A Phase 2 Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of the FLT3 Inhibitor Gilteritinib (ASP2215) Administered as Maintenance Therapy Following Induction/Consolidation Therapy for Subjects with FLT3/ITD AML in First Complete Remission

Protocol for Phase 2 Study of ASP2215

ISN/Protocol 2215-CL-0302

Version 3.0

Incorporating Substantial Amendment 2 [See Section 13]

25 April 2019

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Sponsor:

Astellas Pharma Global Development, Inc. (APGD)

1 Astellas Way

Northbrook, IL 60062

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Investigator:
Investigator information is on file at Astellas

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Table of Contents

List of In-text Tables

I. SIGNATURES

1. SPONSOR'S SIGNATURE

Required signatures (e.g., Protocol authors, Sponsor's reviewers and contributors, etc.) are located in Section 14, Sponsor's Signatures; e-signatures (when applicable) are located at the end of this document.

2. INVESTIGATOR'S SIGNATURE

A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of the FLT3 Inhibitor Gilteritinib (ASP2215) Administered as Maintenance Therapy Following Induction/Consolidation Therapy for Subjects with FLT3/ITD AML in First Complete Remission

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25 April 2019

I have read all pages of this 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 personnel 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: ----------

Address: ----------

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

24h-Contact for Serious Adverse Events (SAEs) See Section 5.5.5	PPD **, MD** PPD **, Global Medical Oncology Science** **Mobile:** PPD **Please fax or email the SAE Worksheet to:** **Astellas Pharma Global Development, Inc.** **Pharmacovigilance** **North America Fax Number: 888-396-3750** **(North America Alternate Fax: 847-317-1241)** **International Fax Number: +44-800-471-5263** **Email: safety-us@astellas.com** **For investigational sites in Japan:** **Japan/Asia Development I, Astellas Pharma Inc.** **Phone: 03-3244-1097** **Fax: 03-3243-5737**
Medical Monitor/Medical Expert:	PPD, MD PPD, Oncology Development Astellas Pharma Global Development Office: PPD Mobile: PPD Email: PPD
Clinical Research Contact (Global):	PPD, Clinical Science Astellas Pharma Global Development, Inc. Office: PPD Cell: PPD E-mail: PPD
Clinical Research Contacts (Japan):	Corporate Name: Astellas Pharma Inc. Location: 2-5-1, Nihonbashi-Honcho, Chuo-ku, Tokyo, Japan Phone No.: 03-3244-1097 Fax: 03-3243-5737 Sponsor's personnel: PPD Contact numbers during nonbusiness hours and for emergency: Phone No.: PPD
Contact Information for the Clinical Research Organization (CRO) Japan:	Corporate Name: Parexel International Location: 6F Kayaba-cho First Building, 1-17-21, Shinkawa, Chuo-ku, Tokyo 104-0033, Japan Phone No.: 03-3537-5493 Fax: 03-6888-1486 CRO's personnel: PPD Contact numbers during nonbusiness hours and for emergency: Phone No.: PPD

III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of Abbreviations
$5HT_1R$	5-hydroxytryptamine receptor 1
$5HT_{2B}R$	5-hydroxytryptamine receptor 2B
ΔQTcF	Fridericia-corrected QT interval corrected relative to baseline
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
ANCOVA	Analysis of Covariance
APGD	Astellas Pharma Global Development, Inc.
APL	Acute promyelocytic leukemia
AST	Aspartate aminotransferase
AUC_{inf}	Area under the concentration-time curve from the time of dosing extrapolated to time infinity
AUST	Astellas United States Technologies
AXL	AXL tyrosine kinase
BCRP	Breast cancer resistance protein
CK	Creatine kinase
C_{max}	Maximum concentration
CNS	Central nervous system
CR	Complete remission
CR1	First complete remission
CRc	Composite complete remission
CRi	Complete remission with incomplete hematologic recovery
CRO	Contract Research Organization
CRp	Complete remission with incomplete platelet recovery
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_t/C_{max}	Tissue concentration/maximum tissue concentration
C_{trough}	Observed trough concentration
CYP	Cytochrome P450
DLT	Dose-limiting toxicities
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviations	Description of Abbreviations
eCRF	Electronic Case Report Form
EFS	Event-free survival
EML4-ALK	Echinoderm microtubule-associated protein-like 4-ALK variant 1
EQ-5D-5L	EuroQol Group-5 Dimension-5 Level Instrument
ER	Emergency room
FACT-An	Functional Assessment of Cancer Therapy-Anemia
FACT-Leu	Functional Assessment of Cancer Therapy-Leukemia
FAS	Full Analysis Set
FLT3	FMS-like tyrosine kinase 3
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GMP	Good Manufacturing Practice
hERG	human ether-à-go-go-related gene
HSCT	Hematopoietic stem cell transplant
IC_{50}	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IND	Investigational new drug
INR	International normalization ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
IRT	Interactive response technology
ITD	Internal tandem duplication
IWG	International Working Group
LA-CRF	Liver Abnormality-Case Report Form
LFT	Liver function test
LLN	Lower limit of normal
LTK	Leukocyte receptor TK
MATE1	Multidrug and toxin extrusion protein 1
MDRD	Modification of Diet in Renal Disease
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scan

Abbreviations	Description of Abbreviations
NCI	National Cancer Institute
NDA	New Drug Application
NGS	Next-generation sequencing
NOAEL	No observed adverse effect level
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
OS	Overall survival
P-gp	P-glycoprotein
PGx	Pharmacogenomics
PKAS	Pharmacokinetic Analysis Set
PPS	Per Protocol Set
PR	Partial remission
PRES	Posterior reversible encephalopathy syndrome
PRO	Patient reported outcome
PT	Preferred term
QTc	Corrected QT interval
QTcF	Fridericia-corrected QT interval
RFS	Relapse-free survival
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
STAT5	Signal transducer and activator of transcription 5
SUSAR	Suspected unexpected serious adverse reaction
TAM	Tyro-3, AXL and Mer
TEAE	Treatment-emergent adverse event
TK	Tyrosine kinase
TLFs	Tables, listings and figures
TRKA	Tropomyosin receptor kinase A
ULN	Upper limit of normal
VAS	Visual analogue scale

Definition of Key Study Terms

Terms	Definition of terms
Baseline	Observed values/findings which are regarded observed starting point for comparison.
Enroll	To register or enter into a clinical trial. NOTE: Once a subject has been enrolled, the clinical trial protocol applies to the subject.
Intervention	The drug, 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, pharmacoeconomics).
Investigational period	Period of time where major interests of protocol objectives are observed, and where the test drug or comparative drug (sometimes without randomization) 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.
Randomization	The process of assigning trial subjects to treatment or control groups using an element of chance to determine assignments in order to reduce bias.
Screen failure	Potential subject who did not meet 1 or more criteria required for participation in a trial.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screening period	Period of time before entering the investigational period, usually from the time of starting a subject signing consent until just before the test drug or comparative drug (sometimes without randomization) 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 quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

IV. SYNOPSIS

Date and Version # of Protocol Synopsis:	25 Apr 2019 / Version 3.0
Sponsor: Astellas Pharma Global Development, Inc. (APGD)	**Protocol Number:** 2215-CL-0302
Name of Study Drug: ASP2215/Gilteritinib	**Phase of Development:** 2
Title of Study: A Phase 2 Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of the FLT3 Inhibitor Gilteritinib (ASP2215) Administered as Maintenance Therapy Following Induction/Consolidation Therapy for Subjects with FLT3/ITD AML in First Complete Remission	
Planned Study Period: From 4Q2016 to 3Q2021	

Study Objectives:

Primary Objective:

The primary objective is to compare relapse-free survival (RFS) between subjects with FMS-like tyrosine kinase 3 (FLT3) / internal tandem duplication (ITD) acute myeloid leukemia (AML) in first complete remission (CR1) without transplant and who are randomized to receive gilteritinib or placebo beginning after completion of induction/consolidation chemotherapy for a 2-year period.

Secondary Objectives:

Key secondary objective is to:

- Compare overall survival (OS) in subjects treated with gilteritinib as maintenance therapy after induction/consolidation with those treated with placebo.

The secondary objectives are to:

Evaluate the safety and efficacy of gilteritinib versus placebo in terms of:

- Event-free survival (EFS), adverse events (AEs), clinical laboratory, vital signs, electrocardiograms (ECGs) and Eastern Cooperative Oncology Group (ECOG) performance scores.
- Examine the relationship of minimal residual disease (MRD), as determined using a next-generation sequencing (NGS) platform specific to FLT3/ITD mutations, with RFS and OS.

Exploratory Objectives:

The exploratory objectives are to:

- Assess relationship between gilteritinib exposure and Fridericia-corrected QT interval (QTcF) for subjects participating in the ECG/PK sampling subset.
- Explore the pharmacokinetics of gilteritinib (and metabolite, if applicable) in study population using a population pharmacokinetics approach.
- Determine FLT3 mutation status at relapse.
- Evaluate the safety and efficacy of gilteritinib in terms of:
  - Patient reported signs, symptoms and impacts of AML (Functional Assessment of Cancer Therapy-Leukemia [FACT-Leu], Functional Assessment of Cancer Therapy-Anemia [FACT-An])
  - EuroQol Group-5 Dimension-5 Level Instrument (EQ-5D-5L)
- Evaluate healthcare resource utilization including hospitalization, intensive care unit (ICU) visits, emergency room (ER) visits, transfusion and use of antibiotics.

Planned Total Number of Study Centers and Locations:

Approximately 200 centers
North America (Canada & US), Europe, Asia/Pacific, Central and South America and rest of world

Study Population:

Subjects with FLT3/ITD AML in CR1 (including complete remission with incomplete platelet recovery [CRp] and complete remission with incomplete hematologic recovery [CRi]) following induction/consolidation therapy

Number of Subjects to be Enrolled/Randomized:

The target sample size is approximately 85 randomized subjects.

Study Design Overview:

This is a phase 2, randomized, placebo-controlled, double-blind, 2-arm study to compare the effect of gilteritinib as maintenance therapy versus placebo after induction/consolidation in subjects with FLT3/ITD AML in CR1 (including CRp and CRi).

Subjects in CR1 (including CRp and CRi) will be approached for this study after induction/consolidation therapy is complete and a decision not to proceed with transplantation is made or a suitable donor could not be identified.

Approximately 85 subjects will be randomized in a 2:1 ratio to receive gilteritinib or placebo.

Randomization will be stratified based on:

- Age < 60 or ≥ 60 years.
- Geographic region, North America or Europe or Asia/Pacific/Central America/South America/ rest of world.
- Presence of MRD at screening; yes or no.
- Use of FLT3 inhibiting agents during induction/consolidation; yes or no.

Subjects will enter the screening period up to 14 days prior to the start of treatment. Subjects will be administered treatment up to 2 years, or until a discontinuation criterion is met.

After treatment discontinuation, subjects will have a 30-day follow-up visit for safety, after which the subjects will enter the long-term follow-up period for collection of subsequent AML treatment, remission status, and survival (cause of death and date of death).

Inclusion/Exclusion Criteria:

Inclusion Criteria at Screening:

A subject is eligible for the clinical 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 consents to allow access to his or her diagnostic bone marrow aspirate or peripheral blood sample and/or the DNA derived from that sample, if available, that may be used to validate a companion diagnostic test for gilteritinib.

4. Subject has confirmed morphologically documented AML, excluding acute promyelocytic leukemia (APL), in CR1 (including CRp and CRi). For the purposes of enrollment, CR will be defined as < 5% blasts in the bone marrow with no morphologic characteristics of acute leukemia (e.g., Auer rods) in the bone marrow with no evidence of extramedullary disease such as central nervous system involvement or granulocytic sarcoma.
5. Subject will not proceed with transplantation as either a decision not to proceed with transplantation has been made either on the recommendation of the treating physician or by the patient or a suitable donor could not be identified.
6. Subject is < 2 months from the start of the last cycle of consolidation and should have completed the recommended number of consolidations per local practice.
7. Subject has had no use of investigational agents, with the exception of FLT3 inhibiting agents during induction and/or consolidation therapy, within the prior 4 weeks.
8. Subject has had presence of the FLT3/ITD activating mutation in the bone marrow or peripheral blood as determined by the local institution at diagnosis.
9. Subject has an ECOG performance status 0 to 2.
10. Subject must meet the following criteria as indicated on the clinical laboratory tests:
    - Serum creatinine ≤ 1.5 × institutional upper limit of normal (ULN), or if serum creatinine outside normal range, then glomerular filtration rate (GFR) > 40 mL/min/1.73m^2 as calculated with the 4-parameter Modification of Diet in Renal Disease (MDRD) equation.
    - Serum total bilirubin ≤ 2.5 mg/dL (43 µmol/L), except for subjects with Gilbert's syndrome.
    - Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3 x ULN.
    - Serum potassium and serum magnesium ≥ institutional lower limit of normal (LLN).
    - Absolute neutrophil count (ANC) ≥ 500/µl and platelets ≥ 20000/µl (unsupported by transfusions).
11. Subject is suitable for oral administration of study drug.
12. Female subject must either:
    - Be of nonchildbearing potential:
        - Postmenopausal (defined as at least 1 year without any menses) prior to screening, or
        - Documented surgically sterile or status posthysterectomy (at least 1 month prior to screening)
    - Or, if of childbearing potential,
        - Agree not to try to become pregnant during the study and for 6 months after the final study drug administration
        - And have a negative urine or serum pregnancy test at screening
        - And, if heterosexually active, agree to consistently use highly effective contraception per locally accepted standards in addition to a barrier method starting at screening and throughout the study period and for 6 months after the final study drug administration.

*Highly effective forms of birth control include:

- Consistent and correct usage of established hormonal contraceptives that inhibit ovulation,
- Established intrauterine device (IUD) or intrauterine system (IUS),
- Bilateral tubal occlusion,
- Vasectomy (A vasectomy is a highly effective contraception method provided the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)
- Male is sterile due to a bilateral orchiectomy.
- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual activity 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 clinical study and the preferred and usual lifestyle of the subject.

*List is not all inclusive. Prior to enrollment, the investigator is responsible for confirming subject will utilize highly effective forms of birth control per locally accepted standards during the protocol defined period.

13. Female subject must agree not to breastfeed starting at screening and throughout the study period, and for 2 months and 1 week after the final study drug administration.
14. Female subject must not donate ova starting at screening and throughout the study period, and for 6 months after the final study drug administration.
15. Male subject and their female partners who are of childbearing potential must be using highly effective contraception per locally accepted standards in addition to a barrier method starting at screening and continue throughout the study period and for 4 months and 1 week after the final study drug administration.
16. Male subject must not donate sperm starting at screening and throughout the study period and for 4 months and 1 week after the final study drug administration.
17. Subject agrees not to participate in another interventional study while on treatment.

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

Exclusion Criteria (at either Screening or Randomization):

A subject will be excluded from participation in this clinical study if any of the following apply:

1. Subject has had prior allogeneic transplant.
2. Subject has QTcF interval > 450 msec (average of triplicate determinations based on central reading).
3. Subject with Long QT Syndrome.
4. Subject with hypokalemia and hypomagnesemia at screening (defined as values below LLN).
5. Subject has clinically active central nervous system leukemia.
6. Subject is known to have human immunodeficiency virus infection.

7. Subject has active hepatitis B or C.
8. Subject has an uncontrolled infection. If a bacterial or viral infection is present, the subject must be receiving definitive therapy and have no signs of progressing infection for 72 hours prior to randomization. If a fungal infection is present, the subject must be receiving definitive systemic anti-fungal therapy and have no signs of progressing infection for 1 week prior to randomization.
9. Subject has progressing infection defined as hemodynamic instability attributable to sepsis or new symptoms, worsening physical signs or radiographic findings attributable to infection. Persisting fever without other signs or symptoms will not be interpreted as progressing infection.
10. Subject has uncontrolled angina, severe uncontrolled ventricular arrhythmias, electrocardiographic evidence of acute ischemia, congestive heart failure New York Heart Association (NYHA) class 3 or 4 or subject has a history of congestive heart failure NYHA class 3 or 4 in the past, unless a screening echocardiogram or multigated acquisition (MUGA) scan performed within 1 month prior to study entry results in a left ventricular ejection fraction that is ≥ 45%.
11. Subject requires treatment with concomitant drugs that are strong inducers of cytochrome P450 (CYP) 3A.
12. Subject requires treatment with concomitant drugs that are strong inhibitors or inducers of P-glycoprotein (P-gp) with the exception of drugs that are considered absolutely essential for the care of the subject.
13. Subject requires treatment with concomitant drugs that target serotonin 5-hydroxytryptamine receptor 1 ($5HT_1R$) or 5-hydroxytryptamine receptor 2B ($5HT_{2B}R$) or sigma nonspecific receptor with the exception of drugs that are considered absolutely essential for the care of the subject.
14. Subject has a serious medical or psychiatric illness likely to interfere with participation in this clinical study.
15. Subject has prior malignancies, except resected basal cell carcinoma or treated cervical carcinoma in situ. Cancer treated with curative intent ≥ 5 years previously will be allowed. Cancer treated with curative intent < 5 years previously will not be allowed.
16. Subject has any condition which, in the investigator's opinion, makes the subject unsuitable for study participation.

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

Investigational Product:

ASP2215/gilteritinib tablets containing 40 mg of active ingredient.

Dose:

120 mg once daily (continuous)

Mode of Administration:

ASP2215/gilteritinib will be administered orally.

Comparative Drug:
Matching placebo tablets.

Dose:
Matching placebo for ASP2215/gilteritinib 120 mg daily (continuous).

Mode of Administration:
Placebo will be administered orally.

Concomitant Medication Restrictions or Requirements:

Treatment with concomitant drugs that are strong inducers of CYP3A is prohibited. Treatment with concomitant drugs that are strong inhibitors or inducers of P-gp and concomitant drugs that target serotonin $5HT_1R$ or $5HT_{2B}R$ 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. Grapefruit juice should not be ingested during study treatment. If strong CYP3A inhibitors are used concomitantly, subjects should be monitored for AEs.

Duration of Treatment:

Gilteritinib or placebo will be given daily for up to 2 years. After treatment discontinuation, subjects will have a 30-day follow-up visit for safety, after which the subjects will enter the long-term follow-up period and be contacted every 3 months until final database lock for collection of subsequent AML treatment, remission status, and survival (cause of death and date of death) information. Study drug will not be provided during the follow-up period.

Discontinuation Criteria from Treatment:

Gilteritinib or placebo therapy will continue for a maximum of 2 years from initiation of therapy until 1 of the following criteria applies:

- Subject declines further study participation (i.e., withdrawal of consent).
- Subject is noncompliant with the protocol based on the investigator or Medical Monitor assessment.
- Subject is found to have significantly deviated from any 1 of the inclusion or exclusion criteria after enrollment (subjects having clinical benefit may be kept in the study after discussion with the Medical Monitor).
- Subject develops an intolerable or unacceptable toxicity.
- Investigator/sub-investigator determines that the continuation of the study treatment will be detrimental to the subject.
- Subject relapses.
- Subject begins other anti-leukemic therapy.
- Subject becomes eligible for and proceeds to transplant.
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Female subject becomes pregnant.
- Death.

The subject will be discontinued from the post 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 subject's 30-day follow-up visit.
- Death.

Endpoints for Evaluation:

Primary Endpoint

The primary efficacy endpoint is RFS per Independent Review Committee (IRC) adjudication, defined as the time from randomization until relapse or death from any cause, whichever comes first. Leukemia relapse will be defined as bone marrow blasts 5% or higher (not attributable to regenerating bone marrow), any circulating blasts, any extramedullary blast foci as per Revised International Working Group (IWG) criteria.

Secondary Endpoints

The key secondary endpoint is:

- OS, defined as the time from randomization until death from any cause.

The secondary endpoints are:

- EFS
- MRD

Safety Endpoints

- AEs
- Serum chemistry, hematology, coagulation and urinalysis
- Vital signs
- ECGs
- Physical examination findings
- ECOG performance status

Exploratory Endpoints

- ECGs at specified visits and time points with time-matched gilteritinib plasma concentrations
- Gilteritinib metabolite concentrations (if applicable)
- FLT3 mutation status at relapse
- Signs, symptoms and impacts of AML as measured with patient-reported outcome instruments
- Healthcare resource utilization including hospitalization, ICU visits, ER visits, transfusion and use of antibiotics.
- Gilteritinib plasma concentrations

Statistical Methods:

Sample Size Justification

The study is a multicenter, double-blind, placebo-controlled, randomized phase 2 trial comparing gilteritinib as maintenance therapy versus placebo in FLT3/ITD AML subjects in CR1. The target number of randomized subjects is 85; approximately 57 in gilteritinib arm and 28 in placebo arm.

The median RFS time in the placebo arm is assumed to be 15 months, based on RATIFY control arm data on subjects with FLT3 mutation achieving CR1 after induction and consolidation. A total of 54 relapse or death events will provide 83.2% power to detect a hazard ratio of 0.5 (corresponding to 24% difference in 2-year RFS rates) with 1-sided significance level of 0.075. The sample size estimation of 85 subjects assumes approximately 2 years of accrual.

Randomization will be stratified by age, geographic region, the presence of minimal residual disease and use of FLT3 inhibiting agents during induction/consolidation.

Age:

- < 60 years
- ≥ 60 years

Geographic Region:

- North America
- Europe
- Asia/Pacific/South and Central America/rest of world

Presence of MRD in the screening bone marrow sample:

- Yes
- No

Use of FLT3 inhibiting agents during induction/consolidation:

- Yes
- No

Efficacy:

Primary Efficacy Analysis

The primary outcome of the trial is RFS per IRC adjudication from the time of randomization, treated as a time to event variable. The primary analysis will be conducted when the planned relapse or death events have been observed. RFS will be compared between arms on full analysis set (FAS) population with all randomized subjects using the stratified log-rank test with strata on age at randomization, screening MRD status, geographic region and use of FLT3 inhibiting agents during induction/consolidation. Kaplan-Meier estimates of RFS will also be described for each arm, along with 95% confidence intervals at 1, 2, and 3 years. The FAS is defined as all subjects who were randomized and the analysis will be based on the randomized treatment arms.

The primary analysis of the primary endpoint will be performed at 1-sided 0.075 significance level to test the null hypothesis that RFS in the gilteritinib arm is worse than or equal to RFS in the placebo arm versus the alternative hypothesis that RFS in the gilteritinib arm is better than RFS in the placebo arm.

In order to evaluate the robustness of the primary analysis of RFS, the sensitivity analyses will be performed as follows:

- Unstratified log-rank test on the FAS
- Stratified Cox proportional hazards model with the same strata as in primary analysis on the FAS
- Same analysis as primary analysis but on the per protocol set (PPS)
- Same analysis as primary analysis on the FAS, but RFS is censored at the last evaluable disease assessment without relapse when relapse or death is documented after more than 1 missed disease assessment.

- Same analysis as primary analysis on the FAS, but RFS is censored at end of treatment.
- Same analysis as primary analysis on the FAS, but RFS is defined by using investigator assessed relapse.

Key Secondary Efficacy Analysis

The key secondary efficacy endpoint of OS will be analyzed on the FAS using a stratified log-rank test with the same strata as in the primary analysis of RFS. With the sequential multiple test procedure to control for overall type I error at the 1-sided 0.075 significance level, formal significance testing of OS will be conducted only if the RFS comparison is statistically significant. Otherwise, OS analysis will be considered exploratory.

For the key secondary endpoint of OS, sensitivity analyses will be performed as below:

- Unstratified log-rank test on the FAS
- Stratified Cox proportional hazards model with the same strata as in primary analysis on the FAS
- Same analysis as primary analysis but on the PPS
- Same analysis as primary analysis on the FAS, but OS is censored at the first hematopoietic stem cell transplant and first subsequent anti-leukemic treatment, whichever occurs first.

Pharmacokinetics:

Sparse (predose) pharmacokinetic samples will be collected in all subjects.

Additional ECGs and/or time-matched plasma samples will be collected in a subset of approximately 40 subjects at the following visits and time points:

- Day 15 – 4 hours (± 1 hour) postdose
- Day 29 – 4 hours (± 1 hour) postdose

Pharmacodynamics:

Not applicable.

Safety:

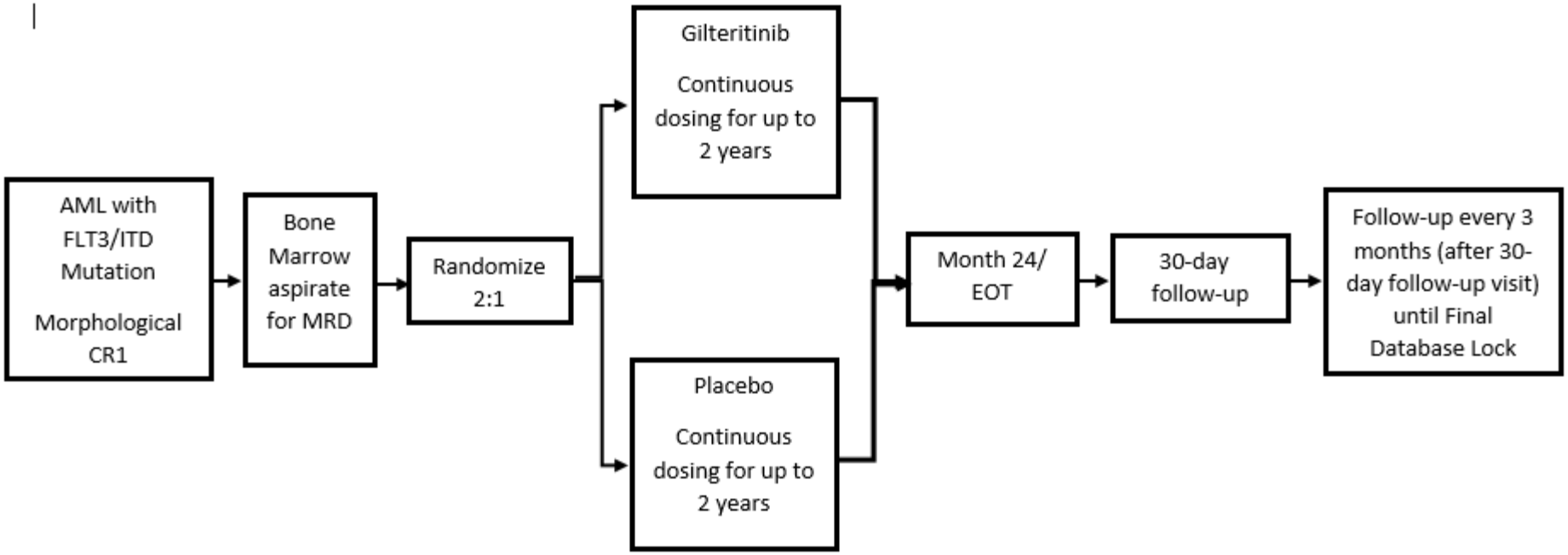
The safety analysis set is defined as all randomized subjects who received at least 1 dose of study treatment.

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 (CTCAE) version 4.03.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart



AML: acute myeloid leukemia; CR1: first complete remission; EOT: end of treatment; FLT3: FMS-like tyrosine kinase 3; ITD: internal tandem duplication; MRD: minimal residual disease.

Table 1 Schedule of Assessments

Assessments	Screening	D1	D8	D9	D15	D29	Months 2-6[a]	Subsequent Visits[a,b] (every 2 months, i.e., Month 8, Month 10, etc.)	Month 24/ EOT[c]	30-Day Follow-up	Long-term Follow-up[d]
Windows	**Day -14 to -1**		**+/- 1d**		**+/-1d**	**+/- 1d**	**+/- 5d**	**+/- 10d**	**+/- 7d**	**+7d**	**+/-7d**
Signed ICF	X										
Medical and Disease History	X										
Randomization		X									
Physical Examination[e]	X	X	X		X	X	X	X	X		
Vital Signs	X	X	X		X	X	X	X	X		
ECOG Performance Status	X						X	X	X		
12-lead ECG[f] (all subjects)	X	X	X	X[g]	X	X	X	X	X		
12-lead ECG – ECG/PK sampling subset – additional time points[h]					X	X					
Chest X-ray (or CT of chest)	X										
Pregnancy Test for WOCBP[i]	X	X					X	X	X		
MUGA or ECHO[j]	X										
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis)[k]	X[k,l]	X	X		X	X	X[k]	X[k]	X[k]		
Thyroid Function Test[m]	X						X[m]	X[m]	X[m]		
Patient reported outcome tools[n]		X					X	X	X		
Resource utilization		X					X	X	X		
FLT3 Mutation Status (local results)[o]	X[o]										
Bone Marrow Biopsy and/ or Aspiration for disease assessment and MRD[p]	X[p]						X[p]	X[p]	X[p]		
PK Sample Collection (all subjects)[q]		X	X		X	X	X	X	X		
PK Sample Collection – ECG/PK sampling subset – additional time points					X[r]	X[r]					
PGx (whole blood and buccal swab)[s]		X									
AE/SAE Assessment	X	X	X		X	X	X	X	X	X[t]	X[u]
Prior and Concomitant Medications[v]	X[v]	X	X		X	X	X	X	X		
Survival and subsequent anti-leukemic treatments and their outcomes										X[t]	X
Gilteritinib or Placebo Dosing at the Clinic[w]		X	X		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; PK: pharmacokinetic; QTcF: Fridericia-corrected QT interval; SAE: serious adverse event; WOCBP: women of childbearing potential.

[a] Visits should be scheduled based on day 1.

[b] After month 6, subjects will be seen every 2 months for the duration of study treatment, up to 2 years (month 8, month 10, month 12, etc.).

[c] If subject relapses and/or permanently discontinues treatment, an end of treatment visit should be conducted within 7 days of last dose.

[d] Telephone contact every 3 months after the 30-day follow-up visit. Additional contacts may be made to support key analyses. Follow-up will continue until the final database lock, which is estimated to occur after the last subject enrolled reaches the 30-day follow-up visit.

[e] Height measurement performed only at screening. Weight measurement should be performed at screening and each monthly visit.

[f] Screening ECG is required. ECG assessment will be evaluated in all subjects before dosing on day 1, day 8, day 15, day 29 and each subsequent visit. 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 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 decisions. If the mean triplicate QTcF is > 500 ms at any time point, the ECG will be repeated (within 2 hours if identified on machine read or as soon as possible if identified by central read).

[g] If the mean QTcF from day 1 to day 8 has increased > 30 ms with no other known etiology, a confirmatory ECG should be performed on day 9. If the day 8 and 9 ECGs confirm the > 30 ms increase in QTcF, then the investigator should assess if a dose modification should occur as per the dose interruption or reduction guideline in the protocol.

[h] For subjects participating in the ECG/PK sampling subset, additional ECGs will be performed 4 hours (+/-1 hour) postdose on day 15 and day 29. The 12-lead ECGs will be recorded in triplicate (3 separate ECGs with 10 minutes resting prior to first ECG and at least 5 minutes apart per time point) and transmitted electronically for central reading. Triplicate ECGs are to be performed prior to obtaining the time-matched PK sample (at day 15 and day 29), therefore must be started at least 10 to 15 minutes before the PK draw.

[i] Woman of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin).

[j] MUGA scans or ECHO are to be performed at screening for subjects with history of congestive heart failure New York Heart Association Class 3 or 4 (unless MUGA scan or ECHO performed within 1 month prior to screening revealed left ventricular ejection fraction ≥ 45%).

[k] Urinalysis is only required at screening. Additional laboratory tests may be performed according to institutional standard of care.

[l] All subjects must be randomized off of central results. Labs can be repeated during the screening period for eligibility.

[m] Thyroid function tests will be repeated after every 2 months of therapy beginning at month 2 (month 2, month 4, month 6, etc.).

[n] Includes EuroQol Group 5-dimension 5-level instrument, Functional Assessment of Cancer Therapy-Anemia and Functional Assessment of Cancer Therapy-Leukemia. If possible, subject reported outcome measures should be performed prior to any other assessments on that visit day.

[o] The documentation of a FLT3-ITD mutation in the past will be used to confirm eligibility criteria at screening. For randomized subjects, if bone marrow aspirate or peripheral blood sample and/or DNA derived from the sample at the time of diagnosis are available, additional testing of this sample may be performed.

Footnotes continued on next page

[p] Bone marrow aspirate is required and bone marrow biopsy in addition is preferred. In case of inadequate aspirate, bone marrow biopsy is required.

Bone marrow samples will be collected at screening and months 3, 6, 12, 18 and 24 and assessed by the local lab. If a subject relapses, a bone marrow sample should also be performed at the time of relapse. Only bone marrow samples showing relapse will be sent to a central lab. If bone marrow aspirate is unobtainable at relapse (e.g., dry tap), a peripheral blood smear should be collected along with bone marrow biopsy and sent to the central lab.

MRD assessment will be performed at screening and months 3, 6, 12, and 24/EOT. MRD performed at EOT should be performed only if the subject discontinued treatment for a reason other than relapse. For MRD, the first 0.25-0.75 mL of bone marrow aspirate will be collected and sent by overnight carrier to a central laboratory. A peripheral blood sample is not acceptable for MRD assessment.

If a subject relapses, FLT3 mutations will be assessed at the time of relapse by a central lab. If bone marrow aspirate is unavailable at relapse, a peripheral blood sample is acceptable to be collected for assessment of FLT3 mutations.

[q] Trough PK samples will be collected in all subjects predose (within 1 hour of dose administration) on day 1, day 8, day 15, day 29, at months 2-6 and every subsequent visit (month 8, month 10, etc.) and at EOT.

[r] For subjects participating in the ECG/PK sampling subset, additional PK sample will be collected 4 hours (+/-1 hour) postdose on day 15 and day 29.

[s] Whole blood and buccal swab collected predose on day 1 for subjects who consent to participate in the PGx study.

[t] Telephone contact with the subject is sufficient unless any assessment must be repeated for resolution of treatment-related AEs.

[u] Only SAE data that is possibly or probably related to study drug will be collected.

[v] Includes medications taken within 28 days prior to day 1.

[w] Gilteritinib or placebo is taken daily at home except for clinic days when it will be taken at the clinic.

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 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 people (11530 men and 7330 women) were to be diagnosed with AML, and 10460 were to die from the disease 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 about 30% to 40% of the overall patient population has long-term disease-free survival [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 syndrome) and comorbidities. Currently, there is no effective cure for the disease.

FMS-like tyrosine kinase 3 (FLT3) is a member of the class III receptor tyrosine kinase (TK) 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]. These activated mutations in FLT3 are oncogenic and show 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].

AXL tyrosine kinase (AXL) is a member of TAM family (Tyro-3, AXL and Mer) receptor TKs and is normally expressed in cells of mesenchymal origin, such as osteoblasts, fibroblasts and blood cells. AXL has been reported to be overexpressed or activated in many cancers, including AML [Linger et al, 2008]. AXL overexpression in AML confers drug resistance [Hong et al, 2008] and is associated with adverse prognosis [Ben-Batalla et al,

2013; Rochlitz et al, 1999]. AXL inhibition suppresses the growth of human FLT3-positive AML in vivo [Park et al, 2013]. In addition, AXL inhibition is also effective against FLT3-negative AML expressing AXL in vivo [Ben-Batalla et al, 2013].

ASP2215/gilteritinib is a new chemical entity discovered by Astellas Pharma Inc. in collaboration with Kotobuki Pharmaceutical Co., Ltd. Gilteritinib has an inhibitory effect on TKs, mainly FLT3, AXL and anaplastic lymphoma kinase (ALK). Gilteritinib demonstrated favorable efficacy in a nonclinical AML model, with complete regression of tumors in the xenograft model mice transplanted with MV4-11, human AML cell line expressing FLT3-ITD, by repeated oral doses. In addition, gilteritinib inhibited the growth of cells expressing either FLT3-ITD, FLT3-D835Y or FLT3-ITD-D835Y.

Considering the high risk of relapse in patients in remission, post-remission therapy aimed at prolonging remission duration is warranted. Allogeneic HSCT is recommended to prevent relapse. However, HSCT is limited to fitter patients with an available donor. For patients who are not undergoing HSCT, maintenance therapy aimed at eradicating residual disease and prolonging disease remission is a possible alternative. Currently, there is no approved or universally accepted maintenance treatment, nor is there a conclusive clinical trial demonstrating the benefit of an agent in maintenance setting for AML with FLT3-ITD. This clinical trial is designed to test the hypothesis that maintenance therapy with a potent FLT3 inhibitor will lead to improved relapse-free survival (RFS) for patients with FLT3/ITD AML in remission after induction/consolidation treatment. The trial is a randomized double-blind study comparing gilteritinib to placebo.

1.2 Nonclinical and Clinical Data

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

1.2.1 Nonclinical Data

1.2.1.1 Summary of In Vitro Pharmacology Studies

Gilteritinib in vitro studies showed the inhibition of activities of a series of tyrosine kinases: FLT3, nucleophosmin 1-ALK, leukocyte receptor TK (LTK), ALK and AXL kinases at 1 and 5 nmol/L, and tropomyosin receptor kinase A (TRKA), ROS, RET and MER kinases at 5 nmol/L by over 50%. Gilteritinib inhibited FLT3, LTK, AXL, echinoderm microtubule-associated protein-like 4-ALK variant 1 (EML4-ALK) and KIT kinase activities with half-maximal inhibitory concentration (IC_{50}) values of 0.291, 0.350, 0.726, 1.2 and 229 nmol/L, respectively.

Gilteritinib inhibited the cell growth of Ba/F3 cells expressing FLT3-ITD, FLT3-D835Y and FLT3-ITD-D835Y (IC_{50} values ranged from 1.6 to 2.1 nmol/L) and the growth of MV4-11 cells, a human AML cell line expressing FLT3-ITD, with an IC_{50} value of 0.92 nmol/L.

In MV4-11 cells, treatment with gilteritinib inhibited FLT3 phosphorylation (phosphorylation levels of 100%, 86%, 19% and 7% with gilteritinib at 0, 0.1, 1, and 10 nmol/L, respectively).

In addition, gilteritinib inhibited phosphorylation of signal transducer and activator of transcription 5 (STAT5), AKT and extracellular signal-regulated kinase in MV4-11 cells. Gilteritinib at 3 and 10 nmol/L significantly increased the population of MV4-11 cells in G1 phase, suggesting that gilteritinib arrests the cell cycle in this cell line. ASP2215 at 10 and 30 nmol/L significantly increased the annexin-V-positive population in MV4-11 cells, indicating that gilteritinib induces apoptosis in this cell line.

Gilteritinib also inhibited cell growth and ALK phosphorylation in NCI-H2228 cells, human non-small cell lung cancer (NSCLC) cells endogenously expressing EML4-ALK.

Gilteritinib inhibited AXL phosphorylation in AXL-overexpressed PC9 (PC9 AXL) cells. The combination treatment of gilteritinib and erlotinib showed more effective growth inhibition in PC9 AXL cells compared to erlotinib alone, suggesting that overexpression of AXL confers resistance to erlotinib in NSCLC cells.

The affinity of gilteritinib to 46 receptors, 5 ion channels, 3 transporters and the inhibitory effect of gilteritinib on 3 enzyme reactions were evaluated. Gilteritinib inhibited radioligand binding to adenosine A1 (rat) receptor, serotonin 5-hydroxytryptamine receptor 1 ($5HT_1R$) receptor (nonselective, rat), serotonin 5-hydroxytryptamine receptor 2B ($5HT_{2B}R$) receptor (human) and sigma receptor (nonselective, guinea pig) with IC_{50} values of 4.57, 4.90, 0.190 and 0.615 μmol/L, respectively. Gilteritinib inhibited human $5HT_{2B}R$ receptor function in a cell function assay with an IC_{50} value of 5.82 μmol/L without showing agonistic activity.

1.2.1.2 Summary of In Vivo Pharmacology Studies

Gilteritinib induced significant growth inhibition of MV4-11 tumors and tumor regression in vivo. At 6 and 10 mg/kg per day, gilteritinib induced complete tumor regression for 4 out of 6 and 6 out of 6 mice, respectively. Body weight of the mice treated with gilteritinib was not affected at any tested doses. After single oral administration of gilteritinib in the xenograft mice, the phosphorylation of FLT3 and STAT5 in MV4-11 tumors was inhibited at doses of 1, 3, 6 and 10 mg/kg.

Gilteritinib in combination with cytarabine and daunorubicin or in combination with cytarabine and idarubicin showed superior antitumor efficacy in mice xenografted with MV4-11 cells compared to gilteritinib alone or to either chemotherapy combinations without gilteritinib.

In the erlotinib-resistant HCC827 tumors, once-daily oral administration of gilteritinib did not inhibit tumor growth; however, in combination with erlotinib, tumor regression was induced by 46% after the 13-day treatment.

1.2.1.3 Summary of Nonclinical Pharmacokinetics

After a single oral administration, C_{max} and AUC_{inf} increased more than dose-proportionally from 1 to 10 mg/kg in rats and slightly more than dose proportionally from 0.3 to 3 mg/kg in dogs. The absolute oral bioavailability was 26.8% at 1 mg/kg in rats and 88.2% at 0.3 mg/kg in dogs.

[^{14}C] - gilteritinib-derived radioactivity in nonpigmented rats was distributed to be the highest in the liver and detectable at 72 hours in many tissues. In pigmented rats, the concentration of radioactivity decreased over time and was below the lower limit of quantification by 4 weeks postdose in most tissues. However, the elimination of radioactivity from the ciliary body and retina and choroid were notably slow, and tissue concentration/maximum tissue concentration (C_t/C_{max}) ratios at 17 weeks postdose were 32.7% and 42.8%, respectively. The plasma protein binding ratios of gilteritinib in mice, rats, rabbits, dogs and monkeys ranged between approximately 75% and 90%, and ranged from 90.2% to 90.5% in humans. The major binding protein in human plasma was human serum albumin.

After oral administration of [^{14}C] - gilteritinib at 1 mg/kg to nonpigmented rats, the urinary and fecal excretion of radioactivity within 168 hours was 1.4% and 89.9% of the dose, respectively. The urinary and biliary excretion of radioactivity within 48 hours was 8.6% and 29.3% of the dose, suggesting that the oral absorption was at least 37.9%. A part of the biliary excretion is assumed to undergo enterohepatic circulation.

Refer to [Section 1.2.2.2] for assessments using human biomaterials.

1.2.1.4 Summary of Nonclinical Safety

In safety pharmacology studies, gilteritinib showed a concentration-dependent suppression effect on the human ether-à-go-go-related gene (hERG) current in hERG-transfected human embryonic kidney 293 cells at concentrations of 3×10^{-6}, 1×10^{-5} and 3×10^{-5} mol/L with compensated suppression rates of 18.1%, 32.8% and 70.7%, respectively. Suppression was not observed at 1×10^{-6} mol/L. The IC_{50} was 1.6×10^{-5} mol/L.

Gilteritinib showed no effects on the central nervous system (CNS) in rats at 10 mg/kg. At 30 mg/kg and higher, decreased urination was noted. In addition, at 100 mg/kg, decreased defecation was noted. The changes in urination and defecation resolved during the recovery period.

Gilteritinib did not show any effect on the cardiovascular or respiratory system in dogs up to 100 mg/kg, or on the CNS at 1 mg/kg. At 3 mg/kg and higher, the following signs were noted: retching at 3 mg/kg, vomiting and positive fecal occult blood at 10 mg/kg and higher, a decrease in the blood Ca^{2+}concentration at 30 mg/kg, and salivation and an increase followed by a decrease in the blood Ca^{2+} concentration at 100 mg/kg. All of the findings recovered.

In the single oral dose toxicity study in rats, the approximate lethal dose level was 300 mg/kg for males and females. The major change was a gastrointestinal hemorrhagic disorder at 100 and 300 mg/kg. Reversibility of the changes noted in the surviving animals was seen.

No definitive single oral dose toxicity study in dogs was conducted. In the 4-week toxicity study in dogs, a dose of 1000 mg/kg per day caused deaths and moribund sacrifices on day 2. The cause of death and moribundity was considered to be deterioration of general condition caused by gastrointestinal hemorrhage.

In the 1-week oral repeated dose toxicity study in rats, interstitial pneumonia in the lung and vacuolar change in the rod-cone layer of the retina were observed in a male at 30 mg/kg per day. In the 13-week oral repeated dose toxicity study in rats, deaths occurred at 20 mg/kg per day in both sexes. Target organ toxicity was identified in the gastrointestinal tract, immune system, hematopoietic system, eye, lung, kidney and liver. The no observed adverse effect level (NOAEL) was lower than 2.5 mg/kg per day for males and females. The changes noted during the dosing period recovered or tended to recover during the 4-week recovery period. The severely toxic dose in 10% of the animals in rats was considered to be 20 mg/kg per day. In the 4-week oral repeated dose study in dogs, mortality occurred at 10 mg/kg per day or more. Target organ toxicity was identified in the gastrointestinal tract, immune system, hematopoietic system, eye, kidney and liver. The NOAEL was 1 mg/kg per day for males and females. Reversibility of most of the test article-related changes was indicated by the end of the 4-week recovery period. The highest non-severely toxic dose in dogs was considered to be 5 mg/kg per day. In the 13-week oral repeated dose study in dogs, mortality occurred at 5 mg/kg per day. Target organ toxicity was identified in the lung, lacrimal gland, urinary bladder, epithelial tissue, gastrointestinal tract, immune system, hematopoietic system, eye, kidney and liver. The NOAEL was 1 mg/kg per day for males and females. Reversibility of most of the test article-related changes was indicated by the end of the 4-week recovery period.

Gilteritinib did not induce gene mutation in the definitive in vitro reversion test in bacteria. Similarly, gilteritinib did not induce chromosomal aberrations in the definitive in vitro chromosomal aberration test in mammalian cells. The definitive in vivo micronucleus test showed that gilteritinib has a potential to induce micronuclei in mice. Based on the results of the battery of genotoxicity studies above, it was concluded that gilteritinib has a potential to induce genotoxicity in vivo.

Gilteritinib showed teratogenic potential and embryo-fetal deaths in the embryo-fetal development study in rats. The NOAEL for dams and embryo-fetal development was 10 mg/kg per day.

Gilteritinib showed no potential to induce phototoxicity to cultured mammalian cells.

1.2.2 Clinical Data

1.2.2.1 Clinical Pharmacokinetics and Pharmacodynamics

The pharmacokinetic parameters of unchanged drug after single and multiple doses of gilteritinib to AML subjects were investigated in the dose escalation cohort of Study 2215-CL-0101. Assessment of C_{trough} over time for individual subjects (both dose escalation and dose expansion cohorts) showed that in most subjects, the trough concentration of gilteritinib appeared to reach steady state by day 15 of multiple administrations of gilteritinib

from 20 to 120 mg once daily. Plasma inhibitory assay from the samples collected predose and postdose on days 1, 8, 15 and 29 demonstrated sustained inhibition of phospho-FLT3 at doses 80 mg and higher.

The effect of strong and moderate cytochrome P450 (CYP)3A4 inhibitors and strong CYP3A4 inducers on gilteritinib exposure was assessed in relapsed or refractory AML subjects (Study 2215-CL-0101) and healthy subjects (Study 2215-CL-0108). In relapsed or refractory AML subjects, there was a less than 2-fold increase in gilteritinib exposure when gilteritinib was coadministered with moderate or strong CYP3A4 inhibitors. In healthy subjects, gilteritinib exposure increased approximately 2-fold when gilteritinib was coadministered with itraconazole, a strong CYP3A4 and P-glycoprotein (P-gp) inhibitor. Coadministration of gilteritinib with rifampicin, a strong CYP3A4 inducer, resulted in an approximate 70% decrease in gilteritinib exposure. Collectively, these data support monitoring subjects who require concomitant medications that are strong CYP3A4 inhibitors and restricting use of concomitant medications that are strong CYP3A4 inducers.

Preliminary results from a drug-drug interaction assessment in a subset of relapsed or refractory AML subjects (2215-CL-0101) indicate cephalexin (MATE 1 substrate) exposure was comparable after single dose administration of cephalexin alone and in combination with gilteritinib (administered once daily). These results suggest coadministration of MATE1 substrates and gilteritinib is not expected to result in a clinically-relevant drug-drug interaction.

A preliminary analysis of the relationship between ASP2215 plasma concentration and Fridericia-corrected QT interval (QTcF) change from baseline (ΔQTcF) was performed on data from the 2215-CL-0101 study (data cutoff 31 Oct 2015). This assessment included 1359 observations from 199 patients. A model-averaging approach was used to develop a robust model to describe and predict the ASP2215 concentration-ΔQTcF relationship. A concentration-related increase in ΔQTcF was observed and the mean ΔQTcF at the mean steady-state C_{max} at 120 mg was predicted to be less than the 10 msec-threshold considered clinically significant. Additionally, 4.1% of relapse/refractory subjects had a maximum post-baseline QTcF interval >500 msec. These data indicate clinically-relevant corrected QT interval (QTc) prolongation is not anticipated.

With increasing dose of gilteritinib, increasing plasma concentrations of creatine kinase (CK) were observed. Comparison of day matched CK corrected relative to baseline with C_{trough} ASP2215 values showed a correlation with a positive slope. Similarly, comparison of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade for CK elevations with gilteritinib C_{trough} values showed increasing incidence of higher CTCAE grades with increasing drug exposure. However, almost all of the elevations were grade 1 and grade 2. Overall, increasing CK plasma concentrations from baseline appeared to correlate with increasing ASP2215 plasma concentrations; the mechanism for this effect is unknown.

1.2.2.2 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-gp but not a substrate for breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP)1B1, OATP1B3 or organic cation transporter (OCT)1. Gilteritinib demonstrated a potential to inhibit BCRP and multidrug and toxin extrusion (MATE)1 at clinically relevant concentrations of gilteritinib. However, preliminary results from the drug-drug interaction assessment of coadministration of gilteritinib and cephalexin, a MATE1 substrate, in relapsed or refractory AML subjects (Study 2215-CL-0101) indicate lack of a clinically-significant interaction between gilteritinib and MATE1 substrates (see Section 1.2.2.1). Based on EMA Guideline on the Investigation of Drug Interaction (Jun 2012), gilteritinib may also inhibit liver transporters OCT1 and OATP1B1 at clinically relevant drug exposures. 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 CYP3A4. Gilteritinib has a potential to induce CYP enzyme activities (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4/5) and mRNA levels (CYP2B6, CYP2C8, CYP2C9 and CYP3A4). However, these results should be interpreted with caution because these effects were not uniformly observed in all donor samples and the concentration-dependency of these effects could not be evaluated. For CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP2D6 inhibition, IC_{50} values were > 100 μmol/L. Very weak direct inhibition of CYP2C19 and CYP3A was observed. Overall, gilteritinib showed minimal direct inhibition of CYP enzymes at clinically relevant concentrations.

1.2.2.3 Clinical Safety

Ongoing study 2215-CL-0101 is an open-label, dose escalation, first-in-human study in subjects with relapsed or refractory AML, with concomitant expansion cohort for multiple doses. One cycle is defined as 28 days and the subject will receive oral gilteritinib daily. The study treatment will continue until 1 of the discontinuation criterion is met.

The starting dose level of gilteritinib was 20 mg daily, and the decision to dose escalate to the next dose level was made based on the assessment of safety variables including occurrence of grade 2 adverse events (AE) or dose-limiting toxicities (DLTs). The maximum tolerated dose (MTD) in the study was determined to be 300 mg.

This study has 2 cohorts of subjects:

- Cohort 1: Dose escalation cohort (20, 40, 80, 120, 200, 300 and 450 mg doses)
- Cohort 2: Dose expansion cohort (20, 40, 80, 120, 200 and 300 mg doses)

As of 31 Oct 2015, of the first 252 subjects that received gilteritinib, the majority of subjects (245 [97.2%]) experienced at least 1 treatment-emergent adverse event (TEAE). Overall, the most frequently reported TEAE (occurring in at least 10% of subjects) include: febrile neutropenia (38.5%), diarrhea (33.7%), anemia (29.0%), fatigue (28.2%), aspartate aminotransferase (AST) increased (23.0%), edema peripheral (22.6%), dyspnea and pyrexia (21.8% each), cough and constipation (18.7% each), epistaxis (17.9%), nausea (17.5%),

dizziness (17.1%), alanine aminotransferase (ALT) increased and hypotension (16.7% each), vomiting (15.9%), hypokalemia (15.1%), hypocalcemia (14.7%), platelet count decreased (13.5%), blood creatinine increased (13.1%), acute myeloid leukemia and hyponatremia (12.7% each), pneumonia (12.3%), sepsis (11.9%), fall (11.5%), arthralgia and hypomagnesemia and thrombocytopenia (11.1% each), blood alkaline phosphatase increased and headache (10.7% each), and hypoxia (10.3%).

A total of 183 (72.6%) subjects experienced at least 1 TEAE considered by the investigator to be possibly or probably related to study drug. Common drug-related TEAEs (occurring in at least 5% of subjects) include diarrhea (16.3%), fatigue (13.1%), increased AST (11.9%), anemia (9.1%), constipation (8.3%), increased ALT (8.3%), peripheral edema (8.3%), decreased platelet count (7.5%), nausea (7.5%), thrombocytopenia (6.7%), vomiting (6.7%), increased creatine phosphokinase (6.3%), dizziness (6.3%), dysgeusia (6.3%) and increased transaminases (6.0%).

Eighty-seven (34.5%) subjects experienced a TEAE that resulted in death: AML in 32 (12.7%) subjects; multi-organ failure in 7 (2.8%) subjects; respiratory failure in 6 (2.4%) subjects; sepsis and septic shock in 4 (1.6%) subjects each, pneumonia, cardiac arrest and intracranial hemorrhage in 3 (1.2%) subjects each; disease progression and renal failure in 2 (0.8%) subjects each; anemia, neutropenia, peripheral edema, bronchopulmonary aspergillosis, enterococcal infection, lung infection, pyoderma, staphylococcal bacteremia, staphylococcal sepsis, malignant neoplasm progression, cerebral ischemia, loss of consciousness, acute respiratory failure, hypoxia, pulmonary embolism, colitis, ventricular fibrillation, ventricular tachycardia, neutropenic colitis, bacteremia, cellulitis, diabetic ketoacidosis, sudden death and hemoptysis each in 1 (0.4%) subject. One event of intracranial hemorrhage, 1 event of septic shock, 1 event of respiratory failure and sepsis, 1 event of pulmonary embolism, 1 event of neutropenia, 1 event of pyoderma, 1 event of ventricular fibrillation and the event of hemoptysis were considered possibly related to gilteritinib by the investigator. One event of respiratory failure was considered probably related to gilteritinib by the investigator.

The majority of subjects (198 [78.6%]) experienced a serious TEAE. Serious TEAEs that occurred in 2 or more subjects include febrile neutropenia (30.6%), AML (12.7%), sepsis (11.9%), pneumonia (9.5%), acute renal failure (8.3%), pyrexia (6.7% each), bacteremia (5.2%), hypotension and respiratory failure (4.8% each), fungal pneumonia (4.0%), diarrhea (3.2%), multi-organ failure, urinary tract infection and hypoxia (2.8% each), subdural hematoma, septic shock, lung infection, cellulitis, gastrointestinal hemorrhage, leukocytosis and syncope (2.4% each), atrial fibrillation (2.0%), anemia, clostridium difficile colitis, cardiac arrest, vomiting, increased AST, hyponatremia and acute febrile neutrophilic dermatosis (1.6% each), upper respiratory tract infection, clostridium difficile infection, skin infection, bronchopulmonary aspergillosis, hyperbilirubinemia, disease progression, small intestinal obstruction, nausea, blood creatine phosphokinase increased, dehydration, squamous cell carcinoma of skin, intracranial hemorrhage, dyspnea, respiratory distress, angioedema, hematoma, renal failure and convulsion (1.2% each), ejection fraction decreased, liver function test (LFT) abnormal, pericardial effusion, tachycardia, transaminases increased, increased

ALT, urosepsis, fall, streptococcal bacteremia, lobar pneumonia, enterococcal bacteremia, clostridial infection, fatigue, mucosal inflammation, pancytopenia, acute graft-versus-host disease in skin, epistaxis, sinusitis, soft tissue infection, staphylococcal bacteremia, back pain, urinary retention, acute respiratory failure, muscular weakness, pleural effusion, pulmonary embolism, renal tubular necrosis, mental status changes and posterior reversible encephalopathy syndrome (PRES [0.8% each]).

Sixty-nine (27.4%) subjects experienced a serious TEAE that was considered related to the study drug by the investigator. Drug-related serious TEAEs that occurred in 2 or more subjects include febrile neutropenia (2.4%), renal failure acute, gastrointestinal hemorrhage and increased AST (1.6% each), blood bilirubin increased, blood creatine phosphokinase increased, hypotension (1.2% each), nausea, LFT abnormal, pyrexia, sepsis, increased ALT, muscular weakness, transaminases increased, small intestinal obstruction, hypoxia, PRES and vomiting (0.8% each).

A preliminary analysis of the relationship between gilteritinib plasma concentration and ΔQTcF was performed on data from the 2215-CL-0101 study (data cutoff 31 Oct 2015). This assessment included 1359 observations from 199 patients. A model-averaging approach was used to develop a robust model to describe and predict the gilteritinib concentration-ΔQTcF relationship. A concentration-related increase in ΔQTcF was observed. The model-predicted increase in mean QTcF is 5.8 msec (1-sided upper 95% CI: 8.0 msec) at the mean steady state C_{max} (282 ng/mL) associated with once daily dosing of 120 mg gilteritinib. These data indicate QTc prolongation is expected to be less than the 10-msec threshold considered clinically significant.

An exposure-related increase in circulating CK concentration relative to baseline was also observed in relapse/refractory AML subjects enrolled in Study 2215-CL-0101. Almost all CK elevations were grade 1 and grade 2, however CTCAE Grade 3 and 4 AEs related to elevated CK occurred in higher gilteritinib dose groups. Similarly, a significant correlation between gilteritinib concentration and aspartate aminotransferase change from baseline (ΔAST) was also observed. However, the incidence of ≥ Grade 3 events related to elevated AST was < 3% (data cutoff 31 Oct 2015).

After the data cutoff, 1 subject in the 200 mg dose group developed altered mental status and 1 episode of seizure with magnetic resonance imaging (MRI) results consistent with PRES. Gilteritinib was discontinued and the subject's symptoms resolved.

There were 2 subjects who experienced retinoic acid syndrome (differentiation syndrome) that was considered by the investigator to be related to gilteritinib. FLT3 inhibitors may differentiate leukemic blasts to mature neutrophils. Subjects who develop differentiation syndrome may present with increases in neutrophil counts, unexplained fever, acute respiratory distress with interstitial pulmonary infiltrates, and/or vascular capillary leak syndrome.

As of 31 Oct 2015, 23 subjects experienced a DLT. All DLTs occurred in the dose expansion cohort, with the exception of 2 subjects in the 450 mg dose escalation cohort that experienced grade 3 increased AST and grade 3 diarrhea. No further subjects will be enrolled in the

450 mg dose group. None of the doses below 450 mg met the criteria for pausing enrollment. The MTD in Study 2215-CL-0101 is considered 300 mg.

1.2.2.4 Clinical Efficacy

In Study 2215-CL-0101, as of 31 Oct 2015, 252 patients have received gilteritinib. Response was assessed based on central assessment supplemented by local assessment (i.e., derived response) and investigator reported response. Patients are included in the dose group of the initial dose received prior to any dose increase or decrease, unless otherwise noted.

Nearly all patients who achieved a derived response of partial remission (PR) or composite complete remission (CRc) at the end of treatment were FLT3-mutation positive. Based on the derived response in the 174 FLT3-mutation positive patients at the end of treatment, 66 (37.9%) patients achieved CRc, and the best overall response rate was 49.4% (i.e., 66/174 patients). Eleven (6.3%) patients achieved CR, 9 (5.2%) patients achieved complete remission with incomplete platelet recovery (CRp), 46 (26.4%) patients achieved complete remission with incomplete hematologic recovery (CRi) and 20 (11.5%) patients achieved PR.

Overall, the majority of CRc and PR events were observed in FLT3-mutation positive patients in dose groups of 80 mg and greater. The derived CRc rate at the end of treatment in the FLT3-mutation positive population at doses of 80 mg and above was 42.5% overall and 41.7%, 51.9%, 37.7%, 33.3% and 0 in the 80, 120, 200, 300 and 450 mg dose groups, respectively.

Median survival for 80, 120, 200, 300 and 450 mg dose groups was 198, 218, 224, 157 and 51 days, respectively.

1.3 Summary of Key Safety Information for Study Drugs

1.3.1 Gilteritinib Data

The nonclinical and clinical studies, which are referred to in this section, are as of the writing of this protocol. Please refer to the current version of the ASP 2215 Investigator's Brochure.

1.3.2 Gilteritinib Nonclinical Data

Major findings in the safety pharmacology studies were vomiting, positive fecal occult blood and increased/decreased blood Ca^{2+} in dogs, and decreased urination and defecation in rats. In the oral 13-week repeated dose toxicity study in rats, and the 4- and 13-week repeated dose toxicity studies in dogs, mortality occurred at 20, 10 and 5 mg/kg per day, respectively. With respect to other major target organ toxicities, effects on the lacrimal gland, urinary bladder, epithelial tissue, gastrointestinal tract, immune system, hematopoietic system, eye, liver, kidney and/or lung were observed in rats and dogs at 2.5 mg/kg per day or more. All major findings were reversible and monitorable.

Gilteritinib has a potential to induce genotoxicity in vivo. Gilteritinib showed teratogenic potential and embryo-fetal deaths in the embryo-fetal development study in rats.

1.3.3 Gilteritinib Clinical Data

Preliminary data from clinical study 2215-CL-0101 demonstrated efficacy in FLT3-mutation positive patients with relapsed/refractory AML, with a tolerable safety profile.

Expected adverse drug reactions for gilteritinib include (by preferred term) peripheral edema, increased blood creatine phosphokinase, increased ALT, increased AST and myopathy (Astellas data on file).

Refer to [Section 1.2.2.3] for a comprehensive summary of safety findings.

1.4 Risk-Benefit Assessment

AML with activating FLT3 mutations such as FLT3-ITD and FLT3 point mutation around D835 decrease the prognosis for AML patients. Even patients who achieve remission with induction chemotherapy have very high risk of relapse. Once relapsed, AML is incurable in most of the patients. Gilteritinib inhibits the growth of cells with FLT3-ITD and FLT3 point mutation (D835). Gilteritinib has shown anti-leukemic activity in an ongoing trial in FLT3-mutation positive AML patients. When used after successful remission induction, gilteritinib can potentially delay or prevent relapse and thus improve the long term outcome.

The potential undesirable effects of gilteritinib in humans based on toxicities observed in the nonclinical studies and in the recent clinical study in subjects with AML are summarized in [Section 1.2.1.4 and Section 1.2.2.3]. As with any investigational agent, subjects may experience side effects that are more severe than those observed in the nonclinical and clinical studies or may experience side effects not observed in nonclinical and clinical studies. Findings of potential concern for clinical trials with gilteritinib include effects on the gastrointestinal tract, immune system, hematopoietic system, eye, liver and kidney.

Subjects will have adequate and appropriate monitoring during this study to monitor for AEs and minimize risk. The Independent Data Monitoring Committee (IDMC) will perform periodic review of the data as documented in the IDMC Charter.

The potential risks identified from the nonclinical and clinical studies are judged to be acceptable in light of the potential benefits. The MTD in clinical study 2215-CL-0101 was determined to be 300 mg, and the recommended phase 2 dose was determined to be 120 mg (please refer to the current ASP2215 Investigator's Brochure for more detailed information). Strict adherence to the eligibility criteria is essential to ensure that appropriate subjects are selected for participation. Equally important is strict adherence to the schedule of safety assessments to ensure that subjects are appropriately monitored.

2 STUDY OBJECTIVE(S), DESIGN, AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective is to compare RFS between subjects with FLT3/ITD AML in first complete remission (CR1) without transplant and who are randomized to receive gilteritinib or placebo beginning after completion of induction/consolidation chemotherapy for a 2-year period.

2.1.2 Secondary Objectives

2.1.2.1 Key Secondary Objective

Compare overall survival (OS) in subjects treated with gilteritinib as maintenance therapy after induction/consolidation with those treated with placebo.

2.1.2.2 Additional Secondary Objectives

The secondary objectives are to evaluate the safety and efficacy of gilteritinib versus placebo in terms of:

- Event-free survival (EFS), AEs, clinical laboratory, vital signs, electrocardiograms (ECGs) and Eastern Cooperative Oncology Group (ECOG) performance scores.
- Examine the relationship of minimal residual disease (MRD), as determined using a next-generation sequencing (NGS) platform specific to FLT3/ITD mutations, with RFS and OS.

2.1.3 Exploratory Objectives

The exploratory objectives are to:

- Assess relationship between gilteritinib exposure and QTcF for subjects participating in the ECG/PK sampling subset.
- Explore the pharmacokinetics of gilteritinib (and metabolite, if applicable) in study population using a population pharmacokinetics approach.
- Determine FLT3 mutation status at relapse.
- Evaluate the safety and efficacy of gilteritinib in terms of:
    - Patient reported signs, symptoms and impacts of AML (Functional Assessment of Cancer Therapy-Leukemia [FACT-Leu], Functional Assessment of Cancer Therapy-Anemia [FACT-An])
    - EuroQol Group-5 Dimension-5 Level Instrument (EQ-5D-5L)
- Evaluate healthcare resource utilization including hospitalization, intensive care unit (ICU) visits, emergency room (ER) visits, transfusion and use of antibiotics

2.2 Study Design and Dose Rationale

2.2.1 Study Design

This is a phase 2, randomized, placebo-controlled, double-blind, 2-arm study to compare the effect of gilteritinib as maintenance therapy versus placebo after induction/consolidation in subjects with FLT3/ITD AML in CR1 (including CRp and CRi). The trial will be conducted at approximately 200 centers in North America, Europe, South America, Central America, and Asia/Pacific and rest of world.

Subjects in CR1 (including CRp and CRi) will be approached for this study after induction/consolidation therapy is complete and a decision not to proceed with transplantation is made or a suitable donor could not be identified.

Approximately 85 subjects will be randomized in a 2:1 ratio to receive gilteritinib or placebo.

Randomization will be stratified based on:

- Age < 60 or ≥ 60 years.
- Geographic region, North America or Europe or Asia/Pacific/Central America/South America/rest of world.
- Presence of MRD at screening, yes or no.
- Use of FLT3 inhibiting agents during induction/consolidation, yes or no.

Subjects will enter the screening period up to 14 days prior to the start of treatment. Subjects will be administered treatment up to 2 years, or until a discontinuation criterion is met.

After treatment discontinuation, subjects will have a 30-day follow-up visit for safety, after which the subjects will enter the long-term follow-up period for collection of subsequent AML treatment, remission status, and survival (cause of death and date of death).

2.2.2 Dose Rationale

Gilteritinib has been evaluated in relapsed and refractory AML patients in the US (clinical study 2215-CL-0101) and Japan (clinical study 2215-CL-0102) at doses from 20 mg to 450 mg. In the US study, the MTD was determined to be 300 mg and in the Japan study, the MTD was determined to be 200 mg; however, 120 mg was selected as the recommended phase 2/3 dose based on comparable efficacy, effective inhibition of target and lower DLT rate. This dose is being used in all ongoing phase 3 trials. Please refer to the current ASP2215 Investigator's Brochure for more detailed information.

2.3 Endpoints

2.3.1 Primary Endpoints

The primary efficacy endpoint is RFS, defined as the time from randomization until relapse or death from any cause, whichever comes first.

Leukemia relapse will be defined as bone marrow blasts 5% or higher (not attributable to regenerating bone marrow), any circulating blasts, any extramedullary blast foci as per Revised International Working Group (IWG) criteria.

2.3.2 Secondary Endpoints

The key secondary efficacy endpoint is:

- OS, defined as the time from randomization until death from any cause.

Additional secondary efficacy endpoints are:

- EFS
- MRD

Safety Endpoints

- AEs
- Serum chemistry, hematology, coagulation and urinalysis
- Vital signs
- ECGs
- Physical examination findings
- ECOG performance status

2.3.3 Exploratory Endpoints

- ECGs at specified visits and time points with time-matched gilteritinib plasma concentrations
- Gilteritinib metabolite concentrations (if applicable)
- FLT3 mutation status at relapse
- Signs, symptoms and impacts of AML as measured with patient-reported outcome instruments
- Healthcare resource utilization including hospitalization, ICU visits, ER visits, transfusion and use of antibiotics.
- Gilteritinib plasma concentrations

3 STUDY POPULATION

3.1 Selection of Study Population

Subjects diagnosed with FLT3/ITD AML in CR1, including CRp and CRi defined in [Appendix 12.6], for whom a decision not to proceed with transplantation has been made, or a suitable donor could not be identified.

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 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 consents to allow access to his or her diagnostic bone marrow aspirate or peripheral blood sample and/or the DNA derived from that sample, if available, that may be used to validate a companion diagnostic test for gilteritinib.
4. Subject has confirmed morphologically documented AML, excluding acute promyelocytic leukemia (APL), in CR1 (including CRp and CRi). For the purposes of enrollment, CR will be defined as < 5% blasts in the bone marrow with no morphologic characteristics of acute leukemia (e.g., Auer rods) in the bone marrow with no evidence of extramedullary disease such as central nervous system involvement or granulocytic sarcoma.
5. Subject will not proceed with transplantation as either a decision not to proceed with transplantation has been made either on the recommendation of the treating physician or by the patient or a suitable donor could not be identified.
6. Subject is < 2 months from the start of the last cycle of consolidation and should have completed the recommended number of consolidations per local practice.
7. Subject has had no use of investigational agents, with the exception of FLT3 inhibiting agents during induction and/or consolidation therapy, within the prior 4 weeks.
8. Subject has had presence of the FLT3/ITD activating mutation in the bone marrow or peripheral blood as determined by the local institution at diagnosis.
9. Subject has an ECOG performance status 0 to 2.
10. Subject must meet the following criteria as indicated on the clinical laboratory tests:
    - Serum creatinine ≤ 1.5 × institutional upper limit of normal (ULN), or if serum creatinine outside normal range, then glomerular filtration rate (GFR) > 40 mL/min/1.73m^2 as calculated with the 4-parameter Modification of Diet in Renal Disease (MDRD) equation.
    - Serum total bilirubin ≤ 2.5 mg/dL (43 µmol/L), except for subjects with Gilbert's syndrome.
    - Serum AST and ALT < 3 x ULN.
    - Serum potassium and serum magnesium ≥ institutional lower limit of normal (LLN).
    - Absolute neutrophil count (ANC) ≥ 500/µl and platelets ≥ 20000/µl (unsupported by transfusions).
11. Subject is suitable for oral administration of study drug.
12. Female subject must either:
    - Be of nonchildbearing potential:
        - Postmenopausal (defined as at least 1 year without any menses) prior to screening, or

    - Documented surgically sterile or status posthysterectomy (at least 1 month prior to screening)
- Or, if of childbearing potential,
    - Agree not to try to become pregnant during the study and for 6 months after the final study drug administration
    - And have a negative urine or serum pregnancy test at screening
    - And, if heterosexually active, agree to consistently use highly effective contraception per locally accepted standards in addition to a barrier method starting at screening and throughout the study period and for 6 months after the final study drug administration.

*Highly effective forms of birth control include:

- Consistent and correct usage of established hormonal contraceptives that inhibit ovulation,
- Established intrauterine device (IUD) or intrauterine system (IUS),
- Bilateral tubal occlusion,
- Vasectomy (A vasectomy is a highly effective contraception method provided the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)
- Male is sterile due to a bilateral orchiectomy.
- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual activity 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 clinical study and the preferred and usual lifestyle of the subject.

*List is not all inclusive. Prior to enrollment, the investigator is responsible for confirming subject will utilize highly effective forms of birth control per locally accepted standards during the protocol defined period

13. Female subject must agree not to breastfeed starting at screening and throughout the study period, and for 2 months and 1 week after the final study drug administration.
14. Female subject must not donate ova starting at screening and throughout the study period, and for 6 months after the final study drug administration.
15. Male subject and their female partners who are of childbearing potential must be using highly effective contraception per locally accepted standards in addition to a barrier method starting at screening and continue throughout the study period and for 4 months and 1 week after the final study drug administration.
16. Male subject must not donate sperm starting at screening and throughout the study period and for 4 months and 1 week after the final study drug administration.
17. Subject agrees not to participate in another interventional 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 has had prior allogeneic transplant.
2. Subject has QTcF interval > 450 msec (average of triplicate determinations based on central reading).
3. Subject with Long QT Syndrome.
4. Subject with hypokalemia and hypomagnesemia at screening (defined as values below LLN).
5. Subject has clinically active CNS leukemia.
6. Subject is known to have human immunodeficiency virus infection.
7. Subject has active hepatitis B or C.
8. Subject has an uncontrolled infection. If a bacterial or viral infection is present, the subject must be receiving definitive therapy and have no signs of progressing infection for 72 hours prior to randomization. If a fungal infection is present, the subject must be receiving definitive systemic anti-fungal therapy and have no signs of progressing infection for 1 week prior to randomization.
9. Subject has progressing infection defined as hemodynamic instability attributable to sepsis or new symptoms, worsening physical signs or radiographic findings attributable to infection. Persisting fever without other signs or symptoms will not be interpreted as progressing infection.
10. Subject has uncontrolled angina, severe uncontrolled ventricular arrhythmias, electrocardiographic evidence of acute ischemia, congestive heart failure New York Heart Association (NYHA) class 3 or 4 or subject has a history of congestive heart failure NYHA class 3 or 4 in the past, unless a screening echocardiogram (ECHO) or multigated acquisition scan (MUGA) performed within 1 month prior to study entry results in a left ventricular ejection fraction that is ≥ 45%.
11. Subject requires treatment with concomitant drugs that are strong inducers of CYP3A.
12. Subject requires treatment with concomitant drugs that are strong inhibitors or inducers of P-glycoprotein (P-gp) with the exception of drugs that are considered absolutely essential for the care of the subject.
13. Subject requires treatment with concomitant drugs that target serotonin $5HT_1R$ or $5HT_{2B}R$ or sigma nonspecific receptor with the exception of drugs that are considered absolutely essential for the care of the subject.
14. Subject has a serious medical or psychiatric illness likely to interfere with participation in this clinical study.

15. Subject has prior malignancies, except resected basal cell carcinoma or treated cervical carcinoma in situ. Cancer treated with curative intent ≥ 5 years previously will be allowed. Cancer treated with curative intent < 5 years previously will not be allowed.
16. Subject has any condition which, in the investigator's opinion, makes the subject unsuitable for study participation.

Waivers to the exclusion criteria will NOT be allowed.

4 TREATMENT(S)

4.1 Identification of Investigational Product(s)

4.1.1 Test Drug(s)

Gilteritinib is an oral drug that is available in a 40 mg tablet. The tablets are contained within a high-density polyethylene bottle.

The study centers will be provided bottles of gilteritinib, each containing 30 tablets. The study site personnel will fill out the label to indicate the dispensing date, subject's dose and the corresponding number of tablets that need to be taken each day. The gilteritinib 40 mg tablet product information is listed in [Table 2].

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 ASP2215 in free form. Gilteritinib Tablets are round light-yellow film-coated tablets.
Lot No.	Described in separately prepared "Study Drug Handling Procedures"
Storage	Gilteritinib should be stored according to labeled storage conditions and should not be stored above the temperature specified on the gilteritinib label. Store in original container.

4.1.2 Comparative Drug(s)

The placebo for gilteritinib (inactive ingredients) will be supplied as a 40 mg placebo to match tablet. The tablets contain mannitol, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, hypromellose (2910), talc, polyethylene glycol 8000, titanium oxide and yellow ferric oxide, which are all well characterized excipients. The placebo tablets are identical in size and appearance to gilteritinib tablets.

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, International Council on Harmonisation (ICH) of Technical Requirements

for Registration of Pharmaceuticals for Human Use Good Clinical Practice (GCP) guidelines and applicable local laws/regulations.

Each bottle will bear a label conforming to regulatory guidelines, GMP and local laws and regulations with identifier the contents as investigational drug.

A qualified person of Astellas Pharma Europe B.V. or sponsor's designee will perform the final release of the medication according to Directive 2003/94/EC Annex 13.

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

Drug inventory and accountability records for the study drugs will be kept by the investigator, head of study site (specific to sites in Japan), 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 drug(s) to any persons except the eligible subjects in this study in accordance with the protocol.
- The investigator or designee will store and take accountability of the study drug(s) in conforming to the procedures for handling the study drugs written by the Sponsor.
- The investigator or designee will prepare and retain records of the study drug's receipt, the inventory at the study site, the use by each subject, and the return to the Sponsor or alternative disposal of unused study drug(s) if approved by Sponsor. These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the study drugs and subjects.
- 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 medication. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility.

Specific to Japan

In Japan, the head of the study site or the study drug storage manager should take accountability of the study drugs as follows:

- The study drug storage manager should store and take accountability of the study drugs in conforming to the procedures for handling the study drugs written by the Sponsor.
- The study drug storage manager should prepare and retain records of the study drug's receipt, the inventory at the study site, the use by each subject and the return to the Sponsor or alternative disposal of unused study drugs. These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable) and the unique code numbers assigned to the study drugs and subjects.
- The study drug storage manager should prepare and retain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all the study drugs supplied from the Sponsor.

4.4 Blinding

This is a double-blind study. Subjects will be randomized to receive gilteritinib or placebo in a double-blind fashion such that the investigator, Sponsor's study management team, clinical staff, nor the subject will know which agent is being administered. The randomization number will be assigned based on information obtained from the Interactive Response Technology (IRT).

4.4.1 Retention of the Assignment Schedule and Procedures for Treatment Code Breaking

The randomization list and study medication blind will be maintained by the IRT system.

The IDMC will be provided access to the dosing assignment for periodic review of the unblinded data as documented in the IDMC Charter.

4.4.2 Breaking the Treatment Code by the Sponsor

The Sponsor may break the treatment code for subjects who experience a Suspected Unexpected Serious Adverse Reaction (SUSAR), in order to determine if the individual case or a group of cases requires expedited regulatory reporting. Individual Emergency Codes will be provided to the limited staff who are responsible to break the codes for all SUSAR cases for reporting purposes.

The treatment code for each randomized subject will be provided by the IRT in the event of a medical emergency requiring knowledge of the treatment assigned to the subject. The time, date, subject number and reason for obtaining any of these codes, and therefore breaking the blind, must be documented in the study file. They must only be requested by the investigator or other persons designated as sub-investigators. No subjects or other study personnel will be made aware of the treatment given to any subject unless a medical emergency necessitates such disclosure.

Unblinding of the study drug should only be considered for participant safety and/or evidence of documented relapse contingent upon knowing the blinded study drug assignment. Astellas Data Science Group will remain blinded.

- Unblinding for patient safety by the investigator or designated sub-investigator must be reported immediately to the Sponsor (Astellas Medical Monitor) and must include an explanation of why the study medication was unblinded. If possible, the Sponsor should be contacted prior to unblinding of the study drug.
- Unblinding for documented relapse by the investigator or designated sub-investigator must be reported to the Sponsor (Astellas Medical Monitor), including an explanation and evidence of relapse prior to unblinding of the study drug. Relapse can be based on the investigator's assessment or the IRC adjudication.

4.5 Assignment and Allocation

Enrollment, randomization and study drug assignment will be performed via IRT. Prior to the initiation of the study treatment, the site staff will contact the IRT in order to determine the randomly assigned treatment. Specific procedures for randomization through the IRT are contained in the study procedures manual.

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

Gilteritinib or placebo are oral tablets that subjects will take once daily without food for continuous daily dosing. Subjects will be instructed to take the daily gilteritinib or placebo dose with water as close to the same time each morning as possible. Dose reductions are permitted (see [Section 5.1.2]). Gilteritinib or placebo can be taken at least 2 hours after or 1 hour before food. Gilteritinib or placebo will be self-administered at home when subjects are not scheduled for clinic visits. If a subject forgets to take a dose in the morning and 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.

Assigned treatment should continue until unacceptable toxicity occurs, or the subject meets a treatment discontinuation criterion as provided in [Section 6.1].

5.1.2 Interruption or Reduction in Dose of the Study Drug(s)

Guidelines for gilteritinib or placebo dose interruption and reduction are provided in [Table 4].

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 4]. 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.

The dose levels potentially used include the following [Table 3].

Table 3 Study Drug Dose Levels

Dose Level (DL)	Gilteritinib/Placebo Dose
DL -2	40 mg
DL -1	80 mg
DL 1 (starting dose)	120 mg

The study drug dose may be initially reduced by 1 dose level per day. The study drug dose can be further reduced by a second dose level. Note that dose reductions should occur in a step-wise manner. Only 2 dose level reductions are permitted.

The study drug will be interrupted if a grade 3 or greater AE occurs and the investigator judges that AE to be possibly or probably related to the study drug. When the grade of AE decreases to ≤ 1, the study drug may be resumed at the next lower dose level, unless the investigator deems the AE was, in retrospect, not related to the study drug, at which point the original dose may be resumed. If an AE occurs that prevents administration of the study drug (e.g., surgery that precludes an oral drug, intubation for respiratory failure), and that AE is judged to be not caused by the study drug, the study drug may be resumed at the original dose when deemed appropriate by the investigator.

Table 4 Guidelines for Study Drug Dose Interruption or Reduction Event

Guidelines for Dose Reduction or Interruption Event	
Event	**Action**
First occurrence: Grade 3 or greater AE possibly or probably related to the study drug	The study drug will be interrupted until resolution of the AE to grade ≤ 1. The participant may then resume treatment at 80 mg per day (resumption at original dose level permitted as detailed in Section 5.1.2).
Second occurrence: Recurrence of the same AE or appearance of a new AE grade 3 or greater probably or possibly due to the study drug	The study drug will be interrupted until resolution of the AE to grade ≤ 1. The participant may resume treatment at 40 mg per day.
Third occurrence: Recurrence of a prior AE or appearance of a new AE grade 3 or greater probably or possibly due to the study drug	The study drug will be discontinued.
Table continued on next page	

Guidelines for Dose Reduction or Interruption Event	
Event	**Action**
At any point, in retrospect, if the investigator determines a prior grade 3 or greater AE which was initially attributed as possibly, or probably related to study drug is now deemed unrelated	The study drug will be re-escalated to dose that the participant was on at the time of the AE.
QTcF > 500 ms	If the mean triplicate QTcF is > 500 ms at any time point, the ECG will be repeated (within 2 hours if identified on machine read or as soon as possible if identified from central reading). Cardiology consult will be obtained as medically indicated. If the repeat ECG confirms a mean of the triplicate QTcF > 500 ms, dosing of study treatment will be interrupted for up to 14 days. While study drug may be interrupted temporarily based on machine read, the central reading should be used for final treatment decisions. If QTcF resolves to ≤ 480 ms by central reading within 14 days from study drug interruption, the participant may resume dosing at the reduced dose of 80 mg (or if currently at 80 mg, reduction to 40 mg).
QTcF day 8 increase > 30 ms	If the mean triplicate QTcF on day 8 has increased > 30 ms compared to the mean triplicate QTcF on day 1 with no other known etiology, then a confirmatory ECG will be performed day 9. If the day 9 mean triplicate QTcF also shows an increase of > 30 ms compared to that of day 1, then dose reduction to 80 mg should be considered.

AE: adverse event; ECG: electrocardiogram; QTcF: Fridericia-corrected QT interval.

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

All medications and concomitant treatments administered from 28 days prior to day 1 through the end of treatment visit must be recorded in the electronic case report form (eCRF). 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 $5HT_1R$ or $5HT_{2B}R$ 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. Grapefruit juice should not be ingested during study treatment. If strong 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 intervals or QTc.

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 12.1]. 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, HSCT, immunotherapy or cellular therapy) are prohibited during therapy with gilteritinib. Participation in another interventional study while on treatment is prohibited.

Refer to [Appendix 12.1 List of Excluded and Cautionary Concomitant Medications] for additional details on excluded medications.

5.1.4 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. Compliance will be verified by the accounting of study drug at each visit after Baseline (day 1). When study drug is administered at the research facility, it will be administered under the supervision of study personnel.

Compliance of the study drug will be monitored by the accounting of unused medication returned by the subject at visits. Compliance will be documented.

The dose of study drug administered to each subject will be recorded on the appropriate form at every visit. Reasons for reduction or interruption will also be recorded when applicable. This information at every visit will be used to assess compliance with the treatment except in cases where directed by protocol or principal investigator (e.g., account for dose interruptions, adjustments, etc.).

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, 2010] version 4.03, 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 and method of diagnosis, bone marrow evaluations, histopathology, cytogenetics, immunophenotyping and cytochemistry, lumbar puncture results if performed (red blood cells, 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 3 Mutation Status

All subjects must have documented FLT3/ITD AML at the time of AML diagnosis. Additionally, FLT3/ITD mutation status will be analyzed using the diagnostic specimen (when available) by a Sponsor-designated central laboratory.

FLT3 mutation status will be analyzed at relapse by a Sponsor-designated central laboratory.

5.2.3.3 Performance Status

The ECOG Scale [Oken et al, 1982] will be used to assess performance status [Table 5] and will be obtained and recorded according to the Schedules of Assessments [Table 1].

Table 5 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 Assessment

5.3.1 Bone Marrow Aspirate and Biopsy

Bone marrow samples will be analyzed locally according to the Schedule of Assessments [Table 1]. Bone marrow aspirate is required and bone marrow biopsy in addition is preferred. In case of inadequate aspirate, bone marrow biopsy is required. If a subject relapses, the relapse bone marrow sample must also be analyzed by a Sponsor-designated central laboratory.

5.3.1.1 Minimal Residual Disease (MRD)

MRD will be analyzed by a Sponsor-designated central laboratory according to the Schedule of Assessments [Table 1]. The first 0.25-0.75 mL of bone marrow aspirate will be collected and

sent by overnight carrier to the central laboratory for assessment of MRD. A peripheral blood sample is not acceptable for MRD assessment.

5.3.2 Relapse

Relapse after CR (including CRp and CRi), is defined as bone marrow blasts 5% or higher (not attributable to regenerating bone marrow), any circulating blasts, any extra-medullary blast foci as per Revised IWG criteria. Relapse events will be adjudicated by an independent review committee and will be used in the efficacy assessments, unless specifically stated otherwise.

5.3.3 Survival Time, Remission Status and Other Efficacy Endpoints

5.3.3.1 Survival Status and Subsequent Anti-leukemic Treatments and Their Outcomes

Information on survival status, remission status, subsequent anti-leukemic treatments and outcomes will be collected for all subjects during long-term follow-up.

The first survival status 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 final database lock, which is estimated to occur when the last subject enrolled reaches the 30-day follow-up visit.

Additional contacts may be made to support key analyses (e.g., final analysis or analyses by the IDMC).

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 serious adverse event (SAE) reporting period or if the death occurs after the SAE reporting period but is determined by the investigator to be related to study drug, then the associated AE with outcome of death will also be reported on the eCRF and SAE Worksheet. If a subject death does not meet the criteria of an SAE, then death and anti-leukemic treatment and outcome up through the date of death should be collected and entered in the eCRF.

5.3.3.2 Overall Survival (OS)

OS is defined as the time from the date of randomization until the date of death from any cause. For surviving subjects, non-events will be censored at the date of last known date alive.

Date of last known date alive is defined as the latest of the following dates: treatment discontinuation date, last dosing administration date, last disease assessment date, last adverse

event (start date or stop date) or the last follow-up date on which the subject was known to be alive.

5.3.3.3 Relapse-free Survival (RFS)

RFS is defined as the time from the date of randomization until the date of documented relapse or death from any cause, whichever occurs first.

If a subject experiences relapse or death, the subject is defined as having RFS event related to either "relapse" or "death," and the event date is the date of relapse or death.

For a subject who is not known to have relapse or death, RFS is censored at the date of last relapse-free assessment date.

5.3.3.4 Event-free Survival (EFS)

EFS is defined as the time from the date of randomization until the date of documented relapse, or discontinuation of the treatment, or initiation of other anti-leukemic treatment or death from any cause, whichever occurs first.

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

If a subject discontinues the treatment or initiates anti-leukemic treatment, the subject is defined as having EFS event and the event date is the date of study drug discontinuation or date of start of anti-leukemic treatment, respectively.

For a subject who is not known to have relapse or death or treatment discontinuation or initiation of the other anti-leukemic treatment, EFS is censored at the date of last relapse-free assessment date.

Subject becomes eligible for and proceeds to transplant will be considered non-event and censored at the time of HSCT.

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 Schedules 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 Adverse Events

AE (including SAE) collection will begin from time of informed consent and continue through 30 days after the last dose of study drug. During the long-term follow-up period, only SAE data that is possibly or probably related to study drug will be collected. SAE data will be collected, at a minimum, 7 days after the date of last dose, if the subject undergoes HSCT. AEs will be documented at each clinic visit, but can be collected at any time. Any AE that meets the definition of an SAE will also be reported on a separate form to the Sponsor. See [Section 5.5 Adverse Events and Other Safety Aspects] for information regarding AE collection and data handling.

5.4.2.1 Adverse Events of Possible Hepatic Origin

See [Appendix 12.2 Liver Safety Monitoring and Assessment] for detailed information on liver abnormalities, monitoring and assessment, if the AE for a subject enrolled in a study and receiving study drug is accompanied by increases in LFTs (e.g., AST, ALT, bilirubin, etc.) or is suspected to be due to hepatic dysfunction.

Subjects with AEs of hepatic origin accompanied by LFT abnormalities should be carefully monitored.

5.4.3 Laboratory Assessments

[Appendix 12.3] contains the laboratory tests that will be performed centrally during the conduct of the study. Refer to the Schedules of Assessments [Table 1] for study visit collection dates. Additional laboratory tests should be performed according to institutional standard of care. Local testing of bone marrow aspirate and/or biopsy at screening and months 3, 6, 12, 18 and 24 and at the time of relapse will be reported in the eCRF. Clinical significance of out-of-range laboratory findings is to be determined and documented by the investigator or delegated sub-investigator who is a qualified physician.

5.4.4 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 Schedules of Assessments [Table 1]. Each physical examination will include the observation and review of body system and include weight at screening and each monthly visit. 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.

5.4.5 Electrocardiogram (ECG)

A 12-lead ECG will be performed during the screening period, predose on day 1, day 8, day 15 and at each subsequent visit. Predose assessments should be taken within 1 hour before drug administration. 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 (see [Section 7.5.5]). The mean of the triplicate ECG from central read should be used for all final treatment decisions and AE reporting.

For day 8 ECG, if the mean QTcF from day 1 to day 8 has increased > 30 ms with no other known etiology, a confirmatory ECG should be performed on day 9. If the day 8 and 9 ECGs confirm the > 30 ms increase in QTcF, then the investigator should assess if study drug dose modification should occur as per the dose interruption or reduction guideline in [Section 5.1.2].

If the mean triplicate QTcF is > 500 ms at any time point, 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 study drug per the interruption or reduction guidelines in [Section 5.1.2].

At a subset of sites, approximately 40 subjects will have additional ECGs as part of the pharmacokinetic sampling substudy. On day 15 and day 29, ECGs will be performed at predose (within 1 hour before study drug) and 4 hours postdose (+/- 1 hour) in triplicate and transmitted electronically for central reading. Triplicate 12 lead ECGs should be obtained after the subject has rested quietly and is awake in a fully supine position (or semirecumbent if supine is not tolerated) for 10 minutes before the first ECG from a triplicate and at least 5 minutes apart per time point.

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 blood draw. At scheduled ECG time points that coincide with other nonpharmacokinetic study procedures, ECG collection should be given priority. At scheduled time points where ECGs coincide with pharmacokinetic sampling, ECGs should be performed prior to pharmacokinetic sample collection ensuring that pharmacokinetic samples are collected at the scheduled time point.

5.4.6 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.

5.4.7 Multigated Acquisition Scan or Echocardiogram

A MUGA or ECHO is to be performed at screening for subjects with a history of NYHA Class 3 or 4 congestive heart failure (unless MUGA or ECHO performed within 1 month prior to screening revealed left ventricular ejection fraction ≥ 45%).

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events (AEs)

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

Some countries may have additional local requirements for events that are required to be reported as AEs or in an expedited manner similar to an SAE. In these cases, it is the investigator's responsibility to ensure these AEs or other reporting requirements are followed and the information is appropriately recorded in the eCRF accordingly.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical examination) should be defined as an AE only if the abnormality meets 1 of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication
- The abnormality or investigational value is clinically significant in the opinion of the investigator.

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 or leads to prolongation of hospitalization (hospitalization for treatment/observation/examination caused by AE is to be considered as serious)
- Other medically important events

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 1 of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also

usually be considered serious. Examples of such events are intensive treatment in an ER or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Safety special situations on the medicinal products administered to the subject as part of the study (e.g., study drug, comparator, background therapy) that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of the medicinal product(s)
- Suspected abuse/misuse of the medicinal product(s)
- Inadvertent or accidental exposure to the medicinal product(s)
- Medication error involving the medicinal product(s) (with or without subject/patient exposure to the Sponsor medicinal product, e.g., name confusion)

All of the special situations noted above should be recorded on the eCRF. Any situation involving these events of interest that also meets the criteria for an SAE should be recorded on the AE page of the eCRF and marked 'serious' and on the SAE worksheet/report.

The Sponsor has a list of events that they classify as "always serious" events. If an AE is reported that is considered to be an event per this classification as "always serious", additional information on the event may be requested.

5.5.3 Criteria for Causal Relationship to the Study Drug

AEs that fall under either "Possible" or "Probable" should be defined as "AEs whose relationship to the study drugs could not be ruled out".

Causal relationship to the study drug	**Criteria for causal relationship**
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on re- administration (rechallenge) or withdrawal (dechallenge).

5.5.4 Criteria for Defining the Severity of an Adverse Event

AEs, including abnormal clinical laboratory values, will be graded using the NCI-CTCAE guidelines (Version 4.03). The items that are not stipulated in the NCI-CTCAE Version 4.03 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)

SAE collection will begin from time of informed consent through 30 days after last dose of study drug. During the long-term follow-up period, only SAE data that the investigator assesses as possibly or probably related to study drug will be collected. SAE data will be collected, at a minimum, 7 days after the date of last dose of study drug, if the subject undergoes HSCT. In the case of an SAE, the investigator must contact the Sponsor by telephone or fax immediately (within 24 hours of awareness).

The investigator should complete and submit an SAE Worksheet containing all information that is required by the Regulatory Authorities to the Sponsor by fax immediately (within 24 hours of awareness). If the faxing of an SAE Worksheet is not possible or is not possible within 24 hours, the local drug safety contact should be informed by phone.

The following paragraph is specific to investigational sites in Japan

For Japan, in the case of an SAE, the investigator or sub-investigator must report to the head of the study site and must contact the delegated contract research organization (CRO) by telephone or fax immediately (within 24 hours of awareness). The investigator should complete and submit JUTOKUNA YUUGAIJISHOU HOUKOKUSHO containing all information that is required by the Regulatory Authorities to the delegated CRO by fax immediately (within 24 hours of awareness) and to the head of the hospital. If the faxing of JUTOKUNA YUUGAIJISHOU HOUKOKUSHO is not possible or is not possible within 24 hours, the delegated CRO should be informed by phone.

For contact details for each country/region, see Section II Contact Details of Key Sponsor's Personnel. Please fax the SAE Worksheet to:

Astellas Pharma Global Development, Inc. (APGD)
Pharmacovigilance
North American Fax number: 888-396-3750

(North American Alternate Fax number: 847-317-1241)
International Fax number: +44-800-471-5263
Email: safety-us@astellas.com

Specific to investigational sites in Japan

JUTOKUNA YUUGAIJISHOU HOUKOKUSHO the SAE Worksheet to:

PAREXEL International
Global Monitoring Operations
Fax number: 03-6888-1486

Japan/Asia Development I, Astellas Pharma Inc.
Phone: 03-3244-1097
Fax number: 03-3243-5737

If there are any questions, or if clarification is needed regarding the SAE, please contact the Sponsor's Medical Monitor/Expert or his/her designee (see 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 and on the eCRF.

The following minimum information is required:

- ISN/Study number,
- Subject number, sex and age,
- The date of report,
- A description of the SAE (event, seriousness of the event), and
- Causal relationship to the study drug.

The Sponsor or Sponsor's designee will submit expedited safety reports (i.e. Investigational New Drug [IND] Safety Reports) to the regulatory agencies (i.e. FDA) as necessary, and will inform the investigators of such regulatory reports. Investigators must submit safety reports as required by their IRB/IEC within timelines set by regional regulations (i.e., EU, electronic Common Technical Document, FDA). Documentation of the submission to and receipt by the IRB/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 SAEs which require submission per local requirements to IRB/IEC/head of the study site.

The heads of the study sites/investigators should provide written documentation of IRB/IEC notification for each report to the Sponsor.

The investigators may contact the Sponsor's Medical Monitor/Expert for any other problem related to the safety, welfare, or rights of the subject.

For SUSAR from a blinded trial, unblinded CIOMS-I report will be submitted to the authorities and IRB/IEC where required.

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.

If during AE follow-up, the AE progresses to an SAE, or if a subject experiences a new SAE, the investigator must immediately report the information to the Sponsor.

Please refer to [Appendix 12.2 Liver Safety Monitoring and Assessment] for detailed instructions on Drug Induced Liver Injury.

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 12.4 Common Serious Adverse Events] for your reference. The list does NOT change your reporting obligations 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 you that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common serious adverse events" as specified in [Appendix 12.4 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 Procedure in Case of Pregnancy

If a female subject or partner of a male subject becomes pregnant during the study dosing period or within 6 months for female subjects and 4 months and 1 week for partners of male subjects from the discontinuation of dosing, the investigator should report the information to the Sponsor as if it is an SAE. 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.

The investigator will follow the medical status of the mother, as well as the fetus, as if the pregnancy is an SAE and will report the outcome to the Sponsor.

When the outcome of the pregnancy falls under the criteria for SAEs [spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including anomaly in a miscarried fetus)], the investigator should respond in accordance with the report procedure for SAEs. Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below.

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

- Death of an infant within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug
- If an infant dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as "possible" by the investigator
- In the case of a delivery of a living newborn, the "normality" of the infant is evaluated at the birth
- Unless a congenital anomaly are identified prior to spontaneous abortion or miscarriage, the embryo or fetus should be assessed for congenital defects by visual examination

If during the conduct of a clinical trial, a male subject makes his partner pregnant, the subject should report the pregnancy to the investigator. The investigator will report the pregnancy to the Sponsor as an SAE.

5.5.9 Emergency Procedures and Management of Overdose

In the event of suspected study drug overdose, the subject should receive supportive care and monitoring. The Medical Monitor/Expert should be contacted as applicable.

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 following 2 paragraphs are specific to investigational sites in Japan:

1. When information is obtained regarding serious and unexpected adverse drug reactions (or other) that are specified in Article 273 of the Enforcement Regulations of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics, in compliance with Article 80-2 Paragraph 6 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics, the Sponsor should inform all the investigators involved in the clinical study, the head of the study site and the regulatory authorities of such information. The head of the study site who receives such information will decide whether the clinical study should be continued after hearing the opinions of the IRB. The investigator will supply the new information to the subjects, in compliance with [Section 8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of Written Information.].
2. In addition to the above item (1), when the head of the study site receives the revisions of the Investigator's Brochure, protocol, or written information, information on the matters covering the quality of the study drug, efficacy and safety, information necessary for conducting the clinical study properly, or documents to be examined by the IRB should be sent to the IRB.

5.5.11 Deviations from the Protocol and Other Actions Taken to Avoid Life-Threatening Risks to Subjects (Specific to Investigational sites in Japan)

The investigator must not deviate from or amend the protocol, excluding an emergency case for avoiding risks to the subjects. When the investigator does not follow the protocol in order to avoid urgent risks for subjects, the investigator should take the following actions.

1. Describe the contents of the deviation or amendment and the reasons for it in a written notice, and immediately send the document stating the deviation or amendment and the reasons to the Sponsor and the head of the study site. Keep a copy of the notice.
2. Consult with the Sponsor at the earliest possibility for cases in which it is necessary to amend the protocol. Obtain approval for a draft of the amended protocol from the IRB and the head of the study site as well as written approval from the Sponsor.

5.6 Test Drug Concentration

5.6.1 Pharmacokinetics

Sparse pharmacokinetic samples will be collected to evaluate gilteritinib plasma concentrations as outlined in the Schedule of Assessments [Table 1].

At a subset of sites, approximately 40 subjects on day 15 and day 29 will have dense pharmacokinetic sampling as outlined in the Schedule of Assessments [Table 1]. Samples will be collected predose (within 1 hour before study drug administration) and 4 hours (± 1 hour) postdose.

Plasma samples may also be used for metabolite profiling of gilteritinib. The reports for the metabolite profiling and identification will not be incorporated into the clinical study report.

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 Patient Reported Outcome Measures

EQ-5D-5L, FACT-Leu, and FACT-An will be assessed during the study period to report the subject's experience of symptoms/treatment and quality of life.

5.7.1.1 EuroQol Group-5 Dimension-5 Level Instrument (EQ-5D-5L)

The EQ-5D-5L is a self-reported questionnaire. The EQ-5D-5L is being used as a measure of respondents' health-related quality of life. The EQ-5D-5L consists of the EuroQol Group-5 Dimension descriptive system and the EuroQol Group Visual Analogue Scale (VAS). The EuroQol Group-5 Dimension descriptive system comprises of 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The VAS records the respondent's self-rated health status on a graduated (0-100)

scale, where the endpoints are labeled 'best imaginable health state' and 'worst imaginable health state' with higher scores for higher health-related quality of life. The EQ-5D-5L will be administered at site visits directly to the subjects via an electronic patient reported outcome (PRO) device during treatment through the end-of-treatment visit. It will be administered as outlined in the Schedule of Assessments [Table 1]. If possible, patient reported outcome measures should be performed prior to any other assessments on that visit day.

5.7.1.2 Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu)

The FACT-Leu [Cella et al, 2012] is designed to measure leukemia-specific signs, symptoms and the impact of leukemia on subjects. The 44-item scale has global and domain scores including physical well-being, social/family well-being, emotional well-being, functional well-being and additional leukemia-specific concerns. The FACT-Leu has a 7-day recall period. The FACT-Leu will be administered at site visits directly to the subjects via an electronic PRO device. It will be administered as outlined in the Schedule of Assessments [Table 1]. If possible, patient reported outcome measures should be performed prior to any other assessments on that visit day.

5.7.1.3 Functional Assessment of Cancer Therapy-Anemia (FACT-An)

The FACT-An is designed to measure patient experiences associated with anemia. It includes 13 items that are designed to measure fatigue associated with anemia and 7 items that assess other symptoms and impacts associated with anemia, such as shortness of breath and dizziness. It also includes the same generic physical well-being, social/family well-being, emotional well-being, functional well-being domains as the FACT-Leu. These redundant scales will not be administered as part of the FACT-An; only the 20 anemia-specific items will be administered.

5.7.1.4 Resource Utilization

Healthcare resource utilization in this study population will include hospitalization, ICU visits, ER visits, transfusion and use of antibiotics. 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 ICU) and type and reason for hospitalization 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 intravenous infusions and type of antibiotic.

5.7.2 Exploratory Biomarker Analyses

5.7.2.1 FLT3 Mutation Status

FLT3/ITD mutation status and allelic ratio will be analyzed using the diagnostic specimen (when available) by a Sponsor-designated central laboratory. All subjects must have documented FLT3/ITD AML at the time of AML diagnosis.

FLT3 mutation status will be analyzed at relapse by a Sponsor-designated central laboratory.

The manufacturer of the FLT companion diagnostic assay will analyze the diagnostic samples (when available) with the FLT3 companion diagnostic assay. The results may be used to seek regulatory approval if a companion diagnostic for FLT3/ITD is indicated for the patient population in this study. All biomarker samples collected 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.

5.7.2.2 Minimal Residual Disease (MRD) Assessment

MRD will be measured from bone marrow samples as outlined in the Schedule of Assessments [Table 1]. FLT3/ITD mutation ratio will be measured in relation to total FLT3. Changes in FLT3/ITD mutation ratio will be compared with baseline/screening samples.

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

Additional protein or genetic biomarkers related to AML and gilteritinib activity may be analyzed.

5.7.3 Whole Blood and Buccal Sample for Future Pharmacogenomic Analysis (Retrospective Pharmacogenomic Analysis) (Optional)

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 randomization, a 3-6 mL sample of 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 (2215-CL-0302),
- Subject number, and
- Purpose and biological matrix (i.e., “biobanking”, “whole blood”, “buccal sample”).

Details on sample collection, labeling, storage and shipment procedures will be provided in a separate Laboratory Manual.

See [Appendix 12.5. Retrospective PGx Substudy] for further details on the banking procedures.

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 screening is approximately 17 mL.

The maximum amount of blood collected for study specific assessments during month 1 is approximately 60 mL.

The maximum amount of blood collected for study specific assessments during months 2 and 4 is approximately 16 mL.

The maximum amount of blood collected for study specific assessments during months 3 and 5 is approximately 14 mL.

The maximum amount of blood collected for study specific assessments during month 6 and beyond is approximately 16 mL.

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

A discontinuation is a subject who enrolled or randomized in the study and for whom study treatment is permanently discontinued prematurely for any reason.

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 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.

Gilteritinib or placebo therapy will continue for a maximum of 2 years from initiation of therapy until 1 of the following criteria applies:

- Subject declines further study participation (i.e., withdrawal of consent).
- Subject is noncompliant with the protocol based on the investigator or Medical Monitor assessment.

- Subject is found to have significantly deviated from any 1 of the inclusion or exclusion criteria after enrollment (subjects having clinical benefit may be kept in the study after discussion with the Medical Monitor).
- Subject develops an intolerable or unacceptable toxicity.
- Investigator/sub-investigator determines that the continuation of the study treatment will be detrimental to the subject.
- Subject relapses.
- Subject begins other anti-leukemic therapy.
- Subject becomes eligible for and proceeds to transplant.
- Subject is lost to follow-up despite reasonable efforts by the investigator to locate the subject.
- Female subject becomes pregnant.
- Death.

Discontinuation Criteria from Post-Treatment 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 subject's 30-day follow-up visit.
- Death.

6.2 Discontinuation of the Site

If an investigator intends to discontinue participation in the study, the investigator must immediately inform the Sponsor (for investigational sites in Japan: and the head of the Study site).

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

The statistical analysis will be coordinated by the responsible biostatistician of APGD-US. 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.

Prior to database lock, a Final Review of Data and Tables, Listings and Figures (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 lock.

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

7.1 Sample Size

The study is a multicenter, double-blind, placebo-controlled, randomized phase 2 trial comparing gilteritinib as maintenance therapy versus placebo in FLT3/ITD AML subjects in CR1. The target number of randomized subjects is approximately 85; 57 in gilteritinib arm and 28 in placebo arm.

The median RFS time in the placebo arm is assumed to be 15 months, based on RATIFY control arm data on subjects with FLT3 mutation achieving CR1 after induction and consolidation. A total of 54 relapse or death events will provide 83.2% power to detect a hazard ratio of 0.5 (corresponding to 24% difference in 2-year RFS rates) with 1-sided significance level of 0.075. The sample size estimation of 85 subjects assumes approximately 2 years of accrual.

7.2 Analysis Set

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 will consist of all subjects who are randomized. This will be the primary analysis set for efficacy analyses. Subjects will be analyzed based on the randomized treatment.

7.2.2 Per Protocol Set (PPS)

The per protocol set 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 key secondary endpoints will be performed on the PPS. Select demographic and baseline characteristics may 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 randomized subjects who took at least 1 dose of study treatment, and will be used for safety analyses. The subjects will be analyzed based on the actual treatment received.

7.2.4 Pharmacokinetic Analysis Set (PKAS)

The pharmacokinetic analysis set (PKAS) consists of the population administered at least 1 dose of gilteritinib, have at least 1 measurable concentration datum and for whom both the date and time of dosing and PK sampling is 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 determined at the Classification Meeting and documented in the Classification Specifications.

7.3 Demographics and Other Baseline Characteristics

7.3.1 Demographics

Demographics and other 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 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.

7.3.3 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.

7.3.4 Prior and Concomitant Medications

The frequency of concomitant medications (prescription, over-the-counter and nutritional supplements) will be summarized by treatment group and preferred term 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.

7.3.5 Subject Disposition

The number and percentage of all subjects during the study will be reported per treatment group for various disposition parameters including analysis sets, reason for treatment discontinuation, reason for study discontinuation, lost to follow-up, and protocol deviation.

7.3.6 Treatment Compliance

Treatment compliance is defined as the total number of doses of study drug 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 for the entire study period for the SAF by treatment group.

7.3.7 Extent of Exposure

Exposure to treatment, measured by the duration of treatment in number of days will be summarized by treatment group on SAF. Duration of exposure to a study drug is defined as: (the last date that subject took study drug – the first dose date + 1). The total dose administered, number and proportion of subjects with dose reduction, and dose interruption will be tabulated.

7.4 Analysis of Efficacy

7.4.1 Analysis of Primary Endpoint

The primary analysis of RFS will be performed at 1-sided 0.075 significance level to test the null hypothesis that RFS in the gilteritinib arm is worse than or equal to RFS in the placebo arm versus the alternative hypothesis that RFS in the gilteritinib arm is better than RFS in the placebo arm. The primary analysis will be conducted when the planned 54 relapse or death events have been observed. The primary efficacy endpoint of RFS will be analyzed on the FAS using the stratified log-rank test with strata on age at randomization, screening MRD status, geographic region and use of FLT3 inhibiting agents during induction/consolidation as described below.

Age:

- < 60 years
- ≥ 60 years

Geographic Region:

- North America
- Europe
- Asia/Pacific/South and Central America/rest of world

Presence of screening MRD:

- Yes
- No

Use of FLT3 inhibiting agents during induction/consolidation:

- Yes
- No

Kaplan-Meier curves will be used to describe the RFS in each arm. Median RFS time and RFS rates at 1, 2, and 3 years along with 95% confidence interval will be estimated from the Kaplan-Meier curves.

In order to evaluate the robustness of the primary analysis of RFS, sensitivity analyses will be performed as below:

- Unstratified log-rank test on the FAS

- Stratified Cox proportional hazards model with the same strata as in primary analysis on the FAS
- Same analysis as primary analysis but on the PPS
- Same analysis as primary analysis on the FAS, but RFS is censored at the last evaluable disease assessment without relapse when relapse or death is documented after more than 1 missed disease assessment.
- Same analysis as primary analysis on the FAS, but RFS is censored at end of treatment.
- Same analysis as primary analysis on the FAS, but RFS is defined by using investigator assessed relapse.

7.4.2 Analysis of Secondary Endpoints

7.4.2.1 Key Secondary Endpoints

The key secondary analysis of OS will be performed at 1-sided 0.075 significance level to test the null hypothesis that OS in the gilteritinib arm is worse than or equal to OS in the placebo arm versus the alternative hypothesis that OS in the gilteritinib arm is better than OS in the placebo arm. The endpoint OS will be analyzed on the FAS using the stratified log-rank test with strata on age at randomization, screening MRD status, geographic region and use of FLT3 inhibiting agents during induction/consolidation.

With the sequential multiple test procedure to control for overall type I error at the 1-sided 0.075 significance level, formal significance testing of OS will be conducted only if the RFS comparison is statistically significant. Otherwise, OS analysis will be considered exploratory.

Kaplan-Meier curves will be used to describe the OS in each arm. Median OS time and OS rates at 1, 2, 3, and 4 years along with 95% confidence interval will be estimated from the Kaplan-Meier curves.

For the key secondary endpoint of OS, sensitivity analyses will be performed as below:

- Unstratified log-rank test on the FAS
- Stratified Cox proportional hazards model with the same strata as in primary analysis on the FAS
- Same analysis as primary analysis but on the PPS
- Same analysis as primary analysis on the FAS, but OS is censored at the first HSCT and first subsequent anti-leukemic treatment, whichever occurs first.

7.4.2.2 Other Secondary Endpoints

- Stratified log-rank test for EFS on the FAS
- Analyze the relationship between MRD and RFS, and that between MRD and OS on the FAS.

7.4.3 Analysis of Exploratory Endpoints

Analysis of covariance (ANCOVA) model will be used to analyze change from baseline to post-baseline visits for the global and domain scores, individual items and item clusters of the FACT-Leu. The same analytic will be used for FACT-An.

ANCOVA model will be used for the change from baseline EQ-5D-5L VAS to post-baseline visits and shift table for the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) from baseline to end-of-treatment visit.

The Cochran-Mantel-Haenszel method will be used for resource utilization status (hospitalization, blood transfusion, antibiotic intravenous infusions, ICU visit, and ER visit). ANOVA model will be used for resource utilization counts (hospital stays, duration of medications, blood transfusions, antibiotic intravenous infusions, ICU visit, and ER visit).

FLT3/ITD mutation status of the diagnostic bone marrow or blood sample will be summarized for local results and central results.

FLT3 mutation status at relapse will be summarized.

7.4.4 Subgroup Analysis

Subgroup analysis will be performed on primary and key secondary efficacy endpoint for age group (< 60 and ≥ 60 years), geographic region (North America, Europe, Asia/Pacific/South and Central America/rest of world), presence of screening MRD (Yes, No), use of FLT3 inhibiting agents during induction/consolidation (Yes, No), sex, baseline ECOG performance status, and race.

7.5 Analysis of Safety

The safety evaluation will be based mainly on AEs, clinical laboratory results, vital sign measurements, ECGs, physical examination findings and ECOG performance status. Descriptive statistics will be used to summarize safety data. All safety data will be summarized by the actual 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 dose of study treatment will be classified as treatment-emergent AEs. AEs will be categorized by SOC and PT using the MedDRA dictionary and will be graded according to the NCI-CTCAE version 4.03.

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 1 grade 3 or higher AE will be summarized by treatment group, SOC and preferred term (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 treatment-emergent events 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 the actual treatment received 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. 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 the actual treatment received 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 ECGs

The 12-lead ECG results will be summarized by treatment group 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.

The correlation between gilteritinib exposure and QTcF for subjects participating in the ECG/PK sampling subset will be analyzed.

7.5.6 ECOG performance scores

ECOG performance scores will be summarized by the actual treatment received and visit.

7.6 Analysis of Pharmacokinetics

Based on pharmacokinetic data obtained within this study, a separate population pharmacokinetic analysis will be performed. Data from this study may be pooled with other studies for analysis. The prospective details of this analysis will be specified in a separate population pharmacokinetic analysis plan.

The plasma concentrations will be summarized for gilteritinib using descriptive statistics, including number of subjects, mean, standard deviation, minimum, median, maximum, geometric mean, and coefficient of variation of the mean and geometric mean. Time-course of drug concentrations will be plotted as appropriate.

Population pharmacokinetic/pharmacodynamic analysis will be performed to assess the relationship between gilteritinib exposure and QTcF. Data from this study may be pooled with other studies for analysis. Details of this analysis will be specified in a separate population pharmacokinetic/pharmacodynamic analysis report.

7.7 Protocol Deviations and Other Analyses

Protocol deviations as defined in [Section 8.1.6 Protocol Deviations] will be summarized for all randomized subjects by treatment group and total as well as by site. 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.

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

Not applicable.

7.9 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 AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 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 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 laboratory will provide the Sponsor or designee with a complete and clean copy of the data.

ECG results are performed 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.

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

Electronic PRO:

Subject diaries and questionnaires will be completed by the subject on an electronic device. The information completed by the subject on the electronic device will be automatically uploaded into a central website. The investigator or site designee should review the diaries and questionnaire data on the website for correct completion while the subject is at the site. The questionnaire data will be transferred electronically to Sponsor or designee at predefined intervals during the study. The vendor will provide Sponsor or designee with a complete and clean copy of the data.

8.1.2 Specification of 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 following information should be included in the source medical records:

- Demographic data (age, sex, race, ethnicity, height and body weight)
- Inclusion and exclusion criteria details
- Participation in study and original signed and dated ICFs
- Visit dates
- Medical history and physical examination details
- Key efficacy and safety data, if applicable (as specified in the protocol)
- AEs and concomitant medication
- Results of relevant examinations (e.g., ECG charts, X-ray films etc.)
- Laboratory printouts (if applicable)
- Dispensing and return of study drug details
- Reason for premature discontinuation (if applicable)
- Randomization number (if applicable)

8.1.3 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/sub-investigator 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.

8.1.4 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, such as source documents (refer to [Section 8.1.2 Specification of 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.

8.1.5 Data Management

Data Management will be coordinated by the 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. eCRF completion will be described in the eCRF instructions. Coding of medical terms and medications will be performed using MedDRA and WHO Drug Dictionary, respectively.

8.1.6 Protocol Deviations

A 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 trial 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.

For the purposes of this protocol, deviations requiring notification to Sponsor are defined as any subject who:

- Entered into the study even though they did not satisfy entry criteria.
- Developed withdrawal criteria during the study and not withdrawn.
- Received wrong treatment or incorrect dose.
- Received excluded concomitant treatment.

When a 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 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.

NOTE: Other deviations outside of the categories defined above that are required to be reported by the IRB/IEC in accordance with local requirements will be reported, as applicable.

8.1.7 End of Trial in All Participating Countries

The end of trial in all participating countries is defined as the last subject's last contact.

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) / Competent Authorities (CA)

GCP requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent 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 IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent 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 IEC/IRB approval prior to implementation of the changes made to the study design at the site. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any SAEs that meet reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to Sponsor.

If required by local regulations, the investigator shall make accurate and adequate written progress reports to the IEC/IRB at appropriate intervals, not exceeding 1 year. The investigator shall make an accurate and adequate final report to the IRB/IEC within 90 days after the close-out visit for APGD-sponsored studies, or for Astellas Pharma Europe

BV/Astellas Pharma Europe Ltd.-sponsored studies within 1 year after last subject out or termination of the study.

8.2.2 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.

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject or his/her guardian or 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 ***(specific to investigational sites in Japan: place a personal seal)*** 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 ***(specific to investigational sites in Japan: or sealed)*** 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.

8.2.3.2 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 adverse drug reaction). The communication must be documented in the subject's medical records and must document whether the subject is willing to remain in the study or not.
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 ***(specific to investigational sites in Japan: place a personal seal)***. A copy of the signed ***(specific to investigational sites in Japan: or sealed)*** 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.

8.2.4 Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the subject to the subject's physician 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.

The Sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number and/or initials 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 will ensure that the use and disclosure of protected health information obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information (i.e., Health Insurance Portability and Accountability Act).

8.3 Administrative Matters

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

Information concerning the study drug, patent applications, processes, unpublished scientific data, the Investigator's Brochure 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.

8.3.2 Documents and Records Related to the Clinical Study

The Sponsor will provide the investigator and/or institution with the following:

- Study protocol (and amendments, where applicable)
- Investigator’s Brochure (and amendments, where applicable)
- CRFs (specific to investigational sites in Japan: and JUTOKUNA YUUGAIJISHOU HOUKOKUSHO)
- Study drug with all necessary documentation
- Study contract

In order to start the study, the investigator and/or study site is required to provide the following documentation to the Sponsor:

- Financial disclosure in compliance with US federal regulation 21CFR Part 54
- Signed and dated FDA form 1572
- Signed Investigator's Statement in this protocol and eCRF
- Current Curricula Vitae of all investigators
- List of sub investigators and collaborators
- IRB approval of the protocol, protocol amendments (if applicable) including a membership list with names and qualification (COPY)
- Specific to investigational sites in Japan: Instruction and decision of the head of the study site
- Study contract
- Laboratory normal reference ranges (if applicable, signed and dated by the responsible laboratory employee)

At the end of the study, the sponsor is responsible for the collection of:

- Unused study documentation,
- Unused study drug

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 New Drug Application (NDA) or discontinuation of the IND). The Sponsor will notify the site/investigator if the NDA/Marketing Authorization Application/J-NDA is approved or if the IND/Investigational Medicinal Product Dossier/CHIKEN TODOKE is discontinued. 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. All data will be entered on the CRFs supplied for each subject.

The following 2 paragraphs are specific to investigational sites in Japan:

The records to be retained at the study sites are the ones listed as essential documents in GCP. These records shall be retained by the head of the study site or the record keeper designated by the head until notice issued by the Sponsor on completion of the retention period is received. These documents are also subject to direct access and should be provided upon request from the Sponsor or regulatory authorities.

The head of the study site will retain the essential documents that should be stored at the study site in an appropriate manner according to the rules of the study site concerned until the date defined in number 1 or number 2 below, whichever comes later.

1. Approval date of marketing of the test drug (if development of the drug is stopped, until 3 years after the decision to discontinue development is notified)
2. Until 3 years after discontinuation or termination of the study.

The following are the major documents to be retained at the study site.

1. Source documents (clinical data, documents, and records for preparing the eCRF) hospital records, medical records, test records, memoranda, administration records, data recorded by automatic measuring instruments, reproductions or transcripts verified as precise copies, microfiche, negative films, microfilms/magnetic media, X-ray films, subject files and study-related records kept at either a pharmacy, a laboratory, or medical technical office, as well as subject registration forms, laboratory test slips including central measurement, worksheets specified by the Sponsor, records of clinical coordinators, and records related to the clinical study selected from those verified in other departments or hospitals.
2. Contracts, written ICFs, written information, and other documents or their copies prepared by the study personnel. A letter of request for clinical study (including a request for continuation/amendment), letter of request for review, notice of clinical study contract, clinical study contract, notification of discontinuation or completion of clinical study, written information for informed consent (including revisions), signed and dated written informed consent (including revisions), Curriculum Vitae of investigators, list of sub-investigators, list of signatures and print of seals (copy), and CRFs (copy), etc.
3. The protocol, documents obtained from the IRB related to the adequacy of conducting the clinical study by the head of the study sites (Article 32-1, MHW Ordinance No. 28), documents obtained from the IRB related to the adequacy of conducting a clinical study whose period exceeds 1 year or the adequacy of continuously conducting the clinical study from which information on adverse drug reactions is obtained, and other documents obtained. An agreed-upon protocol (including revisions), Investigator's Brochure (including revisions), operational procedures for the investigator, materials and information supplied by the Sponsor (e.g., AE report), matters reported by the investigator (revisions of the protocol, AE reports, etc.), operational procedures for the IRB, the list of names of the IRB members, materials for IRB review (including continuous deliberation), IRB review records (including continuous deliberation), and the review result report of the IRB (including continuous deliberation), etc.
4. Records of control for study drugs and other duties related to the clinical study. Procedure for controlling the study drugs, drug inventory and accountability record, vouchers for the receipt and return of the study drugs, and the prescriptions for concomitant medications

The documents of the Efficacy and Safety Evaluation Committee (minutes and SOPs and others) and the judgment committee outside the study sites (minutes and SOPs and others) shall be retained by the Sponsor.

8.3.3 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, Competent Authority approval 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). In Japan, it is followed by the approval of the head of the study site.

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 Informed Consent, written verification of IRB/IEC approval must be forwarded to the Sponsor. An approved copy of the new Informed Consent must also be forwarded to the Sponsor.

8.3.4 Insurance of Subjects and Others

The Sponsor has covered this study by means of an insurance of the study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator's File.

Specific to Japan

If a subject suffers any study-related injury, the Sponsor will compensate appropriately according to the severity and duration of the damage. However, if it was caused intentionally or was due to gross negligence by the study site, the Sponsor will consult with the study site about handling the injury, based on the agreed study contract. Compensation for the study-related injury is provided by the following procedures:

1. If a subject incurs an injury as a result of participation in the clinical study, the study site should provide medical treatment and other necessary measures. The Sponsor should be notified of the injury.
2. When the subject claims compensation from the study site for the above study-related injury, or such compensation may be claimed, the study site should immediately communicate the fact to the Sponsor. Both parties should work together towards compensation settlement.
3. The Sponsor shall pay compensation or indemnification and bear expenses necessary for the settlement as provided in the clinical contract.
4. The Sponsor shall make an arranging for insurance and take measures necessary to ensure the compensation or indemnification mentioned above.

8.3.5 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.

9 QUALITY ASSURANCE

The Sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

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.

10 STUDY ORGANIZATION

10.1 Independent Data-Monitoring Committee (IDMC)

The IDMC will be responsible for the review of subject safety and enrollment rates during periodic review as defined in the IDMC charter.

Members of the IDMC will be independent from the Sponsor and also will not participate as investigators in the trial. Additional details regarding responsibilities and membership requirements will be included in the IDMC charter.

10.2 Independent Review Committee (IRC)

The Independent Review Committee (IRC) will be responsible for adjudicating relapse events for the purpose of RFS endpoint as defined in IRC charter. Members of the IRC will be independent from the Sponsor and also will not participate as investigators in the trial. Additional details regarding responsibilities and membership requirements will be included in the in the IRC charter.

10.3 Other Study Organization

Specific to investigational sites in Japan:

The Japan site contact list is kept as a separate attachment to the protocol.

11 REFERENCES

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12 APPENDICES

12.1 List of Excluded and Cautionary Concomitant Medications

The following list describes medications and foods that are common strong inhibitors of CYP3A. 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 Telaprevir Clarithromycin Telithromycin Conivaptan Itraconazole Ketoconazole Posaconazole Voriconazole Nefazodone

CYP: cytochrome P450.

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

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

CYP: cytochrome P450.

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

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
Affinity or function to $5HT_1R$	Almotriptan Malate Aripiprazole Avitriptan Buspirone Hydrochloride Dihydroergotamine Mesylate Droperidol Eletriptan Hydrobromide Ergoloid Mesylates Ergonovine Maleate Ergotamine Tartrate Frovatriptan Succinate Haloperidol Decanoate Lesopitron Methylergonovine Maleate Methylergotamine Methysergide Maleate Naratriptan Hydrochloride Pizotifen Quetiapine Fumarate Rizatriptan Benzoate Sumatriptan Succinate Tegaserod Maleate Thioridazine Hydrochloride Ziprasidone Hydrochloride Ziprasidone Mesylate Zolmitriptan Zotepine

$5HT_1R$: 5-hydroxytryptamine receptor 1; $5HT_{2B}R$: 5-hydroxytryptamine receptor 2B.

The following list describes medications and foods that are common inhibitors or inducers of P-gp. 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 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 Ziprasadone Lithium Haloperidol

Table continued on next page

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

12.2 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 × ULN, or bilirubin > 2 × ULN, should undergo detailed testing for liver enzymes (including at least ALT, AST, alkaline phosphatase, and total bilirubin). Testing should be repeated within 48-72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central lab regarding moderate and severe liver abnormality to inform the investigator, study monitor 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		Total Bilirubin
Moderate	> 3× ULN	or	> 2× ULN
Severe[a]	> 3× ULN	and	> 2× ULN

ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal
a. See definition of Hy's Law later in this appendix.

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

- ALT or AST > 8× ULN
- ALT or AST > 5× ULN for more than 2 weeks
- ALT or AST > 3× ULN and international normalized ratio (INR) > 1.5 (If INR testing is applicable/evaluated).
- ALT or AST > 3× 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 should complete the Liver Abnormality Case Report Form (LA-CRF) that has been developed globally and can be activated for any study or an appropriate document. Subjects with confirmed abnormal liver function testing should be followed as described below.

Confirmed moderately abnormal LFTs should be repeated 2-3 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 should be recorded as AEs on the AE page of the eCRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Non-alcoholic steatohepatitis is seen in obese hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating aminotransferase levels. The investigator should ensure that the medical history form captures any illness that pre-dates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including non-prescription medication, complementary and alternative medications), alcohol use, recreational drug use, and special diets. Medications, including dose, should be entered on the concomitant medication page of the eCRF. 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 Discontinuation

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

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks
- ALT or AST > 3 × ULN and total bilirubin > 2 × ULN or INR > 1.5 (If INR testing is applicable/evaluated)
- ALT or AST > 3 × 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, drug should be discontinued.

[a] Hy's Law Definition-Drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10–50% 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 times the upper limit of normal ("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 3x ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated alkaline phosphatase) or Gilbert's syndrome [Temple, 2006].

References

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

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12.3 Laboratory Tests

Panel/Assessment	Matrix/Collection Tube	Parameters to be Analyzed
Hematology	Approximately 5 mL into EDTA tube	White Blood Cell Count White Blood Cell Differential Red Blood Cell Count Hemoglobin Hematocrit Mean Corpuscular Volume Platelet Count Mean Corpuscular Hemoglobin Concentration Mean Corpuscular Hemoglobin Blast Count
Chemistry	Approximately 8 mL into serum tube	Sodium Potassium Chloride Bicarbonate Blood Urea Nitrogen Creatinine Uric Acid Glucose Calcium Phosphate Magnesium Albumin Total Protein Alkaline Phosphatase Lactate Dehydrogenase Creatine Kinase Aldolase Triglycerides Total Cholesterol Globulin Liver Function Tests including: Total Bilirubin Alanine Aminotransferase Aspartate Aminotransferase Thyroid function tests including: TSH Free T4
Pregnancy Test	1 mL serum or urine	Human Chorionic Gonadotropin
Coagulation Profile	Approximately 2-4.5 mL into sodium citrate tube	INR (with PT if reported) aPTT Fibrinogen (Screening Only) D-Dimer (Screening Only)

Table continued on next page

Panel/Assessment	Matrix/Collection Tube	Parameters to be Analyzed
Urinalysis	Urine collection cup	Color Appearance Specific Gravity pH Bilirubin Blood Glucose Ketones Leukocyte esterase Nitrite Protein Urobilinogen
Bone Marrow	Aspirate 0.25 – 0.75 mL Blood 1 mL – 3 mL 2 to 3 bedside smears slides and/or biopsy [d]	Blast count and cell counts[a] Flow cytometry for blasts[a] FLT3 mutation status[b, c] MRD[b]
Pharmacokinetic	2 mL blood into dipotassium EDTA tube, processed to 1 mL plasma in transfer tube	Gilteritinib concentration
Pharmacogenomics (for subjects who provide separate PGx consent)	3 mL into EDTA tube Buccal swab	PGx analyses to be determined

aPTT: activated partial thromboplastin time; FLT3: FMS-like tyrosine kinase 3; Free T4: free thyroxine; INR: international normalized ratio; MRD: minimal residual disease; PGx: pharmacogenomics; PT: prothrombin time; TSH: thyroid-stimulating hormone.

a. Performed locally, however relapse sample will also be sent to a central lab for subjects who relapse.

b. Assessed by central laboratory.

c. Performed on historical/diagnostic bone marrow sample and relapse samples only.

d. Required to be sent to central laboratory when local bone marrow assessment shows relapse.

12.4 Common Serious Adverse Events

The following is a list of serious adverse events 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 adverse event meeting the definition of an SAE as detailed in [Section 5.5.2 Definition of Serious Adverse Event]. The purpose of this list is to alert you that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of "common serious adverse events". You are 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 regulatory agencies. If aggregate analysis of these events indicate they occur more frequently with study drug, an expedited IND safety report may be submitted to regulatory agencies.

Serious Adverse Events Caused by Active AML	**Grades usually observed with Active 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	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

Table continued on next page

Serious Adverse Events Caused by Active AML	Grades usually observed with Active AML
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
Libido decreased	0-2
Meningismus	0-5
Seizure	0-5
Somnolence	0-5
Syncope	3
Other AE	
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	0-3
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
Petechiae	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	0-3
Weight loss	0-2

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

12.5 Retrospective Pharmacogenomics Substudy (Optional)

INTRODUCTION

PGx research aims to provide information regarding how naturally occurring changes in a subject's gene and/or expression 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 and/or buccal swab is exploratory. The objective of this research will be to analyze or determine genes of relevance to clinical response, pharmacokinetics, and 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

For healthy volunteers study, subjects who have consented to participate in this study will participate in this PGx sub-study. As part of this sub-study, subjects must provide written consent prior to providing any blood samples that may be used at a later time for genetic analysis.

For patients study, subjects who have consented to participate in this study may participate in this PGx sub-study. As part of this sub-study, subjects must provide separate written consent prior to providing any blood samples that may be used at a later time for genetic analysis.

SAMPLE COLLECTION AND STORAGE

Subjects who consent to participate in this sub-study will provide one 3 ml tube of whole blood per Astellas' instructions. Each sample will be identified by the unique subject number (first code). Samples will be shipped frozen to a designated banking CRO either directly from site or via a central laboratory as directed by Astellas.

PGx ANALYSIS

Details on the potential PGx analysis cannot be established yet. Astellas may initiate the PGx analysis in case 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.

INFORMATION DISCLOSURE TO THE SUBJECTS

Exploratory PGx analysis may be conducted following the conclusion of the clinical study, if applicable. The results of the genetic 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.

12.6 Definition of Complete Remission

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 > 1×10^9/L and platelet count ≥ 100×10^9/L and normal marrow differential with < 5% blasts and they will be RBC and platelet transfusion independent (defined as 1 week without RBC transfusion and platelet transfusion). There should be no evidence of extramedullary leukemia.

Complete remission with incomplete hematologic 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.

Complete remission with incomplete platelet recovery (CRp)

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

13 ATTACHMENT 1: SUBSTANTIAL AMENDMENT 2

The purpose of this amendment is:

Substantial Changes
1. Title and Text Phase Updated
DESCRIPTION OF CHANGE:
The study is changed from a phase 3 to phase 2.
RATIONALE:
The study is changed from Phase 3 to 2 based on the reduction in the sample size.
2. Update the Number of Subjects Enrolled
DESCRIPTION OF CHANGE:
Prior text indicating target numbers for enrollment based on an adaptive design is modified to remove the adaptive design element and provide approximate enrollment numbers moving forward.
RATIONALE:
The sample size is re-calculated per revised assumption of hazard ratio (from 0.6 to 0.5), significance level (from 0.025 to 0.075, 1-sided), expected power (from 90% to 83.2%) and change in planned accrual and follow-up period. The target number of randomized subjects is then reduced from 354 to 85 with 54 relapse-free survival (RFS) events (reduced from 182) expected at the time of primary analysis.
3. Removal of Interim Analysis
DESCRIPTION OF CHANGE:
The interim analysis that was originally planned is removed.
RATIONALE:
The reduction in enrollment size negates the need for an interim analysis.
4. Update of Text for Inclusion Criterion 3
DESCRIPTION OF CHANGE:
Inclusion criterion 3 makes note of a diagnostic test that was previously under development but is now available. The revision reflects this change in the diagnostic test status.
RATIONALE:
To update the criterion to reflect the current status of the diagnostic test.

5. Modification of Duration of Treatment
DESCRIPTION OF CHANGE:
The duration of treatment no longer includes the requirement for a 3-year follow-up (to start after the 30-day follow-up) or for 80% of the subjects to have a relapse-free survival (RFS) event, whichever comes first.
RATIONALE:
The three year follow-up cap has been removed due to the revised timing of the final analysis. Subjects will be followed every three months until the final database lock which is estimated to occur when the last subject enrolled reaches the 30-day follow-up visit.
6. Update of Statistical Methods
DESCRIPTION OF CHANGE:
The primary analysis hypothesis test on the primary endpoint of RFS is changed from the Wald test based on stratified Cox-proportional hazards model to a stratified log-rank test, and the stratified Cox-proportional hazards model is then used as sensitivity analysis. A weighted statistics model (CHW method) will no longer be applied to the primary endpoint analysis.
RATIONALE:
The primary analysis hypothesis test is changed to log-rank test, which doesn't rely on the proportional hazards assumption. The CHW method is no longer applied with interim analysis removed.
7. Change to Unblinding Practice
DESCRIPTION OF CHANGE:
Language is added to clarify the conditions under which unblinding could occur, including in the event of documented relapse.
RATIONALE:
Now that gilteritinib is FDA-approved for relapsed acute myeloid leukemia (AML), it is not ethical to keep the patient unblinded if they relapse, therefore this is removed.

Non-Substantial Changes
1. Minor Administrative-type Changes
DESCRIPTION OF CHANGE:
Include minor administrative-type changes, e.g., typos, format, numbering, consistency throughout the protocol.

RATIONALE:
To provide clarifications to the protocol and to ensure complete understanding of study procedures.
2. Update Contact Information of Key Sponsor's Personnel
DESCRIPTION OF CHANGE:
Names and contact information for key personnel are updated (Section II).
RATIONALE:
As the study has progressed, key personnel have changed; the modifications reflect the current individuals working on this study.

II Amendment Summary of Changes:

Title
WAS:
A Phase 3 Multicenter, Randomized, Double-Blind, Placebo Controlled Trial of the FLT3 Inhibitor Gilteritinib (ASP2215) Administered as Maintenance Therapy Following Induction/Consolidation Therapy for Subjects with FLT3/ITD AML in First Complete Remission Protocol for Phase 3 Study of ASP2215
IS AMENDED TO:
A Phase ~~3~~ **2** Multicenter, Randomized, Double-Blind, Placebo Controlled Trial of the FLT3 Inhibitor Gilteritinib (ASP2215) Administered as Maintenance Therapy Following Induction/Consolidation Therapy for Subjects with FLT3/ITD AML in First Complete Remission Protocol for Phase ~~3~~ **2** Study of ASP2215

List of Abbreviations and Definition of Key Terms *List of Abbreviations*
DELETED
~~IA Interim Analysis~~

IV Synopsis, Planned Study Period
WAS:
From 4Q2016 to 4Q2023
IS AMENDED TO:
From 4Q2016 to ~~4Q2023~~ **3Q2021**

IV Synopsis, Number of Subjects to be Enrolled/Randomized
WAS:
Initial target sample size is 354 randomized subjects. According to the adaptive design, the independent data monitoring committee (IDMC) may recommend to enroll up to a maximum of 444 randomized subjects.
IS AMENDED TO:
~~Initial~~ **The** target sample size is **approximately** ~~354~~ **85** randomized subjects. ~~According to the adaptive design, the independent data monitoring committee (IDMC) may recommend to enroll up to a maximum of 444 randomized subjects.~~

IV Synopsis, Study Design Overview
WAS:
This is a phase 3, randomized, placebo-controlled, double-blind, 2-arm study to compare the effect of gilteritinib as maintenance therapy versus placebo after induction/consolidation in subjects with FLT3/ITD AML in CR1 (including CRp and CRi). Subjects in CR1 (including CRp and CRi) will be approached for this study after induction/consolidation therapy is complete and a decision not to proceed with transplantation is made or a suitable donor could not be identified. Approximately 354 subjects will be randomized in a 2:1 ratio to receive gilteritinib or placebo. Randomization will be stratified based on: ● Age < 60 or ≥ 60 years. ● Geographic region, North America or Europe or Asia/Pacific/Central America/South America/ rest of world. ● Presence of MRD at screening; yes or no. ● Use of FLT3 inhibiting agents during induction/consolidation; yes or no. Subjects will enter the screening period up to 14 days prior to the start of treatment. Subjects will be administered treatment up to 2 years, or until a discontinuation criterion is met. After treatment discontinuation, subjects will have a 30-day follow-up visit for safety, after which the subjects will enter the long-term follow-up period for collection of subsequent AML treatment, remission status, and survival (cause of death and date of death). A formal interim analysis (IA) for sample size re-estimation will be performed by an IDMC when approximately 50% of the total planned RFS event size of 182 (i.e., 91 relapse or death events) have occurred. After IA, the sample size may increase from 354 randomized subjects up to 444 randomized subjects (25% increase).
IS AMENDED TO:
This is a phase ~~3~~ **2**, randomized, placebo-controlled, double-blind, 2-arm study to compare the effect of gilteritinib as maintenance therapy versus placebo after induction/consolidation in subjects with FLT3/ITD AML in CR1 (including CRp and CRi). Subjects in CR1 (including CRp and CRi) will be approached for this study after induction/consolidation therapy is complete and a decision not to proceed with

transplantation is made or a suitable donor could not be identified.

Approximately ~~354~~ **85** subjects will be randomized in a 2:1 ratio to receive gilteritinib or placebo.

Randomization will be stratified based on:

- Age < 60 or ≥ 60 years.
- Geographic region, North America or Europe or Asia/Pacific/Central America/South America/ rest of world.
- Presence of MRD at screening; yes or no.
- Use of FLT3 inhibiting agents during induction/consolidation; yes or no.

Subjects will enter the screening period up to 14 days prior to the start of treatment. Subjects will be administered treatment up to 2 years, or until a discontinuation criterion is met.

After treatment discontinuation, subjects will have a 30-day follow-up visit for safety, after which the subjects will enter the long-term follow-up period for collection of subsequent AML treatment, remission status, and survival (cause of death and date of death).

~~A formal interim analysis (IA) for sample size re-estimation will be performed by an IDMC when approximately 50% of the total planned RFS event size of 182 (i.e., 91 relapse or death events) have occurred. After IA, the sample size may increase from 354 randomized subjects up to 444 randomized subjects (25% increase).~~

IV Synopsis, Inclusion Criteria and 3 Study Population

3.2 Inclusion Criterion #3

WAS:

3. Subject consents to allow access to his or her diagnostic bone marrow aspirate or peripheral blood sample and/or the DNA derived from that sample, if available, that may be used to validate a companion diagnostic test that is being developed in parallel with gilteritinib.

IS AMENDED TO:

3. Subject consents to allow access to his or her diagnostic bone marrow aspirate or peripheral blood sample and/or the DNA derived from that sample, if available, that may be used to validate a companion diagnostic test ~~that is being developed in parallel with~~ **for** gilteritinib.

IV Synopsis, Duration of Treatment
WAS:
Gilteritinib or placebo will be given daily for up to 2 years. Subjects will be followed for up to 3 years after the 30-day follow-up visit, or until 80% of the subjects have an RFS event, whichever comes first. Study drug will not be provided during the follow-up period.
IS AMENDED TO:
Gilteritinib or placebo will be given daily for up to 2 years. ~~Subjects will be followed for up to 3 years after the 30-day follow-up visit, or until 80% of the subjects have an RFS event, whichever comes first.~~ **After treatment discontinuation, subjects will have a 30-day follow-up visit for safety, after which the subjects will enter the long-term follow-up period and be contacted every 3 months until final database lock for collection of subsequent AML treatment, remission status, and survival (cause of death and date of death) information.** Study drug will not be provided during the follow-up period.

IV Synopsis, Endpoints for Evaluation
WAS:
Primary Endpoint The primary efficacy endpoint is RFS, defined as the time from randomization until relapse or death from any cause, whichever comes first. Leukemia relapse will be defined as bone marrow blasts 5% or higher (not attributable to regenerating bone marrow), any circulating blasts, any extramedullary blast foci as per Revised International Working Group (IWG) criteria.
IS AMENDED TO:
Primary Endpoint The primary efficacy endpoint is RFS **per Independent Review Committee (IRC) adjudication**, defined as the time from randomization until relapse or death from any cause, whichever comes first. Leukemia relapse will be defined as bone marrow blasts 5% or higher (not attributable to regenerating bone marrow), any circulating blasts, any extramedullary blast foci as per Revised International Working Group (IWG) criteria.

IV Synopsis, Statistical Methods *Sample Size Justification*
WAS:
The study is a multicenter, double-blind, placebo-controlled, randomized phase 3 trial with 1 planned IA, comparing gilteritinib as maintenance therapy versus placebo, in FLT3/ITD AML subjects in CR1. The initial target number of randomized subjects is 354; 236 in gilteritinib arm and 118 in placebo arm. The median RFS time in the placebo arm is assumed to be 15 months, based on RATIFY control arm data on subjects with FLT3 mutation achieving CR1 after induction and

consolidation. A total of 182 relapse or death events will provide 90% power to detect a hazard ratio of 0.6 (corresponding to 18% difference in 2-year RFS rates) with 1-sided significance level of 0.025. The sample size estimation of 354 subjects assumes approximately 2 years of accrual and 5% drop out per year.

Randomization will be stratified by age, geographic region, the presence of minimal residual disease and use of FLT3 inhibiting agents during induction/consolidation.

Age:
- < 60 years
- ≥ 60 years

Geographic Region:
- North America
- Europe
- Asia/Pacific/South and Central America/rest of world

Presence of MRD in the screening bone marrow sample:
- Yes
- No

Use of FLT3 inhibiting agents during induction/consolidation:
- Yes
- No

A formal IA will be performed when approximately 91 relapse or death events (50% of the planned RFS event size of 182) have occurred in the study.

IS AMENDED TO:

The study is a multicenter, double-blind, placebo-controlled, randomized phase ~~3~~ **2** trial ~~with 1 planned IA,~~ comparing gilteritinib as maintenance therapy versus placebo~~,~~ in FLT3/ITD AML subjects in CR1. The ~~initial~~ target number of randomized subjects is ~~354~~ **85**; **approximately** ~~236~~ **57** in gilteritinib arm and ~~118~~ **28** in placebo arm.

The median RFS time in the placebo arm is assumed to be 15 months, based on RATIFY control arm data on subjects with FLT3 mutation achieving CR1 after induction and consolidation. A total of ~~182~~ **54** relapse or death events will provide ~~90~~ **83.2**% power to detect a hazard ratio of ~~0.6~~ **0.5** (corresponding to ~~18~~ **24**% difference in 2-year RFS rates) with 1-sided significance level of ~~0.025~~ 0.075. The sample size estimation of ~~354~~ **85** subjects assumes approximately 2 years of accrual ~~and 5% drop out per year~~.

Randomization will be stratified by age, geographic region, the presence of minimal residual disease and use of FLT3 inhibiting agents during induction/consolidation.

Age:
- < 60 years
- ≥ 60 years

Geographic Region:
- North America
- Europe
- Asia/Pacific/South and Central America/rest of world

Presence of MRD in the screening bone marrow sample:
- Yes

- No

Use of FLT3 inhibiting agents during induction/consolidation:

- Yes
- No

~~A formal IA will be performed when approximately 91 relapse or death events (50% of the planned RFS event size of 182) have occurred in the study.~~

IV Synopsis, Statistical Methods

Efficacy

WAS:

Primary Efficacy Analysis

The primary outcome of the trial is RFS from the time of randomization, treated as a time to event variable. The primary analysis will be conducted when the planned relapse or death events have been observed. RFS will be compared between arms on full analysis set (FAS) population with all randomized subjects using the stratified Cox proportional hazards model with strata on age at randomization, screening MRD status, geographic region and use of FLT3 inhibiting agents during induction/consolidation. Kaplan-Meier estimates of RFS will also be described for each arm, along with 95% confidence intervals at 1, 2, and 3 years. The FAS is defined as all subjects who were randomized and the analysis will be based on the randomized treatment arms.

The primary analysis of the primary endpoint will be performed at 1-sided 0.025 significance level to test the null hypothesis that RFS in the gilteritinib arm is worse than or equal to RFS in the placebo arm versus the alternative hypothesis that RFS in the gilteritinib arm is better than RFS in the placebo arm. The weighted statistic proposed by Cui, Hung and Wang (1999) will be used for the primary analysis of the primary endpoint at the end of the study.

In order to evaluate the robustness of the primary analysis of RFS, 2 sensitivity analyses will be performed. One sensitivity analysis is the same as the primary analysis except that it censors RFS at the end of treatment. The other sensitivity is the same as the primary analysis except that it censors at the last evaluable disease assessment without relapse when relapse or death is documented after more than 1 missed disease assessment.

Key Secondary Efficacy Analysis

The key secondary efficacy endpoint of OS will be analyzed on the FAS using the stratified Cox proportional hazards model with the same strata as in the primary analysis of RFS. With the sequential multiple test procedure to control for overall type I error at the 1-sided 0.025 significance level, formal significance testing of OS will be conducted only if the RFS comparison is statistically significant. Otherwise, OS analysis will be considered exploratory.

Pharmacokinetics:

Sparse (predose) pharmacokinetic samples will be collected in all subjects.

Additional ECGs and/or time-matched plasma samples will be collected in a subset of approximately 90 subjects (targeting approximately 60 subjects in the gilteritinib arm and 30 subjects in the placebo arm) at the following visits and time points:

- Day 15 – 4 hours (± 1 hour) postdose
- Day 29 – 4 hours (± 1 hour) postdose

Pharmacodynamics:

Not applicable.

Safety:

The safety analysis set is defined as all randomized 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 (CTCAE) version 4.03.

IS AMENDED TO:

Primary Efficacy Analysis

The primary outcome of the trial is RFS **per IRC adjudication** from the time of randomization, treated as a time to event variable. The primary analysis will be conducted when the planned relapse or death events have been observed. RFS will be compared between arms on full analysis set (FAS) population with all randomized subjects using the stratified ~~Cox proportional hazards model~~ **log-rank test** with strata on age at randomization, screening MRD status, geographic region and use of FLT3 inhibiting agents during induction/consolidation. Kaplan-Meier estimates of RFS will also be described for each arm, along with 95% confidence intervals at 1, 2, and 3 years. The FAS is defined as all subjects who were randomized and the analysis will be based on the randomized treatment arms.

The primary analysis of the primary endpoint will be performed at 1-sided 0.025 significance level to test the null hypothesis that RFS in the gilteritinib arm is worse than or equal to RFS in the placebo arm versus the alternative hypothesis that RFS in the gilteritinib arm is better than RFS in the placebo arm. ~~The weighted statistic proposed by Cui, Hung and Wang (1999) will be used for the primary analysis of the primary endpoint at the end of the study.~~

In order to evaluate the robustness of the primary analysis of RFS, ~~2~~ **the** sensitivity analyses will be performed **as follows:**

- **Unstratified log-rank test on the FAS**
- **Stratified Cox proportional hazards model with the same strata as in primary analysis on the FAS**
- **Same analysis as primary analysis but on the per protocol set (PPS)**
- **Same analysis as primary analysis on the FAS, but RFS is censored at the last evaluable disease assessment without relapse when relapse or death is documented after more than 1 missed disease assessment.**
- **Same analysis as primary analysis on the FAS, but RFS is censored at end of treatment.**
- **Same analysis as primary analysis on the FAS, but RFS is defined by using**

investigator assessed relapse.

~~One sensitivity analysis is the same as the primary analysis except that it censors RFS at the end of treatment. The other sensitivity is the same as the primary analysis except that it censors at the last evaluable disease assessment without relapse when relapse or death is documented after more than 1 missed disease assessment.~~

Key Secondary Efficacy Analysis

The key secondary efficacy endpoint of OS will be analyzed on the FAS using ~~the~~ a stratified ~~Cox proportional hazards model~~ **log-rank test** with the same strata as in the primary analysis of RFS. With the sequential multiple test procedure to control for overall type I error at the 1-sided ~~0.025~~ **0.075** significance level, formal significance testing of OS will be conducted only if the RFS comparison is statistically significant. Otherwise, OS analysis will be considered exploratory.

For the key secondary endpoint of OS, sensitivity analyses will be performed as below:

- **Unstratified log-rank test on the FAS**
- **Stratified Cox proportional hazards model with the same strata as in primary analysis on the FAS**
- **Same analysis as primary analysis but on the PPS**
- **Same analysis as primary analysis on the FAS, but OS is censored at the first hematopoietic stem cell transplant and first subsequent anti-leukemic treatment, whichever occurs first.**

Pharmacokinetics:

Sparse (predose) pharmacokinetic samples will be collected in all subjects.

Additional ECGs and/or time-matched plasma samples will be collected in a subset of approximately ~~90~~ **40** subjects ~~(targeting approximately 60 subjects in the gilteritinib arm and 30 subjects in the placebo arm)~~ at the following visits and time points:

- Day 15 – 4 hours (± 1 hour) postdose
- Day 29 – 4 hours (± 1 hour) postdose

Pharmacodynamics:

Not applicable.

Safety:

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

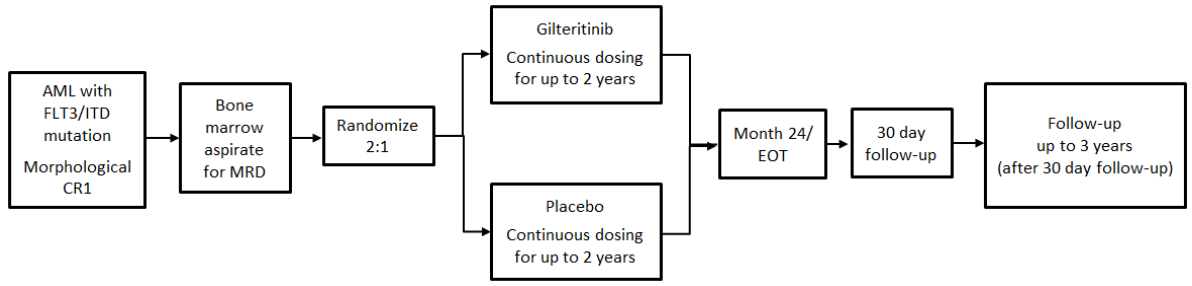
The safety evaluation will be based mainly on AEs, clinical laboratory, vital signs, ECGs and ECOG performance status. Descriptive statistics will be used to summarize safety data. All safety data will be summarized by the actual treatment received.
All summaries of AEs will include only treatment-emergent 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 (CTCAE) version 4.03.

IV Synopsis, Statistical Methods
DELETED
~~Interim Analyses~~: ~~A formal IA will be performed when approximately 91 relapse or death events (50% of the planned RFS event size of 182) have occurred in the study. Since the study is not planned to be terminated based on the efficacy results at the IA, the conservative Gamma (-40) alpha-spending function (Hwang et al, 1990) will be used to allocate 1-sided alpha=5*10-11 to spend at the IA.~~ ~~Details for the IA, monitoring subject safety, enrollment rates and event rates will be contained in the IDMC charter. Recommendations regarding study conduct will be made by the IDMC based on their independent assessment. The IDMC may recommend increasing sample size to a maximum of 444 accordingly based on interim analysis. The adaptive strategy details will be described in the IDMC charter with restricted access.~~ ~~The primary endpoint at the final analysis will be tested at the 1-sided significance level at 0.025 based on Gamma (-40) alpha-spending function, which allocates 1-sided alpha=5*10-11 to the IA.~~

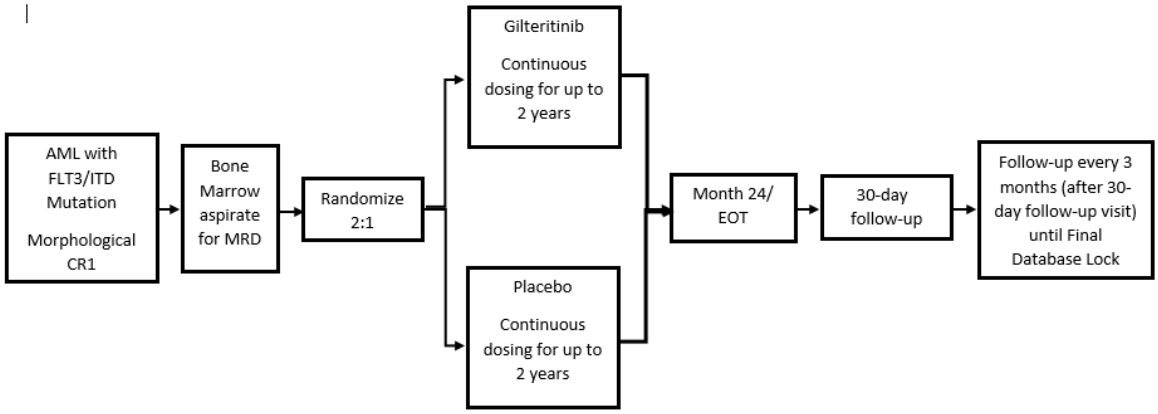
V. Flow Chart and Schedule of Assessments

Flow Chart

WAS:



IS AMENDED TO:



V. Flow Chart and Schedule of Assessments

Table 1 Schedule of Assessments, Footnote d

WAS:

d. Telephone contact every 3 months. 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.

IS AMENDED TO:

d. Telephone contact every 3 months **after the 30-day follow-up visit**. Additional contacts may be made to support key analyses. **Follow-up will continue until the final database lock, which is estimated to occur after the last subject enrolled reaches the 30-day follow-up visit**. ~~Subjects will be followed for up to 3 years after the 30-day follow-up visit.~~

1.3 Summary of Key Safety Information for Study Drugs

1.3.1 Gilteritinib Data

WAS:

The nonclinical and clinical studies, which are referred to in this section, are described in more detail in the ASP2215 Investigator's Brochure [2015].

IS AMENDED TO:

The nonclinical and clinical studies which are referred to in this section are ~~described in more detail in the ASP2215 Investigator's Brochure [2015]~~ **as of the writing of this protocol. Please refer to the current version of the ASP 2215 Investigator's Brochure.**

2.2 Study Design and Dose Rationale

2.2.1 Study Design

WAS:

This is a phase 3, randomized, placebo-controlled, double-blind, 2-arm study to compare the effect of gilteritinib as maintenance therapy versus placebo after induction/ consolidation in subjects with FLT3/ITD AML in CR1 (including CRp and CRi). The trial will be conducted at approximately 200 centers in North America, Europe, South America, Central America, and Asia/Pacific and rest of world.

Subjects in CR1 (including CRp and CRi) will be approached for this study after induction/consolidation therapy is complete and a decision not to proceed with transplantation is made or a suitable donor could not be identified.

Approximately 354 subjects (up to a maximum of 444 subjects) will be randomized in a 2:1 ratio to receive gilteritinib or placebo.

Randomization will be stratified based on:

- Age < 60 or ≥ 60 years.
- Geographic region, North America or Europe or Asia/Pacific/Central America/South America/rest of world.
- Presence of MRD at screening, yes or no.
- Use of FLT3 inhibiting agents during induction/consolidation, yes or no.

Subjects will enter the screening period up to 14 days prior to the start of treatment. Subjects will be administered treatment up to 2 years, or until a discontinuation criterion is met.

After treatment discontinuation, subjects will have a 30-day follow-up visit for safety, after which the subjects will enter the long-term follow-up period for collection of subsequent AML treatment, remission status, and survival (cause of death and date of death).

A formal interim analysis (IA) for sample size re-estimation will be performed by an IDMC when approximately 50% of the total planned RFS event size of 182 (i.e., 91 relapse or death events) have occurred. After IA, the sample size may increase from 354 randomized subjects up to 444 randomized subjects (25% increase).

IS AMENDED TO:

This is a phase ~~3~~ **2**, randomized, placebo-controlled, double-blind, 2-arm study to compare

the effect of gilteritinib as maintenance therapy versus placebo after induction/consolidation in subjects with FLT3/ITD AML in CR1 (including CRp and CRi). The trial will be conducted at approximately 200 centers in North America, Europe, South America, Central America, and Asia/Pacific and rest of world.

Subjects in CR1 (including CRp and CRi) will be approached for this study after induction/consolidation therapy is complete and a decision not to proceed with transplantation is made or a suitable donor could not be identified.

Approximately ~~354~~ **85** subjects ~~(up to a maximum of 444 subjects)~~ will be randomized in a 2:1 ratio to receive gilteritinib or placebo.

Randomization will be stratified based on:

- Age < 60 or ≥ 60 years.
- Geographic region, North America or Europe or Asia/Pacific/Central America/South America/rest of world.
- Presence of MRD at screening, yes or no.
- Use of FLT3 inhibiting agents during induction/consolidation, yes or no.

Subjects will enter the screening period up to 14 days prior to the start of treatment. Subjects will be administered treatment up to 2 years, or until a discontinuation criterion is met.

After treatment discontinuation, subjects will have a 30-day follow-up visit for safety, after which the subjects will enter the long-term follow-up period for collection of subsequent AML treatment, remission status, and survival (cause of death and date of death).

~~A formal interim analysis (IA) for sample size re-estimation will be performed by an IDMC when approximately 50% of the total planned RFS event size of 182 (i.e., 91 relapse or death events) have occurred. After IA, the sample size may increase from 354 randomized subjects up to 444 randomized subjects (25% increase).~~

4.4 Blinding

4.4.2 Breaking the Treatment Code by the Sponsor

WAS:

The Sponsor may break the treatment code for subjects who experience a Suspected Unexpected Serious Adverse Reaction (SUSAR), in order to determine if the individual case or a group of cases requires expedited regulatory reporting. Individual Emergency Codes will be provided to the limited staff who are responsible to break the codes for all SUSAR cases for reporting purposes.

The treatment code for each randomized subject will be provided by the IRT in the event of a medical emergency requiring knowledge of the treatment assigned to the subject. The time, date, subject number and reason for obtaining any of these codes, and therefore breaking the blind, must be documented in the study file. They must only be requested by the investigator or other persons designated as sub-investigators. No subjects or other study personnel will be made aware of the treatment given to any subject unless a medical emergency necessitates such disclosure.

Unblinding of the study medication should only be considered for subject safety or when

critical therapeutic decisions are contingent upon knowing the blinded study drug assignment. Any unblinding by the investigational staff must be reported immediately to the Sponsor and must include an explanation of why the study medication was unblinded. If possible, the Sponsor should be contacted prior to unblinding of the study medication.

IS AMENDED TO:

The Sponsor may break the treatment code for subjects who experience a Suspected Unexpected Serious Adverse Reaction (SUSAR), in order to determine if the individual case or a group of cases requires expedited regulatory reporting. Individual Emergency Codes will be provided to the limited staff who are responsible to break the codes for all SUSAR cases for reporting purposes.

The treatment code for each randomized subject will be provided by the IRT in the event of a medical emergency requiring knowledge of the treatment assigned to the subject. The time, date, subject number and reason for obtaining any of these codes, and therefore breaking the blind, must be documented in the study file. They must only be requested by the investigator or other persons designated as sub-investigators. No subjects or other study personnel will be made aware of the treatment given to any subject unless a medical emergency necessitates such disclosure.

~~Unblinding of the study medication should only be considered for subject safety or when critical therapeutic decisions are contingent upon knowing the blinded study drug assignment. Any unblinding by the investigational staff must be reported immediately to the Sponsor and must include an explanation of why the study medication was unblinded. If possible, the Sponsor should be contacted prior to unblinding of the study medication.~~

Unblinding of the study drug should only be considered for participant safety and/or evidence of documented relapse contingent upon knowing the blinded study drug assignment. Astellas Data Science Group will remain blinded.

- **Unblinding for patient safety by the investigator or designated sub-investigator must be reported immediately to the Sponsor (Astellas Medical Monitor) and must include an explanation of why the study medication was unblinded. If possible, the Sponsor should be contacted prior to unblinding of the study drug.**
- **Unblinding for documented relapse by the investigator or designated sub-investigator must be reported to the Sponsor (Astellas Medical Monitor), including an explanation and evidence of relapse prior to unblinding of the study drug. Relapse can be based on the investigator's assessment or the IRC adjudication.**

5.3 Efficacy Assessment

5.3.3.1 Survival Status and Subsequent Anti-leukemic Treatments and Their Outcomes

WAS:

Information on survival status, remission status, subsequent anti-leukemic treatments and outcomes will be collected for all subjects during long-term follow-up.

The first survival status 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 for up to 3 years after the 30-day follow-up visit, or until 80% of the subjects have an RFS event, whichever comes first.

Additional contacts may be made to support key analyses (e.g., interim/final analysis or analyses by the IDMC).

IS AMENDED TO:

Information on survival status, remission status, subsequent anti-leukemic treatments and outcomes will be collected for all subjects during long-term follow-up.

The first survival status 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 ~~for up to 3 years after the 30-day follow-up visit, or until 80% of the subjects have an RFS event, whichever comes first~~ **until the final database lock, which is estimated to occur when the last subject enrolled reaches the 30-day follow-up visit**.

Additional contacts may be made to support key analyses (e.g., ~~interim/~~final analysis or analyses by the IDMC)

5.4 Safety Assessment

5.4.5 Electrocardiogram (ECG)

WAS:

At a subset of sites, approximately 90 subjects (targeting approximately 60 subjects in the gilteritinib arm and 30 subjects in the placebo arm) will have additional ECGs as part of the pharmacokinetic sampling substudy. On day 15 and day 29, ECGs will be performed at predose (within 1 hour before study drug) and 4 hours postdose (+/- 1 hour) in triplicate and transmitted electronically for central reading. Triplicate 12 lead ECGs should be obtained after the subject has rested quietly and is awake in a fully supine position (or semirecumbent if supine is not tolerated) for 10 minutes before the first ECG from a triplicate and at least 5 minutes apart per time point.

IS AMENDED TO:

At a subset of sites, approximately ~~90~~ **40** subjects ~~(targeting approximately 60 subjects in the gilteritinib arm and 30 subjects in the placebo arm)~~ will have additional ECGs as part of the pharmacokinetic sampling substudy. On day 15 and day 29, ECGs will be performed at predose (within 1 hour before study drug) and 4 hours postdose (+/- 1 hour) in triplicate and transmitted electronically for central reading. Triplicate 12 lead ECGs should be obtained after the subject has rested quietly and is awake in a fully supine position (or semirecumbent if supine is not tolerated) for 10 minutes before the first ECG from a triplicate and at least 5 minutes apart per time point.

5.6 Test Drug Concentration

5.6.1 Pharmacokinetics

WAS:

Sparse pharmacokinetic samples will be collected to evaluate gilteritinib plasma concentrations as outlined in the Schedule of Assessments [Table 1].

At a subset of sites, approximately 90 subjects (targeting approximately 60 subjects in the gilteritinib arm and 30 subjects in the placebo arm) on day 15 and day 29 will have dense pharmacokinetic sampling as outlined in the Schedule of Assessments [Table 1]. Samples will be collected predose (within 1 hour before study drug administration) and 4 hours (± 1 hour) postdose.

IS AMENDED TO:

Sparse pharmacokinetic samples will be collected to evaluate gilteritinib plasma concentrations as outlined in the Schedule of Assessments [Table 1].

At a subset of sites, approximately ~~90~~ **40** subjects ~~(targeting approximately 60 subjects in the gilteritinib arm and 30 subjects in the placebo arm)~~ on day 15 and day 29 will have dense pharmacokinetic sampling as outlined in the Schedule of Assessments [Table 1]. Samples will be collected predose (within 1 hour before study drug administration) and 4 hours (± 1 hour) postdose.

5.7 Other Measurements, Assessments or Methods

5.7.2.1 FLT3 Mutation Status

WAS:

FLT3/ITD mutation status and allelic ratio will be analyzed using the diagnostic specimen (when available) by a Sponsor-designated central laboratory. All subjects must have documented FLT3/ITD AML at the time of AML diagnosis.

FLT3 mutation status will be analyzed at relapse by a Sponsor-designated central laboratory.

The FLT3 Mutation Assay Companion Diagnostic is an investigational use only assay that is being developed in parallel with gilteritinib. The manufacturer of the assay will analyze the diagnostic samples (when available) with the FLT3 companion diagnostic assay. The results may be used to seek regulatory approval if a companion diagnostic for FLT3/ITD is indicated for the patient population in this study. All biomarker samples collected 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.

IS AMENDED TO:

FLT3/ITD mutation status and allelic ratio will be analyzed using the diagnostic specimen (when available) by a Sponsor-designated central laboratory. All subjects must have documented FLT3/ITD AML at the time of AML diagnosis.

FLT3 mutation status will be analyzed at relapse by a Sponsor-designated central laboratory.

~~The FLT3 Mutation Assay Companion Diagnostic is an investigational use only assay that is being developed in parallel with gilteritinib.~~ The manufacturer of the **FLT companion diagnostic** assay will analyze the diagnostic samples (when available) with the FLT3 companion diagnostic assay. The results may be used to seek regulatory approval if a companion diagnostic for FLT3/ITD is indicated for the patient population in this study. All biomarker samples collected 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.

7 STATISTICAL METHODOLOGY

7.1 Sample Size

WAS:

The study is a multicenter, double-blind, placebo-controlled, randomized phase 3 trial with 1 planned IA, comparing gilteritinib as maintenance therapy versus placebo, in FLT3/ITD AML subjects in CR1. The initial target number of randomized subjects is 354; 236 in gilteritinib arm and 118 in placebo arm.

The median RFS time in the placebo arm is assumed to be 15 months, based on RATIFY control arm data on subjects with FLT3 mutation achieving CR1 after induction and consolidation. A total of 182 relapse or death events will provide 90% power to detect a hazard ratio of 0.6 (corresponding to 18% difference in 2-year RFS rates) with 1-sided significance level of 0.025. The sample size estimation of 354 subjects assumes approximately 2 years of accrual and 5% drop out per year.

After IA, the sample size may increase from 354 randomized subjects up to 444 randomized subjects (25% increase).

IS AMENDED TO:

The study is a multicenter, double-blind, placebo-controlled, randomized phase ~~3~~ **2** trial ~~with 1 planned IA,~~ comparing gilteritinib as maintenance therapy versus placebo in FLT3/ITD AML subjects in CR1. The ~~initial~~ target number of randomized subjects is approximately ~~354~~ **85**; ~~236~~ **57** in gilteritinib arm and ~~118~~ **28** in placebo arm.

The median RFS time in the placebo arm is assumed to be 15 months, based on RATIFY control arm data on subjects with FLT3 mutation achieving CR1 after induction and consolidation. A total of ~~182~~ **54** relapse or death events will provide ~~90~~ **83.2**% power to detect a hazard ratio of ~~0.6~~ **0.5** (corresponding to ~~18~~ **24**% difference in 2-year RFS rates) with 1-sided significance level of ~~0.025~~ **0.075**. The sample size estimation of ~~354~~ **85** subjects assumes approximately 2 years of accrual ~~and 5% drop out per year~~.

~~After IA, the sample size may increase from 354 randomized subjects up to 444 randomized subjects (25% increase).~~

7.2 Analysis Set

7.2.4 Pharmacokinetic Analysis Set (PKAS)

WAS:

The pharmacokinetic analysis set (PKAS) consists of the population administered at least 1 dose of study drug (gilteritinib), have at least 1 measurable concentration datum and for whom the time of dosing on the day of sampling is 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 determined at the Classification Meeting and documented in the Classification Specifications.

IS AMENDED TO:

The pharmacokinetic analysis set (PKAS) consists of the population administered at least 1 dose of ~~study drug (~~gilteritinib~~)~~, have at least 1 measurable concentration datum and for whom **both** the **date and** time of dosing ~~on the day of~~ **and PK** sampling is 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 determined at the Classification Meeting and documented in the Classification Specifications.

7.4 Analysis of Efficacy

7.4.1 Analysis of Primary Endpoint

WAS:

The primary analysis of RFS will be performed at 1-sided 0.025 significance level to test the null hypothesis that RFS in the gilteritinib arm is worse than or equal to RFS in the placebo arm versus the alternative hypothesis that RFS in the gilteritinib arm is better than RFS in the placebo arm. The weighted statistic proposed by Cui, Hung and Wang (1999) will be used for the primary analysis of the primary endpoint at the end of the study. The primary analysis will be conducted when the planned 182 relapse or death events have been observed. The primary efficacy endpoint of RFS will be analyzed on the FAS using the stratified Cox proportional hazards model with strata on age at randomization, screening MRD status, geographic region and use of FLT3 inhibiting agents during induction/consolidation as described below.

Age:

- < 60 years
- ≥ 60 years

Geographic Region:

- North America
- Europe
- Asia/Pacific/South and Central America/rest of world

Presence of screening MRD:

- Yes

- No

Use of FLT3 inhibiting agents during induction/consolidation:

- Yes
- No

Kaplan-Meier curves will be used to describe the RFS in each arm. Median RFS time and RFS rates at 1, 2, and 3 years along with 95% confidence interval will be estimated from the Kaplan-Meier curves.

In order to evaluate the robustness of the primary analysis of RFS, sensitivity analyses will be performed as below:

- Unstratified Cox proportional hazards model on the FAS
- Stratified Cox proportional hazards model on the PPS
- Stratified Cox proportional hazards model on the FAS where RFS is censored at the last evaluable disease assessment without relapse when relapse or death is documented after more than 1 missed disease assessment.
- Stratified Cox proportional hazards model on the FAS where RFS is censored at end of treatment.
- Stratified Cox proportional hazards model on the FAS where RFS is defined by using investigator assessed relapse.

IS AMENDED TO:

The primary analysis of RFS will be performed at 1-sided ~~0.025~~ **0.075** significance level to test the null hypothesis that RFS in the gilteritinib arm is worse than or equal to RFS in the placebo arm versus the alternative hypothesis that RFS in the gilteritinib arm is better than RFS in the placebo arm. ~~The weighted statistic proposed by Cui, Hung and Wang (1999) will be used for the primary analysis of the primary endpoint at the end of the study.~~ The primary analysis will be conducted when the planned ~~182~~ **54** relapse or death events have been observed. The primary efficacy endpoint of RFS will be analyzed on the FAS using the stratified ~~Cox proportional hazards model~~ **log-rank test** with strata on age at randomization, screening MRD status, geographic region and use of FLT3 inhibiting agents during induction/consolidation as described below.

Age:

- < 60 years
- ≥ 60 years

Geographic Region:

- North America
- Europe
- Asia/Pacific/South and Central America/rest of world

Presence of screening MRD:

- Yes
- No

Use of FLT3 inhibiting agents during induction/consolidation:

- Yes
- No

Kaplan-Meier curves will be used to describe the RFS in each arm. Median RFS time and RFS rates at 1, 2, and 3 years along with 95% confidence interval will be estimated from the Kaplan-Meier curves.

In order to evaluate the robustness of the primary analysis of RFS, sensitivity analyses will be performed as below:

- Unstratified ~~Cox proportional hazards model~~ **log-rank test** on the FAS
- ~~Stratified Cox proportional hazards model on the PPS~~
- ~~Stratified Cox proportional hazards model on the FAS where RFS is censored at the last evaluable disease assessment without relapse when relapse or death is documented after more than 1 missed disease assessment.~~
- ~~Stratified Cox proportional hazards model on the FAS where RFS is censored at end of treatment.~~
- ~~Stratified Cox proportional hazards model on the FAS where RFS is defined by using investigator assessed relapse.~~
- **Stratified Cox proportional hazards model with the same strata as in primary analysis on the FAS**
- **Same analysis as primary analysis but on the PPS**
- **Same analysis as primary analysis on the FAS, but RFS is censored at the last evaluable disease assessment without relapse when relapse or death is documented after more than 1 missed disease assessment.**
- **Same analysis as primary analysis on the FAS, but RFS is censored at end of treatment.**
- **Same analysis as primary analysis on the FAS, but RFS is defined by using investigator assessed relapse.**

7.4 Analysis of Efficacy

7.4.2.1 Key Secondary Endpoints and 7.4.2.2 Other Secondary Endpoints

WAS:

The key secondary analysis of OS will be performed at 1-sided 0.025 significance level to test the null hypothesis that OS in the gilteritinib arm is worse than or equal to OS in the placebo arm versus the alternative hypothesis that OS in the gilteritinib arm is better than OS in the placebo arm. The endpoint OS will be analyzed on the FAS using the stratified Cox proportional hazards model with strata on age at randomization, screening MRD status, geographic region and use of FLT3 inhibiting agents during induction/consolidation.

With the sequential multiple test procedure to control for overall type I error at the 1-sided 0.025 significance level, formal significance testing of OS will be conducted only if the RFS comparison is statistically significant. Otherwise, OS analysis will be considered exploratory.

Kaplan-Meier curves will be used to describe the OS in each arm. Median OS time and OS rates at 1, 2, 3, and 4 years along with 95% confidence interval will be estimated from the Kaplan-Meier curves.

For the key secondary endpoint of OS, sensitivity analyses will be performed as below:

- Unstratified Cox proportional hazards model on the FAS
- Stratified Cox proportional hazards model on the PPS
- Stratified Cox proportional hazards model on the FAS where OS is censored at the first HSCT and first subsequent anti-leukemic treatment, whichever occurs first.

7.4.2.2 Other Secondary Endpoints

- Stratified Cox proportional hazards model for EFS on the FAS
- Analyze the relationship between MRD and RFS, and that between MRD and OS on the FAS.

IS AMENDED TO:

The key secondary analysis of OS will be performed at 1-sided ~~0.025~~ **0.075** significance level to test the null hypothesis that OS in the gilteritinib arm is worse than or equal to OS in the placebo arm versus the alternative hypothesis that OS in the gilteritinib arm is better than OS in the placebo arm. The endpoint OS will be analyzed on the FAS using the stratified ~~Cox proportional hazards model~~ **log-rank test** with strata on age at randomization, screening MRD status, geographic region and use of FLT3 inhibiting agents during induction/consolidation.

With the sequential multiple test procedure to control for overall type I error at the 1-sided ~~0.025~~ **0.075** significance level, formal significance testing of OS will be conducted only if the RFS comparison is statistically significant. Otherwise, OS analysis will be considered exploratory.

Kaplan-Meier curves will be used to describe the OS in each arm. Median OS time and OS rates at 1, 2, 3, and 4 years along with 95% confidence interval will be estimated from the Kaplan-Meier curves.

For the key secondary endpoint of OS, sensitivity analyses will be performed as below:

- ~~Unstratified Cox proportional hazards model on the FAS~~
- ~~Stratified Cox proportional hazards model on the PPS~~
- ~~Stratified Cox proportional hazards model on the FAS where OS is censored at the first HSCT and first subsequent anti-leukemic treatment, whichever occurs first.~~
- **Unstratified log-rank test on the FAS**
- **Stratified Cox proportional hazards model with the same strata as in primary analysis on the FAS**
- **Same analysis as primary analysis but on the PPS**
- **Same analysis as primary analysis on the FAS, but OS is censored at the first HSCT and first subsequent anti-leukemic treatment, whichever occurs first.**

7.4.2.2 Other Secondary Endpoints

- Stratified ~~Cox proportional hazards model~~ **log-rank test** for EFS on the FAS
- Analyze the relationship between MRD and RFS, and that between MRD and OS on the

FAS.

7 Statistical Methodology

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

WAS:

A formal IA will be performed when approximately 91 relapse or death events (50% of the planned RFS event size of 182) have occurred in the study. Since the study is not planned to be terminated based on the efficacy results at the IA, the conservative Gamma (-40) alpha-spending function (Hwang et al, 1990) will be used to allocate 1-sided alpha=$5*10^{-11}$ to spend at the IA.

Details for the IA, monitoring subject safety, enrollment rates and event rates will be contained in the IDMC Charter. Recommendations regarding study conduct will be made by the IDMC based on their independent assessment. The IDMC may recommend increasing sample size to a maximum of 444 for the whole study accordingly based on interim analysis. The adaptive strategy details will be described in the IDMC charter with restricted access.

The primary endpoint at the final analysis will be tested at the 1-sided significance level at 0.025 based on Gamma (-40) alpha-spending function, which allocates 1-sided alpha=$5*10^{-11}$ to the IA.

IS AMENDED TO:

~~A formal IA will be performed when approximately 91 relapse or death events (50% of the planned RFS event size of 182) have occurred in the study. Since the study is not planned to be terminated based on the efficacy results at the IA, the conservative Gamma (-40) alpha-spending function (Hwang et al, 1990) will be used to allocate 1-sided alpha=$5*10^{-11}$ to spend at the IA.~~

~~Details for the IA, monitoring subject safety, enrollment rates and event rates will be contained in the IDMC Charter. Recommendations regarding study conduct will be made by the IDMC based on their independent assessment. The IDMC may recommend increasing sample size to a maximum of 444 for the whole study accordingly based on interim analysis. The adaptive strategy details will be described in the IDMC charter with restricted access.~~

~~The primary endpoint at the final analysis will be tested at the 1-sided significance level at 0.025 based on Gamma (-40) alpha-spending function, which allocates 1-sided alpha=$5*10^{-11}$ to the IA.~~

Not applicable.

10 Study Organization

10.1 Independent Data-Monitoring Committee (IDMC)

WAS:

The IDMC will be responsible for the review of subject safety, enrollment rates and event (relapse or death) rates during periodic review and interim analysis as defined in the IDMC charter. The IDMC may recommend increasing event size and sample size accordingly based on interim analysis. The adaptive strategy details will be described in the IDMC charter with

restricted access.

Members of the IDMC will be independent from the Sponsor and also will not participate as investigators in the trial. Additional details regarding responsibilities and membership requirements will be included in the IDMC charter.

IS AMENDED TO:

The IDMC will be responsible for the review of subject safety~~,~~ **and** enrollment rates ~~and event (relapse or death)~~ rates during periodic review ~~and interim analysis~~ as defined in the IDMC charter. ~~The IDMC may recommend increasing event size and sample size accordingly based on interim analysis. The adaptive strategy details will be described in the IDMC charter with restricted access.~~

Members of the IDMC will be independent from the Sponsor and also will not participate as investigators in the trial. Additional details regarding responsibilities and membership requirements will be included in the IDMC charter.

11 References

DELETED

~~Cui L, Hung HM, Wang SJ. Modification of sample size in group sequential clinical trials. Biometrics. 1999;55:853–7.~~

12.4 Common Serious Adverse Events

Serious Adverse Events Caused by Active AML

WAS:

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

Other AE	
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
Petechiae	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

IS AMENDED TO:

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

Other AE	
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~~ **3**
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
Petechiae	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~~ **3**
Weight loss	0-2

14 SPONSOR'S SIGNATURES