STATISTICAL ANALYSIS PLAN

Draft Version 1.3, dated 20 Aug-2021

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

NCT03730012

ISN/Protocol: 2215-CL-1101
IND number: 117,548

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I.   LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Concentration-time Curve
AXL	A Receptor Tyrosine Kinase Encoded by the AXL Gene
BMAS	Biomarker Analysis Set
BMI	Body Mass Index
BOIN	Bayesian Optimal Interval Design
CA	Competent Authorities
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
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Concentration Immediately Prior to Dosing at Multiple Dosing
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DEC	Dose Evaluation Committee
DL	Dose Level
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EFS	Event-free survival
EOT	End of Treatment

Abbreviations	Description of abbreviations
FAB	French-American-British
FAS	Full Analysis Set
FLT3	FMS-like Tyrosine Kinase 3
HSCT	Hematopoietic Stem Cell Transplantation
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INR	International Normalized Ratio
IRT	Interactive Response Technology
ISN	International Study Number
MRD	Minimal Residual Disease
MTD	Maximum Tolerated Dose
MUGA	Multigated Acquisition
NCI	National Cancer Institute
OS	Overall Survival
PGx	Pharmacogenomic
PKAS	Pharmacokinetics Analysis Set
PR	Partial Remission
PT	Preferred Term
q2w	Once Every 2 Weeks
QTcF	Fridericia-Corrected QT Interval
RBC	Red Blood Cell
RP2D	Recommended Phase 2 Dose
RTK	Receptor Tyrosine Kinase
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
ULN	Upper Limit of Normal
WHO	World Health Organization
WHO – DD	World Health Organization – Drug Dictionary
WOCBP	Woman of Childbearing Potential

List of Key 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 studyl.
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.

1   INTRODUCTION

This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary, secondary and exploratory endpoints and other data.

The SAP is finalized and signed prior to any of the following: study unblinding, database hard lock, interim analysis, or accumulation of substantial amount of data in an open-label study to ensure lack of bias. For operational efficiency an earlier time is usually targeted. If needed, revisions to the approved SAP may be made prior to database hard lock. Revisions will be version controlled.

This statistical analysis is coordinated by the responsible biostatistician of GD-US. Any changes from the analyses planned in the SAP will be justified in the Clinical Study Report (CSR).

Prior to database hard lock, a final review of data and TLFs meeting will be held to allow a review of the clinical trial 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 hard lock.

2   FLOW CHART AND VISIT SCHEDULE

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┌─────────────────────┐     ┌──────────────────────────┐     ┌────────┐     ┌────────────┐     ┌──────────────┐
│ Enroll up to 12     │     │ Phase 1: gilteritinib      │     │        │     │            │     │ Long-term    │
│ subjects in         │     │ once daily plus            │     │        │     │ 30-day     │     │ follow-up for│
│ phase 1 and up to 49│ ──▶ │ 420 or 840 mg atezolizumab │ ──▶ │ EOT    │ ──▶ │ follow-up  │ ──▶ │ 3 years or   │
│ subjects in phase 2 │     │ q2w. Phase 2:              │     │ Visit  │     │ visit      │     │ until subject│
│ s with Relapsed or  │     │ gilteritinib once daily    │     │        │     │            │     │ death or     │
│ Treatment Refractory│     │ plus atezolizumab q2W      │     │        │     │            │     │ withdrawal   │
│ FLT3 mutated AML    │     │ at RP2D. 28-day cycles in  │     └────────┘     └────────────┘     └──────────────┘
└─────────────────────┘     │ phases 1 and 2 until lack  │
                            │ of clinical benefit or     │
                            │ unacceptable toxicity.     │
                            └──────────────────────────┘
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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			

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.

Footnotes continued on next page

^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 [Protocol 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 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.
^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

3 STUDY OBJECTIVES AND DESIGN

3.1 Study Objectives

3.1.1 Primary Objectives

● 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).

3.1.2 Secondary Objectives

● 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:
  o Gilteritinib trough plasma concentrations (C_{trough})
  o CR rate
  o CR with partial hematologic recovery (CRh)
  o Best response rate (CRc + PR)
  o Duration of remission
  o Event-free Survival (EFS)
  o OS
  o AEs, clinical laboratory results, vital signs, ECGs and Eastern Cooperative Oncology Group (ECOG) performance status scores

3.1.3 Exploratory Objectives

● 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

3.2 Study Design

3.2.1 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 2 Flow Charts and Table 1 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 Table 1. Dose escalation decisions will be made based on DLTs that occur during the first cycle of treatment. 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, 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	120mg 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).

3.2.2   Reduction in Dose of the Study Drug(s)

3.2.2.1 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 3].

The dose levels potentially used include the following [Table 2]:

Table 2   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 3]. 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 3]. 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 3   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 [Protocol 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 $< 25 \times 10^9$/L and/or absolute neutrophil count (ANC) $\leq 0.5 \times 10^9$/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

3.2.2.2 Atezolizumab Dose Interruption

Refer to the following for atezolizumab dose modification recommendations:

Table 4   Recommended Dosage Modifications for Adverse Reactions (Atezolizumab)

Adverse Reaction	Severity of Adverse Reaction[a]	Dosage Modifications
Pneumonitis *[see Warnings and Precautions (5.1) in the package insert]*	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 (5.2) in the package insert]*	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 Prec*autions (5.3) in the package insert]*	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 (5.4) in the package insert]*	Grade 2, 3, or 4	Withhold dose until Grade 1 or resolved and clinically stable on hormone replacement therapy.
Other immune-mediated adverse reactions involving a major organ *[see Warnings and Precautions (5.5) in the package insert]*	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 (5.6) in the package insert]*	Grade 3 or 4	Withhold dose until Grade 1 or resolved
Infusion-Related Reactions [*see Warnings and Precautions (5.7) in the package insert]*	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
Table continued on next page		

Adverse Reaction	Severity of Adverse Reaction[a]	Dosage Modifications
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

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

Refer to the pharmacy manual and package insert for any updates.

3.3   Randomization

This is a non-randomized study. Patient assignment will be performed via Interactive Response Technology (IRT). Prior to the initiation of the study treatment, the site staff will contact the IRT in order to assign the subject to treatment. Specific procedures for assignment, enrollment and registration through the IRT are contained in the study procedures manual.

4   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. 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 Table 2.

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.

5   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.

5.1   Full Analysis Set (FAS)

The full analysis set (FAS) will consist of all subjects who are enrolled in the study andtook
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.

5.2   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.

5.3   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.

5.4   Biomarker Analysis Set (BMAS)

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

6   ANALYSIS VARIABLES

6.1   Efficacy Endpoints

Efficacy analysis will be conducted on the FAS.

6.1.1   Primary Efficacy Endpoint

Composite complete remission (CRc) rate is the primary efficacy endpoint. The definition
will be defined in Section 6.1.4.

6.1.2   Secondary Efficacy Endpoint

● Complete remission (CR) rate
● CR with partial hematologic recovery (CRh) rate

- Duration of remission
- Best response rate
- Event-free survival (EFS)
- Overall survival (OS)

The definition of secondary efficacy endpoint will be defined in Section 6.1.3 and Section 6.1.4.

6.1.3   Response Definition

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

- 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 x 10^9/L and platelet count ≥ 100 x 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 (< 100×10^9/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 < 1×10^9/L with or without complete platelet recovery. RBC and platelet transfusion independence is not required.

- Composite Complete Remission (CRc)

For subjects to be classified as being in CRc at a post-baseline visit, they must either achieve CR, CRp or CRi at the visit.

- Complete Remission with Partial Hematological Recovery (CRh)

For subjects classified as being in CR, except if their ANC is > 0.5 Gi/L and their platelets are > 50 Gi/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 <=2%) 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 (>2%) or 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, up to the time of 2 cycles of treatment period and the EOT Visit will be defined.

● Treatment Failure

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

6.1.4   Definition of Other Efficacy Variables

● CR rate - Defined as the number of subjects with CR divided by the number of subjects in the analysis population. Subjects with unknown or missing response, or who provide no information on response at the end of study will be treated as non-responders and will be included in the denominator when calculating rates.
● CRp rate, CRi rate, CRh rate, PR rate – Defined similarly as CR rate.
● Best response rate – Defined as the number of subjects with CR or CRp or CRi or PR divided by the number of subjects in the analysis population (i.e., CR+ CRp + CRi + PR). Subjects with unknown or missing response, or who provide no information on response at the end of study will be treated as non-responders and will be included in the denominator when calculating rates.
● Duration of remission – This includes duration of CRc, duration of CR, duration of CR/CRh, and duration of response (CRc + PR) by the EOT.

   o Duration of CRc – Defined as the time from the date of either first CRc until the date of documented relapse of any type for subjects who achieve CRc. Subjects who die without report of relapse are considered non-events 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 non-events and censored at the last relapse-free assessment date.

   o Duration of CR, and CR/CRh – Defined similarly as duration of CRc.

   o Duration of response – 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.

- Event-free survival (EFS) – The time from the date of first dose until the date of documented relapse from CR, CRp or CRi, treatment failure or death from any cause, whichever occurs first.

   o 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.

   o 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 first dose.

   o 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).

   o 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.

- Overall survival (OS) - The time from the date of first dose 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.

6.1.5   Definition of Biomarker Variables

- Minimal Residual Disease (MRD)

MRD will be analyzed from bone marrow and blood samples by a Sponsor-designed central laboratory. 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.

FLT3/ITD mutation ratio will be measured in relation to total FLT3. For a subject with multiple ITD mutations, the overall FLT3/ITD mutation ratio will be calculated from the sum of all ITD mutations. Changes in FLT3/ITD mutation ratio from baseline will be compared.

At each visit, the presence of MRD will be "Present" if $\log_{10}$-transformed overall FLT3/ITD mutation ratio is greater than -4; otherwise, the presence of MRD will be "Absent". For subjects with multiple ITD mutations detected, the ratios will be summed.

Additional absolute cut points (e.g., $\log_{10}$-transformed overall FLT3/ITD to total FLT3 ratio of -2, -3, etc.) may be evaluated, as well as the $\log_{10}$ transformed change in FLT3/ITD to total FLT3 ratio at each visit compared to baseline.

Further details of biomarker variables will be specified in a separate biomarker analysis plan.

6.2   Safety Variables

Safety (Development of DLTs and AEs) are the primary endpoints of the study.

The safety and tolerability of ASP2215 will be assessed using:

- Development of DLT
- Adverse events
- Clinical laboratory results (chemistry, hematology, coagulation, urinalysis, serum pregnancy test and bone marrow)
- Vital signs (systolic and diastolic blood pressure, pulse rate and body temperature)
- 12-lead electrocardiogram (ECG)
- Eastern Cooperative Oncology Group (ECOG) performance status scores

6.2.1   Definition of DLT

In Phase 1, a DLT is defined as any of the following events that occur during 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/day 1 through cycle 1/day 28).

- Confirmed Hy's law case
- Any Grade $\geq$ 3 non-hematologic or extramedullary toxicity with the following exceptions:
    o Anorexia or fatigue
    o 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 $\leq$ 2 with standard antiemetic or antidiarrheal medications used at prescribed dose within 7 days of onset
    o Grade 3 mucositis that resolved to grade $\leq$ 2 within 7 days of onset
    o Grade 3 fever with neutropenia, with or without infection*
    o Grade 3 infection*
    o 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) $\leq$ 0.5 x 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 or blood will be considered as a DLT.

6.2.2   Definition of MTD

MTD is defined as the highest dose level where no more than one subject out of six eligible subjects has experienced DLT during the DLT observation period.

6.2.3   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 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 25% 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.

6.2.4   Adverse Events

Any adverse event (AE) recorded on treatment including within 30 days from the last study treatment will be classified as treatment-emergent AE (TEAE) and will be summarized.

A drug-related TEAE is defined as any TEAE with at least possible relationship (possibly or probably related) to study treatment as assessed by the investigator or with missing assessment of the causal relationship

Serious adverse events (SAEs) include adverse events that are flagged as serious by the investigator or sponsor on eCRF, or upgraded by the Sponsor based on review of the Sponsor's list of Always Serious term.

Adverse events of special safety interest (AESI) are defined in the Safety Review Plan for ASP2215.

6.2.5   Other Variables

- Clinical laboratory variables (hematology, chemistry, coagulation, urinalysis, serum pregnancy test and bone marrow)
- Vital signs (systolic and diastolic blood pressure, pulse rate and body temperature)
- 12-lead electrocardiogram (ECG)
- Eastern Cooperative Oncology Group (ECOG) performance status scores

6.3   Pharmacokinetics Variables

Gilteritinib trough plasma concentrations (C_{trough}) samples will be collected for all subjects predose (within 1 h of dose administration) on cycle 1/day 1, 8 and 15, and on days 1 and 15 of each subsequent cycle up to 6 months.

6.4   Pharmacodynamics Variables

Blood samples for FLT3 and AXL will be collected on cycle 1/day 1 predose and postdose at 2 h, between 4 to 6 h, and 24 h.Changes in the activation status of FLT3 and AXL, a receptor tyrosine kinase (RTK), may be assessed before and after treatment.

6.5   Other Variables

● Body Mass Index (BMI)

BMI = weight (kg) / [height (m)]^2

● Duration of exposure
Duration of exposure to a study drug will be calculated in days, using the following formula:

Date of last dose of study drug – Date of first dose + 1 – number of days without drug administration in between.

When the start or stop date is missing, then the exposure will be treated as missing.

● Number of dosing days is defined as the number of days with non-zero dosing
● Cumulative Dose

Cumulative dose (mg) = sum of all doses of study drug taken during the study.

● Average daily dose is defined as (cumulative dose)/(number of dosing days) in "mg/day"
● Dose intensity is defined as (cumulative dose/duration of exposure) in "mg/day" for Gilteritinib and (cumulative dose/duration of exposure*14 days for Atezolizumb.
● Relative dose intensity is defined as (dose intensity/planned dose intensity)*100%.
● Treatment compliance

Treatment compliance of Gilteritinib is defined as:

Total number of doses of gilteritinib actually taken by the number of study drug expected to be taken during the study multiplied by 100.

Treatment compliance of Atezolizumab is defined as:

Total amount of Atezolizumab actually consumed by amount of study drug should been taken multiplied by 100.

● Duration of AML

Duration of AML will be calculated in days using the following formula:

(Enrollment date – date of initial diagnosis of AML) + 1

● Previous and concomitant medication

Previous medication is defined as medication with at least one dose taken before the date of the first dose of study drug.

Concomitant medication is defined as medication with at least one dose taken between the date of first exposure (inclusive) and the date of last exposure (inclusive) of study

drug. The first exposure is from 28 days prior to cycle 1 day 1. The last exposure date is max (the last dosing date for study drug, initial dosing date of the last cycle + 30).

7   STATISTICAL METHODOLOGY

7.1   General Considerations

For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation, median, minimum and maximum. When needed, the use of other percentiles (e.g., 10%, 25%, 75% and 90%) will be mentioned in the relevant section. In addition, for continuous PK parameters, the coefficient of variation will be calculated and for C_{max} and AUC the geometric mean will also be calculated. Frequencies and percentages will be displayed for categorical data. Percentages by categories will be based on the number of subjects with no missing data, i.e. will add up to 100%. Kaplan-Meier survival curves will be displayed for time-to-event variables and median survival time will be estimated with 2-sided 95% confidence interval (CI).

Safety analysis and other summaries based on SAF will be presented by actual treatment received. Pharmacokinetic summaries based on will be presented by actual treatment received. For subjects with dose change, actual treatment refers to the first dose received before dose change.

All data processing, summarization, and analyses will be performed using SAS® Version 9.3 or higher on Unix. Specifications for table, figure, and data listing formats can be found in the TLF specifications for this study.

Baseline is defined as the last available measurement prior to the first dose of study drug. Unless otherwise specified, all summaries and analysis will be presented by phase.

7.2   Study Population

7.2.1   Disposition of Subjects

The following subject data will be presented:

- Number and percentage of subjects with informed consent, discontinued before allocation to treatment, allocated to treatment (overall only);
- Number and percentage of subjects allocated to treatment in each analysis set;
- Number and percentage of subjects completed and discontinued treatment, by primary reason for treatment discontinuation;
- Number and percentage of subjects completed and discontinued the study, by primary reason for study discontinuation;
- Number and percentage of subjects completed and discontinued the post-study period, by primary reason for post-study period discontinuation;

7.2.2   Protocol Deviations

Protocol deviations as defined in the study protocol (Section 8.3 Major Protocol Deviations) will be assessed for all subjects allocated to treatment. The number and percentage of

subjects meeting any criteria will be summarized for each criterion and overall as well as by study site. Subjects deviating from a criterion more than once will be counted once for the corresponding criterion. Any subjects who have more than one protocol deviation will be counted once in the overall summary. A data listing will be provided by site and subject.

The protocol deviation criteria will be uniquely identified in the summary table and listing. The unique identifiers will be 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.

7.2.3   Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized 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.

Number and percentage of subjects allocated to treatment in each country and site will be presented for the SAF.

Descriptive statistics for age, weight, body mass index (BMI), height, and prior FLT3 inhibitor (gilteritinib, quizartinib, crenolanib) at study entry will be presented. Frequency tabulations for sex, ethnicity, region, age group (< 65 years vs. >=65 years) and race will be presented. Demographics and baseline characteristics will be summarized for the SAF.

Frequency tabulations for AML disease history including AML subtype as classified by World Health Organization (WHO) classification and French-American-British (FAB) classification, risk status, antecedent hematological disorder, central nervous system leukemia, FLT3 mutation status will be presented for the SAF.

Medical history other than AML and conditions existing at baseline will be coded in MedDRA and summarized by System Organ Class (SOC) and Preferred Term (PT) as well as by PT alone for the SAF. Baseline conditions are defined as those ongoing at the time of informed consent or arise following the time of informed consent and before the first dose of study drug. For ongoing medical conditions, Common Terminology Criteria for Adverse Events (CTCAE) grade will be provided in listing.

Results from lumbar puncture and MUGA scan, if performed, will be provided in listing.

7.2.4   Previous and Concomitant Medications

Previous medications are coded with World Health Organization – Drug Dictionary (WHO-DD), and will be summarized by therapeutic subgroup (Anatomical Therapeutic Chemical [ATC] 2nd level) and chemical subgroup (ATC 4th level) and preferred WHO name for the SAF.

As with previous medication, concomitant medication will be summarized by therapeutic subgroup (ATC 2nd level), chemical subgroup (ATC 4th level) and preferred WHO name for the SAF. Subjects taking the same medication multiple times will be counted once per medication. A medication which can be classified into several chemical and/or therapeutic subgroups is presented in all chemical and therapeutic subgroups.

Concomitant medication will also be summarized for SAF and presented in decreasing order of frequency based on the total number of subjects who took each medication.

7.2.5   Previous and Concomitant Non-Medication Therapy

Frequency tabulations of subjects with previous non-medication therapy and reason for use will be presented for SAF. Number of previous non-medication therapy received per subject will be summarized using descriptive statistics.

Concomitant non-medication therapy will also be summarized as previous non-medication therapy.

7.3   Study Drugs

7.3.1   Exposure

The following information on drug exposure will be presented for the SAF:

- Descriptive statistics for cumulative amount of the drug subject was exposed to and average daily dose; and
- Number and percent of subject with dose increase, decrease or interruptions.

Duration of exposure will be summarized in two ways.

- Descriptive statistics will be presented.
- Exposure time will be categorized according to the following categories:
  - less than 3 months
  - at least 3 months, less than 6 months
  - at least 6 months, less than 12 months
  - at least 12 months, less than 24 months
  - 24 months or more
  - Unknown.

Counts and percentages of subjects in each of these categories will be summarized for the SAF.

Listing of subjects with dose reduction and interruption will also be provided for SAF.

Descriptive statistics for duration of exposure, cumulative amount of the drug subject was exposed to average daily dose, dose intensity and relative dose intensity will be presented for study drug.

7.3.2   Treatment Compliance

Treatment compliance of gilteritinub is defined as the total number of doses of gilteritinub actually taken by the subject divided by the number of doses of study drug

expected to be taken during the study multiplied by 100. Treatment compliance of Atezolizumab is defined as total amount of Atezolizumab actually consumed by amount of study drug should been taken multiplied by 100. Descriptive statistics for study drug compliance will be presented by dose for the entire study period for the SAF. Overall compliance will be examined for subjects in the SAF whose total study drug count and first and last days of treatment are known.

Percent overall compliance will be summarized in two ways for the SAF:

- Descriptive statistics will be presented by cohort and dose level.
- Percent compliance will be categorized according to the following categories:
  - less than 50%
  - at least 50%, less or equal to 80%
  - greater than 80%
  - Unknown.

Overall compliance will be provided in listing.

7.4   Analysis of Efficacy

Efficacy analysis will be conducted on the FAS.

7.4.1   Analysis of Primary Efficacy Endpoint

The CRc rate will be evaluated according to Simon's minimax two-stage design (Simon, 1989). The null hypothesis that the true CRc rate is 50% will be tested against a one-sided alternative.

In stage I, a total 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 one-sided type I error rate of 0.025 and power of 80% when the true CRc rate is 70%.

The CRc (CR + CRp + CRi) rate will be summarized and its 95% confidence interval will be constructed by Clopper-Pearson method.

7.4.2   Analysis of Secondary Efficacy Endpoint

CR rate, best response rate, duration of remission, OS and EFS will be summarized using descriptive statistics. The CR rate, best response rate with the corresponding 95% confidence interval will be reported. The survival curve and the 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.

The SAS code used to produce median from Kaplan-Meier estimates and corresponding 95% CI will be similar to that shown below:

```
proc lifetest data=adtte plots=(s) outsurv=surv;
time survtime*censor(0);
```

run;

7.4.3   Analysis of Exploratory Efficacy Endpoint

● Evaluate efficacy of gilteritinib given in combination with atezolizumab in terms of minimal residual disease (MRD). MRD analysis will be conducted on the BMAS. MRD will be assessed in relation to the following efficacy variables:
  o CR rate
  o CRc rate
  o EFS
  o Duration of remission
  o OS
● 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

7.5   Analysis of Safety

All analysis of safety will be performed on the SAF, unless specified otherwise.

7.5.1   Adverse Events

Any adverse event (AE) recorded on treatment including within 30 days from the last study treatment will be classified as treatment-emergent AE (TEAE) and will be summarized.

Summaries and listings of TEAEs and Serious TEAEs include SAEs upgraded by the Sponsor based on review of the Sponsor's list of Always Serious terms if any upgrade was done.

The number and percent of subjects experiencing one or more AE(s) will be summarized by SOC and PT using MedDRA and will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. The number and percentage of subjects with at least one grade 3 or higher AE will also be summarized by SOC and PT.

An overview table will include the following details:

● Number and percentage of subjects with TEAEs,
● Number and percentage of subjects with causally drug related TEAEs,
● Number and percentage of subjects with serious TEAEs and Astellas upgraded serious TEAE,
● Number and percentage of subjects with serious drug related TEAEs and Astellas upgraded serious drug related TEAE,
● Number and percentage of subjects with TEAEs leading to permanent discontinuation of study drug,
● Number and percentage of subjects with drug related TEAEs leading to permanent discontinuation of study drug,

- Number of deaths, and
- Number and percentage of subjects with grade 3 or higher TEAEs.

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized by period, cohort and dose level. Summaries will be provided for:

- TEAEs
- Drug related TEAEs,
- Serious TEAEs and Astellas upgraded serious TEAE,
- Drug related serious TEAEs and drug related Astellas upgraded serious TEAE,
- TEAEs leading to permanent discontinuation of study drug,
- Drug related TEAEs leading to permanent discontinuation of study drug,
- TEAEs excluding serious adverse events that equal to or exceed a threshold of 5% in any dose level,
- Common TEAEs that equal to or exceed a threshold of 5% in any dose level, and
- Grade 3 or higher TEAEs.

The number and percentage of subjects with TEAEs, as classified by PT only, will be summarized.

AE summary tables will include subject counts as opposed to AE counts. If a subject experiences more than one episode of a particular AE, the subject will be counted only once for that AE. If a subject has more than one AE that code to the same preferred term, the subject will be counted only once for that preferred term. Similarly, if a subject has more than one AE within a SOC, the subject will be counted only once in that SOC.

The number and percentage of subjects with TEAEs, as classified by SOC and PT will also be summarized by NCI-CTCAE severity grade and by relationship to study drug. In the subject count, if a subject has multiple TEAEs with the same SOC or PT, but with differing severity grade or relationship, then the subject will be counted only once with the worst severity grade and highest degree of relationship, however, if any of the severity grade or relationship values are missing then the subject will be counted only once with missing severity grade or relationship. Drug related TEAEs will be presented in a similar way by severity grade only.

The number and percentage of subjects with adverse events of special safety interest (AESIs)for Atezolizumab will be summarized by PT. See [Appendix 12.7 Adverse Events of Special Interest (AESI) for Atezolizumab] for further details.

All summaries of AEs will include only TEAEs unless otherwise stated. All AEs, deaths, SAEs and withdrawals due to adverse events will be displayed in listings.

7.5.2   Clinical Laboratory Evaluation

The baseline visit is the last measurement taken prior to initial study drug administration.

Quantitative clinical laboratory variables, i.e., hematology, serum chemistry, coagulation and urinalysis will be summarized using mean, standard deviation, minimum, maximum and median at each visit. Additionally, change from baseline will be calculated as the

post-baseline value minus the baseline value and summarized in the same way. Each laboratory result will be classified as low (L), normal (N), or high (H) at each visit according to the laboratory supplied reference ranges.

The number and percentage of subjects below and above reference range will be summarized at each visit.

Frequency tabulations of qualitative clinical laboratory variables (urinalysis) will be presented at each visit.

Clinically significant abnormalities in laboratory values will be presented.

For hematology and chemistry two types of shift tables will be presented:

●   Shift tables of changes based on reference range defined category (low, normal, high) from baseline to each visit as well as worst finding during the treatment period, and

●   Summary shifts of changes based on reference range defined category from baseline to each visit as well as worst finding during the treatment period (shift from high or normal
to low, shift from low or normal to high, categorized increase [shift from low to normal
or from normal to high], categorized no change [value stays in the same reference range],
categorized decrease [shift from high to normal or from normal to low]).

Laboratory results will also be graded using NCI-CTCAE v5.0, where possible. Parameters that have criteria available for both low and high values, i.e., hypo- and hyper-, will be summarized for both criteria. The same subject can be counted for both values if the subject has different laboratory values meeting each criterion. NCI-CTCAE grade of laboratory evaluations will be summarized by number and percentage of subjects for each visit. Shift tables of NCI-CTCAE grade change from baseline to worst post-baseline grade will also be presented.

Laboratory results based on central assessment will be used for summaries as described above. Laboratory results based on local assessment and bone marrow results will be listed only. The laboratory results may be displayed in figures.

7.5.2.1 Liver Enzymes and Total Bilirubin

The following potentially clinically significant criteria in liver function tests for Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), total bilirubin, Aspartate Transaminase (AST) and their combination are defined. The subject's highest value during the study will be used.

Parameter	Criteria
ALT	> 3xULN
	> 5xULN
	> 8xULN
AST	> 3xULN
	> 5xULN
	> 8xULN
ALT or AST	> 3xULN
Total Bilirubin	> 2xULN
ALP	> 1.5xULN
ALT and/or AST AND Total Bilirubin[*]	(ALT and/or AST > 3xULN) and total bilirubin > 2xULN

[*] Combination of values measured within same sample

The number and percentage of subjects with potentially clinically significant values in liver enzymes and total bilirubin will be presented.

7.5.3 Vital Signs

The baseline visit is the last measurement taken prior to initial study drug administration.

Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate and body temperature) will be summarized using mean, standard deviation, minimum, maximum and median by visit. Additionally, change will be calculated as the post-baseline value minus the baseline value and summarized by visit.

Tables for potentially clinically significant vital signs will be generated using baseline value and highest value.

The following potentially clinically significant criteria are defined:

Vital Sign Variable	Criteria
SBP	≥180 mmHg AND ≥20 mmHg change from baseline
DBP	≥105 mmHg AND ≥15 mmHg change from baseline
Pulse Rate	≥120 bpm AND ≥15 bpm change from baseline

7.5.4 Electrocardiograms (ECGs)

12-lead ECGs will be recorded in triplicate at the scheduled time points. Each ECG tracing will be taken at least 5 minutes apart and transmitted electronically to central reading. The mean of the triplicate ECGs from central read should be used for all final treatment decisions, AE reporting and in the summary for analysis at each visit.

ECG variables including changes from baseline will be summarized using mean, standard deviation, minimum, maximum and median at each visit.

Number and percentage of subjects with normal and abnormal results as assessed by central read for the overall interpretation will be tabulated at each visit. A shift analysis table showing shift in overall ECG interpretation from baseline to each time point will be provided. The worst of the three overall ECG interpretations will be used as the time-specific overall ECG interpretation for a subject.

The QT interval corrected for heart rate by Fridericia's formula, QTcF, is defined as: *QTc (F) = QT/(RR)$^{0.33}$*, where RR interval is inversely proportional to heart rate (approximately RR = 60/heart rate).

The QTcF interval will be summarized using frequency tables at each visit for values of clinical importance using the range criteria below.

	QTc Interval Criteria Value (msec)	
	Cumulative Category	**Interval Category**
Normal	≤ 450	≤ 450
Borderline	> 450	> 450 to ≤ 480
Prolonged	> 480	> 480 to ≤ 500
Clinically significant	> 500	> 500

The QTcF interval will also be summarized by the frequencies of subjects with a change from baseline of clinical importance using the criteria identified below. These summaries will be provided at each visit.

Variable	**Change from Baseline**	
	Cumulative Category	**Interval Category**
QTc Interval (msec)	<0	<0
	≥ 0	≥ 0 to ≤ 30
	> 30	> 30 to ≤ 60
	> 60	> 60

Number and percentage of subjects with 12 lead ECG abnormalities at each visit as well as number and percentage of subjects whose 12 lead ECG reading shift from baseline to each visit will be tabulated.

7.5.5   Pregnancies

A detailed listing of all pregnancies will be provided.

7.5.6   Eastern Cooperative Oncology Group (ECOG) Performance Scores

Number of percent of subjects for each category of the ECOG performance status at each assessment time will be provided. Negative change scores indicate an improvement and positive scores indicate a decline in performance.

ECOG performance scores will also be summarized using shift table from baseline to post-baseline assessments.

7.6   Analysis of PK

PK analysis will be conducted on the PKAS.

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, if appropriate, by visit and time point.

7.7   Analysis of Biomarkers

The activation status of FLT3 and AXL will be summarized by dose and change from baseline at each time point.

Immune cell immunophenotyping and blast cell immunophenotyping biomarkers will be summarized by dose and change from baseline at each time point by both absolute number and percentage.

7.8   Subgroups of Interest

Not applicable for this study.

7.9   Other Analyses

Not applicable for this study.

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

Not applicable for this study.

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

7.11.1   Missing Data

Every effort will be made to resolve incomplete dates for death and disease relapse. If a partial date cannot be resolved, the most conservative imputation methods will be used to complete the missing information.

For OS and EFS, missing or incomplete death date will be imputed as the earliest feasible date on or after the date of last contact as the examples shown in the table below. The date of last contact will be obtained as described in Section 6.1.2.

Incomplete Date of Death (YYYY MMM DD)	Date of Last Contact (YYYY MMM DD)	Imputed Date of Death (YYYY MMM DD)
2005 APR ??	2005 MAR 31	2005 APR 01
2005 ??? 13	2005 MAR 31	2005 APR 13
2005 ??? ??	2005 MAR 31	2005 MAR 31
???? APR ??	2005 MAR 31	2005 APR 01
???? APR 13	2005 MAR 31	2005 APR 13
???? ??? ??	2005 MAR 31	2005 MAR 31

Partial relapse dates will be imputed to the first day of the month of the missing parameter but not earlier than the last disease assessment date. A month and year must be present or the date will remain missing.

Missing or partial start and stop dates of adverse events and concomitant medication will be imputed using the following algorithm:

- Imputation rules for partial or missing stop dates:
  - If the month and year are present, then impute as the last day of that month.
  - If only the year is present, impute as December 31 of that year.
  - If the stop date is entirely missing, assume the event or medication is ongoing.
- Imputation rules for partial or missing start dates:

		Stop Date						
		Complete: *yyyymmdd*		**Partial: *yyyymm***		**Partial: *yyyy***		**missing**
Start Date		$<1^{st}$ dose	$\geq 1^{st}$ dose	$<1^{st}$ dose *yyyymm*	$\geq 1^{st}$ dose *yyyymm*	$<1^{st}$ dose *yyyy*	$\geq 1^{st}$ dose *yyyy*	
Partial: *yyyymm*	$= 1^{st}$ dose *yyyymm*	2	1	2	1	n/a	1	1
	$\neq 1^{st}$ dose *yyyymm*		2		2	2	2	2
Partial: *yyyy*	$= 1^{st}$ dose *yyyy*	3	1	3	1	n/a	1	1
	$\neq 1^{st}$ dose *yyyy*		3		3	3	3	3
Missing		4	1	4	1	4	1	1

1 = Impute as the date of first dose; 2 = Impute as the first of the month; 3 = Impute as January 1 of the year; 4 = Impute as January 1 of the stop year

The imputed dates will be used to determine whether an AE is/is not treatment emergent. Listings of AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

7.11.2 Outliers

All values will be included in the analyses.

7.11.3 Visit Windows

Visit windows are allowed for certain visits per the schedule of assessments. Subject data will not be excluded from analyses due to the subject's failure to comply with the visit schedule. The visit windows for assessments are described in the following table.

CRF visit	Visit Window
Screening	D-14 to D-1
Cycle 1 Day 1	No Window
Cycle 1 Day 8	C1D8± 1
Cycle 1 Day 15	No Window
Cycle 2 Day 1	No Window
Cycle 2 Day 15	No Window
Cycle X Day 1	No Window
Cycle X Day 15	No Window
End of Treatment Visit	Last dose date + 7

Scheduled visit will be calculated using number of days relative to the first dose based on 28-day cycles. In the case of multiple observations at a specific visit, the observation which is closest to the target date will be used. If the observations have the same distance to the target visit, the latest one will be used.

7.11.4   Covid-19 Impact Assessment

Assessments affected by the Covid-19 pandemic will be listed for visit-based assessments and for non-visit-based assessments.

For visit-based assessments affected by Covid-19, the listing shows if an assessment was not performed due to Covid-19, if it was out of window, if the assessment was performed at an alternative location or if it was a virtual assessment. Other information and comments reported on assessments affected by Covid-19 are also included.

For non-visit-based assessments affected by Covid-19, subjects who experience any of the following items: treatment discontinuation due to Covid-19, Covid-19 medical history, Covid-19 adverse event, hospitalization due to Covid-19, dose changing due to Covid-19, or Covid-19 death, will be flagged in a listing.

Any events like discontinuation of treatment, medical history, adverse events, hospitalization, dose changing, or death, which are related to Covid-19, will be flagged in the corresponding listing.

8   DOCUMENT REVISION HISTORY

Version	Date	Changes	Comment/rationale for change
1.0	26-Nov-2018	NA	Initial SAP draft
1.1	21-June-2019	NA	SAP updates based on Protocol Amendment 1
1.2	3-June-2020	Remove BSA, Add Prior FLT3 Inhibitor	
1.3	20-Aug-2020	Remove MRD analysis of biomarker Revise treatment compliance for Atezolizumab	

9   REFERENCES

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10   APPENDICES

10.1   Appendix 1: Signatures

Prepared by: _____   Date: _____

        PPD , MS   Date (DD Mmm YYYY)
        PPD
Global Data Science
Astellas Pharma Global Development USA

Approved by: _____   Date: _____

        PPD   MD   Date (DD Mmm YYYY)
        PPD   ,
        PPD
Medical Science-Hematology
Astellas Pharma Global Development USA

                                                  Date: _____

        PPD , PHD   Date (DD Mmm YYYY)
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Global Data Science
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                                                  Date: _____

        PPD   Date (DD Mmm YYYY)
        PPD
Clinical Project management
Astellas Pharma Global Development USA

                                                  Date: _____

        PPD   PHD   Date (DD Mmm YYYY)
        PPD
        PPD
Clinical Pharmacology and Exploratory Development
Astellas Pharma Global Development USA

                                                  Date _____

        PPD   PHD   Date (DD Mmm YYYY)
        PPD
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