Title Page

A MULTI-CENTER CONTINUATION STUDY EVALUATING AZACITIDINE WITH OR WITHOUT GLASDEGIB (PF-04449913) IN PATIENTS WITH PREVIOUSLY UNTREATED ACUTE MYELOID LEUKEMIA, MYELODYSPLASTIC SYNDROME OR CHRONIC MYELOMONOCYTIC LEUKEMIA

Study Intervention Number:	PF-04449913
Study Intervention Name:	Glasdegib
US IND Number:	CCI [redacted]
EudraCT Number:	CCI [redacted]
Protocol Number:	B1371019
Phase:	Phase 3

Short Title: Continuation Study Evaluating Azacitidine With Or Without Glasdegib (PF-04449913) In Patients With Previously Untreated AML, MDS or CMML.

Protocol Amendment Summary of Changes Table

Amendment 6 (02 February 2021)

Overall Rationale for the Amendment: Amendment 6 was necessary to enable (1) any participant in the NINT cohort who (in the investigator's clinical judgement) continues to derive clinical benefit may access study medication(s), and (2) participants previously enrolled in B1371012 who (in the investigator's clinical judgement) continue to derive clinical benefit can enroll in this study purely for continued access to study medication(s).

The protocol amendment summary of changes table for past amendment(s) is provided in Appendix 13.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Amendment 6	02 February 2021	This amendment has extensive changes throughout. An overview of the changes is as follows: (1) The title of the protocol has been updated to indicate only participants in the NINT cohort are continuing in the study starting with this amendment and moving forward that the study is unblinded and not placebo controlled, and participants with MDS or CMML may be included. (2) Efficacy assessments are no longer applicable in this Amendment (Section 3 and Section 8.1). (3) Statistical hypothesis and analysis applicable in previous amendments are no longer applicable in this Amendment. The only reporting is safety analyses (Section 3, Section 8.2, and Section 9). (4) The SOA found in Section 1.3 is replacing the previous SOA and has been revised to decrease the frequency of study procedures while maintaining appropriate assessment of patient safety. (5) INT cohort Population: Given the EDMC futility conclusion, standard of care therapy will be maintained until the end of the Consolidation phase. Experimental therapy will end in the post consolidation phase. (6) Restricted concomitant medications have been updated to further align with the information in the Investigator's Brochure.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		In addition, the following Letters to Investigators that were issued since the release of Amendment 5 are addressed as follows: Letter dated 12 Jun 2019: • The content of this letter was to clarify discrepancies between all versions of the protocol up to and including Amendment 5, and the Japanese translated version of the protocol. The Japanese-translated protocols had additional supportive instructions which did not appear in the English version. • The content of the letter is no longer applicable to this Amendment so is not incorporated in this amendment. The letter is attached to Appendix 13. Letter dated 1 Aug 2019: • The contraception language for male participants (which includes condom use) is included in Section 10.4.1. • The definition of postmenopausal women in Section 5.3.2 has been revised to not include "age 60 or older". • The change in one of the items in footnote for the SOA is no longer applicable in this protocol. Letter dated 09 Apr 2020: • New data capturing scenarios was communicated as a result of COVID-19. The data capture communicated in the letter was in effect in the trial conduct as of the date of the letter until the last participant completed amendment 5 of the protocol. The letter is incorporated in Appendix 13. • For this Amendment (Amendment 6) COVID-related measures are described in Appendix 7.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		Letter dated 21 Oct 2020: • The letter was issued to communicate that EDMC concluded that the intensive cohort would not meet the primary objectives of the study. The content of the letter is summarized in Section 2.2.1 of this amendment.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs.

TABLE OF CONTENTS

LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: Continuation Study Evaluating Azacitidine With or Without Glasdegib (PF-04449913) In Patients With Previously Untreated AML, MDS, or CMML.

Rationale

The B1371012 Parent Study (Amendment 7, 14 June 2018) is closing; however, participants in the MDS expansion cohort continue to demonstrate clinical benefit per their treating investigator, therefore are allowed to continue study intervention under Study B1371019 Protocol Amendment 6.

The B1371019 Protocol (Amendment 5, 12 April 2019) contained 2 cohorts: INT and NINT. The EDMC concluded that glasdegib offered no survival benefit in either the INT or NINT cohorts. There were no unexpected safety findings.

As Per Protocol B1371019 Amendment 5, Section 9, methodology for summary and statistical analyses are detailed in the SAP. Per the SAP, the goals of the interim analyses are to allow early stopping of the study for futility or efficacy. The EDMC reviewed data before the study was unblinded to investigators. Following the EDMC conclusion of futility for both cohorts, investigators and participants on the B1371019 study were unblinded to study treatment prior to starting Amendment 6 and no further study therapy would be given in the INT cohort once consolidation therapy completes. No further follow-up is required past the mandatory 28 days safety follow-up period. .

The purpose of Amendment 6 is to provide continued access to study intervention (azacitidine with or without glasdegib), and collection of safety data for eligible participants who continue to derive a clinical benefit from study treatment in studies B1371019 and B1371012.

1.1.1. INT Cohort Population (Investigator Instructions Communicated for Both Cohorts Following Amendment 5 Study Design)

Study participants - consolidation phase:

- Study participants must be contacted to review treatment therapy.
- May continue to receive consolidation treatment on study (with or without glasdegib) if in the investigator's clinical judgement the participant is deriving clinical benefit.
- Participants receiving consolidation treatment on the study (with or without glasdegib), must be re-consented by signing the IRB/EC approved consent addendum.
- Participants who continue study intervention must follow the protocol and have all procedures and assessments done. Once treatment ends, study participants will be followed for 28 days after last dose or until the date consent is withdrawn, then no further follow-up will be required.

- Once consolidation therapy ends, no further treatment will be given. Following that time, no further follow-up is required outside the 28 day safety reporting period (if consent is not withdrawn).

- Study participants – post consolidation phase:
  - Participants must end study treatment as soon as possible.
  - Participants must sign the IRB/EC approved consent addendum noting that post consolidation treatment will end.
  - Once post-consolidation therapy ends, no further treatment will be given. Participants will be followed for 28 days after last dose or until the date consent is withdrawn. Following that time, no further follow-up is required.

- Study participants -in follow-up (past 28 day safety reporting period):
  - Participants in either cohort (INT or NINT) must end follow-up procedures in the study as soon as possible.

Objectives and Endpoints

Objective	Endpoint
• To monitor the safety and tolerability of the investigational drugs in participants continuing study intervention from this study and participants originating from Study B1371012.	• All AEs and SAEs

Overall Design

Study design is as described in the B1371019 Protocol (Amendment 5, 12 April 2019) and Study B1371012 Protocol (Amendment 7, 14 June 2018). This is an open-label, continuation protocol for eligible NINT cohort participants enrolled in Study B1371019 or Study B1371012 eligible participants.

Number of Participants

A maximum of 34 participants from Study B1371019 and 3 participants originating from Study B1371012 who continue to derive clinical benefit per the treating investigators will be allowed continued access to the study intervention per Amendment 6.

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

Intervention Groups and Duration

- Azacitidine will be administered 75 mg/m^2/day for 7 days every 28 days as per local label or per the IP Manual (or SPC). Azacitidine may be administered by SC injection or IV infusion. Alternate dosing schedules to administer the 7 doses to accommodate participant and treatment center availability are allowed. The starting dose regimen will be the same as the most recent regimen received on the B1371019 or B1371012 study.

- Glasdegib will be orally administered daily (50, 75 or 100 mg) and continuously. The starting dose regimen will be the same as the most recent regimen received on the B1371019 or B1371012 study.

- Study intervention should be continued until objective disease progression or relapse, death, unacceptable toxicity, or participant refusal, whichever occurs first.

Data Monitoring Committee or Other Independent Oversight Committee: None as the EDMC has been retired after study futility conclusions prior to Amendment 6.

Statistical Methods

Detailed methodology for summary and statistical analyses of the safety data collected in this continuation study is outlined in Section 9.

The safety analyses of participants from Study B1371019 and participants originating from Parent Study B1371012 will be conducted separately and independently of each other.

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, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Visit Identifier Abbreviations used in this table may be found in Appendix 15.	**Screening**	**Day 1 (28 day cycles)**	**End of Treatment/Withdrawal**	**1-Month Safety Follow-up**[a]	**Notes**
Visit Window (days)		**-3/+14**	Obtain assessments if not completed in the last week.	**28 days after last dose**	
Data Collection Required on CRF					• ICD date of consent to Amendment 6, dosing information, AEs, and SAEs will be collected on the CRF. • Additional CRFs applicable as described in CRF Completion Guide.
Informed re-consent	X	X			
Study intervention					
Glasdegib		X			• Administered once daily, continuously, at approximately the same time each day • Treatment will be administered in 28-day cycles. Cycle duration may be extended to allow for toxicity resolution.
Azacitidine		X			• Azacitidine will be administered per local label or per IP manual (or SPC). • The starting dose regimen will be the same as the most recent regimen received on the B1371019 or B1371012 study • Treatment can be administered as a SC injection or IV infusion on Days 1-7 (±3 days) per local label. • Alternate dosing schedules to administer the 7 doses to accommodate participant and treatment center availability are allowed.
Serious and nonserious adverse event monitoring	X	X	X	X	• NCI CTCAE version 4.03 will be used.

Visit Identifier Abbreviations used in this table may be found in Appendix 15.	**Screening**	**Day 1 (28 day cycles)**	**End of Treatment/Withdrawal**	**1-Month Safety Follow-up[a]**	**Notes**
Visit Window (days)		**-3/+14**	Obtain assessments if not completed in the last week.	**28 days after last dose**	
Data Collection for the following will be in the Medical Records only (not required on CRF)					
Physical examination/Vitals/ECG	As per Standard of Care at the Study Site				
Clinical Laboratory Assessment	As per Standard of Care at the Study Site				
Pregnancy test/Contraception check	X	X	X		• Male participants with female partner of childbearing potential and female participants who are of childbearing potential will need to affirm that they meet the criteria for correct use of the selected methods of contraception. In addition, the investigator or his or her 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 the participant's partner. Refer to Appendix 4 for contraceptive guidance. Appropriate contraception usage for at least 180 days after the last dose of study intervention is to be confirmed
Disease Assessment	As per Standard of Care at the Study Site				
Concomitant treatment(s)		X	X	X	

a. Study participants will be followed (can be by telephone) for 28 calendar days after the last administration of study treatment to capture any AE/SAEs. There will be no further follow-up required after the 28-day safety reporting period.

2. INTRODUCTION

Protocol Amendment 6 is applicable to all eligible participants from Study B1371019 and participants originating from Study B1371012 continuing on study intervention with azacitidine with or without glasdegib.

Please refer to Protocol Amendment 5, 12 April 2019, for the full protocol design. Glasdegib (PF-04449913) is a novel small molecule inhibitor of the Sonic Hh pathway approved in the US by the FDA in 2018 to be used in combination with LDAC for the treatment of newly-diagnosed AML in adults who are 75 years of age or older or who have comorbidities that may preclude the use of intensive chemotherapy. Glasdegib is being developed for the treatment of hematologic malignancies.

Azacitidine (VIDAZA®) is a chemical analogue of the cytosine nucleoside whose mechanism of action involves inhibition of DNA methyltransferase at low doses, causing hypomethylation of DNA, and direct cytotoxicity in abnormal hematopoietic cells in the bone marrow through its incorporation into DNA and RNA at high doses, resulting in cell death. Use of azacitidine has been approved by the FDA and EMA.

2.1. Study Rationale

The B1371012 Parent Study (Amendment 7, 14 June 2018) is closing; however, participants in the MDS expansion cohort continue to demonstrate clinical benefit per their treating investigator, therefore are allowed to continue study intervention under Study B1371019 Protocol Amendment 6.

The B1371019 Protocol (Amendment 5, 12 April 2019) contained 2 cohorts: INT and NINT. The EDMC concluded that glasdegib offered no survival benefit in either the INT or NINT cohort. There were no unexpected safety findings.

Per Section 9 in Protocol B1371019 Amendment 5, detailed methodology for summary and statistical analyses are detailed in the SAP. Per the SAP, the goal of the interim analyses was to allow early stopping of the study for futility or efficacy. The EDMC reviewed data before the study was unblinded to investigators. Following the EDMC conclusion of futility for both cohorts, all investigators and participants on the B1371019 study were unblinded to study treatment prior to consenting for Amendment 6. No further study therapy would be given in the INT cohort once the standard of care consolidation chemotherapy is completed. No further follow-up is required past the mandatory 28 days safety follow-up period.

The purpose of Amendment 6 is to provide continued access to study intervention (azacitidine with or without glasdegib), and collection of safety data for eligible participants who continue to derive a clinical benefit from study intervention in studies B1371019 and B1371012.

2.2. Background

Study B1371019 was a randomized (1:1), double-blind, multicenter, placebo controlled study evaluating intensive chemotherapy with or without glasdegib (PF-04449913) or azacitidine with or without glasdegib in participants with previously untreated AML.

The goals of the interim analyses were to allow early stopping of the study for futility or efficacy. Following a planned interim analysis on 30 September 2020 for the Intensive cohort, Pfizer accepted the Committee's (EDMC) conclusion that in this trial the randomized arm (7+3 intensive chemotherapy [cytarabine + daunorubicin] + glasdegib) would not meet the primary objective of improving overall survival with respect to intensive chemotherapy alone. No unexpected safety issues were identified. Following EDMC review of the data and conclusion, investigators were unblinded to study treatment following the EDMC conclusion.

The Parent Study B1371012 was a multicenter open label Phase 1b study designed to evaluate the safety, efficacy, PK, and PD of glasdegib when combined with azacitidine in participants with previously untreated Higher Risk MDS, AML, and CMML. This Phase 1b study included 2 components: a safety lead-in cohort and an expansion phase with 2 cohorts. Since the B1371012 study is closing, participants who wish to continue treatment may do so on Study B1371019 Amendment 6.

This amendment describes the procedures for NINT cohort participants from B1371019 and B1371012 who elect to continue to receive study treatment. The Investigator is to follow the guidance below for the conduct of this study.

2.2.1. INT Cohort Population (Investigator Instructions Communicated for Both Cohorts Following Amendment 5 Study Design)

Study participants - consolidation phase:

- Study participants must be contacted to review treatment therapy.
- May continue to receive consolidation treatment on study (with or without glasdegib) if in the investigator's clinical judgement the participant is deriving clinical benefit.
- Participants receiving consolidation treatment on the study (with or without glasdegib), must be re-consented by signing the IRB/EC approved consent addendum.
- Participants who continue study intervention must follow the protocol and have all procedures and assessments done. Once treatment ends, study participants will be followed for 28 days after last dose or until the date consent is withdrawn, then no further follow-up will be required.
- Once consolidation therapy ends, no further treatment will be given. Following that time, no further follow-up is required outside the 28 day safety reporting period (if consent is not withdrawn).

Study participants – post consolidation phase:

- Participants must end study treatment as soon as possible.
- Participants must sign the IRB/EC approved consent addendum noting that post consolidation treatment will end.
- Once post-consolidation therapy ends, no further treatment will be given. Participants will be followed for 28 days after last dose or until the date consent is withdrawn. Following that time, no further follow-up is required.

Study participants -in follow-up (past 28 day safety reporting period):

- Participants in either cohort (INT or NINT) must end follow-up procedures in the study as soon as possible.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of glasdegib may be found in the investigator's brochure, which is the SRSD for this study. The SRSD for azacitidine is the package insert.

2.3.1. Risk Assessment

Risk assessment will be based on continued monitoring and clinical management as per GCP guidelines.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To monitor the safety and tolerability of the investigational drugs in participants continuing study intervention from this study and participants originating from Study B1371012	• All AEs and SAEs

4. STUDY DESIGN

4.1. Overall Design

Study design is as described in the B1371019 Protocol (Amendment 5, 12 April 2019) and Study B1371012 Protocol (Amendment 7, 14 June 2018). This is an open-label, continuation protocol for eligible NINT cohort participants enrolled in Study B1371019 or Study B1371012 eligible participants.

Following a planned interim analysis on 30 September 2020 for the INT cohort, Pfizer accepted the Committee's EDMC conclusion that glasdegib offered no survival benefit.

A maximum of 34 unblinded participants from Study B1371019 and 3 participants originating from Study B1371012 who continue to derive clinical benefit per the treating investigators will be allowed access to the study intervention per Amendment 6.

Amendment 6 is a continuation protocol for NINT cohort participants from Study B1371019 or Study B1371012. A maximum of 34 participants from Study B1371019 and 3 participants from Study B1371012 will continue to receive access to study intervention.

4.2. Scientific Rationale for Study Design

The scientific rationale is as described in the B1371019 Protocol (*Amendment 5, 12 April 2019*) and Study B1371012 Protocol (*Amendment 7, 14 June 2018*).

4.3. Justification for Dose

The doses administered to participants have already been established in the *B1371019 Protocol (Amendment 5, 12 April 2019)* and Study B1371012 Protocol (*Amendment 7, 14 June 2018*).

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 28-day safety follow-up period.

The end of this Study is defined as when all participants have discontinued from study treatment and have completed the Safety Follow-up Period. The safety follow-up period is defined as 28 days after last dose of last study drug. The study may also be terminated at any time at the discretion of the Sponsor.

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:

1. Any participant who continues to demonstrate clinical benefit (as determined by the Principal Investigator) from study treatment with azacitidine with or without glasdegib in this Study or from Study B1371012.
2. 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:

1. 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.
2. Female participants who are pregnant or breastfeeding (if continuing to receive study intervention);
3. Participant has been withdrawn from Study B1371019 and Study B1371012 for any reason (including INT cohort participants required to end study treatment).

5.3. Lifestyle Considerations

5.3.1. Contraception

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

5.3.2. Postmenopausal Defined

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high FSH level in the postmenopausal range (as per the reference range used by the laboratory) may be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods described in Section 10.4.3 if they wish to continue their HRT during the trial. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before trial enrollment.

5.3.3. Sunlight Exposure

Participants will be advised to report any reaction to sun exposed skin. In addition, special precautions will be taken to limit any potential photo irritation effect, by minimizing the participants' exposure to light including high intensity UVB sources such as tanning beds, tanning booths and sunlamps. Participants should be encouraged to apply sunscreen/sunblock daily.

5.4. Screen Failures

Participants who do not meet the inclusion/exclusion criteria will not be permitted to participate in Amendment 6. See Section 8 regarding screening evaluations.

6. STUDY INTERVENTION

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

For the purposes of this study, and per ICH guidelines, investigational product is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33). For the purpose of this study, the study interventions are glasdegib and azacitidine.

6.1. Study Intervention(s) Administered

Intervention Name	Glasdegib	Azacitidine
ARM Name (group of participants receiving a specific treatment (or no treatment)	NA	NA
Type	Drug	Drug
Dose Formulation	Tablet	Powder for injection
Unit Dose Strength(s)	25 mg or 100 mg tablet	100 mg/vial powder for 25 mg/mL suspension for injection
Dosage Level(s)	50, 75 or 100 mg daily	75 mg/m^2/day for 7 days every 28 days, or per the local label, IP Manual (or SPC) or if dose modified
Route of Administration	Oral	IV or SC
Use	Experimental	Other
IMP or NIMP	IMP	NIMP
Sourcing	Provided centrally by the sponsor	In US and Germany drug is sourced by the sites. All other countries, the drug is sourced by the Sponsor.
Packaging and Labeling	Study intervention will be provided in HDPE bottles. Each bottle will be labelled as required per country requirement.	Study intervention will be provided in sealed single-use colorless type 1 glass vials. Each vial will be labelled as required per country requirement.
Current/Former Name(s) or Alias(es)	PF-04449913	NA

6.1.1. Administration

Both glasdegib and azacitidine are administered in 28-day cycles. Cycle duration maybe extended beyond 28 days to allow resolution of toxicities related to study treatments. It is suggested that sites contact the participant via phone anytime there is a dose reduction to confirm that the participant adequately understands the dosing instructions.

Glasdegib will be self-administered by the participant at home, unless otherwise specified. Glasdegib will be administered orally with approximately 8 ounces (240 mL) of water, at the same time each day. Tablets must not be crushed or cut; they must be swallowed whole, not manipulated or not chewed prior to swallowing. If a participant forgets to take their dose at the regularly scheduled time, and if fewer than 10 hours have passed since the scheduled dosing time, that dose should be taken as soon as possible. If more than 10 hours have passed since the scheduled dosing time, the dose should be skipped, and the participant should continue their normal dosing schedule. If a participant misses a day's dose entirely, they must be instructed not to "make it up" the next day. If a participant vomits any time after taking a dose, they must be instructed not to "make it up," but to resume subsequent doses the next day as prescribed. If a participant inadvertently takes 1 extra dose during a day, the

participant should not take the next dose of glasdegib. The participant will be reminded to bring their bottle(s) and participant dosing diary into clinic to evaluate dosing compliance.

Participants requiring glasdegib dose reduction(s) will be administered multiples of 25 mg tablets and should continue taking the glasdegib at the same time each day at the dose prescribed by the Investigator (ie, 75 mg QD and 50 mg QD in the form of three or two 25 mg tablets respectively). In situations where clinical benefit is observed, glasdegib can be reduced below 50 mg QD upon Sponsor approval.

Dose modifications are discussed in Section 6.6.

Study intervention administration details will be recorded on the CRF.

6.1.2. Dosing Regimen

- Azacitidine will be administered 75 mg/m^2/day for 7 days every 28 days on Days 1-7 (±3 days) per local label or per the IP Manual (or SPC). Azacitidine may be administered by SC injection or IV infusion. Alternate dosing schedules to administer the 7 doses to accommodate participant and treatment center availability are allowed. The starting dose regimen will be the same as the most recent regimen received on the B1371019 or B1371012 study.

- Glasdegib 50, 75 or 100 mg will be orally administered daily and continuously. The starting dose regimen will be the same as the most recent regimen received on the B1371012 or B1371019 study.

Dose modifications are discussed in Section 6.6.

6.1.3. Treatment Duration

Treatment with the study treatment should be continued until objective disease progression or relapse, death, unacceptable toxicity, or participant refusal, whichever occurs first.

If glasdegib is permanently discontinued for reasons other than objective disease progression, participant refusal, or consent withdrawal, single agent treatment with azacitidine may be continued if, in the Investigator's judgment, a clinical benefit has been observed and following discussion between the investigator and sponsor.

In cases of unacceptable toxicity or pregnancy, the participant must be withdrawn from study treatment.

6.2. Preparation/Handling/Storage/Accountability

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

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study

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

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

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

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

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

7. See the package insert, or SPC for storage conditions of the azacitidine once reconstituted and/or diluted.

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

9. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

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

6.2.1. Preparation and Dispensing

6.2.1.1. Glasdegib

Glasdegib will be supplied by Pfizer Worldwide Research and Development as 25 mg and 100 mg tablets for oral administration. Supplies will be labelled according to local regulatory requirements.

Glasdegib will be packaged in HDPE bottles and should be handled with care. Each bottle will contain enough medication for a 28 day cycle of daily dosing, plus an additional amount to cover the time between site visits. Participants should be instructed to keep their medication in the bottles provided and not transfer it to any other containers and return the bottles to the site at the next study visit. Site personnel must ensure that participants clearly understand the directions for self-medication.

Study intervention should be dispensed using the IRT system (IWR) that provides a confirmation report containing the participant identification number and DU(s) or container number(s) assigned by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance. The confirmation report must be stored in the site's files.

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

6.2.1.2. Azacitidine

Azacitidine 25 mg/mL powder for suspension for injection will be used in this study. Please refer to the local package insert (or SPC) or the IP manual for detailed formulation, preparation and IV and SC administration instructions.

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

If azacitidine is provided by sponsor, it should be dispensed using the IRT system that provides a confirmation report containing the participant identification number and DU(s) or container number(s) assigned by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, practitioner, or pharmacist) as allowed by local, state, and institutional guidance. The confirmation report must be stored in the site's files.

6.3. Measures to Minimize Bias: Randomization and Blinding

Randomization and blinding are not applicable to this protocol amendment. Participants on Study B1371019 will be unblinded prior to dosing on Amendment 6.

6.4. Study Intervention Compliance

The investigator's site must maintain adequate records documenting the receipt, use, loss, or other disposition of the drug supplies. At each dispensing visit (Cycle 2 Day 1, Cycle 3 Day 1, etc. or when there is a dose reduction), all unused or partially used bottles must be returned by participants to the Investigator. The number of tablets returned by the participant at the end of the cycle will be counted, documented and recorded.

The sponsor or designee will provide guidance on the destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the study site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by sponsor or designee and all destruction must be adequately documented.

For azacitidine, the site should complete the required dosage Preparation Record located in the Investigational Product Manual. The use of the Preparation Record is preferred but it does not preclude the use of an existing appropriate clinical site documentation system. The existing clinical site's documentation system should capture all pertinent/required information on the preparation and administration of the dose including the methodology used to calculate the participant body surface area. This may be used in place of the Preparation Record after approval from the Sponsor.

6.5. Concomitant Therapy

Concomitant medications will be assessed at screening and all clinic visits.

Concomitant treatment considered necessary for the participant's well-being may be given at discretion of the treating physician. If a participant is offered, in accordance with the prevailing local guidelines, a COVID-19 vaccine, **it should be permitted**. This would be recorded as a concomitant medication in the medical records and standard AE collection and reporting processes would be followed.

6.5.1. Restricted or Prohibited Concomitant Medications

The following medications are not allowed during the active study treatment period:

- Agents used to treat AML or MDS;
- Investigational agents; This exclusion **does not apply** to any COVID-19 vaccine.
- CYP3A4/5 Strong Inducers: A drug-drug interaction study in healthy participants with the strong CYP3A4 inducer, rifampin, resulted in a 70% decrease in plasma exposures (AUC_{inf}) and a 35% decrease in peak plasma concentration (C_{max}) of a single 100 mg oral dose of glasdegib. Therefore, coadministration of glasdegib and strong CYP3A4/5 inducers is not permitted. A comprehensive list of strong CYP3A4/5 inducers is provided in Appendix 9. The Sponsor study team should be contacted if there is uncertainty whether a concomitant medication is contraindicated.
- CYP3A4/5 Moderate Inducers (Appendix 9): Avoid concomitant use of glasdegib with moderate CYP3A4 inducers. If use cannot be avoided, double the glasdegib

dose, as tolerated. After the moderate CYP3A4 inducer has been discontinued for 7 days, resume glasdegib dose taken prior to initiating the moderate CYP3A4 inducer.

The following medications have use restrictions during the active study treatment period:

- CYP3A4/5 Inhibitors: In a healthy volunteer study, ketoconazole, a potent CYP3A4/5 inhibitor, produced a 2.4 fold increase in plasma exposure and a 1.4 fold increase in peak plasma concentration of glasdegib. Therefore, a potential exists for drug-drug interactions with CYP3A4/5 inhibitors, and coadministration of glasdegib in combination with strong/ moderate CYP3A4/5 inhibitors is not recommended. Selection of concomitant medication with no or minimal CYP3A4/5 inhibition potential is recommended. Strong/moderate CYP3A4/5 inhibitors (Appendix 10 or Appendix 11) should be used with caution and only if considered medically necessary. If a moderate/strong CYP3A4/5 inhibitor is to be initiated in addition to glasdegib, the guidance provided in Appendix 6.
- Drugs with a known risk of TdP: Glasdegib has been shown to have the potential to prolong the QTc interval in preclinical studies. In the first in participant study as single agent, Grade 3 QTcF prolongation was observed at the highest doses tested (400 mg and 600 mg). While the glasdegib dose evaluated in this study is 100 mg, the concomitant administration of glasdegib and drugs with a known risk of Tdp should be avoided whenever possible. A list of such drugs is provided in Appendix 12. Use of these drugs is not recommended unless there are no alternatives. If a TdP drug is to be initiated in addition to glasdegib the guidance provided in Section 6.6.1 dose modifications for QT prolongation per Table 3 must be followed.
- QT prolonging medications (without a risk of TdP) should be avoided whenever possible.
- Concomitant administration of multiple moderate/strong CYP3A4/5 inhibitors, TdP drugs, and/or QT prolonging medications (without a risk of TdP) is not recommended.

6.5.2. Permitted Concomitant Medications

6.5.2.1. Best Supportive Therapy

BST administration is permitted according to institutional guidelines for all participants on study. BST will be provided by the site and may vary depending on the participant's signs and symptoms, site current practice, and country practice. It includes medications and supportive measures that may palliate disease related symptoms, improve quality of life and treat bacterial, fungal or viral infections. BST may include:

- Blood transfusions;
- Platelet transfusions;
- Antibiotics;
- Antifungal agents;
- Antiviral agents.

6.5.2.2. Hematopoietic Growth Factors

Hematopoietic growth factors (eg, G-CSF, GM-CSF) may be used according to local practice and guidelines.

6.5.2.3. Antiemetic and Antidiarrheal Therapy

Participants should be pre-medicated with anti-emetics for nausea and vomiting before each dose of azacitidine in all cycles according to local practice and guidelines.

Primary prophylaxis of diarrhea is permitted at the Investigator's discretion. The choice of the prophylactic drug is up to the investigator assuming the drug is not contraindicated as described in Section 6.5.1.

6.5.3. Surgery

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and glasdegib required to minimize the risk of impaired wound healing and bleeding has not been determined. Stopping glasdegib is recommended at least 7 days prior to surgery. Post-operatively, the decision to reinitiate glasdegib treatment is up to the Investigator with Sponsor approval and should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

6.5.4. HSCT

Participants who are eligible for HSCT will undergo HSCT per local standard of care.

For post disease remission HSCT, glasdegib will be interrupted at least 28 days before HSCT (date of stem cell infusion).

Glasdegib may be resumed 30-60 days post HSCT once there is ANC engraftment, no ≥ Grade 2 ongoing GVHD, and no ongoing SAEs in the judgement of the investigator.

6.6. Dose Modification

Every effort should be made to administer the study drug treatment according to the planned dose and schedule.

In the event of Grade 3 or Grade 4 non-hematologic, study-treatment-related toxicity, dosing may be delayed and/or dose reduced. The glasdegib dose should be reduced 1 dose level at a time, in increments of 25 mg (75 mg QD, 50 mg QD, in the form of 3 or 2 x 25 mg tablets respectively). Glasdegib does not need to be delayed or dose reduced for hematologic, study-treatment-related toxicity.

Glasdegib may be interrupted or permanently discontinued for any reason as per GCP. Glasdegib should be permanently discontinued if:

interruptions are for more than 28 consecutive days when not required by the protocol (ie, HSCT period).

Dose escalations will not be allowed following glasdegib/placebo dose reductions. Dose modifications may occur in 3 ways:

Within a cycle: Dosing interruption until adequate recovery followed by dose reduction (if required) of glasdegib during a given treatment cycle.

Between cycles: The next treatment cycle may be delayed if toxicity from the preceding cycle persists.

In the next cycle: Dose reduction may be required based on toxicities experienced in the previous cycle.

When chemotherapy is given, a Cycle is determined by chemotherapy administration schedule. A Cycle is 28 days, but will be extended if there are dose delays or modifications in the chemotherapy backbone.

6.6.1. Glasdegib

Glasdegib does not need to be delayed or dose reduced for hematologic toxicity deemed unrelated/unlikely related to glasdegib by the investigator.

Participants experiencing Grade 3 or 4 nonhematological toxicities potentially attributable to glasdegib should have their glasdegib treatment interrupted regardless of when it occurs in the cycle until the toxicity resolves or returns to baseline or ≤Grade 1, as described in Table 2. If these parameters have not been met following >28 consecutive days of dose interruption, glasdegib should be permanently discontinued. If glasdegib treatment is permanently discontinued, participants may continue single agent treatment with azacitidine, if according to the investigator's judgment a clinical benefit has been observed, and following discussion between the investigator and the sponsor.

Appropriate follow-up assessments should be implemented until adequate recovery (toxicity resolves or returns to baseline) occurs.

Depending on when the adverse event resolved, treatment interruption may lead to the participant missing all subsequent planned doses of glasdegib within the cycle. If the AE leading to treatment interruption recovers within the same cycle, recommencement of dosing in that cycle is allowed. The need for a dose reduction at the time of treatment resumption should be based on the criteria outlined in Table 2, unless specifically agreed otherwise following discussion between the investigator and the sponsor. If a dose reduction for glasdegib is applied in the same cycle, the participant may need to receive a new supply of drug. Glasdegib doses omitted for toxicity will not be replaced within that cycle (eg, cycles will not be prolonged beyond the 28 days to make up for any missed glasdegib doses during that cycle).

Glasdegib may be interrupted or permanently discontinued for any reason as per GCP. Glasdegib should be permanently discontinued if interruptions are for more than 28 consecutive days. In the event of glasdegib treatment interruption for reasons other than

treatment-related toxicity (eg, elective surgery) for a duration >28 days, the details of treatment resumption will be determined in consultation with the Sponsor.

Dose reduction of glasdegib by 1 or, if necessary, 2 dose levels (Table 1) will be allowed depending on the type and severity of toxicity encountered. **NOTE**: In the specific situations where clinical benefit is observed, glasdegib can be reduced below 50 mg QD upon discussion with the sponsor. All dose modifications/adjustments must be clearly documented in the participant's notes and eCRF.

Once the glasdegib dose has been reduced, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Dose re-escalation is not allowed. Deviations from any of the dose modifications must be discussed and agreed with the sponsor Medical Monitor.

Table 1. Available Dose Levels

Glasdegib (mg QD)
100
75
50
25 *

* **NOTE**: If clinical benefit is observed, glasdegib may be reduced below 50 mg QD following Sponsor approval.

Dose modifications for treatment-related- non-hematologic toxicities (excluding QTc prolongation, muscle spasms, and myalgia) are outlined in Table 2.

Table 2. Dose Modifications for Non Hematologic Toxicities (Excluding QTc Prolongation, Muscle Spasms, and Myalgia)

Toxicity (NCI CTCAE version 4.03)	Glasdegib
≥ Grade 3 toxicity (nausea, vomiting, and/or diarrhea must persist at ≥ Grade 3 (despite maximal appropriate medical therapy) to require dose modification).	Hold glasdegib until toxicity has recovered to baseline or ≤ Grade 1. **First episode**: Decrease by 1 dose level **Second episode**: Decrease by 1 dose level **Third episode**: Permanently discontinue
Potential drug induced liver injury/Hy's Law (as defined in Appendix 5).	Interrupt glasdegib dosing. If an alternative cause is found, restarting of glasdegib at the same dose may be considered.
Confirmed drug induced liver injury/Hy's Law (as defined in Appendix 5).	Glasdegib should be permanently discontinued.

Participants will be closely monitored for potential cardiovascular symptoms per standard of care. Appropriate monitoring should include clinical examinations, vital signs, routine ECGs, and AE monitoring. In case of QTcF prolongation, concomitant conditions such as electrolyte imbalances, hypoxia, or use of medications affecting the QT interval should be ruled out and/or corrected. In case of clinically significant toxicities, glasdegib administration should be interrupted and the dose reduced as indicated in Table 3.

Concomitant administration of glasdegib with strong/moderate CYP3A4/5 inhibitors (Appendix 10 or Appendix 11) and drugs with known risk of TdP (Appendix 12) is not recommended due to the potential for drug-drug interaction to prolong the QTc interval. However, if it is medically necessary for participants to use these medications please refer to Appendix 6 for monitoring procedures. Investigators must be aware of the QTcF prolonging potential of all medications that participants on study are taking, and should take appropriate action when clinically indicated. Given the potential for QTcF prolongation, the measurement and immediate correction of electrolyte abnormalities such as potassium and magnesium, and of other reversible causes of QTcF prolongation such as hypoxia, are especially important. In the event that the QTcF interval is prolonged beyond 480 msec (CTCAE v. 4.03 ≥Grade 2), Table 3 must be referenced and actioned. Additional ECG and cardiac consultation should be obtained if clinically indicated.

Table 3. Glasdegib Dose Modifications for mQTcF Prolongation

CTCAE v 4.03	Grade 1	Grade 2	Grade 3	G ade 4
ECG QTc interval prolonged*	450-480 msec	481-500 msec	≥501 msec on at least 2 separate ECGs	QTc ≥501 msec or >60 msec change from baseline and TdP or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia

*The severity of QTc prolongation assessment is to be determined by calculating a mean QT of 3 consecutive ECGs performed approximately 2 minutes (but no longer than 5 minutes) apart using the Frederica correction method (mQTcF).
**Please see Section 8.3.9 for protocol specified SAE reporting requirement of Grade 3 or 4 mQTcF prolongation.

Category	Action	Grade 1	Grade 2	Grade 3	Grade 4
General management	Assess electrolyte levels and supplement as clinically indicated		X	X	X
	Review and adjust concomitant medications with known QTc interval-prolonging effects		X	X	X
ECG monitoring	Monitor ECGs at least weekly for 2 weeks following resolution of mQTcF prolongation to ≤480 msec		X	X	X
Initial glasdegib action	Discontinue and do not rechallenge				X
	Interrupt treatment			X	
	Continue treatment at same dose	X	X		

Table 3. Glasdegib Dose Modifications for mQTcF Prolongation

Resume glasdegib dosing	If **no** prior glasdegib dose interruption related to QTcF prolongation has occurred, resume at a reduced dose of 75 mg once daily when mQTcF interval returns to within 30 msec of baseline or ≤480 msec			X	
	If **1** prior glasdegib dose interruption related to QTcF prolongation has occurred, resume at a reduced dose of 50 mg once daily when mQTcF interval returns to within 30 msec of baseline or ≤480 msec			X	
Discontinue glasdegib permanently	If **2** prior glasdegib dose interruptions related to QTcF prolongation have occurred			X	

Dose modifications for glasdegib in case of drug class related AEs are outlined in Table 4.

Table 4. Dose Modifications for Glasdegib in Case of Drug Class Related AEs

Muscle Spasms or Myalgia	**Grade 1**	**Grade 2**	**Grade 3**
Glasdegib	Continue at same dose level. Administer oral rehydration solutions containing electrolytes.[a] Consider other appropriate interventions (eg, anti-spasmodics) as per institutional guidelines. Evaluate levels of: CK, Vit B6, Vit D, ferritin, transferrin and electrolytes (Na, K, Mg, Ca and P).[b] If CK is elevated, evaluate urine and serum myoglobin, CK isoenzymes, and serum creatinine.	Continue at same dose level. Administer oral re-hydration salts containing electrolytes.[a] Consider other appropriate interventions (eg, anti-spasmodics) as per institutional guidelines. Evaluate levels of: CK, Vit B6, Vit D, ferritin, transferrin and electrolytes (Na, K, Mg, Ca and P).[b] If CK is elevated, evaluate urine and serum myoglobin, CK isoenzymes, and serum creatinine. If event persists, hold dose until resolution to Grade ⩽1.	Hold dose. Administer oral re-hydration salts containing electrolytes.[a] Consider other appropriate interventions (eg, anti-spasmodics) as per institutional guidelines. Evaluate levels of: CK, Vit B6, Vit D, ferritin, transferrin and electrolytes (Na, K, Mg, Ca and P).[b] If CK is elevated, evaluate urine and serum myoglobin, CK isoenzymes, and serum creatinine. Upon resolution to Grade ⩽ 1, restart study treatment at next lower dose level. If the event does not resolve within 3 weeks to Grade ⩽1, at the discretion of the Investigator the dose may be restarted at the next lower

Table 4. Dose Modifications for Glasdegib in Case of Drug Class Related AEs

Muscle Spasms or Myalgia	Grade 1	Grade 2	Grade 3
		Upon resolution, restart at prior dose, or for prolonged muscle spasms, consider reducing dose by one dose level.	dose level or the participant may be permanently discontinued from study treatment.

a. Electrolyte replacement drinks should include Na, K, Mg, Ca and P. Consideration should be given to ensuring adequate hydration prior to bedtime, and whenever fluid intake is decreased for a prolonged duration.
b. Labs may be drawn between protocol visits.
In the event of alopecia or dysgeusia, investigator discretion should be applied with respect to dose interruption and/or dose reduction of glasdegib as preliminary analysis of available clinical data suggests that these events are not dose dependent.

6.6.2. Azacitidine

For azacitidine dose modification, refer to the local package insert (or SPC) or IP Manual.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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

- Objective disease progression or relapse
- Participant refusal
- Consent withdrawal
- Unacceptable toxicity
- Pregnancy
- Initiation of another anti-cancer treatment

If study intervention is definitively discontinued, the participant will not remain in the study for further evaluation. See the SoA for data to be collected at the time of discontinuation of study intervention.

Note that discontinuation of study intervention does not represent withdrawal from the study. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for 28 calendar days after the last dose of study treatment administration. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

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

7.2. Participant Discontinuation/Withdrawal From the Study

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

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- Progressive Disease;
- Pregnancy;
- Global deterioration of health status;
- Unacceptable toxicity
- Withdrawal of consent;
- Significant noncompliance.

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

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

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

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

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

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed. Refer to Appendix 7 for alternative measures during the COVID-19 pandemic.

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.

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

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

8.1. Efficacy Assessments

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/Vital Signs/ECG

Physical examinations and vital signs will be performed as per standard of care at the Study Center but will not be recorded in the CRF. A finding representing an AE will be recorded in the AE CRF as described in Section 8.3.1.

ECG values of potential clinical concern are listed in Appendix 6: ECG.

8.2.2. Clinical Safety Laboratory Assessments

Timing and frequency of clinical safety laboratory tests are to be performed per standard of care and at any time during the study to assess any perceived safety issues. Appendix 2 includes laboratory tests recommended to determine dosing eligibility.

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

8.2.3. Pregnancy Testing

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

8.2.4. Disease Assessment

Imaging and tumor assessments will be conducted per the site's standard of care and will not be recorded in the CRF. A finding representing an AE will be recorded in the AE CRF as described in Section 8.3.1.

8.2.5. One Month Safety Follow-up

For follow-up procedures see SoA and Section 8.

Study participants will be followed for 28 calendar days after the last administration of study treatment to capture any potential AEs leading to permanent study treatment discontinuation/SAEs.

In the event a participant is unable to return to the clinic for the follow-up visit, telephone contact with the participant to assess AEs and treatment is expected. If laboratory assessments are needed to follow up unresolved AEs, retrieval of assessments performed at an institution local to the participant is acceptable. No further follow-up is required after the 28 day safety reporting period.

8.3. Adverse Events and Serious Adverse Events

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

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see Section 7.1).

Each participant/parent/legal guardian/legally authorized representative 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 and Pfizer concurs with that assessment.

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

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

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

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

8.3.1.1. Reporting SAEs to Pfizer Safety

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

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

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

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

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

If a participant begins a new anticancer therapy, the recording period for nonserious AEs ends at the time the new treatment is started; however, SAEs must continue to be recorded on the CRF during the above-indicated active collection period. Note that a switch to a commercially available version of the study intervention is considered as a new anticancer therapy for the purposes of SAE reporting.

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

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

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

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

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

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

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted

should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 5 terminal half-lives 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 preprocedural test findings are conclusive for a congenital anomaly and the findings are reported).

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

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

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

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

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

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

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

8.3.5.3. Occupational Exposure

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

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

8.3.6. Cardiovascular and Death Events

Not applicable.

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

Lack of efficacy is reportable to Pfizer Safety **only** if associated with an SAE. Refer to Appendix 3, Section 10.3.1 for additional information.

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.
- If the dose administered is >120% of the scheduled dose, <80% of the scheduled dose, or dosed outside a 28 day window. If the drug is administered as incorrect formulation (ie, pills cut in half instead of administering a lower dosage tablet, pills crushed and administered via feeding tube without direction from Sponsor).

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF.

Medication errors will NOT include:

- Cases where commercial backbone drug was used instead of supplied stock;
- Cases where the wrong lot number of drug was dispensed;
- Dose modifications outlined in Section 6.6.

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.**

8.3.11. Protocol-Specified Serious Adverse Events

All cases of Grade 3 or 4 mQTcF prolongation regardless of causality and treatment arm must be reported as an SAE for up to 28 calendar days after the last dose of study drug administered. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections, and will be handled as SAEs in the safety database.

8.4. Treatment of Overdose

For this study, an overdose is considered >120% of the scheduled dose of study treatment.

There is no specific treatment for an overdose. Management of glasdegib overdose should include symptomatic treatment and ECG monitoring.

In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.

2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities for at least 5 half-lives or 28 calendar days after the overdose of study intervention (whichever is longer). Closely monitor the participant for any AEs/SAEs.

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

4. Overdose is reportable to Safety **only when associated with an SAE.**

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

8.5. Pharmacokinetics

No pharmacokinetic assessments will be conducted.

8.6. Pharmacodynamics

No pharmacodynamic assessments will be conducted.

8.7. Genetics

No genetic assessments will be conducted.

8.8. Biomarkers

No biomarker assessments will be conducted.

8.9. Immunogenicity Assessments

No immunogenicity assessments will be conducted.

8.10. Health Economics

No health economic assessments will be conducted

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined below.

9.1. Statistical Hypotheses

Not applicable.

9.2. Sample Size Determination

Not applicable.

9.3. Analysis Sets

9.3.1. Safety Analysis Set

The safety analyses of participants from Study B1371019 and participants originating from Parent Study B1371012 will be conducted separately and independently of each other.

The safety analysis set will include all participants who receive at least one dose of study treatment after consenting to this Protocol Amendment 6.

9.4. Statistical Analyses

This section is a summary of the planned statistical analyses of the safety endpoints.

9.4.1. Safety Endpoint(s)

All participants who receive any study treatment (safety analysis set) will be included in the summaries and listings of safety data. Overall safety profile and tolerability of azacitidine or glasdegib + azacitidine will be characterized by type, frequency, severity, seriousness, timing, and relationship to study therapy of AEs.

AEs will be classified using the MedDRA classification system. The severity of the toxicities will be graded according to the NCI CTCAE version 4.03.

In all summaries, emphasis will be placed on TEAEs (events occurring from Amendment 6 consent up to last dose + 28 days). AEs will be summarized by the frequency of participants experiencing TEAEs corresponding to body systems and MedDRA preferred term and by worst NCI CTCAE (version 4.03) grade.

AEs leading to permanent discontinuation of any study treatment, and SAEs will be considered with special attention. AE reporting, including SUSARs, will be carried out in accordance with applicable local regulations. Reasons for discontinuation from study treatment will be summarized by the frequency of participants with each reason described.

Descriptive statistics ie, number of non-missing values and number of missing values (ie, n [missing]), mean, median, SD, minimum, maximum and first and third quartile (Q1 and Q3) for treatment duration ([last dose date - first dose date after Amendment 6 consent +1]/7) will be provided.

9.5. Interim Analyses

The interim analyses were performed prior to Amendment 6.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

The EDMC was retired after study futility conclusions prior to Amendment 6.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

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

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

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

The investigator will be responsible for the following:

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

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

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

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

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

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

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

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

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

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date 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 or the participant's legally authorized representative.

10.1.4. Data Protection

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

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

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

10.1.5. Dissemination of Clinical Study Data

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

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

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in 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 available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

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

10.1.6. Data Quality Assurance

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

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

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

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s) and

their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

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

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

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

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

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

10.1.7. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The

investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the clinical monitoring plan.

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

10.1.8. Study and Site Start and Closure

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

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

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

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

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

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

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

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

10.1.9. Publication Policy

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

The investigator agrees to refer to the primary publication in any subsequent publications such as secondary manuscripts, and submits all manuscripts or abstracts to the sponsor 30 days before submission. This allows the sponsor to protect proprietary information and to

provide comments and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study- or Pfizer intervention-related information necessary for the appropriate scientific presentation or understanding of the study results.

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

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

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

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

10.1.10. Sponsor’s Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

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

10.2. Appendix 2: Clinical Laboratory Tests

Clinical laboratory tests will be conducted as per standard of care at the individual Study site. They will not be collected in the CRF. The laboratory tests described in the table below are recommended to determine participant dosing eligibility. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues. As per the investigator's evaluation, if any laboratory test is determined as an AE or SAE, this should be reported to the Sponsor as described in Appendix 3.

Hematology	**Blood Chemistry**	**Urinalysis (microscopic analysis[a])**	**Coagulation Tests**
Hemoglobin	ALT	If urine dipstick is positive for protein, perform U/A with microscopy. If U/A with microscopy shows ≥2+ protein, collect 24-hour urine for protein.	aPTT
Platelets	AST	Urine dipstick positive for urine blood: Collect a U/A with microscopy (unless dipstick hematuria can be explained by local bleeding such as menses).	INR
WBC	Alk Phos	Specific Gravity	
Neutrophils	Sodium	pH	
Lymphocytes	Potassium	Protein	
Monocytes	Magnesium	Glucose	
Eosinophils	Chloride	RBC	
Basophils	Calcium	WBC	
Blast Count	Total Bilirubin	Ketones	
	BUN or Urea	Leukocyte Esterase	
	Creatinine	Nitrite	
	Uric Acid		
	Glucose (non-fasting)		
	Albumin		
	Total Protein		
	Phosphorus		
	LDH		
	CPK		
	Bicarbonate		

a. Only if urine dipstick is positive for blood, protein, nitrites, or leukocyte esterase. if the dipstick is positive for blood, protein, nitrites and leukocytes, suggestive of UTI, then send sample for laboratory microscopy and culture.

Investigators must document their review of each laboratory safety report.

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 conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
• The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or SAE if they fulfill the definition of an AE or SAE and meet the requirements as per Section 8.3.8.1. Also, “lack of efficacy” or “failure of expected pharmacological action” does not constitute an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen. • Worsening of signs and symptoms of the malignancy under study should be recorded as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.

10.3.2. Definition of SAE

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

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

a. Results in death

b. Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

- Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the active collection period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF, and as an SAE with CTCAE Grade 5 (see the Assessment of Intensity section).
- If the HIV-related disease has a fatal outcome during the study or within the active collection period, then the event leading to death must be recorded as an AE on the CRF and as an SAE.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

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

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs on the CT SAE Report Form to Pfizer Safety. 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, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study based on NCI CTCAE Version 4.03:

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.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

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

10.3.4. Reporting of SAEs

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

10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 180 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s) ***plus*** an additional 90 days (a spermatogenesis cycle):

- Refrain from donating sperm.

PLUS either**:**

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

OR

- Must agree to use contraception/barrier as detailed below.
  - Agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.
- Use of an additional highly effective contraceptive method with a failure rate of <1% per year as described below in Section 10.4.4 for a female partner of childbearing potential.

10.4.2. Female Participant Reproductive Inclusion Criteria

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:
  - Is not a WOCBP (see definitions below in Section 10.4.3).
  - OR
  - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described below during the intervention period and for at least 180 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
  - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with high user dependency, as described below during the intervention period and for at least 180 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention(s). In addition, a second effective method of contraception, as described below, must be used. The investigator should evaluate

the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

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

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

10.4.3. Woman of Childbearing Potential

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

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

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

1. Premenarchal.
2. 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.

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

- Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

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

Highly Effective Methods That Have Low User Dependency

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

Highly Effective Methods That Are User Dependent

1. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral;
    - Intravaginal;
    - Transdermal;
    - Injectable.
2. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.
3. Sexual abstinence:
    - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be

evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

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

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

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

Potential Cases of Drug-Induced Liver Injury

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

LFTs are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

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

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

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.
- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).
    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

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

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

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

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

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

10.6. Appendix 6: 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

- 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 patients 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 patients 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
• QTcF prolongation >500 msec. • 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.

10.7. Appendix 7: Alternative Measures During Public Emergencies

The alternative study measures described in this section are to be followed during public emergencies, including the COVID-19 pandemic. This appendix applies for the duration of the COVID-19 pandemic globally and will become effective for other public emergencies only upon written notification from Pfizer.

Use of these alternative study measures are expected to cease upon the return of business as usual circumstances (including the lifting of any quarantines and travel bans/advisories).

Details for entering the data in the CRF are described in the CRF Completion Guidelines.

10.7.1. Telehealth Visits

In the event that in-clinic study visits cannot be conducted, every effort should be made to follow up on the safety of study participants at scheduled visits per the Schedule of Activities or unscheduled visits. Telehealth visits may be used to continue to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit:

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer Section 8.3 and Appendix 3.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4 and Section 10.7.2.1 of this appendix regarding pregnancy tests.

Study participants must be reminded to promptly notify site staff about any change in their health status.

10.7.2. Alternative Facilities for Safety Assessments

10.7.2.1. Laboratory Testing

If a study participant is unable to visit the site for protocol-specified safety laboratory evaluations, testing may be conducted at a local laboratory if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. The following safety laboratory evaluations may be performed at a local laboratory:

- Hematology
- Chemistry

- Coagulation: PT/INR, PTT/aPTT
- Urinalysis

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records.

If a participant requiring pregnancy testing cannot visit a local laboratory for pregnancy testing, a home urine pregnancy testing kit with a sensitivity of at least 25 IU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome should be documented in the participant's source documents/medical records. Confirm that the participant is adhering to the contraception method(s) required in the protocol.

10.7.3. Study Intervention

If the safety of a trial participant is at risk because they cannot complete required evaluations or adhere to critical mitigation steps, then discontinuing that participant from study intervention must be considered.

Study intervention may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for the study intervention. Pfizer does not permit the shipment of study intervention by mail. The tracking record of shipments and the chain of custody of study intervention must be kept in the participant's source documents/medical records.

The following is recommended for the administration of study intervention for participants who have active [confirmed (positive by regulatory authority-approved test) or presumed (test pending/clinical suspicion)] SARS-CoV2 infection:

- For symptomatic participants with active SARS-CoV2 infection, study intervention should be delayed for at least 14 days from the start of symptoms. This delay is intended to allow the resolution of symptoms of SARS-CoV2 infection.
- Prior to restarting treatment, the participant should be afebrile for 72 hours, and SARS-CoV2-related symptoms should have recovered to ≤ Grade 1 for a minimum of 72 hours. Notify the study team when treatment is restarted.
- Continue to consider potential drug-drug interactions as described in Section 6.5 for any concomitant medication administered for treatment of SARS-CoV2 infection.

10.7.4. Adverse Events and Serious Adverse Events

If a participant has COVID-19 during the study, this should be reported as an AE or SAE and appropriate medical intervention provided. Study treatment should continue unless the

investigator/treating physician is concerned about the safety of the participant, in which case temporary or permanent discontinuation may be required.

It is recommended that the investigator discuss temporary or permanent discontinuation of study intervention with the study medical monitor.

10.8. Appendix 8: France Contrat Unique

1. GCP Training

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

2. Study Intervention

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

3. Urgent Safety Measures

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

4. Termination Rights

   Pfizer retains the right to discontinue development of PF-04449913 at any time.

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

10.9. Appendix 9: Strong and Moderate CYP3A4/5 Inducers

Strong CYP3A4/5 Inducers	
Inducer	**Therapeutic Class**
Rifampin	Antibiotics
Ivosidenib	Antineoplastics
Rifapentine	Antibiotics
Avasimibe	Antilipedimics
Phenytoin	Anticonvulsants
Carbamazepine	Anticonvulsants
Phenobarbital	Anticonvulsants
Enzalutamide	Antiandrogens
Apalutamide	Antiandrogens
St. John's Wort	Herbal Medications
Mitotane	Antineoplastics
Lumacaftor	Cystic Fibrosis Treatments
Moderate CYP3A4/5 Inducers	
Inducer	**Therapeutic Class**
Semagacestat	Alzheimer's Treatments
Bosentan	Endothelin Receptor Antagonist
Genistein	Food Product
Thioridazine	Antipsychotics
Nafcillin	Antibiotics
Daclatasvir and asunaprevir and beclabuvir	Antivirals
Lopinavir	Protease Inhibitor
Tipranavir and ritonavir	Protease Inhibitors
Modafinil	Psychostimulant
Efavirenz	NNRTI
Etravirine	NNRTI
Lersivirine	NNRTI
Talviraline	NNRTI
PF-06282999	Myeloperoxidase Inactivators
Telotristat ethyl	Antidiarrheals
Lesinurad	Antigout and Uricosuric Agents
Dabrafenib	Kinase Inhibitors
Cenobamate	Anticonvulsant
Rifabutin	Antibiotic
Lorlatinib	Kinase Inhibitor
Elagolix	GnRH Antagonist

Source: University of Washington Drug Interaction Database. "Copyright University of Washington 2005-2018, UW Metabolism and Transport Drug Interaction Database, Oct2020".

10.10. Appendix 10: Strong CYP3A4/5 Inhibitors

Strong CYP3A4/5 Inhibitors	
Inhibitor	**Therapeutic Class**
Ketoconazole	Antifungal
Itraconazole	Antifungal
Voriconazole	Antifungal
Posaconazole	Antifungal
Troleandomycin	Antibiotics
Clarithromycin	Antibiotics
Telithromycin	Antibiotics
Mibefradil	Calcium Channel Blocker
Conivaptan	Diuretics
Nefazodone	Antidepressants
Cobicistat	--
Indinavir/Ritonavir	Protease Inhibitors
Tipranavir/Ritonavir	Protease Inhibitors
Ritonavir	Protease Inhibitors
Indinavir	Protease Inhibitors
Nelfinavir	Protease Inhibitors
Saquinavir	Protease Inhibitors
Saquinavir/Ritonavir	Protease Inhibitors
Lopinavir/Ritonavir	Protease Inhibitors
Telaprevir	Antivirals
Boceprevir	Antivirals
Danoprevir/Ritonavir	Antivirals
VIEKIRA PAK	Antivirals
Elvitegravir/Ritonavir	Treatment of AIDS
LCL161	Cancer treatment
Idelalisib	Kinase Inhibitors
Ribociclib	Kinase Inhibitors
Grapefruit Juice DS	Food Products
Mifepristone	Antiprogestins
Ceritinib	Kinase Inhibitor
Tucatinib	Kinase Inhibitor

Source: University of Washington Drug Interaction Database. “Copyright University of Washington 2005 2018. UW Metabolism and Transport Drug Interaction Database, October 2020.”

10.11. Appendix 11: Moderate CYP3A4/5 Inhibitors

Moderate CYP3A4/5 Inhibitors	
Inhibitor	**Therapeutic Class**
Fluconazole	Antifungals
Ravuconazole	Antifungals
Isavuconazole	Antifungals
Erythromycin	Antibiotics
Ciprofloxacin	Antibiotics
Diltiazem	Calcium Channel Blockers
Verapamil	Calcium Channel Blockers
Dronedarone	Antiarrhythmics
Aprepitant	Antiemetics
Casopitant	Antiemetics
Netupitant	Antiemetics
Tofisopam	Benzodiazepines
Cyclosporine	Immunosuppressant
Schisandra sphenanthera	Herbal Medication
ACT-178882	Renin Inhibitor
Cimetidine	H2 Receptor Antagonist
FK1706	Central Nervous System Agent
Faldaprevir	Antivirals
Letermovir	Antivirals
Crizotinib	Kinase Inhibitor
Nilotinib	Kinase Inhibitor
Atazanivir/Ritonavir	Protease Inhibitor
Darunavir	Protease Inhibitor
Darunavir/Ritonavir	Protease Inhibitor
Atazanavir	Protease Inhibitor
Fedratinib	Kinase Inhibitor
Imatinib	Antineoplastic agent
GSK2647544	Alzheimer's Disease & Dementia Treatments
Grapefruit Juice	Food Products
Duvelisib	Kinase Inhibitor
ACT-539313	Hypnotic - Sedative
Lefamulin	Antibiotic
Istradefylline	Other Antiparkinsonians
Voxelotor	Hemoglobin S Polymerization Inhibitor

Source: University of Washington Drug Interaction Database. “Copyright University of Washington 2005-2018. UW Metabolism and Transport Drug Interaction Database, October 2020.”

10.12. Appendix 12: List of Drugs with Known Risk of Torsade de Pointes

The following drugs are known to have the risk of Torsade de Pointes due to QTc prolongation and their current use in combination with glasdegib is not recommended. If any of these drugs are considered to be medically necessary, then they should be used with caution in combination with glasdegib.

Generic Name	Drug Class	Therapeutic Use	Route
Aclarubicin (Only on Non US Market)	Anti-cancer	Cancer	injection
Amiodarone	Anti-arrhythmic	Abnormal heart rhythm	oral, injection
Anagrelide	Phosphodiesterase 3 inhibitor	Thrombocythemia	oral
Arsenic trioxide	Anti-cancer	Leukemia	injection
Astemizole (Removed from Market)	Antihistamine	Allergic rhinitis	oral
Azithromycin	Antibiotic	Bacterial infection	oral, injection
Bepridil (Removed from Market)	Anti-anginal	Heart pain	oral
Chloroquine	Anti-malarial	Malaria infection	oral
Chlorpromazine	Anti-psychotic/Anti-emetic	Schizophrenia, nausea, many others	oral, injection, suppository
Cilostazol	Phosphodiesterase 3 inhibitor	Intermittent claudication	oral
Ciprofloxacin	Antibiotic	Bacterial Infection	oral, injection
Cisapride (Removed from market)	GI stimulant	Increase GI motility	oral
Citalopram	Anti-depressant, SSRI	Depression	oral
Clarithromycin	Antibiotic	Bacterial infection	oral, inhaled
Cocaine	Local anesthetic	Anesthesia (topical)	oral, nasal
Disopyramide	Anti-arrhythmic	Abnormal heart rhythm	oral, injection
Dofetilide	Anti-arrhythmic	Abnormal heart rhythm	oral

Generic Name	Drug Class	Therapeutic Use	Route
Domperidone (Only on Non US market)	Anti-emetic	Nausea, vomiting	oral, injection, suppository
Donepezil	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)	oral
Dronedarone	Anti-arrhythmic	Atrial Fibrillation	oral
Droperidol	Anti-psychotic/Anti-emetic	Anesthesia adjunct, nausea	injection
Erythromycin	Antibiotic	Bacterial infection; increase GI motility	oral, injection
Escitalopram	Anti-depressant, SSRI	Major depression/ Anxiety disorders	oral
Flecainide	Anti-arrhythmic	Abnormal heart rhythm	oral
Fluconazole	Anti-fungal	Fungal infection	oral, injection
Gatifloxacin (Removed from market)	Antibiotic	Bacterial infection	oral, injection
Grepafloxacin (Removed from market)	Antibiotic	Bacterial infection	oral
Halofantrine (Only on Non US market)	Anti-malarial	Malaria infection	oral
Haloperidol	Anti-psychotic	Schizophrenia, agitation	oral, injection
Hydroquinidine	Anti-arrhythmic	Arrhythmia	oral
Ibogaine (Only on Non US market)	Psychedelic	Narcotic addiction, unproven	oral
Ibutilide	Anti-arrhythmic	Abnormal heart rhythm	injection
Levofloxacin	Antibiotic	Bacterial infection	oral, injection
Levomepromazine (methotrimeprazine) (Only on Non US Market)	Anti-psychotic	Schizophrenia	oral, injection
Levomethadyl acetate (Removed from market)	Opiate	Narcotic dependence	oral
Levosulpiride (Only on Non US market)	Anti-psychotic	Schizophrenia	oral, injection

Generic Name	Drug Class	Therapeutic Use	Route
Mesoridazine (Removed from market)	Anti-psychotic	Schizophrenia	oral
Methadone	Opiate	Pain control, narcotic dependence	oral, injection
Meglumine Antimonite	Anti-parasitic	Leishmaniasis	injection
Moxifloxacin	Antibiotic	Bacterial infection	oral, injection
Nifekalant	Anti-arrhythmic	Arrhythmia	oral
Ondansetron	Anti-emetic	Nausea, vomiting	oral, injection
Oxaliplatin	Anti-cancer	Cancer	injection
Papaverine HCl (Intra-coronary)	Vasodilator, Coronary	Diagnostic adjunct	injection
Pentamidine	Anti-fungal	Pneumocystis pneumonia	injection, inhaled
Pimozide	Anti-psychotic	Tourette's tics	oral
Probucol (Removed from market)	Antilipemic	Hypercholesterolemia	oral
Procainamide	Anti-arrhythmic	Abnormal heart rhythm	injection
Propofol	Anesthetic, general	Anesthesia	injection
Quinidine	Anti-arrhythmic	Abnormal heart rhythm	oral, injection
Roxithromycin (Only on Non US market)	Antibiotic	Bacterial infection	oral
Sevoflurane	Anesthetic, general	Anesthesia	inhaled
Sertinidole	Anti-psychotic	Schizophrenia, anxiety	oral
Sotalol	Anti-arrhythmic	Abnormal heart rhythm	oral
Sparfloxacin (Removed from market)	Antibiotic	Bacterial infection	oral
Sulpiride (Only on Non US market)	Anti-psychotic, atypical	Schizophrenia	oral, inhaled
Sultopride (Only on Non US market)	Anti-psychotic, atypical	Schizophrenia	oral, injection
Terfenadine (Removed from market)	Antihistamine	Allergic rhinitis	oral

Generic Name	Drug Class	Therapeutic Use	Route
Terlipressin (Only on Non US market)	Vacoconstrictor	Septic shock	injection
Terodiline (Only on Non US market)	Muscle relaxant	Bladder spasm	oral
Thioridazine	Anti-psychotic	Schizophrenia	oral
Vandetanib	Anti-cancer	Thyroid cancer	oral

Source: CredibleMeds.org (http://crediblemeds.org/healthcare providers/drug list/?rf=All). TdP risk category filtered on Drugs with known TdP risk. December 2020.

10.13. Appendix 13: Protocol Amendment History

The protocol Amendment Summary of Changes Table for the current amendment is located directly before the TOC. The protocol amendment summary of changes tables for past amendment(s) can be found below:

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
Amendment 5	12 April 2019	Note that 2 tables have been removed from the introduction section, resulting in updated table numbers. Schedule of Activities: Tables 1 and 3, Footnote 1: clarify that assessments performed as standard of care within 28 days of randomization do not need to be repeated to be used for screening. Tables 1 and 3, Footnote 4: clarified that Response Assessment includes assessment of EMD (eg, disease in CSF). Table 1, Footnotes 6 and 7: clarified that weekly hematology and chemistry tests must continue weekly until the next phase of study/treatment begins. Table 1, Footnote 14 and Table 3, Footnote 13: Morning dosing of therapy is preferred but not mandatory, rationale for change added to Section 5.5.1.1. Tables 1 and 3, Deleted individual rows for each Patient Reported Outcome survey since they are administered together and are outlined in footnote and Section 7.4. Table 1, Footnote 32 and Table 3, Footnote 36: added “if able” to the PRO collection during HSCT period. Table 3 and Section 5.5.1.3: Participants enrolled in the Non Intensive study may undergo HSCT per local standard of care and at the Investigator’s discretion. Table 1, Footnotes 26, 27, 38 and Table 3, Footnotes 24, 25, 31: Updated with text related to China samples.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		Table 1, Footnote 19, Table 3, Footnote 16 and Section 7.2.3: Bone marrow assessments within 3 weeks of growth factor administration are evaluable and do not need to be repeated. Original text that these BM assessments would not be considered evaluable has been deleted. Introduction: Background (Section 1.2) and Rationale sections have been separated and updated to reflect current data and IB. Removed Nonclinical Toxicology text (Section 1.2.3). Clinical Development (Section 1.2.4): Removed Table 5 and Table 6. Safety and Efficacy sections removed and new section inserted describing Glasdegib Clinical Pharmacology. Updates to relevant clinical studies with glasdegib made to provide relevant background. Data from thorough QTc study included. Section 4.2, Inclusion/Exclusion: Inclusion #1: Clarified that participants with FLT3+ AML not receiving and not intended to receive a FLT3 inhibitor during study participation are allowed per regulatory agreement. Inclusion #5: Removed ATRA since it is meant to treat APL and removed anageride. Text added, continuation or resumption of hydroxyurea or leukapheresis after described time period must be approved by the Sponsor. Exclusion #1: Clarified that APL is associated with t(15;17). Exclusion #2: Clarified that the mutation must be known. Exclusion #4: QTc exclusion does not apply to participants with cardiac pacemaker. • Exclusion #14: Removed local radiation as an excluded treatment modality during the screening period.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		Section 4.3: Text added defining Screen Failures as participants who consent to participate in the clinical study but are not subsequently randomized. Added data collection required for Screen Failure participants. Section 4.4.1: Text updated to require one method of birth control, consistent with sponsor requirements. Language added to clarify Investigator responsibility for reproductive capability assessment. Table 6: Updated to include abstinence. Section 4.4.2: Added to provide postmenopausal definition. Section 5.2 Breaking the Blind: Text now reflects that CRF does not collect Break blind data, but that this will be documented within the source. Additionally, participants may not continue on study treatment once an investigator breaks the blind for that participant. Section 5.5.1.2: Clarification text added regarding the timing and terms of bone marrow assessments. Section 5.5.2: Adverse events and concomitant medications will not be collected during long-term follow-up. Table 10 Glasdegib/placebo Dose Modifications for mean QTcF Prolongation: updated in alignment with the USPI. Also added comment that mQTcF dose mods do not apply to participants with cardiac pacemakers. Figure 2: Updated for clarity and to align terms with CRF fields. Figure 3: Updated with addition of option for HSCT. Section 5.8.1: Removed requirement of discussion with Medical Monitor for the concomitant use of CYP3A4 inhibitors/inhibitors. Section 5.8.2.2: Removed text requiring a repeat BM assessment if done within 3 weeks from last

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		dose of growth factor. Growth factors may be given per local standard of care and local label. Section 6.4, Table 1, Footnote 31 and Table 3, Footnote 29: Text added regarding the use of public records for long term survival follow-up as allowed by local law. Section 7.2.1: Additional text describing the AML response assessment added for clarity. Section 7.2.2: Text added allowing post baseline genetic assessments to be limited to abnormalities noted at baseline and molecular assessments to follow standard of care. CCI [redacted] Add Section 7.3.2: Biomarker Assessments: Updated to reflect current biomarker plans. Section 7.4: Updates to account for hospitalized participant schedules, participants with visual problems, and clarification that for patients hospitalized or with a timepoint falling on a weekend or holiday, PRO questionnaires may be performed on the next business day. Section 7.1.4: Re-screening is allowed. Section 9: 9.1: clarified percentage of patients censored for OS used in the sample size determination. 9.2: clarified all analyses of intensive and nonintensive chemotherapy participants will be conducted separately and independently of each other. 9.3.1 : added region (rest of world versus China) as a stratification factor to the primary and secondary analyses for intensive patients due to potentially different rates of stem cell transplantation. 9.3.2 : clarified all secondary PRO and efficacy endpoints will be based on the full analysis set unless stated otherwise; clarified method for calculating confidence intervals for binary efficacy

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		endpoints; removed Kaplan-Meier analysis for time to response as analysis is for responders only; clarified censoring for those without event-free survival events; clarified which event-free survival methods are for responders only. 9.4: clarified transfusion conversion rate is analyzed in the safety analysis set. 9.5.1: clarified safety analyses are analyzed in both intensive and non-intensive studies. 9.7: clarified DMC will convene at least once yearly per DMC charter. Clarified throughout document that restarting glasdegib/placebo Post HSCT requires no **ongoing** ≥ Grade 2 GVHD. Section 14: Added text regarding options for Non-Intensive participants to continue treatment at study end. Appendix 1: Added abbreviation for HGRAC. Appendix 4: Updates for clarity and readability. Appendices 5, 6, 7, 8 and references updated. General spelling, grammar, repetitions and formatting corrected.
Amendment 4	02 July 2018	Amendment 4 changes will be applicable to participants enrolling in Germany. German ethics committee requested collection of unrelated SAEs during the HSCT period. This edit was made in Section 8.1. Section 9.5.1: deleted text impacted by update to Section 8.1.
Amendment 3	01 March 2018	All changes were made prior to start of the study in response to regulatory requests except where indicated. Other minor changes were added for clarity. Added BRIGHT AML1019 study logo to cover page.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		Endpoints: clarified response definition by defining CRi or better to include CR (including $CR_{MRD\text{-}negative}$) or CRi for intensive chemotherapy participants, and CR (including $CR_{MRD\text{-}negative}$), CRh, or CRi for non-intensive chemotherapy participants. CRh or better is only defined for non-intensive chemotherapy participants as CR (including $CR_{MRD\text{-}negative}$) or CRh. Also updated Section 9.3 (and subsections) and Appendix 4 with these definitions. Schedule of Activities: • Clarified that bone marrow assessments for study assessments other than disease classification must be done after informed consent signed in footnotes, as specified in the Protocol Administrative Change Letter, dated 20 Dec 2017. • Added whole blood collection for immunophenotyping and molecular profiling on Day 1, prior to dosing study drug to provide a baseline sample to compare to future samples for MRD assessment. • Removed whole blood collection for pharmacogenomic analysis from intensive and non-intensive chemotherapy studies because pharmacogenomic analysis of drug metabolizing enzymes and transporters was no longer a priority for this study as it was unlikely to provide valuable information that would inform either safety or efficacy. Also removed Section in protocol defining this analysis. • Added additional times when bone marrow samples must be collected post consolidation for the Intensive Study so MRD status may be confirmed in a timely manner. • Table 3: blood chemistry deleted from follow-up visits; added in error.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		Section 1.2.3: Edited text for glasdegib nonclinical toxicity to align with updated data. Inclusion criterion #5: specified anti-cancer agents for clarity in response to regulatory request. Exclusion criteria #7: removed right bundle branch blocks as this is common and it should not be excluded. Section 4.3.1: Added a requirement for a backup contraception method in response to regulatory request. Section 5.4.1.3: removed subcutaneous route for cytarabine since this will not be an option. Removed term *allogeneic* because either autologous or allogeneic HSCT is allowed during the Intensive Chemotherapy Study per regulatory feedback. Section 5.8.1: re-organized CYP3A4/5 inducers so bullet appears under proper heading. Table 11 now specifies that glasdegib/placebo should be permanently discontinued for all cases of confirmed DILI/Hy's Law and potential cases require glasdegib/placebo dose interruption and potential restarting. Added in response to regulatory request. Table 14 now includes required bicarbonate testing to determine dose reductions per azacitidine label, per regulatory request. Also clarified indication for U/A with microscopic evaluation and 24-hour urine protein. Sections 7.1.7: removed additional QTc monitoring requirements if a moderate/strong CYP3A4/5 inhibitor or TdP drug administered during study since additional monitoring was not required. Section 9.3: Changes in the PRO section were made to improve clarity regarding planned analyses per regulatory request. Other changes

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		clarified method by which response will be analyzed. Removed section specifying end of trial in a member state because LSLV will be considered the end of trial in all participating countries. Removed due to regulatory request. Appendix 16 added per country specific requirement in France. General spelling, grammar, and consistency issues corrected throughout the protocol.
Amendment 2	15 November 2017	All changes were made prior to start of the study in response to FDA request except where indicated. Other minor changes were added for clarity. Secondary endpoints updated: • CR/CRh was added to duration of response assessment to match statistical analysis section. • CR/CRh was added to time to response assessment to match statistical analysis section. • Schedule of Activities (Intensive study): Pregnancy testing added for Day 1 of each Consolidation Cycle with single agent cytarabine and Day 1 of each cycle where single agent glasdegib/placebo administered to ensure appropriate safety monitoring. • Schedule of Activities (Intensive and Nonintensive studies): Immunophenotyping was removed because it is not required for any study analysis. Immunophenotyping was also removed from Sections 7.1 and 7.2.2 for consistency. X's added to tables so tables now match footnotes indicating specified instances AEs and SAEs may be collected during the follow-up period. Table 2 and Table 4 now provide time windows for assessments allowing sites flexibility in obtaining assessments without jeopardizing data.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		Other minor footnote clarifications to ensure consistency with tables. Inclusion Criterion #4: removed bullet indicating that the criterion does not apply to participants with bundle branch blocks and is otherwise asymptomatic. This conflicted with an exclusion criterion and was confusing. Exclusion Criterion #4: specified that a participant could not participate in other clinical studies involving other investigational drugs to clarify that this did not apply to glasdegib in this study. Section 5.4.1.2: Reduced the text describing the azacitidine supply to match information supplied for other chemotherapy drugs in this study. Edits added for clarity, instructing sites to follow local regulations. Section 5.5.5 updated per FDA request to provide more information regarding glasdegib/placebo dose modifications. • Corrected typographical error in Section 5.5.5.1 indicating that glasdegib or placebo does not need to be delayed or dose reduced for hematologic, study treatment related toxicity. • Specified dose escalations will not be allowed following glasdegib/placebo dose reductions. • Added Section 5.5.5.2 for dosing interruptions for glasdegib/placebo non-hematological toxicities. • Section 5.8.1: corrected a typographical error, removing word permitted. Section 7.1.3: Added text specifying that assessment of acute GVHD will be graded by standard criteria based on the Consensus conference on acute GVHD grading and assessment of chronic GVHD will be assessed based on the NIH criteria with associated

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		references. Grading and Staging for acute GVHD is summarized in Appendix 15. • Section 7.1.4: Clarified that laboratory tests only need to be obtained during screening, and there is no need to repeat these tests on Day 1 if performed within 3 days prior to randomization. • Section 7.1.7: specified type of ECGs (supine) for clarity. • Section 7.4.3 updated per FDA request: • Changed PGIS from a 7 point scale to a 4 point scale. The FDA recommended that Pfizer revise the PGIS to 4 response options (eg, absent (no symptoms), mild, moderate, and severe) so patients can easily distinguish severity. • Section 9.2.5: updated for clarity; now specifies Intensive and Nonintensive studies. • Section 9.3.2: updated per FDA request, specifying type of analysis required for fatigue and to correct minor errors. This section also includes an update to correct a typographical error: Method 1 sensitivity analysis for EFS must include CRi and Method 4 must not include CRi for the Intensive Study. For the Nonintensive study, Method 2 for the EFS definition now specifies CR or CRi will be evaluated following up to 6 cycles of therapy. Now specifies the Brookmeyer and Crowley method will be used to evaluate EFS for clarity. PK Parameters now specify C_{trough} will be reported for glasdegib metabolites, if relevant. Though there is no activity anticipated for the N-desmethyl metabolite (M3) that is <10% in circulation; possible metabolite measurement is added, if applicable as a conservative approach.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		Appendix 4 updated to match data analysis section for consistency: • Absence of CRh added to SD definition. • Treatment failure definitions added for Intensive and Non-intensive studies. • Appendix 11 updated to address FDA comments: PGIS now includes question regarding leukemia symptoms. General spelling, grammar, and consistency issues corrected throughout the protocol.
Amendment 1	19 September 2017	All changes were made prior to start of the study and made per FDA comments except where indicated. Other minor changes were added for clarity. Schedule of Activities for the Intensive and Non-intensive Studies and applied throughout protocol: • For bone marrow assessments, bone marrow aspirates are required; however, we now added preference for bone marrow biopsies in addition to aspirates. In the event of an inadequate aspirate, a bone marrow biopsy is required. • Baseline genetics edits made for clarification that known genetics at the time of randomization will be used to stratify participants. • Red blood cell and platelet transfusion history required 8 and not 24 weeks prior to randomization for the nonintensive study only. • Added windows for follow-up assessments. Schedule of Activities for the Intensive Study only:

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		• Removed collection of prior transfusions; only collect during study. • Changed from every 28 day to weekly chemistries. • Consolidation with cytarabine changed from 13 g/m^2 to 3 g/m^2 for adults <60 years and 1 g/m^2 for adults ≥60 years. • Following HSCT, participants will not be allowed to have ≥Grade 2 GVHD before resuming glasdegib/placebo. PGIC not collected at baseline for non-intensive study, updated as a correction Table 2: Made a correction by adding the time, 1 hour post-dose, for the column labeled "Glasdegib following chemotherapy". Cycle ≥1, Day 1 Secondary Endpoint (Section 2 and throughout protocol): added CR with partial hematologic recovery (CRh) for the Non-intensive study only. CCI [redacted] Inclusion Criterion 5: removed one single dose of Ara-C of up to 2 grams for control of blasts counts. Exclusion Criterion 10: clarified that dose equivalent of ≥550 mg/m^2 of daunorubicin is a criterion for the Intensive Chemotherapy study only. Dose Modifications (Section 5.5.5): clarified glasdegib or placebo does not be delayed or dose reduced for Grade 3/Grade 4 nonhematologic, study treatment related toxicity and should be permanently discontinued if interruptions are for more than 28 consecutive days. Concurrent administration of herbal preparations prohibited (Section 5.8.1), added as a clarification since it is already an exclusion criterion.

Document History		
Document	**Version Date**	**Summary and Rationale for Changes**
		Prophylactic Intrathecal Chemotherapy allowed per investigator discretion in Permitted Concomitant Medications in Section 5.8.2. Efficacy Assessments (Section 7.2) now includes definition for CR with partial hematologic recovery for the Non-intensive study. Immunophenotyping and Genetics (Section 7.2.2) clarifications added regarding requirement to stratify based on known genetic risk classification at the time of randomization. Section 9.3.2: Added updated definitions for EFS and includes CR/CRh as response (in duration of response and time to response endpoints) for the nonintensive study. Added additional sensitivity analyses for EFS. Appendix 4: Added response definition for CRh and clarified CRi requires either criteria for residual neutropenia or thrombocytopenia must be met. Appendix 14: added ELN Risk Stratification by Genetics table. General spelling and grammar issues corrected. CCI [redacted]
Original protocol	27 July 2017	N/A

10.14. Appendix 14: Letters Sent to Investigators After Amendment 5

The following letters were sent to investigators after Amendment 5, but the content of the letters are no longer relevant in this amendment:

Letter dated 12 Jun 2019

Letter dated 09 Apr 2020

10.15. Appendix 15: Abbreviations

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

Abbreviation	Term
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
AML	acute myeloid leukemia
APL	acute promyelocytic leukemia
aPTT	activated partial thromboplastin time
Ara-C	cytarabine
AST	aspartate aminotransferase
ATRA	all-trans retinoic acid
AUC	area under the plasma concentration curve
AUC_{inf}	area under the plasma concentration-time profile from time 0 to infinity
AV	atrioventricular
BM	bone marrow
BST	Best Supportive Therapy
BUN	blood urea nitrogen
Ca	calcium
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
C_{max}	maximum plasma concentration
CMML	chronic myelomonocytic leukemia
COVID-19	Coronavirus Disease 2019
CPK	creatine phosphokinase
CR	complete remission
CRF	case report form
CRh	complete remission with partial hematologic recovery
CRi	complete remission with incomplete hematologic recovery
$CR_{MRD-neg}$	complete remission with negative minimal residual disease
CRO	contract research organization
CSF	cerebrospinal fluid
CSR	clinical study report
CT	Clinical Trial
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	plasma trough concentration
CYP	cytochrome P450
DILI	drug-induced liver injury
DNA	deoxyribonucleic acid
DU	dispensable units

Abbreviation	Term
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDP	Exposure During Pregnancy
EDMC	External Data Monitoring Committee
EFS	event-free survival
ELN	European Leukemia Net
EMA	European Medicines Agency
EMD	Extra Medulary Disease
EU	European Union
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration (United States)
FLT3-ITD	fms-like tyrosine kinase internal tandem duplication
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GGT	gamma-glutamyl transferase
GM-CSF	granulocyte macrophage colony-stimulating factor
GnRH	gonadotropin-releasing hormone
GVHD	graft-versus-host disease
HDPE	high-density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HGRAC	Human Genetics Resources Administration of China
Hh	Hedgehog
HI	hematologic improvement
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
HSCT	hematopoietic stem cell transplant
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	investigational medicinal product
IND	investigational new drug application
INR	international normalized ratio
INT	intensive
IP	investigational product
IPAL	Investigational Product Accountability Log
IRB	Institutional Review Board
IRT	interactive response technology
IWR	Interactive Web Response

Abbreviation	Term
IV	intravenous
IVR	Interactive Voice Response
K	potassium
LDAC	low dose cytarabine
LDH	lactate dehydrogenase
LFT	liver function test
LIC	lead-in cohort
LS	least squares
LSLV	last subject last visit
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
Mg	magnesium
mQTcF	mean QTcF
MRD	minimal residual disease
NA	not applicable
Na	sodium
NCI	National Cancer Institute
NIH	National Institutes of Health
NIMP	non-investigational medicinal product
NINT	non-intensive
NNRTI	non-nucleoside reverse transcriptase inhibitors
OS	overall survival
PD	pharmacodynamics
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Symptoms
PK	Pharmacokinetics
PRO	patient reported outcomes
PT	prothrombin time
PTT	partial thromboplastin time
PVC	premature ventricular contraction/complex
Q	quartile
QD	once a day
QTc	corrected QT
QTcF	corrected QT (Fridericia method)
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV2	severe acute respiratory syndrome coronavirus 2
SC	Subcutaneous
SD	standard deviation
SoA	schedule of activities
SOP	standard operating procedure

Abbreviation	Term
SPC	Summary of Product Characteristics
SRSD	single reference safety document
SSRI	selective serotonin reuptake inhibitor
SUSAR	suspected unexpected serious adverse reactions
TBili	total bilirubin
TdP	Torsade de Pointes
TEAE	treatment emergent adverse event
TOC	Table of Contents
U/A	urinalysis
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
UTI	urinary tract infection
UVB	ultraviolet B light
UV	University of Washington
Vit	vitamin
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman of childbearing potential

11. REFERENCES (Not Applicable)