Phase 1/2 Study of ASP2215 (Gilteritinib) Combined with Atezolizumab in Patients with Relapsed or Treatment Refractory FLT3 Mutated Acute Myeloid Leukemia (AML)

Protocol for Phase 1/2 Study of ASP2215

ISN/Protocol 2215-CL-1101

Version 3.2

Incorporating Nonsubstantial Amendment 3 [See Section 13]

09 Dec 2020

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Sponsor:

Astellas Pharma Global Development, Inc. (APGD)

1 Astellas Way
Northbrook, IL 60062

Protocol History:

Version 1.0 Original [21Jun2018]
Version 1.1 Incorporating Nonsubstantial Amendment 1 [17Oct2018]
Version 2.0 Incorporating Substantial Amendment 1 [15Jan2019]
Version 3.0 Incorporating Substantial Amendment 2 [05Dec2019]
Version 3.1 Incorporating Nonsubstantial Amendment 2 [24Mar2020]

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I. SIGNATURES

1. SPONSOR'S SIGNATURES

Required signatures (e.g., Protocol authors and contributors, etc.) are located in [Section 14 Sponsor Signature].

2. INVESTIGATOR'S SIGNATURE

Phase 1/2 Study of ASP2215 (Gilteritinib) Combined with Atezolizumab in Patients with Relapsed or Treatment Refractory FLT3 Mutated Acute Myeloid Leukemia (AML)

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I have read all pages of this clinical study protocol for which Astellas is the sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local regulations. I will also ensure that subinvestigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: .....

Date (DD Mmm YYYY)

Printed Name: .....

<Insert name and qualification of the investigator>

Address:	

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

24h-Contact for Serious Adverse Events (SAEs) See [Section 5.5.5 Reporting of Serious Adverse Events] for SAE Fax Number and Email	**PPD MD** **PPD, Medical Oncology Science** **Astellas Pharma Global Development, Inc.** **Mobile: PPD** **Please fax or email the SAE Worksheet to:** **Astellas Pharma Global Development, Inc.** **Pharmacovigilance** **Fax number: 1-888-396-3750** **Alternate Fax number: 1-847-317-1241** **Email: safety-us@astellas.com**
Medical Monitor/Study Physician:	PPD MD PPD Medical Oncology Science Astellas Pharma Global Development, Inc. Office: PPD Mobile: PPD Email: PPD PPD PhD PPD Medical Sciences Parexel International 8 Federal Street Billerica, MA, 01821 Office: PPD Mobile: PPD
Clinical Research Contact:	PPD PPD Phone: PPD Email: PPD

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
ADR	adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{inf}	area under the concentration-time curve from the time of dosing extrapolated to time infinity
AUC_{last}	area under the concentration-time curve from the time of dosing up to the time of the last measurable concentration
AUC_{tau}	area under the concentration-time curve from the time of dosing to the start of the next dosing interval at multiple dose conditions
AUST	Astellas United States Technologies (AUST)
AXL	a receptor tyrosine kinase encoded by the AXL gene
BCRP	breast cancer resistance protein
BMAS	biomarker analysis set
CA	Competent Authorities
cEC	Concerned Ethics Committee
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL/F	apparent total clearance after extravascular dosing
C_{max}	maximum concentration
CR	complete remission
CRc	composite complete remission
CRh	complete remission with partial hematologic recovery
CRi	complete remission with incomplete hematologic recovery
CRp	complete remission without platelet recovery
CRF	case report form
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	concentration immediately prior to dosing at multiple dosing
CV	coefficient of variation

Abbreviations	Description of abbreviations
CYP	cytochrome P450
DEC	Dose Evaluation Committee
DLT	dose limiting toxicity
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EEA	European Economic Area
EFS	event-free survival
EOT	end of treatment
FAS	full analysis set
FEV_1	forced expiratory volume in the first second
FLT3	FMS-like tyrosine kinase 3
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
GVHD	graft-versus-host disease
HSCT	hematopoietic stem cell transplantation
IB	Investigator's Brochure
IC_{50}	concentration of an inhibitor where the response (or binding) is reduced by half
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISN	international study number
ITD	internal tandem duplication
LA-CRF	liver abnormality case report form
LFT	liver function tests
MATE	multidrug and toxin extrusion
MDS	myelodysplastic syndrome
MRD	minimal residual disease
MTD	maximum tolerated dose
MUGA	multigated acquisition
NCI	National Cancer Institute
NYHA	New York Heart Association

Abbreviations	Description of abbreviations
OCT	organic cation transporter
OATP	organic anion transporting polypeptide
OS	overall survival
P-gp	P-glycoprotein
PD-L1	programmed death-ligand 1
PGx	pharmacogenomic
PKAS	pharmacokinetics analysis set
PPS	per protocol set
PR	partial remission
q2w	once every 2 weeks
QTcF	Fridericia-corrected QT interval
RBC	red blood cell
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAF	safety analysis set
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedures
SPC	summary of product characteristics
SUSAR	suspected unexpected serious adverse reactions
$t_{½}$	terminal elimination half-life
TBL	total bilirubin
TEAE	treatment-emergent adverse event
t_{max}	time of the maximum concentration
ULN	upper limit of normal
USM	urgent safety measure
V_z/F	apparent volume of distribution during the terminal elimination phase after extravascular dosing
WOCBP	woman of childbearing potential

Definition of Key Study Terms

Terms	Definition of terms
Baseline	Assessments of subjects as they enter a study before they receive any treatment.
Endpoint	Variable that pertains to the efficacy or safety evaluations of a study.
Enroll	To register or enter a subject into a clinical study. NOTE: Once a subject has received the study drug or placebo, the clinical study protocol applies to the subject.
Intervention	The drug, device, therapy or process under investigation in a clinical study that is believed to have an effect on outcomes of interest in a study (e.g., health-related quality of life, efficacy, safety and pharmacoeconomics).
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test drug or comparative drug is usually given to a subject, and continues until the last assessment after completing administration of the test drug or comparative drug.
Post investigational period	Period of time after the last assessment of the protocol. Follow-up observations for sustained adverse events and/or survival are done in this period.
Screening	A process of active consideration of potential subjects for enrollment in a study.
Screen failure	Potential subject who did not meet 1 or more criteria required for participation in a study.
Screening period	Period of time before entering the investigational period, usually from the time when a subject signs the consent until just before the test drug or comparative drug is given to a subject.
Study period	Period of time from the first site initiation date to the last site completing the study.
Variable	Any entity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

IV. SYNOPSIS

Date and Version No of Protocol Synopsis:	09 Dec 2020, Version 3.2
Sponsor: Astellas Pharma Global Development Inc. (APGD)	**Protocol Number:** 2215-CL-1101
Name of Study Drug: ASP2215/Gilteritinib	**Phase of Development:** Phase 1/2
Title of Study: Phase 1/2 Study of ASP2215 (Gilteritinib) Combined with Atezolizumab in Patients with Relapsed or Treatment Refractory FLT3 Mutated Acute Myeloid Leukemia (AML)	
Planned Study Period: From 4Q2018 to 2Q2024.	

Study Objective(s):

The primary objectives are to:

- Determine the safety and tolerability of gilteritinib given in combination with atezolizumab in subjects with relapsed or treatment refractory FMS-like tyrosine kinase 3 (FLT3) mutated acute myeloid leukemia (AML).
- Determine the composite complete remission (CRc) rate for subjects with relapsed or treatment refractory FLT3 mutated AML who either discontinued the study or completed 2 cycles of gilteritinib given in combination with atezolizumab. CRc is defined as a complete remission (CR), complete remission without platelet recovery (CRp) or complete remission with incomplete hematologic recovery (CRi).

The secondary objectives are to:

- Characterize the pharmacokinetics of gilteritinib and its active metabolites (if appropriate) when given in combination with atezolizumab.
- Evaluate the safety and efficacy of gilteritinib in combination with atezolizumab in terms of:
  - Gilteritinib trough plasma concentrations (C_{trough})
  - CR rate
  - CR with partial hematologic recovery (CRh)
  - Best response rate (CRc + partial remission [PR])
  - Duration of remission
  - Event-free Survival (EFS)
  - Overall Survival (OS)
  - Adverse events (AEs), clinical laboratory results, vital signs, electrocardiograms (ECGs), and Eastern Cooperative Oncology Group (ECOG) performance status scores

The exploratory objectives are to:

- Evaluate efficacy of gilteritinib given in combination with atezolizumab in terms of minimal residual disease (MRD)
- Evaluate potential genomic, proteomic and/or other biomarkers that may correlate with treatment outcome
- Evaluate pharmacodynamic biomarkers of treatment effect
- Evaluate immune cell populations and AML blasts by immunophenotyping in relation to treatment effects

Planned Total Number of Study Centers and Location(s):

15 sites in the United States

Study Population:
Patients with relapsed or treatment refractory FLT3 mutated AML.

Number of Subjects to be Enrolled:
Up to 61 subjects who are evaluable for response including up to 12 subjects in the phase 1 portion and up to 49 subjects in the phase 2 portion.

Study Design Overview:
This is an open-label, single arm, phase 1/2 study to evaluate the safety and efficacy of combining gilteritinib with atezolizumab for subjects with relapsed or treatment refractory FLT3 mutated AML. This study will have 2 phases.

Phase 1:

The phase 1 portion of this study is a dose-escalation phase with a 3 + 3 design to establish the recommended phase 2 dose (RP2D) of gilteritinib given in combination with atezolizumab. Up to 12 subjects will be enrolled in cohorts of 3 to 6 subjects to determine the RP2D following the dose levels of the combination treatment outlined in the table below. Dose escalation decisions will be made based on DLTs that occur during the first cycle of treatment. A cycle is defined as 28 days. The treatment will consist of 3 distinct periods; remission induction, consolidation and maintenance.

The dose limiting toxicity (DLT) observation period will be from cycle 1/day 1 through cycle 1/day 28. Evaluable subjects are defined as subjects who experience a DLT or in the absence of DLT, receive at least 23/28 doses of gilteritinib and at least 1/2 doses of atezolizumab. Subjects who are later discovered not to meet eligibility criteria or are not evaluable for DLT may be replaced.

Dose evaluation rules based on the 3 + 3 design and dose escalation rules are as follows:

Number of Subjects with DLT at the Given Dose During the DLT Observation Period	Escalation Decision Rules
0 of 3 or ≤ 1 of 6 subjects	Escalate and enter up to 3 subjects at the next dose level, if next dose level available. If at dose level 2, determine if RP2D.
1 of 3 subjects	Enter up to 3 subjects at the same dose level.
≥ 2 subjects	De-escalate or stop escalating.

DLT: dose limiting toxicity; RP2D: recommended phase 2 dose

The Dose Evaluation Committee (DEC) will consist of the sponsor, principal investigators, and if appropriate, expert consultants who will be responsible for the review of safety data through the DLT observation period for each cohort. The decision will be made by the DEC to escalate to the next planned dose level, to remain at the same dose level, de-escalate to the dose level below or stop escalation. The RP2D will be selected based on the DEC's review of all available data at each dose level, including safety and pharmacokinetic data (if available), and the RP2D will become the minimum safe and biologically effective dose level. Additional details regarding responsibilities and membership requirements will be included in the Subject Enrollment and DEC Plan. The subjects in the first cohort will be treated with gilteritinib 120 mg orally once daily and atezolizumab 420 mg once every 2 weeks by intravenous infusion. The subjects in the second cohort will be dosed based on the results of the first cohort and according to the dose level table below.

Dose Level	Dose- Atezolizumab	Dose- Gilteritinib
1	420 mg q2w	120 mg once daily
-1	420 mg q2w	80 mg once daily
2	840 mg q2w	120 mg once daily

q2w: once every 2 weeks

Phase 2:

In the phase 2 portion with 2 stages, up to 49 subjects will be enrolled. The subjects will be treated with gilteritinib and atezolizumab at the RP2D. In the first stage, 22 subjects will be enrolled. The subjects enrolled at the first stage of phase 2 will be used to calculate the CRc rate for the first stage. If the minimum CRc rate criterion (i.e., at least 12 CRc responders out of 22 subjects) is met, an additional 27 subjects will be enrolled for the second stage.

Inclusion/Exclusion Criteria:

Inclusion:

Subject is eligible for the study if all of the following apply:

1. Institutional Review Board-/Independent Ethics Committee-approved written Informed Consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act Authorization for United States sites) must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject is considered an adult according to local regulation at the time of signing informed consent form (ICF).
3. Subject has defined AML by the WHO criteria (2017) and fulfills one of the following:
   - Refractory to at least 1 cycle of induction chemotherapy
   - Relapsed after achieving remission with a prior therapy
4. Subject is positive for FLT3 mutation in bone marrow or blood after completion of subject's last interventional treatment as determined by the local institution.
5. Subject has an ECOG performance status ≤ 2 at screening.
6. Subject must meet the following criteria as indicated on the clinical laboratory tests:
   - Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x upper limit of normal (ULN)
   - Serum total bilirubin ≤ 1.5 x ULN
   - Serum creatinine ≤ 1.5 x ULN or an estimated glomerular filtration rate of > 50 mL/min as calculated by the Modification of Diet in Renal Disease equation.
7. Subject is suitable for oral administration of study drug.
8. A female subject is eligible to participate if she is not pregnant [see Appendix 12.3 Contraception Requirements] and at least one of the following conditions applies:
   - Not a woman of childbearing potential (WOCBP) as defined in [Appendix 12.3 Contraception Requirements]
     OR
   - WOCBP who agrees to follow the contraceptive guidance as defined in [Appendix 12.3 Contraception Requirements] throughout the treatment period and for at least 180 days after the final study drug administration.
9. Female subject must agree not to breastfeed starting at screening and throughout the study period, and for at least 180 days after the final study drug administration.

10. Female subject must not donate ova starting at screening and throughout the study period, and for at least 180 days after the final study drug administration.
11. A male subject must not donate sperm starting at screening and throughout the treatment period, and for at least 120 days after the final study drug administration.
12. A male subject with female partner(s) of child-bearing potential must agree to use contraception as detailed in [Appendix 12.3 Contraception Requirements] during the treatment period, and for at least 120 days after the final study drug administration.
13. Male subject with a pregnant or breastfeeding partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy or time partner is breastfeeding throughout the treatment period, and for 120 days after the final study drug administration
14. Subject agrees not to participate in another interventional study while on treatment.

Waivers to the inclusion criteria will **NOT** be allowed.

Exclusion:

Subject will be excluded from participation if any of the following apply:

1. Subject was diagnosed as acute promyelocytic leukemia.
2. Subject has BCR-ABL-positive leukemia (chronic myelogenous leukemia in blast crisis).
3. Subject has AML secondary to prior chemotherapy for other neoplasms (except for myelodysplastic syndrome [MDS]).
4. Subject has clinically active central nervous system leukemia.
5. Subject has uncontrolled or significant cardiovascular disease, including:
   - A myocardial infarction within 12 months
   - Uncontrolled angina within 6 months
   - History of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, torsades de pointes) or any history of arrhythmia
   - Uncontrolled hypertension
6. Subject has baseline left ventricular ejection fraction (LVEF) that is < 45%.
7. Subject has mean of triplicate Fridericia-corrected QT interval (QTcF) > 450 ms at screening based on central reading.
8. Subject has congenital or acquired Long QT Syndrome at screening.
9. Subject has hypokalemia and/or hypomagnesemia at screening (defined as values below institutional lower limit of normal).
10. Subject has been diagnosed with another malignancy that requires concurrent treatment or hepatic malignancy regardless of the need for treatment.
11. Subject has clinically significant coagulation abnormality unless secondary to AML in the opinion of the investigator.
12. Subject is receiving or plans to receive concomitant chemotherapy or immunotherapy other than as specified in the protocol.
13. Subject has had major surgery within 4 weeks prior to the first study dose.
14. Subject has radiation therapy within 4 weeks prior to the first study dose.
15. Subject requires treatment with concomitant drugs that are strong inducers of CYP3A.
16. Subject has known pulmonary disease with diffusion capacity of lung for carbon monoxide ≤ 65%, forced expiratory volume in the first second (FEV_1) ≤ 65%, dyspnea at rest or requiring oxygen or any pleural neoplasm.

17. Subject with systemic fungal, bacterial, viral or other uncontrolled infection that is exhibiting ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics or other treatment. The patient needs to be off pressors and have negative blood cultures for 48 hours.
18. Subject has not recovered from any prior therapy related toxicities, as determined by investigator.
19. Subject is known to have human immunodeficiency virus infection.
20. Subject has active hepatitis B or C or other active hepatic disorder.
21. Subject has previously been treated with gilteritinib, quizartinib or crenolanib (will only apply to subjects enrolled in the phase 2 portion of the study).
22. Subject has active clinically significant graft-versus-host disease (GVHD) or is on treatment with systemic corticosteroids for GVHD.
23. Subject has relapsed after allogeneic HSCT.
24. Subject has an active autoimmune disorder that in the opinion of the investigator makes the subject unsuitable for study treatment or participation.
25. Subject has any condition, which, in the investigator's opinion, makes the subject unsuitable for study participation, including any contraindications of atezolizumab listed in the current Investigator's Brochure (IB).

Waivers to the exclusion criteria will **NOT** be allowed.

Investigational Product(s):

Gilteritinib tablets containing 40 mg of active ingredients

Atezolizumab vials containing 60 mg/mL (1200 mg/20 mL) of active ingredients

Dose(s):

Subjects will be treated with gilteritinib 120 mg or 80 mg once daily and atezolizumab 420 mg or 840 mg once every 2 weeks for the phase 1 portion of the study. The primary objective will be to establish an RP2D of gilteritinib in combination with atezolizumab. The RP2D will be determined by the DEC and will be the minimum safe and biologically effective dose level based on data from the phase 1 portion of the study.

In the phase 2 portion, the subjects will be treated with gilteritinib and atezolizumab at RP2D.

Mode of Administration:

Gilteritinib will be administered orally.

Atezolizumab will be administered by intravenous infusion over 60 minutes, and if the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

Comparative Drug(s):

Not applicable

Concomitant Medication Restrictions or Requirements:

The following medications are *prohibited* during the course of the program:

- Strong inducers of CYP3A.
- Therapies to treat AML including, but not limited to:
  - Chemotherapy
  - Immunotherapy, cellular therapy or vaccines

  Exceptions: Hydroxyurea, intrathecal chemotherapy, cranial irradiation, localized radiation for palliation.
- Any other investigational agent for AML.

Caution is advised when considering the concomitant use of the following medications:

- Medications known to prolong QT or QTcF intervals.
- Strong inhibitors or inducers of P-glycoprotein and concomitant drugs that target serotonin $5HT_{2B}R$ are to be avoided with the exception of drugs that are considered absolutely essential for the care of the subject.
- Treatment with concomitant drugs that are strong inhibitors of CYP3A should be avoided with the exception of antibiotics, antifungals and antivirals that are used as standard of care to prevent or treat infections. If CYP3A inhibitors are used concomitantly, subjects should be closely monitored for AEs.

Precaution is advised in the use of gilteritinib (ASP2215) with concomitant drugs that are substrates of breast cancer resistance protein, since the transporter has been shown to be inhibited by gilteritinib (ASP2215) in in vitro studies.

Duration of Treatment:

Subjects will be treated until they no longer derive clinical benefit in the judgment of the treating physician, have unacceptable toxicity, undergo hematopoietic stem cell transplantation (HSCT), or meet 1 of the discontinuation criteria; whichever occurs first.

Definition of Dose Limiting Toxicity:

In phase 1, a DLT is defined as any of the following events that occur within the observation period (cycle 1/day 1 through cycle 1/day 28) and that is considered to be possibly or probably related to study regimen. In phase 2, the DLT observation period is the first treatment cycle (cycle 1/day1 through cycle 1/day28).

- Confirmed Hy's law case
- Any Grade ≥ 3 non-hematologic or extramedullary toxicity with the following exceptions:
  - Anorexia or fatigue
  - Grade 3 nausea and/or vomiting if not requiring tube feeding or TPN, or diarrhea if not requiring or prolonging hospitalization that can be managed to grade ≤ 2 with standard antiemetic or antidiarrheal medications used at prescribed dose within 7 days of onset
  - Grade 3 mucositis that resolved to grade ≤ 2 within 7 days of onset
  - Grade 3 fever with neutropenia, with or without infection*
  - Grade 3 infection*
  - Grade 3 infusion-related toxicity, if successfully managed and resolves within 72 hours.

*Toxicities are excluded only if the event is an expected direct complication of cytopenias due to the active underlying leukemia.

Hematologic toxicity will not be considered as a DLT. However, prolonged myelosuppression defined as absolute neutrophil count (ANC) ≤ 0.5×10^9/L for more than 21 days from the onset of severe neutropenia in the absence of evidence of active leukemia in the marrow and blood will be considered as a DLT.

Discontinuation of Treatment:

Subjects who meet any of the following criteria during the study will be withdrawn from study treatment:

- Subject declines further study participation (i.e., withdrawal of consent).
- Subject is non-compliant with protocol based on the investigator or medical monitor assessment.
- Subject is found to have significantly deviated from any one of the inclusion or exclusion criteria after enrollment (subjects having clinical benefit and no DLT may be kept in the study after discussion with the medical monitor).

- Subject develops an unacceptable study DLT or serious adverse event (SAE) requiring discontinuation of treatment.
- Subject has not achieved PR or CRc, and in the opinion of the investigator, is no longer deriving clinical benefit after 6 cycles of therapy.
- Gilteritinib dose is interrupted for greater than 15 days. Subjects may be allowed to continue treatment after discussions with the medical monitor if the interruption was not due to a gilteritinib related AE.
- Subject receives any antileukemic therapy (including HSCT) other than the assigned treatment, with the exception of hydroxyurea up to 5 g daily for up to 2 weeks, prophylactic intrathecal chemotherapy or cranial irradiation.
- Investigator/subinvestigator determines that the continuation of the study treatment will be detrimental to the subject.
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Female subject becomes pregnant.
- Death.
- Subject is receiving gilteritinib, atezolizumab, or the combination of gilteritinib + atezolizumab and has progressive disease, recurrence under treatment, and in the opinion of the investigator the subject is no longer deriving clinical benefit.

The subject will be discontinued from the long term treatment period if any of the following occur:

- Subject declines further study participation (i.e., withdraws consent)
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- More than 3 years has passed from the End of Treatment (EOT) Visit.
- Death

Endpoints for Evaluation:

Primary:

- Safety and tolerability (development of DLTs and AEs and define RP2D)
- CRc rate

Secondary:

- Gilteritinib trough plasma concentrations (C_{trough})
- CR rate
- CR with partial hematologic recovery (CRh)
- Best response rate
- Duration of remission
- EFS
- OS
- AEs, clinical laboratory results, vital signs, ECGs and ECOG

Exploratory:

- MRD in relation to clinical outcomes
- Evaluate potential genomic, proteomic and/or other biomarkers that may correlate with treatment outcome
- Evaluate pharmacodynamic biomarkers of treatment effect
- Evaluate immune cell populations and AML blasts by immunophenotyping in relation to treatment effects

Statistical Methods:

Sample Size Justification:

Phase 1

The sample size in phase 1 is based on 3+3 design and not based on power calculation.

Phase 2

Simon's 2-stage design [Simon, 1989] will be used in the study to evaluate the efficacy in terms of CRc rate for the selected combination dose level of gilteritinib and atezolizumab. The null hypothesis that the true CRc rate is 50% will be tested against a 1-sided alternative. In the first stage, the CRc of 22 subjects will be evaluated. If there are 11 or fewer subjects with CRc from these 22 subjects by the end of cycle 2, the study will be stopped. Otherwise, 27 additional subjects will be accrued for a total of 49 subjects evaluable for calculation of CRc rate. The null hypothesis will be rejected if 32 or more subjects with CRc are observed in the 49 subjects by the end of cycle 2. This design yields a 1-sided type I error rate of 0.025 and power of 80% when the true CRc rate is 70%. The sample size was calculated in East® Version 6.4.

Bayesian Posterior Probability for Safety Monitoring in Phase 2:

A Bayesian posterior probability will be used for safety monitoring during the whole treatment period. Subjects in phase 1 and phase 2 cohorts who complete the DLT observation period or experience DLTs will be included in the model-fitting process to provide the complete safety information. The DLT rate will be reviewed as the last subject of each cohort of 7 DLT-evaluable subjects completes the first treatment cycle. The estimated DLT rates based on the Bayesian beta-binomial model will be provided for safety monitoring in the dose expansion cohort. If the DLT rate for the expanded dose level is equal or higher than 20% with a posterior probability of 80%, then the enrollment to the expansion cohort will be paused and the safety will be reassessed by the DEC. If the reassessment warrants, enrollment to the expansion cohort may be continued at the current dose level or 1 lower dose level. Safety evaluation will be conducted separately for induction, consolidation and maintenance phases.

With a non-informative prior, Beta(1,1) distribution, the numbers of DLTs for each cohort of 7 DLT-evaluable subjects, which trigger the enrollment pause for toxicities review, are listed in the following table:

DLT-evaluable Subjects	Number of DLTs
7	3
14	4
21	6
28	8
35	9
42	11
49	12

DLT: dose-limiting toxicity

Efficacy:

Response to treatment will be defined per modified Cheson criteria [2003] as outlined below for up to the end of 2 cycles and end of treatment.

Composite Complete Remission (CRc) rate

Defined as the rate of all complete and incomplete remission (i.e., CR+ CRp + CRi).

Complete Remission (CR)

For subjects to be classified as being in CR, they must have bone marrow regenerating normal hematopoietic cells and achieve a morphologic leukemia-free state and must have an ANC $> 1 \times 10^9$/L and platelet count $\geq 100 \times 10^9$/L, and normal marrow differential with < 5% blasts, and they must be red blood cell (RBC) and platelet transfusion independent (defined as 1 week without RBC transfusion and 1 week without platelet transfusion prior to disease assessment. There should be no evidence of extramedullary leukemia.

Complete Remission with Incomplete Platelet Recovery (CRp)

For subjects classified as being in CRp, they must achieve CR except for incomplete platelet recovery ($< 100 \times 10^9$/L).

Complete Remission with Incomplete Hematological Recovery (CRi)

For subjects to be classified as being in CRi, they must fulfill all the criteria for CR except for incomplete hematological recovery with residual neutropenia $< 1 \times 10^9$/L with or without complete platelet recovery. RBC and platelet transfusion independence is not required.

Complete Remission with Partial Hematologic Recovery (CRh)

For subjects classified as being in CR, except if their ANC is $> 0.5 \times 10^9$/L and their platelets are $> 50 \times 10^9$/L.

Partial Remission (PR)

For subjects to be classified as being in PR, they must have bone marrow regenerating normal hematopoietic cells with evidence of peripheral recovery with no (or only a few regenerating) circulating blasts and with a decrease of at least 50% in the percentage of blasts in the bone marrow aspirate/biopsy with the total marrow blasts between 5% and 25%.

Relapse

Relapse after CR, CRp or CRi is defined as a reappearance of leukemic blasts in the peripheral blood or ≥ 5% blasts in the bone marrow aspirate/biopsy not attributable to any other cause or reappearance or new appearance of extramedullary leukemia.

Relapse after PR is similarly defined with reappearance of significant numbers of peripheral blasts and an increase in the percentage of blasts in the bone marrow aspirate/biopsy to > 25% not attributable to any other cause or reappearance or new appearance of extramedullary leukemia.

Best Response

Best response is defined as the best-measured response (CR, CRp, CRi or PR) post-treatment. Two best responses will be defined.

Pharmacokinetics:

Gilteritinib trough plasma concentrations (C_{trough})

Pharmacodynamics:

Changes in the activation status of FLT3 and AXL, a receptor tyrosine kinase (RTK), may be assessed before and after treatment.

Safety:

The safety analysis set is defined as all enrolled subjects who received at least 1 dose of study treatment.

The safety evaluation will be based mainly on AEs, clinical laboratory, vital signs, ECGs and ECOG performance status. Descriptive statistics will be used to summarize safety data. All safety data will be summarized by the actual treatment received.

All summaries of AEs will include only treatment-emergent events unless otherwise stated. AEs will be categorized by SOC and preferred term using MedDRA and will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

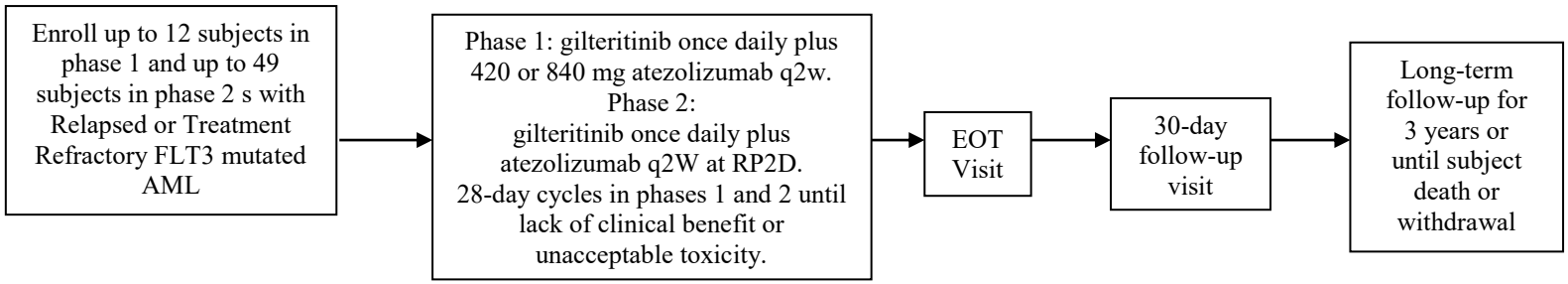
During phase 1, DLT assessment will occur during cycle 1 only. AEs (toxicities) will be graded according to the CTCAE version 5.0.

Interim analyses:

No interim analysis is planned.

V. FLOW CHARTS AND SCHEDULE OF ASSESSMENTS

Phases 1 and 2



AML: acute myeloid leukemia; EOT: end of treatment; FLT3: FMS-like tyrosine kinase 3; q2w: every 2 weeks; RP2D: recommended phase 2 dose.

Table 1 Schedule of Assessments

Assessments	Screening	C1D1	C1D8 [a]	C1 D15 [a]	Subsequent Cycles D1	Subsequent Cycles D15[a]	EOT[b]	30-Day Follow-up	Long-term Follow-up[c]
Windows	Day -14 to -1		± 1d				± 7d	+ 7d	± 7d
Signed ICF	X								
Medical and Disease History	X								
Enrollment		X							
Physical Examination[d]	X	X	X	X	X	X	X		
Vital Signs	X	X	X	X	X	X	X		
ECOG Performance Status[e]	X	X		X	X	X	X		
12-lead ECG[f]	X	X	X	X	X	X	X		
Chest X-ray (or CT of chest)	X								
Pregnancy Test for WOCBP[g]	X	X			X		X		
MUGA or ECHO	X								
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis)[h,i]	X[h]	X[h,i]	X[i]	X[i]	X	X	X		
Thyroid Function Test[j]	X				X[j]		X[j]		
Resource utilization		X			X		X		
FLT3 Mutation Status[k]	X[k]								
Bone Marrow Biopsy and/or Aspiration for disease assessment and MRD[l]	X[l]				X[l]		X[l]		
Pharmacokinetic Sample Collection[m]		X	X	X	X	X			
Blood Sample for FLT3 and AXL[n]		X							
Blood Sample for Immune Cell Immunophenotyping[o]		X		X	X[o]		X		
Blood Sample for Blast Cell Immunophenotyping[o]		X		X	X[o]		X		
PGx (whole blood and buccal swab)[p]		X							
AE/SAE Assessment	X	X	X	X	X	X	X	X[q]	X[r]
Prior and Concomitant Medications[s]	X	X	X	X	X	X	X	X[r]	
Survival and subsequent anti-leukemic treatments and their outcomes								X[q]	X
Gilteritinib Dosing at the Clinic[t]		X	X	X	X	X			
Subject Diary for Gilteritinib[u]		X			X				
Atezolizumab Dosing at the Clinic		X		X	X	X			

Footnotes appear on next page

AE: adverse event; CT: computed tomography; D: day; ECG: electrocardiogram; ECHO: echocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end of treatment; FLT3: FMS-like tyrosine kinase 3; ICF: informed consent form; MRD: minimal residual disease; MUGA: multigated acquisition scan; PGx: pharmacogenomics; QTcF: Fridericia-corrected QT interval; SAE: serious adverse event; WOCBP: women of childbearing potential.

a. Visits should be scheduled based on day 1.
b. If subject permanently discontinues treatment, an EOT Visit should be conducted within 7 days of last dose of study drug.
c. Telephone contact every 3 months, from the date of the 30-day follow-up visit additional contacts may be made to support key analyses. Subjects will be followed for up to 3 years after the 30-day follow-up visit.
d. Height measurement performed only at screening. Weight measurement should be performed at screening and at day 1 of each cycle.
e. Subject has an ECOG performance status ≤ 2 at screening to be eligible to enroll in study.
f. ECG assessment will be evaluated at screening, predose on cycle 1 days 1, 8 and 15, and days 1 and 15 of each subsequent visit and at EOT. Predose assessments should be taken within 1 hour before drug administration. The 12-lead ECGs will be recorded in triplicate (3 separate ECGs with 10 min resting prior to first ECG and at least 5 min apart per time point), and transmitted electronically for central reading. The mean QTcF of the triplicate ECG tracings based on central reading will be used for all treatment decisions. If the mean triplicate QTcF is > 500 ms at any time point, the ECG will be repeated (within 2 h if identified on machine read or as soon as possible if identified by central read). See [Section 5.4.4] for further guidance on treatment decision.
g. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin).
h. Subjects may be screened and enrolled from local labs only. However, clinical laboratory samples must also be submitted for central read. Laboratory tests and/or ECGs can be repeated during the screening period. In the event that the central laboratory results received after randomization are not within eligibility parameters, the subject will still be considered eligible, if local labs met the eligibility criteria, and will not be considered a protocol deviation. Local laboratory results that support eligibility and dosing decisions must be entered into the clinical database. If local laboratory is to be used to support dosing decisions, local laboratory tests will include complete blood count with differential and clinical chemistries (e.g., potassium levels, magnesium levels, glucose, serum creatinine, alanine aminotransferase and aspartate aminotransferase). Additional assessments may be done centrally or locally to monitor AEs or as required by dose modification requirements.
i. Urinalysis is only required at screening. Uric acid will be tested in cycle 1 only on days 1, 8 and 15. Additional laboratory tests may be performed according to institutional standard of care.
j. Thyroid function tests will be repeated after every 2 cycles beginning at cycle 3 (cycle 3/day 1, cycle 5/day 1, cycle 7/day 1, etc.).
k. Subject is positive for FLT3 mutation in bone marrow or blood after completion of the subject's last interventional treatment as determined by the local institution.
l. Bone marrow samples will be collected at screening, cycle 2/day 1, and cycle 3/day 1. For subjects who do not achieve a CR, CRp or CRi, the bone marrow assessments will be repeated on day 1 of every 2 subsequent cycles. For subjects who achieve a CRc (CR, CRp or CRi), bone marrow will be repeated 1 month after the date of remission and every 3 subsequent cycles or if there is suspicion of relapse in the whole blood. Bone marrow samples are also required at the EOT Visit and as clinically indicated. If bone marrow aspirate is unobtainable due to technical difficulties such as dry tap, a tube of whole blood (EDTA) along with bone marrow biopsy should be collected instead. Remaining bone marrow aspirate and/or whole blood samples will be used for MRD analysis and may be used for other biomarker analyses in relation to treatment outcome. If bone marrow aspirate is unobtainable at relapse (e.g., dry tap), a peripheral blood smear should be collected along with bone marrow biopsy. All samples will be sent to the central lab for analysis.
m. Trough pharmacokinetic samples will be collected for all subjects predose (within 1 h of dose administration) on cycle 1/days 1, 8 and 15, and on days 1 and 15 of each subsequent cycle up to 6 months.
n. Blood samples for FLT3 and AXL samples will be collected on cycle 1/day 1 predose and postdose at 2 h, between 4 to 6 h, and 24 h.
o. Blood samples for immune and blast cell immunophenotyping will be collected pre-dose at cycle 1 on days 1 and 15, cycle 2/day 1, cycle 3/day 1 and EOT.
p. Whole blood and buccal swab will be collected pre-dose on day 1 for subjects who consent to participate in the PGx study.
q. Telephone contact with the subject is sufficient unless any assessment must be repeated for resolution of treatment-related AEs.

Footnotes continued on next page

r. Only SAE data that is possibly or probably related to study drug will be collected. Any concomitant medications related to SAEs will be collected.
s. Includes medications taken within 28 days prior to day 1.
t. Gilteritinib is taken once daily at home except for clinic days when it will be taken at the clinic.
u. Subject diary for gilteritinib is to be given to the subject on day 1 of every cycle. Subjects should complete as instructed.

1 INTRODUCTION

1.1 Background

Over 90% of leukemia cases are diagnosed in adults 20 years of age and older, among whom the most common types are chronic lymphocytic leukemia (35%) and acute myeloid leukemia (AML; 32%) [American Cancer Society, 2014]. The median age at diagnosis for leukemia is 67 years of age, with 54% of patients diagnosed at 65 years or older [O'Donnell et al, 2012]. It was estimated that 18860 (11530 men and 7330 women) were to be diagnosed with and 10460 were to die of AML in 2014 in the United States [American Cancer Society, 2014]. While 60% to 80% of younger patients achieve a complete remission (CR) with standard therapy, only 30% to 40% of such patients are alive and disease-free at 5 years because relapsing AML subsequent to CR is common [Tallman, 2005]. Outcomes are worse for patients aged 60 years or over, with CR rates in the range of 40% to 55% and poor long-term survival rates. Along with age, remission rates and overall survival (OS) depend on a number of other factors, including cytogenetics, previous bone marrow disorders (such as myelodysplastic syndromes) and comorbidities.

FMS-like tyrosine kinase 3 (FLT3) is a member of the class III receptor tyrosine kinase family that is normally expressed on the surface of hematopoietic progenitor cells. FLT3 and its ligand play an important role in proliferation, survival and differentiation of multipotent stem cells. FLT3 is overexpressed in the majority of AML cases. In addition, activated FLT3 with internal tandem duplication (ITD) in and around the juxtamembrane domain and tyrosine kinase domain mutations at around D835 in the activation loop are present in 28% to 34% and 11% to 14% of AML cases, respectively [Schlenk & Döhner, 2009] transforming activity in cells [Yamamoto et al, 2001]. Patients with FLT3-ITD mutation show poor prognosis in clinical studies, with a higher relapse rate, a shorter duration of remission from initial therapy (6 months versus 11.5 months for those without FLT3-ITD mutations), as well as reduced disease-free survival (16% to 27% versus 41% at 5 years) and OS (15% to 31% versus 42% at 5 years) [Patel et al, 2012; Gale et al, 2008; Yanada et al, 2005; Tiesmeier et al, 2004; Moreno et al, 2003]. The incidence of relapse after hematopoietic stem cell transplant (HSCT) is also higher for patients with FLT3-ITD (30% versus 16% at 2 years for those without FLT3-ITD mutations) [Brunet et al, 2012]. Similar to their prognosis for first-line therapy, patients with relapsed/refractory FLT3-mutation positive AML have lower remission rates with salvage chemotherapy, shorter durations of remission to second relapse and decreased OS relative to FLT3-mutation negative patients [Konig & Levis, 2015; Chevallier et al, 2011; Levis et al, 2011].

In a recent international randomized phase III study of elacytarabine versus investigator choice in patients with relapsed/refractory AML, the CR rate in the control arm was only 12% [Roboz et al, 2014]. In this study, the treatment options available in the control arm (physician's choice) reflect contemporary clinical practice, rather than a strict selection of only patients that are eligible for intensive salvage regimens. As a result, this control arm should more appropriately represent what can be expected in standard clinical practice.

AXL, a receptor tyrosine kinase, has been detected in AML and has been shown to play a role in mediating migration and invasiveness of cancer cells. Inhibition of AXL has been shown to increase apoptosis and inhibit proliferation of FLT3-ITD and FLT3 wild-type AML cell lines and primary AML cells in vitro and reduced tumor burden and prolonged survival in mouse models [Janning et al, 2015].

Gilteritinib

XOSPATA (gilteritinib) tablets have been approved by FDA, EMA and MHLW for the treatment of adult patients who have relapsed or refractory AML with a FLT3 mutation.

Gilteritinib has an inhibitory effect on tyrosine kinases, mainly FLT3, AXL, LTK and ALK.

Gilteritinib demonstrated favorable efficacy in a nonclinical AML model, with complete regression of tumors in the xenograft model mice transplanted with MV4-11, by repeated oral doses. In addition, gilteritinib inhibited the growth of Ba/F3 cells expressing either FLT3-ITD, FLT3-D835Y or FLT3-ITD-D835Y with similar activities. Gilteritinib has been studied in relapsed or refractory AML patients in a phase 1/2 study. In the study, patients with FLT3 mutated AML receiving 80 mg or higher dose had a complete composite remission (CRc) rate of 41% and median OS of 31 weeks [Perl et al, 2017]. Furthermore, 16% of the patients tested were in complete molecular remission by FLT3-ITD based minimal residual disease (MRD) assay [Levis 2018]. Based on promising activity observed in the phase 1/2 study in AML patients, a phase 3 study in relapsed or refractory AML is currently ongoing.

Programmed Death-Ligand 1/PD-1 Inhibitors

Agents that target the programmed death-ligand 1 (PD-L1)/PD-1 axis have shown broad activity and durable responses in multiple tumor types, holding the promise of delivering immune-based therapy to almost all patients with cancer. To date, patients with solid tumors have been the focus of most clinical studies that use immune checkpoint inhibitors; however, data are emerging that these therapeutics are active in hematological malignancies. Significant preliminary activity with nivolumab has been seen in relapsed/refractory Hodgkin's lymphoma [Ansell et al, 2015]. In this ongoing phase I study, an overall response rate (ORR) of 87% was seen in patients with heavily pre-treated Hodgkin's lymphoma (n = 23). Most patients had undergone prior autologous stem cell transplant and received brentuximab vedotin. Pembrolizumab has shown similar activity in Hodgkin's lymphoma [Moskowitz et al, 2014]. Nivolumab has also been studied in a variety of relapsed/refractory lymphoid histologies (B-cell lymphoma, T-cell lymphoma, and multiple myeloma) [Lesokhin et al, 2014]. The most significant responses were seen in the diffuse large B-cell lymphoma and follicular lymphoma subgroups. Additionally, Nivolumab in combination with azacytadine achieved 22% CRc and median OS of 6.8 months in patients with relapsed or refractory AML [Daver et al, 2017].

Atezolizumab is a PD-L1 blocking antibody that previously received FDA accelerated approval for the treatment of locally advanced or metastatic urothelial carcinoma that has progressed after platinum-containing chemotherapy. On October 18, 2016, FDA approved atezolizumab for the treatment of patients with metastatic non-small cell lung cancer whose

disease progressed during or following platinum-containing chemotherapy. Currently, there have not been any results released of clinical studies with atezolizumab in AML. However, atezoluzimab monotherapy has been tested in patients with advanced myeloid malignancies [Gerds et al, 2018] and preliminary results showed an overall response rate of 62% for the atezolizumab-azacitidine arm at a dosing schedule of 840 mg intravenous every 2 weeks. Also, as previously described, studies with other checkpoint inhibitors have demonstrated clinical activity, including CRs in AML in the post-HSCT setting. Therefore, atezolizumab, as a typical PD-L1 inhibitor, was selected to be evaluated as combination therapy with gilteritinib to treat patients with relapsed/refractory FLT3 mutated AML.

1.2 Nonclinical and Clinical Data

Nonclinical and clinical data for gilteritinib (ASP2215) available as of the writing of this protocol are summarized below. Please refer to the current version of the Gilteritinib (ASP2215) Investigator's Brochure (IB).

1.2.1 Nonclinical Data – Gilteritinib

Refer to the current IB for a summary of nonclinical data on gilteritinib.

1.2.2 Nonclinical Data – Atezolizumab

Refer to the current IB for nonclinical data on atezolizumab.

1.2.3 Clinical Data - Gilteritinib

1.2.3.1 Studies Using Human Biomaterials

In Caco-2 cells, the permeability of gilteritinib was between that of known low and high permeability markers. Gilteritinib was a substrate for P-glycoprotein (P-gp), but not a substrate for breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP)1B1, OATP1B3 or organic cation transporter (OCT)1. No major human-specific gilteritinib metabolites were formed by liver microsomes or hepatocytes. The main enzyme involved in the metabolism of gilteritinib was estimated to be cytochrome P450 (CYP)3A4.

In in vitro studies, gilteritinib showed inhibitory effects on P-gp, BCRP, OATP1B1, OCT1, OCT2, multidrug and toxin extrusion (MATE)1 and MATE2-K. Gilteritinib showed direct inhibition of CYP2C19 and CYP3A4, and induction potential on CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4/5. The interactions that may be clinically relevant include the potential to inhibit CYP3A, BCRP, and P-gp in the small intestine, OCT1 in the liver, and MATE1 in the kidney. Clinical assessments were performed to evaluate the effect of gilteritinib on a MATE1 substrate and a CYP3A substrate. Results are described in [Section 1.2.3.2 Clinical Pharmacokinetics and Pharmacodynamics].

1.2.3.2 Clinical Pharmacokinetics and Pharmacodynamics

In study 2215-CL-0101, a phase 1/2 study in patients with relapsed/refractory AML, FLT3 mutational status was collected locally from the patient's record.

With regards to gilteritinib pharmacokinetics, median t_{max} was observed between 2 and 6 hours following single and repeat dosing. At a dose of 120 mg, the median C_{max} at day 15 was approximately 282 ng/mL and the median AUC at day 15 was approximately 6180 ng·h/mL. The estimated $t_{1/2}$ across dose levels based on R_{ac} ranged from 45 to 159 hours. Approximately dose proportional pharmacokinetics were observed following once daily administration of gilteritinib over the range evaluated (20 to 450 mg).

The effect of gilteritinib on the pharmacokinetics of midazolam, a CYP3A4 substrate, was investigated in patients with relapsed/refractory AML. Midazolam exposure was comparable when midazolam was administered alone or in combination with gilteritinib. The results suggest coadministration of gilteritinib and a CYP3A4 substrate is not expected to result in a clinically-relevant drug-drug interaction.

An assessment of the effect of gilteritinib on the pharmacokinetics of cephalexin, a MATE1 substrate, was also performed in patients with relapsed/refractory AML. Cephalexin exposure and renal excretion were comparable when cephalexin was administered alone or in combination with gilteritinib. These results indicated a clinically-relevant interaction is not expected when gilteritinib is coadministered with a MATE1 substrate.

The potential for drug-drug interactions was investigated in healthy subjects or patients with relapsed/refractory AML. The effect of ITZ (a strong CYP3A4 inhibitor), FLZ (a moderate CYP3A4 inhibitor) and RIF (a strong CYP inducer) on the pharmacokinetics of gilteritinib, a CYP3A4 and P-gp substrate, were evaluated in healthy adult subjects. Coadministration of gilteritinib with ITZ significantly increased gilteritinib exposure (approximately 2.21-fold) via a reduction in CL/F. As anticipated, a smaller increase in gilteritinib systemic exposure (approximately 1.43-fold) was observed following coadministration gilteritinib with FLZ. Furthermore, RIF significantly decreased gilteritinib systemic exposure (approximately 70%). In summary, coadministration of gilteritinib with a strong CYP3A4 inhibitor or inducer may result in significantly greater or lesser, respectively, gilteritinib systemic exposure.

The effect of food on gilteritinib pharmacokinetics was examined in phase 1 study 2215-CL-0113 in healthy adult subjects. Although the geometric mean C_{max} decreased approximately 26% under fed conditions, overall exposure of gilteritinib was comparable under fasted and fed conditions as evidenced by the less than 10% difference in AUC. Indices of overall gilteritinib exposure decreased approximately 10% (AUC_{inf} and AUC_{last}) and absorption was delayed (2-hour increase in median t_{max}) when gilteritinib was administered with a high-fat meal relative to fasted conditions. Gilteritinib $t_{1/2}$, CL/F and VZ/F were comparable in the fasted and fed treatment groups. Hence, gilteritinib can be administered without regard to food.

1.2.3.3 Clinical Safety

All patients receiving the study drug experienced at least 1 AE, and 91.7% (22/24) of patients experienced a drug-related AE. Common AEs, occurring in ≥ 20% of all patients, were hepatic function abnormal and blood creatine phosphokinase increased (37.5%, 9/24), blood lactate dehydrogenase increased (33.3%, 8/24), diarrhea and pyrexia (29.2%, 7/24) and

febrile neutropenia, stomatitis, renal impairment and hypertension (20.8%, 5/24). Of these common AEs, hepatic function abnormal, blood creatine phosphokinase increased and diarrhea appeared to have increased incidence with increasing doses. The majority of the common AEs were considered by the investigator to be related to study drug.

1.2.3.4 Clinical Efficacy

Results from study 2215-CL-0101 indicate that of the 252 patients who received at least 1 dose of gilteritinib, the majority of composite complete remission (CRc) and partial remission (PR) events were observed in FLT3 mutation-positive AML patients in dose groups of 80 mg and greater. The derived response rate (CRc + PR) at the EOT in the 191 FLT3 mutation-positive patients was 48.7% overall and 66.7%, 55.4%, 47.2%, 60.0% and 50.0% in the 80 mg, 120 mg, 200 mg, 300 mg and 450 mg dose groups, respectively.

Of the 249 patients who received at least 1 dose of gilteritinib in study 2215-CL-0101 who were evaluated for efficacy, the majority of CRc and PR responses were observed in FLT3 mutation-positive patients in dose groups of 80 mg and greater. The derived response rate (CRc + PR) at the end of treatment (EOT) in the 191 FLT3 mutation-positive patients was 48.7% overall and 66.7%, 55.4%, 47.2%, 60.0% and 50.0% in the 80 mg, 120 mg, 200 mg, 300 mg and 450 mg dose groups, respectively.

After gilteritinib treatment at doses ranging from 20 mg to 300 mg per day, a CRc rate of 36.8% and a response rate of 47.4% was attained. Patients in the 200 mg dose group had the highest CRc and response rate, of 57.1% (for both measures) at EOT. At EOT, 3 of the FLT3 mutation-positive patients achieved CRc (60.0%) and the response rate in this group was 80.0%. Across all dose groups, the median duration of CRc was 86.5 days and the median duration of remission was 113.5 days.

Study 2215-CL-0301, is a phase 3, open-label, randomized study comparing the efficacy and safety of gilteritinib monotherapy to salvage chemotherapy in patients with FLT3- mutated AML who are refractory to or have relapsed after first-line AML therapy.

As of the data cutoff date of 17 Sep 2018, OS was significantly longer in the gilteritinib arm (median, 9.3 months) compared with the salvage chemotherapy arm (median, 5.6 months) using a Kaplan-Meier estimate (HR: 0.637; 95% CI: 0.490, 0.830; 1-sided P-value 0.0004). The survival probability was higher in the gilteritinib arm compared with the salvage chemotherapy arm at 6 months (65.5% versus 48.9%) and 12 months (37.1% versus 16.7%).

1.2.4 Clinical Data – Atezolizumab

Refer to the current IB for clinical data on atezolizumab.

1.3 Summary of Key Safety Information for Study Drugs

1.3.1 Key Safety Information - Gilteritinib

The nonclinical and clinical studies, which are referred to in this section, are described in more detail in the ASP2215 IB.

Study 2215-CL-0101 demonstrated efficacy in FLT3 mutation-positive patients with relapsed/refractory AML, with a tolerable safety profile.

Expected ADRs for gilteritinib include the preferred terms of diarrhea, edema peripheral, blood creatine phosphokinase increased, ALT increased, AST increased, myopathy, electro-cardiogram (ECG), QT prolongation and posterior reversible encephalopathy syndrome.

Refer to [Section 1.2.3.3 Clinical Safety] and the IB for a comprehensive summary of safety findings.

The majority of patients (249 [98.8%]) in study 2215-CL-0101 experienced at least 1 treatment-emergent adverse event (TEAE), and 188 (74.6%) of patients experienced at least 1 TEAE considered by the investigator to be possibly or probably related to study drug. Common TEAEs (occurring in at least 10% of patients) included febrile neutropenia, thrombocytopenia, constipation, diarrhea, nausea, stomatitis, vomiting, asthenia, fatigue, peripheral edema, pyrexia, pneumonia, sepsis, fall, alanine aminotransferase (ALT) increased, AST increased, blood alkaline phosphatase (ALP) increased, blood creatinine increased, neutrophil count decreased, platelet count decreased, appetite decreased, hypoalbuminemia, hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, arthralgia, AML, dizziness, dysgeusia, headache, cough, dyspnea, epistaxis, hypoxia and hypotension. Other than TEAEs that were determined to be ADRs, no clear dose-dependent patterns were observed for overall TEAEs, TEAEs of grade 3 or higher, drug-related TEAEs, serious TEAEs or drug-related serious TEAEs. Peripheral edema, increases in circulating creatine kinase (CK), increases in circulating ALT and AST, myopathy, diarrhea, prolonged QT and posterior reversible encephalopathy syndrome were identified as ADRs that may be expected for gilteritinib.

Ninety-five patients experienced a TEAE with an outcome of death; of these, 1 event of each of the following: intracranial hemorrhage, pulmonary embolism, septic shock, neutropenia, ventricular fibrillation and hemoptysis were considered possibly related to gilteritinib and 1 event of respiratory failure was considered probably related to gilteritinib by the investigator. Additionally, 1 event of bacteremia recorded as grade 3 with a fatal outcome was considered possibly related to gilteritinib by the investigator. Twenty-eight patients experienced dose limiting toxicities (DLTs). None of the doses below 450 mg met the criteria for pausing enrollment. Thus, the maximum tolerated dose (MTD) in study 2215-CL-0101 is considered to be 300 mg.

As of the final analysis data cutoff date of 17 Sep 2018, 246 patients had received at least 1 dose of gilteritinib 120 mg and 109 patients had received at least 1 dose of salvage chemotherapy in Study 2215-CL-0301. 100% (246/246) of patients in the gilteritinib arm and 98.2% (107/109) of patients in the salvage chemotherapy arm experienced at least 1 TEAE. When adjusted for number of events (E) per patient year (PY) with PY defined as the total duration of exposures time in year, the E/PY of drug related TEAEs were higher in patients treated with salvage chemotherapy compared to patients treated with gilteritinib (47.23 vs 16.52).

The most frequent TEAEs in the gilteritinib arm were anemia, febrile neutropenia, pyrexia, ALT increased, AST increased, diarrhea, nausea and constipation. The most frequent TEAEs in the salvage chemotherapy arm were febrile neutropenia, anemia, nausea, diarrhea and pyrexia. Diarrhea, blood creatine phosphokinase increased, ALT increased and AST increased and edema peripheral and myalgia have been identified as expected adverse reactions for gilteritinib.

The data below is from a cutoff date of 17 Sep 2018:

When adjusted for number of events (E) per patient year (PY) with PY defined as the total duration of exposures time in year, the E/PY of drug related TEAEs leading to death were higher in patients treated with salvage chemotherapy compared to patients treated with gilteritinib (0.67 vs 0.12). The most frequent TEAEs leading to death in the gilteritinib arm by PT were AML, septic, sepsis, cardiac arrest and lung infection and pneumonia.

1.3.2 Key Safety Information - Atezolizumab

Detailed information on the toxicities and common AEs associated with atezolizumab can be found within the current IB.

In a 15-day intravenous (dosing frequency days 1, 8 and 15) toxicity study in mice, the major toxicological finding was minimal sciatic neuropathy (vacuolation and lymphocytic infiltration) at doses ≥ 10 mg/kg observed at the end of dosing and 4-week recovery period.

In repeated 8-week subcutaneous/intravenous and 26 week intravenous toxicity studies (dosing frequency: weekly) in cynomolgus monkeys, the major toxicological finding was minimal to mild multifocal arteritis/periarteritis in multiple organs including the heart, aorta, kidney, liver, pancreas, epididymis, gastrointestinal tract, skin, tongue, and female reproductive organs. The findings were reversible following a 3-month recovery period. In the 26-week study, female monkeys administered 50 mg/kg intravenous atezolizumab experienced irregular menstruation during the dosing period, including an increase in mean menstrual cycle length compared to controls and a corresponding lack of newly formed corpora lutea.

The PD-1/PD-L1 pathway is known to play an important role to maintain immune tolerance to the fetal allograft and inhibiting this pathway could cause adverse effects on pregnancy such as abortion and/or stillbirth [Poulet et al, 2016].

Preliminary data in myelodysplastic syndrome (MDS) patients of atezolizumab 840 mg every 2 weeks dose in combination with azacitidine [Gerds et al, 2018] showed that the most common adverse events (AEs) were febrile neutropenia (4/11), neutropenia (3/11) and anemia (1/11). Additionally, preliminary data of atezolizumab 840 mg every 2 weeks dose in combination with guadecitabine in MDS patients [O'Connell et al, 2018] showed that the most common AEs were again hematologic; neutropenia, thrombocytopenia and leukopenia.

1.4 Risk Benefit Assessment

Approximately 30% of adult AML subjects are refractory to induction therapy. Furthermore, of those who achieve CR, approximately 75% will relapse. Subjects with AML with FLT3 mutations comprise an especially poor prognosis group. Generally, there is no established standard for relapsed subjects with FLT3 mutations and less than 20% will achieve CR with subsequent treatment. Duration of remission for the small minority who achieve remission is also limited with most of the subjects relapsing.

In phase 1/2 Study 2215-CL-0101, ASP2215 has resulted in CRc in over 40% of subjects receiving 80 mg or higher dose. The median survival was over 7 months in 120 mg dose level. The majority of subjects in the study have received multiple treatments prior to receiving ASP2215. Furthermore, ASP2215 was well tolerated at the proposed doses in this study.

The drug interaction potential of atezolizumab is unknown [TECENTRIQ® prescribing information, 2016]. Atezolizumab is not expected to have direct impact on CYP and other drug metabolizing enzymes or transporters. In addition, atezolizumab is not expected to modulate cytokine levels, which could exert an indirect impact on CYP450 activities. No significant or clinically meaningful drug-drug interaction is expected when atezolizumab is co-administered with ASP2215, a CYP3A and P-gp substrate.

Given the lack of progress in AML drug development, the high, unmet medical need among all AML patient populations, and the promise of immune checkpoint inhibitors, the overall risk-benefit profile is favorable and justifies further exploration of atezolizumab in AML. On the basis of their mechanism of action, drugs such as atezolizumab have the potential to confer the benefits of a HSCT (i.e., GVL) with a much more tolerable side effect profile (i.e., lack of graft versus host disease).

Subjects with AML who relapse or do not respond to initial treatment have a very poor prognosis. Although there are various chemotherapy options available, they are by no means curative. The response to salvage chemotherapy is poor, and especially for subjects with FLT3 mutation. Although it is not known whether combination of ASP2215 with atezolizumab would lead to longer survival, in light of the very poor prognosis of relapsed or refractory AML subjects with FLT3 mutations, the potential for combination treatment to improve outcome outweighs the risk of potential toxicities.

2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS

2.1 Study Objective(s)

2.1.1 Primary Objectives

The primary objectives are to:

- Determine the safety and tolerability of gilteritinib given in combination with atezolizumab in subjects with relapsed or treatment refractory FLT3 mutated AML.
- Determine the CRc rate for subjects with relapsed or treatment refractory FLT3 mutated AML who either discontinued the study or completed 2 cycles of gilteritinib given in combination with atezolizumab. CRc is defined as a CR, complete remission without platelet recovery (CRp) or complete remission with incomplete hematologic recovery (CRi).

2.1.2 Secondary Objectives

The secondary objectives are to:

- Characterize the pharmacokinetics of gilteritinib and its active metabolites (if appropriate) when given in combination with atezolizumab.
- Evaluate the safety and efficacy of gilteritinib in combination with atezolizumab in terms of:
    - Gilteritinib trough plasma concentrations (C_{trough})
    - CR rate
    - CR with partial hematologic recovery (CRh)
    - Best response rate (CRc + PR)
    - Duration of remission
    - Event-free Survival (EFS)
    - OS
    - AEs, clinical laboratory results, vital signs, ECGs and Eastern Cooperative Oncology Group (ECOG) performance status scores

2.1.3 Exploratory Objectives

The exploratory objectives are to:

- Evaluate efficacy of gilteritinib given in combination with atezolizumab in terms of MRD
- Evaluate potential genomic, proteomic and/or other biomarkers that may correlate with treatment outcome
- Evaluate pharmacodynamic biomarkers of treatment effect
- Evaluate immune cell populations and AML blasts by immunophenotyping in relation to treatment effects

2.2 Study Design and Dose Rationale

2.2.1 Study Design

This is an open-label, single arm, phase 1/2 study to evaluate the safety and efficacy of combining gilteritinib with atezolizumab for subjects with relapsed or treatment refractory FLT3 mutated AML. This study will have 2 phases. Refer to [Section V Flow Charts and Schedule of Assessments] for details of design.

Phase 1:

The phase 1 portion of this study is a dose- escalation phase with a 3 + 3 design to establish the recommended phase 2 dose (RP2D) of gilteritinib given in combination with atezolizumab. Up to 12 subjects will be enrolled in cohorts of 3 to 6 subjects to determine the RP2D following the dose levels of the combination treatment outlined in the table below. Dose escalation decisions will be made based on DLTs that occur during the first cycle of treatment. A cycle is defined as 28 days. The treatment will consist of 3 distinct periods; remission induction, consolidation and maintenance.

The DLT observation period will be from cycle 1/day 1 through cycle 1/day 28. Evaluable subjects are defined as subjects who experience a DLT or in the absence of DLT, receive at least 23/28 doses of gilteritinib and at least 1/2 doses of atezolizumab. Subjects who are later discovered not to meet eligibility criteria or are not evaluable for DLT may be replaced.

Dose evaluation rules based on the 3 + 3 design and dose escalation rules are as follows:

Number of Subjects with DLT at the Given Dose During the DLT Observation Period	**Escalation Decision Rules**
0 of 3 or ≤ 1 of 6 subjects	Escalate and enter up to 3 subjects at the next dose level, if next dose level available. If at dose level 2, determine if RP2D.
1 of 3 subjects	Enter up to 3 subjects at the same dose level.
≥ 2 subjects	De-escalate or stop escalating.

DLT: dose limiting toxicity

The Dose Evaluation Committee (DEC) will consist of the sponsor, principal investigators, and if appropriate, expert consultants who will be responsible for the review of safety data through the DLT observation period for 3 or 6 evaluable subjects for each cohort. The decision will be made by the DEC to escalate to the next planned dose level, to remain at the same dose level, de-escalate to the dose level below or stop escalation. The RP2D will be selected based on the DEC's review of all available data at each dose level, including safety and pharmacokinetic data (if available), and the RP2D will become the minimum safe and biologically effective dose level. Additional details regarding responsibilities and membership requirements will be included in the Subject Enrollment and DEC Plan.

The subjects in the first cohort will be treated with gilteritinib 120 mg orally once daily and atezolizumab 420 mg once every 2 weeks by intravenous infusion. The subjects in the second

cohort phase will be dosed based on the results of the first cohort and according to the dose level table below.

Dose Level	Dose-Atezolizumab	Dose-Gilteritinib
1	420 mg q2w	120 mg once daily
-1	420 mg q2w	80 mg once daily
2	840 mg q2w	120 mg once daily

Subjects will be administered treatment until a discontinuation criterion is met. If 1 treatment is discontinued due to toxicity, the subject may continue on the other as monotherapy until a discontinuation criterion is met. Subjects will have an (EOT) visit within 7 days after last dose of study drug, followed by a 30-day follow up for safety, after which the subjects will enter the long-term follow-up period of up to 3 years for collection of subsequent AML treatment, remission status and survival (cause of death and date of death).

Phase 2:

In the phase 2 portion with 2 stages, up to 49 subjects will be enrolled. The subjects will be treated with gilteritinib and atezolizumab at the RP2D. In the first stage, 22 subjects will be enrolled. The subjects enrolled at the first stage of phase 2 will be used to calculate the CRc rate for the first stage. If the minimum CRc rate criterion (i.e., at least 12 CRc responders out of 22 subjects) is met, an additional 27 subjects will be enrolled for the second stage.

Subjects will enter the screening period up to 14 days prior to the start of treatment.

Subjects will be administered treatment until discontinuation criterion is met. If 1 treatment is discontinued due to toxicity, the subject may continue on the other as monotherapy until discontinuation criteria is met. Subjects will have an (EOT) visit within 7 days after last dose of study drug, followed by a 30-day follow up for safety, after which the subjects will enter the long-term follow-up period of up to 3 years for collection of subsequent AML treatment, remission status and survival (cause of death and date of death).

2.2.2 Dose Rationale

In the first-in-human phase 1/2 clinical study 2215-CL-0101, relapsed/refractory AML subjects were treated with gilteritinib at doses ranging from 20 to 450 mg administered once daily. The primary objectives for this study were to determine the safety and pharmacokinetics of gilteritinib following single and repeat dosing. In addition, preliminary efficacy as assessed by response rates was evaluated.

Clinical safety data indicated an MTD of 300 mg. Clinical efficacy data supports doses of 120 mg and greater to ensure efficacy in FLT3-mutation positive subjects. PIA has shown substantial reduction of phospho-FLT3, with > 90% inhibition at doses of 80 mg or greater. Although, none of the dose levels within the expansion cohort reached the threshold to stop enrollment (> 20% DLT with posterior probability of 80%), 120 mg and 200 mg doses especially had low DLT rates. However, CK and AST elevations correlating with increasing dose and increasing exposure were observed. Overall, 120 mg provides a good balance of

ensuring effective drug levels for virtually all subjects with a low incidence of safety concerns.

Doses of 80 mg and 120 mg gilteritinib given in combination with atezolizumab is chosen as a starting dose for the escalation cohort to maintain a more efficacious gilteritinib dose while confirming the safety of the combination in a population that is not able to tolerate intense therapy.

For atezolizumab, simulations [Bai et al, 2012] do not suggest any clinically meaningful differences in exposure following a fixed dose compared with a body weight-adjusted dose. On the basis of this analysis, a fixed dose of 1200 mg once every 3 weeks (equivalent to a weight based dose of 15 mg/kg once every 3 weeks) was defined as the RP2D.

For the once every 2 weeks dosing interval, the fixed dose of 840 mg once every 2 weeks is expected to be equivalent to that of 1200 mg every 3 weeks, the approved dosage for atezolizumab [Tecentriq prescribing information, 2016]. A 2-week dosing schedule is being used to better align AML treatment and evaluation schedule with gilteritinib. The fixed dose of 1200 mg once every 3 weeks (equivalent to an average body-weight based dose of 15 mg/kg once every 3 weeks) was selected on the basis of both nonclinical studies [Deng et al, 2016] and available clinical pharmacokinetic, efficacy and safety data (refer to the Atezolizumab IB for details).

The initial dose of atezolizumab to be tested in combination with gilteritinib will be 420 mg once every 2 weeks to determine the RP2D following the dose levels of the combination treatment outlined in Section 2.2.1. Dose escalation decisions will be made based on DLTs that occur during the first cycle of treatment.

2.3 Endpoints

2.3.1 Primary Endpoints

- Safety and tolerability (development of DLTs and AEs and define RP2D)
- CRc rate

2.3.2 Secondary Endpoints

- Gilteritinib trough plasma concentrations (C_{trough})
- CR rate
- CR with partial hematologic recovery (CRh)
- Best response rate
- Duration of remission
- EFS
- OS
- AEs, clinical laboratory results, vital signs, ECGs and ECOG

2.3.3 Exploratory Endpoints

- MRD in relation to clinical outcomes
- Evaluate potential genomic, proteomic and/or other biomarkers that may correlate with treatment outcome

- Evaluate pharmacodynamic biomarkers of treatment effect
- Evaluate immune cell populations and AML blasts by immunophenotyping in relation to treatment effects

3 STUDY POPULATION

3.1 Selection of Study Population

The study population will consist of a total of up to 61 adults, male and female. Subjects with relapsed or treatment refractory FLT3 mutated AML will be enrolled in this study.

Verification of inclusion and exclusion criteria for a subject's participation in this study is to be determined by the principal or a sub-investigator.

3.2 Inclusion Criteria

Subject is eligible for the study if all of the following apply:

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act Authorization for US sites) must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).

2. Subject is considered an adult according to local regulation at the time of signing informed consent form (ICF).

3. Subject has defined AML by the WHO criteria (2017) and fulfills one of the following:

- Refractory to at least 1 cycle of induction chemotherapy
- Relapsed after achieving remission with a prior therapy

4. Subject is positive for FLT3 mutation in bone marrow or blood after completion of the subject's last interventional treatment as determined by the local institution.

5. Subject has an ECOG performance status ≤ 2 at screening.

6. Subject must meet the following criteria as indicated on the clinical laboratory tests:

- Serum AST and ALT ≤ 2.5 x upper limit of normal (ULN)
- Serum total bilirubin (TBL) ≤ 1.5 x ULN
- Serum creatinine ≤ 1.5 x ULN or an estimated glomerular filtration rate of > 50 mL/min as calculated by the Modification of Diet in Renal Disease equation.

7. Subject is suitable for oral administration of study drug.

8. A female subject is eligible to participate if she is not pregnant [see Appendix 12.3 Contraception Requirements] and at least one of the following conditions applies:

- Not a woman of childbearing potential (WOCBP) as defined in [Appendix 12.3 Contraception Requirements]

OR

- WOCBP who agrees to follow the contraceptive guidance as defined in [Appendix 12.3 Contraception Requirements] throughout the treatment period and for at least 180 days after the final study drug administration.

9. Female subject must agree not to breastfeed starting at screening and throughout the study period, and for at least 180 days after the final study drug administration.

10. Female subject must not donate ova starting at screening and throughout the study period, and for at least 180 days after the final study drug administration.

11. A male subject must not donate sperm starting at screening and throughout the treatment period, and for at least 120 days after the final study drug administration.

12. A male subject with female partner(s) of child-bearing potential must agree to use contraception as detailed in [Appendix 12.3 Contraception Requirements] during the treatment period, and for at least 120 days after the final study drug administration.

13. Male subject with a pregnant or breastfeeding partner(s) must agree to remain abstinent or use a condom for the duration of the pregnancy or time partner is breastfeeding throughout the treatment period, and for 120 days after the final study drug administration.

14. Subject agrees not to participate in another investigational study while on treatment.

Waivers to the inclusion criteria will **NOT** be allowed.

3.3 Exclusion Criteria

Subject will be excluded from participation if any of the following apply:

1. Subject was diagnosed as acute promyelocytic leukemia.
2. Subject has BCR-ABL-positive leukemia (chronic myelogenous leukemia in blast crisis).

3. Subject has AML secondary to prior chemotherapy for other neoplasms (except for MDS).

4. Subject has clinically active central nervous system leukemia.

5. Subject has uncontrolled or significant cardiovascular disease, including:

- A myocardial infarction within 12 months
- Uncontrolled angina within 6 months
- History of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, torsades de pointes) or any history of arrhythmia
- Uncontrolled hypertension

6. Subject has baseline left ventricular ejection fraction (LVEF) that is < 45%.

7. Subject has mean triplicate Fridericia-corrected QT interval (QTcF) > 450 ms at screening based on central reading.

8. Subject has congenital or acquired Long QT Syndrome at screening.

9. Subject has hypokalemia and/or hypomagnesemia at screening (defined as values below institutional lower limit of normal).

10. Subject has been diagnosed with another malignancy that requires concurrent treatment or hepatic malignancy regardless of the need for treatment.

11. Subject has clinically significant coagulation abnormality unless secondary to AML in the opinion of the investigator.

12. Subject is receiving or plans to receive concomitant chemotherapy or immunotherapy other than as specified in the protocol.

13. Subject has had major surgery within 4 weeks prior to the first study dose.

14. Subject has radiation therapy within 4 weeks prior to the first study dose.

15. Subject requires treatment with concomitant drugs that are strong inducers of CYP3A.

16. Subject has known pulmonary disease with diffusion capacity of lung for carbon monoxide ≤ 65%, forced expiratory volume in the first second (FEV_1) ≤ 65%, dyspnea at rest or requiring oxygen or any pleural neoplasm.

17. Subject with systemic fungal, bacterial, viral or other uncontrolled infection that is exhibiting ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics or other treatment. The patient needs to be off pressors and have negative blood cultures for 48 hours.

18. Subject has not recovered from any prior therapy related toxicities, as determined by investigator

19. Subject is known to have human immunodeficiency virus infection.

20. Subject has active hepatitis B or C or other active hepatic disorder.

21. Subject has previously been treated with gilteritinib, quizartinib or crenolanib (will only apply to subjects enrolled in the phase 2 portion of the study).

22. Subject has active clinically significant graft-versus-host disease (GVHD) or is on treatment with systemic corticosteroids for GVHD.

23. Subject has relapsed after allogeneic HSCT.

24. Subject has an active autoimmune disorder that in the opinion of the investigator makes the subject unsuitable for study treatment or participation.

25. Subject has any condition, which, in the investigator's opinion, makes the subject unsuitable for study participation, including any contraindications of atezolizumab listed in the current IB.

Waivers to the exclusion criteria will **NOT** be allowed.

4 TREATMENT(S)

4.1 Identification of Investigational Product(s)

4.1.1 Study Drug(s)

Gilteritinib will be provided by the sponsor in high-density polyethylene bottles each containing 30 tablets of 40 mg gilteritinib (see Table 2). The study site personnel will fill out the label to indicate the number of tablets that need to be taken each day based on the assigned dose. Additional information and guidance is provided in the pharmacy manual.

Table 2 Test Drug (Gilteritinib Tablets, 40 mg)

Test Drug	Gilteritinib Tablets, 40 mg
Code name	ASP2215
Active ingredient	Chemical name: $C_{29}H_{44}N_8O_3$•1/2 $C_4H_4O_4$
Composition and dosage form	One tablet contains 40 mg of gilteritinib in free form. gilteritinib tablets are round light-yellow film-coated tablets.
Lot no.	Described in separately prepared “Study Drug Handling Procedures”
Storage	Bottled gilteritinib should be stored according to labeled storage instructions. Store in original container.

Atezolizumab will be provided by the sponsor as 1200 mg/20 mL solution in vials for intravenous infusion [Table 3]. Refer to the current IB.

Table 3 Test Drug (Atezolizumab)

Comparative Drug	Atezolizumab
Code Name	TECENTRIQ®
Active ingredient	Atezolizumab
Composition and dosage form	TECENTRIQ 1200 mg/20 mL solution for intravenous infusion
Lot No.	Refer to drug product.
Storage	Refer to current IB.

4.2 Packaging and Labeling

Gilteritinib used in this study will be prepared, packaged, and labeled under the responsibility of qualified staff at Astellas Pharma Global Development, Inc. (APGD) – Astellas United States Technologies (AUST) or sponsor’s designee in accordance with APGD-AUST or sponsor’s designee Standard Operating Procedures (SOPs), Good Manufacturing Practice (GMP) guidelines, ICH Good Clinical Practice (GCP) guidelines, and applicable local laws/regulations.

Each bottle of gilteritinib will bear a label conforming to regulatory guidelines, GMP and local laws and regulations that identifies the contents as investigational drug.

Atezolizumab will be supplied by the sponsor and will be packaged and labeled under the responsibility of qualified staff at APGD – AUST or sponsor’s designee in accordance with APGD-AUST or sponsor’s designee SOPs, GMP guidelines, ICH GCP guidelines, and applicable local laws/regulations.

Each atezolizumab 1200 mg/20 mL vial will bear a label conforming to regulatory guidelines, GMP and local laws and regulations that identifies the contents as investigational drug. Each labeled vial of atezolizumab 1200 mg/20 mL will be packaged into a 1x carton that also bears a label conforming to regulatory guidelines, GMP and local laws and regulations that identifies the contents as investigational drug.

4.3 Study Drug Handling

Current ICH GCP Guidelines require the investigator to ensure that study drug deliveries from the sponsor are received by the investigator or designee and that:

- Such deliveries are recorded,
- Study drug is handled and stored according to labeled storage conditions,
- Study drug with appropriate expiry/retest only is dispensed to study subjects in accordance with the protocol, and
- Any unused study drug is returned to the sponsor or standard procedures for the alternative disposition of unused study drug are followed.

Study drug inventory and accountability records will be kept by the investigator or designee. Study drug accountability throughout the study must be documented and reconciled. The following guidelines are therefore pertinent:

- The investigator or designee agrees not to supply study drugs to any persons except the eligible subjects in this study in accordance with the protocol.
- The investigator or designee will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these study drugs.
- A study drug inventory will be maintained by the investigator or designee. The inventory will include details of material received and a clear record of when they were dispensed and to which subject.
- At the conclusion or termination of this study, the investigator or designee agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and/or returned study drug. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility.
- The site staff must return unused study drug including gilteritinib and atezolizumab supplied by the sponsor back to the sponsor or designee at the end of the study or upon expiration.

4.4 Blinding

This section is not applicable as this is an open label study.

4.5 Assignment and Allocation

Enrollment and study drug assignment will be performed via Interactive Response Technology (IRT).

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drug(s) and Other Medication(s)

5.1.1 Dose/Dose Regimen and Administration Period

5.1.1.1 Gilteritinib Dosing

Gilteritinib is an oral tablet that subjects will take once daily. Subjects will be instructed to take the daily gilteritinib dose with water as close to the same time each morning as possible. Dose reductions are permitted [see Section 5.1.2 Reduction in Dose of the Study Drug(s)]. Gilteritinib will be taken in the clinic on visit days, and self-administered at home when subjects are not scheduled for clinic visits. If a subject forgets to take a dose in the morning and is within 6 hours of the planned dosing time, they should be instructed to take their dose. If the subject forgets to take their daily dose and more than 6 hours has passed the planned dosing time, they should be instructed to wait for the next morning to dose. If vomiting occurs after dosing, the subject should not receive another dose, but just wait until the next morning to dose.

Subjects will be treated with gilteritinib at either 120 mg or 80 mg once daily for the phase 1 portion of the study. The primary objective will be to establish an RP2D of gilteritinib in combination with atezolizumab. The RP2D will be determined by the DEC and will be the minimum safe and biologically effective dose level based on data from the phase 1 portion of the study.

In the phase 2 portion, the subjects will be treated with gilteritinib once daily at RP2D. All subjects will be treated until they no longer derive clinical benefit in the judgment of the treating physician, have unacceptable toxicity, undergo HSCT, or meet 1 of the discontinuation criteria; whichever occurs first.

5.1.1.2 Gilteritinib Subject Diary

Each subject will be given a subject diary on day 1 of each cycle. Subjects should complete the diary as instructed.

5.1.1.3 Atezolizumab Dosing

Atezolizumab at a dose of 420 mg or 840 mg via intravenous infusion will be administered once every 2 weeks for the phase 1 portion. Based on the results of the phase 1 portion, Atezolizumab may be dosed at 420 mg or 840 mg via intravenous infusion administered once every 2 weeks for the phase 2 portion of the study.

Administer the assigned dose as an intravenous infusion over 60 minutes every 2 weeks. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

Refer to the pharmacy manual and current IB for administration instructions.

The route of administration of atezolizumab outside of label instructions is not recommended and is a clinical decision of the investigator.

Atezolizumab will be prepared according to the current IB.

Atezolizumab treatment should continue until the subject no longer receives clinical benefit from therapy in the opinion of the investigator, unacceptable toxicity occurs or the subject meets a treatment discontinuation criterion.

5.1.1.4 Combination Dosing

On days where both gilteritinib and atezolizumab are dosed, gilteritinib is to be taken first, then atezolizumab second, when subject is in the clinic. It should be noted that trough pharmacokinetic samples should be collected within 1 hour prior to gilteritinib dosing, and time points for blood samples collected for FLT3 and AXL (cycle 1/day 1 – pre-dose and post-dose at 2 hours, between 4 to 6 hours and 24 hours) are relative to gilteritinib dose administration. If in the opinion of the investigator the subject no longer receives clinical benefit from or experiences unacceptable toxicity that is related to either gilteritinib or atezolizumab, then the subject may discontinue either gilteritinib or atezolizumab and continue to receive the other agent.

5.1.2 Reduction in Dose of the Study Drug(s)

5.1.2.1 Gilteritinib Dose Reduction

Gilteritinib dose cannot be reduced during the DLT observation period (cycle 1/day 1 through cycle 1/day 28) of the phase 1 portion of the study.

Guidelines for gilteritinib dose interruption and reduction for the phase 2 portion are provided in [Table 5].

The dose levels potentially used include the following [Table 4]:

Table 4 Gilteritinib Dose Levels

Dose Level (DL)	Gilteritinib Dose
DL - 0	120 mg[a]
DL – 1	80 mg
DL – 2	40 mg

[a] Starting dose for gilteritinib

The gilteritinib dose may be initially reduced by 1 dose level per day. The gilteritinib dose can be further reduced by a second dose level if the subject has already experienced clinical benefit. Note that dose reductions should occur in a step-wise manner. Only 2 dose level reductions are permitted. Dose reduction can occur during the treatment cycle based on the dose reduction guideline in [Table 5]. Additionally, if the investigator deems it necessary to ensure subject safety, dosing may be interrupted or reduced for reasons other than those provided in [Table 5]. In the unusual circumstance that dosing is interrupted or reduced for reasons not specified in the tables, the investigator should promptly inform the study medical monitor or his/her designee. If the gilteritinib dose has been reduced for related toxicities, it cannot be re-escalated. Any subjects that have been off treatment for more than 14 days other

than for HSCT or a study drug related AE, may only resume treatment after discussion with the medical monitor.

Table 5 Guidelines for Gilteritinib Dose Interruption or Reduction Event

Gilteritinib Dosing Instructions	
Nonhematological Events	
Grade 3 toxicity at least possibly related to gilteritinib	Dosing will be interrupted for up to 14 days. If the AE resolves to ≤ grade 1 within 14 days, the subject may resume dosing at the reduced dose.
Grade 4 toxicity at least possibly related to gilteritinib	Treatment will be discontinued.
QTcF > 500 ms	See [Section 5.4.4]
Myelosuppression	
Myelosuppression in the presence of CR, CRp or CRi	Dose may be reduced without interruption if the following criteria are met: Subject has received a minimum of 2 cycles of gilteritinib Platelets < 25×10^9/L and/or absolute neutrophil count (ANC) ≤ 0.5×10^9/L Marrow blasts < 5% No evidence of extramedullary disease Further dose reduction is permitted if dosing 1 full cycle at the reduced dose has not resulted in the desired hematologic recovery.

AE: adverse event; CR: complete remission; CRc: composite complete remission; CRi: complete remission with incomplete hematologic recovery; CRp: complete remission with incomplete platelet recovery; ECG: electrocardiogram; QTcF: Fridericia-corrected QT interval

5.1.3 Atezolizumab Dose Interruption

Refer to the following for atezolizumab dose modification recommendations:

Table 6 Recommended Dosage Modifications for Adverse Reactions (Atezolizumab)

Adverse Reaction	Severity of Adverse Reaction[a]	Dosage Modifications
Pneumonitis *[see Warnings and Precautions (6.3) in the current IB]*	Grade 2	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)
	Grade 3 or 4	Permanently discontinue
Hepatitis *[see Warnings and Precautions (6.3) in the current IB]*	AST or ALT > 3 and ≤ 8 x ULN or total bilirubin > 1.5 and ≤ 3 x ULN	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)
	AST or ALT > 8 x ULN or total bilirubin > 3 x ULN	Permanently discontinue
Colitis or diarrhea *[see Warnings and Precautions (6.3) in the current IB.]*	Grade 2 or 3	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)
	Grade 4	Permanently discontinue
Endocrinopathies (including but not limited to hypophysitis, adrenal insufficiency, hyperthyroidism, and type 1 diabetes mellitus) *[see Warnings and Precautions (6.3) in the current IB]*	Grade 2, 3, or 4	Withhold dose until Grade 1 or resolved and clinically stable on hormone replacement therapy.
Table continued on next page		

Adverse Reaction	Severity of Adverse Reaction[a]	Dosage Modifications
Other immune-mediated adverse reactions involving a major organ *[see Warnings and Precautions (6.3) in the current IB]*	Grade 3	Withhold dose until Grade 1 or resolved and corticosteroid dose is less than or equal to prednisone 10 mg per day (or equivalent)
	Grade 4	Permanently discontinue
Infections *[see Warnings and Precautions (6.3) in the current IB]*	Grade 3 or 4	Withhold dose until Grade 1 or resolved
Infusion-Related Reactions *[see Warnings and Precautions (6.3) in the current IB]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue
Persistent Grade 2 or 3 adverse reaction (excluding endocrinopathies)	Grade 2 or 3 adverse reaction that does not recover to Grade 0 or 1 within 12 weeks after last TECENTRIQ dose	Permanently discontinue
Inability to taper corticosteroid	Inability to reduce to less than or equal to prednisone 10 mg per day (or equivalent) within 12 weeks after last TECENTRIQ dose	Permanently discontinue
Recurrent Grade 3 or 4 adverse reaction	Recurrent Grade 3 or 4 (severe or life- threatening) adverse reaction	Permanently discontinue
Previously experienced a skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents	Grade 3 or 4 (severe or life-threatening reaction)	Caution when considering the use of atezolizumab
Suspected cutaneous adverse reactions	Grade 3 or 4	Refer to a dermatologist for further diagnosis and management
	SJS or TEN	Withhold dose until confirmation of diagnosis
Confirmed SJS or TEN	Any Grade	Permanently discontinue

SJS: Stevens-Johnson Syndrome; TEN: Toxic Epidermal Necrolysis

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0

Refer to the pharmacy manual or current IB for any updates.

5.1.3.1 Additional Dosing Interruption Guidelines

- Cycle 1: If the cycle 1/day 15 dose of atezolizumab is withheld due to, a treatment-related AE then the cycle 1/day 15 dose should be skipped and atezolizumab administration resumed at day 1 of the next cycle, if the treatment-related event has resolved or returned to grade 1.
- Subsequent cycles 2 and beyond: if the day 1 and/or day 15 dose of atezolizumab in a cycle is delayed due to a treatment-related AE, then atezolizumab administration should be skipped until the next scheduled atezolizumab dose (e.g., day 1 or day 15) of a cycle.

- In subsequent cycles, atezolizumab and gilteritinib may be interrupted for situations other than treatment related AEs such as medical/surgical events or logistical reasons not related to study therapy. Subjects should be placed back on study therapy within 14 days of the scheduled interruption, unless otherwise discussed with the medical monitor. The reason for interruption should be documented in the subject's study record.

5.1.4 Previous and Concomitant Treatment (Medication and Non-Medication Therapy)

All medications and concomitant treatments administered from 28 days prior to cycle 1/day 1 through the EOT Visit must be recorded in the electronic case report form (eCRF). Concomitant medications should be collected for reported or ongoing AE/serious adverse events (SAEs) through 30 days after the last dose of study drug for subjects who have discontinued treatment. For subjects who undergo HSCT, concomitant medications should be collected for reported or ongoing AE/SAEs through start of conditioning treatment or 30 days after the last dose of study drug, whichever comes first. Treatment with concomitant drugs that are strong inducers of CYP3A are prohibited. Treatment with concomitant drugs that are strong inhibitors or inducers of P-gp and concomitant drugs that target serotonin $5HT_{2B}R$ or sigma nonspecific receptor are to be avoided with the exception of drugs that are considered absolutely essential for the care of the subject. Treatment with concomitant drugs that are strong inhibitors of CYP3A should be avoided with the exception of antibiotics, antifungals and antivirals that are used as standard of care to prevent or treat infections. If CYP3A inhibitors are used concomitantly, subjects should be closely monitored for AEs.

Precaution should be used in use of gilteritinib with concomitant drugs that are known to prolong QT or QTc intervals.

Precaution should be used in use of gilteritinib with concomitant drugs that are substrates of BCRP, since the transporter has been shown to be inhibited by gilteritinib in in vitro studies.

Common strong CYP3A inhibitors, strong CYP3A inducers, drugs targeting the serotonin receptor, P-gp inhibitors or inducers and drugs known to prolong QT or QTc intervals are listed in [Appendix 12.4 List of Prohibited and/or Cautionary Concomitant Medications]. The investigator should consult individual labels for all drugs that the subject is taking to evaluate if they fall into any of the above named categories. For concomitant drugs that have the potential to prolong QT or QTc intervals, a cardiology consult should be obtained as medically indicated. Any other treatments of AML (including but not limited to chemotherapy, radiotherapy, surgery, immunotherapy or cellular therapy) are prohibited during therapy with gilteritinib with the exception of hydroxyurea up to 5 g daily for up to 2 weeks to keep the absolute blast count below 50×10^9/L, prophylactic intrathecal chemotherapy or cranial irradiation. Participation in another interventional study while on treatment is prohibited.

Refer to [Appendix 12.4 List of Prohibited and/or Cautionary Concomitant Medications], as well as the country specific atezolizumab package insert for additional details on excluded or cautionary use of medications.

5.1.5 Treatment Compliance

Study subjects should be counseled on the need to meet 100% compliance with study drug. Investigator or designee should ensure that study subjects meet this goal throughout the study period. When study drug is administered at the research facility, it will be administered under the supervision of study personnel.

Compliance of gilteritinib will be monitored by the accounting of unused medication returned by the subject at visits and the subject diary. Compliance will be documented in EDC and IRT.

Reasons for dose reduction or interruption will also be recorded in the eCRF.

Treatment compliance should be monitored closely and deviation in compliance should be reported to the sponsor, except in cases where directed by protocol or principal investigator (e.g., account for dose interruptions, adjustments, etc.).

5.1.6 Criteria for Continuation of Treatment

Not applicable for this study.

5.1.7 Restrictions During the Study

See Inclusion/Exclusion Criteria in [Sections 3.2 and 3.3].

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

Demographic information will be collected for all subjects and will include age, sex, race and ethnicity.

5.2.2 Medical History

Medical history includes all significant medical conditions other than AML that have resolved prior to informed consent. Conditions that are ongoing at the time of consent will be collected as baseline conditions on the Medical History eCRF. Details that will be collected include the onset date, recovery date and CTCAE grade [National Cancer Institute, 2017], if applicable for ongoing conditions.

5.2.3 Diagnosis of the Target Disease, Severity, and Duration of Disease

5.2.3.1 Disease History

AML diagnosis and studies related to AML subtype classification will be collected and will include date, bone marrow evaluations, histopathology, cytogenetics, immunophenotyping and cytochemistry, lumbar puncture results if performed (RBCs, white blood cells with differential, cytospin results) and related genetic syndromes. Dates for diagnostic procedures will be collected.

5.2.3.2 FMS-like Tyrosine Kinase Mutation Status

All subjects must have documented FLT3 mutation by the local institution after completion of the subject's last interventional treatment.

Bone marrow/blood sampling, processing, storage and shipment instructions will be provided in the Laboratory Manual. Refer to the Laboratory Manual for more detailed information.

5.2.4 Performance Status

The ECOG Scale [Oken et al, 1982] will be used to assess performance status [Table 7] and will be obtained and recorded according to the Schedule of Assessments [Table 1].

Table 7 ECOG Performance Status

Grade	Description
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

ECOG: Eastern Cooperative Oncology Group

5.3 Efficacy Assessments

5.3.1 Bone Marrow Aspirate and Biopsy

Bone marrow samples will be collected at screening, cycle 2/day 1 and cycle 3/day 1. For subjects who do not achieve a CR, CRp or CRi, the bone marrow assessments will be repeated on day 1 of every 2 subsequent cycles. For subjects who achieve a CRc (CR, CRp or CRi), bone marrow will be repeated 1 month after the date of remission and every 3 subsequent cycles or if there is suspicion of relapse in the whole blood. Bone marrow samples are also required at the EOT Visit and as clinically indicated. If bone marrow aspirate is unobtainable due to technical difficulties such as dry tap, a tube of whole blood (ethylenediaminetetraacetic acid [EDTA]) along with bone marrow biopsy should be collected instead. Remaining bone marrow aspirate and/or whole blood samples will be used for MRD analysis and may be used for other biomarker analyses in relation to treatment outcomes [described in Section 5.7] If bone marrow aspirate is unobtainable at relapse (e.g., dry tap), a peripheral blood smear should be collected along with bone marrow biopsy lab. All samples will be sent to the central lab. Refer to the laboratory manual for additional details.

5.3.2 Response Assessments

Response to treatment will be defined per modified Cheson criteria [Cheson et al, 2003] as outlined below for up to the end of 2 cycles and end of treatment.

5.3.2.1 Composite Complete Remission (CRc) rate

Defined as the rate of all complete and incomplete remission (i.e., CR+ CRp + CRi).

5.3.2.2 Complete Remission (CR)

For subjects to be classified as being in CR, they must have bone marrow regenerating normal hematopoietic cells and achieve a morphologic leukemia-free state and must have an absolute neutrophil count (ANC) > 1×10^9/L and platelet count ≥ 100×10^9/L, and normal marrow differential with < 5% blasts, and they must be red blood cell (RBC) and platelet transfusion independent (defined as 1 week without RBC transfusion and 1 week without platelet transfusion). There should be no evidence of extramedullary leukemia.

5.3.2.3 Complete Remission with Incomplete Platelet Recovery (CRp)

For subjects classified as being in CRp, they must achieve CR except for incomplete platelet recovery (< 100×10^9/L).

5.3.2.4 Complete Remission with Incomplete Hematological Recovery (CRi)

For subjects to be classified as being in CRi, they must fulfill all the criteria for CR except for incomplete hematological recovery with residual neutropenia < 1×10^9/L with or without complete platelet recovery. RBC and platelet transfusion independence is not required.

5.3.2.5 Complete Remission with Partial Hematologic Recovery (CRh)

For subjects classified as being in CR, except if their ANC is > 0.5×10^9/L and their platelets are > 50×10^9/L.

5.3.2.6 Partial Remission (PR)

For subjects to be classified as being in PR, they must have bone marrow regenerating normal hematopoietic cells with evidence of peripheral recovery with no (or only a few regenerating) circulating blasts and with a decrease of at least 50% in the percentage of blasts in the bone marrow aspirate/biopsy with the total marrow blasts between 5% and 25%.

5.3.2.7 Relapse

Relapse after CR, CRp or CRi is defined as a reappearance of leukemic blasts in the peripheral blood or ≥ 5% blasts in the bone marrow aspirate/biopsy not attributable to any other cause or reappearance or new appearance of extramedullary leukemia.

Relapse after PR is similarly defined with reappearance of significant numbers of peripheral blasts and an increase in the percentage of blasts in the bone marrow aspirate/biopsy to > 25% not attributable to any other cause or reappearance or new appearance of extramedullary leukemia.

5.3.2.8 Treatment Failure

Treatment failure is defined as lack of CR, CRp or CRi, and is determined at the EOT.

5.3.2.9 Best Response

Best response is defined as the best-measured response (CR, CRp, CRi or PR) post treatment. Two best responses will be defined.

5.3.3 Survival Time, Duration of Response and Other Efficacy Endpoints

5.3.3.1 Survival Status and Subsequent Antileukemic Treatments and Their Outcomes

Information on survival status, subsequent antileukemic treatments (including HSCT) and outcomes will be collected for all subjects during long-term follow-up.

The first survival status assessment will occur at the 30-day follow up. After the 30-day follow up, the subject or caregiver will continue to be contacted via telephone by site personnel for follow-up every 3 months. Data may be supplemented by site records when available at the time of the contact (e.g., treatment records, outcomes). Follow-up will continue until the data cut-off date for final analysis, which is estimated to be up to 3 years of follow-up for some subjects. Additional contacts may be made to support key analyses (e.g., final analysis).

Reasonable effort should be made to contact any subjects lost to follow-up during the course of the study in order to complete study-related assessments and retrieve any outstanding data and study drug. Following unsuccessful telephone contact, an effort to contact the subject by mail using a method that provides proof of receipt should be attempted. Contact via an alternate, preapproved contact is permissible if the subject is not reachable. Such efforts should be documented in the source documents.

If a subject death occurs during the SAE reporting period or if the death occurs after the SAE reporting period but is determined by the investigator to be related to study regimen (gilteritinib and/or atezolizumab), then the associated AE with outcome of death will also be reported on the AE eCRF and SAE Worksheet. If a subject death does not meet the criteria of an SAE, then death and antileukemic treatment and outcome up through the date of death should be collected and entered in the eCRF.

5.3.3.2 Overall Survival

OS is defined as the time from the date of enrollment until the date of death from any cause. For a subject who is not known to have died by the end-of-study follow-up, OS is censored at the date of last contact.

Date of last contact is defined as the death date or the latest of the following dates: treatment discontinuation date, last dosing administration date, last disease assessment date or the last follow-up date on which the subject was known to be alive.

5.3.3.3 Event-free Survival

EFS is defined as the time from the date of enrollment until the date of documented relapse from CR, CRp or CRi, treatment failure or death from any cause, whichever occurs first.

If a subject experiences relapse or death the subject is defined as having an EFS event related to either “relapse” or “death,” and the event date is the date of relapse or death.

If a subject who discontinues the treatment due to treatment failure during the first 2 treatment cycles, and the subject has no previous response of CR, CRp or CRi, the subject is defined as having an EFS event and the event date is the date of enrollment.

If a subject who discontinues the treatment due to treatment failure after the 2 treatment cycles, and the subject has no previous response of CR, CRp or CRi, the subject is defined as having an EFS event and the event date is the date of end of the 2nd treatment cycle evaluation date (i.e., cycle 3/day 1 bone marrow evaluation).

For a subject who is not known to have relapse or treatment failure or death, EFS is censored at the date of last relapse-free assessment date. Subject is not censored at HSCT.

5.3.3.4 Duration of Remission

Duration of remission includes duration of CRc, CR, CRi, CRp and response (CRc + PR).

Duration of CRc is defined as the time from the date of first CRc until the date of documented relapse for subjects who achieve CRc. Subjects who die without report of relapse are considered nonevents and censored at their last relapse-free disease assessment date. Subjects who come off study for an allogeneic HSCT will be considered nonevents and censored at the time of HSCT. Other subjects who do not relapse on study are considered nonevents and censored at the last relapse-free disease assessment date.

The duration of CR, CRp or CRi is defined similarly as duration of CRc.

Duration of response is defined as the time from the date of either first CRc or PR until the date of documented relapse of any type for subjects who achieve CRc or PR. Subjects who die without report of relapse are considered nonevents and censored at their last relapse-free disease assessment date. Subjects who come off study for an allogeneic HSCT will be considered nonevents and censored at the time of HSCT. Other subjects who do not relapse on study are considered nonevents and censored at the last relapse-free assessment date.

5.4 Safety Assessment

5.4.1 Vital Signs

Vital signs, including systolic and diastolic blood pressures (mmHg), radial pulse rate (beats/minute) and temperature will be obtained and recorded at the times specified in the Schedule of Assessments [Table 1]. All vital sign measurements will be obtained with the subject in the sitting or supine position.

If clinically significant vital sign changes from baseline (pretreatment) are noted, the changes will be documented as AEs on the AE page of the eCRF. Clinical significance will be defined as a variation in vital signs, which has medical relevance that could result in an alteration in medical care. The investigator will continue to monitor the subject until the parameter returns to grade ≤ 1 or to the baseline (pretreatment) value or until the investigator determines that follow up is no longer medically necessary

5.4.2 Laboratory Assessments

Refer to [Appendix 12.8 Laboratory Assessment] and laboratory manual for a list of the laboratory tests that will be performed during the conduct of the study. Refer to the Schedule of Assessments [Table 1] for study visit collection dates. Local laboratory tests can be used at screening for eligibility for serum chemistry, hematology, urinalysis and coagulation only. In

the event that the central laboratory results received after enrollment are not within eligibility parameters, the subject will still be considered eligible if local labs met the eligibility criteria and not considered a protocol deviation. Additional laboratory tests should be performed according to institutional standard of care. Local testing of hematology and bone marrow aspirate and/or biopsy at screening and day 1 of each cycle will be reported in the eCRF. Hematology results will need to be assessed prior to dosing.

Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator/subinvestigator who is a qualified physician.

5.4.3 Physical Examination

Standard, full physical examinations will be performed to assess general appearance, skin, eyes, ears, nose, throat, neck, cardiovascular, chest and lungs, abdomen, musculoskeletal, neurologic status, mental status and lymphatic systems. Genitourinary and rectal system examinations are to be performed only if clinically indicated. Physical examinations will be conducted at the visits outlined in the Schedule of Assessments [Table 1]. Each physical examination will include the observation and review of body system, weight at screening and on day 1 of each cycle. Height is only required at screening. If clinically significant worsening of findings from predose (day 1) is noted at any study visit, the changes will be documented as AEs on the AE page of the eCRF. Clinical significance is defined as any variation in physical findings, which has medical relevance that could result in an alteration in medical care. The investigator will continue to monitor the subject until the parameter returns to grade ≤ 1 or to the baseline (pretreatment) condition or until the investigator determines that follow up is no longer medically necessary.

5.4.4 Electrocardiogram

A 12-lead ECG will be performed during the screening period, predose of cycle 1/day 1, cycle 1/day 8, cycle 1/day 15, day 1 of each subsequent cycle, day 15 of each subsequent cycle and at the EOT visit. Predose assessments should be taken within 1 hour before gilteritinib alone or in combination with atezolizumab administration on the days when the combination is given. The 12-lead ECGs will be recorded in triplicate (3 separate ECGs, 10 minutes resting prior to first ECG and at least 5 minutes apart per time point) and transmitted electronically for central reading. The mean QTcF of the triplicate ECG tracings based on central reading will be used for all treatment interruption and reduction decisions.

If the mean triplicate QTcF is > 500 ms at any time point, on local read, the ECG will be repeated (within 2 hours if identified on machine read or as soon as possible if identified from central read). Cardiology consult will be obtained as medically indicated. If QTcF > 500 ms is confirmed, then the investigator will interrupt and reduce gilteritinib per the interruption or reduction guidelines in [Section 5.1.2 Reduction in Dose of the Study Drug(s)].

ECGs are to be performed prior to obtaining the time-matched pharmacokinetic sample, therefore, the ECGs must be started at least 10 to 15 minutes before the pharmacokinetic draw. Whenever a study procedure coincides with the scheduled time point for an ECG

triplicate, the study activities will ideally be undertaken in a fixed sequence: ECG triplicate first, vital signs (blood pressure and heart rate) second and any type of blood draw as the last assessment. This order of events is not mandatory and can be changed if required in order to accommodate pharmacokinetic time points.

5.4.5 Chest X-ray or Computed Tomography Scan

Chest X-ray or computed tomography (CT) scan is to be performed at screening. A chest X-ray (or CT of chest) does not need to be repeated if performed within 2 weeks prior to start of screening.

5.4.6 Multigated Acquisition Scan or Echocardiogram

A multigated acquisition scan (MUGA) or ECHO (as per standard of care) is to be performed at screening for all subjects.

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events

An AE is any untoward medical occurrence in a subject administered a study drug, and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease (new or exacerbated) temporally associated with the use of a medicinal product whether or not considered related to the medicinal product.

In order to identify any events that may be associated with study procedures and could lead to a change in the conduct of the study, Astellas collects AEs even if the subject has not received study drug treatment. AE collection begins after the signing of the ICF and will be collected until 30 days after the last dose of study drug or the subject is determined to be a screen failure.

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

5.5.1.1 Abnormal Laboratory Findings

Any abnormal laboratory test result (e.g., hematology, clinical chemistry or urinalysis) or other safety assessment (e.g., ECGs, radiographic scans, vital signs measurements, physical examination), including those that worsen from baseline, that is considered to be clinically significant in the medical and scientific judgment of the investigator and not related to underlying disease, is to be reported as an SAE or AE (also referred to as an [S]AE).

Any clinically significant abnormal laboratory finding or other abnormal safety assessment, which is associated with the underlying disease does not require reporting as an (S)AE, unless judged by the investigator to be more severe than expected for the subject’s condition.

Repeating an abnormal laboratory test or other safety assessment, in the absence of any of the above criteria, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

5.5.1.2 Potential Cases of Drug-Induced Liver Injury

Refer to [Appendix 12.5 Liver Safety Monitoring and Assessment] for detailed instructions on Drug Induced Liver Injury (DILI). Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) concurrent or with abnormal elevations in TBL that meet the criteria outlined in [Appendix 12.5 Liver Safety Monitoring and Assessment], in the absence of other causes of liver injury, are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and are always to be considered important medical events and reported per [Section 5.5.5 Reporting of Serious Adverse Events].

5.5.1.3 Disease Progression and Study Endpoints

Under this protocol, the following event(s) will not be considered as an (S)AE:

- Disease Progression: events including defined study endpoints that are clearly consistent with the expected pattern of progression of the underlying disease are not to be recorded as AEs. If there is any uncertainty as to whether an event is due to anticipated disease progression and/or if there is evidence suggesting a causal relationship between the study drug and the event, it should be reported as an (S)AE. All deaths up to 30 days after the last dose of study drug must be reported as an SAE, even if attributed to disease progression.
- Pre-planned and elective hospitalizations or procedures for diagnostic, therapeutic or surgical procedures for a pre-existing condition that did not worsen during the course of the clinical study. These procedures are collected per the eCRF Completion Guidelines.

5.5.2 Definition of Serious Adverse Events (SAEs)

An AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Results in death
- Is life-threatening (an AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Results in congenital anomaly or birth defect
- Requires inpatient hospitalization (except for planned procedures as allowed per study) or leads to prolongation of hospitalization (except if prolongation of planned hospitalization is not caused by an AE). Hospitalization for treatment/observation/examination caused by AE is to be considered as serious.)
- Other medically important events (defined in paragraph below)

Medical and scientific judgment should be exercised in deciding whether expedited 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 subject or may require intervention to prevent one of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, usually are considered serious. Examples of such events are 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.

5.5.2.1 Always Serious Adverse Events

The sponsor has a list of events that they classify as "always serious" events. If an AE is reported that is considered by the sponsor to be an SAE per this classification as "always serious", additional information on the event (e.g., investigator confirmation of seriousness, causality) will be requested.

5.5.3 Criteria for Causal Relationship to Study Drug

A medically qualified investigator is obligated to assess the relationship between each study drug and each occurrence of each (S)AE. This medically qualified investigator will use medical judgment, as well as the Reference Safety Information (RSI) to determine the relationship. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The medically qualified investigator is requested to provide an explanation for the causality assessment for each (S)AE and must document in the medical notes that he/she has reviewed the (S)AE and has provided an assessment of causality.

Following a review of the relevant data, the causal relationship between the study drug and each (S)AE will be assessed by answering '**yes**' or '**no**' to the question "**Do you consider that there is a reasonable possibility that the event may have been caused by the study drug**".

When making an assessment of causality, the following factors are to be considered when deciding if there is evidence and/or arguments to suggest there is a 'reasonable possibility' that an (S)AE may have been caused by the study drug (rather than a relationship cannot be ruled out) or if there is evidence to reasonably deny a causal relationship:

- Plausible temporal relationship between exposure to the study drug and (S)AE onset and/or resolution. Has the subject actually received the study drug? Did the (S)AE occur in a reasonable temporal relationship to the administration of the study drug?
- Plausibility; i.e., could the event been caused by the study drug? Consider biologic and/or pharmacologic mechanism, half-life, literature evidence, drug class, preclinical and clinical study data, etc.
- Dechallenge/Dose reduction/Rechallenge:
    - Did the (S)AE resolve or improve after stopping or reducing the dose of the suspect drug? Also consider the impact of treatment for the event when evaluating a dechallenge experience.

  - Did the (S)AE reoccur if the suspected drug was reintroduced after having been stopped?
- Laboratory or other test results; a specific lab investigation supports the assessment of the relationship between the (S)AE and the study drug (e.g., based on values pre-, during and post-treatment)
- Available alternative explanations independent of study drug exposure; such as other concomitant drugs, past medical history, concurrent or underlying disease, risk factors including medical and family history, season, location, etc. and strength of the alternative explanation

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/delegated contract research organization (CRO). However, it is very important that the medically qualified investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor/delegated CRO. With limited or insufficient information about the event to make an informed medical judgment and in absence of any indication or evidence to establish a causal relationship, a causality assessment of 'no' is to be considered. In such instance, the investigator is expected to obtain additional information regarding the event as soon as possible and to re-evaluate the causality upon receipt of additional information. The medically qualified investigator may revise his/her assessment of causality in light of new information regarding the SAE and shall send an SAE follow-up report and update the eCRF with the new information and updated causality assessment.

5.5.4 Criteria for Defining the Severity of an Adverse Event

AEs, including abnormal clinical laboratory values, will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE) guidelines (version 5.0). The items that are not stipulated in the NCI-CTCAE version 5.0 will be assessed according to the criteria below and entered into the eCRF:

Grade	Assessment Standard
1-Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations noted; intervention not indicated.
2-Moderate	Local or noninvasive intervention indicated.
3-Severe	Medically significant but not immediately life threatening, hospitalization or prolonged hospitalization.
4-Life Threatening	Life threatening consequences, urgent intervention indicated
5-Death	Death related to AE

5.5.5 Reporting of Serious Adverse Events (SAEs)

The collection of AEs and the expedited reporting of SAEs will start following receipt of the ICF and will continue until 30 days after last administration of study drug or the subject is determined to be a screen failure.

In the case of a SAE, the investigator must contact the sponsor/delegated CRO by fax or email immediately (within 24 hours of awareness).

The investigator must complete and submit an SAE worksheet containing all information that is required by local and/or regional regulations to the sponsor/delegated CRO by email or fax immediately (within 24 hours of awareness).

The SAE worksheet must be signed by a medically qualified investigator (as identified on Delegation of Authority Log). Signature confirms accuracy and completeness of the SAE data, as well as the investigator causality assessment including the explanation for the causality assessment.

For contact details, see [Section II Contact Details of Key Sponsor's Personnel]. Fax or email the SAE/Special Situations Worksheet to:

Astellas Pharma Global Development, Inc.
Global Pharmacovigilance
Fax number 888-396-3750
Alternate Fax: 847-317-1241
Email: safety-us@astellas.com

If there are any questions or if clarification is needed regarding the SAE, please contact the sponsor's medical monitor/study physician or his/her designee [Section II Contact Details of Key Sponsor's Personnel].

Follow-up information for the event should be sent promptly (within 7 days of the initial notification).

Full details of the SAE should be recorded on the medical records, SAE/Special Situation Worksheet and on the (e)CRF. The following minimum information is required:

- International Study Number (ISN)/Study number,
- Subject number, sex and age,
- The date of report,
- A description of the SAE (event, seriousness criteria),
- Causal relationship to the study drug (including reason), and
- The drug provided (if any)

The sponsor or sponsor's designee will medically evaluate the SAE and determine if the report meets the requirements for expedited reporting based on seriousness, causality, and expectedness of the events (e.g., Suspected Unexpected Serious Adverse Reaction (SUSAR) reporting) according to current local/regional regulatory requirements in participating countries. The sponsor or sponsor's designee will submit expedited safety reports (e.g., IND Safety Reports, SUSAR, Council for International Organizations of Medical Sciences [CIOMS]-I) to Competent Authorities (CA) and concerned Ethics Committee (cEC) per current local regulations, and will inform the investigators of such regulatory reports as required. Investigators must submit safety reports as required by their IRB/local IEC within timelines set by regional regulations (e.g., EMA, FDA) where required. Documentation of the submission to and receipt by the IRB/local IEC of expedited safety reports should be retained by the site.

The sponsor/delegated CRO will notify all investigators responsible for ongoing clinical studies with the study drug of all SUSARs which require submission per local requirements IRB/local IEC.

The investigators should provide written documentation of IRB/IEC notification for each report to the sponsor.

The investigator may contact the sponsor's medical monitor/study physician for any other problem related to the safety, welfare or rights of the subject.

5.5.6 Follow-up of Adverse Events

All AEs occurring during or after the subject has discontinued the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized by the investigator.

If after the protocol defined AE collection period [see Section 5.5.1 Definition of Adverse Event], an AE progresses to a SAE or the investigator learns of any (S)AE including death, where he/she considers there is reasonable possibility it is related to the study drug treatment or study participation, the investigator must promptly notify the sponsor.

5.5.7 Monitoring of Common Serious Adverse Events

Common SAEs are SAEs commonly anticipated to occur in the study population independent of drug exposure. SAEs classified as “common” are provided in [Appendix 12.6 Common Serious Adverse Events] for reference. The list does NOT change the investigator’s reporting obligations, nor his obligations to perform a causality assessment, or prevent the need to report an AE meeting the definition of an SAE as detailed above. The purpose of this list is to alert the investigator that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of “common SAEs” as specified in [Appendix 12.6 Common Serious Adverse Events]. The sponsor will monitor these events throughout the course of the study for any change in frequency. Any changes to this list will be communicated to the participating investigational sites. Investigators must report individual occurrences of these events as stated in [Section 5.5.5 Reporting of Serious Adverse Events].

5.5.8 Adverse Events of Special Interest (AESI) (Immediately Reportable to the Sponsor)

AEs of special interest (AESI) are required to be reported by the investigator to the sponsor immediately (i.e., no more than 24 hours after learning of the event). AEs of special interest are provided in the [Appendix 12.7 Adverse Events of Special Interest for Atezolizumab] for reference.

After initiation of study treatment, AEs of special interest will continue to be reported until 30 days after the last dose of study treatment. The AEs of special interest are to be collected via the SAE/Special Situation worksheet and reported within 24 hours as described in [Section 5.5.5 Reporting of SAEs].

5.5.9 Special Situations

Certain Special Situations observed in association with the study drug(s), such as incorrect administration (e.g., wrong dose of study drug) are collected in the eCRF, as Protocol Deviation per [Section 8.3 Major Protocol Deviations] or may require special reporting, as described below. These Special Situations are not considered AEs, but do require to be communicated to Astellas as per the timelines defined below.

If a Special Situation is associated with, or results in, an AE, the AE is to be assessed separately from the Special Situation and captured as an AE in the eCRF. If the AE meets the definition of a SAE, the SAE is to be reported as described in [Section 5.5.5 Reporting of Serious Adverse Events] and the details of the associated Special Situation are to be included in the clinical description on the SAE worksheet.

The Special Situations are:

- Pregnancy
- Medication Error, Overdose and "Off-label use"
- Misuse/abuse
- Occupational exposure
- Suspected Drug-Drug interaction

5.5.9.1 Pregnancy

If a female subject becomes pregnant during the study dosing period or within 180 days from the discontinuation of dosing, the investigator is to report the information to the sponsor/delegated CRO according to the timelines in [Section 5.5.5 Reporting of Serious Adverse Events] using the Pregnancy Reporting Form and in the eCRF.

The investigator will attempt to collect pregnancy information on any female partner of a male subject who becomes pregnant during the study dosing period or within 180 days from the discontinuation of dosing and report the information to sponsor/delegated CRO according to the timelines in [Section 5.5.5 Reporting of Serious Adverse Events] using the Pregnancy Reporting Form.

The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data etc., should be included in this information.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or termination (including elective termination) of a pregnancy is to be reported for a female study subject as an AE in the eCRF or SAE per [Section 5.5.5 Reporting of Serious Adverse Events]. For (S)AEs experienced by a female partner of a male subject, (S)AEs are to be reported via the Pregnancy Reporting Form.

Additional information regarding the outcome of a pregnancy when also categorized as an SAE is mentioned below:

- "Spontaneous abortion" includes miscarriage, abortion and missed abortion.

- Death of a newborn or infant within 1 month after birth is to be reported as an SAE regardless of its relationship with the study drug.
- If an infant dies more than 1 month after the birth, is to be reported if a relationship between the death and intrauterine exposure to the study drug is judged as ″possible″ by the investigator.
- Congenital anomaly (including anomaly in miscarried fetus)

Unless a congenital anomaly is identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination. (S)AEs experienced by the newborn/infant should be reported via the Pregnancy Reporting Form. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date.

5.5.9.2 Medication Error, Overdose and "Off-Label Use"

If a Medication Error, Overdose or "Off label Use" (i.e., use outside of what is stated in the protocol) is suspected, refer to Section 8.3 Major Protocol Deviations. Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of a SAE, the SAE is also to be reported as described in [Section 5.5.5 Reporting of Serious Adverse Events] together with the details of the medication error, overdose and/or "Off-Label Use".

In the event of suspected gilteritinib overdose, the subject should receive supportive care and monitoring. The medical monitor should be contacted as applicable.

In the event of suspected overdose of atezolizumab, refer to Section 6.10 in the current IB.

5.5.9.3 Misuse/Abuse

If misuse or abuse of the study drug(s) is suspected, the investigator must forward the Special Situation worksheet to the delegated CRO by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of a SAE, the SAE is also to be reported as described in [Section 5.5.5 Reporting of Serious Adverse Events] together with details of the misuse or abuse of the study drug(s).

5.5.9.4 Occupational Exposure

If occupational exposure (e.g., inadvertent exposure to the study drug(s) of site staff whilst preparing it for administration to the subject) to the study drug(s) occurs, the investigator must forward the Special Situation worksheet to delegated CRO by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs occurring to the individual associated with or resulting from the Special Situation are to be reported on the Special Situations worksheet.

5.5.9.5 Suspected Drug-Drug Interaction

If a suspected drug-drug interaction associated with the study drug(s) is suspected, the investigator must forward the Special Situation worksheet to the delegated CRO by fax or email immediately (within 24 hours of awareness). Any associated (S)AEs are to be reported in the eCRF. If the AE meets the definition of a SAE, the SAE is also to be reported as

described in [Section 5.5.5 Reporting of Serious Adverse Events] together with details of the suspected drug-drug interaction.

5.5.10 Supply of New Information Affecting the Conduct of the Study

When new information becomes available necessary for conducting the clinical study properly, the sponsor will inform all investigators involved in the clinical study, as well as the regulatory authorities. Investigators should inform the IRB/IEC of such information when needed.

The investigator will also inform the subjects, who will be required to sign an updated ICF in order to continue in the clinical study.

5.5.11 Urgent Safety Measures

An Urgent Safety Measure (USM) is an intervention, which is not defined by the protocol and can be put in place with immediate effect without needing to gain prior approval by the sponsor, relevant CA, IRB/IEC, where applicable, in order to protect study participants from any immediate hazard to their health and/or safety. Either the investigator or the sponsor can initiate an USM. The cause of an USM can be safety, product or procedure related.

5.5.12 Reporting Urgent Safety Measures

In the event of a potential USM, the investigator must contact the Astellas Study Physician (within 24 hours of awareness). Full details of the potential USM are to be recorded in the subject's medical records. The sponsor may request additional information related to the event to support their evaluation.

If the event is confirmed to be an USM the sponsor will take appropriate action to ensure the safety and welfare of the subjects. These actions may include, but are not limited to, a change in study procedures or study treatment, halting further enrollment in the study or stopping the study in its entirety. The sponsor or sponsor's designee will notify the cEC within the timelines required per current local regulations, and will inform the investigators as required. When required, investigators must notify their IRB/IEC within timelines set by regional regulations.

5.6 Test Drug Concentration

5.6.1 Pharmacokinetics

Pharmacokinetic samples will be collected at predose for all subjects to evaluate gilteritinib plasma concentrations as outlined in the Schedule of Assessments [Table 1].

For each sample, 2 mL of blood will be collected and processed.

Blood sampling, processing, storage and shipment instructions will be provided in the Laboratory Manual. Samples will be shipped to and analyzed by a sponsor-designated analytical laboratory. Please refer to the Laboratory Manual for more detailed information on this topic.

5.7 Other Measurements, Assessments or Methods

5.7.1 Blood and Buccal Swab Sample for Banked Pharmacogenomic Sample Analysis

Pharmacogenomic (PGx) research may be conducted in the future to analyze or determine genes of relevance to clinical response, pharmacokinetics and toxicity/safety issues. After enrollment, a whole blood and buccal swab sample will be collected for subjects who provide separate consent. Samples will be shipped to a sponsor-designated banking CRO.

Labels should uniquely identify each sample and contain at least:

- Protocol number (i.e., 2215-CL-1101)
- Subject number and
- Purpose and biological matrix (i.e., “biobanking,” “buccal sample”)

Details on sample collection, labeling, storage and shipment procedures will be provided in a separate Laboratory Manual. See [Appendix 12.7 Adverse Events of Special Interest (AESI) for Atezolizumab] for further details on the banking procedures.

5.7.2 Exploratory Biomarker

Bone marrow aspirate samples

Samples will be analyzed for MRD at any time point. Samples will be analyzed for FLT3 mutational status at screening/baseline and EOT, and may be analyzed for FLT3 mutational status at other time points. Samples may be analyzed for mutations in AML related genes and changes in proteins in relation to treatment effects at screening/baseline and EOT, and may be analyzed for mutations in AML related genes and changes in proteins in relation to treatment effects at other time points. Samples may be used for method development or validation of diagnostic assays related to study treatment.

Blood samples

Samples may be analyzed for MRD at any time point. Samples may be analyzed for FLT3 mutational status at screening/baseline and EOT, and may be analyzed for FLT3 mutational status at other time points. Samples may be analyzed for mutations in AML related genes and changes in proteins in relation to treatment effects at screening/baseline and EOT, and may be analyzed for mutations in AML related genes and changes in protein expression in relation to treatment effects at other time points.

Samples will be assessed for activation status of FLT3 and AXL, AML blast cell phenotyping and immunophenotyping for immune cell populations including, but not limited to, lymphocyte subsets, dendritic cells, natural killer cells, regulatory T cells and T lymphocyte subsets. Samples may be used for method development or validation of diagnostic assays related to study treatments.

Bone marrow/blood sampling, processing, storage and shipment instructions will be provided in the Laboratory Manual. Samples will be shipped to and analyzed by a sponsor-designated analytical laboratory. Samples will be stored for a period up to 15 years following study

database hard lock. Please refer to the Laboratory Manual for more detailed information on this topic.

5.7.3 Resource Utilization

Resource utilization in this study population will include analysis of data on hospitalization, blood transfusion, antibiotic IV infusions, medication for AEs and opioid usage. Details on hospitalizations and other relevant resource utilization will be collected at each study visit as indicated in the Schedule of Assessments [Table 1].

For each hospitalization, reason, admission and discharge dates, ward type (normal vs intensive care unit) will be recorded in the eCRF.

The following other resource utilization will be recorded in the eCRF: number of blood transfusions, number of units of each transfusion, number of antibiotic IV infusions, type of antibiotic, start/end dates of antibiotic treatment, type of medication for AEs, mode of administration of medication for AEs (oral, IV, etc.), start/end dates of medication for AEs, type of opioid medication, mode of administration of opioids, (oral, IV, etc.), start/end dates of opioids.

5.8 Total Amount of Blood

The total amount of blood collected for study assessments for each subject will vary depending on how long they stay on treatment.

At any time during the study, if any laboratory abnormalities are found for a subject, if results are needed before central laboratory results are available or for disease assessment, then additional blood may be drawn for monitoring.

Additional blood beyond standard monitoring that will be drawn for this study will include draws for eligibility assessment, serum chemistry, hematology, coagulation and pregnancy test at specific study defined time points, pharmacokinetics and bioanalytical sampling.

The maximum amount of blood collected for study specific assessments during the screening and cycle 1 period is approximately 42 mL.

The maximum amount of blood collected for study specific assessments in cycle 2 and beyond is approximately 36 mL per cycle.

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s) From Study Treatment

A discontinuation from treatment is a subject who enrolled in the study and for whom both study treatments are permanently discontinued for any reason. If one treatment is discontinued due to toxicity, the subject may continue on the other as monotherapy until discontinuation criteria is met. The reason for discontinuation from study treatment must be documented in the subject's medical records.

All subjects who discontinue study treatment will remain in the study and must continue to be followed for protocol specific follow-up procedures as outlined in [Table 1 Schedule of Assessments]. The only exception to this is when the subject specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information.

All participants who discontinue study treatment are to be followed for up to 3 years after their EOT, death or the final analysis, whichever occurs first per [Table 1 Schedule of Assessments].

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to discontinue the subject from study treatment or to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

If a subject is discontinued from the study with an ongoing AE or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until the condition stabilizes or no longer is clinically significant.

Subjects who meet any of the following criteria during the study will be withdrawn from study treatment:

- Subject declines further study participation (i.e., withdrawal of consent).
- Subject is non-compliant with protocol based on the investigator or medical monitor assessment.
- Subject is found to have significantly deviated from any one of the inclusion or exclusion criteria after enrollment (subjects having clinical benefit and no DLT may be kept in the study after discussion with the medical monitor).
- Subject develops an unacceptable study drug-related toxicity (DLT) or SAE requiring discontinuation of treatment.
- Subject receives any antileukemic therapy (including HSCT) other than the assigned treatment, with the exception of hydroxyurea up to 5 g daily for up to 2 weeks, prophylactic intrathecal chemotherapy or cranial irradiation.
- Subject has not achieved a PR or CRc, and in the opinion of the investigator, is no longer deriving clinical benefit after 6 cycles of therapy.
- Investigator/subinvestigator determines that the continuation of the study treatment will be detrimental to the subject.
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Female subject becomes pregnant.
- Death
- Subject is receiving gilteritinib, atezolizumab, or the combination of gilteritinib + atezolizumab and has progressive disease, recurrence under treatment, or no response, and in the opinion of the investigator the subject is no longer deriving clinical benefit.

Discontinuation criteria from long term follow-up for individual subjects:

- Subject declines further study participation (i.e., withdraws consent)
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- More than 3 years has passed from the EOT Visit.
- Death

6.1.1 Lost to Follow Up

Every reasonable effort is to be made to contact any subject lost to follow up during the course of the study to complete study-related assessments, record outstanding data, and retrieve study drug.

6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the sponsor.

6.3 Discontinuation of the Study

The sponsor may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. Advance notice is not required if the study is stopped due to safety concerns. If the sponsor terminates the study for safety reasons, the sponsor will immediately notify the investigator and subsequently provide written instructions for study termination.

7 STATISTICAL METHODOLOGY

A statistical analysis plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures to be produced. The SAP will be finalized before the database soft lock at the latest. Any changes from the analyses planned in SAP will be justified in the clinical study report.

In general, continuous data will be summarized with descriptive statistics (number of subjects, mean, SD, minimum, median and maximum), and frequency and percentage for categorical data.

Baseline will be defined as the last observation prior to first dose, unless otherwise specified.

Prior to database lock, a Final Review of Data and Tables, Listings and Figures Meeting will be held to allow a review of the clinical study data and to verify the data that will be used for analysis set classification. If required, consequences for the statistical analysis will be discussed and documented. A meeting to determine analysis set classifications may also be held prior to database lock.

7.1 Sample Size

This is an open-label, single arm study. No interim analysis and 1 final analysis are planned.

Phase 1

The sample size in phase 1 is based on 3+3 design and not based on power calculation.

Phase 2

Simon's 2-stage design [Simon, 1989] will be used in the study to evaluate the efficacy in terms of CRc rate for the selected combination dose level of gilteritinib and atezolizumab. The null hypothesis that the true CRc rate is 50% will be tested against a 1-sided alternative. In the first stage, the CRc of 22 subjects will be evaluated. If there are 11 or fewer subjects with CRc from these 22 subjects by the end of cycle 2, the study will be stopped. Otherwise, 27 additional subjects will be accrued for a total of 49 subjects evaluable for calculation of CRc rate. The null hypothesis will be rejected if 32 or more subjects with CRc are observed in the 49 subjects by the end of cycle 2. This design yields a 1-sided type I error rate of 0.025 and power of 80% when the true CRc rate is 70%. The sample size was calculated in East® Version 6.4.

Bayesian Posterior Probability for Safety Monitoring in Phase 2:

A Bayesian posterior probability will be used for safety monitoring during the whole treatment period. Subjects in phase 1 and phase 2 cohorts who complete the DLT observation period or experience DLTs will be included in the model-fitting process to provide the complete safety information. The DLT rate will be reviewed as the last subject of each cohort of 7 DLT-evaluable subjects completes the first treatment cycle. The estimated DLT rates based on the Bayesian beta-binomial model will be provided for safety monitoring in the dose expansion cohort. If the DLT rate for the expanded dose level is equal or higher than 20% with a posterior probability of 80%, then the enrollment to the expansion cohort will be paused and the safety will be reassessed by the DEC. If the reassessment warrants, enrollment to the expansion cohort may be continued at the current dose level or 1 lower dose level. Safety evaluation will be conducted separately for induction, consolidation and maintenance phases.

With a non-informative prior, Beta(1,1) distribution, the numbers of DLTs for each cohort of 7 DLT-evaluable subjects, which trigger the enrollment pause for toxicities review, are listed in the following table:

DLT-evaluable Subjects	Number of DLTs
7	3
14	4
21	6
28	8
35	9
42	11
49	12

DLT: dose-limiting toxicity

7.2 Analysis Sets

Detailed criteria for analysis sets will be laid out in Classification Specifications and the allocation of subjects to analysis sets will be determined prior to database hard-lock.

7.2.1 Full Analysis Set (FAS)

The full analysis set (FAS) will consist of all subjects who are enrolled in the study and took at least 1 dose of study drug. The FAS will be used for efficacy analyses. Subjects will be analyzed based on the actual treatment received.

7.2.2 Per Protocol Set (PPS)

The per protocol set (PPS) will consist of the subset of the FAS who do not meet criteria for PPS exclusion. These criteria are to capture relevant non-adherence to the protocol and will be defined in the SAP. The sensitivity analyses for the primary and some secondary endpoints may be performed on the PPS. Select demographic and baseline characteristics will also be summarized for the PPS.

7.2.3 Safety Analysis Set (SAF)

For the statistical summary of the safety data, the safety analysis set (SAF) will be used. The SAF consists of all subjects who took at least 1 dose of study drug (gilteritinib or atezolizumab) and will be used for safety analyses. The subjects will be analyzed based on the actual treatment received. The FAS and SAF are the same for this study.

7.2.4 Pharmacokinetics Analysis Set (PKAS)

The pharmacokinetics analysis set (PKAS) consists of the administered population for which sufficient plasma concentration data is available to facilitate derivation of at least one pharmacokinetic parameter and for whom at least 1 plasma concentration datum is available and both the date and time of dosing on the day of pharmacokinetic sampling and the date and time of sampling are known. Additional subjects may be excluded from the PKAS at the discretion of the pharmacokineticist. Any formal definitions for exclusion of subjects or time-points from the PKAS will be documented in the in the Classification Specifications and determined the Classification Meeting.

7.2.5 Biomarker Analysis Set (BMAS)

The biomarker analysis set (BMAS) will include the subjects from the administered population for whom sufficient biomarker measurements were collected.

7.3 Demographics and Baseline Characteristics

7.3.1 Demographics

Demographics and baseline characteristics will be summarized by treatment group for the SAF. Descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum for continuous endpoints and frequency and percentage for categorical endpoints.

7.3.2 Subject Disposition

The number and percentage of all subjects during the study will be reported per treatment group, study drug administration, subject completion, premature discontinuation and major protocol violations.

7.3.3 Previous and Concomitant Medications

The frequency of concomitant medications (prescription, over-the-counter and nutritional supplements) will be summarized by treatment group and PT for SAF. Medications will be coded using the WHO drug dictionary. Medications will be counted by the number of subjects who took each medication. A subject taking the same medication multiple times will only be counted once for that medication. Medications will be presented in decreasing order of frequency based on the total number of subjects who took each medication.

7.3.4 Medical History

A detailed medical history for each subject will be obtained during screening period and will be summarized by treatment group for the SAF

7.3.5 Disease History

Each subject's complete cancer history will be listed. The number and percentage of subjects will be used to summarize the AML subtype and FLT3 mutation status.

7.3.6 Treatment Compliance

Treatment compliance is defined as the total number of doses of gilteritinib in combination with atezolizumab actually taken by the subject divided by the number of doses of study drug expected to be taken during the study multiplied by 100. Descriptive statistics for study drug compliance will be presented by dose for the entire study period for the SAF by treatment group.

7.3.7 Extent of Exposure

Drug exposure including duration of exposure, cumulative dose, average daily dose, dose intensity and relative dose intensity will be summarized by treatment group. The number and

proportion of subjects with dose reduction, dose escalation and dose interruption will be tabulated. Details of the calculation will be provided in SAP.

7.4 Analysis of Efficacy

Efficacy analysis will be conducted on the FAS and PPS in which FAS will be considered as primary and PPS as supportive.

7.4.1 Analysis of Efficacy Variables

CRc rate, CR rate, best response rate, duration of remission, EFS and OS, will be summarized using descriptive statistics. The CRc rate, CR rate, best response rate with the corresponding 95% confidence interval will be reported by treatment group. The survival curve and median time for time-to-event variables will be estimated using the Kaplan-Meier method and will be reported along with the corresponding 95% confidence interval by treatment group.

7.5 Analysis of Safety

The safety evaluation will be based mainly on AEs, clinical laboratory results, vital sign measurements, ECGs and ECOG performance scores. Descriptive statistics will be used to summarize safety data. All safety data will be summarized by treatment received and the analyses will be performed on the SAF.

7.5.1 Adverse Events

All AEs recorded on treatment including within 30 days from the last study treatment will be summarized. AEs will be categorized by SOC and PT using the MedDRA dictionary and will be graded according to the NCI CTCAE version 5.0.

The number and percent of subjects experiencing 1 or more AE(s) will be summarized by treatment group, SOC and PT. The number and percentage of subjects with at least one grade 3 or higher AE will be summarized by treatment group, SOC and PT.

Distribution of the maximum severity (grade) and treatment-related AEs will be summarized by treatment group, SOC and PT. Distribution of SAEs, discontinuations due to AE and deaths on study will be presented for each treatment group.

Additional summary tables will be generated for the following population subsets: subjects with SAEs including deaths, subjects who discontinue due to AEs and investigator-attributed relationship to study drug for AEs and SAEs.

All summaries of AEs will include only TEAEs unless otherwise stated. Listings of AEs, SAEs, deaths and withdrawals due to AEs will be presented.

7.5.2 Laboratory Assessments

Clinical laboratory evaluations (including serum chemistry, hematology, coagulation and urinalysis) and their changes from baseline will be summarized by treatment group using descriptive statistics. Clinically significant abnormalities in laboratory values will be presented for each treatment. Shift tables will present shift from baseline to worst grade for

selected variables using the NCI-CTCAE grade and laboratory reference range indicator. Frequency of subjects with laboratory values outside normal range will be generated in addition to tabulation of worst toxicity grade.

7.5.3 Vital Signs

Descriptive statistics will be used to summarize vital sign results and changes from baseline by treatment group and time point.

7.5.4 Physical Examination

Physical examination findings will be listed by the actual treatment received. All clinically significant abnormal findings will be recorded as medical history or AEs and graded using NCI-CTCAE guidelines.

7.5.5 Routine 12-lead Electrocardiograms

The 12-lead ECG results will be summarized by the actual treatment received and time point. Overall ECG interpretation will be summarized for each time point. A shift analysis table showing shifts from baseline in overall ECG (normal, abnormal) will be provided. ECG parameters and their change from baseline will be summarized by treatment group using descriptive statistics.

7.6 Analysis of Pharmacokinetics

Descriptive statistics (e.g., N, mean, standard deviation, minimum, median, maximum, coefficient of variation [CV], geometric mean, and geometric CV) will be provided for trough plasma concentrations (C_{trough}) of gilteritinib and possible metabolite(s), if appropriate, by treatment, visit and time point.

7.7 Analysis of Pharmacodynamics

Changes in the activation status of FLT3 and AXL may be assessed before and after treatment.

7.8 Analysis of Biomarkers

MRD will be assessed in relation to the following efficacy variables: CRc rate, CR rate, EFS, Duration of remission and OS.

FLT3 mutational status at baseline and EOT, as well as mutations in other AML related genes and protein expression will be assessed in relation to CRc rate, CR rate, EFS, Duration of remission and OS.

Baseline levels and changes from baseline in immune cell populations and AML blasts by immunophenotyping will be assessed in relation to CRc rate, CR rate and OS.

7.9 Major Protocol Deviations and Other Analyses

Major protocol deviations as defined in [Section 8.3 Major Protocol Deviations] will be provided in a data listing.

The major protocol deviation criteria will be uniquely identified as follows:

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

7.10 Interim Analysis (and Early Discontinuation of the Clinical Study)

No formal interim analysis is planned.

7.11 Handling of Missing Data, Outliers, Visit Windows, and Other Information

Imputation methods for missing data, if applicable, and the definitions for windows to be used for analyses by visit will be outlined in the SAP.

8 OPERATIONAL CONSIDERATIONS

8.1 Data Collection

The investigator or site designee will enter data collected using an Electronic Data Capture system. In the interest of collecting data in the most efficient manner, the investigator or site designee should record data (including laboratory values, if applicable) in the eCRF within 5 days after the subject's visit.

The investigator or site designee is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. These documents should be appropriately maintained by the site.

The monitor should verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them.

Certain laboratory tests are performed at a central laboratory per the Schedule of Assessments [Table 1]. Laboratory data performed at a central laboratory will be transferred electronically to the sponsor or designee at predefined intervals during the study. The Central laboratory will provide the sponsor or designee with a complete and clean copy of the data.

ECG results will be read at a central ECG reading laboratory. Central ECG read data will be transferred electronically to the sponsor or designee at predefined intervals during the study. The central ECG laboratory will provide the sponsor or designee with a complete and clean copy of the data.

The investigator or designee will be responsible for eCRF completion and that all data and queries are accurate, complete and are verifiable with the source. The source should be appropriately maintained by the clinical unit.

Electronic data sources and any supporting documents should be available for review/retrieval by the sponsor/designee at any given time.

8.2 Screen Failures

For screen failures the demographic data, reason for failing, informed consent, inclusion and exclusion criteria and AEs will be collected in the eCRF.

8.3 Major Protocol Deviations

A major protocol deviation is generally an unplanned excursion from the protocol that is not implemented or intended as a systematic change. The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol and must protect the rights, safety, and welfare of subjects. The investigator should not implement any deviation from, or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to study subjects.

A protocol waiver is a documented prospective approval of a request from an investigator to deviate from the protocol. Protocol waivers are strictly prohibited.

The major protocol deviation criteria are as follows:

PD1 - Entered into the study even though they did not satisfy entry criteria,

PD2 - Developed withdrawal criteria during the study and was not withdrawn,

PD3 - Received wrong treatment or incorrect dose,

PD4 - Received excluded concomitant treatment.

When a major deviation from the protocol is identified for an individual subject, the investigator or designee must ensure the sponsor is notified. The sponsor will follow-up with the investigator, as applicable, to assess the deviation and the possible impact to the safety and/or efficacy of the subject to determine subject continuation in the study.

If a major deviation impacts the safety of a subject, the investigator must contact the sponsor immediately.

The investigator will also assure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will be provided to the sponsor and maintained within the trial master file.

9 END OF TRIAL

The end of the study is defined as the last visit or scheduled procedure shown in the Schedule of Assessments [Table 1] for the last study participant in the study.

10 STUDY ORGANIZATION

10.1 Independent Data-Monitoring Committee (IDMC) | Data and Safety Monitoring Board (DSMB) | Monitoring Committee | Adjudication Committee | Other Evaluation Committee(s)

This section is not applicable to this study.

10.2 Other Study Organization

A DEC consisting of sponsor representatives and investigators will convene once a dose level cohort completes the DLT observation period and the data are available for review.

Additional details regarding responsibilities, membership requirements and safety review time points will be included in the DEC Plan.

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12 APPENDICES

12.1 Ethical, Regulatory, and Study Oversight Considerations

12.1.1 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

12.1.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

GCP requires that the clinical protocol, any protocol amendments, the IB, the ICF and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IRB/IEC. The IRB/IEC will review the ethical, scientific and medical appropriateness of the study before it is conducted. IRB/IEC approval of the protocol, ICF and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any substantial amendments to the protocol will require IRB/IEC approval before implementation, except for changes necessary to eliminate an immediate hazard to subjects.

The investigator will be responsible for the following:

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

12.1.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments: substantial amendments and/or non-substantial amendments. Depending on the nature of the amendment, either IRB/IEC or notification may be required. The changes will become effective only after the approval of the sponsor, the investigator, the regulatory authority and the IRB/IEC (if applicable).

Amendments to this protocol must be signed by the sponsor and the investigator. Written verification of IRB/IEC approval will be obtained before any amendment is implemented which affects subject safety or the evaluation of safety, and/or efficacy. Modifications to the protocol that are administrative in nature do not require IRB/IEC approval, but will be submitted to the IRB/IEC for their information, if required by local regulations.

If there are changes to the ICF, written verification of IRB/IEC approval must be forwarded to the sponsor. An approved copy of the new ICF must also be forwarded to the sponsor.

12.1.4 Financial Disclosure

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

12.1.5 Informed Consent of Subjects

12.1.5.1 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject or his/her legal representative, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject or his/her guardian or legal representative, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor regulatory authorities and other applicable individuals upon request.

12.1.5.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

1. The investigator or his/her representative will immediately inform the subject orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue to participate in the study (e.g., report of serious drug ADR). The communication must be documented in the subject's medical records and whether the subject is willing to remain in the study or not must be confirmed and documented.
2. The investigator must update their ICF and submit it for approval to the IRB/IEC. The investigator or his/her representative must obtain written informed consent from the subject on all updated ICFs throughout their participation in the study. The investigator or his/her designee must re-consent subjects with the updated ICF even if relevant information was provided orally. The investigator or his/her representative who obtained the written informed consent and the subject should sign and date the ICF. A copy of the signed ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must be made in the subject's records documenting the re-consent process.

12.1.6 Source Documents

Source data must be available at the site to document the existence of the study subjects and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The investigator is responsible for ensuring the source data are attributable, legible, contemporaneous, original, accurate and complete whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, achieved, retrieved or transmitted electronically via computerized systems (and/or other kind of electric devices) as part of regulated clinical study activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records, protocol related assessments, AE tracking, and/or drug accountability.

Paper records from electronic systems used in place of electronic format must be certified copies. A certified copy must be an exact copy and must have all the same attributes and information as the original. Certified copies must include signature and date of the individual completing the certification. Certified copies must be a complete and chronological set of study records (including notes, attachments, and audit trail information (if applicable). All printed records must be kept in the subject file and available for archive.

12.1.7 Record Retention

The investigator will archive all study data (e.g., subject identification code list, source data, eCRFs and investigator's file) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation (for US sites, 2 years after approval of the NDA or discontinuation of the IND). The investigator agrees to obtain the sponsor's agreement prior to disposal, moving, or transferring of any study-related records. The sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes.

12.1.8 Subject Confidentiality and Privacy

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited unless otherwise the subject provides written consent or approval. Additional medical information may be given only after approval of the subject to the investigator or to other appropriate medical personnel responsible for the subject's well-being.

The sponsor shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

Even though any individuals involved in the study, including the study monitors and auditors, may get to know matters related to subject's privacy due to direct access to source documents, or from other sources, they may not leak the content to third parties.

The sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number will identify subject data retrieved by the sponsor. However, the sponsor requires the investigator to permit the sponsor, sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The sponsor agrees to comply and process personal data in accordance with all applicable privacy laws and regulations, including, without limitation, the Personal Information Protection Law in Japan and Privacy laws in the US. If the services will involve the collection or processing of personal data (as defined by applicable data protection legislation) within the European Economic Area (EEA), then sponsor shall serve as the controller of such data, as defined by the EU Data Protection Directive, and investigator and/or third party shall act only under the instructions of the sponsor in regard to personal data If sponsor is not based in the EEA, sponsor must appoint a third party to act as its local data protection representative or arrange for a co-controller established in the EU for data protection purposes in order to comply with the Directive.

12.1.9 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, the IB and other pertinent information is confidential and remains the property of the sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator may use this information for the purpose of the study only. It is understood by the investigator that the sponsor will use the information obtained during the clinical study in connection with the development of the drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the sponsor with all data obtained during the study.

Publication of the study results is discussed in the clinical study agreement.

12.1.10 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final study report which forms part of a marketing authorization application be signed by the representative for the coordinating investigator(s) or the principal investigator(s). The representative for the coordinating investigator (s) or the principal investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for coordinating investigator(s) or the principal investigator(s) will be selected from the participating investigators by the sponsor prior to database lock.

12.2 Procedure for Clinical Study Quality Control

12.2.1 Clinical Study Monitoring

The sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the investigator/subinvestigator are accurate and complete and that they are verifiable with study-related records such as source documents. The sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

12.2.2 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the sponsor or delegated CRO as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records including source documents when they are requested by the sponsor monitors and auditors, the IRB/IEC, or regulatory authorities. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

12.2.3 Data Management

Data Management will be coordinated by the Global Data Science department of the sponsor in accordance with the SOPs for data management. All study specific processes and definitions will be documented by Data Management. Completion of the eCRF will be described in the eCRF Completion Guidelines. Coding of medical terms and medications will be performed using MedDRA and WHO Drug Dictionary respectively.

12.2.4 Quality Assurance

The sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that studies are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s). Where applicable, the quality assurance and quality control systems and written SOPs of the CRO will be applied.

The sponsor or sponsor's designee may arrange to audit the clinical study at any or all investigational sites and facilities. The audit may include on-site review of regulatory documents, case report forms, and source documents. Direct access to these documents will be required by the auditors.

12.3 Contraception Requirements

WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Schedule of Assessments.

WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION DEFINITIONS (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following (at least 1 month prior to screening):
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Post-menopausal

Documentation of any of these categories can come from the site personnel's review of the female subject's medical records, medical examination, or medical history interview.

A postmenopausal state is defined as at least 12 months after last regular menstrual bleeding without an alternative medical cause.

- In case the last regular menstrual bleeding cannot be clearly determined, confirmation with repeated FSH measurements of at least > 40 IU/L (or higher per local institutional guidelines), is required.

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

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

One of the highly effective methods of contraception listed below is required at the time of informed consent and until the end of relevant systemic exposure, defined as 180 days after the final study drug administration[a]

Highly Effective Contraceptive Methods (Failure rate of < 1% per year when used consistently and correctly) [b]

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

- oral
- intravaginal
- transdermal

Progestogen-only hormonal contraception associated with inhibition of ovulation

- oral
- injectable
- implantable

Hormonal methods of contraception containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)

- intrauterine device (IUD)
- bilateral tubal occlusion

Male is sterile due to a bilateral orchiectomy

Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male 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.)*

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 drug. 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. It is not necessary to use any other method of contraception when complete abstinence is elected.*

[a] Local laws and regulations may require use of alternative and/or additional contraception methods.

[b] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL.

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during treatment and until the end of relevant systemic exposure defined as 120 days after final drug administration.*****

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to remain abstinent use a condom during treatment and until end of relevant systemic exposure defined as 120 days after final drug administration.
- Female partners of male participants who have not undergone a vasectomy with the absence of sperm confirmed or a bilateral orchiectomy should consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 180 days after final drug administration.

12.4 List of Prohibited and/or Concomitant Medications to be Use with Caution

Treatment with concomitant drugs that are strong inducers of CYP3A are **prohibited.** The following list describes medications and foods that are common strong inducers of CYP3A. This list should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity to induce CYP3A.

Strong CYP3A Inducers

Drug Type	Generic Drug Name
Antiepileptic, Anticonvulsant	Carbamazepine Phenytoin
Antibiotic	Rifampicin
Food/Juice Supplement	St. John's Wort

Source: Table 4 in FDA Draft Guidance for Industry – Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Recommendations (February 2012)
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf.
CYP: cytochrome P450.

The following list describes medications and foods that are common strong inhibitors of CYP3A and should be used with caution. This list should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity to inhibit CYP3A.

Strong CYP3A Inhibitors

Drug Type	Generic Drug Name
Human Immunodeficiency Virus Protease Inhibitors	Indinavir Nelfinavir Lopinavir/ritonavir Ritonavir Saquinavir
Food/Juice	Grapefruit juice
Others	Boceprevir Clarithromycin Conivaptan Itraconazole Ketoconazole Nefazodone Posaconazole Telaprevir Telithromycin Voriconazole

Source: Table 3 in FDA Draft Guidance for Industry – Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Recommendations (February 2012)
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm292362.pdf.
CYP: cytochrome P450.

The following list describes medications that target serotonin receptors. This list should not be considered all inclusive. Consult individual drug labels for specific information on whether a compound targets serotonin receptors.

Drugs Targeting Serotonin Receptors

Drug Type	Generic Drug Name
Affinity or function to $5HT_{2B}R$	Eletriptan Hydrobromide

$5HT_{2B}R$: 5-hydroxytryptamine receptor 2B

The following list describes medications and foods that are common inhibitors or inducers of P-gp and should be used with caution. This list should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity to inhibit or induce P-gp.

P-gp Inhibitors or Inducers

Transporter	Gene	Inhibitor	Inducer
P-gp	*ABCB1*	Amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, verapamil	Avasimibe, carbamazepine, phenytoin, rifampin, St John's wort, tipranavir/ritonavir

P-gp: P-glycoprotein

Source: Table 12 in http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664 htm#major

Drugs Targeting Sigma (nonspecific) Receptor (sigma R)

No list of drugs that target sigma nonspecific receptor is provided. Please consult individual drug labels for specific information on whether a compound targets sigma nonspecific receptors.

Drugs That May Prolong QT or QTc

The following list describes drugs that are known to prolong QT or QTc. This list should not be considered all inclusive. Consult individual drug labels for specific information on whether a compound is known to prolong QT or QTc.

Drug Type	**Generic Drug Name**
Class IA antiarrhythmics	Quinidine Procainamide Disopyramide
Class IC antiarrhythmics	Flecainide Propafenone Moricizine
Class III antiarrhythmics	Amiodarone Sotalol Bretylium Ibutilide Dofetilide
Antipsychotics	Thioridazine Mesoridazine Chlorpromazine Prochlorperazine Trifluoperazine Fluphenazine Perphenazine Pimozide Risperidone
Antipsychotics	Ziprasadone Lithium Haloperidol
Tricyclic/tetracyclic antidepressants	Amitriptyline Desipramine Doxepin Dosulepin hydrochloride Imipramine Maprotiline
Selective serotonin and norepinephrine reuptake inhibitors (SSNRIs) antidepressants	Venlafaxine
Macrolide antibiotics	Azithromycin Erythromycin Clarithromycin Dirithromycin Roxithromycin Tulathromycin
Fluoroquinolone antibiotics	Moxifloxacin Gatifloxacin
Azole antifungals	Ketoconazole Fluconazole Itraconazole Posaconazole Voriconazole
Table continued on next page	

Drug Type	**Generic Drug Name**
Antimalarials	Amodiaquine Atovaquone Chloroquine Doxycycline Halofantrine Mefloquine Proguanil Primaquine Pyrimethamine Quinine Sulphadoxine
Antiprotozoals	Pentamidine
Antiemetics	Droperidol Dolasetron Granisetron Ondansetron
Antiestrogens	Tamoxifen
Immunosuppressants	Tacrolimus

Source:
Yap GY, Camm AJ. Drug induced qt prolongation and torsades de pointes. Heart. 2003;89:1363-1372.

12.5 Liver Safety Monitoring and Assessment

Any subject enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases to > 3 x ULN or TBL > 2 x ULN should undergo detailed testing for liver enzymes (including at least ALT, AST, ALP, and TBL). Testing should be repeated within 72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central laboratory regarding moderate and severe liver abnormality to inform the investigator and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

Confirmed abnormalities will be characterized as moderate and severe where ULN:

	ALT or AST		**TBL**
Moderate	> 3 x ULN	or	> 2 x ULN
Severe	> 3 x ULN	and	> 2 x ULN

In addition, the subject should be considered to have severe hepatic abnormalities for any of the following:

- ALT or AST > 8 x ULN.
- ALT or AST > 5 x ULN for more than 2 weeks.
- ALT or AST > 3 x ULN and International Normalized Ratio (INR) > 1.5 (If INR testing is applicable/evaluated).
- ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

The investigator may determine that abnormal liver function results, other than as described above, may qualify as moderate or severe abnormalities and require additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and severe abnormalities in hepatic functions should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination and laboratory tests. The site staff is to complete the liver abnormality case report form (LA-CRF). Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal liver function tests (LFTs) should be repeated 2 to 3 times weekly then weekly or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.

Severe hepatic liver function abnormalities as defined above, in the absence of another etiology, may be considered an important medical event and may be reported as a SAE. The sponsor should be contacted and informed of all subjects for whom severe hepatic liver function abnormalities possibly attributable to study drug are observed.

To further assess abnormal hepatic laboratory findings, the investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new-onset diseases is to be recorded as "AEs" within the (e)CRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis is seen in obese hyperlipoproteinemic and/or diabetic subjects, and may be associated with fluctuating AT levels. The investigator should ensure that the medical history form captures any illness that predates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including nonprescription medication, complementary and alternative medications), alcohol use, recreational drug use and special diets. Medications, is to be entered in the (e)CRF. Information on alcohol, other substance use and diet should be entered on the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents.
- Based on the subject's history, other testing may be appropriate including:
    - Acute viral hepatitis (A, B, C, D, E or other infectious agents),
    - Ultrasound or other imaging to assess biliary tract disease,
    - Other laboratory tests including INR, direct bilirubin.
- Consider gastroenterology or hepatology consultations.
- Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study Treatment Discontinuation

In the absence of an explanation for increased LFT's, such as viral hepatitis, preexisting or acute liver disease, or exposure to other agents associated with liver injury, the subject may be discontinued from study treatment. The investigator may determine that it is not in the subject's best interest to continue study treatment. Discontinuation of study treatment should be considered if:

- ALT or AST > 8 x ULN.
- ALT or AST > 5 x ULN for more than 2 weeks.
- ALT or AST > 3 x ULN and TBL > 2 x ULN or INR > 1.5) (If INR testing is applicable/evaluated).
- ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

In addition, if close monitoring for a subject with moderate or severe hepatic laboratory tests is not possible, study treatment should be discontinued.

*Hy's Law Definition: Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10 to 50% mortality (or transplant).

The 2 "requirements" for Hy's Law are:

1) Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations higher 3 x ULN ("2 x ULN elevations are too common in treated and untreated patients to be discriminating").

2) Cases of increased bilirubin (at least 2 x ULN) with concurrent transaminase elevations at least 3 x ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated ALP) or Gilbert's syndrome [Temple, 2006].

FDA Guidance for Industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation"2009:

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo.
2. Among study subjects showing such AT elevations, often with ATs much greater than 3 x ULN, one or more also show elevation of serum TBL to > 2 x ULN, without initial findings of cholestasis (elevated serum ALP).
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury. [Guidance for Industry titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" issued by FDA on July 2009]

References

Temple R. Hy's law: Predicting Serious Hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006 April;15(Suppl 4):241-3.

Guidance for Industry titled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" issued by FDA on July 2009.

12.6 Common Serious Adverse Events

The following is a list of SAEs that the sponsor considers to be associated with the disease state being studied. The list does NOT change your reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed in [Section 5.5.2 Definition of Serious Adverse Events]. The purpose of this list is to alert the investigator that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common SAEs". The investigator is required to follow the requirements detailed in [Section 5.5.5 Reporting of Serious Adverse Events].

For IND safety reporting, single occurrences of the following events may be excluded from expedited reporting to the FDA. If aggregate analysis of these events indicate they occur more frequently with study drug, an expedited IND safety report may be submitted to the FDA.

Serious Adverse Events Caused by AML	**Grades Usually Observed with AML**
Hematologic AE	
Anemia	0 - 4
Bone marrow hypocellular	0 - 4
CD4 lymphocytes decreased	0 - 4
Disseminated intravascular coagulation	0 - 3
Leukocytosis	0 - 4
Lymphocyte count decreased	0 - 4
Lymphocyte count increased	0 - 4
Neutropenia	0 - 4
Neutrophil count decreased	0 - 4
Platelet count decreased	0 - 4
Purpura	0 - 3
Thrombocytopenia	0 - 4
White blood cell decreased	0 - 4
Infection-related AE	
Bacterial infection (regardless of organ-system involved or specific bacterial cause)	0 - 3
Chills	0 - 3
Cough	0 - 3
Febrile neutropenia (without infection)	0 - 4
Fever	0 - 5
Flu-like symptoms	0 - 3
Fungal infections (regardless of organ-system involved or fungal cause)	0 - 3
Mucositis	0 - 4
Periodontal disease	0 - 3
Pneumonia	0 - 5
Sepsis/septicemia/bacteremia (all causes)	0 - 5
Sinusitis	0 - 4
Sore throat	0 - 3
Psychiatric and Nervous System Related AE	
Anxiety	0 - 2
Cognitive disturbance	0 - 3
Confusion	0 - 5
Depressed level of consciousness	0 - 5
Depression	0 - 3
Table continued on next page	

Serious Adverse Events Caused by AML	Grades Usually Observed with AML
Libido decreased	0 - 2
Meningismus	0 - 5
Seizure	0 - 5
Somnolence	0 - 5
Syncope	3
Other AEs	
Activated partial thromboplastin time prolonged	0 - 2
Alanine aminotransferase increased	0 - 2
Alkaline phosphatase increased	0 - 2
Anorexia	0 - 2
Aspartate aminotransferase increased	0 - 2
Blood bilirubin increased	0 - 2
Bone and/or joint pain	0 - 2
Bruising	0 - 2
Bleeding/hemorrhage	0 - 5
Diarrhea	0 - 2
Dyspnea	0 - 5
Fatigue	0 - 3
Flushing	0 - 2
Gamma-glutamyltransferase increased	0 - 1
GVHD-acute and chronic	0 - 2
Hypertrophied gums	0 - 1
Hyperuricemia	0 - 1
Hypokalemia	0 - 2
Hypotension	0 - 2
Hypoxia	0 - 3
INR increased	0 - 1
Lactate dehydrogenase increased	0 - 2
Malaise	0 - 2
Multiorgan failure	0 - 5
Nausea	0 - 2
Oral dysesthesia	0 - 2
Petichiae	0 - 2
Pruritus	0 - 3
Skin and subcutaneous tissue disorders	0 - 3
Transient ischemic attacks	0 - 2
Tumor lysis syndrome	3 - 5
Vasculitis	0 - 5
Vomiting	0 - 2
Weight loss	0 - 2

AE: adverse event; AML: acute myeloid leukemia; GVHD: graft-versus-host disease;
INR: international normalization ratio

12.7 Adverse Events of Special Interest (AESI) for Atezolizumab

Adverse events of special interest (AESI) are required to be reported by the investigator to the sponsor immediately (i.e., no more than 24 hours after learning of the event). AEs of special interest are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.5.1.2 Potential Cases of Drug-Induced Liver Injury)
- Suspected transmission of an infectious agent by the study treatment, as defined below:
    - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a subject exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT > 10 × ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness, systemic inflammatory response syndrome, and systemic immune activation
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions are a known risk (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

12.8 Laboratory Assessments

Panel/Assessment	Parameters to be Analyzed
Hematology	White Blood Cell Count[a] White Blood Cell Differential[a] Red Blood Cell Count Hemoglobin[a] Hematocrit[a] Mean Corpuscular Volume Platelet Count[a] Mean Corpuscular Hemoglobin Concentration Mean Corpuscular Hemoglobin Blast count
Chemistry	Sodium Potassium Chloride Bicarbonate Blood Urea Nitrogen Creatinine Uric Acid[b] Glucose Calcium Phosphate Magnesium Albumin Total Protein Alkaline Phosphatase Lactate Dehydrogenase Creatine Kinase Triglycerides Total Cholesterol Liver Function Tests including: Total Bilirubin Alanine Aminotransferase Aspartate Aminotransferase Thyroid Function Tests including TSH and Free T4
Serum Pregnancy Test	Human Chorionic Gonadotropin
Coagulation Profile (PT/INR, D-dimer, fibrinogen)	INR (with PT if reported) aPTT Fibrinogen (screening only) D-dimer (screening only)
Table continued on next page	

Footnotes

Panel/Assessment	Parameters to be Analyzed
Urinalysis	Color Appearance Specific Gravity pH Bilirubin Blood Glucose Ketones Leukocyte Esterase Nitrite Protein Urobilinogen
Bone Marrow	Blast Count and Cell Counts[a] Flow Cytometry for Blasts Minimal Residual Disease Exploratory biomarkers (protein or genomic) related to study treatment
Pharmacokinetics	Gilteritinib concentration
Pharmacogenomics (For subjects who provide separate PGx consent)	PGx analyses to be determined.
FLT3 and AXL	Phospho-FLT3 and Phospho-AXL
Immune cell population immunophenotyping	Lymphocyte subsets, dendritic cells, natural killer cells, T-cell subsets, T-regulatory cells
Blast cell immunophenotyping	Blast cell immunophenotyping

aPTT: activated partial thromboplastin time; FLT3: FMS-like tyrosine kinase;
INR: international normalized ratio; PGx: pharmacogenomic; PT: prothrombin time; T4: thyroxine;
TSH: thyroid stimulating hormone.

a. In addition to the central read of these values, available local results will also be entered into the electronic case report form.

b. On days 1, 8 and 15 in cycle 1.

12.9 Pharmacogenomic (PGx) Analysis With Banked Sample (Optional)

INTRODUCTION

PGx research aims to provide information regarding how naturally occurring differences in a subject's gene and/or expression of genes based on genetic variation may impact what treatment options are best suited for the subject. Through investigation of PGx by technologies such as genotyping, gene sequencing, statistical genetics and Genome-Wide Association Studies, the relationship between gene profiles and a drug's kinetics, efficacy or toxicity may be better understood. As many diseases may be influenced by 1 or more genetic variations, PGx research may identify which genes are involved in determining the way a subject may or may not respond to a drug.

OBJECTIVES

The PGx research that may be conducted in the future with acquired blood samples is exploratory. The objective of this research will be to analyze or determine genes of relevance to clinical response, pharmacokinetics and/or toxicity/safety issues.

By analyzing genetic variations, it may be possible to predict an individual subject's response to treatment in terms of efficacy and/or toxicity.

SUBJECT PARTICIPATION

Subjects who have consented to participate in this study may participate in this PGx sub-study. Subjects must provide written consent prior to providing any blood samples that may be used at a later time for PGx analysis.

SAMPLE COLLECTION AND STORAGE

Subjects who consent to participate in this sub-study will provide one tube of whole blood of approximately 4 – 6 mL per Astellas' instructions. Each sample will be identified by the unique subject number. Samples will be shipped to a designated banking CRO as directed by Astellas.

PGx ANALYSIS

Details on the potential PGx analysis cannot be established yet. Astellas may initiate the PGx analysis if evidence suggests that genetic variants may be influencing the drug's kinetics, efficacy and/or safety.

DISPOSAL OF PGx SAMPLES/DATA

All PGx samples collected will be stored for a period of up to 15 years following study database hardlock. If there is no requirement for analysis, the whole blood sample will be destroyed after the planned storage period. The subject has the right to withdraw consent at any time. When a subject's withdraw notification is received, the PGx sample will be destroyed. The results of any PGx analysis conducted on a sample prior to its withdrawal will be retained at Astellas indefinitely unless otherwise specified by local regulation.

INFORMATION DISCLOSURE TO THE SUBJECTS

Exploratory PGx analysis may be conducted following the conclusion of the clinical study, if applicable. The results of the PGx analysis will not be provided to any investigators or subjects, nor can the results be requested at a later date. Any information that is obtained from the PGx analysis will be the property of Astellas.

12.10 Clinical Study Continuity

INTRODUCTION

The purpose of this appendix is to provide acceptable alternate methods to assess safety and efficacy parameters, as appropriate, in the event the clinical study is interrupted at the country, state, site or participant level during any crisis (e.g., natural disaster, pandemic).

BENEFIT-RISK RATIONALE

Maintaining the safety of clinical study participants and delivering continuity of care in the clinical study setting is paramount during any crisis. The site is expected to follow the protocol and associated Schedule of Assessments [Table 1] unless the site principal investigator discusses the need with the Astellas medical monitor to implement the alternate measures.

The approach outlined within this appendix defines which assessments are required to maintain a favorable benefit/risk to the participant, to maintain overall study integrity and to provide acceptable alternate methods to complete the study required assessments and procedures if study activities are unable to be performed as described in Section 5 due to a crisis.

INFORMED CONSENT

Participants who need to follow any or all of the alternate measures outlined in this Appendix will be required to provide informed consent, which explicitly informs them of the nature of and rationale for these changes, and gain their agreement to continue participation in the study prior to the implementation of any of these changes. In the event the urgency of implementing the alternate measures does not allow for the participant to provide written consent prior to implementation, the principal investigator or designee will obtain oral agreement from the subject followed by written documentation as soon as is feasible. A separate addendum to the study informed consent will be provided to document the participant's consent of the changes.

PARTICIPANT PROCEDURES ASSESSMENT

Sites with participants who are currently enrolled into this clinical study may consider implementing the alternate methods outlined below if one or more of the following conditions are met due to the crisis:

- Regional or local travel has been restricted, inclusive of mandatory shelter in place measures, which makes participant travel to/from the study site nearly impossible
- Site facilities have been closed for clinical study conduct
- Site has been restricted to treating patients with conditions outside of the scope of the study
- Site personnel have temporarily relocated the conduct of the study to a location that place a burden on the participant with respect to time and travel

- Participant(s) have temporarily relocated from the current study site to an alternate study site to avoid placing a burden on the participant with respect to travel
- Participant(s) have temporarily relocated from their home location and the new distances from the site would cause undue burden with respect to time and travel
- Participant has risk factors for which traveling to the site poses an additional risk to the participant's health and safety

Adherence to the original protocol as reflected in the Schedule of Assessment [Table 1] is expected, where plausible, in the case of a crisis. The alternate measures as noted in [Table 8] below are only permissible in the event of a crisis, and after discussing the need with the Astellas medical monitor or designee to implement the alternate measures. This is to allow for continuity of receiving study drug and maintaining critical safety and efficacy assessments for patients participating in the study at a time of crisis.

If one or more of the alternate measures noted below is implemented for a participant, the site should document in the participant's source document the justification for implementing the alternate measure and the actual alternate measures that were implemented, along with the corresponding time point(s).

All other assessments should be completed as outlined in [Table 1].

Table 8 Alternative Schedule of Assessments in Response to a Crisis

Critical Assessments	Alternate Approach(es)	Critical Time points						Follow-up	
Cycle Day		**C1D1**	**C1D8**	**C1D1**	**Subsequent Cycles D1**	**Subsequent Cycles D15**	**EOT**	**30-Day Follow-up**	**Long-term Follow-up**
General Study Procedures									
Weight	Can be obtained at local clinic	X			X				
Physical Examination	Since atezolizumab needs to be given every 2 weeks in the clinic, this will be captured in the clinic. In the event the visit is missed, this can be captured during the telehealth visit.	X	X	X	X	X	X		
Vital Signs	Since atezolizumab needs to be given every 2 weeks in the clinic, this will be captured in the clinic. In the event the visit is missed, information may be captured during telehealth visits if a patient has adequate monitoring instruments and knowledgeable and able to obtain measurements	X	X	X	X	X	X		
ECOG Performance Status	Since atezolizumab needs to be given every 2 weeks in the clinic, this will be captured in the clinic. In the event the visit is missed, information can be captured during telehealth visits.	X		X	X	X	X		
AE/SAE Assessment	Since atezolizumab needs to be given every 2 weeks in the clinic, this will be obtained in the clinic. In the event the visit is missed or the patient cannot come to the clinic, telehealth visits will be allowed for non-dosing visits. Please refer to protocol schedule of assessments.	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	Since atezolizumab needs to be given every 2 weeks in the clinic, this will be obtained in the clinic. In the event the visit is missed or the patient cannot come to the clinic, telehealth visits will be allowed for non-dosing visits. Please refer to protocol schedule of assessments.	X	X	X	X	X	X	X	
Electrocardiograms									
12-lead ECG	Since atezolizumab needs to be given every 2 weeks in the clinic, this will be obtained in the clinic. In the event the visit is missed or cannot be made, ECG in triplicates performed in local facility is acceptable if results can be made available to investigative site.	X	X	X	X	X	X		

Table continued on next page

Critical Assessments	Alternate Approach(es)	Critical Time points						Follow-up	
Cycle Day		**C1D1**	**C1D8**	**C1D1**	**Subsequent Cycles D1**	**Subsequent Cycles D15**	**EOT**	**30-Day Follow-up**	**Long-term Follow-up**
Blood and Urine Collection									
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis)	Since atezolizumab needs to be given every 2 weeks in the clinic, this will be obtained in the clinic. In the event the visit is missed, or the patient cannot come to the clinic, the collection of samples at local facility is acceptable if the results can be made available to investigative site.	X	X	X	X	X	X		
Thyroid Function Test	Since atezolizumab needs to be given every 2 weeks in the clinic, this will be obtained in the clinic. In the event the visit is missed, or the patient cannot come to the clinic, the collection of samples at local facility is acceptable if the results can be made available to investigative site.				X		X		
Pharmacokinetic Sample Collection	Since atezolizumab needs to be given every 2 weeks in the clinic. This will be obtained in the clinic.	X	X	X	X	X			
Blood Sample for FLT3 and AXL	This is an exploratory endpoint. There are no alternative approaches for this assessment. If the 24 post-dose sample is not feasible, it is okay.	X							
Blood Sample for Immune Cell Immunophenotyping	In general biomarker samples are collected on atezolizumab treatment days and do not require a unique visit to the study site. These samples cannot be stored. If samples cannot be received by central lab then they should not be collected	X		X	X		X		
Blood Sample for Blast Cell Immunophenotyping	In general biomarker samples are collected on atezolizumab treatment days and do not require a unique visit to the study site. These samples cannot be stored. If samples cannot be received by central lab then they should not be collected	X		X	X		X		
PGx (whole blood and buccal swab)	This samples are collected on an atezolizumab treatment day. If the samples can be collected but the central lab cannot receive samples, samples can be stored at sites until shipping is accepted again	X							

Table continued on next page

Critical Assessments	Alternate Approach(es)	Critical Time points						Follow-up	
Cycle Day		**C1D1**	**C1D8**	**C1D1**	**Subsequent Cycles D1**	**Subsequent Cycles D15**	**EOT**	**30-Day Follow-up**	**Long-term Follow-up**
Pregnancy Test for WOCBP	Since atezolizumab needs to be given every 2 weeks in the clinic, this will be obtained in the clinic. In the event the visit is missed, or the patient cannot come to the clinic, the collection of samples at local facility is acceptable if the results can be made available to investigative site.	X			X		X		
Treatment									
Gilteritinib Dosing at the Clinic	Patient will be taken off study and the patient can take commercially available gilteritinib off study or receive other alternative therapies for R/R AML albeit the options are limited and not very effective. Delivery from site to patient if the patient is just on gilteritinib monotherapy is also possible.	X	X	X	X	X			
Atezolizumab Dosing at the Clinic	All atezolizumab dose needs to be administered in the clinic at every 2 week intervals. The protocol allows for patients to continue treatment with gilteritinib alone if the patient had issues related to tolerability of other clinical considerations related to atezolizumab.	X		X	X	X			
Tissue Collection									
Bone Marrow Biopsy and/or Aspiration for disease assessment and MRD	Bone marrow assessment to be performed in the clinic. In the event this is not possible, bone marrow biopsy performed in a local facility is acceptable if results can be made available to investigative site.				X		X		
Diary									
Subject Diary for Gilteritinib	Diary can be shipped directly to the patient. Accountability can be performed during the telehealth visit.	X			X				

AE: adverse event; AML: acute myeloid leukemia; AXL; a receptor tyrosine kinase encoded by the AXL gene; C: cycle; D: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end of treatment; FLT3: FMS-like tyrosine kinase 3; MRD: minimal residual disease; PGx: pharmacogenomics; R/R: relapsed or refractory; SAE: serious adverse event; WOCBP: women of childbearing potential.

INVESTIGATIONAL PRODUCT SUPPLY

If any of the conditions outlined above in the Participants Procedures Assessment are met, one or all of the following mitigating strategies will be employed, as needed, to ensure continuity of study supply to the participants:

- Increase stock of study drug on site to reduce number of shipments required, if site space will allow
- Use of locally available atezolizumab brands
- Direct-to-Participant shipments of study drug from the site to the participant's home (ASP2215 only)

DATA COLLECTION REQUIREMENTS

Additional data may be collected in order to indicate how participation in the study may have been affected by a crisis and to accommodate data collection resulting from alternate measures implemented to manage the conduct of the study and participant safety.

- Critical assessments for safety and efficacy based on study endpoints to be identified as missing or altered (performed virtually, at alternative locations, out of window, or other modifications) due to the crisis

13 ATTACHMENT 1: NONSUBSTANTIAL AMENDMENT 3

I. The purpose of this amendment is:

Nonsubstantial Changes
1. Update Key Sponsor Personnel
DESCRIPTION OF CHANGE:
Contact details for clinical research contact are revised.
RATIONALE:
Contact details of sponsor personnel are updated based on changes to study personnel.
2. Update Recommended Dose Modifications for Adverse Reactions
DESCRIPTION OF CHANGE:
Table 6 is expanded to add rows for the following adverse reactions: • Skin adverse reaction while on prior treatment with another immune-stimulatory anticancer agent • Suspected cutaneous adverse reaction • Confirmed Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis
RATIONALE:
To include appropriate management of severe dermatological events, as well as to specify severe cutaneous adverse reactions to be a known risk with atezolizumab.
3. Update Definition of Pharmacokinetics Analysis Set (PKAS)
DESCRIPTION OF CHANGE:
The definition of PKAS is revised to include *and for whom at least 1 plasma concentration datum is available and both the date and time of dosing on the day of pharmacokinetic sampling and the date and time of sampling are known*.
RATIONALE:
Only the plasma concentration sample with both date and time of sampling and date and time of dosing available is valid for pharmacokinetic analysis.
4. Note that Severe Cutaneous Reactions are Known Risk
DESCRIPTION OF CHANGE:
In Section 12.7, it is noted that severe cutaneous reactions are a known risk.
RATIONALE:
Severe cutaneous reactions is upgraded from a potential risk to an identified risk by the Atezolizumab manufacturer.

5. Add Appendix for Clinical Study Continuity
DESCRIPTION OF CHANGE:
A Clinical Study Continuity appendix is added to the protocol. This appendix contains procedures for continuity of care during a crisis. An alternative schedule of assessments is provided.
RATIONALE:
This appendix is added to provide acceptable alternate methods to assess safety and efficacy parameters in the event the clinical study is interrupted at the country, state, site or participant level during any crisis (e.g., natural disaster or pandemic).
6. Minor Administrative-type Changes
DESCRIPTION OF CHANGE:
Include minor administrative-type changes (e.g., typos, format, numbering and consistency throughout the protocol).
RATIONALE:
To provide clarifications to the protocol and to ensure better definition of the study procedures.

II. Amendment Summary of Changes:

II Contact Details of Key Sponsor's Personnel

WAS:

Clinical Research Contact:	Jason Moresco, MBA Clinical Study Manager on assignment with Astellas Phone: 262-331-1613 Email: jason.moresco@astellas.com

IS AMENDED TO:

Clinical Research Contact:	**Dhruva Patel**~~Jason Moresco, MBA~~ Clinical Study Manager ~~on assignment with Astellas~~ Phone: **1-224-205-8837**~~262 331 1613~~ Email: **dhruva.patel**~~jason.moresco~~@astellas.com

5 Treatments and Evaluation
5.1.3 Atezolizumab Dose Interruption, Table 6 Recommended Dosage Modifications for Adverse Reactions (Atezolizumab)

ADDED:

Adverse Reaction	Severity of Adverse Reaction[a]	Dosage Modifications
Previously experienced a skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents	**Grade 3 or 4 (severe or life-threatening reaction)**	**Caution when considering the use of atezolizumab**
Suspected cutaneous adverse reactions	**Grade 3 or 4**	**Refer to a dermatologist for further diagnosis and management**
	SJS or TEN	**Withhold dose until confirmation of diagnosis**
Confirmed SJS or TEN	**Any Grade**	**Permanently discontinue**

SJS: Stevens-Johnson Syndrome; TEN: Toxic Epidermal Necrolysis

IV Synopsis and 5 Treatments and Evaluation
5.3.2 Response Assessments

WAS:

Response to treatment will be defined per modified Cheson criteria [Cheson et al, 2003] as outlined below.

IS AMENDED TO:

Response to treatment will be defined per modified Cheson criteria [Cheson et al, 2003] as outlined below **for up to the end of 2 cycles and end of treatment**.

IV Synopsis and 5 Treatments and Evaluation *5.3.2.5 Complete Remission with Partial Hematologic Recovery (CRh)*
WAS:
For subjects classified as being in CR, except if their ANC is > 0.5 Gi/L and their platelets are > 50 Gi/L.
IS AMENDED TO:
For subjects classified as being in CR, except if their ANC is > 0.5 × ~~Gi~~**10^9**/L and their platelets are > 50 × ~~Gi~~**10^9**/L.

IV Synopsis and 5 Treatments and Evaluation *5.3.2.9 Best Response*
WAS:
Two best responses, up to the time of 2 cycles of treatment period and the EOT Visit will be defined.
IS AMENDED TO:
Two best responses~~, up to the time of 2 cycles of treatment period and the EOT Visit~~ will be defined.

7 Statistical Methodology *7.2.4 Pharmacokinetics Analysis Set (PKAS)*
WAS:
The pharmacokinetics analysis set (PKAS) consists of the administered population for which sufficient plasma concentration data is available to facilitate derivation of at least one pharmacokinetic parameter and for whom the time of dosing on the day os sampling is known.
IS AMENDED TO:
The pharmacokinetics analysis set (PKAS) consists of the administered population for which sufficient plasma concentration data is available to facilitate derivation of at least one pharmacokinetic parameter and for whom **at least 1 plasma concentration datum is available and both the date and time of dosing on the day of pharmacokinetic sampling and the date and time of sampling are known**~~the time of dosing on the day os sampling is known~~.

12 Appendices *12.7 Adverse Events of Special Interest (AESI) for Atezolizumab*
WAS:
• Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic

epidermal necrolysis)
IS AMENDED TO:
• Severe cutaneous reactions **are a known risk** (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

12 Appendices
ADDED:
12.10 Clinical Study Continuity **INTRODUCTION** **The purpose of this appendix is to provide acceptable alternate methods to assess safety and efficacy parameters, as appropriate, in the event the clinical study is interrupted at the country, state, site or participant level during any crisis (e.g., natural disaster, pandemic).** **BENEFIT-RISK RATIONALE** **Maintaining the safety of clinical study participants and delivering continuity of care in the clinical study setting is paramount during any crisis. The site is expected to follow the protocol and associated Schedule of Assessments [Table 1] unless the site principal investigator discusses the need with the Astellas medical monitor to implement the alternate measures.** **The approach outlined within this appendix defines which assessments are required to maintain a favorable benefit/risk to the participant, to maintain overall study integrity and to provide acceptable alternate methods to complete the study required assessments and procedures if study activities are unable to be performed as described in Section 5 due to a crisis.** **INFORMED CONSENT** **Participants who need to follow any or all of the alternate measures outlined in this Appendix will be required to provide informed consent, which explicitly informs them of the nature of and rationale for these changes, and gain their agreement to continue participation in the study prior to the implementation of any of these changes. In the event the urgency of implementing the alternate measures does not allow for the participant to provide written consent prior to implementation, the principal investigator or designee will obtain oral agreement from the subject followed by written documentation as soon as is feasible. A separate addendum to the study informed consent will be provided to document the participant's consent of the changes.** **PARTICIPANT PROCEDURES ASSESSMENT** **Sites with participants who are currently enrolled into this clinical study may consider implementing the alternate methods outlined below if one or more of the following conditions are met due to the crisis:**

- **Regional or local travel has been restricted, inclusive of mandatory shelter in place measures, which makes participant travel to/from the study site nearly impossible**
- **Site facilities have been closed for clinical study conduct**
- **Site has been restricted to treating patients with conditions outside of the scope of the study**
- **Site personnel have temporarily relocated the conduct of the study to a location that place a burden on the participant with respect to time and travel**
- **Participant(s) have temporarily relocated from the current study site to an alternate study site to avoid placing a burden on the participant with respect to travel**
- **Participant(s) have temporarily relocated from their home location and the new distances from the site would cause undue burden with respect to time and travel**
- **Participant has risk factors for which traveling to the site poses an additional risk to the participant's health and safety**

Adherence to the original protocol as reflected in the Schedule of Assessment [Table 1] is expected, where plausible, in the case of a crisis. The alternate measures as noted in [Table 8] below are only permissible in the event of a crisis, and after discussing the need with the Astellas medical monitor or designee to implement the alternate measures. This is to allow for continuity of receiving study drug and maintaining critical safety and efficacy assessments for patients participating in the study at a time of crisis.

If one or more of the alternate measures noted below is implemented for a participant, the site should document in the participant's source document the justification for implementing the alternate measure and the actual alternate measures that were implemented, along with the corresponding time point(s).

All other assessments should be completed as outlined in [Table 1].

12 Appendices

ADDED:

Table 8 Alternative Schedule of Assessments in Response to a Crisis

Critical Assessments	Alternate Approach(es)	Critical Time points						Follow-up	
Cycle Day		C1D1	C1D8	C1D1	Subsequent Cycles D1	Subsequent Cycles D15	EOT	30-Day Follow-up	Long-term Follow-up
General Study Procedures									
Weight	Can be obtained at local clinic	X			X				
Physical Examination	Since atezolizumab needs to be given every 2 weeks in the clinic, this will be captured in the clinic. In the event the visit is missed, this can be captured during the telehealth visit.	X	X	X	X	X	X		
Vital Signs	Since atezolizumab needs to be given every 2 weeks in the clinic, this will be captured in the clinic. In the event the visit is missed, information may be captured during telehealth visits if a patient has adequate monitoring instruments and knowledgeable and able to obtain measurements	X	X	X	X	X	X		
ECOG Performance Status	Since atezolizumab needs to be given every 2 weeks in the clinic, this will be captured in the clinic. In the event the visit is missed, information can be captured during telehealth visits.	X		X	X	X	X		
AE/SAE Assessment	Since atezolizumab needs to be given every 2 weeks in the clinic, this will be obtained in the clinic. In the event the visit is missed or the patient cannot come to the clinic, telehealth visits will be allowed for non-dosing visits. Please refer to protocol schedule of assessments.	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	Since atezolizumab needs to be given every 2 weeks in the clinic, this will be obtained in the clinic. In the event the visit is missed or the patient cannot come to the clinic, telehealth visits will be allowed for non-dosing visits. Please refer to protocol schedule of assessments.	X	X	X	X	X	X	X	
Electrocardiograms									

12-lead ECG	**Since atezolizumab needs to be given every 2 weeks in the clinic, this will be obtained in the clinic. In the event the visit is missed or cannot be made, ECG in triplicates performed in local facility is acceptable if results can be made available to investigative site.**	**X**	**X**	**X**	**X**	**X**	**X**		
Blood and Urine Collection									
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis)	**Since atezolizumab needs to be given every 2 weeks in the clinic, this will be obtained in the clinic. In the event the visit is missed, or the patient cannot come to the clinic, the collection of samples at local facility is acceptable if the results can be made available to investigative site.**	**X**	**X**	**X**	**X**	**X**	**X**		
Thyroid Function Test	**Since atezolizumab needs to be given every 2 weeks in the clinic, this will be obtained in the clinic. In the event the visit is missed, or the patient cannot come to the clinic, the collection of samples at local facility is acceptable if the results can be made available to investigative site.**				**X**		**X**		
Pharmacokinetic Sample Collection	**Since atezolizumab needs to be given every 2 weeks in the clinic, this will be obtained in the clinic.**	**X**	**X**	**X**	**X**	**X**			
Blood Sample for FLT3 and AXL	**This is an exploratory endpoint. There are no alternative approaches for this assessment. If the 24 post-dose sample is not feasible, it is okay.**	**X**							
Blood Sample for Immune Cell Immunophenotyping	**In general biomarker samples are collected on atezolizumab treatment days and do not require a unique visit to the study site. These samples cannot be stored. If samples cannot be received by central lab then they should not be collected**	**X**		**X**	**X**		**X**		
Blood Sample for Blast Cell Immunophenotyping	**In general biomarker samples are collected on atezolizumab treatment days and do not require a unique visit to the study site. These samples cannot be stored. If samples cannot be received by central lab then they should not be collected**	**X**		**X**	**X**		**X**		
PGx (whole blood and buccal swab)	**This samples are collected on an atezolizumab treatment day. If the samples can be collected but the central lab cannot receive samples, samples can be stored at sites until shipping is accepted again**	**X**							
Pregnancy Test for WOCBP	**Since atezolizumab needs to be given every 2 weeks in the clinic, this will be obtained in the clinic. In the event the visit is missed, or the patient cannot come to the clinic, the collection of samples at local facility is acceptable if the results can be made available to investigative site.**	**X**			**X**		**X**		

Treatment									
Gilteritinib Dosing at the Clinic	**Patient will be taken off study and the patient can take commercially available gilteritinib off study or receive other alternative therapies for R/R AML albeit the options are limited and not very effective. Delivery from site to patient if the patient is just on gilteritinib monotherapy is also possible.**	**X**	**X**	**X**	**X**	**X**			
Atezolizumab Dosing at the Clinic	**All atezolizumab dose needs to be administered in the clinic at every 2 week intervals. The protocol allows for patients to continue treatment with gilteritinib alone if the patient had issues related to tolerability of other clinical considerations related to atezolizumab.**	**X**		**X**	**X**	**X**			
Tissue Collection									
Bone Marrow Biopsy and/or Aspiration for disease assessment and MRD	**Bone marrow assessment to be performed in the clinic. In the event this is not possible, bone marrow biopsy performed in a local facility is acceptable if results can be made available to investigative site.**				**X**		**X**		
Diary									
Subject Diary for Gilteritinib	**Diary can be shipped directly to the patient. Accountability can be performed during the telehealth visit.**	**X**			**X**				

AE: adverse event; AML: acute myeloid leukemia; AXL; a receptor tyrosine kinase encoded by the AXL gene; C: cycle; D: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOT: end of treatment; FLT3: FMS-like tyrosine kinase 3; MRD: minimal residual disease; PGx: pharmacogenomics; R/R: relapsed or refractory; SAE: serious adverse event; WOCBP: women of childbearing potential.

INVESTIGATIONAL PRODUCT SUPPLY

If any of the conditions outlined above in the Participants Procedures Assessment are met, one or all of the following mitigating strategies will be employed, as needed, to ensure continuity of study supply to the participants:

- **Increase stock of study drug on site to reduce number of shipments required, if site space will allow**
- **Use of locally available atezolizumab brands**
- **Direct-to-Participant shipments of study drug from the site to the participant's home (ASP2215 only)**

DATA COLLECTION REQUIREMENTS

Additional data may be collected in order to indicate how participation in the study may have been affected by a crisis and to accommodate data collection resulting from alternate measures implemented to manage the conduct of the study and participant safety.

- **Critical assessments for safety and efficacy based on study endpoints to be identified as missing or altered (performed virtually, at alternative locations, out of window, or other modifications) due to the crisis**

III. Nonsubstantial Amendment Rationale:

Rationale for Nonsubstantial Designation
All revisions made to the protocol are administrative in nature and do not impact the safety or scientific value of the clinical study.

14 SPONSOR SIGNATURES

Astellas Signatories

(Electronic signatures are attached at the end of the document.)

PPD, MD
PPD
Medical Sciences

PPD, PhD
PPD
Data Science