 4	Permanently discontinue binimetinib.
Other Adverse Reactions (including hemorrhage)	
Recurrent Grade 2 or First occurrence of any Grade 3	Withhold binimetinib for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, resume at reduced dose. • If no improvement, permanently discontinue.
First occurrence of any Grade 4	Permanently discontinue binimetinib or withhold for up to 4 weeks. • If improves to Grade 0-1 or to pretreatment/baseline levels, then resume at a reduced dose. • If no improvement, permanently discontinue binimetinib.
Recurrent Grade 3	Consider permanently discontinuing binimetinib.
Recurrent Grade 4	Permanently discontinue binimetinib.

b. For AEs that may be related to both binimetinib and PF-07284890, guidance is provided for the other agent also. If binimetinib is permanently discontinued, PF-07284890 may be continued unless otherwise indicated in Table 5 above.

6.7. Intervention After the End of the Study

As this is a first-in-human clinical trial, no post-trial study intervention is currently planned to be provided to study participants at the end of the study. Depending on the overall development path, the sponsor will make an effort to provide post-trial study intervention to appropriate participants who are tolerating treatment and continuing to experience clinical benefit.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following:

- Objective disease progression (participants continuing to derive clinical benefit may be permitted to continue treatment, see Section 7.1.1 for requirements);
- Global deterioration of health status requiring discontinuation;
- Unacceptable toxicity;
- Pregnancy;
- Significant protocol violation;
- Lost to followup;
- Participant refused further treatment;
- Study terminated by sponsor;
- Death.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, disease assessments, subsequent anticancer therapies, and survival. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

After participants have discontinued treatment for any reason, they will be contacted approximately every 3 months until withdrawal of consent, the participant is lost to follow-up (Section 7.3), death or defined End of Study (Section 4.3.5). If participants withdraw consent for study intervention they will continue to be contacted for survival status unless they specifically request that they not be contacted. If the participant refuses to be contacted, attempts to determine survival status should be made via access to public records where permitted by local laws (Section 7.2.1).

Examples of AEs requiring dose modification/study intervention discontinuation are provided in Table 5 and Table 6.

7.1.1. Request to Continue Study Intervention

If the investigator feels the participant is still deriving benefit from study intervention, then discuss with the sponsor to elect treatment for the participant at the same dose or 1 dose lower until such benefit no longer exists. For a patient to continue treatment past disease progression all of the following criteria must be met:

- Absence of unacceptable toxicity;
- Absence of clinical symptoms or signs indicating clinically significant disease progression;
- No decline in performance status;
- Absence of rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention; and
- Patient provides informed consent to continue therapy.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include:

- Completed study followup;
- Study terminated by sponsor;
- Lost to followup;

- Refused further follow-up;
- Withdrawal of consent by parent/legal guardian or assent by an adolescent who has provided assent during any phase of the study.
- Death.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are enrolled and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

The participant will be permanently discontinued both from the study intervention and from the study at that time.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent/assent (see Section 7.2.1) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails 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 attend 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 or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether 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. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICD 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.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

8.1. Efficacy Assessments

8.1.1. Tumor Response Assessments

8.1.1.1. Non-glioma Primary Tumors

Tumor assessments will include all known or suspected disease sites. Imaging will include contrast-enhanced chest, abdomen and pelvis CT or MRI scans; brain MRI scan for participants with known or suspected brain metastases; bone scan and/or bone x-rays for participants with known or suspected bone metastases. For participants with known CT contrast allergy, a non contrast CT of the chest with contrast enhanced abdominal and pelvic MRI can be used. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

Anti-tumor activity will be assessed through radiological tumor assessments conducted at Screening, C3D1, then every other cycle/Q6W ±1 week through Cycle 17 (ie, for 1 year), and every 4 cycles/Q12W ±1 week after Cycle 17 until progressive disease, withdrawal of consent, initiation of subsequent anticancer therapy, participant is lost to follow-up, death, or defined end of study. Anti-tumor activity will also be assessed whenever disease progression is suspected (eg, symptomatic deterioration), and at the time of withdrawal from treatment (if not done in the previous 8 weeks). MRI of spinal cord will only occur at Screening for participants with known or suspected disease at baseline. For patients without brain involvement, assessment of overall response will be made using RECIST version 1.1 (see Appendix 11).[42] For patients with intracranial disease, assessment of overall, extracranial, and intracranial response will made using mRECIST version 1.1 (see Appendix 12).

All participants' files and radiologic images must be available for source verification and for potential peer review, including by independent central review.

If simultaneous CT-PET scans are used, it must be a spiral-CT scan of the same diagnostic quality as dedicated CT scans (ie, without PET). PET data will not be used for primary tumor response assessments.

8.1.1.2. Glioma

Imaging will conform with requirements for RANO and assessment of disease at baseline and on study will include review of brain MRI scans performed per institutional imaging protocol sequence. MRI of spinal cord will only occur at Screening for participants with known or suspected disease at baseline. The same imaging technique used to characterize each identified and reported lesion at baseline will be employed in the following tumor assessments.

Anti-tumor activity will be assessed through MRI assessments conducted at Screening, C3D1, then every other cycle/Q6W ±1 week through Cycle 17 (ie, for 1 year), and every 4 cycles/Q12W ±1 week after Cycle 17 until progressive disease, withdrawal of consent, initiation of subsequent anticancer therapy, participant is lost to follow-up, death, or defined end of study. Anti-tumor activity will also be assessed based on corticosteroid usage and whenever disease progression is suspected (eg, deterioration of clinical status), and at the time of withdrawal from treatment (if not done in the previous 8 weeks). Assessment of overall response will be made using RANO[43,44] for HGG or LGG, as applicable [see Appendix 13]).

All participants' files and radiologic images must be available for source verification and for potential peer review, including by independent central review.

8.1.2. Management of Incidental Findings

An incidental finding is one unknown to the participant that has potential health or reproductive importance, which is discovered unexpectedly in the course of a research study, but is unrelated to the purpose and beyond the aims of the study.

Images may be reviewed by a central review facility. If done, the purpose of this review is to evaluate images for independent assessment of efficacy. Central image review is not a complete medical review of the participant; therefore, no incidental findings will be shared with the PI, site staff, or the participant. All safety reviews will be the sole responsibility of site staff.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Safety assessments will include collection of AEs, SAEs, vital signs and physical examinations, ECG (12-lead), ECHO scans, ophthalmic examinations, dermatologic examinations, neurologic examinations, and laboratory assessments, including pregnancy tests and verification of concomitant treatments.

Assessment of AEs will include the type, incidence, severity (as graded by NCI CTCAE version 5.0), timing, seriousness, and relatedness.

8.2.1. Physical Examinations

Participants will have a physical examination to include weight, assessment of ECOG status and height; height will be measured at Screening only. All physical examinations occurring on dosing days must be performed prior to study drug administration.

A complete physical examination will include, at a minimum, assessments of the general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast and pelvic examinations will be performed.

A brief physical examination should be targeted as clinically indicated and include at a minimum lungs, cardiovascular system, and abdomen (liver and spleen).

A complete physical examination will be performed at Screening. Subsequent brief physical examination may be performed as directed by symptoms.

Investigators should pay special attention to clinical signs related to previous serious illnesses. Findings of all physical examinations should be recorded in the source documents, and any change from baseline considered by the investigator to be clinically significant should be recorded as an AE in the CRF.

Tanner Stage should be assessed in adolescent participants at Screening and at the time points specified in the SoA. Once a participant reaches Tanner Stage 5, assessment is no longer necessary. See 10.22 for Tanner Stage Definition.

8.2.2. Dermatological Examinations

Dermatological evaluations will be performed at the site by the investigator to monitor for the possible development of keratoacanthoma and/or squamous cell carcinoma, as these have been reported to occur with selective BRAF inhibitor treatment.[45] A full dermatologic examination will be performed at Screening. The on treatment assessment may be performed pre-dose or postdose at the time points specified in the SoA. In addition, dermatologic screening for skin malignancies will be performed every 6 weeks until EOT and then every 9 weeks from EOT until 6 months after the last dose of PF-07284890.

In case of the occurrence of keratoacanthoma or squamous cell carcinoma, participants will undergo complete surgical excision of the skin lesion following institutional standards. Dermatologic evaluations will be performed by a dermatologist as clinically indicated.

8.2.3. Opthalmic Examinations

8.2.3.1. Testing at Screening and During the Treatment Period

Full ophthalmic examination will be performed by an ophthalmologist at Screening (SoA) including best corrected visual acuity, slit lamp examination, intraocular pressure, dilated fundoscopy and OCT. Examination of the retina is required (especially to identify findings

associated with RPED, serous detachment of the retina and RVO). The ophthalmic evaluation should be repeated at any point during the treatment period as clinically indicated.

During the treatment period, visual acuity testing will be performed on Day 1 of each cycle.

8.2.3.2. Additional Opthalmic Testing

Participants with clinical suspicion of retinal abnormalities of any grade (eg, RPED, serous detachment of the retina, RVO, photopsia, metamorphopsia, impairment of visual acuity) **must** complete at least 1 of the following additional assessments:

- For non-vascular abnormalities: OCT (spectral domain OCT recommended);
- For vascular abnormalities: fluorescein angiography of the central 30 degrees.

Images/results of the ophthalmic examinations (at a minimum, optical coherence tomography and/or fluorescein angiography) must be sent to the investigational site and be maintained in the participant's source document file. These images/results must be made available upon sponsor request.

8.2.4. Neurologic Examinations

Neurologic examinations will be performed as indicated in the SoA and will include mental status, cranial nerves, gait (eg, rise from chair without hands, walk on toes and heels, tandem heel to toe), reflexes (eg, at triceps, biceps, brachioradialis, patellar, ankle and plantar, Babinski), motor (eg, muscle strength in all 4 extremities, presence of extraneous movements), sensation (eg, to light touch in all 4 extremities, vibration and pinprick at great toes) and balance/coordination (eg, Romberg, finger-to-nose). Neurological symptoms to inquire about may include (but are not limited to) changes in speech, memory, sleep, cognition, and/or vision.

8.2.5. ECOG Performance Status

Criteria are provided in Appendix 14.

8.2.6. Vital Signs and Weight

Vital signs (to be taken consistently before or at least 30 minutes after blood collection for laboratory tests) and weight will be measured per institutional standards. Vital signs will include temperature, systolic and diastolic blood pressure, pulse rate and respiratory rate. All vital sign measurements on dosing days must be performed prior to study drug administration.

Blood pressure and pulse rate measurements will be assessed sitting with a completely automated device. Manual techniques will be used only if an automated device is not available. Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cellphones).

Weight should be measured in a consistent fashion (eg, with the same scale if feasible), and with outerwear and shoes removed.

8.2.7. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10-second rhythm strip) should be collected at times specified in the Pharmacokinetic Sampling and ECGs Schedule tables using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTcF intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) is not recommended given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for approximately 10 minutes in a supine position, and the patient should remain in this position while the ECGs are conducted. When an ECG is to be performed at the same time point as a blood collection, the ECG is to be performed first. The ECG measurement at any time point will be used for AE grading and recommended dose modifications.

A single ECG should be performed during Screening and may be repeated twice more (performed approximately 2 minutes apart) if the initial QTcF value is >470 msec. If more than 3 ECGs are performed during Screening, this should be reviewed with the sponsor's medical monitor to confirm eligibility. For eligibility, the QTcF interval at Screening and at C1D1 pre-dose must be ≤470 msec (for triplicate ECGs, the average QTcF must be ≤470 msec). The pre-dose ECGs on C1D1 will be considered baseline.

Three consecutive ECGs performed approximately 2 minutes apart to determine the mean QTcF interval will be performed at pre-dose (within approximately15 min before the pre-dose PK sample) and at 2 hours (±10 min) after dose on C1D1 and C1D15 and, during Phase 1a of the study when PF-07284890 is administered QD and PK sampling necessitates a pre-dose visit on C1D2, at 24 hours after the C1D1 dose on C1D2 (ie, within 30 minutes prior to the dose on C1D2) the ECG will be collected pre-dose (within approximately 15 minutes before the pre-dose PK sample). Triplicate ECGs will also be performed at 2 hours (±30 minutes) after dosing on Day 1 of Cycles 2-6 as specified in the SoA section of this protocol.

Pre-dose ECGs should be performed within approximately 15 minutes before the pre-dose PK sample. The 2 hour time point is intended to approximate the T_{max} of PF-07284890, but based on initial PK data the time of the triplicate ECGs may be adjusted to better match the T_{max} via a PACL to the investigators.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) the mean value from the triplicate measurements or the value from any single measurement for any postdose QTcF interval is increased by ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QTcF value is >500 msec for any scheduled ECG. If either of these conditions occurs, then a single ECG measurement must be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat

measurement. In addition, if verified QTcF values continue to exceed the criteria above, immediate correction for reversible causes including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTcF interval should be performed.

If the QTcF interval reverts to ≤470 msec, and in the judgment of the investigator(s) and sponsor, it is determined that the cause(s) of QTcF prolongation is something other than study intervention, treatment may be continued with regular ECG monitoring. If in that time frame the QTcF intervals rise above the threshold values, the study intervention will be held until the QTcF interval decreases to below the threshold values. Participants will then restart the study intervention at the next lowest dose level. If the QTc interval has still not decreased to the baseline value on Cycle 1 Day 1 pre-dose after 2 weeks, or if at any time a participant has a QTcF interval >500 msec or becomes symptomatic, the participant will be removed from the study. Additional triplicate ECGs may be performed as clinically indicated.

ECG data will be submitted to a central laboratory for measurement. The final ECG report from the central laboratory should be maintained in the participant's source documentation and be the final interpretation of the ECG recording. Any clinically significant changes from the baseline/Cycle 1 Day 1 pre-dose ECG may potentially be AEs (Appendix 7) and should be evaluated further, as clinically warranted.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTcF value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

If a participant experiences a cardiac or neurologic AE (specifically syncope, dizziness, seizures, or stroke), an ECG (triplicate) should be obtained at the time of the event.

ECG values of potential clinical concern are listed in Appendix 7.

8.2.8. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

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 CRF. Clinically significant abnormal laboratory findings are those which are not associated with

the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention 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.

See Appendix 6 for suggested actions and follow-up assessments in the event of potential drug-induced liver injury.

If Cycle 1 Day 1 requires assessment of clinical laboratory values and those were performed for Screening in the prior 7 days, those laboratory assessments are not required to be repeated.

8.2.9. Echocardiogram

Cardiac ejection fraction and cardiac valve morphology will be assessed by transthoracic ECHO at the time points specified in the SoA. The same method should be used throughout the study. Participants who develop signs/symptoms of CHF at any point during the study are required to have an evaluation of LVEF measurements by ECHO and should be monitored per institutional guidelines.

8.2.10. Pregnancy Testing

Pregnancy tests may be urine or serum tests as specified in the SoA, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at Screening, appropriate contraception must be commenced and a second negative pregnancy test result will be required at the baseline visit prior to the participant's receiving the study treatment. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

8.2.11. Additional Assessments for Adolescent Participants

Tanner Stage:

See Section 8.2.1 and 10.22 Appendix 22: Tanner Staging.

Measurements of LH, FSH, and Estradiol (female) or Testosterone (male):

For female participants who are less than Tanner Stage 4 (ie, Tanner Stage 1-3), serum for measurement of LH, FSH, and estradiol levels should be performed at Screening, every 4 cycles thereafter, and at the End of Treatment visit. For male participants who are less than Tanner Stage 4 (ie, Tanner Stage 1-3), serum for measurement of LH, FSH, and testosterone levels should be performed at Screening, every 4 cycles thereafter, and at the End of Treatment visit.

Suicidal Ideation and Behavior Risk Monitoring:

No additional screening or detection methods are recommended. Families and caregivers of participants must be instructed to monitor participants for the emergence of suicidal ideation and behavior, and to report such symptoms immediately to the investigator.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in Appendix 3.

AEs 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 to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant will be questioned about the occurrence of AEs in a nonleading manner. In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent/assent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including a minimum of 30 calendar days, except as indicated below, after the last administration of the study intervention.

During the survival follow-up period in this study, only SAEs will be actively elicited and collected after completion of the active collection period described above. The SAEs identified during survival follow-up will be reported to Pfizer Safety on the CT SAE Report Form only if considered reasonably related to the study intervention.

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent/assent for the collection of future information, the active collection period ends when consent/assent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the CT SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the CT SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.3.1 are reported to Pfizer Safety on the CT SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

If a participant begins a new anticancer therapy, SAEs occurring during the above-indicated active collection period must still be reported to Pfizer Safety irrespective of any intervening treatment. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for purposes of SAE reporting.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent/assent as described in Section 8.3.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

If a participant begins a new anticancer therapy, the recording period for nonserious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period. Note that a switch to a

commercially available version of the study intervention is considered as a new anticancer therapy for the purposes of SAE reporting.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in Appendix 3.

8.3.4. 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 intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
  - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation or skin contact.
  - A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until a time period that is at least 5 terminal halflives after the last dose (until the half-life is determined from clinical data, this should be at least until the time of last follow-up).
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedural test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the CT SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness regardless of whether there is an associated SAE. The information must be reported using the CT SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable to this study.

8.3.7. Disease-Related Events and/or Disease-Related Outcome Not Qualifying as AEs or SAEs

Not applicable to this study.

8.3.8. Adverse Events of Special Interest

PF-07284890: there are no AEs of Special Interest at this time (as no patients have been dosed at the time of the writing of this protocol version); this section will be updated as data emerges from the ongoing study.

Binimetinib AEs of Special Interest, listed as--Category (AESI)--according to MedDRA Version 21.0: cardiac events (bradycardia, left ventricular dysfunction), dermatologic events (acneiform dermatitis, nail disorders, rash, severe cutaneous adverse reactions, skin infections), edema events (peripheral edema), hemorrhage (hemorrhage), hypertension (hypertension), liver events (hepatic failure, lifer function test abnormalities), ophthalmic events (retinal vein occlusion, retinopathy excluding RVO), pneumonitis events (pneumonitis), venous thromboembolism (venous thromboembolism).

Adverse events of special interest (AESIs) are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes.

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.3.1 through 8.3.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

8.3.8.1. Lack of Efficacy

Not applicable to this study.

8.3.9. Medical Device Deficiencies

Not applicable to this study.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE.**

Other examples include, but are not limited to:

- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

8.4. Treatment of Overdose

For this study, any dose of PF-07284890 or binimetinib greater than the prescribed regimen for the participant within a 24-hour time period ±6 hours will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of PF-07284890 and/or binimetinib (whichever is longer).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**
5. Obtain a blood sample for PK analysis within 7 days from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis).

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

For participants receiving only PF-07284890, blood samples of approximately 3 mL, to provide a minimum of 1.2 mL plasma, will be collected. For participants receiving PF-07284890 and binimetinib, blood samples of approximately 5 mL, to provide a minimum of 2 mL plasma, will be collected. The samples will be collected as specified in the Pharmacokinetic Sampling and ECGs Schedule tables. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times of PK samples may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples within the sampling time window specified in the Pharmacokinetic Sampling and ECGs Schedule tables will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF/DCT. If a scheduled blood sample collection cannot be completed for any reason, the missed sample time may be re-scheduled with agreement of the clinical investigator, participant, and sponsor.

Plasma PK samples will be used to evaluate the PK of PF-07284890 (and binimetinib in participants receiving the combination). For participants receiving only PF-07284890, the plasma PK sample will be used as 1 aliquot approximately 1 mL in volume (1 sample for measuring PF-07284890). For participants receiving PF-07284890 and binimetinib, each plasma PK sample will be divided into 2 aliquots approximately 1 mL in volume each (1 sample for measuring PF-07284890 and 1 sample for measuring binimetinib). Samples collected for analyses of plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

Genetic analyses will not be performed on these plasma samples unless consent for this analysis was obtained. Participant confidentiality will be maintained.

An optional CSF sample of 5 mL is to be collected any time CSF is sampled as part of SOC. If feasible CSF samples are to be collected on PK days (C1D1 and C1D15), ideally 2 to 4 hours post-dose. If CSF samples are obtained on days that are not PK days, if possible an additional PK sample will be collected at approximately the same time. The exact times of the administration of the dose before the CSF sample collection, of the CSF sample collection itself, and if appropriate of the unscheduled PK sample collection should be recorded. CSF samples, obtained only when performed as part of SOC, will be used to evaluate the CSF levels of PF-07284890, and may be used for CCI analysis, if the amount collected is sufficient. Each CSF sample will be divided into 2 aliquots, 1 sample approximately 1 mL in volume for measuring PF-07284890 and 1 sample at least 4 mL for analyzing CCI. The sample collected for analysis of PF-07284890 concentration may also be used to determine the binimetinib concentration. Germline genetic analyses will not be performed on these CSF samples unless consent for this was included in the informed consent/assent. Participant confidentiality will be maintained.

Samples collected for measurement of plasma concentrations of PF-07284890 (and binimetinib in participants receiving the combination) and of CSF concentrations of PF-07284890 will be analyzed using validated analytical methods in compliance with applicable SOPs. Potential metabolites in plasma samples may be analyzed with either validated or exploratory methods.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping

conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Any changes in the timing or addition or removal of time points for any planned study PK assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.6. Pharmacodynamics

PD parameters will be evaluated in this study. See Section 8.8 Biomarkers.

Blood samples of approximately 20 mL, to provide a minimum of approximately 8 mL plasma volume, will be collected for measurement of [redacted] (total amount) and BRAF V600 mutation according to the SoA.

As part of understanding the PD of the study intervention, samples may be used for evaluation of the bioanalytical method, as well as for other internal exploratory purposes.

Samples will be analyzed using a validated analytical method in compliance with applicable SOPs.

The PD samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PD sample handling procedure (eg, sample collection and processing steps, interim storage, or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Details on PD samples and analysis can be found in the Laboratory Manual.

8.7. Genetics

8.7.1. BRAF Testing

Participants will be eligible for the study based on documented evidence of a *BRAF* V600 mutation in tumor tissue or blood (eg, [redacted]) obtained during the course of normal clinical care in a CLIA or similarly certified laboratory at any time prior to Screening. Only PCR and NGS-based local assays results will be acceptable. A molecular report clearly documenting the presence of the BRAF V600 mutation (and any other molecular findings from samples as performed during the normal course of clinical care) must be provided for confirmation that testing meets eligibility. BRAF V600 mutation confirmation (eg, by central testing) is not required for study eligibility, but may be performed retrospectively using submitted tumor tissue and/or baseline blood sample (ie, "blood sample for BRAF CDx"; see SoA and Section 8.7.2) at a Pfizer designated central laboratory.

8.7.2. Archived Tissue Sample/Blood Sample for CDx

Confirmation of the availability of adequate tumor tissue (primary or metastatic, archival), if possible from the same sample that was used to perform local BRAF mutation testing, must be provided for all participants enrolled in the study and submitted to the sponsor. Adequate is defined as: FFPE tumor tissue block, newly collected fixed biopsy sample, or a minimum of 15 unstained slides ideally with at least 20% tumor nuclei content.

This sample may be utilized for CDx development, but will not be used for determining eligibility.

If an archival tumor sample is not available, a fresh tumor biopsy should be obtained if biopsy can be performed safely (in the opinion of the investigator); if biopsy cannot be performed safely, the participant may be eligible if other Inclusions/Exclusion Criteria are met). If a fresh biopsy is taken, the biopsy should be from a nontarget lesion when possible.

Slide sections should be freshly cut (ie, ideally no more than 30 days prior to shipment to the central laboratory), 4-5 µm thick and mounted on positively-charged microscope slides (SuperFrost Plus glass slides are recommended).

Discuss with the sponsor if less then this number of or quality of these slides is available.

A peripheral blood sample (20 mL) will also be collected during Screening (Blood Sample for CDx, see SoA).

Samples collected from this study may be used as part of the development of an in vitro diagnostic assay in accordance with FDA's Quality System Regulations and Design Control requirements. Any tumor samples remaining after testing for BRAF V600 and/or a blood sample collected during Screening may be used for companion diagnostic development and Health Authority registration, and to assess the concordance between the results for BRAF V600 status obtained using the central laboratory assay and the companion diagnostic assay which will be submitted for premarket approval.

Although it is anticipated that most samples will be consumed by planned analyses during the course of the study, any unused samples may be stored at a facility selected by the sponsor for a maximum of 10 years (or according to local regulations) following the last participant's last visit for the study unless prohibited by local regulations or ethics committee decision.

Additional information regarding tissue specimen requirements, sample handling and shipment will be provided in the laboratory manual.

8.7.3. Specified Genetics

A 20-mL blood sample for DNA isolation will be collected at the time points for [redacted] blood collection are provided in the SoA, and at disease progression. DNA samples will be analyzed for the purpose of quantifying cfDNA, BRAF V600 mutations and other mutations correlated with response and resistance to treatment.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant.

Genetic testing may also be performed on CSF samples collected and remaining plasma samples for CDx (Blood Sample for CDx, see SoA) for the purpose of quantifying cfDNA, BRAF V600 mutations and other mutations correlated with response and resistance.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the laboratory manual.

8.7.4. Pharmacogenetics

A 6-mL blood sample prior to the first dose of study drug will be obtained for pharmacogenetics analysis. Genetic variant analysis of the CCI will be performed to investigate the correlation between various genotypes on PF-07284890 exposure. Other genetic analyses on genes that are related to the disease or PF-07284890 metabolism and action may also be performed using these samples. This sample collection is required in this study. It is included in the main consent and is not optional unless otherwise indicated by local IRB/EC or Health Authority requirements.

8.7.5. Banked Biospecimens for Genetics

A 4 mL blood sample optimized for DNA isolation Prep D1 will be collected as local regulations and IRBs/ECs allow.

Banked Biospecimens may be used for research related to the study intervention(s) and cancer. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the banked samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the laboratory manual.

8.8. Biomarkers

Biospecimens collected for pharmacodynamic and other biomarker assessments may include peripheral blood and tumor tissues, and may be used to analyze DNA, RNA, or proteins, for achieving planned biomarker objectives. Refer to the SoA for sample collection time points and Study/Laboratory Manual for sample processing and shipping. The following biospecimen types are planned to be collected in support of study objectives. Additional biospecimens collected over the course of participant disease management may be submitted for biomarker analyses.

8.8.1. Optional De Novo Tumor Biopsies

Tumor biospecimens from de novo biopsies will be used to analyze candidate nucleic acid and protein biomarkers for their ability to identify those participants who are most likely to benefit from treatment with the study drugs. Optional tumor biopsies (obtained prior to C1D1, between C1D8 and C2D15, and at disease progression) will be used to measure

changes from baseline in [redacted]. Inhibition of BRAF kinase activity is expected to block downstream signaling leading to a decrease of [redacted] as measured by immunohistochemistry of tissue samples. Additional protein markers of cell cycle proteins and apoptosis may be measured as molecular changes in cell proliferation. Biopsy samples may also be used to identify acquired changes in tumor DNA that could identify mechanisms of resistance to study drugs.

Additional biomarkers may include, but are not limited to target expression, nucleic acid analyses, as well as cell types and constituents of the TME.

These biopsies will only be obtained in participants in whom biopsy is safe to perform in the opinion of the investigator, and only with the participant's informed consent/assent. If a participant requires a resection of tumor tissue (eg, in the brain) as part of standard of care of their disease (not a study procedure) while on study treatment, the participant may provide optional consent to submit this tissue or a portion of this tissue to the study for analysis. Additionally, the participant may consent to collection of an optional time-matched PK sample collected near the time of the tumor tissue collection.

Additional information on tissue collection procedures can be found in the Laboratory/Study Manual.

8.8.2. Whole Blood, Plasma Biomarkers

Peripheral blood and derivatives may be used to characterize cell phenotypes, measure soluble proteins and analyze nucleic acids to support study objectives. Examples may include cell-free DNA, and cytokines. Total cfDNA in plasma samples will be quantified and BRAF V600 mutant allele fraction will be measured by PCR or NGS from the cfDNA/plasma sample. Mutant allele fractions may be reported as number of mutant copies or the percentage of mutant copies from total reads. Reduction in tumor volume is expected to result in a decrease in shed DNA from tumors as measured by cfDNA and the specific BRAF V600 mutant clones as measured by BRAF V600 mutant [redacted]. Additional analyses, including additional nucleic acid analyses, may be warranted based on emerging data. Plasma samples at EOT/disease progression will be used to identify acquired changes in [redacted] that could identify mechanisms of resistance to study drugs.

8.9. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in an SAP, which will be maintained by the sponsor.

The data will be summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, safety observations and measurements, pharmacokinetic and biomarker measurements.

9.1. Statistical Hypotheses

There will be no formal hypothesis testing in this study.

9.2. Sample Size Determination

Total number of participants for Phase 1a and Phase 1b combined, is estimated to be approximately 120-138.

9.2.1. Phase 1a Dose Escalation

According to criteria to declare the MTD, approximately 35 participants will be enrolled. However, the total number of participants will depend on the number of dose levels needed to determine the MTD/recommended dose for further study and number of participants evaluable for DLT at each dose level, for both the monotherapy and the combination therapy dose escalations.

9.2.2. Phase 1b Dose Expansion

Approximately 20 participants will be enrolled to each of Cohorts 1-4. For Cohort 5, 40 participants, for Cohort 6, 10 participants may be enrolled. Optional Cohort 7, if needed, may enroll 6-8 participants.

- Cohort 1 will include participants with asymptomatic brain metastases and no prior BRAF inhibitor therapy. This cohort will include melanoma participants. For this cohort, the table below shows the probabilities that the true ORR is within a specific interval, given an observed response. For example, assuming the observed ORR is at 40% (8/ 20), assuming a non-informative prior (ie, Jeffrey's prior), a sample size of 20 evaluable participants will yield 65%% Bayesian posterior probability that the 'True ORR' is between 30% and 50%.

Observed ORR	P(ORR) 0-30%	P(ORR) 30-50%	P(ORR) 50-100%
2/20 (10%)	0.982	0.018	0
4/20 (20%)	0.835	0.162	0.003
6/20 (30%)	0.487	0.478	0.035
8/20 (40%)	0.164	0.650	0.186
10/20 (50%)	0.029	0.471	0.5
12/20 (60%)	0.003	0.183	0.814

- Cohort 2 will include participants with symptomatic brain metastases and no prior BRAF inhibitor therapy. This cohort will include melanoma participants. Since these participants are more advanced relative to their brain metastases, we expect more variability in their clinical outcome, including variability relative to tumor type. Therefore, with the approximately 20 participants anticipated, the table below shows

the probabilities that the true ORR is within a specific interval, given an observed response. For example, assuming the observed ORR is at 40% (8/20), assuming a non-informative prior (ie, Jeffrey's prior), a sample size of 20 evaluable participants will yield 65% Bayesian posterior probability that the 'True ORR' is between 30% and 50%.

Observed ORR	P(ORR) 0-30%	P(ORR) 30-50%	P(ORR) 50-100%
2/20 (10%)	0.982	0.018	0
4/20 (20%)	0.835	0.162	0.003
6/20 (30%)	0.487	0.478	0.035
8/20 (40%)	0.164	0.65	0.186
10/20 (50%)	0.029	0.471	0.5
12/20 (60%)	0.003	0.183	0.814

- Cohorts 3 and 4 will include participants (Cohort 3 with asymptomatic brain metastases, Cohort 4 with symptomatic brain metastases) with prior BRAF inhibitor therapy. These 2 cohorts will include melanoma participants. Since these participants have received prior BRAF inhibitors, in addition to other prior therapies, we expect variability in their clinical outcome. For both Cohort 3 and 4, the plan is to enroll approximately 20 participants in each cohort with melanoma. The table below shows the probability that the true ORR is within a specific interval, given an observed response. For example, assuming the observed ORR is at 40% (8/20), assuming a non-informative prior (ie, Jeffrey's prior), a sample size of 20 evaluable participants will yield 65% Bayesian posterior probability that 'True ORR' is between 30% and 50%.

Observed ORR	P(ORR) 0-30%	P(ORR) 30-50%	P(ORR) 50-100%
2/20 (10%)	0.982	0.018	0
4/20 (20%)	0.835	0.162	0.003
6/20 (30%)	0.487	0.478	0.035
8/20 (40%)	0.164	0.65	0.186
10/20 (50%)	0.029	0.471	0.5
12/20 (60%)	0.003	0.183	0.814

- Cohort 5 will include a mixture of tumor types, any brain disease (ie no brain disease, symptomatic or asymptomatic brain metastases) and with or without prior BRAF inhibitor therapy. Participants with the following tumor types are likely to enroll to this cohort: NSCLC, gliomas (low and high grade), cholangiocarcinoma, anaplastic thyroid cancer, and papillary thyroid cancer. We plan to enroll approximately 40 participants into this cohort. Therefore, we anticipate that for a given tumor type the sample size will be at most n=10. The table below shows the probability that the true ORR is within a specific interval, given an observed response. For example, assuming the observed ORR is at 30% (3/10) for a given tumor type, assuming a non-informative prior (ie, Jeffrey's prior), a sample size of 10 evaluable participants will yield 41.7% Bayesian posterior probability to demonstrate that 'True ORR' is between 30% and 50%. If we observe a relatively high response rate of 60% (6/10)

in any given group, assuming a non-informative prior (ie, Jeffrey's prior), a sample size of 10 evaluable participants will yield 73.5% Bayesian posterior probability that 'True ORR' is between 60% and 100%.

Observed ORR	P(ORR) 0-30%	P(ORR) 30-50%	P(ORR) 50-100%
1/10 (10%)	0.926	0.07	0.004
2/10 (20%)	0.745	0.229	0.026
3/10 (30%)	0.481	0.417	0.102
4/10 (40%)	0.238	0.497	0.265
5/10 (50%)	0.088	0.412	0.5
6/10 (60%)	0.023	0.241	0.735

9.2.3. Optional Phase 1b DDI SubStudy

Assuming the intra-participant AUC variability is approximately 30% for midazolam, based on a 2-sided significance level of 0.05, a sample size of at least 8 participants in the DDI Study Expansion Cohort will provide 90% power to detect approximately 1.5-fold or greater change in midazolam AUC when midazolam is coadministered with PF-07284890 (test condition) as compared to midazolam administered alone before the first PF-07284890 dose (reference condition). Approximately 10 participants will be enrolled. See Appendix 15.

9.2.4. Optional Food-effect Substudy

The food-effect substudy is designed to qualitatively assess safety of administration of PF-07284890 with food at a recommended dose for further study .Approximately 6-8 participants will be enrolled. See Appendix 16: A Food-effect SubStudy.

1. Full analysis set.

   The full analysis set includes all enrolled participants.

   "Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent/assent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

2. Safety analysis set.

   The safety analysis set includes all enrolled participants who receive at least 1 dose of study intervention. Unless otherwise specified the safety analysis set will be the default analysis set used for all analyses.

3. Per protocol analysis set (evaluable for MTD).

   The per protocol analysis set includes all enrolled participants who had at least 1 dose of study treatment and either experienced DLT or do not have major treatment deviations during the DLT observation period.

4. mITT Population.

   The mITT is the analysis population that will follow the ITT principle and include participants receiving at least 1 dose of study intervention with baseline assessment and at least 1 post baseline assessment, disease progression, or death before the first tumor assessment. The mITT population may be used for interim analysis and conference presentations when the study is still ongoing.

5. PK analysis sets.

   The PK parameter analysis population is defined as all enrolled participants treated who do not have protocol deviations influencing PK assessment, and have sufficient information to estimate at least 1 of the PK parameters of interest.

   The PK concentration population is defined as all enrolled participants who are treated and have at least 1 analyte concentration.

6. Response Evaluable Set.

   The response evaluable population will include all participants who received at least 1 dose of study treatment and had baseline disease assessment and at least 1 post baseline disease assessment.

7. PD/Biomarker analysis set(s).

   The PD/Biomarker analysis population is defined as all enrolled participants with at least 1 of the PD/Biomarkers evaluated at pre and/or post dose.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1. Primary Endpoint(s)

9.3.1.1. Phase 1a: Maximum Tolerated Dose Determination

Determination of MTD will be performed using Per-protocol analysis set (evaluable for MTD).

The dose escalation in the Phase 1a of the study will be guided by a Bayesian analysis of DLT. Toxicity in monotherapy is modeled using a 2 parameter logistic regression for the probability of a participant experiencing a DLT at the given dose. Toxicity in the combination-therapy dose escalation is modeled using a 5 parameter logistic regression (which includes an interaction parameter) for the probability of a participant experiencing a DLT at the given combination dose. A mixture of weakly informative prior distribution based on nonclinical/expert opinion information and an MAP prior based on encorafenib

historical data will be used to define the prior distribution for the PF-07284890 monotherapy dose escalation. The MAP prior for the logistic model parameters for this study is the conditional distribution of the parameters given the historical data.

The PF-07284890 toxicity data collected in the monotherapy dose escalation will be used by the BLRM combination to guide the PF-07284890+binimetinib dose escalation.

After each cohort of participants, the posterior distribution for the risk of DLT for new participants at different doses of interest for PF-07284890 will be evaluated, in the mono- and combination therapy dose escalations separately. The posterior distributions will be summarized to provide the posterior probability that the risk of DLT lies within the following intervals:

Under-dosing:	[0, 0.16]
Target dosing:	[0.16, 0.33]
Overdosing:	[0.33, 1]

Dosing decisions are guided by the EWOC principal. A dose may only be used for newly enrolled participants if the risk of overdosing at that dose is less than 25%.

Prior distributions:

MAP prior distribution based on historical encorafenib DLT information will be chosen for the logistic parameters for the monotherapy dose escalation of PF-07284890 and the PF-07284890 toxicity data collected in the monotherapy dose escalation will be used by the BLRM combination to guide the PF-07284890+binimetinib dose escalation, see Section 10.9, Appendix 9.

Starting dose:

The starting dose for the monotherapy PF-07284890 is 50 mg QD. This dose satisfies the EWOC criterion. A full assessment of the prior risk to participants is given in Section 10.9, Appendix 9.

Criteria to declare MTD:

The sponsor estimates that the maximum number of participants in the Phase 1a dose escalation portion of the trial (for monotherapy and combination with binimetinib) is 35 participants. However, the actual number may be more or less based on observed PK and safety. The Phase 1a part of the trial can declare an MTD when the following criteria are met:

- At least 6 participants have been treated at the recommended MTD/recommended dose for further study for both the mono- and the combination therapy escalations.

- The dose *d* for PF-07284890 satisfies 1 of the following conditions for each the mono- and the combination therapy escalation part:
  - The probability of target toxicity at dose d exceeds 50%, ie, $Pr(0.16 \leq \pi d < 0.33) \geq 50\%$, or
  - A minimum of 15 participants have been treated in Phase 1a.

9.3.1.2. Phase 1b: Overall Response and Intracranial Response

The Response Evaluable Set will be used for all response related analyses. The primary endpoint of overall response by RECIST version 1.1 and intracranial response by mRECIST version 1.1 (RANO for HGG or LGG) will be summarized and listed by expansion cohort and disease type.

9.3.2. Secondary Endpoint(s)

9.3.2.1. Efficacy Analysis

Response Evaluable Set will be used for all response related analyses including overall and intracranial tumor response, DoR, PFS, DFS (intracranial) and TTR. Tumor response will be presented in the form of participant data listings that include, but are not limited to tumor type, dose on Day 1, tumor response at each visit, and best overall response. OS will be reported on the Full Analysis Set as well as on the mITT.

For Phase 1a, the following secondary endpoints will be reported for efficacy: overall response by RECIST version 1.1 and intracranial response by mRECIST version 1.1 (RANO for HGG or LGG).

For Phase 1b, the secondary efficacy endpoints of Disease Control Rate (overall and intracranial), PFS (overall and intracranial), OS, DoR (overall and intracranial) and TTR (overall and intracranial) will be summarized (also graphically where appropriate) and listed by expansion cohort and disease type.

9.3.2.2. Single-Dose and Steady-State PF-07284890 and Binimetinib Pharmacokinetic Analysis

Plasma concentrations of PF-07284890 will be summarized descriptively (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean and its associated coefficient of variation) by dose, cycle, day and nominal time. This summarization will also be reported for PF-07284890 administered alone and coadministered with binimetinib. Plasma concentrations of binimetinib will be summarized descriptively (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean and its associated coefficient of variation) by dose of PF-07284890, cycle, day and nominal time, and again by cycle, day and nominal time.

Individual participant plasma concentration-time data within a dose interval after Cycle 1 Day 1 and Cycle 1 Day 15 will be analyzed using noncompartmental methods to determine single- and multiple- dose PK parameters for PF-07284890 (and binimetinib when coadministered). For Phase 1a and Phase 1b Cohort 6 participants, single-dose PK parameters to be estimated will include the plasma C_{max}, T_{max}, and AUC_{last}, and if data permit, AUC_{inf}, $t_{½}$, CL/F, and V_z/F. Multiple-dose PK parameters to be estimated will include $C_{ss,max}$, $T_{ss,max}$, $AUC_{ss,\tau}$, plasma $C_{ss,min}$, CL_{ss}/F, and if data permit, V_{ss}/F, $t_{1/2}$, and R_{ac}. For Phase 1b Cohort 1-5 participants, single-dose PK parameters to be estimated will include the plasma C_{max} and T_{max}. Multiple-dose PK parameters to be estimated will include $C_{ss,max}$, T_{max}, plasma $C_{ss,min}$, and R_{ac}. For PF-07284890, the single dose and steady-state PK parameters will be summarized descriptively (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean and its associated coefficient of variation) by dose level, cycle and day. This summarization will also be reported for PF-07284890 administered alone and coadministered with binimetinib. For binimetinib the single dose and steady-state PK parameters will be summarized descriptively (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean and its associated coefficient of variation) by dose of PF-07284890, cycle and day, and again by cycle and day.

For Phase 1a, PF-07284890 dose normalized AUC_{inf} (AUC_{τ} at steady state), AUC_{last} and C_{max} will be plotted against dose (using a logarithmic scale) by cycle and day. These plots will include individual participant values and the geometric means for each dose. The plots will also be done separately for single agent PF-07284890 and PF-07284890 coadministered with binimetinib.

Urine drug concentrations of PF-07284890 (urine PK will be analyzed during DDI substudy, see Appendix 15) as well as urine volume, amount in the urine, and renal clearance will be summarized by descriptive statistics (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean and its associated coefficient of variation).

9.3.2.3. Single-Dose Midazolam Pharmacokinetic Analysis

For Phase 1b Cohort 6, plasma concentrations of midazolam will be summarized descriptively (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean and its associated coefficient of variation) by day and nominal time.

Individual participant plasma concentration-time data for midazolam on Day -7, Cycle 1 Day 1 and Cycle 1 Day 15 will be analyzed using noncompartmental methods to determine single-dose PK parameters. PK parameters to be estimated will include the plasma C_{max}, T_{max}, and AUC_{last}, and if data permit, AUC_{inf}, $t_{½}$, CL/F, and V_z/F. Midazolam PK parameters will be summarized descriptively (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean and its associated coefficient of variation) by day.

If appropriate, a mixed effects model will then be used to analyze natural log-transformed midazolam AUC_{last}. This model will have a fixed effect term for treatment, with participants considered random. Compound symmetry will be assumed and estimation will use REML. The difference in treatment means will be determined along with their associated 90% CI. If appropriate, midazolam C_{max} and AUC_{last} will also be analyzed using a mixed effects model with a fixed effect of treatment and participant as random. There will be no such statistical analyses of other parameters (eg, T_{max}, CL/F, and $t_{½}$).

9.3.2.4. Pharmacodynamic Analyses

PD analysis described in Section 8.6 (ie, CCI [redacted] in optional paired tumor biopsies) will be summarized by descriptive statistics.

9.3.3. Tertiary/Exploratory Endpoint(s)

9.3.3.1. PK-QTc Relationship

Matched PK and ECG data from Phase 1a may be used to investigate any possible relationship between PF-07284890 exposure (as measured by PK assessments of PF-07284890 plasma concentration) and QT prolongation. To investigate the possible relationship between PF-07284890 concentration and change from baseline in QTcF, hereafter denoted ΔQTcF, a linear mixed effect model will be used to quantify the relationship between ΔQTcF and time-matched plasma concentrations of PF-07284890. Time-matched PK and triplicate ECG data will be used in the analysis. The model will be of the form:

$$\Delta QTcF = a + b \times \text{Baseline QTcF} + c \times Cp$$

where Cp is the logarithm of time-matched plasma concentration of PF-07284890, a is the intercept, b and c are the slope for Baseline QTcF and Cp, respectively. 90% CI around b and c will be determined. Coadministration of binimetinib will be tested as a covariate. Additional model structures may be tested as appropriate. The ΔQTcF at C_{max} of the RDE will be calculated.

9.3.3.2. CSF Concentration

The concentration of PF-07284890 in CSF, as well as time-matched PK samples, will be listed for individual subjects. As CSF samples are only obtained when they are needed as part of standard of care, these data may only be obtained for a small number of patients. Additionally, the time of the CSF samples relative to drug administration will be inconsistent. Given the challenges, these data will not be summarized.

9.3.4. Other Safety Analyses

All safety analyses will be performed on the safety population. Summaries and analyses of safety parameters will include all participants in the safety analysis set.

AEs, ECGs, BP, HR, ECHO and safety laboratory data will be reviewed and summarized on an ongoing basis during the study to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and HR abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination and neurological examination information, as applicable, collected during the course of the study will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

9.3.4.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters QT interval, heart rate, QTc interval, PR interval, and QRS complex will be summarized by treatment and time.

The number (%) of participants with maximum postdose QTcF values and mFaximum increases from baseline in the following categories will be tabulated by treatment:

Safety QTcF Assessment

Degree of Prolongation	Mild (msec)	Moderate (msec)	Severe (msec)
Absolute value	>450-480	>480-500	>500
Increase from baseline		30-60	>60

The mean of the replicate measurements will be used to represent a single observation at that time point. If any of the 3 individual ECG tracings has a QTc value >500 msec, but the mean of the triplicates is not >500 msec, the data from the participant's individual tracing will be described in a safety section of the CSR in order to place the >500-msec value in appropriate clinical context. However, values from individual tracings within triplicate measurements that are >500 msec will not be included in the categorical analysis unless the average from the triplicate measurements is also >500 msec. Changes from baseline will be defined as the change between the postdose QTc value and the average of the time-matched baseline triplicate values on Day -1, or the average of the predose triplicate values on Day 1.

The analysis of ECG results will be based on participants in the safety analysis set with baseline (ie, pre-dose on Cycle 1 Day 1) and on-treatment ECG data.

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. Any data obtained from ECGs repeated for safety reasons after the nominal time-points will not be averaged along with the preceding triplicates. Interval measurements from repeated ECGs will be included in the outlier analysis (categorical analysis) as individual values obtained at unscheduled time points.

QT intervals will be corrected for HR (QTc) using standard correction factors (ie, Fridericia's (default correction), Bazett's, and possibly a study-specific factor, as appropriate). Data will be summarized and listed for QT, HR, RR, PR, QRS, QTcF (and other correction factors, eg, QTcB as appropriate), and by study treatment (ie, monotherapy versus combination therapy) and dose. Individual QT (all evaluated corrections) intervals will be listed by study treatment, time and dose. The most appropriate correction factor will be selected and used for the following analyses of central tendency and outliers and used for the study conclusions. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute corrected QT interval and changes from baseline in corrected QT after treatment by study treatment, dose and time point. Details of additional analysis (if any) will be specified in SAP.

9.3.4.2. Adverse Events

AEs will be graded by the investigator according to the CTCAE version 5.0 and coded using MedDRA. Adverse event data will be reported in tables and listings. Summaries of AE by mapped terms, appropriate thesaurus level, toxicity grade, and seriousness and relationship to study treatment will be presented, as well as summaries of AEs leading to death and premature withdrawal from study treatment. The number and percentage of participants who experienced any AE, SAE, treatment related AE, and treatment related SAE will be summarized according to worst toxicity grades. The summaries will present AEs both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). Listings of DLTs and deaths will be provided.

9.3.4.3. Laboratory Test Abnormalities

The number and percentage of participants who experienced laboratory test abnormalities will be summarized according to worst toxicity grade observed for each laboratory assay. The analyses will summarize laboratory tests both on the entire study period and by cycle (Cycle 1 and Cycles beyond 1). For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

9.3.5. Other Analyse(s)

Pharmacogenomic or biomarker data from Banked Biospecimens may be collected during or after the trial and retained for future analyses; the results of such analyses are not planned to be included in the CSR.

Analysis of Biomarker Endpoints

For CCI and biopsy samples, summary statistics (eg, the mean and standard deviation, median, and minimum/maximum levels of continuous, and frequencies and percentages of categorical biomarker measures) will be determined at baseline and post-treatment. Further analysis will be specified in SAP.

Clinically relevant and interpretable biomarker assessments generated for Primary and Secondary objectives will be summarized in the CSR. Other biomarker data might be summarized in a separate technical document.

Population Pharmacokinetic Analysis or PK/PD Modeling

PK and PD data from this study may be analyzed using compartmental modeling approaches and may also be pooled with data from other studies to investigate any association between PF-07284890 exposure and biomarkers or significant safety and/or efficacy endpoints. The results of these analyses, if performed, may be reported separately.

9.4. Interim Analyses

No formal interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating PK/PD modeling, and/or supporting clinical development.

9.5. Data Monitoring Committee or Other Independent Oversight Committee

This study will not use a DMC.

Phase 1a:

In the phase 1a dose escalation, members will convene a DLRM for dose escalation decisions. The actual dose selected at each dose decision may be at or below the BLRM recommended dose as determined by the members of the DLRM after considering all available safety, PK and PD information. The membership of the DLRM will be composed, at a minimum, of all study investigator(s) or medically qualified designee with patients participating in the dose level under review and Pfizer Global Clinical Lead, Pfizer Study Clinician, and Pfizer Study Manager. If a representative of an individual site(s) does not participate in the DLRM, their input may be obtained in writing afterward. The membership must reach consensus (either at the meeting or through written communication) on the dose escalation decision. Additional members may be added as needed (eg, Clinical Pharmacologist Lead, Translational Oncology, Safety Risk Lead or designee and Pfizer Biostatistic representative).

All available study data including demographics, medical history, concomitant medications, AEs, ECGs, vital signs, laboratory results, and emerging PK or PD data will be reviewed. Data to be reviewed may not be verified.

Phase 1b:

In the Phase 1b dose expansion, the study will use a safety review committee (SRC) comprised of internal and external members to assess safety as well as efficacy of dose expansion cohorts. The SRC will be responsible for ongoing monitoring of the safety of participants and will meet regularly to assess the totality of the safety information in the

development program. The SRC will also be responsible for prespecified and ad hoc assessments of safety and futility of each cohort, analysis of incoming expedited safety reports, development of cumulative summaries of all adverse events, and making recommendations to the sponsor regarding protocol modifications. The recommendations made by the SRC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC 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/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

- In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.
- In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent/Assent Process

The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study. The participant or his/her legally authorized representative should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent/assent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her legally authorized representative is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant or his or her legally authorized representative.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her legally authorized representative is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent/assent was obtained before the participant was enrolled in the study and the date the written consent/assent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or the participant's legally authorized representative.

A participant who is rescreened is not required to sign another ICD if the rescreening occurs within 28 days from the previous ICD signature date.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow specimens to be used for additional research. Participants who decline to participate in this optional additional research will not provide this separate signature.

Adolescent Participants:

The investigator or his/her representative will explain the nature of the study to the participant and his/her parent(s)/legal guardian and answer all questions regarding the study. The participant and his/her parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

When consent is obtained from a participant's parent(s)/legal guardian, the participant's assent (affirmative agreement) must be subsequently obtained when the participant has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a participant's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the participant's assent may be waived with source documentation of the reason assent was not obtained. If the study participant does not provide his or her own assent, the source documents must record why the participant did not provide assent (for example, minor child), how the investigator determined that the person signing the consent was the participant's parent(s)/legal guardian, the consent signer's relationship to the study participant, and that the participant's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If study participants are minors who reach the age of majority during the study, as recognized under local law, they must be reconsented as adults to remain in the study. If the enrollment of emancipated minors is permitted by the IRB/EC and local law, they must provide documentation of legal status to give consent without the permission of a legally authorized representative.

Participants and their parent(s)/legal guardian must be informed that their participation is voluntary. Participant's parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant's parent(s)/legal guardian and the study participant as applicable is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant's parent(s)/legal guardian must be informed that the participant's 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's parent(s)/legal guardian.

The participant's parent(s)/legal guardian must be informed that the participant's medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant's parent(s)/legal guardian is fully informed about his or her right to access and correct his or her child's personal data and to withdraw consent for the processing of his or her child's personal data keeping in mind the privacy rights that may restrict access of older adolescents medical records by their parent(s)/legal guardian in certain regions.

The source documentation must include a statement that written informed consent and as applicable, assent, was obtained before the participant was enrolled in the study and the date the written consent/assent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Parent(s)/legal guardian and the participant must be reconsented to the most current version of the ICD(s)/assent during their participation in the study.

A copy of the ICD(s) and assent, if written, must be provided to the parent(s)/legal guardian and the participant.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical

code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.5. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in participants) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since

01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.6. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the Clinical Monitoring Plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF 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 ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. 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. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.7. 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 site.

Data reported on the CRF or entered in the eCRF that are 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.

Definition of what constitutes source data can be found in the Clinical Monitoring Plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor 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.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.9. Publication Policy

The results of this study may be published or presented at scientific meetings by the investigator after publication of the overall study results or 1 year after the end of the study (or study termination), whichever comes first.

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

For all publications relating to the study, the investigator will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors.

The sponsor will comply with the requirements for publication of the overall study results covering all investigator sites. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship of publications for the overall study results will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

If publication is addressed in the clinical study agreement, the publication policy set out in this section will not apply.

10.1.10. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation/study portal or other electronic system.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent/assent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 7. Safety Laboratory Tests

Hematology	Chemistry	Serology (at screening only)	Coagulation	Urinalysis	Pregnancy Test	Ad hoc Central Lab Cytokine Analysis
Hemoglobin	ALT	HBV	PT/INR	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urobilinogen Urine bilirubin Microscopy[a]	For female participants of childbearing potential	IL-6, IL-10, IL- 2, sIL2R, IL-12, IL-4, IL-5, IL-10, IL-13, IL-17, IL-1b, IL-8, IFNγ, and TNF-α
Hematocrit	AST	HCV	PTT			
Total RBC count	bicarbonate	HIV (if applicable)				
Platelets	CRP					
WBC	Alk Phos					
Absolute Neutrophils	Sodium					
Absolute Lymphocytes	Potassium					
Absolute Monocytes	Magnesium					**Optional Ad hoc Local Lab Cytokine Analysis**
Absolute Eosinophils	Chloride					
Absolute Basophils	Total calcium					IL-6
Troponin (for participants receiving binimetinib)	Total bilirubin***					IL-1β
	Total Protein					IL-10
	BUN					TNFα
	Creatinine					
	Uric Acid					
	Glucose (nonfasted)					
	LDH					
	Albumin					

Table 7. Safety Laboratory Tests

Hematology	Chemistry	Serology (at screening only)	Coagulation	Urinalysis	Pregnancy Test	Ad hoc Central Lab Cytokine Analysis
	Phosphorus or Phosphate					
	Creatine Kinase (CK)					

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.

*** For potential Hy's Law cases, in addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, PT/INR, alkaline phosphatase, total bile acids and acetaminophen drug and/or protein adduct levels.

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 CRF.

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

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE:
  - Is associated with accompanying symptoms;
  - Requires additional diagnostic testing or medical/surgical intervention;
  - Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention 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 intervention 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.

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 (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen. • Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

10.3.2. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. 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 that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is

serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. 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 (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. 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 intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with CTCAE Grade 5 (see the Assessment of Intensity section).
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the CT SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the

exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

GRADE	Clinical Description of Severity
1	MILD adverse event
2	MODERATE adverse event
3	SEVERE adverse event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO adverse event

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is

very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology, if requested.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as the data become available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via CT SAE Report Form

- Facsimile transmission of the CT SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which *corresponds to the time needed to eliminate* reproductive safety risk of the *study intervention(s):*

- Refrain from donating sperm.

PLUS either:

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a longterm and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP of male participants (refer to the list of highly effective methods below in Section 10.4.4).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in Section 10.4.3).

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described below during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). *The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.*

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with high user dependency, as described below during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). In addition, a second effective method of contraception, as

described below, must be used. The investigator should evluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

- A WOCBP agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

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

Women in the following categories are <u>not</u> considered WOCBP:

1. Premenopausal female with 1 of the following:

   - Documented hysterectomy;
   - Documented bilateral salpingectomy;
   - Documented bilateral oophorectomy.

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

   Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female.

   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
     - High FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.

- Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen 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.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner.
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

1. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation.
    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.
2. Progestogen-only hormone contraception associated with inhibition of ovulation.
    - Oral;
    - Injectable.

3. Sexual abstinence.

    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. 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.

One of the following effective barrier methods must be used in addition to the highly effective methods listed above that are user dependent:

- Male or female condom with or without spermicide;
- Cervical cap, diaphragm, or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.
- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.
- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to study intervention or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.
- The results of genetic analyses may be reported in the CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained as indicated:
  - Samples for specified genetic analysis (see Section 8.7.3) will be stored for up to 15 years or other period as per local requirements.
  - Samples for banking will be stored indefinitely or for another period as per local requirements.
- Participants may withdraw their consent for the storage and/or use of their Banked Biospecimens at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.
- Banked Biospecimens will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held at the study site and will not be provided to the sample bank.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury, but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are an "adaptor" or are "susceptible."

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

  - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

  - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: ECG Findings of Potential Clinical Concern

ECG Findings That May Qualify as Adverse Events
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 msec. • New prolongation of QTcF to >480 msec (absolute) or by ≥60 msec from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30 seconds' duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That May Qualify as Serious Adverse Events

• QTcF prolongation >500 msec.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset left bundle branch block (QRS >120 msec).
• New-onset right bundle branch block (QRS >120 msec).
• Symptomatic bradycardia.
• Asystole:
  • In awake, symptom-free participants in sinus rhythm, with documented periods of asystole ≥3.0 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node.
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more pauses of at least 5 seconds or longer.
  • Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.
• Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).

- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (heart rate <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm (such as torsades de pointes)).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as Serious Adverse Events

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30 seconds' duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The enumerated list of major events of potential clinical concern are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all inclusive of what to be reported as AEs/SAEs.

10.8. Appendix 8: Country-Specific Requirements

10.8.1. France Contrat Unique

1. GCP Training

   Before enrolling any participants, the investigator and any subinvestigators will complete the Pfizer-provided Good Clinical Practice training course ("Pfizer GCP Training") or training deemed equivalent by Pfizer. Any investigators who later join the study will do the same before performing study-related duties. For studies of applicable duration, the investigator and subinvestigators will complete Pfizer GCP Training or equivalent every 3 years during the term of the study, or more often if there are significant changes to the ICH GCP guidelines or course materials.

2. Study Intervention

   No participants or third-party payers will be charged for study intervention.

3. Urgent Safety Measures

   In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

4. Termination Rights

   Pfizer retains the right to discontinue development of PF-07284890 at any time.

The investigator agrees to abide by the ethical principles set forth in the World Health Organization's *Guiding Principles for Human Cell, Tissue and Organ Transplantation* (WHA63.22) (http://www.who.int/transplantation/en/) with regard to the study.

10.9. Appendix 9: Detailed Dose Escalation/De-Escalation Scheme for BLRM Design

Bayesian design using EWOC will guide the dose escalation for PF-07284890 monotherapy as well as for its combinations with binimetinib. The use of Bayesian response adaptive designs for Phase 1 studies has been advocated for and is one of the key elements of the FDA's Critical Path Initiative.[47,48]

The BLRM will be set-up separately for the dose-toxicity relationship of PF-07284890 when administered as monotherapy and in combination with binimetinib. This Bayesian analysis will be based on the dose limiting toxicity data (absence or presence of DLT) during the first cycle (DLT observation period) accumulated throughout the dose escalation. This appendix provides the details of the statistical model, the description of prior distribution. The results of the Bayesian analyses and respective dosing decisions for some hypothetical data scenarios, and a simulation study of the operating characteristics of the model could be found in the separate Technical supplement to this appendix.

10.9.1. Statistical Models

During Phase 1a dose escalation, BLRM with EWOC will be used to describe the DLT relationship of PF-07284890 monotherapy, to describe the DLT relationship of PF-07284890 + binimetinib, and to guide the decision to escalate the dose of PF-07284890.

10.9.2. Prior Specifications for Monotherapy BLRM

In the monotherapy dose escalation portion of Phase 1a, the DLT relationship of PF-07284890 given as a single agent will be described by a 2-parameter BLRM formulated as follows:

$$\text{logit}\big(\pi(d)\big) = \log(\alpha) + \beta \log\left(\frac{d}{d^*}\right)$$

Where, π(d) is the probability that a patient has a DLT during the first cycle (21 days) when PF-07284890 is given as single agent. The parameter d* is the reference dose in the model and is used to scale the doses of PF-07284890. The α, β >0 are the parameters of the model such that α (>0) is the PF-07284890 odds of a DLT at d^*; and β (>0) is the increase in the log-odds of a DLT by a unit increase in log-dose.

The Bayesian approach requires the specification of prior distributions for the model parameters $\log(\alpha)$ and $\log(\beta)$. Available preclinical toxicology makes it difficult to predict toxicity profile of PF-07284890 single agent in humans. Available toxicity data from a similar compound (encorafenib) will be used and combined with a weakly informative prior allowing for considerable uncertainty, so that the a-priori range for the parameters covers a wide range of plausible values.

10.9.3. Prior Specifications for Combination BLRM

In the combination-therapy dose escalation portion of Phase 1a, the DLT relationship of PF-07284890 and binimetinib given as a combination-therapy will be described by a 5-parameter BLRM formulated as follows:

- PF-07284890 single agent toxicity, represented by parameters α_1, and β_1:

$$\text{logit}(\pi_1(d_1)) = \log(\alpha_1) + \beta_1 \log\left(\frac{d_1}{d_1^*}\right)$$

- The single agent toxicity of the combination partner, binimetinib, represented by parameters α_2, and β_2:

$$\text{logit}(\pi_2(d_2)) = \log(\alpha_2) + \beta_2 \log\left(\frac{d_2}{d_2^*}\right)$$

where $\pi_1(d_1)$ and $\pi_2(d_2)$ are the probability that a patient has a DLT during the first cycle of combination treatment with PF-07284890 and the combination partner, binimetinib at dose d_1 and d_2 respectively and where d_1^* and d_2^* are the PF-07284890 and combination partner reference doses.

Then, the dose-DLT relationship of the combination is defined as:

$$Odds(\pi_{12}(d_1, d_2)) = \frac{\pi_{12}(d_1, d_2)}{1 - \pi_{12}(d_1, d_2)} = \exp(\eta \frac{d_1}{d_1^*} \frac{d_2}{d_2^*}) \left[\frac{\pi_1(d_1) + \pi_2(d_2) - \pi_1(d_1)\pi_2(d_2)}{(1 - \pi_1(d_1))(1 - \pi_2(d_2))}\right]$$

where η is the interaction parameter between PF-07284890 and its combination partner. The drug combination may produce a toxic effect whose magnitude is less than (protective, $\eta < 0$), equal to (no interaction, $\eta = 0$), or greater than (synergistic, $\eta > 0$) that obtained by the treatments acting independently.

The Bayesian approach requires the specification of prior distributions for the model parameters $\log(\alpha_1)$, $\log(\beta_1)$, $\log(\alpha_2)$, $\log(\beta_2)$ and the interaction parameter η.

The prior for $\log(\alpha_1)$, $\log(\beta_1)$ will be based on emerging DLT data from PF-07284890 in the monotherapy portion of Phase 1a. The prior for $\log(\alpha_2)$, $\log(\beta_2)$ will be based on safety data available in the literature for binimetinib for the combination part of Phase 1a. A weakly informative prior for the interaction parameter η will be used reflecting the current uncertainty about the interaction.

Meta-Analytic-Predictive Priors Approach

A MAP prior may be used to define the prior for any or all of the dose cohorts in the dose escalation in order to account for heterogeneity between the available DLT data and the actual study protocol population and treatment regimen/schedule. A MAP prior maybe used instead of, or in addition to a weakly informative prior to form a weighted mixture prior and account for uncertainty. A mixture prior can take the form:

$$p \times BVN_{MAP} + (1-p) \times BVN_{Weak}$$

The weights of the mixture prior are driven by clinical judgement. The aim of the MAP prior approach for treatment i is to derive a prior distribution for the logistic parameters $(\log(\alpha_i^*), \log(\beta_i^*))$ using prior DLT data, available from previously conducted trial, or from the same study but with another regimen.

Let r_i and n_i be the number of participants with a DLT, and the total number of participants at dose d_i in the DLT data available from the historical trial. The corresponding probability of a DLT is π_{di}. The model specifications are as follows:

$$r_i \mid \pi_{di} \sim \text{Bin}(\pi_{di}, n_i)$$

$$\text{logit}(\pi_{di}) = \log(\alpha_i) + \beta_i \log(d_i/d^*)$$

$$\left(log(\alpha_i), log(\beta_1)\right) \mid \mu, \psi \sim \text{BVN}(\mu_i, \psi_i)$$

$$\left(log(\alpha_i^*), log(\beta_i^*)\right) \mid \mu, \psi \sim \text{BVN}(\mu_i, \psi_i)$$

The parameter $\mu_i = (\mu_{i1}, \mu_{i2})$ is the mean for the logistic parameters, and ψ_i is the between-regimen/study covariance matrix. Covariance matrix ψ_i is defined by the standard deviations (t_{i1}, t_{i2}), and correlation r_i.

The following priors will be used for these parameters:

normal priors for μ_{i1} and μ_{i2};

log-normal priors for t_{i1} and t_{i2}, and

a uniform prior for r_i.

To further specify the details of these distributions the principles described in Neuenschwander et.al., 2014[49] will be followed. The MAP prior for model parameters of PF-07284890, $\left(log(\alpha_i^*), log(\beta_i^*)\right)$, is the predictive distribution.

$$\left(log(\alpha_i^*), log(\beta_i^*)\right) \mid (r_i, n_i)$$

Since the predictive distribution is not available analytically, the MCMC method is used to simulate values from this distribution. This is implemented using JAGS version 4.10.

Sensitivity analysis

Despite being prespecified in the protocol, some AEs that fall into the category of DLTs may need to be considered differently. Conversely, some AEs that are not defined as a DLT per protocol should be considered by the dose escalation algorithm. Accordingly, the new concept of an "equivocal" DLT or AE is introduced: most AE/DLTs are considered "unequivocal," but certain types of AEs/DLTs are considered to be "equivocal." To mitigate the risk of dichotomizing and misclassifying DLTs, the sensitivity analysis that uses those weighted equivocal DLT/AE data into the BLRM model estimation will also be performed. The BLRM model uses all the equivocal and unequivocal AE/DLT data, but the variability associated with equivocal AEs/DLTs (less interpretable) is increased. So, the model recommendations are more heavily weighted towards unequivocal data. See below for the posterior distribution of the BLRM model parameters based on the theory of power prior.

Suppose n participants treated at dose d with m unequivocal DLTs and r equivocal DLTs/AEs, and the weight w for the equivocal data, then based on the power prior,

$$Posterior\ (\alpha, \beta \mid d, m, r, w) \ \propto L\ (m \mid \alpha, \beta, d, w) \times L\ (r \mid \alpha, \beta, d, w)\ w \times prior\ (\alpha, \beta)$$
$$\propto p\ (\alpha, \beta, d)^m \times [1 - p\ (\alpha, \beta, d)]^{n-r-m} \times p\ (\alpha, \beta, d)^{rw} \times prior\ (\alpha, \beta),$$

where L is the likelihood of the observed DLT data, and $p\ (\alpha, \beta, d)$ is the probability of DLT at dose d that is modeled by logistic regression in BLRM. To achieve the equality sign, appropriate normalizing constant is required. The contribution of equivocal AEs/DLTs to the data (likelihood) and the Bayesian posterior estimation of the MTD are weighted; the weight parameter controls the influence and can be interpreted as a precision parameter for the equivocal AE/DLT data, similar to the scale parameter in the power prior for the Bayesian historical borrowing. The weight for an equivocal DLT is decreased (eg, 1 decreased to 0.5) and the weight for an equivocal AE (non-DLT by protocol) is increased (eg, 0 increased to 0.5). To maintain the integrity of a trial, the weight is pre-specified as 0.5 in the analysis. If all the investigators and the sponsor agree on the equivocal DLT/AE data, the DLT weighting approach could be the primary dose escalation method. This DLT weighting approach provides a flexible and powerful tool that may incorporate the clinician's valuable experience with some specific DLTs/AEs and improve MTD estimation in dose-escalation trials.

10.10. Appendix 10: Anti-epileptic Medication

Table 8. Mechanism of Elimination of Anti-Epileptic Agents and Potential for PF-07284890 to Alter Their PK[a] [37,50,51]

Anti-epileptic drug	Mechanism of elimination	Potential DDI with PF-07284890	Guidance
Older			
Carbamazepine[b]	CYP3A4	Possible interaction	Use with caution
Ethosuximide	CYP3A4	Possible interaction	Use with caution
Phenytoin[b]	CYP2C9/CYP2C19	Possible interaction (CYP2C9)	Use with caution
Phenobarbital[b]	CYP2C9	Possible interaction	Use with caution
Primidone[b]	CYP2C9	Possible interaction	Use with caution
Sodium valproate[b]	Several UGTs	No apparent mechanism	May be used
Newer			
Lamotrigine	UGTs	No apparent mechanism	May be used
Oxcarbazepine[b]	Cytosolic enzymes in the liver	Possible impact on metabolites through P-gp, but no apparent clinical relevance	May be used
Gabapentin	Renal (elimination proportional to CLcr)	No apparent mechanism	May be used
Topiramate[b]	Renal (not P-gp substrate in vitro)	No apparent mechanism	May be used
Levetiracetam	Renal (correlated to CLcr)	No apparent mechanism	May be used
Zonisamide	CYP3A4	Possible interaction	Use with caution
Vigabatrin	Renal (not P-gp substrate in vitro)	No apparent mechanism	May be used
Pregabalin	Renal (elimination proportional to CLcr)	No apparent mechanism	May be used
Tiagabine	CYP3A4	Possible interaction	Use with caution
Lacosamide	CYP2C19	No apparent mechanism	May be used
Eslicarbazepine[b]	UGTs	No apparent mechanism	May be used
Perampanel[b]	CYP3A4	Possible interaction	Use with caution
Retigabine	Arylamine N-acetyl transferase-2	No apparent mechanism	May be used
Rufinamide[b]	Carboxylesterases	No apparent mechanism	May be used

a. Based on in vitro data of PF-07284890 as a perpetrator of DDIs.
b. These drugs cannot be used in the Phase 1b Cohort 6 DDI substudy with midazolam until after Cycle 1 due to induction and/or inhibition of CYP3A, which could alter midazolam PK.

10.11. Appendix 11: Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1

At baseline, individual tumor lesions will be categorized by the investigator as either measurable or not, according to the criteria summarized below:

1. Measurable Lesions.

Lesions that can be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm for lesions other than lymph nodes and assessed by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm for lesions assessed clinically by caliper measurement (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm for lesions assessed by chest X-ray.
- 15 mm in short axis for lymph nodes when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

2. Non-measurable Lesions.

Non-measurable lesions include small lesions (longest diameter <10 mm or pathological lymph nodes with a ≥10 but <15 mm short axis) as well as truly non-measurable lesions. Truly non-measurable lesions include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses identified by physical examination and not measurable by reproducible imaging techniques.

Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

3. Special Considerations Regarding Specific Lesions.

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same participant, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Solitary lesions:

- If a measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Recording Tumor Measurements

All measurable lesions up to a maximum of 2 lesions per organ and up to 5 in total and representative of all involved organs should be identified as target lesions and measured and recorded at baseline and at the stipulated intervals during treatment. Target lesions should be selected on the basis of their size (lesions with the longest diameters) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically).

The longest diameter will be recorded for each target lesion. The sum of the longest diameter of all target lesions will be calculated and recorded as the baseline sum diameter to be used as reference to further characterize the objective tumor response of the measurable dimension of the disease during treatment.

One (1) exception to the above described approach is related to pathological lymph nodes. Pathological lymph nodes are defined as measurable lesions and may be identified as target lesions if the criterion of a short axis of ≥15 mm by CT scan is met. Only the short axis of these nodes will contribute to the baseline sum. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Definition of Tumor Response

Target Lesions

Response in target lesions is defined as follows:

- Complete Response (CR): disappearance of all target lesions.
- Partial Response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered a sign of progression.
- Stable Disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that participants with CR may not have a total sum of 'zero' on the CRF.

Non-Target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Response in non-target lesions is defined as follows:

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of 1or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression).

Cytology, histology

These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in germ cell tumors). When effusions are known to be a potential adverse effect of treatment (eg, taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response or stable disease and progressive disease.

For participants having effusions or ascites, only cases having cytological proof of malignancy should be recorded on the CRF. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be recorded on the CRF.

New Lesions

The appearance of new malignant lesions indicates PD. New lesion should be unequivocal (eg, not attributable to differences in imaging technique, or change in imaging modality or findings not attributable to tumor). If a new lesion is equivocal, for example due to its small size, continued therapy and follow-up assessment will clarify the etiology of the disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Confirmation of Tumor Response

Confirmation of response is required for non-randomized trials with primary endpoint of response but is not required in randomized studies since the control arm serves as appropriate means of interpretation of data.

Determination of Overall Response by the RECIST version 1.1 Criteria

When both target and non-target lesions are present, individual assessments will be recorded separately. The overall assessment of response will involve all parameters as depicted in Table 9.

Table 9. Response Evaluation Criteria in Solid Tumors

Target lesions	Non-target 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
Any	Any	Yes	PD

Abbreviations: CR = complete response; NE = not evaluable; SD = stable disease; PD = progressive disease; PR = partial response.

Best overall response

The best overall response is determined once all the data for the participant is known. Best response in trials in which confirmation of complete or partial response is not required (ie, randomized trails) is defined as the best response across all time points (for example, a participant who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be the best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the participant's best response depends on the subsequent assessments. For example, a participant who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same participant lost to follow-up after the first SD assessment would be considered not evaluable.

When confirmation of CR and PR is required (ie, non-randomized trials with primary endpoint of response), the best overall response is defined according to the tumor response along the study. Complete or partial responses may be claimed only if the criteria for each are met at a following time point as specified in the protocol (generally 4 weeks later).

Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such participants is to be determined by evaluation of target and non-target lesions.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response.

10.12. Appendix 12: Modified Response Evaluation Criteria in Solid Tumors (mRECIST) version 1.1

1. Modifications to RECIST v1.1 for Assessment of Brain Lesions

The modifications to RECIST v1.1 impact the number and the minimal size of the target brain lesions selected at baseline. Up to 5 additional lesions within the brain may be selected as target lesions; all brain lesions beyond these 5 target lesions will be regarded as nontarget lesions. Patients with intracranial disease will have up to 10 total target lesions (5 extracranial, 5 intracranial) for evaluation. Measurable lesions are defined as those that can be accurately measured in at least 1 dimension with the longest diameter ≥5 mm when evaluated with gadolinium-enhanced MRI.

Gadolinium-enhanced MRI is the only imaging modality accepted for the assessment of brain lesions.

- The technical specification of the MRI scanning sequence will be optimized for the evaluation of brain lesions, which must be measured in the same anatomic plane using the same imaging examinations. Whenever possible the same scanner should be used.[42]

- As a modification to RECIST v1.1, target lesions as small as 5 mm may be selected, however the scanning should follow RECIST v1.1: contiguous slices of maximum thickness corresponding to half the size of the lesion. All measurements must be taken and recorded in millimeters (mm) using a ruler or calipers.

- Image Acquisition guidelines provide the slice thickness requirements that should be used following RECIST v1.1 criteria.

2. Evaluation of Target Brain Lesions

Definitions for assessment of target brain lesion(s) are as follows:

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters (eg, percent change from baseline).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum of diameters* recorded since the treatment started (eg, percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase of at least 5 mm.

Not Evaluable (NE): Cannot be classified by 1 of the 4 preceding definitions.

- Special Notes on the Assessment of Target Brain Lesions:

If a target brain lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance. However, if the response status were PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

3. Evaluation of Non-target Brain Lesions

Definitions for assessment of non-target brain lesion(s) are as follows:

Complete Response (CR): Disappearance of all non-target lesions.

Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) identified as a site of disease.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions.

Not Applicable (N/A): No non-target brain lesions at baseline.

Not Evaluable (NE): Cannot be classified by 1 of the 4 preceding definitions.

- Special Notes on the Assessment of Non-target Brain Lesions:

Non-target brain lesions that are not assessed at a particular timepoint based on the SoA should be excluded from the response determination (eg, non-target response does not have to be "Not Evaluable").

4. New Lesions

New brain malignancies denoting disease progression must be unequivocal. Lesions identified in follow up in an anatomical location not scanned at baseline are considered new lesions.

Any equivocal new lesion should continue to be followed. Treatment can continue at the discretion of the investigator until the next scheduled assessment. If at the next assessment the new lesion is considered to be unequivocal, progression should be documented.

5. Time Point Response for Brain Lesions

Table 10 presents the intracranial response at an individual time point for all possible combinations of tumor response in target and non-target brain lesions, with or without the appearance of new brain lesions for participants with measurable intracranial disease at baseline.

Participants with a global deterioration of health status that requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Objective response status is determined by evaluations of disease burden. Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (eg, fine needle aspirate or biopsy) to confirm the CR.

Table 10. Evaluation of Brain Lesion Response

Target Lesions	Non-target Lesions	New Lesions	Response
CR	CR	No	**CR**
CR	Non-CR/Non-PD or NE	No	**PR**
PR	Non-PD or NE	No	**PR**
SD	Non-PD or NE	No	**SD**
NE	Non-PD	No	**NE**
PD	Any	Yes or No	**PD**
Any	PD	Yes or No	**PD**
Any	Any	Yes	**PD**

6. Best Overall Brain Metastasis Response: All Time Points for Brain Lesions

The best overall brain metastasis response is defined as the best response recorded from the start of treatment until progression of brain metastasis and will be determined programmatically by the sponsor based on the investigator's assessment of brain metastasis response at each time point. Only tumor assessments performed before the start of any subsequent anticancer therapies and not later than 30 days after last dose of study drug will be considered in the assessment of best overall brain metastasis response. Clinical deterioration or clinical progression noted on the completion eCRF will not be considered as documented disease progression.

To be assigned a status of brain metastasis SD, follow-up disease assessment must meet the SD criteria at least once after the first dose of study treatment for a minimum of 6 weeks.

If the minimum time for SD is not met, the best response will depend on subsequent assessments. For example, if an assessment of PD follows the assessment of SD and SD does not meet the minimum time requirement, the best response will be PD. Alternatively,

participants lost to follow-up after an SD assessment who do not meet the minimum time criterion will be considered NE.

7. Extracranial Target, Non-target, New Lesion Assessment and Response

RECIST 1.1 guidelines will be used for assessment of target, non-target, and new lesions for extracranial response

Definitions for assessment of response for extracranial target lesion(s) are as follows:

- Complete Response (CR): Disappearance of all target lesions.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (eg, percent change from baseline).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (eg, percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 mm.
- Not Evaluable (NE): Cannot be classified by one of the four preceding definitions.
- If an extracranial target lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance. However, if the response status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

Definitions for assessment of response for extracranial non-target lesions are as follows:

- Complete Response (CR): The disappearance of all non-target lesions.
- Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) identified as a site of disease.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.
- Not Applicable (NA): No extracranial non-target lesions at baseline.

- Not Evaluable (NE): Cannot be classified by one of the four preceding definitions.

Note:

Extracranial non-target lesions which are not assessed at a particular time point based on the assessment schedule should be excluded from the response determination (that is, the non-target response does not have to be "Not Evaluable" if the non-target lesions were not scheduled for assessment at a particular time point).

Table 11. Evaluation of Extracranial Lesion Response

Target Lesions	Non-target Lesions	New Lesions	Extracranial Response
CR	CR	No	**CR**
CR	Non-CR/Non-PD or NE	No	**PR**
PR	Non-PD or NE	No	**PR**
SD	Non-PD or NE	No	**SD**
NE	Non-PD	No	**NE**
PD	Any	Yes or No	**PD**
Any	PD	Yes or No	**PD**
Any	Any	Yes	**PD**

8. Overall Target, Non-target, and New Lesion Assessment and Response

Overall target lesion response is based on all (that is, intracranial and extracranial) target lesions, up to 10 total as a modification to RECIST 1.1. The sum of longest diameters of all target lesions will be used to determine overall response.

Definitions for assessment of response for target lesion(s) based on modified RECIST 1.1 are as follows:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes must be <10 mm in the short axis.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (eg, percent change from baseline).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (eg, percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5 mm.
- Not Applicable (NA): No extracranial target lesions at baseline.

- Not Evaluable (NE): Cannot be classified by one of the 5 preceding definitions.

Note:

- If lymph nodes are documented as target lesions the short axis is added into the sum of the diameters (eg, sum of diameters is the sum of the longest diameters for non-nodal lesions and the short axis for nodal lesions). When lymph nodes decrease to non-pathological size (short axis <10 mm) they should still have a measurement reported in order not to overstate progression.

- If at a given assessment time point all target lesions identified at baseline are not assessed, sum of the diameters cannot be calculated for purposes of assessing CR, PR, or SD, or for use as the nadir for future assessments. However, the sum of the diameters of the assessed lesions and the percent change from nadir should be calculated to ensure that progression has not been documented. If an assessment of PD cannot be made, the response assessment should be NE.

- All target lesions (nodal and non-nodal) should have their measurements recorded even when very small (eg, 2 mm). If lesions are present but too small to measure, 5 mm should be recorded and should contribute to the sum of the diameters, unless it is likely that the lesion has disappeared in which case 0 mm should be reported.

- If a target lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance. However, if the response status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

Overall non-target lesion response is based on all (that is, intracranial and extracranial) non-target lesions.

Definitions for assessment of response for non-target lesions are as follows:

- Complete Response (CR): The disappearance of all non-target lesions. All lymph nodes identified as a site of disease at baseline must be non-pathological (eg, <10 mm short axis).

- Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) or lymph nodes identified as a site of disease at baseline ≥10 mm short axis.

- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.

- Not Applicable (NA): No intracranial or extracranial non-target lesions at baseline.

- Not Evaluable (NE): Cannot be classified by one of the five preceding definitions.

Note:

- In the presence of measurable disease, progression on the basis of solely non-target disease requires substantial worsening such that even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

- In the presence of non-measurable only disease considerations should be given to whether or not the increase in overall disease burden is comparable in magnitude to the increase that would be required to declare PD for measurable disease.

- Sites of non-target lesions which are not assessed at a particular timepoint based on the assessment schedule should be excluded from the response determination (ie, non-target response does not have to be "Not Evaluable").

New intracranial or extracranial malignancies denoting disease progression must be unequivocal. Lesions identified in follow-up in an anatomical location not scanned at baseline are considered new lesions.

Any equivocal new lesions should continue to be followed. Treatment can continue at the discretion of the investigator until the next scheduled assessment. If at the next assessment the new lesion is considered to be unequivocal, progression should be documented.

Table 12. Evaluation of Overall Response (mRECIST)

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
NE	Non-PD or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

10.13. Appendix 13: Response Assessment in Neuro-Oncology (RANO)

RANO for HGG[43]

Efficacy evaluations using the Macdonald criteria involve post-contrast MRI findings, non contrast T1 and T2 fluid attenuated inversion recovery (FLAIR) images, use of corticosteroid dose, and neurological examination as defined below:

Complete Response (CR) – ALL of the following:

- Complete disappearance of all enhancing measurable and non-measurable disease sustained for ≥4 weeks.
- No new lesions.
- Stable or improved non-enhancing (T2/FLAIR) lesions.
- Offsteroids.
- Neurological condition stable or improved.

Partial Response (PR) – ALL of the following:

- Greater than or equal to 50% decrease compared to baseline in the sum of the perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks.
- No progression of non-measurable disease.
- No new lesions.
- Stable or improved nonenhancing (T2/FLAIR) lesions on the same or lower dose of corticosteroids compared with baseline scan.
- The corticosteroid dose at the time of the scan evaluation should be no greater than the dose at the time of the baseline scan.
- Neurological condition stable or improved.

Progressive Disease (PD) – ANY of the following:

- Greater than or equal to 25% increase in the sum of the products of perpendicular diameters of enhancing lesions compared to the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing dose of corticosteroids.*

- Significant increase in T2/FLAIR nonenhancing lesion on stable or increasing dose of corticosteroids compared with baseline scan or best response following initiation of therapy,* not due to co-morbid events (eg, radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects).
- Any new lesion.
- Clinical deterioration not attributable to other causes apart from the tumor (eg, seizures, medication side effects, complications of therapy, cerebrovascular events, infection, etc.) or changes in corticosteroid dose.
- Failure to return for evaluation due to death or deteriorating condition.
- Clear progression of non-measurable disease.

*Stable doses of corticosteroids includes patients not on corticosteroids.

Stable Disease (SD):

- Does not qualify for CR, PR, or PD.
- Stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose has been increased, the last scan considered to show SD will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
- Stable clinically.

Table 13. Overall Response Criteria (RANO HGG)

	CR	PR	SD	PD[a]
T1-Gd	None	≥50%↓	<25%↑- <50%↓	≥25%↑*
T2/FLAIR	Stable or ↓	Stable or ↓	Stable or ↓	↑*
New Lesion	None	None	None	Present*
Corticosteroids	None	Stable or ↓	Stable or ↓	NA
Clinical Status	Stable or ↑	Stable or ↑	Stable or ↑	↓*
Requirement of response	All	All	All	Any*

↓: decrease; ↑: increase

a. Progression occurs when any of the criteria with * are present; NA: increase in corticosteroid dose alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

RANO for LGG[44]

Diffuse low grade glioma (LGG) are defined by WHO as diffuse infiltrative grade II glioma (eg, astrocytoma, oligodendroglioma, mixed oligoastrocytoma) and are predominantly radiographically non-contrast enhancing tumors that are best visualized on fluid attenuated inversion recovery (FLAIR) and T2-weighted images.

Basic MRI protocol should include:

- Axial FLAIR (canthomeatal alignment).
- Axial T2.
- Coronal T1.
- Post-gadolinium chelate (contrast per local clinical practice).

Efficacy evaluations are as defined below:

Complete Response (CR) – ALL of the following:

- Complete disappearance of the lesion on T2 or FLAIR imaging (if enhancement had been present, it must have resolved completely).
- No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effects, and no new or increased enhancement.
- Off corticosteroids or only physiological replacement doses.
- Must be stable or improved clinically.

Partial Response (PR) – ALL of the following:

- Greater than or equal to 50% decrease compared to baseline in the sum of the perpendicular diameters of the lesion on T2 or FLAIR imaging sustained for at least 4 weeks.
- No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effects, no new or increased enhancement.
- The corticosteroid dose should be no greater than the dose at the time of the baseline scan and should be stable or improved clinically.

Minor Response – ALL of the following:

- Decrease of the area of non-enhancing lesion on T2 or FLAIR MR imaging between 25% and 50% compared to baseline.

- No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effect, and no new or increased enhancement.
- The corticosteroid dose should not be greater than the dose at time of baseline scan and should be stable or improved clinically.

Stable disease – ALL of the following:

- Does not qualify for CR, PR, minor response, or PD.
- Stable area of non-enhancing abnormalities on T2 or FLAIR MR imaging.
- No new lesions, no new T2 or FLAIR abnormalities apart from those consistent with radiation effect, and no new or increased enhancement.
- The corticosteroid dose should not be greater than the dose at time of baseline scan and should be stable or improved clinically.

Progressive Disease (PD) – ANY of the following:

- New lesions or increase of enhancement (radiological evidence of malignant transformation).
- Greater than or equal to 25% increase of the T2 or FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared to baseline scan or best response after initiation of therapy, not attributable to radiation effect or to comorbid events.
- Definite clinical deterioration not attributable to other causes apart from the tumor, or decrease in corticosteroid dose.
- Failure to return for evaluation because of death or deteriorating condition unless caused by documented non-related disorders.

Table 14. Overall Response Criteria (RANO LGG)

	CR	PR	MR	SD	PD
T2/FLAIR	None	≥50%↓	25%↓- <50%↓	<25%↓ - <25%↑	≥25%↑*
New Lesion	None	None	None	None	Present*
Corticosteroids	None	Stable or ↓	Stable or ↓	Stable or ↓	NA**
Clinical Status	Stable or ↑	Stable or ↑	Stable or ↑	Stable or ↑	↓*
Requirement of response	All	All	All	All	Any*

↓: decrease; ↑: increase; CR: complete response; PR: partial response; MR: minor response; SD: stable disease; PD: progressive disease; NA: not applicable
* Progression occurs when any of the criteria with * are present
** NA: increase in corticosteroid dose alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

10.14. Appendix 14: ECOG Classification of Performance Status

ECOG PS Grade	Definition
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework or office work.
2	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	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

10.15. Appendix 15: A Drug-Drug Interaction Substudy

The objective of this DDI substudy is to evaluate the effect of single and repeated administration of PF-07284890 in combination with binimetinib on CYP3A activity using orally administered midazolam as a probe CYP3A substrate.

10.15.1. Rationale for Evaluation of Midazolam PK Interaction

PF-07284890 showed competitive and time-dependent inhibition as well as induction of CYP3A in vitro. As a result, there is a potential that PF-07284890 may alter PK in concomitantly administered medicines metabolized by CYP3A4, possibly increasing or decreasing their exposures. To evaluate the effect of single and repeated administration of PF-07284890 on CYP3A activity, the single dose PK of oral midazolam will be evaluated before Cycle 1 Day 1, and during repeat administration (Cycle 1 Day 15) of PF-07284890 in combination with binimetinib at recommended dose and schedule for further study. Although binimetinib will be coadministered, it is not expected to impact the DDI results, since binimetinib has been demonstrated not to alter the exposure of midazolam.

Midazolam is a benzodiazepine used clinically for conscious sedation. It is specifically metabolized by CYP3A and is widely used as an in vivo probe for CYP3A activity. An oral formulation of midazolam is used to evaluate the effects on CYP3A activity in the GI tract and the liver. The resulting information will be used to determine whether any restrictions or dose modifications of concomitant medications are appropriate in future studies.

10.15.2. Study Design

This is an open-label fixed-sequence study. Approximately 10 participants will be enrolled. Participants will receive a single, 2 mg oral dose of midazolam on Day -7. PF-07284890 at the recommended dose for combination with binimetinib (45 mg BID) (see Section 4.3.4), will be initiated on C1D1. Participants will then receive a single oral dose of midazolam on C1D1 and C1D15. Blood PK sampling will be conducted from 0 to 8 hours on Day -7, C1D1 and C1D15. Urine PK sampling will be conducted on C1D15.

10.15.3. Rationale for the Design

PK sampling will be conducted on Day -7, C1D1 and C1D15 so that the effect of PF-07284890 in combination with binimetinib can be assessed for both single and repeat dosing, due to PF-07284890 inhibition, time-dependent inhibition, and induction of CYP3A potentially causing a different interaction on Day 1 compared to steady state.

10.15.4. Participant Population

In addition to all of the inclusion criteria outlined in Section 5.1, this additional inclusion criteria apply:

- Brain involvement if present must be: (1) neurologically asymptomatic from brain lesions for at least 14 days prior to the start of study treatment; (2) if requiring steroids to control neurological symptoms, on a stable to decreasing dose of steroids

for 14 days prior to the start of study treatment; and (3) no prophylactic or preventative anti-epileptic therapy to prevent neurological symptoms caused by brain lesions. Exception: anti-epileptic therapy to prevent neurological symptoms caused by a preexisting condition and not related to brain involvement is allowed (see Section 6.5 for allowed/prohibited concomitant medications, including anti-epileptic therapy).

In addition to all of the exclusion criteria outlined in Section 5.2, this additional exclusion criteria apply:

- Current use or anticipated need in Cycle 1 for drugs that are known CYP3A inhibitors, including the administration within 10 days or 5 half-lives, whichever is longer, or CYP3A inducers, including the administration within 5 half-lives plus 10 days, prior to first dose of midazolam. Refer to Section 6.5 for further details. See Appendix 18 for example strong CYP3A inhibitors and inducers.

10.15.5. Treatment Administration

Oral midazolam syrup will be supplied to sites. Midazolam will be administered in an oral syringe after administration of study agents. Refer to the Pharmacy Manual for additional information.

Refer to Section 6.1 for administration directions for the other study drug(s).

10.15.6. Additional Concomitant Medications Prohibited Through the End of Cycle 1

Participants on this substudy must follow the guidance in the protocol Section 6.5. Additionally, they must follow the follow restrictions through the end of Cycle 1 to allow a robust assessment of PF-07284890 on midazolam PK.

Because inhibition of CYP3A4/5 isoenzymes may increase midazolam exposure, the use of CYP3A4/5 inhibitors is prohibited through the end of Cycle 1. Strong CYP3A4/5 inhibitors may include grapefruit juice or grapefruit/grapefruit related citrus fruits (eg, Seville oranges, pomelos), ketoconazole, miconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin, indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, fosamprenavir, nefazodone, lopinavir, troleandomycin, mibefradil, and conivaptan. Moderate CYP3A4 inhibitors may include erythromycin, verapamil, atazanavir, fluconazole, darunavir, diltiazem, delavirdine, aprepitant, imatinib, tofisopam, ciprofloxacin, and cimetidine.[37] See Appendix 18 for example strong CYP3A inhibitors.

Because induction of CYP3A4/5 isoenzymes may decrease midazolam exposure, the use CYP3A4/5 inducers is prohibited through the end of Cycle 1. Strong CYP3A4/5 inducers may include phenobarbital, rifampin, phenytoin, carbamazepine, rifabutin, rifapentine, clevidipine, and St. John's Wort.[37] Moderate CYP3A4/5 inducers may include bosentan, efavirenz, etravirine, modafinil, and nafcillin. See Appendix 18 for example strong CYP3A inducers.

Consumption of grapefruit, pomegranates, star fruits, Seville oranges or products containing the juice of each starting from Day -14 through the DDI phase (Day 28) is prohibited, due to potential CYP3A4 interaction with the study drugs. Orange juice is allowed.

Certain anti-epileptic medications may be administered if clinically indicated, consistent with Inclusion/Exclusion Criteria and not subject to drug-drug interactions with study medications. Guidance for anti-epileptic medications that can be used on study is provided in Appendix 10. Because certain anti-epileptic medications induce or inhibit CYP3A4, they cannot be used until after Cycle 1.

During the DDI phase of the study, drinks and food containing caffeine must be excluded 48 hours before PK assessments and the day of PK assessments (ie, Days -9 to -7, -2 to C1D1, C1D13 to C1D15).

10.15.7. Additional PK Assessment

PK assessments (for plasma and CSF) will be conducted as described in Section 8.5, except for the following differences. Blood samples of approximately 8 mL, to provide a minimum of 3.2 mL plasma, will be collected. The samples will be collected as specified in the Pharmacokinetic Sampling and ECGs Schedule table. Plasma PK samples will be used to evaluate the PK of midazolam, PF-07284890 and binimetinib. Each plasma PK sample will be divided into 3 aliquots approximately 1 mL in volume each (1 sample for measuring midazolam, 1 sample for measuring PF-07284890 and 1 sample for measuring binimetinib). Samples collected for analyses of plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method, or for other internal exploratory purposes.

Additionally, a pre-dose urine sample and a post-dose 8-hour urine collection will be obtained on Cycle 1 Day 15 as specified in the Pharmacokinetic Sampling and ECGs Schedule table. The amount of urine collected over 8 hours will be recorded in the CRF. From each of the pre-dose urine sample and the post-dose 8-hour collection, 1 aliquot of approximately 8 mL will be transferred to a 10 mL sample tube for determination of PF-07284890 concentration. The urine samples may be used for additional exploratory analyses (eg, concentration of a metabolite of PF-07284890 in urine). Additional details will be found in the Laboratory Manual.

Samples collected for measurement of urine concentrations of PF-07284890 will be analyzed using a validated analytical method in compliance with applicable SOPs. Potential metabolites in urine samples may be analyzed with either validated or exploratory methods.

10.15.8. Safety Assessments

Safety assessments will include collection of AEs, SAEs, vital signs and physical examinations, ECG (12-lead), ECHO scans, ophthalmic examinations, dermatologic examinations, neurologic examinations, and laboratory assessments, including pregnancy tests and verification of concomitant treatments.

Safety assessments are summarized in the DDI SoA (see Section 10.15.11).

10.15.9. Sample Size

Assuming the intra-participant AUC variability is approximately 30% for midazolam, based on a 2-sided significance level of 0.05, a sample size of at least 8 participants in the DDI Study Expansion Cohort will provide 90% power to detect approximately 1.5-fold or greater change in midazolam AUC when midazolam is coadministered with PF-07284890 (test condition) as compared to midazolam administered alone before the first PF-07284890 dose (reference condition). Approximately 10 participants will be enrolled.

10.15.10. PK Data Analysis

The PF-07284890 and binimetinib PK analysis will be conducted as described in Section 9.3.2.2. Additional details of the midazolam PK analysis are found in Section 9.3.2.3. Plasma concentrations of midazolam will be summarized descriptively (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean and its associated coefficient of variation) by day and nominal time. Plasma concentration-time data of midazolam after each dose will be analyzed using non-compartmental methods to estimate the following PK parameters in individual participants: C_{max}, T_{max}, AUC_{last}, and, if data permit, $t_{½}$, AUC_{inf}, CL/F and V_z/F. PK parameters will be summarized descriptively (n, mean, standard deviation, coefficient of variation, median, minimum, maximum, geometric mean and its associated coefficient of variation) by day.

If appropriate, a mixed effects model will then be used to analyze natural log-transformed midazolam AUC_{last}. Also if appropriate, midazolam C_{max} and AUC_{last} will also be analyzed using a mixed effects model with a fixed effect of treatment and participant as random.

10.15.11. Schedule of Activities for the DDI SubStudy

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each assessment required for compliance with the protocol.

Once a participant completes C2D1, refer to Section 1.3 for subsequent visit activities.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

			Cycle duration = 21 days		
			Cycle 1		Cycle 2-x
Visit Identifier[a]	Screening[1]	Lead-in	Day 1	Day 15	Day 1[b]
Visit Window	Day -35 to Day -8	Day -7	-3 days[c]	No window	±3 days
Informed consent/assent[2]	X				
Inclusion/exclusion criteria	X	X			
Demography and baseline characteristics	X				
Documentation of BRAF V600 mutation[3]	X				
Archived tumor sample[4]	X				
Fresh tumor sample (optional and only if consent provided, for pharmacodynamic analysis)[5]	X			C1D8 (window: ±28 days)	
Whole blood (matched normal)[6]	X				
Blood sample for CDx[7]	X				
Blood sample for CCI (Specified Genetics)[8]	X		X	X	X
HBV and HCV serology testing and HIV where applicable	X				
LH, FSH, and Estradiol for female adolescents or LH, FSH, and Testosterone for male adolescents (Phase 1b)	X				Every 4 cycles (±1 week)
Oncology history	X				
Medical history, prior systemic cancer therapies, radiation and surgeries	X				
Physical examination (Including height at screening only)[9,34]	X	X	X		X
Tanner Stage (phase 1b)	X				Every 4 cycles (±1 week)

			Cycle duration = 21 days		
			Cycle 1		Cycle 2-x
Visit Identifier[a]	**Screening**[1]	**Lead-in**	**Day 1**	**Day 15**	**Day 1**[b]
Visit Window	**Day -35 to Day -8**	**Day -7**	**-3 days**[c]	**No window**	**±3 days**
Full ophthalmic examination[10,34]	X		If clinically indicated (note: visual acuity should be tested by the treating physician on Day 1 of every cycle)		
Dermatologic examination[11,34]	X	X	X		X (C2D1, C3D1, then every other cycle/Q6W)
Neurologic examination[12]		X	X	X	X (C2D1, C2D15, Day 1 of C3-C8, then if clinically indicated)
Vital signs and weight[13]	X	X	X	X	X
ECOG PS[14,34]	X		X		X
Contact IWRS	X	X	X		X
Laboratory					
Hematology[15]	X	X	X	X	X
Blood chemistry (troponin measured only for participants receiving binimetinib)[16]	X	X	X	X	X
Coagulation (aPTT, INR/PT)[17]	X	X	X	X	X (C2D1, C2D15, Day 1 of C3-C8, then if clinically indicated)
Urinalysis[18]	X				X (Starting C3D1 if clinically indicated)
Serum FSH[19]	X				
Serum pregnancy test[20]	X				
Urine pregnancy test[34]			X		X
Contraception check[21]	X		X		X
Single 12-lead ECG[22]	X				
Triplicate 12-lead ECG[23]		X	X	X	X (Day 1 of Cycles 2-6)
ECHO[24]	X				X (C2D1, C6D1, then every 4 cycles/Q12W)

			Cycle duration = 21 days		
			Cycle 1		Cycle 2-x
Visit Identifier[a]	Screening[1]	Lead-in	Day 1	Day 15	Day 1[b]
Visit Window	Day -35 to Day -8	Day -7	-3 days[c]	No window	±3 days
Treatment[25]					
Administer midazolam (AM dose in clinic)		X	X	X	
Administer PF-07284890 and binimetinib (AM dose in clinic)			X	X	X (Day 1 of Cycles 2-6 on PK sampling/ ECG days)
Dispense PF-07284890 and binimetinib			X		X
Administer PF-07284890 and binimetinib			Continuously in 21-day cycles (recommended dose for further study and regimen for PF-07284890; 45 mg BID for binimetinib)		
Review dosing diary and assess drug compliance				X	X
Tumor assessments					
CT or MRI imaging[26]	X		every 6 weeks (2 cycles) ±1 week for 1 year (through Cycle 17) then every 12 weeks ±1 week thereafter		
Other clinical assessments					
Prior and concomitant medication[27]	X	→	→	→	→
Serious and nonserious AE monitoring[28]	X	→	→	→	→
PK blood sampling[29]		X	X	X	X
PK urine sampling[30]				X	
PK CSF sampling[31]			Any time CSF is sampled as part of SOC		
Pharmacogenetics sampling[32]	X				
Pfizer Prep D1 Banked Biospecimen(s)[33]	X				

a. Day relative to start of study intervention (Day 1).
b. For activities/assessments after C2D1, please refer to Section 1.3. C2D1 visit is the end of the DDI substudy assessment.
c. -3 day window is to allow assessments and examinations to occur up to 3 days before initiation of study drug(s) (C1D1) unless otherwise stated (eg, triplicate pre-dose ECG should occur per PK SOA). Follow the PK sampling schedule in relation to the dosing of the study drugs, which should occur 7 days after the first dose of midazolam.

Abbreviations used in this table may be found in Appendix 21.

1. **Screening:** To be obtained within 28 days prior to study entry.
2. **Informed Consent/Assent:** Must be obtained prior to undergoing any study specific procedures. The duration of obtaining ICD should be changed if the screening window is revised.
3. **Documentation of BRAF V600 Mutation**: tissue or blood (eg, CCI) results performed during normal course of clinical care in CLIA or similarly certified laboratory (ie, local testing). Redacted molecular report(s) must be provided during Screening.

4. **Tissue Sample:** Confirmation of availability of adequate tumor tissue for submission to the sponsor. If multiple specimens are available, the most recently obtained is preferred. If participants do not have sufficient archival tissue, a fresh biopsy should be obtained if it can be performed safely in the opinion of the investigator. If adequate archive tissue is not available and a fresh biopsy cannot be performed safely, participants may still be eligible if all other eligibility criteria are met. See Section 8.7.1 for tissue requirements.
5. **Fresh Tumor Sample (Optional):** For participants who provide informed consent/assent for optional biopsy; may be obtained prior to starting treatment, between C1D8 and C2D15, and at EOT (as close to the date of radiographic disease progression as possible if feasible). If feasible, on-treatment and EOT biopsies should be obtained within 2-4 hours after dosing. See Section 8.8.1.
6. **Whole Blood:** as control for tumor molecular analysis.
7. **Blood Sample for CDx:** See Section 8.7.2.
8. **Blood Sample for** CCI **(Specified Geneticss):** Blood sample (CCI) should also be collected at radiographic progression. See Section 8.7.3.
9. **Physical Examination**: Height will be measured at Screening only. Complete physical examination will be performed at initial examination only. Brief, symptom-directed physical examinations will be performed subsequently. See Section 8.2.1.
10. **Full Ophthalmic Examination**: Repeat ophthalmic examination will be performed only if clinically indicated. Visual acuity should be tested by the treating physician on Day 1 of every cycle. See Section 8.2.3.
11. **Dermatologic Examination**: See Section 8.2.2.
12. **Neurologic Examination**: Neurologic examination will be performed on Day 1 and Day 15 of Cycles 1-2. Additional examination will be conducted if clinically indicated. See Section 8.2.4.
13. **Vital Signs:** BP and pulse rate to be recorded in sitting position. See Section 8.2.6.
14. **ECOG PS:** See Appendix 14 for ECOG classification of performance status. See Section 8.2.5.
15. **Hematology**: No need to repeat on C1D1 if Screening assessment performed within 7 days. See Appendix 2 Clinical Laboratory Tests.
16. **Blood Chemistry**: No need to repeat on C1D1 if Screening assessment performed within 7 days prior to that date. See Appendix 2 Clinical Laboratory Tests.
17. **Coagulation**: No need to repeat on C1D1 if Screening assessment performed within 7 days prior to that date. See Appendix 2 Clinical Laboratory Tests. Participants on anticoagulation treatment should have parameters monitored throughout the study as clinically indicated.
18. **Urinalysis:** Dipstick is acceptable at minimum at Screening, C2D1 and EOT visit. See Appendix 2 Clinical Laboratory Tests.
19. **Serum FSH:** High FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.
20. **Pregnancy Test**: Serum pregnancy test will be performed within 24 hours prior to C1D1. Details are described in Section 8.2.10.
21. **Contraception Check:** See Section 5.3.3.
22. **Single 12-Lead ECG:** Single ECG will be performed during Screening to determine eligibility. May be repeated up to twice more (performed approximately 2 minutes apart) if the initial QTcF value is >470 msec; if 3 ECGs are performed, the average QTcF should be ≤470 msec to be eligible.
23. **Triplicate 12-Lead ECG**: For eligibility, the QTcF interval at Screening and C1D1 pre-dose must be ≤470 msec. Additional ECGs may be performed as clinically indicated. The timing of ECG collection may be adjusted based on emerging data. Details of ECG guidance, including obtaining additional ECGs to confirm specific abnormalities, is provided in Section 8.2.7. Details provided in table below when ECDs are obtained at the same time as the PK sample.

24. **ECHO**: ECHO scans will be performed at Screening, Day 1 of Cycle 2. Evaluation of the heart valves should be included and any baseline and treatment-emergent findings should be clearly documented and evaluated for consideration of AE (including grade according to NCI CTCAE version 5.0 and relation to study interventions). See Section 8.2.9.
25. **Study Intervention**: PF-07284890 and binimetinib will be dispensed with dosing diary. Participants will receive a single, 2 mg oral dose of midazolam on Day -7. PF-07284890 at the recommended dose and regimen for combination with binimetinib (45 mg BID), will be initiated on Day 1, continuously in a 21-day cycle. Participants will then receive a single oral dose of midazolam on Day 1 and Day 15. Study intervention will be described in Section 6 and Section 10.15.5.
26. **Tumor Assessments**: Tumor assessments will include all known or suspected disease sites. MRI of brain, contrast-enhanced CT or MRI of chest, abdomen and pelvis will be performed at Screening, C3D1, then every other cycle/Q6W ±1 week. CR or PR confirmation assessments must take place at least 4 weeks after the initial response and may be performed a minimum of 4 weeks (28 days) after the initial scan showing a CR or PR at the discretion of the investigator, with the next scan performed according to the original schedule. See Section 8.1.1.
27. **Prior and Concomitant Medication**: all concomitant medications and NonDrug Supportive Interventions should be recorded on the CRF.
28. **AE Assessments**: AEs should be documented and recorded at each visit using the NCI CTCAE version 5.0. Assessment of AEs should include questions pertaining to the incidence, severity, and timing of visual changes (eg, flashes or color changes), palpitions, and bruising or bleeding. The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent/assent through and including a minimum of 28 calendar days after the last study intervention administration. If the participant begins a new anticancer therapy, the period for recording non-serious AEs on the CRF ends at the time the new treatment is started. However, any SAEs occurring during the active collection period must still be reported to Pfizer Safety and recorded on the CRF, irrespective of any intervening treatment. See Section 8.3.
29. **PK Blood Sampling:** Details provided in the table below. Also, see Section 8.5.
30. **PK Urine Sampling**: Urine PK sampling will be conducted on C1D15.
31. **PK CSF Sampling**: Details provided in the table below. Also, see Section 8.5.
32. **Pharmacogenomics sampling**: Pharmacogenomic samples will be obtained during Screening. See Section 8.7.4.
33. **Pfizer Prep D1 Banked Biospecimen(s):** See Section 8.7.5.
34. Assessment does not need to be repeated if performed within 72 hours prior to Cycle 1 Day 1 (ie, first day of dosing).

Pharmacokinetic Sampling and ECGs for Cohort 6 in Phase 1b

								Study Treatment (cycle duration = 21 days)													
								Cycle 1												Cycle 2-6	
Visit Identifier	Screening	Lead-in						Day 1						Day 15						Day 1[a]	
	Day -35 to Day -8	Day -7						No window						(±3 days)						(±3 days)	
Hours Before/After Dose		0[b]	0.5	1	2	4	8	0[b]	0.5	1	2	4	8	0[b]	0.5	1	2	4	8	0[b]	2
Study intervention administration (PF-07284890 and binimetinib)[1]								X						X						X	
Study intervention administration, CYP3A probe midazolam[1]		X						X						X							
PK blood plasma sampling[2]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine for PK[3]														X	X	X	X	X	X		
PK CSF sampling[4]								Any time CSF is sampled as part of SOC													
Singlet 12-lead ECG	X																				
Triplicate 12-lead ECG[5]		X			X			X			X			X			X				X

a. C2D1 visit is the end of the DDI phase safety assessment. For activities/assessments after C2D1, please refer to Section 1.3.

b. Predose sample collection.

1. **Study drug/Midzolam Administration**: On PK days, morning dose of the study agents will be administered in the clinic. Midazolam will be administered after administration of study agents.
2. **PK Sampling:** Blood will be collected for determining the concentration of midazolam on Lead-in Day -7, and midazolam, PF-07284890 and binimetinib C1D1 and C1D15 at pre-dose (within 30 min before the dose), 30 min (±2 min), 1 hour (±5 min), 2 hour (within 15 minutes after the last of the triplicate ECGs scheduled at that time point), 4 hour (±10 min), and 8 hour (±20 min) postdose. On Day 1 of C2-C6, PK samples will also be obtained pre-dose (within 30 min) and at 2 hours (within 15 minutes following the last of the triplicate ECGs scheduled at that time point) postdose. A PK sample will also be obtained during the EOT visit and at the time of CSF sampling (when CSF sampling is not done on a PK day) if possible. Additional PK samples may be obtained at other timepoints if clinically indicated. Detailed instruction of sample collection, processing and shipment will be provided in the Lab Manual. See Section 8.5.
3. **Urine for PK Sampling:** The predose urine sample will be separate from the subsequent collection. All urine collected over the 0 to 8 hour period will be pooled.
4. **PK CSF Sampling**: PK CSF samples will be collected for participants in whom CSF sampling is being performed as part of SOC. If feasible samples should be collected on any PK day, ideally 2 to 4 hours after dosing on any PK day, with the time collected relative to dosing clearly indicated on the requisition. If the CSF sample is collected but not on a PK day, an additional PK sample should be collected soon after if possible. See Section 8.5.

5. **12 Lead ECG:** A singlet ECG will be collected at Screening. Triplicate ECGs will be collected at pre-dose (within approximately 15 minutes before the pre-dose PK sample) and at 2 hours (±10 min) after dosing on C1D1 and C1D15, and at 2 hours (±30 min) postdose on Day 1 of Cycles 2-6 (intended to approximate the T_{max} of PF-07284890), with 3 consecutive 12 lead ECGs performed approximately 2 minutes apart to determine mean QTcF interval. When ECGs are obtained at the same time as a PK sample, the ECGs must be completed before the PK sample is taken. Additional ECGs will be performed as clinically indicated. The timing of ECG collection may be adjusted based on emerging data. Details of ECG guidance, including obtaining additional ECGs to confirm specific abnormalities, are provided in Section 8.2.7.

10.16. Appendix 16: A Food-effect SubStudy

10.16.1. Rational for Evaluation of Food Effect

Food can have a significant impact on drug pharmacokinetics, and therefore on drug safety and efficacy. The effect of food on PF-07284890 PK is being assessed in healthy participants in Study C4471002 (more details provided in 4.2.6). If the food effect shows an increase in exposures, the data from this study will be used to determine the dose in the fed state that is equivalent to the fasted state MTD/RDE. If the observed food effect is substantial and clinically significant, ie, increases the relative bioavailability by more than 2-fold, more data may be needed to determine whether the equivalent dose for the fed state achieves the proper exposure and is safe with repeat administration. For this reason, the effect of food on PF-07284890 PK and safety will be characterized in this substudy if food causes more than a 2-fold increase in AUC in C4471002.

10.16.2. Study Design

This substudy will be conducted within C4471001 in Cohort 7 participants to assess the safety and PK of administration of a recommend dose for further study when administered with food. Approximately 6-8 participants (PK evaluable) are required for the food-effect assessment, and participants who are inevaluable for this PK substudy may be replaced by the Sponsor.

The PF-07284890 dose in the fed state equivalent to the MTD/RDE dose in the fasted state for a positive food effect will be determined from C4471002 PK data (low-fat meal versus fasted) based on the ratio of LSM of the AUC values. If the ratio, expressed as percent of reference, comparing the low-fat meal (test) to the fasted state (reference) is <125%, the dose in the fed state will be the same as the dose in the fasted state. However, if the ratio is ≥125%, the dose in the fed state will be adjusted based on exposures matching, assuming linear PK, and taking into consideration tablet strengths. For example, if AUC for the fed state (low fat meal) is 200% that of the fasted state, then a 50% decrease in dose will be deemed appropriate.

Within Cohort 7, all participants will be administered PF-07284890 in a fed state. PK sampling times, which include additional PK sampling are described below. Investigational product will be administered with approximately 8 ounces (240 ml) of water within approximately 30 minutes after the start of the meal/snack. The patient should be instructed to record compliance with the requirements to administer drug with food in the dosing diary. Study staff should monitor compliance at each visit and record this in the CRF. The effects of controlled meals were examined in Study C4471002 (ie, standard low-fat and high-fat meals as described in FDA guidance). The goal of this substudy is to determine exposures for a typical meal, and patients should eat something typical for them. Examples of meals/snacks that a patient could consume at a minimum prior to their PK samples include:

- One boiled egg, one packet of flavored instant oatmeal made with water, and 8 oz of milk (1 percent fat) – FDA low-fat meal.

- Cheese, dried fruit, crackers and coke.

Patients are not precluded from eating a larger, high-calorie meal. The above are only examples of snacks/meals that would be acceptable. The schedule of activities will be as described in Section 1.3, but the Pharmacokinetic Sampling and ECGs Schedule noted there will be replaced by Table 15 Schedule of Activities for Food-effect Substudy as noted below.

Based on these data, the effect of food will be evaluated to determine safety and tolerability of the equivalent dose at the MTD/RDE when administered with food. The SRC will be convened after 6 to 8 patients have been treated for at least 21 days to assess safety and tolerability and available PK data. If well tolerated, a PACL may be used to replace the fasting requirement with an instruction for administration of PF-07284890 with food. If exposures are not as expected, the equivalent dose may be further adjusted based on the data from this substudy cohort.

10.16.3. Participant Population

In addition to all of the inclusion criteria outlined in Section 5.1, these additional inclusion criteria apply:

- Brain involvement if present must be: (1) neurologically asymptomatic from brain lesions for at least 14 days prior to the start of study treatment; (2) if requiring steroids to control neurological symptoms, on a stable to decreasing dose of steroids for 14 days prior to the start of study treatment; and (3) no prophylactic or preventative anti-epileptic therapy to prevent neurological symptoms caused by brain lesions. Exception: anti-epileptic therapy to prevent neurological symptoms caused by a preexisting condition and not related to brain involvement is allowed (see Section 6.5 for allowed/prohibited concomitant medications, including anti-epileptic therapy).

In addition to all of the exclusion criteria outlined in Section 5.2, this additional exclusion criterion applies:

- Current use or anticipated need in Cycle 1 for drugs that are known CYP3A inhibitors, including the administration within 10 days or 5 half-lives, whichever is longer, or CYP3A inducers, including the administration within 5 half-lives plus 10 days, prior to first dose of midazolam. Refer to Section 6.5 for further details. See Appendix 18 for examples of strong CYP3A inhibitors and inducers.

10.16.4. Additional PK Assessments

Although the substudy will be conducted in Phase 1b, Cohort 7, additional PK sampling will be done, consistent with PK sampling in Phase 1a dose escalation as shown in Table 15.

10.16.5. Safety Assessments

Safety assessments are described in Section 8.2.

10.16.6. Additional PK Assessments

The analysis of PK-07284890 PK data will be conducted as described in Section 9.3.2.2.

10.16.7. Statistical Analyses

PF-07284890 PK parameters (AUC_8 and C_{max}) will be compared to data from Phase 1a in the fasted state at all dose levels but focusing on the MTD/RDE dose level to determine whether the PK at the equivalent dose in this fed state substudy are as expected.

10.16.8. Transition to Fed State Administration

PK and safety will be assessed for this cohort as per the current protocol/SoA. The dose in the fed state determined equivalent to the fasted state MTD/RDE will be adjusted if exposure and/or tolerability data indicate such an adjustment is needed.

If the PK data from this food-effect substudy indicate with food PK for PF-07284890 has a potential benefit for patients (eg, if exposures are more consistent in the fed state or if C_{trough} values are higher for similar exposures and tolerability) and is well tolerated, the instructions for administering PF-07284890 in the fed state at the appropriate equivalent dose to the MTD/RDE will be introduced into Phase 1b under the current amendment. The fed state equivalent dose will be communicated to the study investigators. Participants who started taking PF-07284890 in the fasted state may transition to the fed state at an equivalent dose after the fed state equivalent dose has been determined and tolerability has been verified in the food-effect substudy cohort.

Table 15. Pharmacokinetic, ECG and Selected Biomarker Sampling for Food-effect Substudy

		Study Treatment (cycle duration = 21 days)															
		1st Cycle Combination Therapy												Cycles 2-6		Subsequent Cycles	
Visit Identifier	Screening	Day 1						Day 15						Day 1		Day 1	EOT
	Day -28 to Day -1	No window						(±3 days)						(±3 days)		(±3 days)	(±7 days)
Hours Before/After Dose		0[a]	1	2	4	6	8	0[a]	1	2	4	6	8	0[a]	2	0[a]	
Administration of study intervention (PF-07284890, or PF-07284890 and binimetinib), AM dose in clinic		X						X						X		X	
PK blood plasma sampling[1]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK and genetic biomarker CSF sampling[2]	Any time CSF is sampled as part of SOC																
Singlet 12-lead ECG[3]	X																
Triplicate 12-lead ECG[3]		X		X				X		X					X		

1. PK Sampling for Participants participating in the food-effect substudy: Blood will be collected for determining the concentration of PF-07284890 (and for binimetinib in patients receiving the combination) on C1D1 and on C1D15 at pre-dose (within 30 min before the dose), 1 hour (±5 min), 2 hour (within 15 minutes after the last of the triplicate ECGs scheduled at that time point), 4 hour (±30 min), 6 hour (±40 min), and 8 hour (±60 min) postdose. On Day 1 of C2-C6, PK samples will also be obtained pre-dose (within 30 min prior to dose) and at 2 hours (within 15 minutes following the last of the triplicate ECGs scheduled at that time point) postdose. On Day 1 of subsequent cycles, PK samples will also be obtained pre-dose (within 30 min prior to dose). A PK sample will also be obtained during the EOT visit. Additional PK samples may be obtained at other timepoints if clinically indicated.
2. PK CSF Sampling: PK CSF samples will be collected for participants in whom CSF sampling is being performed as part of SOC. If possible, samples should be collected on any PK day, ideally 2 to 4 hours after dosing on any PK day, with the time collected relative to dosing clearly indicated on the requisition and/or eCRF. If the CSF sample is collected but not on a PK day, an additional PK sample should be collected soon after if possible. See Section 8.4.
3. 12-Lead ECG: A singlet ECG will be collected at Screening. Triplicate ECGs will be collected at pre-dose (within approximately 15 minutes before the pre-dose PK sample) and at 2 hours (±10 min) after dosing on C1D1 and C1D15; and at 2 hours (±30 min) postdose on Day 1 of Cycles 2-6 (intended to approximate the T_{max} of PF-07284890), with 3 consecutive 12 lead ECGs performed approximately 2 minutes apart to determine mean QTcF interval. When ECGs are obtained at the same time as a PK sample, the ECGs must be completed before the PK sample is taken. Additional ECGs will be performed as clinically indicated. The timing of ECG collection may be adjusted based on emerging data. Details of ECG guidance, including obtaining additional ECGs to confirm specific abnormalities, are provided in Section 8.2.6. When ECGs are obtained at the same time as a PK sample, the ECGs must be completed before the PK sample is taken.

10.17. Appendix 17: Prohibited Concomitant Medications That May Result in DDI

The prohibited concomitant medications listed below should not be taken with PF-07284890 throughout the conduct of the study, and some have a required washout period as listed in the table.

The Pfizer study team is to be notified of any prohibited medications taken during the study. After consulting with the sponsor, the investigator will make a judgment on the ongoing participation of any participant with prohibited medication use during the study.

This list of drugs prohibited for potential DDI concerns with the IMP may be revised during the course of the study with written notification from the sponsor, to include or exclude specific drugs or drug categories for various reasons (eg, emerging DDI results for the IMP, availability of new information in literature on the DDI potential of other drugs).

This is not an all-inclusive list. Site staff should consult with the sponsor or designee with any questions regarding potential DDI.

Investigators should consult the product label for any other medication used during the study for information regarding medication that is prohibited for concomitant use.

Investigators should consult the SRSD for binimetinib for information regarding medication that is prohibited for concomitant use.

Table 16. Prohibited Concomitant Medications that May Result in DDI

Drug Category	Drugs	Guidance	Required Washout Period Prior to the First Dose of PF-07284890
PF-07284890 as Victim of DDI			
CCI [redacted]			
Proton pump inhibitors	dexlansoprazole esomeprazole ilaprazole ▪ lansoprazole omeprazole pantoprazole rabeprazole	Prohibited	7 days

PF-07284890 as Perpetrator of DDI			
CYP3A substrates that have a narrow therapeutic index (NTI)	alfentanil amiodarone argatroban astemizole [a] carbamazepine cisapride [a] cyclosporine dihydroergotamine ergotamine fentanyl (excluding transdermal patch) pimozide quinidine sirolimus tacrolimus terfenadine	Prohibited	N/A

a. Not approved in the US as of October 2020, but may be available in other countries including Korea, China and Mexico.

10.18. Appendix 18: Strong CYP3A Inhibitors and Inducers

This list is not considered to be exhaustive. Although it contains only strong inhibitors and inducers, all CYP3A inhibitors and inducers are prohibited through the end of Cycle 1 for participants in the DDI substudy Phase 1b Cohort 6. Any questions regarding use of CYP3A inhibitors and inducers should be directed to the Sponsor study team.

CYP3A Inhibitors	CYP3A Inducers
HIV antivirals	**HIV antivirals**
Indinavir	Nevirapine
Nelfinavir	**Miscellaneous**
Ritonavir	Barbiturates
Saquinavir	Carbamazepine
Boceprevir	Glucocorticoids (systemic)
Lopinavir/ritonavir	Oxcarbazepine
Amprenavir	Phenobarbital
Atazanavir	Phenytoin
Telaprevir	Rifabutin
Darunavir/ritonavir	Rifampin
Fosamprenavir	St. John's wort[1]
Tiprinavir/ritonavir	Troglitazone
Antibiotics	Nafcillin
Clarithromycin	Avasimibe[2]
Troleandomycin	Enzalutamide
Telithromycin	Mitotane
Rifapentine	Clevidipine
Anti-infective	
Itraconazole	
Ketoconazole	
Posaconazole	
Voriconazole	
Miconazole	
Miscellaneous	
Nefazodone	
Grapefruit juice[3]	
Conivaptan	
Mibefradil[4]	
Idelalisib	

1. The effect of St. John's wort varies widely and is preparation-dependent.
2. Not a marketed drug.
3. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).
4. Withdrawn from the United States market.

10.19. Appendix 19: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the pCOVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

10.19.1. Eligibility

While SARS-CoV2 testing is not mandated for this study, local clinical practice standards for testing should be followed. A patient should be excluded if he/she has a positive test result for SARS-CoV2 infection, is known to have asymptomatic infection, or is suspected of having SARS-CoV2. Patients with active infections are excluded from study participation as per Exclusion Criterion 7. When the infection resolves, the patient may be considered for re-screening.

10.19.2. Teleheath Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4 and Section 10.19.3.1 of this appendix regarding pregnancy tests.

Study participants must be reminded to promptly notify site staff about any change in their health status.

10.19.3. Alternative Facilities for Safety Assessments

10.19.3.1. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

If a participant requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 mIU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

10.19.3.2. Imaging

If the participant is unable to visit the study site for safety imaging assessment(s), the participant may visit an alternative facility to have the safety imaging assessment(s) performed. Qualified study site personnel must order, receive, and review results.

10.19.3.3. Electrocardiograms

If the participant is unable to visit the study site for ECGs, the participant may visit an alternative facility to have the ECGs performed. Qualified study site personnel must order, receive, and review results.

10.19.4. Opthalmic Exams

If the participant is unable to visit the study site for ophthalmic exams, the participant may visit an alternative facility to have the ophthalmic exams performed. A consistent reader should be used across the study whenever possible. Qualified study site personnel must order, receive, and review results.

10.19.5. Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

PF-07284890 and/or binimetinib may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for the study intervention. Pfizer does not permit the shipment of study intervention by mail. The tracking record of shipments and the chain of custody of study intervention must be kept in the participant's source documents/medical records.

In the event that the ongoing COVID-19 pandemic precludes the participant visiting the clinical site in person, study medication may be shipped directly to the participant under the following conditions:

- The participant has completed at least 2 cycles of their current study regimen (ie, if receiving monotherapy, has received at least 2 cycles of monotherapy; if combination therapy, the participant needs to have received at least 2 cycles of combination therapy);
- Based on the opinion of the investigator, there are no ongoing safety issues that would put the participant at risk; and
- Local institutional standards allow the shipment of study medication to the participant.

The following is recommended for the administration of the study intervention for participants who have active confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion) SARS-CoV2 infection:

- For symptomatic participants with active SARS-CoV2 infection, the study intervention should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of SARS-CoV2 infection.
- Prior to restarting treatment, the participant should be afebrile for 72 hours, and SARS-CoV2-related symptoms should have recovered to ≤ Grade 1 for a minimum of 72 hours. Notify the study team when treatment is restarted.
- Continue to consider potential drug-drug interactions as described in Section 6.5, Appendix 17: Prohibited Concomitant Medications That May Result in DDI, and Appendix 18: Strong CYP3A Inhibitors and Inducers for any concomitant medication administered for treatment of SARS-CoV2 infection.

10.19.6. Home Health Visits

A home health care service may be utilized to facilitate scheduled visits per the Schedule of Activities. Home health visits include a healthcare provider conducting an in-person study visit at the participant's location, rather than an in-person study visit at the site. The following may be performed during a home health visit:

- Review and record study intervention;

- Review and record any new concomitant medications or changes in concomitant medications since the last contact;
- Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4 and Section 10.19.3.1 of this appendix regarding pregnancy tests;
- ECG;
- Vital signs;
- Physical assessment; and/or
- Laboratory sample, PK/PD sample, and biomarker sample collection.

10.19.7. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an adverse event (AE) or serious adverse events (SAE) and appropriate medical intervention provided. Temporary discontinuation of the study intervention may be medically appropriate until the participant has recovered from COVID-19.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

10.19.8. Efficacy Assessments

If the participant is unable to visit the study site for imaging assessments (eg, CT, MRI), the participant may visit an alternative facility to have the imaging assessments performed, preferably with consistent imaging modality used throughout the study. Qualified study site personnel must order, receive, and review results.

10.20. Appendix 20: Protocol Amendment Summary of Changes Table

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC). The protocol amendment summary of changes tables for past amendment(s) can be found below

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Amendment 2	14 January 2021	Section 1.2 Schema, Figure 2: Adjusted schema to more align with planned study design. Section 1.3 Schedule of Activities: Added Cycle 1, Day 8 safety assessments to ensure adequate safety monitoring during the first cycle of treatment. Adjusted CCI sample timepoints to align with cycle frequency instead of tumor assessment frequency in order to increase site and participant convenience. Clarified serum and urine pregnancy testing guidance and requirements. Section 5.1 Inclusion Criteria: Clarified criterion 5. Section 5.2 Exclusion Criteria: Updated criterion 14 with additional information to shorten the window prior to study start for participants with a PE or DVT who are stable, asymptomatic and stable on anticoagulant treatment since the potential risk of additional coagulation risk is lower in this population. Section 6.1.1 Administration: Added definition of a missed dose for clarification. Section 6.5.9 Surgery: Clarified guidance for participants undergoing a tumor biopsy and coadministration of the study drug(s). Section 8.8.1 Optional De Novo Tumor Biopsies: Added option for participant to submit resected tumor tissue obtained as

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		part of standard of care along with a time-matched PK sample. Allowing this option provides the study with more opportunities to obtain tissue samples while not increasing the number of procedures a participant must endure. Section 9.6 Data Monitoring Committee or Other Independent Oversight Committee: Given the clinical data available for other BRAF and MEK inhibitor combinations and the preclinical data for PF-07284890, an independent SRC with a charter is not warranted. The study will utilize a Dose Level Review Meeting consisting of participating investigators and members of the sponsor study team to determine dose escalation decisions. Other minor typographical changes and clarifications have been made throughout and Section 1.1 Synopsis has been updated for consistency with the body of the protocol.
Amendment 1	03 August 2020	Section 1.1 (Synopsis), Section 1.2 (Schema), and Section 1.3 (Schedule of Activities): Edits made to make text consistent with changes made throughout the body of the protocol. Section 1.3 (Schedule of Activities) and Section 10.15.11 (SoA DDI SubStudy): Updated main SoA footnote #30 and SoA DDI Substudy footnote #28 to explicitly outline additional questions that should be part of the AE assessment. Section 2.3 (Benefit/Risk Assessment): Added potential risks associated with

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		PF-07284890 and risks associated with approved BRAF inhibitors. Section 3 (Objectives and Endpoints): Corrected typographical error in Phase 1a Secondary Objective. Section 4.1 (Overall Design): Updated to clarify the parameters required to identify the starting dose of PF-07284890 in the combination dose escalation and to add statement related to continued treatment past disease progression. Section 4.1 (Overall Design) and Section 7.1 (Discontinuation of Study Intervention and Participant Discontinuation/Withdrawl): Included additional criteria to be met for participants to continue on study treatment past disease progression and added language related to survival follow-up activities. Section 4.2.1 (Rationale for Dose Escalation Approach) and Section 4.3.2.1 (Monotherapy Dose Escalation): Clarified criteria for 3-fold dose escalation of PF-07284890 and maximal increase allowed after reaching 300 mg dose. Section 4.3.2.3 (Intrapatient Dose Escalation): Clarified that binimetinib may be added to patients receiving PF-07284890 monotherapy if the dose combination has previously met BLRM/EWOC criteria in the combination dose escalation portion of the study. Section 4.3.3 (DLT Definition): Included additional DLT definitions and clarified existing DLTs.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		Section 5.1 (Inclusion Criteria): Modified Criteria 5, 6, and 10. Section 5.2 (Exclusion Criteria): Added Criterion 19 to exclude participants in dose escalation with a history of pneumonitis that required steroids or active pneumonitis. Modified Criteria 6, 8 and 10. Section 6.5.8 (Corticosteroids): Reduced maximal allowable steroid dosing to control/treat symptoms from brain metastases/primary brain tumor to maintain an acceptable risk:benefit profile and make consistent with practice guidelines. Section 6.6.4 (Dose Reductions): Guidance was added to Table 5 to address potential CNS effects. Section 8.1.1 (Tumor Response Assessments): Clarified timing of tumor assessments. Section 8.2.4 (Neurologic Examinations): Added neurological symptoms that should be assessed for during the neurologic exams. Symptoms added are consistent with CNS effects in DLT criteria. Section 10.17 (Appendix 17 Abbreviations): Updated to include acronyms added with amendment. Other minor typographical changes and clarifications have been made throughout.
Original protocol	12 June 2020	N/A

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative clarification letter.

10.21. Appendix 21: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
ΔQTcF	Change in corrected QT (Fridericia method)
ADL	activities of daily living
AE	adverse event
AESI	Adverse event of special interest
AIDS	acquired immunodeficiency syndrome
Alk Phos	alkaline phosphatase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT/APTT	activated Partial Thromboplastin Time
ARAF	A-Raf Proto-Oncogene
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATC	anaplastic thyroid cancer
ATP	adenosine triphosphate
AUC	area under the curve
AUC_{0-24}	area under the plasma concentration-time curve from time 0 extrapolated to 24 hours
AUC_{0-12}	area under the plasma concentration-time curve from time 0 extrapolated to 12 hours
AUC_{8}	area under the plasma concentration-time curve from 0 to 8 hours post-dose
AUC_{inf}	area under the plasma concentration-time curve from time 0 extrapolated to infinity
AUC_{last}	area under the plasma concentration-time curve from time 0 to the last time point of quantifiable concentration
$AUCss,\tau$	area under the plasma concentration-time curve over the dosing interval at steady state
$AUCsd,\tau$	area under the plasma concentration-time curve over the dosing interval from a single dose
AV	atrioventricular
BCRP	breast cancer resistance protein
BID	twice daily
BLRM	Bayesian logistic regression model
BP	blood pressure
bpm	beats per minute
β-HCG	beta human chorionic gonadotropin
BRAF	B-type Raf proto-oncogene
BRAFi	BRAF inhibitor

Abbreviation	Term
BSEP	Bile Salt Export Pump
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
C1D2	Cycle 1 Day 2
C1D8	Cycle 1 Day 8
C1D13	Cycle 1 Day 13
C1D15	Cycle 1 Day 15
C2-C6	Cycle 2 through Cycle 6
C2D1	Cycle 2 Day 1
C2D15	Cycle 2 Day 15
C3D1	Cycle 3 Day 1
C6D1	Cycle 6 Day 1
CAP	College of American Pathologists
CD4	cluster of differentiation 4
CDx	companion diagonostic
cfDNA	cell-free DNA
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL	clearance
CL/F	apparent oral clearance
CLcr	creatinine clearance
CLIA	Clinical Laboratory Improvement Amendments
CLss/F	apparent oral clearance at steady state
C_{max}	maximum observed concentration
C_{trough}	observed concentration at trough
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
Cp	plasma concentration
CPK	creatine phosphokinase
CR	complete response
CRAF	Raf-1 proto-oncogene
CRC	colorectal cancer
CRF	case report form
CRO	contract research organization
CRP	c-reactive protein
CRS	cytokine release syndrome
CSF	cerebrospinal fluid
CSR	clinical study report

Abbreviation	Term
$C_{ss,max}$	peak plasma concentration at steady state
$C_{ss,min}$	trough plasma concentration at steady state
CT	clinical trial
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CCI	[redacted]
CYP	cytochromes P450
DCR	disease control rate
DCT	data collection tool
DDI	drug-drug interaction
DFS	disease-free survival
DILI	drug-induced liver injury
DL	dose level
DLRM	Dose Level Review Meeting
DLT	dose-limiting toxicity
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DoR	duration of response
DU	dispensable unit
DVT	deep venous thrombosis
EC	ethics committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDP	exposure during pregnancy
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EOT	end of treatment
ERK	extracellular signal-regulated kinase
EU	European Union
EudraCT	European Clinical Trials Database
EWOC	escalation with overdose control
FDA	Food and Drug Administration (United States)
FFPE	formalin-fixed paraffin-embedded
FLAIR	fluid attenuated inversion recovery
FOB	functional observational battery
FSH	follicle-stimulating hormone
GBM	glioblastoma
GCP	Good Clinical Practice
Gd	gadolinium
GGT	gamma-glutamyl transferase

Abbreviation	Term
GI	gastrointestinal
GLP	Good Laboratory Practices
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
Hct	hematocrit
HCV	hepatitis C virus
CCI	[redacted]
hERG	human ether-a-go-go related gene
HFSR	hand-foot skin reaction
Hgb	hemoglobin
HGG	high-grade gliomas
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
IC_{70}	70% inhibitory concentration
IC_{90}	90% inhibitory concentration
ICD	informed consent document
ICH	International Council for Harmonisation
ICI	immune checkpoint inhibitor
ID	identification
IFN	interferon-gamma
IL	interleukin
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intent to treat
IV	intravenous
IWR	interactive Web-based response
IWRS	interactive Web-based response system
K_i	inhibitory constant
k_{inact}	maximum rate of enzyme inactivation
K_I	concentration of inhibitor which gives half the maximal rate of inactivation
LBBB	left bundle branch block

Abbreviation	Term
LDH	lactate dehydrogenase
LFT	liver function test
LGG	low-grade glioma
LH	luteinizing hormone
LLC-PK1	Lilly Laboratories cell porcine kidney 1
LLN	lower limit of normal
LSM	Limited Sampling Model
LV	left ventricular
LVEF	left ventricular ejection fraction
MAP	meta-analytic-predictive
MAPK	Mitogen-Activated Protein Kinase
MATE	multidrug and toxin extrusion
MDR1	multidrug resistance gene 1
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated and extracellular signal-regulated kinase
mITT	modified intent to treat
mRECIST	modified Response Evaluation Criteria in Solid Tumors
MR	Minor response
MRI	magnetic resonance imaging
MRP2	multidrug resistance-associated protein 2
MTD	maximum tolerated dose
n	number
N/A	not applicable
NCI	National Cancer Institute
NE	not evaluated
NGS	next-generation sequencing
NIMP	non-investigational medicinal product
NOAEL	no-observed-adverse-effect level
NSCLC	non-small cell lung cancer
NSR	non-significant risk
NTI	Narrow Therapeutic Index
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	optical coherence tomography; organic cation transporter
ORR	overall response rate
OS	overall survival
P(ORR)	probability of ORR
PA	pilocytic astrocytoma
PACL	protocol administrative change letter
PCR	polymerase chain reaction
PD	pharmacodynamics(s); disease progression
PE	pulmonary embolism, physical examination

Abbreviation	Term
CCI	
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PI	primary investigator
PK	pharmacokinetic(s)
PPI	proton pump inhibitor
PR	partial response
PR2D	Recommended Phase 2 Dose
PS	performance status
CCI	
PT	prothrombin time
PTC	papillary thyroid cancer
PTT	partial thromboplastin time
PVC	premature ventricular contraction/complex
PXA	pleiomorphic xanthoastrocytoma
Q6W	once every 6 weeks
Q9W	once every 9 weeks
Q12W	once every 12 weeks
QD	once daily
QTc	corrected QT
QTcB	corrected QT (Bazett method)
QTcF	corrected QT (Fridericia method)
Qual	qualitative
R_{ac}	accumulation ratio
RAF	rapidly accelerated fibrosarcoma
RANO	Response Assessment in Neuro-Oncology
RBC	red blood cell
RDE	recommended dose for expansion
RECIST	Response Evaluation Criteria in Solid Tumors
REML	Restricted Maximum Likelihood Estimation
RP2D	recommended phase 2 dose
RPED	retinal pigment epithelial detachment
RVO	retinal vein occlusion
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results program
sIL-2R	soluble interleukin 2 receptor
SoA	schedule of activities
SOC	standard-of-care

Abbreviation	Term
SOP	standard operating procedure
SRC	Safety Review Committee
SRS	sterotactic radiosurgery
SRSD	single reference safety document
STD	severely toxic dose
STD_{10}	severely toxic dose in 10% of the animals
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
TBili	total bilirubin
TK	toxicokinetics
TNF	tumor necrosis factor
T_{max}	time to maximum plasma concentration
$T_{ss,max}$	time to maximum plasma concentration at steady state
TME	tumor microenvironment
TTR	time to response
UGT	UDP-glucuronosyltransferase
ULN	upper limit of normal
US	United States
UV	ultraviolet
UVB	ultraviolet B
V_{ss}	volume of distribution at steady state
Vss/F	apparent volume of distribution at steady state
V_z/F	apparent volume of distribution
WBC	white blood cell
WBRT	whole brain irradiation
WHO	World Health Organization
WOCBP	woman of childbearing potential

10.22. Appendix 22: Tanner Staging

Pubic Hair: Male and Female

- Pubic Hair Stage 1: Prepubertal. The vellus over the pubis is similar to that on the abdomen. This hair has not yet developed the characteristics of pubic hair.
- Pubic Hair Stage 2: There is sparse growth of long, slightly pigmented downy hair, straight or only slightly curled, mainly at the base of the penis (in males).
- Pubic Hair Stage 3: The hair is considerably darker, coarser, and more curled. It is spread sparsely over the pubis.
- Pubic Hair Stage 4: The hair is adult in type, but the area over which it is present is smaller than in most adults. It has not yet spread to the medial thighs or along the linea alba (in males).
- Pubic Hair Stage 5: The hair is adult in quality and quantity and has the classical triangular distribution in females. It may spread to the medial surface of the thighs.

Breasts: Females

- Breast Stage 1: There is no development. Only the nipple is elevated.
- Breast Stage 2: The "breast bud" stage, the areola widens, slightly darkens, and elevates from the rest of the breast. A bud of glandular tissue is palpable below the nipple.
- Breast Stage 3: The breast and areola further enlarge, presenting a rounded contour. There is no change of contour between the nipple and areola and the rest of the breast. The diameter of breast tissue is still smaller than in a mature breast.
- Breast Stage 4: The breast continues to grow. The papilla and areola project to form a secondary mound above the rest of the breast.
- Breast Stage 5: The mature adult stage. The secondary mound disappears. Some females never progress to Stage 5.

Genitals: Males

- Genital Stage 1: Prepubertal. Penis, testes, and scrotum are about the same size and proportions as in early childhood. It is important to take into account whether the penis is uncircumcised when assessing penile growth, as the uncircumcised penis may appear larger than it really is.

- Genital Stage 2: Only the testes and scrotum have begun to enlarge from the early childhood size. The penis is still prepubertal in appearance. The texture of the scrotal skin is beginning to become thinner and the skin appears redder due to increased vascularization.

- Genital Stage 3: There is further growth of the testes and scrotum. The penis is also beginning to grow, mainly in length with some increase in breadth. It can be difficult to distinguish between Stages 2 and 3.

- Genital Stage 4: The penis enlarges further in length and breadth and the glans becomes more prominent. The testes and scrotum are larger. There is further darkening of the scrotal skin.

- Genital Stage 5: The penis, testes, and scrotum are adult in size and shape.

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