A PHASE 1, RANDOMIZED, OPEN-LABEL, 3-PERIOD, 4-SEQUENCE, CROSSOVER, SINGLE-DOSE STUDY TO COMPARE THE BIOAVAILABILITY OF ORALLY ADMINISTERED BOSUTINIB CAPSULES AND TO ESTIMATE THE EFFECT OF FOOD ON BOSUTINIB CAPSULE

Study Intervention Number:	PF-05208763
Study Intervention Name:	Bosutinib
US IND Number:	CCI
EudraCT Number:	N/A
ClinicalTrials.gov ID:	N/A
Protocol Number:	B1871062
Phase:	1

Brief Title: Evaluation of the Relative Bioavailability of Bosutinib Capsules Under Fed Condition and Estimation of Food Effect on Orally Administered Bosutinib Capsule

Document History

Document	Version Date
Amendment 1	16 June 2021
Original protocol	12 April 2021

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

Protocol Amendment Summary of Changes Table

Amendment 1 (16 June 2021)

Overall Rationale for the Amendment: Per request from the US Food and Drug Administration, exclusion criterion was revised.

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion Criteria	The following changes were made to exclusion criterion #11: • Add unit for eGFR; • Criteria updated to exclude participants with abnormal liver functions tests (ALT or AST) and serum (total and direct) bilirubin levels as well as amalyse and lipase level > ULN.	Revised based on the US Food and Drug Administration recommendation.
Section 10.2 Appendix 2: Clinical Laboratory Tests	Added amalyse and lipase in the chemistry column in Table 6.	Revised based on the US Food and Drug Administration recommendation.
Section 10.4.4 Contraception Methods	"Injectable" hormonal contraception associated with inhibition of ovulation was removed from **Highly Effective Methods That Are User Dependent** #6.	Updated to reflect the internal process update per Clinical Trial Facilitation Group Guidance.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Brief Title: Evaluation of the Relative Bioavailability of Bosutinib Capsules Under Fed Condition and Estimation of Food Effect on Orally Administered Bosutinib Capsule

Background and Rationale

Bosutinib (PF-05208763, Bosulif®) is an orally active Src/Abl kinase inhibitor indicated for the treatment of adult patients with Ph+ CML.

The pediatric development program for bosutinib is being conducted in accordance with the requirements of the EU PIP (000727PIP01-09-M03) and Pediatric Written Request (Amendment 2 dated 30 October 2019). In the pediatric development program for bosutinib, a capsule formulation has been developed as an age-appropriate dosage form and is available in 25, 50, and 100 mg dose strengths. The 25 and 50 mg capsule strengths are currently being used in the ongoing Phase 1/2 pediatric study (ITCC-054/COG AAML1921, also known as BCHILD) along with the commercial immediate release film-coated tablets of 100 and 500 mg strengths to allow for BSA-based dosing over a wide pediatric age range (1 to <18 years). The highest capsule strength of 100 mg for the age-appropriate dosage form is not currently being used in the pediatric study but is intended for commercial use. The purpose of this study is to support the bridging of current clinical 25 mg capsule and proposed commercial 100 mg capsule in healthy participants under fed condition and to evaluate the effect of food on bosutinib plasma pharmacokinetics following administration of the proposed commercial 100 mg capsule strength. The relative bioavailability study will be conducted in the fed state since bosutinib is currently labeled to be administered with food.

Objectives and Endpoints

Objectives	Endpoints
Primary:	**Primary:**
• To estimate the bioavailability of a single 100 mg capsule relative to four 25 mg capsules of bosutinib under fed condition in adult healthy participants. • To estimate the effect of a high-fat, high-calorie meal on the bioavailability of a single 100 mg capsule of bosutinib relative to fasted condition in adult healthy participants.	• Plasma AUC_{inf} and C_{max} for bosutinib. (AUC_{last} will be used as the primary estimate if AUC_{inf} cannot be reliably estimated).
Secondary:	**Secondary:**
• To evaluate the plasma PK of bosutinib when administered as capsule formulation to healthy participants under fasted and fed conditions. • To evaluate the safety and tolerability of bosutinib when administered as capsule formulation to healthy participants under fasted and fed conditions.	• Plasma AUC_{last}, T_{max}, CL/F, V_z/F and $t_{½}$ for bosutinib. • Safety laboratory tests and AE monitoring.

Overall Design

This will be a Phase 1, randomized, open-label, 3-period, 4-sequence, crossover, single-dose study in healthy participants.

Number of Participants

Approximately 28 participants (7 participants per sequence) will be enrolled to study intervention. If there are participants who withdraw or discontinue treatment and are considered to be non-evaluable with respect to the primary PK objective, additional participants can be enrolled at the discretion of the investigator upon consultation with the sponsor.

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and screening. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. 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

Treatment Sequence	Period 1	Washout	Period 2	Washout	Period 3
1 (n=7)	A	At least 14 days between successive bosutinib doses	B	At least 14 days between successive bosutinib doses	C
2 (n=7)	B		A		C
3 (n=7)	A		B		N/A
4 (n=7)	B		A		N/A

Treatment A: 1 × 100 mg capsule under fed condition.
Treatment B: 4 × 25 mg capsules under fed condition.
Treatment C: 1 × 100 mg capsule under fasted condition.

Since the mean plasma elimination $t_{½}$ of bosutinib is approximately 34 hours (range 18 to 55 hours), there will be a minimum 14-day washout period between successive bosutinib doses.

Blood samples for bosutinib PK analysis will be collected predose and at 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72, 96, and 144 hours post the bosutinib dose in each period.

Participants will be on the study for up to 13 weeks, including the screening and follow-up periods. Participants will be screened within 28 days prior to the first dose of the IP and if all entry criteria are fulfilled, the participants will report to the CRU on the day prior to Day 1 dosing (Day -1) of each period. For Treatments A and B, following an overnight fast of at least 10 hours, on Day 1 of each period, participants will receive a high-fat and high-calorie breakfast prior to dosing which will need to be completely consumed within 20 minutes. For Treatment C, participants will be dosed after an overnight fast of at least 10 hours. Bosutinib will be administered as intact capsules with approximately 240 mL of ambient temperature water. Intact capsules will be swallowed and not chewed.

Participants will be confined in the CRU for a minimum of 5 days until completion of the 72-hour PK sample collection on Day 4 in each period. Participants will be discharged at the discretion of the investigator. Participants may be eligible for discharge on Day 4 of each period at the discretion of the investigator following collection of bosutinib PK sampling at 72 hours post dosing and completion of all other required assessments. Alternatively, if participants remain in the CRU until the completion of the 96-hour PK sample collection, the Day 4 discharge assessments will be delayed until Day 5; if participants remain in the CRU until the completion of the 144-hour PK sample collection, the Day 4 or 5 discharge assessments will be delayed until Day 7. The investigator could choose to confine participants in the CRU and discharge them following the 96-hour PK sample on Day 5 or 144-hour PK sample on Day 7. Participants discharged on Day 5 will be required to return to the CRU for outpatient visit on Day 7 of each period. Alternatively, participants may be discharged from the CRU on Day 4, provided that they are able to return for outpatient visits on Days 5 and 7 during each treatment period. A follow-up phone call will be made at least 28 calendar days and up to 35 calendar days after the last administration of the study intervention to capture any potential AEs and confirm appropriate contraceptive usage.

Data Monitoring Committee or Other Independent Oversight Committee: No

Statistical Methods

Natural logarithm-transformed bosutinib AUC_{inf}, AUC_{last} and C_{max} will be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

The following 2 comparisons will be performed:

- Treatment B (Test) vs Treatment A (Reference)
- Treatment A (Test) vs Treatment C (Reference)

The plasma PK parameters AUC_{inf}, C_{max}, AUC_{last}, T_{max}, CL/F, V_z/F and $t_{½}$ of bosutinib will be summarized descriptively by treatment. For AUC_{inf}, AUC_{last} and C_{max}, a listing of the individual participant ratios (Test-Reference) will be provided for the 2 comparisons described above. Individual participant bosutinib PK parameters for AUC_{inf}, AUC_{last} and C_{max} will be plotted by treatment and overlaid with geometric mean. Bosutinib plasma concentrations will be listed and summarized descriptively by PK sampling time and treatment. Individual participant and median profiles of the concentration-time data will be plotted by treatment. For summary statistics and median plots by sampling time, the nominal PK sampling time will be used; for individual participant plots by time, the actual PK sampling time will be used.

AEs, ECG, BP, pulse rate, 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 pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

1.2. Schema

Not applicable.

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 procedure and assessment required for compliance with the protocol.

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

Table 1. Schedule of Activities

Visit Identifier[a]	Screening	Periods 1 through 3							Follow-up[b]	Early Termination/ Discontinuation
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 7[c]**	**28-35 Days**	
Hours After Dose			0[d]	24	48	72	96	144		
Informed consent	X									
Review inclusion/exclusion criteria	X	X[e]								
CRU confinement		X	→	→	→	X[f]	X[f]			
Outpatient visit to CRU[g]							X[f]	X[f]		
Demography (including measurement of height and weight)	X									
Medical history[h]	X	X								
Physical exam[i]	X	X						X		
BP, temperature and pulse rate[j]	X		X					X		X
Single 12-Lead ECG[k]	X		X					X		X
Safety laboratory[l]	X	X				X[f]	X[f]	X		X
Contraception check	X	X				X[f]	X[f]	X	X	X
FSH[m]	X									
Urine drug screening	X	X								

Table 1. Schedule of Activities

Visit Identifier[a]	Screening	Periods 1 through 3							Follow-up[b]	Early Termination/ Discontinuation
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 7[c]**	**28-35 Days**	
Hours After Dose			0[d]	24	48	72	96	144		
HIV, HBsAg, HCVAb, HBcAb	X									
COVID-19 questionnaire[n]	X	X					X	X		
COVID-19 testing[o]	X	X				X	X[f]	X		
COVID-19 check temperature[p]	X	X	X	X	X	X	X	X		X
Bosutinib administration[q]			X							
PK blood sampling			See Table 2 for detailed sampling times							X
Serious and nonserious AE monitoring	X	→	→	→	→	→	→	X	X	X
Prior/concomitant treatments	X	→	→	→	→	→	→	X	X	X
Retained Research Samples (Prep D1)[r]			X							
CRU discharge						X[f]	X[f]	X[f]		

Abbreviations used in this table may be found in Appendix 8: Abbreviations.

a. **Visit Identifier:** Day relative to start of study intervention, ie, bosutinib dosing (Day 1).
b. **Follow-up**: May occur via telephone and must occur at least 28 calendar days and up to 35 calendar days after the last administration of the study intervention.
c. **Day 7 (Period 3)**: Will be used as the end of study visit including at a minimum: safety labs, ECG assessment, BP, temperature and pulse rate assessments, the last PK sample collection, assessment of participant-reported AEs, a review of concomitant treatments, contraception check and COVID-19 testing, COVID-19 questionnaire, COVID-19 check temperature, and brief physical examination.
d. **Day 1 0h:** Activities to be performed predose.
e. **Review inclusion/exclusion criteria**: Period 1 only. Review any changes from Screening.
f. **CRU confinement:** Participants will be required to stay in the CRU for at least 72 hours following bosutinib dosing in each period and allowed to remain in the CRU through the collection of the 96-hour PK sample on Day 5 or 144-hour PK sample on Day 7. Participants may be eligible for discharge on Day 4 of each period at the discretion of the investigator following collection of bosutinib PK sampling at 72 hours post dosing and completion of all other required assessments. Alternatively, if participants remain in the CRU until the completion of the 96-hour PK sample collection, the Day 4 discharge assessments described above will be delayed until Day 5; if participants remain in the CRU until the completion of the 144 hour PK sample collection, the Day 4 or 5 discharge assessments described above will be delayed until Day 7.

Table 1. Schedule of Activities

Visit Identifier[a]	Screening	Periods 1 through 3							Follow-up[b]	Early Termination/ Discontinuation
Days Relative to Day 1	Day -28 to Day -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 7[c]	28-35 Days	
Hours After Dose			0[d]	24	48	72	96	144		

g. **Outpatient visit:** Participants who are discharged on Day 4 will be required to return to the CRU for outpatient visits on Days 5 and 7 during each treatment period. If participants are confined to the CRU until completion of the 96-hour PK sample and discharged on Day 5, they will be required to return to the CRU for outpatient visit on Day 7 during each treatment period.

h. **Medical history:** Include history of alcohol abuse, binge drinking, tobacco, electronic smoking device, licit and illicit drug use or dependence within 6 months of Screening. For Day -1, records would be reviewed or updated only.

i. **Physical exam:** Complete physical examination must either be conducted at Screening or upon admission of Period 1 only, and brief physical examination must be performed on Day 7 of each period. Brief physical examinations may be performed as appropriate at other times at the investigator's discretion if there are findings during the previous examination, new/open AEs, or upon discharge/early termination/discontinuation.

j. **Vital signs:** Collected at screening, at predose on Day 1 of Periods 1 and 3, and Day 7 of Period 3, or upon discharge/early termination/discontinuation.

k. **Single 12-Lead ECG:** Collected at screening, at predose on Day 1 of Period 1 and Day 7 of Period 3, or upon discharge/early termination/discontinuation.

l. **Safety laboratory:** Must be collected within 28 days prior to first administration (see Section 8.2.4). Safety laboratory assessments including urinalysis, hematology, and chemistry will be performed following at least 4 hours fasting. Safety laboratory samples will be collected prior to discharge/early termination/discontinuation or if the reason for discontinuation is related to an AE if applicable. Additional laboratory assessments may be required to evaluate potential cases of Hy's Law or AE as deemed necessary by the investigator. Refer to Table 6 in Section 10.2.

m. **FSH**: Will be performed at screening for postmenopausal (amenorrheic for at least 12 consecutive months) women only.

n. **COVID-19 questionnaire:** Check exposure to SARS-CoV-2, and COVID-19 related signs and symptoms. COVID-19 questionnaires on Days 5 and 7 are only required for outpatient visits during each period.

o. **COVID-19 testing:** The testing for COVID-19 pathogen by PCR will be performed on Day -1 and Day 4 of each period and other timepoints as deemed necessary to assess the safety at the discretion of the investigator. COVID-19 testings on Days 5 and 7 are only required for outpatient visits during each period.

p. **COVID-19 check temperature:** To be done during any visit to the CRU and at least daily during residence.

q. **Bosutinib administration**: Dosing under fed condition (Treatments A and B) or under fasted condition (Treatment C). Each period will be separated by at least a 14-day washout interval from bosutinib dosing in the prior period

r. **Prep D1 Retained Research Samples for Genetics:** Period 1 only. If Prep D1 is not collected on the designated collection day, collect at the next available time point when biospecimens are being collected in conjunction with a participant visit.

Table 2. Pharmacokinetic Sampling Schema

Visit Identifier	**Periods 1 through 3**														
Study Day	**1**								**2**		**3**		**4**	**5**	**7**
Hours After Dose	**0[a]**	**1**	**2**	**3**	**4**	**6**	**8**	**12**	**24**	**36**	**48**	**60**	**72**	**96**	**144**
Bosutinib administration	X														
PK blood sampling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. Predose PK samples collected any time prior to bosutinib dosing on Day 1 of each period.

2. INTRODUCTION

Bosutinib (PF-05208763) is an orally active Src/Abl kinase inhibitor indicated for the treatment of adult patients with Ph+ CML.

2.1. Study Rationale

The pediatric development program for bosutinib (Bosulif®) is being conducted in accordance with the requirements of the EU PIP (000727PIP01-09-M03) and Pediatric Written Request (Amendment 2 dated 30 October 2019). In the pediatric development program for bosutinib, a capsule formulation has been developed as an age-appropriate dosage form and is available in 25, 50, and 100 mg dose strengths. The 25 and 50 mg capsule strengths are currently being used in the ongoing Phase 1/2 pediatric study (ITCC-054/COG AAML1921, also known as BCHILD) along with the commercial immediate release film-coated tablets of 100 and 500 mg strengths to allow for BSA-based dosing over a wide pediatric age range (1 to <18 years). The highest capsule strength of 100 mg for the age-appropriate dosage form is not currently being used in the pediatric study but is intended for commercial use. The purpose of this study is to support the bridging of current clinical 25 mg capsule and proposed commercial 100 mg capsule in healthy participants under fed condition and also to evaluate the effect of food on bosutinib plasma pharmacokinetics following administration of the proposed commercial 100 mg capsule strength. The relative bioavailability study will be conducted in the fed state since bosutinib is currently labeled to be administered with food.

2.2. Background

2.2.1. Clinical Overview

Bosutinib (PF-05208763) is an orally active Src/Abl kinase inhibitor with potent antiproliferative and proapoptotic activity in cultured chronic myelogenous leukemia cells, and antiproliferative activity in primitive progenitor chronic myelogenous leukemia cells from patients. Bosutinib is approved in the US for the treatment of newly diagnosed CP Ph+ CML (400 mg once daily), and adult patients with CP, AP or blast phase Ph+ CML with resistance or intolerance to prior therapy (500 mg once daily); and received initial conditional marketing authorization in the EU for the treatment of adult patients CP, AP, and blast phase Ph+ CML previously treated with 1 or more TKIs, and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options, and an extended indication for patients with newly-diagnosed CP Ph+ CML. Bosutinib exhibits dose proportional increases in AUC and C_{max} over the oral dose range of 200 to 800 mg in both patients with Ph+ CML and healthy participants under fed conditions. Bosutinib absorption was relatively slow, with a median T_{max} of 6 hours, and mean $t_{½}$ was 33 to 39 hours after single oral doses, for healthy participants. Food increases plasma exposures of bosutinib and appears to improve tolerability of bosutinib. Bosutinib is recommended to be taken with food.

Bosutinib has shown an acceptable safety profile in the Phase 1, Phase 2, and Phase 3 studies. As of 11 January 2019, bosutinib has been administered as a single dose in 17 clinical pharmacology and biopharmaceutic studies in healthy participants. In general, AEs with bosutinib have included predominantly low-grade GI toxicities and general

symptoms such as fatigue and asthenia. Other frequent AEs include rash and increases in plasma levels of hepatic transaminases (ALT and AST). In the studies conducted in healthy participants, the most frequently reported TEAEs were GI disorders and nervous system disorders, including diarrhea, nausea, headache, and dizziness. The majority of these AEs were mild or moderate in severity.

Additional information for this compound may be found in the SRSD, which for this study is the IB[1].

2.3. Benefit/Risk Assessment

Bosutinib will not provide any clinical benefit to healthy participants. This study is designed primarily to generate PK data for bosutinib capsule of different strengths (25 mg clinical capsule and 100 mg age-appropriate dosage form) and when 100 mg age-appropriate dosage form administered with and without food as intact capsule to enable pediatric clinical development. In this study, bosutinib will be administered at single doses of 100 mg.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of bosutinib may be found in the current version of the IB, which is the SRSD for this study.

Overall, single 100 mg doses of bosutinib in healthy participants are expected to be safe and well tolerated in this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention Bosutinib		
Potential risk of decline in renal function (eGFR).	The potential risk is based on AEs reported in Ph+ CML patients as included in the IB.	Eligibility criteria have been selected to ensure that only appropriate participants are included in the study (see Section 5). Clinical laboratory results will be monitored on an ongoing basis. This is a single-dose study and renal effect with bosutinib is seen only with continuous dosing.
Potential risk of elevations in serum transaminases (ALT, AST).	The potential risk is based on AEs reported in Ph+ CML patients as included in the IB.	Eligibility criteria have been selected to ensure that only appropriate participants are included in the study (see Section 5). Clinical laboratory results will be monitored on an ongoing basis. Instructions for managing potential cases of drug-induced liver injury are provided (see Appendix 6). This is a single-dose

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention Bosutinib		
		study and hepatic effect with bosutinib is seen only with continuous dosing.
Potential risk to fetus.	Studies in animals have shown reproductive toxicity.	WOCBP and male participants who are unwilling or unable to use a highly effective method of contraception as defined in the study protocol will be excluded (See Sections 5.1, 5.2 and Appendix 4: Contraceptive and Barrier Guidance).

2.3.2. Benefit Assessment

For healthy participants in this study, no clinical benefit is expected.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to study participants, the potential risks identified in association with administration of bosutinib is clinically acceptable.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To estimate the bioavailability of a single 100 mg capsule relative to four 25 mg capsules of bosutinib under fed condition in adult healthy participants. • To estimate the effect of a high-fat, high-calorie meal on the bioavailability of a single 100 mg capsule of bosutinib relative to fasted condition in adult healthy participants.	• Plasma AUC_{inf} and C_{max} for bosutinib. (AUC_{last} will be used as the primary estimate if AUC_{inf} cannot be reliably estimated).
Secondary:	**Secondary:**
• To evaluate the plasma PK of bosutinib when administered as capsule formulation to healthy participants under fasted and fed conditions. • To evaluate the safety and tolerability of bosutinib when administered as capsule formulation to healthy participants under fasted and fed conditions.	• Plasma AUC_{last}, T_{max}, CL/F, V_z/F and $t_{½}$ for bosutinib. • Safety laboratory tests and AE monitoring.

4. STUDY DESIGN

4.1. Overall Design

This will be a Phase 1, randomized, open-label, 3-period, 4-sequence, crossover, single-dose study in approximately 28 healthy participants (7 participants per sequence). Participants will be randomized to 1 of the 4 sequences of treatment described in Table 3.

Table 3. Study design and treatment

Treatment Sequence	Period 1	Washout	Period 2	Washout	Period 3
1 (n=7)	A	At least 14 days between successive bosutinib doses	B	At least 14 days between successive bosutinib doses	C
2 (n=7)	B		A		C
3 (n=7)	A		B		N/A
4 (n=7)	B		A		N/A

Table 3. Study design and treatment

Treatment Sequence	Period 1	Washout	Period 2	Washout	Period 3

Treatment A: 1 × 100 mg capsule under fed condition.
Treatment B: 4 × 25 mg capsules under fed condition.
Treatment C: 1 × 100 mg capsule under fasted condition.

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and screening. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity after screening. 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.

Since the mean plasma elimination $t_{½}$ of bosutinib is approximately 34 hours (range 18 to 55 hours), there will be a minimum 14-day washout period between each successive bosutinib doses.

Blood samples for bosutinib PK analysis will be collected at the timepoints specified in the SoA.

Participants will remain in the study for up to 13 weeks, including the screening and follow-up periods. Participants will be screened within 28 days of the first dose of IP and if all entry criteria are fulfilled, the participants will report to the CRU on the day prior to Day 1 dosing (Day -1) of each period. For Treatments A and B, following an overnight fast of at least 10 hours, on Day 1 of each period, participants will receive a high-fat and high-calorie breakfast prior to dosing which will need to be completely consumed within 20 minutes. For Treatment C, participants will be dosed after an overnight fast of at least 10 hours. Bosutinib will be administered as intact capsules with approximately 240 mL of ambient temperature water. Intact capsules will be swallowed and not chewed.

Participants will be confined in the CRU for a minimum of 5 days until completion of the 72-hour PK sample collection on Day 4 in each period. Participants will be discharged at the discretion of the investigator. Participants may be eligible for discharge on Day 4 of each period at the discretion of the investigator following collection of bosutinib PK sampling at 72 hours post dosing and completion of all other required assessments. Alternatively, if participants remain in the CRU until the completion of the 96-hour PK sample collection, the Day 4 discharge assessments will be delayed until Day 5; if participants remain in the CRU until the completion of the 144 hour PK sample collection, the Day 4 or 5 discharge assessments will be delayed until Day 7. The investigator could choose to confine participants in the CRU and discharge them following the 96-hour PK sample on Day 5 or 144-hour PK sample on Day 7. Participants discharged on Day 5 will be required to return to the CRU for outpatient visit on Day 7 of each period. Alternatively, participants may be discharged from the CRU on Day 4, provided that they are able to return for outpatient visits on Days 5 and 7 during each treatment period. A follow-up phone call will be made at least

28 calendar days and up to 35 calendar days after the last administration of the IP to capture any potential AE and confirm appropriate contraceptive usage.

Tolerability and safety will be assessed for all treatments by monitoring AEs, ECGs, BP, pulse rate and safety laboratory data.

If there are participants who withdraw or discontinue treatment and are considered to be non-evaluable with respect to the primary PK objective, additional participants can be enrolled at the discretion of the investigator upon consultation with the sponsor.

4.2. Scientific Rationale for Study Design

The current study aims to determine the oral bioavailability of the age-appropriate 100 mg capsule relative to the 25 mg clinical capsules when orally administered under fed condition in healthy participants and also to characterize the effect of food on the plasma pharmacokinetics of bosutinib following administration of the proposed 100 mg commercial capsule.

The study is being designed as a crossover study to account for any period effects. Between each sequential dosing of bosutinib, a minimum of 14-day washout is proposed to minimize any residual bosutinib concentrations prior to start of the next period, as bosutinib has a plasma elimination $t_{½}$ of approximately 34 hours.

Bosutinib is currently labeled to be administered with food for improved tolerability. Therefore, the evaluation of relative bioavailability assessment in Treatments A and B will be conducted under fed condition using a high-fat, high-calorie meal[2,3].

Based on findings from animal studies and its mechanism of action, bosutinib can cause fetal harm when administered to a pregnant woman, therefore, females of child-bearing potential will be excluded from the study. In addition, the use of a highly effective method of contraception is required for male participants with female partners of child bearing potential (see Appendix 4).

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

CCI [redacted]

4.3. Justification for Dose

In the current study, bosutinib will be administered at a single dose of 100 mg (100 mg age-appropriate capsule formulation or four 25 mg clinical capsules) as intact capsules.

To achieve similar plasma exposure to the adult approved doses, the anticipated doses of bosutinib for administration in children and adolescents of 1-<18 years will be in the range of 50 to 600 mg based on BSA-based dosing. CCI [redacted] The 25, 50 and 100 mg capsules are manufactured from a common blend. The provision of a range of capsule and tablet strengths will provide the flexibility in dosing across this pediatric population. While the lower capsule strengths of 25 and 50 mg are currently used in the pediatric study along with the 100 and 400 mg tablets, the 100 mg age-appropriate capsule strength is planned to be available for commercial use in addition to the 100 mg clinical tablet. To bridge the clinical capsule and proposed commercial capsule formulation, this study will evaluate the relative bioavailability of 1 × 100 mg age-appropriate capsule, the highest capsule strength intended to be marketed, and 4 × 25 mg clinical age-appropriate capsule.

In addition, the 100 mg dose is also in the anticipated clinical dose range of 50 to 600 mg in pediatric patients.

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 visit and the investigator has reviewed the final safety data and determines that no additional evaluation is required.

The end of the study is defined as the date of the last visit of the last participant in the study.

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.

5.1. Inclusion Criteria

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

Age and Sex:

1. Female participants of non-childbearing potential and/or male participants must be 18 to 55 years of age, inclusive, at the time of signing the ICD.

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

Type of Participant and Disease Characteristics:

2. Male and female participants who are overtly healthy as determined by medical evaluation including a detailed medical history, complete physical examination, vital signs which include BP and pulse rate measurement, clinical laboratory tests, and ECG.

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

Weight:

4. BMI of 17.5 to 30.5 kg/m^2; and a total body weight >50 kg (110 lb).

Informed Consent:

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

5.2. Exclusion Criteria

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

Medical Conditions:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal (eg, ulcerative colitis, irritable bowel syndrome, Crohn's disease), cardiovascular, hepatic, psychiatric, neurological, dermatological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

2. Any condition possibly affecting drug absorption (eg, gastrectomy, cholecystectomy).

3. History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, HBcAb or HCVAb. As an exception, a positive HBsAb as a result of participant vaccination is permissible.

4. 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.

5. A history of hypersensitivity to the active compounds or to any inactive ingredients (excipients) contained in the formulations.

Prior/Concomitant Therapy:

6. Use of prescription or nonprescription drugs and dietary and herbal supplements within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention.

   Proton pump inhibitors must be discontinued at least 14 days prior to the first dose of study medication.

   Hormone replacement therapy must be discontinued at least 28 days prior to the first dose of study intervention.

   Refer to Section 6.8 for additional details.

Prior/Concurrent Clinical Study Experience:

7. Previous administration with an investigational drug within 30 days (or as determined by the local requirement) or 5 half-lives preceding the first dose of study intervention used in this study (whichever is longer).

Diagnostic Assessments:

8. A positive urine drug test.

9. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

10. Baseline 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, baseline QTcF interval >450 msec, complete LBBB, signs of an acute or indeterminate age- myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second or -third-degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If the baseline uncorrected QT interval is >450 msec, this interval should be rate corrected using the Fridericia method and the resulting QTcF should be used for decision making and reporting. If QTcF exceeds 450 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. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding participants.

11. Participants with **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat test, if deemed necessary:

    - eGFR (CKD-EPI) <90 mL/min/1.73 m^2;
    - AST **or** ALT level > ULN;
    - Serum (total and direct) bilirubin level > ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN;
    - Amylase and lipase level > ULN.

Other Exclusions:

12. History of alcohol abuse or binge drinking and/or any other licit or illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces [240 mL] beer, 1 ounce [30 mL] of 40% spirit or 3 ounces [90 mL] of wine).

13. Use of tobacco/nicotine containing products, electronic smoking device in excess of the equivalent of 5 cigarettes/day.

14. Male participants with partners currently pregnant; male participants able to father children who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of IP.

15. Blood donation (excluding plasma donations) of approximately 1 pint (500 mL) or more within 60 days prior to dosing.

16. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.

17. 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.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations.

- For Treatments A and B, following an overnight fast of at least 10 hours, a high-fat (approximately 50% of total caloric content of the meal), high-calorie (approximately 800 to 1000 calories) breakfast will be provided 30 minutes prior to bosutinib dosing on Day 1. This test meal should derive approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively. Participants should consume breakfast completely within 20 minutes, and bosutinib administered 10 minutes after. There will be no restrictions on intake of water prior to and after dosing.

- For Treatment C, following an overnight fast of at least 10 hours, participants will continue to fast until administration of bosutinib. Water will be permitted until 1 hour prior to bosutinib administration and may be consumed without restriction beginning 1 hour after bosutinib dosing on Day 1.

- Lunch will be provided approximately 4 hours after dosing on Day 1 of each period.

- Dinner will be provided approximately 9 to 10 hours after dosing on Day 1 of each period.

- An evening snack may be permitted.

- Participants will refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to the first dose of study intervention until collection of the final PK blood sample in each period.

- With the exception of the high-fat/high-calorie meal administered prior to dosing on Day 1 of each period for Treatments A and B, while participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.

5.3.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from caffeine-containing products for 24 hours prior to the start of dosing and during confinement in the CRU.

- Participants will abstain from alcohol for 24 hours prior (or as specified above for red wine) to admission to the CRU and continue abstaining from alcohol until collection of the final PK sample of each study period. Participants may undergo an alcohol urine test or blood alcohol test at the discretion of the investigator.

- Participants will abstain from the use of tobacco- or nicotine-containing products for 24 hours prior to dosing and during confinement in the CRU.

5.3.3. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

- In order to standardize the conditions on PK sampling days, participants will be required to refrain from lying down (except when required for BP, pulse rate, and ECG measurements), eating, and drinking beverages other than water during the first 4 hours after dosing.

5.3.4. 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 partner(s) from the permitted list of contraception methods (see Appendix 4 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 schedule of activities (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) considering that their risk for pregnancy may have changed since the last visit. 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 randomly assigned to study intervention/enrolled in the study. Screen failure data are collected and remain as source and are not reported to the clinical database.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened if prior reason for not meeting the eligibility criteria has been resolved.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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 intervention refers to bosutinib. The term IP may be used synonymously with study intervention.

6.1. Study Intervention(s) Administered

For this study, the study intervention is bosutinib, which will be administered as intact capsules.

Bosutinib 100 and 25 mg capsules will be supplied to the CRU in multi-dose containers and administered to participants in single dose labeled containers (in sufficient number to allow unopened containers to be kept as retains).

Bosutinib 100 and 25 mg capsules will be supplied to the CRU as packaged bottles and labeled according to local regulatory requirements. The bottles will be provided to the site for dispensing by the pharmacy. A brief description of the bosutinib formulations supplied in this study is provided in Table 4.

Table 4. Summary of Bosutinib Formulation

Description	Label Names	Material ID/ Lot Number	IP to Package	Route of Administration
PF-05208763 100 mg Size 0 (White OP/Swedish.Orange OP) hard	PF-05208763 100 mg Capsules	D1900094/ 20-DP-00370	100 mg × 1 bosutinib capsule	Oral
PF-05208763 25 mg Size 3 (White OP/Yellow OP) hard gelatin	PF-05208763 25 mg Capsules	D1900092/ 20-DP-00368	25 mg × 4 bosutinib capsules	Oral

6.1.1. Administration

IPs will be administered orally and according to the conditions described in the SoA section and Meals and Dietary Restrictions section 5.3.1of this protocol.

Treatments A and B (Fed): Following an overnight fast of at least 10 hours and after the collection of predose bosutinib PK sample on Day 1, participants will receive a high-fat, high-calorie breakfast approximately 30 minutes prior to dosing which should be completed within approximately 20 minutes as outlined in Section 5.3.1 (Meals and Dietary Restrictions). The participants will then receive IP at approximately 0800 hours (±2 hours), approximately 10 minutes after the completion of the breakfast.

Treatment C (Fasted): Following an overnight fast of at least 10 hours and after the collection of predose bosutinib PK sample on Day 1, participants will receive IP at approximately 0800 hours (±2 hours).

Investigator site personnel will administer IP during each period with ambient temperature water of approximately 240 mL. Participants will swallow the intact capsule whole, and will not manipulate or chew the capsule prior to swallowing.

In order to standardize the conditions on PK sampling days, all participants will be required to refrain from lying down (except when required for BP, pulse rate, and ECG

measurements), eating, and drinking beverages other than water during the first 4 hours after dosing.

6.2. Preparation, Handling, Storage, and 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 and is in the CRU local procedures.

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. 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.

7. Further guidance and information for the final disposition of unused study interventions are provided by CRU or as per local procedures. 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.

8. All retain capsules should be stored by the investigator site or with a third-party vendor. Sample retention is the responsibility of the entity performing the study.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery.

6.2.1. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the study intervention ready for administration or dispensing to the participant by qualified staff. Dispensing is defined as the provision of study intervention, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider, participant in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

Bosutinib capsules will be prepared at the CRU in the individual dosing containers by 2 operators, 1 of whom is an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist). Prepared doses will be provided in unit dose containers and labeled in accordance with Pfizer regulations and the clinical site's labeling requirements.

Only qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of IPs.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

The investigator will assign participant numbers to the participants as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the participant will receive the study treatment regimen assigned to the corresponding randomization number.

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. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

6.5. Dose Modification

Dose modification for bosutinib is not allowed.

6.6. Continued Access to Study Intervention After the End of the Study

No intervention will be provided to study participants at the end of their study participation.

6.7. Treatment of Overdose

For this study, any dose of bosutinib greater than 800 mg within a 24-hour time period will be considered an overdose.

Experience with bosutinib overdose in clinical studies to date was limited to isolated cases. There were no reports of any SAEs associated with bosutinib overdoses. Participants who may inadvertently receive an overdose of bosutinib in this study should be observed and given appropriate supportive treatment.

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

1. Contact the Pfizer 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 bosutinib (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 Pfizer Safety **only when associated with an SAE.**

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.

6.8. Concomitant Therapy

Use of prescription or nonprescription drugs and dietary and herbal supplements are prohibited within 7 days or 5 half-lives (whichever is longer) prior to the first dose of study intervention. Limited use of nonprescription medications that are not believed to affect participant safety or the overall results of the study may be permitted on a case-by-case basis following approval by the sponsor. Acetaminophen/paracetamol may be used at doses of ≤1 g/day.

Proton pump inhibitors must be discontinued at least 14 days prior to the first dose of study medication and is prohibited for the duration of the study.

Females using hormonal contraceptives or taking hormone replacement therapy may be eligible to participate in this study if they are willing to discontinue therapy at least 28 days prior to the first dose of study treatment and remain off hormonal therapy for the duration of the study. Depo-Provera® must be discontinued at least 6 months prior to the first dose of study treatment.

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 28 days before the first dose of study intervention will be documented as a prior treatment. Treatments taken after the first dose of study intervention will be documented as concomitant treatments.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Since this is a single-dose study, this section is not applicable.

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 include the following:

- Refused further study procedures;
- Lost to follow-up;
- Death;
- Study terminated by sponsor.

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/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

The participant will be permanently discontinued from the study intervention and 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 (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.

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 return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study;

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

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

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.

Participants will be screened within 28 days prior to administration of the study intervention to confirm that they meet the study population criteria for the study. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then participants do not require rescreening if the laboratory results obtained prior to first dose administration meet eligibility criteria.

A participant who qualified for this protocol but did not enroll from an earlier cohort/group may be used in a subsequent cohort/group without rescreening, provided laboratory results obtained prior to the first dose administration meet eligibility criteria for this study. In addition, other clinical assessments or specimen collections, eg, retained research samples, may be used without repeat collection, as appropriate.

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.

If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (pulse rate and BP) should be collected prior to the insertion of the catheter.

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.

The total blood sampling volume for individual participants in this study is approximately 210 mL. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

To prepare for study participation, participants will be instructed on the information in the Lifestyle Considerations and Concomitant Therapy sections of the protocol.

8.1. Efficacy Assessments

Not applicable.

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.

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

A brief physical examination will include, at a minimum, assessments of general appearance, the respiratory and cardiovascular systems, and participant-reported symptoms.

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

Height and weight will also be measured and recorded as per the SoA. For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Participants must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

Physical examination findings collected during the study will be considered source data and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.3.1 to 8.3.3.

8.2.2. Vital Signs

Supine BP will be measured with the participant’s arm supported at the level of the heart, and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Participants should be instructed not to speak during measurements.

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and pulse rate is acceptable; however, when done manually, pulse rate will be measured in the brachial/radial artery for at least

30 seconds. When the timing of these measurements coincides with a blood collection, BP and pulse rate should be obtained prior to the nominal time of the blood collection.

Additional collection times, or changes to collection times, of BP and pulse rate will be permitted, as necessary, to ensure appropriate collection of safety data.

8.2.2.1. Temperature

Temperature will be measured orally. No eating, drinking, or smoking is allowed for 15 minutes prior to the measurement.

8.2.3. Electrocardiograms

Standard 12-lead ECGs utilizing limb leads (with a 10 second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the heart rate and measures PR, QT, and QTc intervals and QRS complex. Alternative lead placement methodology using torso leads (eg, Mason-Likar) should not be used 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 at least 5 minutes in a supine position.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline (Period 1, Day 1 predose) measurements. Additional ECG monitoring will occur if a) a postdose QTc interval is increased by ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG. If either of these conditions occurs, then 2 additional ECGs will be collected approximately 2 to 4 minutes apart to confirm the original measurement. If the QTc values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a postdose QTc interval remains ≥60 msec from the baseline **and** is >450 msec; or b) an absolute QTc value is ≥500 msec for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTc intervals get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTc intervals do not return to less than the criterion listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

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 QTc value is prolonged, as defined above, repeat measurements may not be necessary if a qualified medical provider's interpretation determines that the QTc values are in the acceptable range.

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

8.2.4. 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 28 calendar 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.

Participants may undergo random urine drug testing at the discretion of the investigator. Drug testing conducted prior to dosing must be negative for participants to receive study intervention.

8.2.5. COVID-19 specific assessments

Participants will be tested for SARS-CoV-2 infection by PCR prior to being admitted to the clinic for confinement and a subsequent SARS-CoV-2 test will be performed after 4 days (ie, upon completion of 4 × 24 hours in house), or if they develop COVID-19 like symptoms. Additional testing may be required by local regulations or by the Principal Investigator.

8.3. Adverse Events, Serious Adverse Events, and Other Safety Reporting

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

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the Investigator or other healthcare providers (clinical signs, test results, etc).

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 (see Section 7.1).

During the active collection period as described in Section 8.3.1, 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, 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 28 calendar days after the last administration of 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.

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 for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant permanently discontinues or temporarily discontinues study 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 information on 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.

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 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.

Reporting of AEs and SAEs for participants who fail screening are subject to the CRF requirements as described in Section 5.4.

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 or 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 toward 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. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure, occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include exposure during pregnancy, exposure during breastfeeding, and occupational exposure.

Any such exposure to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- 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 EDP:
    - 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'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 28 days after the last dose.

- 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 preprocedure 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 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

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the CT SAE Report Form regardless of whether there is an associated SAE. Since the information about the occupational exposure 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 must be maintained in the investigator site file.

8.3.6. Cardiovascular and Death Events

Not applicable.

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

Not applicable.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

This section is not applicable because efficacy is not expected in the study population.

8.3.9. Medical Device Deficiencies

Not applicable.

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.

Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

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.**

8.4. Pharmacokinetics

Blood samples of approximately 3 mL each, to provide approximately 1.0 mL plasma, will be collected for measurement of plasma concentrations of bosutinib as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times 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 up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) 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. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing 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.

Blood samples collected in this study will be used to evaluate the plasma PK of bosutinib. CCI [redacted]

Genetic analyses will not be performed on these plasma samples. Participant confidentiality will be maintained.

Samples collected for measurement of plasma concentrations of bosutinib will be analyzed using a validated analytical method in compliance with applicable SOPs.

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.

CCI [redacted]

8.7. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.8. 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 a SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypotheses

Not applicable.

9.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
PK Concentration	The PK concentration population is defined as all participants randomized and treated who have at least 1 bosutinib concentration in at least 1 treatment period.
PK Parameter	The PK parameter analysis population is defined as all participants randomized and treated who have at least 1 of the bosutinib PK parameters of primary interest in at least 1 treatment period.
Safety	All participants randomly assigned to study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually received.

9.3. Statistical Analyses

The SAP will be developed and finalized prior to database lock 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. Pharmacokinetics Endpoint(s)

PK parameters for bosutinib following single dose administration will be derived from the concentration time profiles using non-compartmental methods as data permit. The various bosutinib PK parameters to be assessed in this study; their definition, and method of

determination are outlined in Table 5. In all cases, actual PK sampling times will be used in the derivation of PK parameters.

Table 5. Definitions of PK Parameters

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})	Linear-log trapezoidal method
AUC_{inf}[a]	Area under the plasma concentration-time curve from time zero extrapolated to infinite time	$AUC_{last} + (C_{last*}/k_{el})$ where C_{last}* is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis and k_{el} is the terminal phase rate constant calculated by a linear regression through at least 3 data points in the terminal phase of the log-linear concentration-time curve.
C_{max}	Maximum plasma concentration	Observed directly from the data
T_{max}	Time for C_{max}	Observed directly from the data as time of first occurrence
$t_{½}$[a]	Terminal elimination half-life	$Log_e(2)/k_{el,}$ only those data points judged to describe the terminal log-linear decline will be used in the regression.
CL/F[a]	Apparent clearance after oral dose	$Dose/AUC_{inf}$ after oral dose
V_z/F[a]	Apparent volume of distribution after oral dose	$Dose/(AUC_{inf}*k_{el})$ after oral dose

a. As data permits.

Natural logarithm-transformed $AUC_{inf,}$ AUC_{last} and C_{max} will be analyzed using a mixed effect model with sequence, period and treatment as fixed effects and participant within sequence as a random effect. Estimates of the adjusted mean differences (Test-Reference) and corresponding 90% CIs will be obtained from the model. The adjusted mean differences and 90% CIs for the differences will be exponentiated to provide estimates of the ratio of adjusted geometric means (Test/Reference) and 90% CIs for the ratios.

The following 2 comparisons will be performed:

- Treatment B (Test) vs Treatment A (Reference)
- Treatment A (Test) vs Treatment C (Reference)

The plasma PK parameters AUC_{inf}, C_{max}, AUC_{last}, T_{max}, CL/F, V_z/F and $t_{½}$ of bosutinib will be summarized descriptively by treatment. For AUC_{inf}, AUC_{last} and C_{max}, a listing of the individual participant ratios (Test-Reference) will be provided for the 2 comparisons described above. Individual participant bosutinib PK parameters for AUC_{inf}, AUC_{last} and C_{max} will be plotted by treatment and overlaid with geometric mean. Bosutinib plasma

concentrations will be listed and summarized descriptively by PK sampling time and treatment. Individual participant and median profiles of the concentration-time data will be plotted by treatment. For summary statistics and median plots by sampling time, the nominal PK sampling time will be used; for individual participant plots by time, the actual PK sampling time will be used.

If an individual participant has a known cause for biased estimate of a PK parameter (due for example to an event such as vomiting before all of the drug is absorbed in the body), this will be footnoted in summary tables and will not be included in the calculation of summary statistics or statistical analyses. Participants who vomited at or before 2 times of median T_{max} after drug administration may be excluded from PK analysis.

CCI [redacted]

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.

9.5. Sample Size Determination

A sample size of 28 participants will provide 90% confidence intervals for the difference between treatments of ±0.0786 and of ±0.1196 on the natural logarithmic scale for AUC_{inf}

and $\log_e C_{max}$ respectively with 90% coverage probability. The following table presents the width of 90% confidence interval for different estimated effects:

Parameter	Estimated Effect (100*Test/Reference)	90% CI	CI Width
AUC_{inf}	80%	0.7395, 0.8655	0.1260
	90%	0.8319, 0.9736	0.1417
	95%	0.8782, 1.0277	0.1496
	100%	0.9244, 1.0818	0.1574
	105%	0.9706, 1.1359	0.1653
	110%	1.0168, 1.1900	0.1732
	120%	1.1092, 1.2982	0.1889
C_{max}	80%	0.7098, 0.9017	0.1918
	90%	0.7985, 1.0144	0.2158
	95%	0.8429, 1.0707	0.2278
	100%	0.8873, 1.1271	0.2398
	105%	0.9316, 1.1834	0.2518
	110%	0.9760, 1.2398	0.2638
	120%	1.0647, 1.3525	0.2878

These calculations are based on estimates of within-subject standard deviations of 0.1560 and 0.2373 for $\log_e AUC_{inf}$ and $\log_e C_{max}$ respectively, as average intra-subject standard deviations obtained from previously completed bosutinib crossover studies with similar formulations and under similar conditions (clinical studies B1871016, B1871024, B1871035, and B1871061).

If there are participants who withdraw or discontinue treatment and are considered to be non-evaluable with respect to the primary PK objective, additional participants can be enrolled at the discretion of the investigator upon consultation with the sponsor.

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, 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.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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 GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (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 the ICH GCP guidelines that the investigator becomes aware of.

10.1.2. Financial Disclosure

Not applicable.

10.1.3. Informed Consent Process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. The participant 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 will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant 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.

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 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 was obtained before the participant was enrolled in the study and the date on which the written consent 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. Participants who are rescreened are required to sign a new ICD.

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 ID. 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. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use a DMC.

10.1.6. 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 patients) 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 data from these trials available 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.

10.1.7. 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.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

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, including definition of study critical data items and processes (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, virtual, or on-site monitoring), are provided in the data management plan maintained and utilized by the sponsor or designee.

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

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.

10.1.8. 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.

In this study, the CRF will serve as the source document. A document must be available at the investigative site that identifies those data that will be recorded on the CRF and for which the CRF will be the source document.

Definition of what constitutes source data and its origin can be found in the Source Document Locator, which is maintained by the sponsor's designee (Pfizer CRU).

Description of the use of the computerized system is documented in the Source Document Locator, which is maintained by the sponsor's designee (Pfizer CRU).

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

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 guidelines, and all applicable regulatory requirements.

10.1.9. 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 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 the ICH 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.

10.1.10. 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.

10.1.11. 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 CTMS.

To facilitate access to appropriately qualified medical personnel for study-related medical questions or problems, participants are provided with an Emergency Contact Card (ECC) at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, and (c) site emergency phone number active 24 hours/day, 7 days per week.

The ECC is intended to augment, not replace, the established communication pathways between the investigator, site staff, and study team. The ECC is to be used by healthcare professionals not involved in the research study only, as a means of reaching the investigator or site staff related to the care of a participant.

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 6. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin	BUN/urea and creatinine	Local Dipstick:	Urine drug screening[b]
Hematocrit	eGFR (CKD-EPI)	pH	COVID-19 testing
RBC count	Glucose (fasting)	Glucose (qual)	**At Screening Only**
MCV	Calcium	Protein (qual)	FSH[c]
MCH	Sodium	Blood (qual)	HBsAg
MCHC	Potassium	Ketones	HBcAb
Platelet count	Chloride	Nitrites	HCVAb
WBC count	Total CO_2 (bicarbonate)	Leukocyte esterase	HIV
Total neutrophils (abs)	AST, ALT	Urobilinogen	
Eosinophils (abs)	Total bilirubin	Urine bilirubin	
Monocytes (abs)	Alkaline phosphatase		
Basophils (abs)	Uric acid	Laboratory:	
Lymphocytes (abs)	Albumin	Microscopy[a]	
	Total protein		
	Amylase		
	Lipase		

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase.
b. The minimum requirement for drug screening includes cocaine, THC, opiates/opioidsbenzodiazepines, and amphetamines (others are site and study specific).
c. For confirmation of postmenopausal status only.

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 <u>Meeting</u> 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 condition 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 or 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 that 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.

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
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 admitted (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 or significant 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), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Is a 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 participant 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.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that 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.

10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the CT SAE Report Form to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious 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	All AEs/SAEs associated with exposure during pregnancy or breastfeeding **Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF.	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE). **
Environmental or occupational exposure to the product under study to a non-participant (not involving EDP or EDB).	None. Exposure to a study non-participant is not collected on the CRF.	The exposure (whether or not there is an associated AE or SAE) must be reported.***

* **EDP** (with or without an associated AE or SAE): any pregnancy information is reported to Pfizer Safety using CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.

** **EDB** is reported to Pfizer Safety using the CT SAE Report Form which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or Occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the CT SAE Report Form.

- When an AE or 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 or 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 or 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 or SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL. Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.

- 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.

- 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 or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or 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.

- New or updated information will be recorded in the originally submitted documents.
- 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) 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 off-line 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 off-line, 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 and Barrier 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 long-term and persistent basis) and agree to remain abstinent.

  OR

- Must agree to use contraception/barrier as detailed below:

  - Agree to use a male condom when having sexual intercourse with a woman of childbearing potential who is not currently pregnant.

- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners 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 a WOCBP (see definitions below in Section 10.4.3).

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a WOCBP.

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 not 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.
     - A 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 WOCBP partners of male participants 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 (eg, bilateral tubal ligation).

5. Vasectomized partner.

    - A 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

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation.

    - Oral;

    - Intravaginal;

    - Transdermal.

7. Progestogen-only hormone contraception associated with inhibition of ovulation.

    - Oral;

    - Injectable.

8. 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).

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[redacted]

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 “adaptors” 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 Hy's law cases, 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, or 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, 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 <u>May</u> Qualify as AEs

- 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 <u>May</u> Qualify as SAEs

- 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 SAEs

- 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: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
Abl	Abelson
abs	absolute
ADL	activity of daily living
AE	adverse event
ALT	alanine aminotransferase
AP	accelerated phase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{inf}	area under the plasma concentration-time curve from time zero extrapolated to infinite time
AUC_{last}	area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration
AV	atrioventricular
BBS	Biospecimen Banking System
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BSA	body surface area
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{last}	last quantifiable concentration
C_{last*}	predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
CL/F	apparent clearance after oral dose
C_{max}	maximum plasma concentration
CML	chronic myeloid leukemia
CO_2	carbon dioxide
COVID-19	coronavirus disease 2019
CP	chronic phase
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
CT	clinical trial

Abbreviation	Term
CTMS	clinical trial management system
DCT	data collection tool
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
EC	ethics committee
ECC	Emergency Contact Card
ECG	electrocardiogram
EDB	exposure during breastfeeding
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EudraCT	European Clinical Trials Database
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ID	Identification
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IV	intravenous
k_{el}	terminal phase rate constant
LBBB	left bundle branch block
LFT	liver function test
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration

Abbreviation	Term
MCV	mean corpuscular volume
msec	millisecond
N/A	not applicable
PCR	polymerase chain reaction
Ph+	Philadelphia chromosome positive
PIP	Pediatric Investigation Plan (EU)
PK	pharmacokinetic(s)
PR interval	time from the beginning of the P wave to the beginning of QRS complex
PT	prothrombin time
PVC	premature ventricular contraction
QRS	time from ECG Q wave to the end of the S wave corresponding to ventricle depolarization
QT	time from the beginning of the QRS complex to the end of the T wave
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
qual	qualitative
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCr	serum creatinine
SoA	schedule of activities
SOP	standard operating procedure
Src	sarcoma
SRSD	single-reference safety document
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	terminal elimination half-life
TBili	total bilirubin
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
T_{max}	time for C_{max}
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
US	United States
V_z/F	apparent volume of distribution after oral dose
WBC	white blood cell
WOCBP	woman of childbearing potential

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