BLOOD AND MARROW TRANSPLANT CLINICAL TRIALS NETWORK

A Multi-center, Randomized, Double-blind, Placebo-controlled Phase III Trial of the FLT3 Inhibitor Gilteritinib Administered as Maintenance Therapy Following Allogeneic Transplant for Patients with FLT3/ITD AML

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Other participating sites will include BMT CTN Affiliate sites in the US and Canada as well as sites in Europe and Asia -Pacific.

List of Abbreviations

$5HT_1R$	5-hydroxytryptamine receptor 1
$5HT_{2B}R$	5-hydroxytryptamine receptor 2B
AE	Adverse event
ALL	Acute lymphocytic leukemia
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
APGD	Astellas Pharma Global Development
AST	Aspartate aminotransferase
AUST	Astellas US Technologies
BCRP	Breast cancer resistance protein
BM	Bone marrow
BMT	Bone marrow transplant
BMT CTN	Blood and Marrow Transplant Clinical Trials Network
C_{trough}	Concentration at the end of the dosing interval
CBC	Complete blood count
CIBMTR	Center for International Blood and Marrow Transplant Research
CK	Creatine kinase
CMV	Cytomegalovirus
CPAP	Continuous positive airway pressure
CR	Complete remission
CR1	First morphologic complete remission
CRF	Case report form
CRc	Composite complete remission rate
CRi	Complete remission with incomplete hematologic recovery
CRO	Contract research organization
CRp	Complete remission with incomplete platelet recovery
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCC	Data Coordinating Center
DLCO	Diffusing capacity of the lung for carbon monoxide
DLI	Donor lymphocyte infusion
DLT	Dose limiting toxicity
DSMB	Data Safety Monitoring Board
EBMT	European Society for Blood and Marrow Transplantation
ECG	Electrocardiogram
eCRF	Electronic case report form
EFS	Event-free survival
EQ-5D-5L	EuroQol Group-5 Dimension-5 Level
FACT-BMT	Functional Assessment of Cancer Therapy-Bone Marrow Transplant
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-Leu	Functional Assessment of Cancer Therapy-Leukemia
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FL	FLT3 ligand
FLT3	FMS-like tyrosine kinase 3

GCP	Good Clinical Practice
GEE	Generalized estimating equations
GFR	Glomerular filtration rate
GMP	Good Manufacturing Practice
GVHD	Graft-versus-host disease
GVL	Graft-versus-leukemia
HBV	Hepatitis B virus
HCT	Hematopoietic cell transplant
HIV	Human immunodeficiency virus
HQL	Health-related quality of life
HR	Hazard ratio
HTLV	Human T-lymphotropic virus
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Council on Harmonisation
ID	Identifier
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalization ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITD	Internal tandem duplication
ITT	Intention-to-treat
LA-CRF	Liver Abnormality-CRF
LFS	Leukemia-free survival
LFT	Liver function test
MAC	Myeloablative conditioning
MRD	Minimal residual disease
MTD	Maximum tolerated dose
NAAT	Nucleic acid amplification test
NCCN	National Comprehensive Cancer Network
NDA	New Drug Application
NGS	Next-generation sequencing
NHLBI	National Heart, Lung and Blood Institute
NMA	Non-myeloablative conditioning
NRM	Non-relapse mortality
NYHA	New York Heart Association
OS	Overall survival
P-gp	P-glycoprotein
PB	Peripheral blood
PCR	Polymerase chain reaction
PKAS	Pharmacokinetic analysis set
PPS	Per protocol set
PRES	Posterior reversible encephalopathy syndrome
PT	Preferred term
QTcF	Fridericia-corrected QT interval
R-IWG	Revised International Working Group
RFS	Relapse-free survival
RIC	Reduced intensity conditioning

SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System Organ Class
SOP	Standard Operating Procedure
SPRT	Sequential probability ratio test
SUSAR	Suspected unexpected serious adverse reaction
T_4	Free thyroxine
TBL	Total bilirubin
TKI	Tyrosine kinase inhibitor
Tregs	Regulatory T-cells
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
URD	Unrelated donor
VAS	Visual analog scale
WBC	White blood cell count

PROTOCOL SYNOPSIS

BMT CTN PROTOCOL 1506 / ASTELLAS PROTOCOL 2215-CL-0304

A Multi-center, Randomized, Double-blind, Placebo-controlled Phase III Trial of the FLT3 Inhibitor Gilteritinib Administered as Maintenance Therapy Following Allogeneic Transplant for Patients with FLT3/ITD AML

Study Chairpersons: Yi-Bin Chen, Mark Levis

Study Design: This is a double-blind, placebo-controlled, randomized, multi-center Phase III trial which participants with FMS-like tyrosine kinase 3 (FLT3) / internal tandem duplication (ITD) (FLT3/ITD) acute myeloid leukemia (AML) in first morphologic complete remission (CR1) undergo allogeneic hematopoietic cell transplant (HCT) and are randomized to receive gilteritinib or placebo beginning after the time of engraftment for a two year period. Participants will be stratified according to 3 factors: 1) conditioning regimen intensity (myeloablative vs reduced intensity/non-myeloablative), 2) time from first day of hematopoietic cell infusion to randomization (30-60 days vs 61-90 days) and 3) presence vs absence of or unknown minimal residual disease (MRD) from a pre-registration bone marrow (BM) aspirate.

Primary Objective: The primary objective is to compare relapse-free survival (RFS) between participants with FLT3/ITD AML in CR1 who undergo HCT and are randomized to receive gilteritinib or placebo beginning after the time of engraftment for a two year period.

Secondary Objectives:

1. To determine the safety and tolerability of gilteritinib after HCT.
2. To compare overall survival (OS), non-relapse mortality (NRM) and event-free survival (EFS) (where events include relapse, death, stopping therapy and administration of donor lymphocyte infusion (DLI) or new therapy for suspicion of disease) in participants treated with gilteritinib as maintenance therapy after HCT compared to those treated with placebo.
3. To compare 6-month cumulative incidence of grades II-IV and III-IV acute graft-versus-host disease (GVHD) and 12-month and 24-month cumulative incidence of mild, moderate, and severe chronic GVHD in participants treated with gilteritinib as maintenance therapy after HCT compared to those treated with placebo.
4. To examine the effect of pre- and post-transplant MRD on RFS and OS.

5. To compare incidence and severity of infection in participants treated with gilteritinib as maintenance therapy after HCT compared to those treated with placebo.

Eligibility Criteria: Patients who are legal adults by local regulation with a diagnosis of AML harboring a FLT3/ITD mutation. Participants must be in CR1 prior to transplant, as defined by < 5% blasts in the BM with no morphologic characteristics of acute leukemia (e.g., Auer rods) in the BM with no evidence of extra-medullary leukemia. Participants must begin preparative chemotherapy for allogeneic transplant as consolidation therapy within 30 days after the confirmatory registration BM aspirate. In order to receive the study drug, participants must achieve engraftment, defined as absolute neutrophil count (ANC) ≥ 500 cells/μL and non-transfused platelet count ≥ 20000/μL. Participants must be registered for the study prior to the start of conditioning for the transplant. Participants will be allowed to receive any conditioning regimen, any GVHD prophylaxis regimen, and HCT from any graft- or donor-source. Registered participants who are not randomized will be replaced.

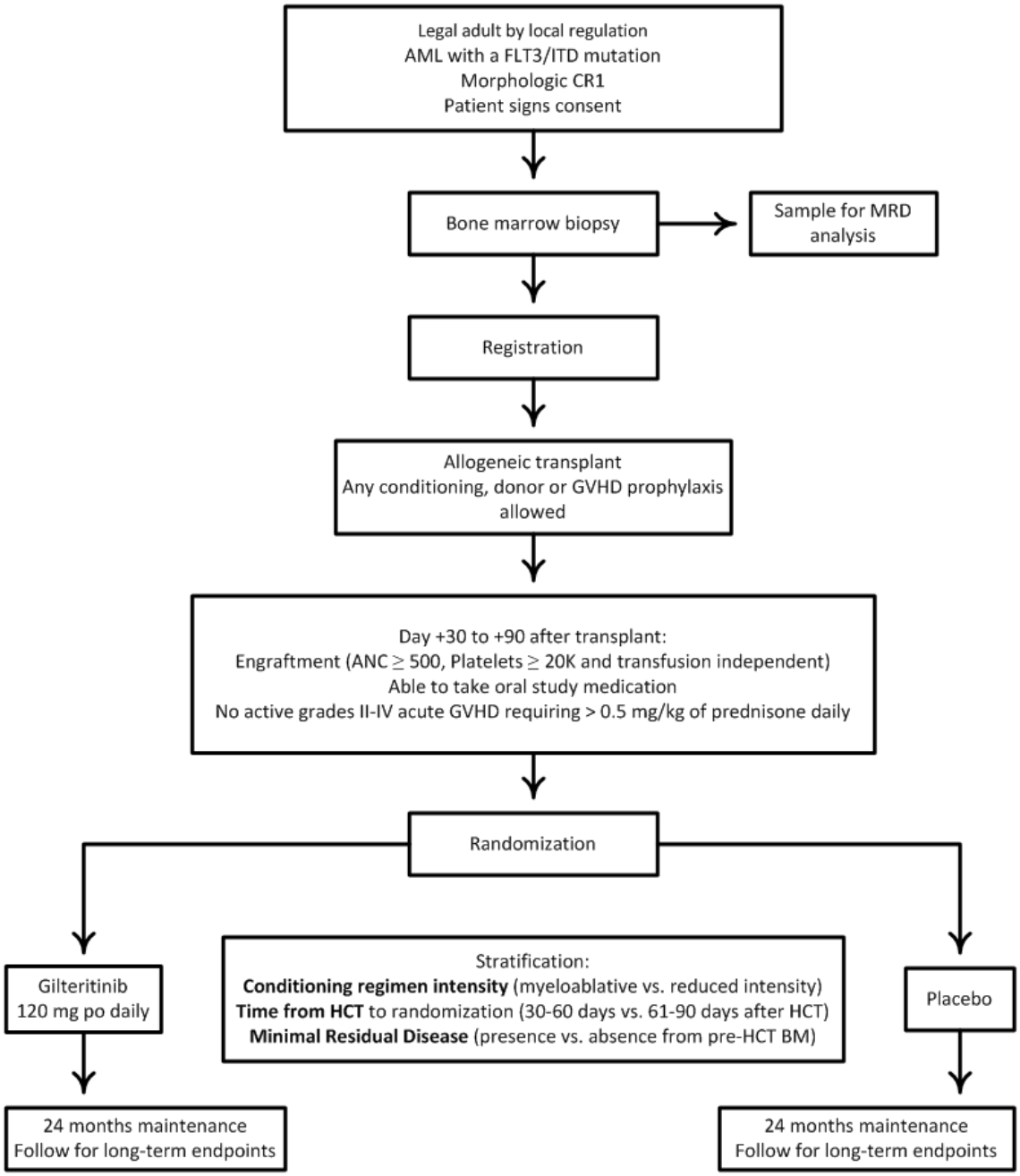
Treatment Description: A BM aspirate and/or biopsy will be obtained after engraftment is achieved, but prior to initiation of the study drug, to confirm an ongoing leukemia-free state. Between days +30 and +90 after the start day of transplant (day 0), participants will be randomized and initiate study drug, gilteritinib 120 mg orally per day or placebo (target initiation time is between days 30 to 45 post HCT). Study drug treatment will continue for 24 months from the start of therapy.

Accrual Objective: This clinical trial will randomize 173 participants per arm (346 total participants).

Study Duration: The estimated accrual period is 24 months. Participants will be treated and assessed for up to 2 years following initiation of study drug. After completion of treatment, participants will be followed for relapse and survival for up to 5 years after the last participant is randomized or until 80% of RFS events occur, whichever comes first. For an individual participant, follow-up will last for 3 to 7 years depending on when they start and stop treatment.

Lab Correlates: DNA will be prepared from pre- and post-transplant BM aspirate samples for analysis of MRD using a next-generation sequencing (NGS) assay. Where available, DNA from the participant's diagnostic BM aspirate, or blood if aspirate is not available, will be analyzed for FLT3/ITD mutant-to-wild type allelic ratio. The same diagnostic specimen will be analyzed for AML-associated mutations using an NGS platform.

OUTLINE OF TREATMENT PLAN



Abbreviations: AML: acute myeloid leukemia; ANC: absolute neutrophil count; BM: bone marrow; CR1: first morphologic complete remission; FLT3: FMS-like tyrosine kinase 3; GVHD: graft-versus-host disease; HCT: hematopoietic cell transplant; ITD: internal tandem duplication; MRD: minimal residual disease.

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CHAPTER 1

1. BACKGROUND AND RATIONALE

1.1. Introduction

Acute myeloid leukemia (AML) is an aggressive hematopoietic malignancy that confers a generally poor prognosis. Although it can occur in children, its peak incidence is during the seventh decade of life. There are roughly 21000 new cases per year in the US[1] and it has a similar incidence in other developed countries, including Europe. AML patients are now routinely stratified at diagnosis into different risk categories based on screening for recurrent genetic abnormalities which define unique subtypes of the disease. Overall survival (OS) for AML patients has been increasing each decade, particularly for patients under age 60, presumably because of improvements in supportive care, tailoring therapy according to risk category, and advances in hematopoietic cell transplant (HCT) techniques[2] However, relapse post-allogeneic HCT remains a significant challenge, and novel treatment strategies are needed in the post-transplant setting, especially for those with poor prognosis AML.

Activating mutations of the FMS-like tyrosine kinase 3 (FLT3) receptor are one of the most common genetic lesions in AML, and are associated with an overall poor prognosis[3] The most common mutation, found in 23% of de novo AML, is a FLT3/internal tandem duplication (ITD), usually localized to the juxtamembrane domain. Point mutations in the kinase domain, typically at residue aspartate 835, are found in 7% of cases and only rarely are both mutations seen concurrently at initial diagnosis. Both mutations constitutively activate FLT3 and, in the case of ITD mutations, lead to aberrant downstream signaling. FLT3 mutations are believed to act as second, or cooperating hits in leukemogenesis[4][5] most often occurring with NPM1 mutations and in the context of a diploid karyotype. De novo AML at diagnosis is polyclonal, the relative allelic burden of each mutation reflects the mixture of different sub-clones[5] Patients with FLT3/ITD AML who present with a high FLT3 mutant allelic burden fare much more poorly than their counterparts with low or intermediate allelic ratios[6][7] FLT3/ITD AML patients typically present with leukocytosis and a hypercellular bone marrow (BM), and they respond to conventional induction chemotherapy with remission rates similar to that seen in other subtypes. However, they are much more likely to relapse and relapse quickly; the presence of a FLT3/ITD mutation at relapse is one of the worst prognostic features known.[8][9]

Given the aggressive nature of the disease and the exceptionally poor prognosis at relapse, allogeneic transplant in first remission is now widely recommended for patients with FLT3 mutations.[10] Allogeneic transplant is the most effective post-remission therapy for reducing the risk of relapse in AML, and the preponderance of literature (as well as National Comprehensive Cancer Network [NCCN] guidelines) supports this approach for FLT3/ITD AML. However, the literature also suggests that while allogeneic transplant reduces the risk of relapse in comparison to consolidation chemotherapy, it is less effective for FLT3/ITD AML than for other AML subtypes, that is, patients with a FLT3/ITD mutation are more likely to relapse following allogeneic transplant than AML patients lacking a FLT3/ITD

mutation.[10] This may be a reflection of the fact that patients with FLT3/ITD AML tend to have a higher disease burden even in remission (with higher rates of minimal residual disease [MRD]). Furthermore, there are recent data suggesting that for patients with a high FLT3 mutant allelic burden, even allogeneic transplant confers little benefit.[7] Therefore, the currently accepted paradigm of induction chemotherapy followed by consolidation with allogeneic transplant remains inadequate for many patients.

FLT3 tyrosine kinase inhibitors (TKIs) have been studied extensively over the past several years.[11] First generation, multi-targeted TKIs such as lestaurtinib and midostaurin had only modest activity, but more recent drugs have shown significant clinical activity as single agents. Effective, sustained FLT3 inhibition induces clearance of peripheral blasts and terminal myeloid differentiation of marrow blasts in patients with relapsed or refractory FLT3/ITD AML. Agents such as sorafenib, quizartinib, crenolanib, and gilteritinib can induce a complete remission (CR) or, more commonly, a CR with incomplete count recovery, in up to half of relapsed patients, and several pivotal randomized trials of these drugs are currently underway. Importantly, there is a growing body of literature suggesting that FLT3 TKIs can confer clinical benefit in the post-transplant setting.[12,13] There have been numerous published reports in which patients relapsing after an allogeneic transplant achieved durable remissions following single agent treatment with sorafenib. Moreover, the use of FLT3 inhibition as maintenance therapy after allogeneic transplant for FLT3/ITD AML patients has now been formally studied in non-randomized studies with both sorafenib and quizartinib through single-arm studies[14,15] and a randomized maintenance study with midostaurin (NCT01883362) is currently accruing. All of these studies have shown that maintenance with any FLT3 TKI studied has been, thus far, safe and well-tolerated.

The data supporting the use of FLT3 inhibition in the post-transplant setting are entirely based on single arm studies or case series. The observed benefits could result from two potential mechanisms. The first is inhibition of an essential kinase in residual AML cells present in the post-transplant BM. While FLT3 inhibition may simply lead to suppressed growth of these residual tumor cells, the FLT3 TKI may synergize with any graft-versus-leukemia (GVL) effect that exists during the maintenance therapy. This is the same mechanism believed to account for the benefit of BCR-ABL inhibitors used in the post-transplant setting for Ph+ acute lymphocytic leukemia (Ph+ ALL) or high risk chronic myeloid leukemia.[16,17]

The second possible mechanism is immunologic. Graft-versus-host disease (GVHD) is one of the major morbidities of allogeneic transplant, but its collateral effect, namely GVL, forms the basis for much of the therapeutic benefit of allogeneic transplant.[18] GVHD/GVL is thought to be mediated by donor T-cells, counterbalanced by regulatory T-cells (Tregs), notably the subset characterized by flow cytometry as CD4+/CD25+/FoxP3+.[19] Treg homeostasis is directly controlled by myeloid dendritic cells,[20] which in turn are dependent on FLT3 ligand (FL, the cognate ligand for the FLT3 receptor) for proliferation.[21] Increases in FL, therefore, have the effect of expanding the Treg population,[22] which is postulated to suppress GVHD. Conversely, FLT3 inhibition would be expected to augment GVHD/GVL. While this theoretically could result in significant toxicity to the patient, thus far none of the

clinical studies have reported worsening GVHD as a limitation of the maintenance therapy with FLT3 TKIs. Interestingly, in a recent study, 8 out of 22 patients treated with sorafenib post-transplant developed a skin rash consistent with GVHD after starting sorafenib.[14] The rash resolved in all cases after cessation of sorafenib.

In summary, allogeneic transplant is currently the most effective consolidation therapy for patients with FLT3/ITD AML, but relapse after transplant remains a significant problem. FLT3 inhibitors have demonstrated clinical activity in this disease, and their use in the post-transplant setting appears to be safe and tolerable. The underlying hypothesis of this clinical trial is that maintenance therapy with a potent FLT3 inhibitor after allogeneic transplant will lead to improved relapse-free survival (RFS) for patients with FLT3/ITD AML. This multi-center international clinical trial is designed to prove or disprove this hypothesis by randomizing FLT3/ITD AML patients who have completed an allogeneic transplant to maintenance therapy with a FLT3 TKI versus placebo, in double-blind fashion. Of the FLT3 TKIs in current clinical development, there are five that would be reasonable choices to study in this context: midostaurin,[23] sorafenib,[23] crenolanib,[24] quizartinib,[25] and gilteritinib.[26] Due to less favorable side effect profiles, sorafenib (hand-foot syndrome and gastrointestinal toxicity) and both midostaurin and crenolanib (nausea requiring pre-medication) would be problematic in a placebo-controlled trial. Although it is extremely well-tolerated by patients, quizartinib is associated with QT prolongation and myelosuppression, both of which could complicate the care of post-transplant patients. Gilteritinib (ASP2215) causes minimal side effects, and neither widespread QT prolongation nor myelosuppression were noted in a trial enrolling more than 250 patients. Furthermore, it has been administered as maintenance therapy to 16 patients post-transplant, and no significant safety signals were noted. Of all 5 compounds, quizartinib and gilteritinib have proven to be the most effective at inhibiting FLT3 in vivo, and gilteritinib appears to be the most tolerable. Gilteritinib, therefore, represents the best candidate for this trial.

1.2. Gilteritinib (ASP2215)

1.2.1. ASP2215 Mechanism of Action

Gilteritinib (ASP2215) is a novel small molecule pyrazinecarboxamide derivative with inhibitory activity against FLT3. It has inhibitory activity against the two most common FLT3-activating mutations (ITD and kinase domain). It is active against most resistance-conferring point mutant forms of FLT3 that arise during therapy with type 2 inhibitors such as sorafenib or quizartinib, specifically the kinase domain mutations at residue D835 and the gatekeeper mutation at residue F691.[27] It is more than 10-fold less potent against KIT. Among 79 tyrosine kinases tested, ASP2215 hemifumarate inhibited activities of FLT3, NPM1-ALK, LTK, ALK and AXL kinases at 1 and 5 nmol/L, and TRKA, ROS, RET and MER kinases at 5 nmol/L by over 50%. The half maximal inhibitory concentration (IC_{50}) values for FLT3, EML4-ALK, and KIT kinases were 0.291, 1.2, and 229 nmol/L, respectively. ASP2215 hemifumarate inhibited the cell growth of Ba/F3 cells expressing FLT3-ITD, FLT3-D835Y, and FLT3-ITD-D835Y with IC_{50} values of 1.8, 1.6, and 2.1 nmol/L, respectively. ASP2215 hemifumarate inhibited the growth of MV4-11 cells with an

IC_{50} value of 0.92 nmol/L. In MV4-11 cells, treatment of ASP2215 hemifumarate at 0, 0.1, 1, and 10 nmol/L resulted in FLT3 phosphorylation of 100%, 86%, 19%, and 7%, respectively. ASP2215 hemifumarate induced significant growth inhibition of MV4-11 tumors and tumor regression in vivo. Further, ASP2215 hemifumarate at 6 and 10 mg/kg per day induced complete tumor regression for 4 and 6 out of 6 mice, respectively. Body weight of the mice treated with ASP2215 hemifumarate was not affected at any tested doses.

1.2.2. ASP2215 Pharmacokinetics

The main enzyme involved in the metabolism of ASP2215 is estimated to be cytochrome P450 (CYP)3A4. ASP2215 has an induction potential of 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. ASP2215 has direct inhibitory effects on CYP2C19 and CYP3A4, but not direct inhibitory effects on CYP1A2, CYP2B6, CYP2C8, CYP2C9, or CYP2D6. After oral administration of [^{14}C] ASP2215 hemifumarate at 1 mg/kg to rats, 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. ASP2215 is a substrate for P-glycoprotein (P-gp), but not for breast cancer resistance protein (BCRP). ASP2215 has the potential of P-gp and BCRP inhibition. In AML patients treated in the 2215-CL-0101 Phase 1/2 study, the mean half-life of ASP2215 was greater than 48 hours.

1.2.3. ASP2215 Formulation

Please refer to the current version of the ASP2215 Investigator's Brochure for details on gilteritinib tablet formulation.

1.2.4. ASP2215 Clinical Experience

In a phase 1/2 trial of oral gilteritinib enrolling 198 adult patients with relapsed/refractory AML (127 of whom harbored FLT3 mutations), the composite complete remission rate (CRc; CR = CR with incomplete platelet recovery [CRp] + CR with incomplete hematologic recovery [CRi]) was 47% in patients treated with the FLT3-inhibitory dose of 80 mg or higher. The maximum tolerated dose (MTD) was 300 mg per day, and the dose limiting toxicity (diarrhea, elevated aspartate aminotransferase [AST]) was seen at 450 mg per day. The median duration of response was 126 days. Please refer to the current version of the ASP2215 Investigator's Brochure for more detailed information.

1.2.5. ASP2215 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.

1.3. Rationale

This multi-center phase III clinical trial will evaluate the impact of maintenance therapy with the FLT3 inhibitor gilteritinib on the RFS of participants with FLT3/ITD AML who have successfully undergone allogeneic transplant. A dose of 120 mg has been chosen on the basis of a monotherapy trial, which demonstrated complete FLT3 inhibition in FLT3/ITD AML patients.[26] A maintenance period of 2 years has been chosen based on Center for International Blood and Marrow Transplant Research (CIBMTR) data that indicate the vast majority of relapses occur by this time after allogeneic HCT. Because it is placebo-controlled and double-blinded, the results that emerge from this study will establish whether or not FLT3 inhibition in this setting can prevent relapse, and whether or not it has an impact on GVHD in these participants. Additionally, the trial may establish the utility of monitoring MRD using a next-generation sequencing (NGS) platform. A validated MRD assay would represent an important advance for the field, as it would allow for the design of more efficient trials testing novel agents in the treatment of FLT3/ITD AML.

CHAPTER 2

2. STUDY DESIGN

2.1. Study Overview

The study is a two-arm, double-blind, placebo-controlled, randomized, multi-center trial in which participants with FLT3/ITD AML in first morphologic CR (CR1) undergoing allogeneic HCT will be randomized to receive gilteritinib or placebo 30 to 90 days after HCT for a two year period. Participants will be stratified according to: 1) conditioning regimen intensity (myeloablative vs reduced intensity/non-myeloablative), 2) time from first day of hematopoietic cell infusion to randomization (30-60 days vs 61-90 days) and 3) presence vs absence of or unknown MRD from the most recent pre-registration BM aspirate.

2.2. Hypothesis and Specific Objectives

2.2.1. Hypothesis

The underlying hypothesis of this clinical trial is that maintenance therapy with a FLT3 inhibitor after allogeneic transplant will lead to improved RFS for participants with FLT3/ITD AML in CR1. The hypothesis will be tested by randomizing participants with FLT3/ITD AML who have undergone allogeneic transplant and are in CR1 to one of two arms, in double-blind fashion: 1) maintenance therapy with 120 mg per day of the FLT3 inhibitor, gilteritinib; or 2) placebo.

2.2.2. Study Objectives

2.2.2.1. The primary objective is to compare RFS between participants with FLT3/ITD AML in CR1 who undergo HCT and are randomized to receive gilteritinib or placebo beginning after the time of engraftment for a two year period.

2.2.2.2. Secondary objectives include:

- To determine the safety and tolerability of gilteritinib after HCT.
- To compare OS, non-relapse mortality (NRM) and event-free survival (EFS) (where events include relapse, death, stopping therapy and administration of donor lymphocyte infusion (DLI) or new therapy for suspicion of disease) in participants treated with gilteritinib as maintenance therapy after HCT compared to those treated with placebo.
- To compare 6-month cumulative incidence of grades II-IV and III-IV acute GVHD and 12-month and 24-month cumulative incidence of mild, moderate, and severe chronic GVHD in participants treated with gilteritinib as maintenance therapy after HCT compared to those treated with placebo.
- To examine the effect of pre- and post-transplant MRD on RFS and OS.
- To compare incidence and severity of infection in participants treated with gilteritinib as maintenance therapy after HCT compared to those treated with placebo.

2.2.2.3. Exploratory objectives include:

- To examine health-related quality of life (HQL).
- To examine healthcare resource utilization.
- To estimate the proportion of participants who are willing and able to be randomized to maintenance and describe the frequencies of events that preclude randomization.
- To assess gilteritinib pharmacokinetics using population pharmacokinetic modeling
- To evaluate FLT3 mutation status and other potential genomic and/or other biomarkers that may correlate to treatment outcome.

2.3.Participant Eligibility

This trial will have a three-step enrollment process:

- Enrollment into the screening segment will occur after informed consent is signed
- Registration will occur prior to HCT after all registration eligibility criteria are met
- Randomization will occur after HCT once the participant is ready to begin the study drug and after all randomization eligibility criteria are met

2.3.1. Registration Eligibility Criteria

Registration will be done prior to HCT.

2.3.1.1. Registration Inclusion Criteria

A participant is eligible for registration to the clinical study if all of the following apply:

1. Participant is considered a suitable candidate for HCT and has an acceptable source of allogeneic donor cells, as defined per institutional practice (allogeneic HCT for any donor source [matched sibling, unrelated donor (URD), mismatched URD, related haploidentical, or umbilical cord blood] and any graft source [umbilical cord, BM, peripheral blood (PB)], and any conditioning [myeloablative conditioning (MAC), reduced intensity conditioning (RIC), or non-myeloablative conditioning (NMA)] will be permitted).
2. Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved written informed consent and privacy language as per national regulations (e.g., Health Insurance Portability and Accountability Act Authorization (HIPAA) for US sites) obtained from the participant or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
3. Participant is considered a legal adult by local regulation at the time of signing informed consent form (ICF).
4. Participant consents to allow access to his or her diagnostic BM aspirate or PB sample and/or the DNA derived from that sample, if available, that may be used to validate a companion diagnostic that is being developed in parallel with gilteritinib.
5. Participant has confirmed, morphologically documented AML in CR1. For the purposes of registration, CR1 will be defined as < 5% blasts in the BM with no morphologic

characteristics of acute leukemia (e.g., Auer Rods) in the BM with no evidence of extramedullary disease such as central nervous system involvement or granulocytic sarcoma.

a. Participant has not received more than 2 cycles of induction chemotherapy to achieve CR1. The induction cycles can be the same regimen or different regimens. The regimen(s) may contain conventional agents, investigational agents, or a combination of both.
b. Participants with CR with incomplete count recovery (CRp or CRi) are allowed. Incomplete platelet recovery (CRp) is defined as CR with platelet count $< 100 \times 10^9$/L. Incomplete blood count recovery (CRi) is defined as CR with residual neutropenia $< 1 \times 10^9$/L with or without complete platelet recovery. Red blood cell count (RBC) and platelet transfusion independence is not required.
c. The maximum time allowed from establishment of CR1 to registration is 12 months.

6. Participant has presence of the FLT3/ITD activating mutation in the BM or PB as determined by the local institution at diagnosis.
7. Participant must meet the following criteria as indicated on the clinical laboratory tests:
    a. Serum creatinine within normal range, or if serum creatinine outside normal range, then glomerular filtration rate (GFR) > 40 mL/min/1.73m^2 as calculated with the Cockcroft-Gault equation with adjustment if total body weight is ≥ 125% of ideal body weight.
    b. Total bilirubin (TBL) ≤ 2.5 mg/dL, except for participants with Gilbert's syndrome.
    c. Serum AST and/or alanine aminotransferase (ALT) < 3 x institutional upper limit of normal (ULN).
8. Participant has left ventricular ejection fraction (LVEF) at rest ≥ 40%.
9. Participant has diffusing capacity of the lung for carbon monoxide (DLCO) (corrected for hemoglobin) ≥ 50% predicted and/or forced expiratory volume in 1 second (FEV1) ≥ 50% predicted.
10. Female participants must either:
    - Be of non-childbearing potential:
        - postmenopausal (defined as at least 1 year without menses) prior to screening, or
        - documented as surgically sterilized (at least 1 month prior to the screening visit)
    - 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 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.

11. Female participants must agree not to breastfeed or donate ova throughout the study drug treatment period and for 6 months after the final study drug administration.
12. Male participants (even if surgically sterilized), and their partners who are women of childbearing potential must be using highly effective contraception in addition to a barrier method throughout the study drug treatment period and for 127 days after the final study drug administration.
13. Male participants must not donate sperm throughout the study drug treatment period and for 127 days after the final study drug administration.
14. Participant is able to take an oral medication.
15. Participant agrees not to participate in another interventional study while on treatment.

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

2.3.1.2. Registration Exclusion Criteria

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

1. Participant has had a prior allogeneic transplant.
2. Participant has Karnofsky performance status score < 70% (APPENDIX F).
3. Participant requires treatment with concomitant drugs that are strong inducers of CYP3A (APPENDIX H) within 14 days of start of study drug.
4. Participant 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 participant (APPENDIX H).
5. Participant has a Fridericia-corrected QT interval (QTcF) > 450 msec (average of triplicate determinations) per central read.
6. Participant has long QT Syndrome at screening.
7. Participant has a known infection with human immunodeficiency virus (HIV).
8. Participant has active hepatitis B infection as determined by nucleic acid amplification test (NAAT) or surface antigen assay. Participants who have acquired immunity from past exposure (HBcAb positive/HBsAb positive/HBsAg negative) are eligible.
9. Participant has active hepatitis C infection as determined by NAAT. NAAT must be performed if the participant has positive serology for hepatitis C. Participants who have had past exposure and have no detectable virus either through spontaneous clearance or treatment are eligible.

10. Participant has an uncontrolled infection. If a bacterial or viral infection is present, the participant must be receiving definitive therapy and have no signs of progressing infection for 72 hours prior to registration. If a fungal infection is present, the participant must be receiving definitive systemic anti-fungal therapy and have no signs of progressing infection for 1 week prior to registration.
    - Progressing infection is 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.
11. Participant has had a myocardial infarction within 6 months prior to registration or New York Heart Association (NYHA) Class III or IV heart failure (APPENDIX D), uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia.
12. Participant has a serious medical or psychiatric illness likely to interfere with participation in this clinical study.
13. Participant is breast feeding or pregnant.
14. Participant has prior malignancies, except lobular breast carcinoma in situ, fully resected basal cell or squamous cell carcinoma of skin 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.

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

2.3.2. Randomization Eligibility Criteria

After engraftment, participants will undergo a BM aspirate and/or biopsy to ensure continued CR status. Engraftment is defined as absolute neutrophil count (ANC) ≥ 500 cells/μL and platelets ≥ 20000/μL on 3 consecutive measurements (each occurring at least 1 day apart). The participant must not have had a platelet transfusion within 7 days prior to the first measurement.

BM aspirate and/or biopsy must be performed ≤ 30 days prior to randomization and can be repeated if necessary to meet the 30 day requirement. Aspirate is required and BM biopsy in addition is preferred. If aspirate is unobtainable (e.g., dry tap), BM biopsy is required. Once aspirate and/or biopsy confirm continued morphological CR status, participants can then proceed to randomization.

2.3.2.1. Randomization Inclusion Criteria

To be randomized, participants must meet the following criteria:

A. Participant is ≥ 30 days and ≤ 90 days from hematopoietic cell infusion.
B. Participant has achieved engraftment. Engraftment is defined as ANC ≥ 500 cells/μL and platelets ≥ 20000/μL on 3 consecutive measurements (each occurring at least 1 day apart). The participant must not have had a platelet transfusion within 7 days prior to the first measurement.

C. Participant has confirmed ongoing morphologically documented AML in CR1. For the purposes of randomization, CR1 will be defined as < 5% blasts with no morphologic characteristics of acute leukemia (e.g., Auer Rods) in the BM with no evidence of extramedullary disease such as central nervous system involvement or granulocytic sarcoma.
D. Participant meets the following criteria as indicated on the clinical laboratory tests:
   - Serum creatinine within normal range, or if serum creatinine outside normal range, then GFR > 40 mL/min/1.73m^2 as calculated with the Cockcroft-Gault equation with adjustment if total body weight is ≥ 125% of ideal body weight.
   - TBL ≤ 2.5 mg/dL, except for participants with Gilbert's syndrome.
   - Serum AST and/or ALT < 3 x institutional ULN.
   - Serum potassium and magnesium greater than or equal to the institutional lower limit of normal.
E. If the participant has developed overall grades II-IV acute GVHD, the following criteria must be met to be randomized:
   - No requirement of > 0.5 mg/kg of prednisone (or equivalent) daily dose within 1 week of randomization
   - No escalation of systemic immunosuppression in terms of increase of corticosteroids or addition of new agent/modality within 2 weeks of randomization (Note that increasing calcineurin inhibitors or sirolimus to achieve therapeutic trough levels is allowed. Topical skin and topical gastrointestinal steroids are allowed.)
F. Participant is able to take oral medication

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

2.3.2.2. Randomization Exclusion Criteria

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

A. Participant requires treatment with concomitant drugs that are strong inducers of CYP3A (APPENDIX H) within 14 days of starting study drug.
B. Participant requires treatment with concomitant drugs that target serotonin 5HT$_1$R or 5HT$_{2B}$R or sigma nonspecific receptor with the exception of drugs that are considered by the investigator to be absolutely essential for the care of the participant and for which no acceptable alternative exists (APPENDIX H).
C. Participant has a QTcF interval > 450 msec (average of triplicate determinations) by central read.
D. Participant has a need for supplemental oxygen with the exception of using previously existing non-invasive continuous positive airway pressure (CPAP) at night.
E. Participant has used investigational agents within 4 weeks of randomization.
F. Participant has used experimental therapy for acute GVHD within 4 weeks of randomization. If unsure of the definition of "experimental", discussion with the one of the protocol chairs is recommended.
G. Participant has an uncontrolled infection. If a bacterial or viral infection is present, the participant 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

participant must be receiving definitive systemic anti-fungal therapy and have no signs of progressing infection for 1 week prior to randomization.

- Progressing infection is 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.

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

2.3.3. Inclusion of Women, Minorities and Other Underrepresented Populations

The inclusion and exclusion criteria listed above should have no effect on the enrollment of these traditionally underrepresented groups in clinical studies. Accrual of women and minorities will be monitored to determine whether rates of enrollment are reflective of the distribution of potentially eligible women and minorities in the population served.

2.4. Treatment Plan

Randomization should occur anytime between days 30 to 90 after day zero (the day of allograft infusion) of HCT. BM aspirate and/or biopsy after engraftment after HCT must be done to confirm ongoing remission and must be performed ≤ 30 days prior to randomization. **Please note that the recommended window to randomize participants is between 30 to 45 days after HCT**, but the protocol allows randomization up to day +90 after HCT. Study drug should be started within 24 hours of randomization. Day 1 of the treatment period is defined as the date of randomization. Study drug will be administered on an outpatient basis but may be continued in the inpatient setting if participants require inpatient evaluation. Expected toxicities and potential risks as well as dose modifications for gilteritinib are described in Sections 2.7 and 2.8 (Dose Modifications and Participant Risks). No investigational or commercial agents or therapies other than study drug may be administered with the intent to treat the participant's malignancy.

2.4.1. Agent Administration - Gilteritinib versus Placebo

Gilteritinib or placebo is an oral tablet and participants will take 3, 40 mg tablets once daily in the morning for continuous daily dosing. Participants will be instructed to take the daily dose with water as close to the same time each morning as possible. Gilteritinib or placebo can be taken at least 2 hours after or 1 hour before consuming food. Study drug will be self-administered at home when participants are not scheduled for clinic visits. If participant is scheduled for a clinic visit, they will take their medication after the pharmacokinetic blood draw. If a participant forgets to take a dose in the morning (or their pharmacokinetic blood draw is on that day) and it is within 6 hours of the planned dosing time, he/she will be instructed to take his/her dose. If the participant forgets to take the daily dose (or their pharmacokinetic blood draw is on that day) and more than 6 hours has passed the planned dosing time, he/she will be instructed to wait for the next morning to dose. If vomiting occurs after dosing, the participant should not receive another dose, but should wait until the

next morning to dose. Missed or vomited doses will not be replaced. (Refer to Section 2.7 for information on dose modifications).

2.4.2. Duration of Therapy

Gilteritinib or placebo therapy will continue for a maximum of 24 months from randomization or until one of the following criteria applies:

- Disease relapse
- Unacceptable adverse event (AE)(s),
- Participant decides to withdraw from treatment
- Participant does not follow instructions
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the opinion of the treating investigator.
- Participant begins other anti-leukemic therapy.

If the participant discontinues treatment early, then the reason for treatment discontinuation and the date the participant was removed must be documented in the study-specific case report form (CRF). Alternative care options will be discussed with the participant. Participants removed from treatment for unacceptable AEs will be followed until resolution or stabilization of the AE.

Participants that discontinue treatment early will continue to be followed for relapse, if not yet documented, and survival.

Table 1 below further clarifies the impact of scenarios on event definitions for time-to-event analyses and action on specific events and treatment:

Table 1 Event Categorizations for Specific Scenarios

Scenario	Event for Relapse-Free Survival (primary endpoint)	Event for Event-Free Survival	Study Drug
Death	Yes	Yes	Stop
Drug discontinuation	No	Yes	Stop
Bone marrow blasts ≥ 5%	Yes	Yes	Stop
Circulating blasts	Yes	Yes	Stop
Extramedullary blast foci	Yes	Yes	Stop
Detectable disease (via cytogenetics, flow cytometry or PCR) not meeting R-IWG criteria[35] for relapse - **No clinical action taken**	No	No	Continue
Immunosuppression rapidly tapered or stopped because of detectable disease (via cytogenetics, flow cytometry or PCR), not meeting R-IWG criteria for relapse	No	No	Continue
Hypomethylating agents, chemotherapy, oral anticancer agents, DLI or cellular therapies given because of detectable disease (via cytogenetics, flow cytometry or PCR), not meeting R-IWG criteria for relapse	No	Yes	Stop
DLI given for infectious complications*	No	No	Continue
DLI given for modulation of T cell chimerism in the peri-transplant or the post-transplant period per institutional protocol is allowed.	No	No	Continue

DLI: donor lymphocytic infusion; PCR: polymerase chain reaction; RFS: relapse-free survival; R-IWG: Revised International Working Group

*DLI given for modulation of T cell chimerism in the peri-transplant or the post-transplant period per institutional protocol is allowed.

2.4.3. Duration of Follow-Up

Participants will return to the clinic for study visits while on study drug for up to 2 years. After study drug is discontinued, participants will be followed for relapse and survival for 5 years from the time of randomization of the last participant or until 80% of RFS events have occurred. For an individual participant, this may be between 3 to 7 years of follow-up depending on when they start and stop study drug.

2.4.4. Criteria for Removal from Study

Participants will be withdrawn from study drug when any of the criteria listed in Section 2.4.2 applies. Participants who complete 24 months of study drug and those who discontinue study drug early will continue to be followed for survival and other outcomes until one of the following criteria is met:

- Participant decides to withdraw consent for further follow-up on survival and other outcomes.
- Participant is lost to follow-up despite reasonable efforts by the investigator to locate the participant.

- 5 years have passed from the last participant randomized.
- 80% of RFS events have occurred.
- Death.

The reason for study removal and the date the participant was removed must be documented in the study-specific CRF.

2.5. Graft-versus-host Disease (GVHD) during Therapy

If a participant develops new onset GVHD, or experiences an increase in the severity of pre-existing GVHD requiring an escalation of immunosuppressive medication, every effort should be made to continue the study drug without any dose reduction. If the participant is unable to take oral medications as a result of GVHD, the study drug can be withheld until the participant is able to resume oral medications.

2.5.1. Management of Acute GVHD

Acute GVHD should be managed per institutional guidelines. Therapies considered standard are allowed and use of investigational therapy while on study drug is prohibited. Discussion with one of the protocol chairs is recommended if uncertainty exists.

2.5.2. Management of Chronic GVHD

Chronic GVHD should be managed per institutional guidelines. Therapies considered standard are allowed and use of investigational therapy while on treatment is prohibited. Discussion with one of the protocol chairs is recommended if uncertainty exists.

2.6. General Concomitant Medication and Supportive Care Guidelines

All medications and concomitant treatments administered from 7 days prior to treatment day 1 through the end of treatment visit must be recorded in the electronic case report form (eCRF).

2.6.1. Antimicrobials

Antibacterial, antiviral and antifungal prophylaxis during and after allogeneic HCT are recommended and can be administered based on local institutional guidelines.

2.6.2. Tapering of GVHD Prophylaxis

Institutional practice should be followed for tapering immunosuppressive therapy in the absence of GVHD. There are no formal recommendations given that participants receiving HCT from any type of donor, after any conditioning and receiving any GVHD prophylaxis regimen are eligible.

2.6.3. Donor Lymphocyte Infusions

Pre-emptive/prophylactic administration of donor lymphocytes for disease progression is not permitted in this protocol. DLI for infectious complications is allowed. DLI given for modulation of T cell chimerism in the peri-transplant or the post-transplant period per institutional protocol is allowed.

2.6.4. Prohibited Therapy

Concomitant use of other anti-cancer therapies, other anti-AML maintenance, or investigational agents is not permitted while participants are receiving study drug during the treatment phase of the study. Participation in another interventional study while on treatment is prohibited. Treatment with concomitant drugs that are strong inducers of CYP3A within 14 days of start of study drug are prohibited. These are listed in Table 2 below:

Table 2 Strong CYP3A Inducers

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

CYP: cytochrome P450

2.6.5. Other Concomitant Treatment (Medication and Non-medication Therapy)

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 should be avoided with the exception of drugs that are considered absolutely essential for the care of the participant. 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, participants should be closely monitored for AEs.

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

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

Common strong CYP3A inhibitors, strong CYP3A inducers, drugs targeting the serotonin receptor, P-gp inhibitors or inducers, and drugs known to prolong QT or QTc intervals are listed in APPENDIX H. The investigator should consult individual labels for all drugs that the participant is taking to evaluate if they fall into any of the above named categories.

Participants undergoing allogeneic transplantation are expected to be receiving treatment with a number of approved drugs that are known to be CYP3A substrates and/or inhibitors. Because gilteritinib is also a CYP3A4 substrate, drug-drug interactions between the study drug and conventional agents (e.g., azoles) are anticipated. Participating centers will adhere to institutional practice regarding the monitoring of serum levels of immunosuppressive agents such as tacrolimus or azoles. Regardless of which concomitant medications are administered, there will be no dose modification of gilteritinib in the absence of drug-related toxicity.

2.7. Dose Modifications

All AEs occurring after randomization will be reported and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The study drug will be interrupted if a grade 3 or greater AE occurs and the local principal investigator judges that AE to be possibly, probably or definitely related to the study drug. When the grade of AE decreases to baseline or grade ≤ 1, the study drug may be resumed at the next lower dose level, unless the local investigator deems the AE was, in retrospect, unlikely to be or 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 local investigator. Guidelines for dose interruption and reduction are provided in Table 3.

Table 3 Guidelines for Dose Reduction 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 baseline or grade ≤ 1. The participant may then resume with one dose level reduction (to 80 mg or if currently at 80 mg to 40 mg per day). If participant is at 40 mg per day at the time of the event, then study drug will be discontinued. Resumption at original dose level permitted as detailed in Section 2.7.
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 baseline or grade ≤1. The participant may resume treatment at 40 mg per day. If participant is at 40 mg per day at the time of the event, then study drug will be discontinued.
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.
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 the 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, the participant may resume dosing at the reduced dose of 80 mg (or if currently at 80 mg, reduction to 40 mg).
Table continued on next page	

Event	Action
QTcF day 8 increase > 30 ms	If the mean triplicate QTcF on day 8 has increased > 30 ms compared to the mean triplicate QTcF of the pre-randomization ECG 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 the pre-randomization ECG, then dose reduction by 1 dose level should be considered.

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

2.8. Participant Risks

2.8.1. Therapy Toxicities

Please refer to the current ASP2215 Investigators Brochure for details on therapy toxicities.

2.9. Study Drug Supply

2.9.1. Gilteritinib

Gilteritinib is an oral drug that is available in a 40 mg tablet. In addition to the active ingredient, gilteritinib 40 mg tablets contain well-characterized excipients. Gilteritinib tablets are round light-yellow film-coated tablets. Refer to the current ASP2215 Investigator's Brochure for further details.

2.9.2. Placebo

Placebo tablets are identical in size and appearance to gilteritinib tablets and contain well-characterized excipients. Refer to the current ASP2215 Investigator's Brochure for further details.

2.9.3. Packaging and Labeling

All study drug used in this study will be prepared, packaged, and labeled under the responsibility of qualified staff at Astellas Pharma Global Development (APGD)-Astellas US Technology (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) 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 which identifies the contents as investigational drug. Temperature logs must be maintained by the site with the storage temperatures recorded daily (at minimum). Study centers will be provided bottles containing blinded study drug (gilteritinib or placebo). Refer to the current Pharmacy Manual for further details on storage.

2.9.4. 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:

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

Study drug inventory and accountability records for the study drugs will be kept by the investigator, or designee. Study drug accountability throughout the study must be documented and reconciled.

The following guidelines are therefore pertinent:

- The investigator agrees not to supply study drugs to any persons except the eligible participants in this study in accordance with the protocol.
- The investigator or designee will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these study drugs.
- A study drug inventory will be maintained by the investigator or designee. The inventory will include details of material received and a clear record of when they were dispensed and to which participant.
- At the conclusion or termination of this study, the investigator or designee agrees to conduct a final drug supply inventory and to record the results of this inventory on the drug accountability record. It must be possible to reconcile delivery records with those of used and/or returned study drug. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility.
- The site must return study drug to the Sponsor or designee (after reconciliation by the site monitor) at the end of the study or upon expiration. In rare cases, study drug may be destroyed at the study site only if agreed upon by the Sponsor. A copy of the standard institutional procedure for destroying investigational drugs will be provided to the sponsor or designee upon request.

The following paragraph is specific to investigational sites in 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.

2.9.5. Blinding

This is a double-blind study. Participants 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 participant will know which agent is being administered. The randomization number will be assigned based on information obtained from the Interactive Response Technology (IRT) system and Advantage eClinical^{SM}.

2.9.6. Retention of the Assignment Schedule

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

The Data Safety Monitoring Board (DSMB) will be provided access to the dosing assignment for periodic review of the unblinded data as documented in the DSMB Charter and the study-specific DSMB Charter Addendum.

2.9.7. Breaking the Treatment Code by the Sponsor

The Sponsor may break the treatment code for participants 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 for breaking the codes for all SUSAR cases for reporting purposes.

The treatment code for each randomized participant will be provided by the IRT in the event of medical emergency requiring knowledge of the treatment assigned to the participant. The time, date, participant 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 participants or other study personnel will be made aware of the treatment given to any participant 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.

- 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.

CHAPTER 3

3. STUDY ENDPOINTS

3.1. Primary Endpoint

The primary endpoint of this study is RFS. RFS will be measured from time of randomization to either leukemia relapse or death, whichever comes first. **Leukemia relapse will be defined as BM blasts 5% or higher (not attributable to regenerating BM), any circulating blasts (not attributable to regenerating BM or growth factors), or any extra-medullary blast foci as per Revised International Working Group (R-IWG) criteria.** Documentation to support relapse diagnosis must be submitted to the Blinded Endpoint Adjudication Committee. Relapse documentation will be dependent on the type of relapse and may include but is not limited to: bone marrow biopsy reports, flow cytometry reports, tissue biopsy reports, and cerebrospinal fluid analysis reports.

RFS (or leukemia-free survival; LFS) is the best predictor of both OS for AML patients who are in remission and/or have undergone allogeneic transplant. A tight correlation between LFS and OS has been demonstrated to exist in AML patients treated with maintenance therapy,[28] and a strong association between relapse after transplant and poor survival is well-established in the literature.[29][30][31] RFS is particularly relevant for the participants in this study, as the presence of a FLT3/ITD mutation at relapse is one of the worst prognostic features in AML. Greater than 80% of patients who relapse after allogeneic transplant do so within 2 years of transplant.[31] Specifically, relapses among transplanted FLT3/ITD+ patients generally occur early in post-transplant course; from European Society for Blood and Marrow Transplantation (EBMT) and CIBMTR data, their incidence after 2 years of follow-up in this group is rare.[32]

The absence of relapse is also important for maintaining quality of life. At relapse after transplant, the majority of patients undergo intensive therapy, which entails considerable morbidity, is largely ineffective to generate durable leukemic control, and is not uncommonly fatal due to toxicity.[31] Investigational use of FLT3 inhibitors, as well as off-label use of sorafenib, is increasingly used in the place of traditional cytotoxic agents to treat post-transplant FLT3/ITD+ AML relapse. While available data show this approach to treat overt relapse has clinical activity and generally limited toxicity, the durability of both disease- and symptom-control is modest, which remains a concern. Whether FLT3 inhibitors therapy of clinical relapse extends OS beyond that achieved with standard chemotherapy is to date unproven. As well, rigorous quality of life comparisons among participants randomized to FLT3 inhibitors and traditional chemotherapy approaches have not yet been performed.

Overall, it is expected that survival of participants who relapse after treatment on this protocol will be poor, regardless of whether they receive cytotoxic agents, FLT3 inhibitors, and/or cellular therapies such as DLIs. The vast majority of AML patients who relapse after transplant either die of their disease or die during attempts to re-achieve subsequent remissions. RFS therefore remains the single most important endpoint in a trial of post-

transplant AML patients in remission, as it correlates with both prolongation of survival and with quality of life after transplant.

3.2. Secondary Endpoints

3.2.1. Safety and Tolerability of Gilteritinib after HCT

All grade ≥ 3 toxicities according to CTCAE version 4.03 will be tabulated for each treatment arm. The proportion of participants developing grade ≥ 3 AEs across treatment arms will be compared. In addition, the incidence of all grade 1 to 4 toxicities according to CTCAE version 4.03 will be tabulated for each treatment arm and compared. Clinical laboratory evaluations and change from baseline will be described and compared. Electrocardiogram (ECG) results and change from baseline will be described and compared. Karnofsky Performance Status scores will be described and compared. The duration of drug use and dose of drug use will also be compared.

3.2.2. Overall Survival (OS)

Time to OS is defined as the time to death from any cause after randomization. For surviving participants, non-events will be censored at the last known alive date.

3.2.3. Non-relapse Mortality

An event for this endpoint is death without evidence of disease progression or recurrence.

3.2.4. Event-free Survival (EFS)

The cumulative incidence at 12 months and 24 months after randomization of EFS will be described and compared. Events for EFS are as defined in Section 2.4.2.

3.2.5. Cumulative Incidence of Acute GVHD

The cumulative incidence at 6 months after randomization of grades II-IV and grades III-IV acute GVHD will be described and compared. Acute GVHD will be graded according to diagnosis and severity scoring used by the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) (APPENDIX I).

3.2.6. Cumulative Incidence of Chronic GVHD

The cumulative incidence at 12 months and 24 months after randomization of chronic GVHD will be described and compared. Chronic GVHD will be graded according to diagnosis and severity scoring from the NIH 2014 Consensus Criteria (APPENDIX I).

3.2.7. Detection of Minimal Residual Disease (MRD)

The cumulative incidence of detection of FLT3/ITD MRD in participants who are FLT3/ITD MRD undetectable prior to randomization will be described. Similarly, the pattern of eradication of FLT3/ITD MRD in participants who have detectable FLT3/ITD MRD prior to randomization will be described.

3.2.8. Incidence and Severity of Infection

The cumulative incidence of CTCAE grades 3 to 5 infection in participants will be described and compared.

3.3. Exploratory Endpoints

3.3.1. Health-related Quality of Life

The Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) version 4.0 instrument is comprised of a general core questionnaire, the Functional Assessment of Cancer Therapy-General (FACT-G), which evaluates the HQL of participants receiving treatment for cancer, and a transplant-specific module, bone marrow transplant (BMT) Concerns, that addresses disease and treatment-related questions specific to BMT. The FACT-G consists of four subscales developed and normed in cancer participants: Physical Well-being, Social/Family Well-being, Emotional Well-being, and Functional Well-being. Each subscale is positively scored, with higher scores indicating better functioning. The FACT-BMT Total, which is the grand total of all items in the FACT-G and BMT modules, will be used as the outcome measure in summarizing the FACT-BMT data.

The Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu) is a modular approach to assess patient HQL and leukemia-specific symptoms using a 'core' set of questions (FACT-G), as well as a cancer site-specific leukemia subscale.[33,34] The FACT-G will be administered as part of the FACT-BMT and it will not be repeated in the FACT-Leu. Only the leukemia-specific subscale consisting of 17 items that assess patient concerns relating to leukemia (FACT-Leu) will be administered. Higher scores are reflective of better HQL. The FACT-Leu total score (score range: 0-176; combining FACT-Leu with the FACT-G scores from the FACT-BMT) will be used in analysis.

The EuroQol Group-5 Dimension-5 Level (EQ-5D-5L) is a self-reported questionnaire. The EQ-5D-5L is being used as a measure of respondents' HQL. 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 HQL.

HQL will be described from pre-transplant to last follow-up at 24 months after randomization. Additionally, HQL will be compared between the maintenance arms utilizing the FACT-BMT self-report, transplant-specific questionnaire, FACT-Leu, and the EQ-5D-5L. The questionnaires will be scored according to standard procedures. The self-report questionnaires will be completed prior to transplant, prior to randomization, on day 29, and at months 3, 6, 12, 18, and 24 after randomization. Comparisons of quality of life will be done between maintenance arms at each of the time points after randomization.

3.3.2. Resource Utilization

Resource utilization will be assessed from randomization through end of treatment and will include hospitalization or emergency department visits (duration, underlying reasons, and setting specified: general ward, ICU, etc.), antibiotic use, and medication for AEs.

3.3.3. Rate of Non-randomization

The proportion of participants and reason for not achieving randomization 90 days post allogeneic HCT will be described.

3.3.4. Gilteritinib Pharmacokinetics

Gilteritinib concentrations will be measured at specified time points and used to perform population pharmacokinetic analysis.

3.3.5. FLT3 Mutation Status at Relapse

FLT3 mutation(s) will be assessed from BM aspirates or blood samples obtained at time of relapse.

3.3.6. FLT3/ITD Allelic Frequencies

FLT3/ITD allelic frequencies will be analyzed using the diagnostic specimens when available.

3.3.7. Correlative Studies

The presence or absence of additional AML-associated genomic and/or other biomarkers that may correlate to treatment outcome may be analyzed using the BM samples from diagnosis, during treatment, and the blood or BM samples from the time of relapse. Correlative analyses with other trial endpoints may be performed. In addition, future studies may be performed using the samples.

CHAPTER 4

4. PARTICIPANT REGISTRATION, ENROLLMENT AND EVALUATION

4.1. Approaching Participants, Eligibility Screening and Obtaining Consent

Potential participants will be approached for this study after the decision to proceed with transplantation is made and a suitable donor is identified. The principal investigator or designee at each study site will evaluate participant eligibility. Informed consent will be obtained via a signature on the IRB or IEC approved consent form prior to performing study specific procedures and within 84 days before the start of the pre-transplant conditioning regimen. Once the participant has provided and signed consent, the participant will be enrolled in the screening segment of Advantage eClinical and assigned a participant identification number. After consent, a BM aspirate and biopsy will be obtained. The pre-transplant conditioning regimen must begin ≤ 30 days after this biopsy. The first 2 cc of BM aspirate will be collected and sent to the central laboratory for assessment of MRD. The remainder of the aspirate and the core biopsy will be used to confirm ongoing remission prior to transplant. Aspirate is required and BM biopsy in addition is preferred. If aspirate is unobtainable (e.g., dry tap), BM biopsy is required. Once CR and other eligibility criteria (per Section 2.3.1.1) are confirmed, the participant will be registered through the Advantage eClinical system.

4.2. Determination of Eligibility for Randomization

Beginning on day 30 and no later than day 90 after the first infusion of hematopoietic cells, the study site principal investigator or designee will determine if the participant is eligible to begin the study drug per criteria in Section 2.3.2. The recommendation is for participants to start as soon as medically able after HCT with a recommended window of randomization at days 30 to 45 after HCT. Also note that a repeat BM aspirate and biopsy is required after engraftment to ensure that the participant remains in CR. If eligibility is confirmed, the participant is randomized and begins study drug within 24 hours of randomization.

4.3. Randomization Procedure

Participants will be randomized using the IRT system. Upon successful completion of the enrollment form, the confirmation of randomization will be displayed.

Participants will be stratified by: 1) conditioning regimen intensity (myeloablative vs reduced intensity/non-myeloablative), 2) time from day 0 of HCT to randomization (30-60 days vs 61-90 days), and 3) presence or absence of or unknown MRD on pre-HCT BM aspirate (most recent aspirate should be used). Conditioning regimen intensity is defined using the CIBMTR Guidelines[36] (APPENDIX L). The conditioning regimen used for stratification may be adjudicated by the protocol chairs and protocol officer according to the Conditioning Regimen Adjudication Charter or the regimen does not appear in APPENDIX L or follow its guidance.

4.4. Participant Evaluations

4.4.1. Pre-transplant Evaluations and Requirements

The following observations will be made ≤ **30 days before initiating the pre-transplant conditioning regimen and prior to registration: (unless otherwise specified).**

1. Medical and Disease History (including documented FLT3/ITD mutation positive status from original diagnosis)
2. Physical examination, including vital signs (blood pressure), height and weight
3. Karnofsky performance status score (APPENDIX F)
4. HCT-specific Comorbidity Index score (APPENDIX G)
5. CBC and white blood cell count (WBC) with differential. CBC includes hemoglobin, hematocrit and platelets. WBC with differential includes relative and ANCs, relative and absolute lymphocyte counts and blasts
6. Liver functions and blood chemistries: sodium, potassium, chloride, bicarbonate, albumin, blood urea and/or blood urea nitrogen, glucose, serum creatinine, magnesium, phosphate, calcium, TBL, alkaline phosphatase (ALP), AST, ALT and CK. The corrected calcium will be calculated in the CRF
7. Thyroid function: thyroid stimulating hormone (TSH) and free thyroxine (T_4)
8. Estimated creatinine clearance, using the Cockcroft-Gault formula and actual body weight
9. Infectious disease markers (may be performed ≤ 42 days before the start of the pre-transplant conditioning regimen): cytomegalovirus (CMV) antibody, Hepatitis panel (HepB surface antigen, HepB core antibody, HepC antibody). Additional markers may be performed according to local standard. If any of the hepatitis B tests are positive, then a hepatitis B virus (HBV) DNA test is required
10. ECG (may be performed ≤ 42 days before the start of the pre-transplant conditioning regimen). 12-lead ECGs will be recorded in triplicate (3 separate ECGs, 10 minutes resting prior to first ECG and at least 5 minutes apart per time point) and transmitted electronically for central reading. The mean QTcF of the triplicate ECG tracings from central read must be used for eligibility, all final treatment decisions and AE reporting.
11. Echocardiogram or multigated acquisition scan (as per standard of care) for LVEF (may be performed ≤ 84 days before the start of the pre-transplant conditioning regimen)
12. Pulmonary function tests, including DLCO and/or FEV1 (may be performed ≤ 84 days before the start of the pre-transplant conditioning regimen)
13. Pregnancy test (serum hCG) for women of childbearing potential as defined in Section 2.3.1.1 (must be performed ≤ 7 days prior to the start of the pre-transplant conditioning regimen)
14. HQL assessments (FACT-BMT, FACT-Leu and EQ-5D-5L)

4.4.2. Pre-transplant Bone Marrow Aspirate and Biopsy

After the participant signs consent and prior to registration, a BM aspiration and/or biopsy is performed in order to:

1. Obtain first 2 cc of BM aspirate sample for analysis of MRD
2. Obtain 5 cc (or per institutional requirement) BM aspirate and/or biopsy to confirm CR. Aspirate is required and BM biopsy in addition is preferred. If aspirate is unobtainable (e.g., dry tap), BM biopsy is required.

The BM aspirate and/or biopsy are to be performed ≤ 30 days prior to the start of the pre-transplant conditioning regimen. Details on the MRD laboratory sample collection will be detailed in the Laboratory Manual(s).

Once this BM biopsy confirms CR and all other eligibility is confirmed, the participant can be registered.

4.4.3. Evaluations after Transplant and Prior to Randomization

The following evaluations to determine eligibility for randomization to maintenance therapy or establish baseline at randomization, will be done after engraftment and **≤ 14 days prior to randomization (unless otherwise specified).**

1. Medical and Disease History. Details on conditioning regimen, HCT, and engraftment will also be collected.
2. Physical examination, including vital signs (blood pressure), and weight
3. Triplicate ECG. Central read for ECG is used for eligibility. It is advised that the ECG is scheduled at least 3 days prior to the planned randomization date.
4. Karnofsky performance status score (APPENDIX F)
5. CBC and WBC with differential. CBC includes hemoglobin, hematocrit and platelets. WBC with differential includes relative and ANCs, relative and absolute lymphocyte counts and blasts.
6. Liver functions and blood chemistries: sodium, potassium, chloride, bicarbonate, albumin, blood urea and/or blood urea nitrogen, glucose, serum creatinine, magnesium, phosphate, calcium, TBL, ALP, AST, ALT and CK
7. Thyroid function: TSH and T_4
8. Pregnancy test (serum hCG) for women of childbearing potential as defined in Section 2.3.1.1 (must be ≤ 72 hours before randomization)
9. BM evaluation: BM aspirate for MRD and BM aspirate and/or biopsy for confirmation of CR (may be completed ≤ 30 days before randomization). For confirmation of CR, aspirate is required and BM biopsy in addition is preferred. If aspirate is unobtainable (e.g., dry tap), a BM biopsy is required.
10. Formal assessment of acute and chronic GVHD (APPENDIX I)

11. Infection assessment
12. Concomitant medication review
13. HQL (FACT-BMT, FACT-Leu and EQ-5D-5L)

4.4.4. Evaluations during Treatment

Upon initiation of study drug, weekly laboratory monitoring, toxicity assessment and GVHD assessment is required for the first 4 weeks. Monitoring and assessment is then required once every month for the following 5 months of treatment and then once every 2 months for the second 6 months of treatment, and then every 3 months for the second year of treatment. Unscheduled visits and laboratory monitoring may occur as needed. Participants who discontinue treatment early will have assessments performed according to the month 24 visit, with the exception of BM aspiration and/or biopsy, which will continue to be performed according to institutional standard of care through first relapse. If a participant discontinues for relapse, an End of Treatment (EOT) MRD sample is not required.

The following required observations are performed after initiation of maintenance therapy. **These evaluations will occur at all study visits (unless otherwise specified)**. Please also refer to Table 4.

1. Physical examination including vital signs (blood pressure) and weight
2. Triplicate ECG. If the mean triplicate QTcF on day 8 has increased > 30 ms compared to the mean triplicate QTcF of the pre-randomization ECG with no other known etiology, then a confirmatory ECG will be performed on day 9. If the day 9 mean triplicate QTcF also shows an increase of > 30 ms compared to that of the pre-randomization ECG, then dose reduction by 1 dose level should be considered.
3. Karnofsky performance status score (APPENDIX F)
4. CBC and WBC with differential. CBC includes hemoglobin, hematocrit and platelets. WBC with differential includes relative and ANCs, relative and absolute lymphocyte counts and blasts.
5. Liver functions and blood chemistries: sodium, potassium, chloride, bicarbonate, albumin, blood urea and/or blood urea nitrogen, glucose, serum creatinine, magnesium, phosphate, calcium, TBL, ALP, AST, ALT and CK. The corrected calcium will be calculated in the eCRF.
6. Thyroid function: TSH and T_4
7. Pregnancy test (serum hCG) for women of childbearing potential to be performed
8. BM evaluation: a BM aspirate for MRD and a BM aspirate and/or biopsy for disease evaluation. For disease evaluation, a BM aspirate is required and BM biopsy in addition is preferred. If aspirate is unobtainable (e.g., dry tap), a BM biopsy is required. An MRD sample is not required at EOT if a participant discontinues treatment due to relapse. Documentation to support relapse diagnosis must be submitted to the Blinded Endpoint Adjudication Committee. Relapse documentation will be dependent on the type of relapse and may include but is not limited to: bone marrow biopsy reports, flow cytometry reports, tissue biopsy reports, and cerebrospinal fluid analysis reports. BM will be collected at the following time points after randomization:

a. 3 months ± 1 week
b. 6 months ± 1 week
c. 12 months ± 2 weeks
d. 18 months ± 4 weeks
e. 24 months ± 4 weeks

9. AE/serious adverse event (SAE) assessment
10. Symptom-driven acute and chronic GVHD assessment. Information on acute and chronic GVHD will be collected at all study visits.
11. Infection assessment
12. Concomitant medication review
13. HQL (FACT-BMT, FACT-Leu and EQ-5D-5L) at day 29, and at 3, 6, 12, 18 and 24 months after randomization
14. Resource Utilization: Beginning at randomization through EOT details on antibiotic use, medications used for AEs, hospitalizations and emergency department visits will be collected.
15. Pharmacokinetic samples for gilteritinib will be collected on treatment day 8 predose, day 15 predose, day 29 predose and predose at every subsequent treatment visit in the ongoing treatment period (within 0.5 hour before drug administration). Details on laboratory sample collection will be detailed in the Laboratory Manual.
16. If disease recurs, a sample of PB or BM aspirate, whichever is available, should be sent to the reference lab for detection of FLT3 mutations as detailed in the Laboratory Manual. Information on subsequent AML therapies will be collected.

4.4.5. Evaluations after Treatment

Participants who complete treatment, or who discontinue early from treatment, will continue to be followed for relapse (if not yet occurred) and survival assessments. A 30-day follow-up (+ 7 days) will be conducted for safety follow-up. Additional contacts may be required for data sweeps. The following observations are required after study drug has been discontinued.

1. Safety follow-up at the 30-day follow-up only.
2. Disease evaluation according to institutional standard of care until relapse. If disease recurs, a sample of PB or BM aspirate, whichever is available, should be sent to the reference lab for detection for FLT3 mutations as detailed in the Laboratory Manual. Information on first disease relapse including laboratory results and reports will be collected. Documentation to support relapse diagnosis must be submitted to the Blinded Endpoint Adjudication Committee. Relapse documentation will be dependent on the type of relapse and may include but is not limited to the following: bone marrow biopsy reports, flow cytometry reports, tissue biopsy reports, and cerebrospinal fluid analysis reports. Information on subsequent AML therapies will be collected.
3. Survival Contact - every 3 months (± 2 weeks) after EOT for up to 5 years after the last participant is randomized or when 80% of RFS events, whichever occurs first.

Table 4 Schedule of Assessments

	Pre-HCT		HCT	Treatment Period															Follow-up	
HCT Day	D-42 to conditionin	D-30 to conditionin	0	After Engraftment																
Treatment Day/Month				Day -14 to RAND[a]	D1	D8	D15	D22	D29	M2	M3	M4, M5	M6	M8, M10	M12	M15	M18	M21	M24/ EOT [b]	30D FU	Q3M FU
Informed Consent [c]	X																			
Medical and Disease History [d]		X		X																
Randomization in IRT					X[a]															
Physical Examination		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Karnofsky PSS		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HCT-specific Comorbidity Index		X																		
Infectious Disease markers [e]	X																			
CBC and WBC with differential, LFTs and chemistries, thyroid function tests [f]		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test (serum hCG) for WOCBP [g]		X [g]		X [g]					X	X	X	X	X	X	X	X	X	X	X	
BM Aspiration for MRD		X		X [h]							X		X		X		X		X	
BM Aspiration and/or Biopsy [i]		X		X [h]							X[p]		X[p]		X[p]		X[p]		X[p]	
Triplicate 12-lead ECG [j]	X			X [j]		X [k]	X	X	X	X	X	X	X	X	X	X	X	X	X	
MUGA or Echocardiogram	X [l]																			
Pulmonary Function Tests: FEV1 and/or DLCO	X [l]																			

Table continued on next page

	Pre-HCT		HCT	Treatment Period															Follow-up	
HCT Day	D-42 to conditionin	D-30 to conditionin	0	After Engraftment																
Treatment Day/Month				Day -14 to RAND[a]	D1	D8	D15	D22	D29	M2	M3	M4, M5	M6	M8, M10	M12	M15	M18	M21	M24/ EOT [b]	30D FU	Q3M FU
AE/SAE Assessment [m]				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Acute GVHD assessment				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chronic GVHD assessment				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Infection Assessment				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Health-related QOL [n]		X		X					X		X		X		X		X		X		
Resource Utilization						X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Pharmacokinetic sample collection [o]						X	X		X	X	X	X	X	X	X	X	X	X	X		
Study Drug Administration in the Clinic					X	X	X		X	X	X	X	X	X	X	X	X	X	X		
Collection of Samples from First Relapse																			X[p]	X[p]	X[p]
Contact for Relapse and Survival																					X[p]

Abbreviations: Ab: antibody; AE: adverse event; BM: bone marrow; CBC: complete blood count; CMV: cytomegalovirus; D: Day; DLCO: diffusion capacity of lung for carbon monoxide; ECG: electrocardiogram; Echo: echocardiogram; EOT: End of Treatment; FEV1: forced expiratory volume in 1 second; FU: follow-up; GVHD: graft-versus-host disease; HBV: hepatitis B virus; hCG: human chorionic gonadotropin; HCT: hematopoietic cell transplant; HepB: hepatitis B; HepC: hepatitis C; LFT: liver function test; M: month; MRD: minimal residual disease; MUGA: multigated acquisition scan; PFT: pulmonary function test; PSS: performance status score; QOL: quality of life; QTcF: Fridericia-corrected QT interval; RAND: randomization; SAE: serious adverse event; sAg: surface antigen; T_4: free thyroxine; TFT: thyroid function test; TSH: thyroid stimulating hormone; WBC: white blood cell count; WOCBP: women of childbearing potential

Footnotes continued on next page

Footnotes:

a. Randomization to occur 30 – 90 days after start date of HCT. Day 1 of the treatment period is defined as the date of randomization. Study drug should begin within 24 hours of randomization

b. Participants who discontinue treatment early will have assessments performed according to the month 24 visit, with the exception of BM aspirate and/or biopsy, which will continue to be performed according to the time points in Section 4.4.4 through relapse. An EOT MRD sample is not required if the participant discontinues treatment due to relapse.

c. Informed consent must be obtained within 84 days prior to the start of the pre-transplant conditioning regimen.

d. Results of FLT3 mutation local testing do not affect eligibility at this time point as participants will be in CR. The documentation of an FLT3-ITD mutation in the past will satisfy eligibility criteria. Additionally, medical history will include any abnormality that occurs until randomization.

e. Infectious disease markers to include CMV Ab, HepB sAg, HepB Core Ab, HepC Ab. Additional markers may be performed per local standard. If any of the HepB tests is positive, then an HBV DNA test is required.

f. CBC includes hemoglobin, hematocrit and platelets. WBC with differential includes relative and ANCs, relative and absolute lymphocyte counts and blasts. Serum chemistry includes sodium, potassium, chloride, bicarbonate, albumin, blood urea and/or blood urea nitrogen, creatinine, glucose, calcium, phosphate, magnesium, and creatine kinase. Liver function tests include AST, ALT, ALP and total bilirubin. TFTs include TSH and T_4. The corrected calcium will be calculated in the CRF.

g. WOCBP must have a negative serum pregnancy test. Pre-registration pregnancy test must be performed ≤ 7 days prior to the start of the pre-transplant conditioning regimen and within 72 hours of randomization.

h. Pre-randomization BM aspirate may be performed ≤ 30 days prior to randomization.

i. Aspirate is required and BM biopsy in addition is preferred. If aspirate is unobtainable (e.g., dry tap), a BM biopsy is required.

j. 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). The mean QTcF of the triplicate ECG tracings based on central reading will be used for eligibility, all final treatment decisions and AE reporting. It is advised that the ECG be scheduled at least 3 days prior to the planned randomization date.

k. If the mean triplicate QTcF on day 8 has increased > 30 ms compared to the mean triplicate QTcF of the pre-randomization ECG with no other known etiology, then a confirmatory ECG will be performed on day 9. If the day 9 mean triplicate QTcF also shows an increase of > 30 ms compared to that of the pre-randomization ECG, then dose reduction by 1 dose level should be considered.

l. PFTs and MUGA or Echo may be performed up to 84 days prior to the start of the pre-transplant conditioning regimen.

m. AEs and SAEs will be collected from the time of randomization through 30 days after the last dose of study drug. In addition, investigators should report any SAE that occurs after consent and prior to randomization that is assessed as related to invasive study-related procedures apart from the HCT, as well as any SAEs assessed as related to study drug that happen after the 30-day follow-up period.

n. Health-related quality of life questionnaires include FACT-BMT, FACT-Leu and EQ-5D-5L.

o. Pharmacokinetic samples for gilteritinib will be collected within 0.5 hours before drug administration.

p. Documentation to support relapse diagnosis must be submitted to the Blinded Endpoint Adjudication Committee. Relapse documentation will be dependent on the type of relapse and may include but is not limited to: bone marrow biopsy reports, flow cytometry reports, tissue biopsy reports, and cerebrospinal fluid analysis reports.

Footnotes continued on next page

Please note the following allowed windows for visits/assessments listed in the table above:
Day 8, 15, 22 and 29: ± 1 business day
Months 2-6: ± 1 week
Months 8, 10, 12 are ± 2 weeks
Months 15, 18, 21, 24: ± 4 weeks
30-day follow-up: + 7 days
Every 3 months follow-up: ± 2 weeks
The monthly visits refer to the end of each month – i.e., Month 2 occurs at the end of the 2nd month of treatment, etc.

4.4.6. Evaluations for Non-Randomized Participants

For participants who registered, but are not randomized, the reason for not proceeding to randomization will be recorded in Advantage eClinical.

4.4.7. Evaluations for Participants who are Randomized but do not Start Study Drug

Participants who are randomized but do not start therapy must only be followed for relapse and survival according to the long-term follow-up instructions in Table 4.

4.5. Data Reporting

4.5.1. Criteria for Forms Submission

Forms that are not entered into Advantage eClinical within the specified time will be considered delinquent. A missing form will be requested either until the form is entered into the Advantage eClinical and integrated into the Data Coordinating Center's (DCC) master database, or until an exception is granted and entered into the Missing Form Exception File.

4.5.2. Reporting Participant Death

If a participant death occurs during the SAE collection period (see Section 4.6), information must be entered into Advantage eClinical within 24 hours of knowledge of the participant's death. If a participant death occurs during the long-term follow-up period, information must be entered into Advantage eClinical according to the standard entry timelines. If the cause of death is unknown at that time, it does not need to be recorded at that time. However, once the cause of death is determined, the form must be updated in Advantage eClinical.

4.6. AE Reporting

AE reporting requirements are summarized below and further information regarding AEs is described in APPENDIX K. AEs and SAEs will be collected from the time of randomization through 30 days after the last dose of study drug. In addition, investigators should report any SAE that occurs after consent and prior to randomization that is assessed as related to invasive study-related procedures apart from the HCT, as well as any SAEs assessed as related to study drug that happens after the 30 day follow-up period. All AEs are to be followed up until resolved, judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized.

4.6.1. Definition of AEs

An AE is defined as any untoward medical occurrence in a participant 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.

GVHD and infection are collected on separate CRFs because they are separate endpoints. Events of GVHD and infection are not to be reported as AEs for this study unless they meet one of the following:

- Meet one or more of the SAE criteria in Section 4.6.2 and be related to study drug
- Result in death between the first dose of study medication through 30 days after the last dose of study drug (inclusive), regardless of relationship to study drug.

Some countries may have additional local requirements for reporting events 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 reported via the web-based electronic data capture system, Advantage eClinical accordingly.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical exam) 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.

See APPENDIX J for detailed information on monitoring and assessment of liver abnormalities.

4.6.2. Definition of SAEs

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

- Death
- Is life threatening (an AE is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death)
- Persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly or birth defect
- Requires 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 that may not be immediately life-threatening or result in death/hospitalization, but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations. These events, including those that may result in

disability/incapacity, should also be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of drug dependency or drug abuse.

For this study, GVHD and infection are only to be reported as SAEs if one of the following conditions is met: 1) the event is both related to study drug and also meets the definition of SAEs above, or 2) the event results in death that occurs within 30 days after the last dose of study drug.

AML relapse will not be reported as an AE/SAE term unless it is the cause of a death that occurs between the first day of study drug though 30 days after the last dose of study drug (inclusive).

Special situations related to the medicinal products administered to the participant as part of the study (e.g., study drug) 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)
- Occupational exposure to the medicinal product(s)
- Medication error involving the medicinal product(s) (with or without participant exposure to the Sponsor medicinal product, e.g., name confusion)
- Off-label use
- Lack of effect
- Exposure via breast milk
- (Suspicion of) transmission of an infectious agent
- Drug-drug interaction

All serious events and special situations noted above must be reported through the expedited AE reporting system via Advantage eClinical and **must be reported within 24 hours of knowledge of the event**. If there are network outages, a paper copy of the AE form must be completed and emailed to 1506safety@emmes.com to initiate Sponsor review. Once the system is available, the event information must be entered into the system.

The Sponsor also has a list of events classified as "always serious" events. If an AE is considered to be an event per this classification as "always serious," additional information on the event may be requested and the event will be requested to be reported through the expedited AE reporting system via Advantage eClinical. In the event an AE is classified as "always serious", the determination of serious and reporting through the expedited AE reporting system is per the opinion of the investigator.

4.6.2.1. SAE Reporting in Japan

For Japan, the investigator or sub-investigator must also 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.

Fax the JUTOKUNA YUUGAIJISHOU HOUKOKUSHO to the CRO:

PAREXEL International
Global Monitoring Operations
Fax: 03-6888-3348

The investigator or sub-investigator must also report the event in Advantage eClinical. The minimal identifiable information must be reported within 48 hours of awareness, followed by full information within 5 business days of awareness.

4.6.3. Criteria for Causal Relationship to the Study Drug

AEs that fall under either "Possible" or "Probable" should be defined as "AE whose relationship to the study drugs could not be ruled out". Table 5 lists the causal relationship to the study drug and the criteria for the causal relationship.

Table 5 Criteria for Causal Relationship

Causal Relationship to the Study Drug	Criteria for Causal Relationship
Not Related	A clinical event, including laboratory test abnormality, with a temporal relationship to study 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 study 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 study drug, unlikely to be attributed to concurrent disease or other drugs or chemicals and which follows a clinically reasonable response on re-administration (re-challenge) or withdrawal (de-challenge).

4.6.4. Criteria for Defining the Severity of an AE

AEs, including abnormal clinical laboratory values, will be graded using the CTCAE guidelines (version 4.03). The items that are not stipulated in the CTCAE version 4.03 will be assessed according to the criteria below in Table 6 and entered into the web-based electronic data capture system, Advantage eClinical.

Table 6 Definition for Severity of an AE

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 the AE

4.6.5. Criteria for Defining Expectedness

For the purposes of regulatory reporting, expected SAEs are those that are listed in the Investigational Brochure.

4.6.6. AE Reporting Guidelines

AEs must be reported regardless of whether a relationship exists between the AE and the use of the study drug.

From the time of screening until randomization, only deaths should be reported during this time frame on the appropriate event-driven CRF in Advantage eClinical. In addition, investigators should report any SAE that occurs after consent and prior to randomization that is assessed as related to invasive study-related procedures apart from the HCT. From the time of randomization through 30 days after the end of study drug, non-serious AEs are required to be reported via event-driven forms in Advantage eClinical. SAEs, irrespective of the attribution of the event to the study drug/procedure/treatment, will be reported through the expedited AE reporting system via Advantage eClinical, and will be graded according to the CTCAE Version 4.03. **SAEs must be reported within 24 hours of knowledge of the event.** The National Heart, Lung and Blood Institute (NHLBI) Data and Safety Monitoring Board will receive summary reports of all unexpected SAEs in an expedited manner and a summary of all adverse experiences at least twice yearly.

For this study, GVHD and infection are only to be reported as SAEs if one of the following conditions is met: 1) the event is both related to study drug and also meets the definition of SAEs above, or 2) the event results in death that occurs within 30 days after the last dose of study drug.

AML relapse will not be reported as an AE/SAE term unless it is the cause of a death that occurs between the first day of study drug though 30 days after the last dose of study drug (inclusive).

4.6.7. Monitoring of Common SAEs

Common SAEs are those events anticipated to occur in the study population independent of drug exposure. SAEs classified as "common" are provided in APPENDIX K Common SAEs for reference. The list does NOT change reporting obligations or prevent the need to report an SAE as detailed above. The purpose of this list is to provide events reported as SAEs that

may not require expedited reporting to the regulatory authorities based on the classification of "common SAEs." Investigators must report individual occurrences of these events as stated in Section 4.6.5.

Any changes to this list or changes in frequency of the events will be communicated to the participating investigational sites.

4.6.8. Procedure in Case of Pregnancy

If a female participant becomes pregnant during the study dosing period or within 6 months from the discontinuation of dosing or partner of a male participant becomes pregnant during the study dosing period or within 127 days from the discontinuation of dosing, the investigator should report the information through the expedited AE reporting system via Advantage eClinical. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result, neonatal data and other related information will be requested. If a participant becomes pregnant during the study dosing period, the study drug will be discontinued.

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. 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

Information will be collected at the time of delivery/birth and 6 months and 12 months after birth.

4.6.9. Emergency Procedures and Management of Overdose

In the event of suspected gilteritinib (ASP2215) overdose, the participant should receive supportive care and monitoring. The Sponsor Medical Monitor or Study Chair should be contacted.

CHAPTER 5

5. STATISTICAL CONSIDERATIONS

5.1. Study Design and Objectives

The study is a double-blind, placebo-controlled, randomized Phase III, multi-center trial comparing gilteritinib as maintenance therapy vs placebo, in FLT3/ITD AML participants in first morphologic CR who are undergoing an HCT. Randomization will start between days 30 and 90 after HCT, after the participant has engrafted. The target number of participants randomized is 346, 173 for each arm. To account for an anticipated 35% dropout between enrollment (at transplant) and randomization post-transplant, 532 participants are expected to enroll at the time of transplant in order to get the targeted number randomized.

5.1.1. Accrual

It is estimated that approximately 2 years of accrual will be necessary to enroll the targeted sample size.

5.1.2. Randomization

Participants will be randomized at a ratio of 1:1 between the treatment arm and the placebo arm using permuted blocks of random sizes. Randomization will be stratified by the conditioning regimen intensity (myeloablative vs reduced intensity/non-myeloablative), time from transplant to randomization (30-60 days vs 61-90 days), and the presence of MRD (present vs absent/unknown) based on the pre-transplant BM aspirate.

5.1.3. Primary Endpoint

The primary endpoint is RFS, treated as a time to event outcome. The primary analysis will be performed using the intent-to-treat principle so that all randomized participants will be included in the analysis. Leukemia relapse or death will be considered failures for this endpoint, which will be adjudicated by a blinded endpoint review committee. The Blinded Endpoint Review Committee will assess relapse according to the Blinded Endpoint Review Committee Charter.

5.1.4. Primary Hypothesis

The primary null hypothesis is that there is no difference in RFS between the treatment arm and placebo. Using a hazard ratio (HR) to denote the RFS primary endpoint for the treatment arm compared to the placebo, the primary hypotheses are:

$$H_{0:} \quad HR = 1 \text{ vs } H_{a:} \; HR \neq 1$$

This hypothesis will be tested at a 0.05 significance level.

5.1.5. Duration of Follow-up

All participants may remain on treatment for up to 2 years after randomization. After treatment discontinuation, long-term follow-up for relapse and/or death will occur until 5 whichever comes first.

5.1.6. Definition of Analysis Populations

5.1.6.1. Efficacy Analysis Population

The intention-to-treat (ITT) population will serve as the population for primary efficacy analysis. All randomized participants will be included in this population. Participants will be included in the treatment group to which they are randomized. Participants who are randomized but do not start therapy will not be replaced.

5.1.6.2. Per Protocol Set

The per protocol set (PPS) will consist of the subset of the ITT who do not meet criteria for PPS exclusion listed in the SAP. The sensitivity analyses for the primary and key secondary endpoints will be performed on the PPS. Select demographic and baseline characteristics will also be summarized for the PPS.

5.1.6.3. Safety Analysis Population

The safety analysis population will serve as the population for all summaries of the safety data. The safety analysis population consists of all participants who took at least 1 dose of study drug (gilteritinib or placebo). Participants will be analyzed based on the actual treatment received.

5.1.6.4. Pharmacokinetic Analysis Population

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 participants may be excluded from the PKAS at the discretion of the pharmacokineticist. Any formal definitions for exclusion of participants or time-points from the PKAS will be documented in the Classification Specifications and determined at the Classification Meeting.

5.2. Sample Size and Power Considerations

The primary analysis will be done using stratified log-rank tests, with the randomization factors used as stratification variables. RFS in the control group is assumed to be 67% at 1 year, 59% at 2 years, and 55% at 3 years, based on CIBMTR data on patients with FLT3/ITD mutation transplanted in CR1 who were alive and progression free at 60 days. A total of 122 events provide 85% power to detect a HR of 0.57 (corresponding to a 15% difference in 2 year RFS) with two-sided significance level of 0.05. This assumes that the survival function in the control group has piecewise constant hazard functions in each interval, that the treatment arm has proportional hazards with a HR of 0.57, and maximum follow-up of 3 years (Note that CIBMTR data indicates that very few events occur after 3 years so there is little benefit in longer follow-up). Assuming approximately 2 years of accrual and 5% drop out rate per year, 346 participants need to be enrolled to ensure a high likelihood of obtaining 122 events.

5.3. Interim Analysis and Stopping Guidelines

Policies and composition of the DSMB are described in the DSMB Charter and the study-specific DSMB Charter Addendum. No interim efficacy or futility analyses are planned.

RFS with immature data may be subject to overestimation; the data are not robust and is rarely reproducible when more mature data are available. For this reason, early evaluation may lead to stopping the trial too early, and therefore the DSMB will not stop the trial due to differences in RFS. Toxicity, AEs, and other safety endpoints will be monitored regularly and reported to the DSMB at each meeting.

5.3.1. Guidelines for Safety Monitoring

Monitoring of a key safety endpoint will be conducted monthly, and if rates significantly exceed preset thresholds, the NHLBI will be notified so that the DSMB can be advised. The stopping guideline serves as trigger for consultation with the DSMB for additional review and are not formal "stopping rules" that would mandate automatic closure of study enrollment.

The key safety endpoint for this study is mortality. The rate of mortality will be monitored up to 90 days post-randomization separately in each of the two treatment arms. At least three events must be observed in order to trigger review. The expected probability of mortality within 90 days post randomization among FLT3+ AML patients who are alive without progression at day 60 post-transplant is $\leq$ 15%, based on CIBMTR data. Each month, the null hypothesis that the 90-day mortality rate is less than or equal to 15% is tested. An extension of the sequential probability ratio test (SPRT) for censored exponential data will be used for monitoring, as described in greater detail below and in APPENDIX E.

This sequential testing procedure conserves type I error at 5% across all of the monthly examinations for a treatment arm. The SPRT can be represented graphically. At each monthly interim analysis, the total time on study in months (x axis) is plotted against the total number of endpoints (y axis) (e.g., participants experiencing death). The continuation region of the SPRT is defined by two parallel lines. Only the upper boundary will be used for monitoring to protect against excessive 90-day mortality. If the graph falls above the upper boundary, the SPRT rejects the null hypothesis, and concludes that there are more events than predicted by the observed time on study. Otherwise, the SPRT continues until enrollment reaches the maximum of 173 participants per arm.

This procedure assumes a censored exponential distribution for the time until death during the first 90 days, and censors follow-up time after 90 days. Only deaths that occur on or before the participant has been followed for 90 days are counted. Total time on study is computed as time from randomization to death, or to 90 days, whichever comes first, summed for all participants on study.

The usual measures of performance of an SPRT are the error probabilities α and β of rejecting H_0 when $\theta = \theta_0$ and of accepting H_1 when $\theta = \theta_1$, respectively, and the expected sample size $E(N|\theta_i)$. The tests to be used in this protocol were developed from the following SPRT:

A SPRT contrasting 15% versus 25% 90-day rate of mortality results in decision boundaries with a common slope of 0.073 and an upper intercept of 4.251, with nominal type I and II errors of 7.5% and 15%, respectively.

The actual operating characteristics of the truncated test, shown in Table 7, were determined in a simulation study that assumed uniform accrual of 173 individuals over a 24 month time period, and exponential time to failure after randomization.

Table 7 Operating Characteristics of Sequential Testing Procedure from a Simulation Study with 10000 Replications

DAY 90 MORTALITY

True 90-Day Rate	15%	20%	25%
Probability Reject Null	0.047	0.427	0.901
Mean Month Stopped	26.2	21.0	12.5
Mean # Endpoints in 90 Days	25.2	26.9	19.8
Mean # Participants Enrolled	168.5	139.0	87.9

For example, the testing procedure rejects the null hypothesis in favor of the alternative 5% of the time when the true 90-day mortality rate is 15%, and 90% of the time when the rate is 25%. This corresponds to a type I error rate of $\alpha = 0.05$ and a type II error rate of $\beta = 0.1$. When the true 90-day mortality rate is 25%, on average, the DSMB will be consulted 12 months after opening, when 20 events have been observed in 88 participants.

5.4. Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized for all participants. Characteristics to be examined are: age, gender, race/ethnicity (if available), performance status, MRD status, CMV status, HCT-specific comorbidity index, time from diagnosis to transplantation, time from CR to randomization, time from transplant to randomization, donor type, conditioning regimen and intensity, graft type, HLA matching, GVHD prophylaxis regimen, presence of GVHD prior to randomization, treatment used for GVHD, and time to ANC recovery.

5.5. Analysis Plan

5.5.1. Participant Disposition

The number and percentage of all participants who receive any study drug, who complete the study, and who discontinue the study prematurely, will be reported per treatment group, along with reasons for discontinuation.

5.5.2. Analysis of the Primary Endpoint

The primary outcome of the trial is RFS from the time of randomization, treated as a time to event variable. Participants going off study drug without prior documentation of a RFS event will continue to be followed for RFS, and this additional follow-up will be included in the primary analysis. Participants without a RFS event but lost to follow-up will be censored at last date of follow-up. The primary analysis will be conducted when 122 events have been observed for the primary endpoint. RFS will be compared between groups in the ITT population using the stratified log-rank test, stratified on conditioning regimen intensity, time from transplant to randomization, and pre-transplant MRD status. The HR, along with

confidence intervals, will be estimated from a stratified Cox model with treatment as a covariate, and using the same strata variables. Kaplan-Meier estimates of RFS will also be described for each group, along with confidence intervals at 1, 2, and 3 years. In order to evaluate the robustness of the primary endpoint analysis of RFS, several sensitivity analyses will be performed. The first sensitivity analysis is the same as the primary analysis except that it censors at the last disease assessment without relapse when relapse or death is documented after more than one missed disease assessment and it censors patients going off treatment without prior documentation of a RFS event at their last disease assessment before going off treatment. The second sensitivity analysis utilizes EFS (as described in Section 5.5.3.4) rather than RFS. These sensitivity analyses will be conducted using the same methods as for the primary endpoint. A sensitivity analysis will also be conducted to assess whether any random imbalances in the intensity of preparative regimen or the planned GVHD prophylaxis affected the RFS outcome, by adding these variables as covariates into the stratified Cox model. Finally, the proportional hazards assumption for the Cox model using graphical methods and time-dependent covariates will be assessed and if there is evidence that this assumption is violated, adjusted RFS curves will be generated, and adjusted RFS probabilities will be compared between the groups at 2 and 3 years.

5.5.3. Analysis of Secondary Endpoints

5.5.3.1. Overall Survival

OS will be a key secondary endpoint, with explicit control of the type I error rate through a gatekeeper approach. Formal significance testing of OS will be conducted if the RFS comparison is statistically significant. Otherwise, survival analyses will be considered exploratory. OS curves from time of randomization will be estimated using the Kaplan-Meier estimator applied to the ITT population, and compared between treatment groups using the stratified log-rank test, with the same strata variables as for the primary endpoint. The HR, along with confidence intervals, will be estimated from a stratified Cox model with treatment group as a covariate. Surviving participants will be censored at the last known alive date.

Additional analyses assessing the impact of crossover after unblinding on OS will be performed. Details of these analyses will be provided in the SAP.

5.5.3.2. Non-relapse Mortality (NRM)

Incidence of NRM will be estimated using the cumulative incidence function, treating relapse/progression as a competing risk. Incidence of NRM will be compared between the treatment arms using a Fine and Gray model, adjusting for strata variables of conditioning regimen intensity (myeloablative vs reduced intensity/non-myeloablative), time from transplant to randomization, and pre-transplant MRD status.

5.5.3.3. Relapse

Incidence of relapse will be estimated using cumulative incidence function, treating death in remission as a competing risk. Incidence of relapse/progression will be compared between the treatment arms using a Fine and Gray model, adjusting for strata variables of conditioning

regimen intensity (myeloablative vs reduced intensity/non-myeloablative), time from transplant to randomization, and pre-transplant MRD status.

5.5.3.4. Event-free Survival (EFS)

EFS will be estimated using the Kaplan-Meier estimator applied to the ITT population, and compared between treatment groups using the stratified log-rank test, with the same strata variables as for the primary endpoint. The HR, along with confidence intervals, will be estimated from a stratified Cox model with treatment group as a covariate. The reason for participants starting new therapies, and the types of new therapies given will be described in each arm. EFS considers discontinuation of study drug or initiation of an anticancer treatment to be an event.

5.5.3.5. Acute GVHD of Grades II-IV and III-IV

Cumulative incidence of new onset acute GVHD or worsening in the grade of acute GVHD at the time of randomization by one point (e.g., grade II acute GVHD at the time of randomization, progressing to grade III or more after randomization) will be estimated from the time of randomization using the cumulative incidence function, treating death prior to acute GVHD as the competing risk. Cumulative incidence of acute GVHD will be compared between treatment arms using a Fine and Gray model, adjusting for strata variables of conditioning regimen intensity (myeloablative vs reduced intensity/non-myeloablative), time from transplant to randomization, and pre-transplant MRD status. An additional analysis will be performed treating death and relapse without documentation of an acute GVHD event as a competing risk.

5.5.3.6. Chronic GVHD

Cumulative incidence of new onset chronic GVHD from the time of randomization or worsening in the grade of chronic GVHD at the time of randomization by one point (e.g., mild chronic GVHD at the time of randomization, progressing to moderate or severe chronic GVHD after randomization) will be estimated using the cumulative incidence function, treating death prior to chronic GVHD as the competing risk. Cumulative incidence of chronic GVHD will be compared between treatment arms using a Fine and Gray model, adjusting for strata variables of conditioning regimen intensity (myeloablative vs reduced intensity/non-myeloablative), time from transplant to randomization, and pre-transplant MRD status.

5.5.3.7. Infection

The number of infections and the number of patients experiencing infections will be tabulated by type of infection, severity and time period after transplant. The cumulative incidence of CTCAE grade 3 to 5 infections, treating death (grade 5) as a competing event, will be compared among the treatment arms using Gray's test.

5.5.3.8. Relative Dose Intensity

Relative Dose Intensity is defined as the percentage of the planned number of doses of study drug which are actually taken by the participant. Descriptive statistics for study drug compliance will be presented for the safety population by treatment group.

5.5.3.9. Extent of Exposure

Exposure to treatment, measured by the duration of treatment in number of months, will be summarized by treatment group using the safety population. The number and proportion of participants with dose reduction and dose interruption will be tabulated.

5.5.3.10. Safety and Tolerability

5.5.3.10.1. *Adverse Events*

All AEs recorded on treatment including within 30 days from the last study treatment will be summarized. AEs will be categorized by System Organ Class (SOC) and preferred term (PT) using the MedDRA dictionary and will be graded according to the CTCAE version 4.03.

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

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

Additional summary tables will be generated for the following population subsets: participants with SAEs including deaths, participants 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.

5.5.3.10.2. *Laboratory Assessments*

Clinical laboratory evaluations (including serum chemistry, LFTs, thyroid tests, hematology) and their changes from baseline will be summarized by treatment 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 CTCAE grade and laboratory reference range indicator. Frequency of participants with laboratory values outside normal range will be generated in addition to tabulation of worst toxicity grade.

5.5.3.10.3. *Physical Examination*

All clinically significant abnormal findings will be recorded as medical history, AEs, infection or GVHD and graded using either CTCAE guidelines or according to standard criteria for GVHD.

5.5.3.10.4. ***Electrocardiograms***

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.

5.5.3.11. Karnofsky Performance Status Scores

Karnofsky performance status scores will be summarized by treatment group and visit.

5.5.3.12. Post- transplant MRD Status

The cumulative incidence of detection of MRD in participants who are MRD undetectable prior to randomization will be described in each group and compared between treatment arms using Gray's test; death without detection of MRD will be treated as a competing risk. Similarly, the time until eradication of MRD in participants who have detectable MRD prior to randomization will also be described and compared between treatment arms using Gray's test; death without eradication of MRD will be treated as a competing risk.

5.5.4. Analysis of Exploratory Endpoints

5.5.4.1. Health-Related Quality of Life (HQL)

HQL will be measured on day -30, day -14, day 29, month 3, month 6, month 12, month 18 and EOT (month 24) using three instruments: the FACT-BMT, FACT-Leu, and EQ-5D-5L. HQL at each time point will be summarized using simple descriptive statistics (mean, SD) and simple comparisons between treatment arms will be performed using t-tests. Analysis will be done separately for each instrument/summary scale using a Bonferroni adjusted significance level (0.05/4). All models will be adjusted for baseline HQL. Partly conditional regression conditioning on being alive at each time point will be used to compare the longitudinal HQL measurements over time between the treatment groups. Interactions with time will be tested for and if significant, treatment effects will be estimated separately for each time point. The missing data pattern of the HQL measurements will be examined using graphical techniques and logistic regression models conditional on survival. At each time point, estimates of the difference in HQL between the treatments conditional on survival at that time point will be obtained using inverse probability of censoring weighted generalized estimating equations (GEE) with independent estimating equations to account for missing data.

5.5.4.2. Healthcare Resource Utilization

Descriptive analyses of healthcare resource utilization will be conducted for antibiotic use, medication for AEs, and hospitalization including the total and average number and duration of hospitalizations. Additional analyses may be performed and reported separately.

5.5.4.3. Subgroup Analysis

Subgroup analyses will be conducted for RFS for each of the following variables: pre-transplant MRD status at enrollment, MRD status at randomization, age, gender, region,

FLT3-ITD allelic ratio from the diagnostic sample, incidence of FLT3 mutation at relapse, conditioning intensity and GVHD prophylaxis. Interaction tests between treatment group and subgroup will be conducted within a Cox proportional hazards regression model with treatment, subgroup, and a treatment*subgroup interaction term. Plots of Kaplan-Meier estimates of RFS by treatment will be shown separately for each level of the subgroup, and a forest plot will be used to show the HR's for each subgroup.

5.5.4.4. Gilteritinib Plasma Pharmacokinetics

Gilteritinib plasma concentrations will be summarized by treatment, visit, and time point (in hours). 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.

5.5.5. Handling of Missing Data, Outliers, Visit Windows and Other Information

As a general principle, no imputation of missing data will occur during analysis. Exceptions are the start and stop dates of AEs and concomitant medication. The imputed dates will be used to determine whether an AE is/is not treatment-emergent or a medication is/is not concomitant. Listings of the AEs and concomitant medications will present the actual partial dates; imputed dates will not be shown.

The definition for windows to be used for analyses by visit, if applicable, will be outlined in the statistical analysis plan (SAP).

APPENDIX A
HUMAN SUBJECTS

APPENDIX A
HUMAN SUBJECTS

1. Participant Consent

A conference will be held with the participant, and family if available, to discuss this study and alternative treatments available for the treatment of the underlying disease. The conference will be conducted by the Principal Investigator or other designated physician. Potential risks associated with the study treatments should be discussed as objectively as possible. Consent will be obtained using an IRB/IEC-approved consent.

The Sponsors will provide a template of the consent form to each center. Each center will customize the template according to their local requirements and submit it for review by the local IRB or IEC. The delegated clinical research organizations and APGD will verify the adequacy of the consent forms prior to submission to the IRB or IEC. Each center must provide evidence of IRB or IEC approval.

2. Confidentiality

Confidentiality will be maintained by masking individual names and assigning a participant identifier code. The code relaying the participant's identity with the identifier (ID) code will be kept separately at the center. The ID code will be transmitted to the network.

3. Participation of Women and Minorities and Other Populations

Women and ethnic minorities and other populations will be included in this study. Accrual of women and minorities at each center will be monitored to determine whether their rates of enrollment are reflective of the distribution of potentially eligible women and minorities expected from data reported to the CIBMTR and from published data on incidence of AML in these groups. Centers will be notified if their rates differ significantly from those expected and asked to develop appropriate recruitment strategies.

APPENDIX B
INVESTIGATOR'S SIGNATURE

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A Multi-center, Randomized, Double-blind, Placebo-controlled Phase III Trial of the FLT3 Inhibitor Gilteritinib Administered as Maintenance Therapy Following Allogeneic Transplant for Patients with FLT3/ITD AML

BMT CTN PROTOCOL 1506

ASTELLAS PROTOCOL 2215-CL-0304

Version 3.0, March 15, 2019

Protocol History:

Version 1.0 23Sep2016
Version 1.1 [JP] Nonsubstantial Amendment 1 dated 09Nov2016
Version 1.1 [FR] Nonsubstantial Amendment 2 dated 03Nov2016
Version 1.1 [UK] Nonsubstantial Amendment 3 dated 20Mar2017
Version 1.1 [DE] Nonsubstantial Amendment 4 dated 03May2017
Version 1.2 [FR] Nonsubstantial Amendment 5 dated 19Jul2017
Version 2.0 Substantial Amendment 1 dated 20Nov2017
Version 2.1 Nonsubstantial Amendment 6 dated 19Feb2018

I have read all pages of this clinical study protocol. 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 ICH GCP guidelines and applicable local regulations. I will also ensure that subinvestigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

Principal Investigator:

Signature: ----------

Date (DD Mmm YYYY)

Printed Name: ----------

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

APPENDIX C

OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

APPENDIX C

OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

1. Clinical Study Quality Control

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 transcribe data (including laboratory values, if applicable) in the electronic case report form (eCRF) in a timely manner after the participant visit unless otherwise noted. The BMT CTN DCC will be reviewing form submission regularly and will follow-up to assure data is submitted promptly.

The investigator or site designee is responsible for ensuring 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 will verify a subset of the data in the eCRFs with source documents and confirm that there are no inconsistencies between them.

Study Documentation

Study documentation includes, but is not limited to, all CRFs, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and signed protocol and amendments, IRB/IEC correspondence and approved current and previous consent forms and signed participant consent forms.

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. The original recording of an observation should be retained as the source document. If the original recording of an observation is the electronic record, that will be considered the source.

Clinical Study Monitoring

The Sponsors or delegated CROs are responsible for monitoring the clinical study to ensure that the participant's human rights, safety and well-being are protected, that the study is properly conducted in adherence with 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 Sponsors or delegated CROs are responsible for assigning study monitor(s) to this study for proper monitoring. The protocol will be monitored in accordance with planned monitoring procedures.

Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the Sponsor or delegated CROs as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records and documentation when they

are requested by the Sponsor monitors and auditors, the IRB/IEC or regulatory authorities. The confidentiality of the participant's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

Quality Assurance

The Sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that the trial is 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, CRFs and source documents. Direct access to these documents will be required by the auditors.

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 participants. The investigator should not implement any deviation from or changes of, the protocol, unless it is necessary to eliminate an immediate hazard to study participants.

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 participant who:

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

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

If a deviation impacts the safety of a participant, 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 require reporting to the IRB/IEC in accordance with local requirements will be reported, as applicable.

The following is specific to investigational sites in Japan:

Deviations from the Protocol and Other Actions Taken to Avoid Life-Threatening Risks to Subjects

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.

2. Ethics and Protection of Participant Confidentiality

Institutional Review Board/Independent Ethics Committee/Competent Authorities

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

Any substantial amendments to the protocol will require IRB/IEC approval 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., SUSAR and any additional reports required by local regulations) to the IRB/IEC of any changes that affect the conduct of the study and/or increase the risk to participants. Written documentation of the submission to the IRB/IEC should also be provided to the Sponsor.

If required by local regulations, the investigator shall make accurate and adequate written progress reports to the IRB/IEC 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.

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.

Informed Consent of Participants

Participant Information and Consent

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the participant, the informed consent statement will be reviewed and signed (***Specific to investigational sites in Japan:*** place a personal seal), and dated by the participant 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) informed consent form (ICF) will be given to the participant and the original will be placed in the participant's medical record. An entry must also be made in the participant's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the participant 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.

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

The investigator or his/her representative will immediately inform the participant orally whenever new information becomes available that may be relevant to the participant's consent or may influence the participant'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 participant's medical records and must document whether the participant is willing to remain in the study or not.

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 participant on all updated ICFs throughout their participation in the study. The investigator or his/her designee must re-consent participants 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 participant 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 participant and the original will be placed in the participant's medical record. An entry must be made in the participant's records documenting the reconsent process.

The following items 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 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 Pharmaceutical Affairs Law, 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 the information provided above [Supply of New and Important Information Influencing the Subject's Consent and Revision of the 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, these documents should be sent to the IRB.

Participant Confidentiality

Individual participant 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 participant to the participant's physician or to other appropriate medical personnel responsible for the participant's well-being.

The Sponsor affirms the participant'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 (PHI) obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information (i.e., HIPAA).

3. Administrative Matters

Arrangement for Use of Information

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 Astellas. 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 Sponsors 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.

Documents and Records Related to the Clinical Study

The investigator will archive all study data (e.g., Participant 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 investigational new drug (IND). The Sponsor will notify the site/investigator if the NDA/Marketing Authorisation 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.

The investigator and Sponsor will mutually agree upon the storage format for the retention of electronic data

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 1. or 2. below, whichever comes later.

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

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.

Insurance of Participants 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.

The following paragraph is specific to investigational sites in 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.

APPENDIX D
NEW YORK HEART ASSOCIATION CLASSIFICATION OF CARDIAC DISEASE

APPENDIX D

NEW YORK HEART ASSOCIATION CLASSIFICATION OF CARDIAC DISEASE

NYHA Class	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g., no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20–100 m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while *at rest*. Mostly bedbound patients.

Source: The Criteria Committee of the New York Heart Association. (1994). Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston: Little & Co. 1994;253–56.

APPENDIX E
DERIVATION OF A SEQUENTIAL TEST STATISTIC FOR CENSORED EXPONENTIAL DATA

APPENDIX E
DERIVATION OF A SEQUENTIAL TEST STATISTIC FOR CENSORED EXPONENTIAL DATA

Background – The Sequential Probability Ratio Test

Let $f(.,\theta)$ be the density function for random variable X. According to Neyman and Pearson, the most powerful test of $H_0:\theta=\theta_o$ versus $H_1:\theta=\theta_1$ decides in favor of H_1 or H_0 if $L_n>c_\alpha$ or $L_n<c_\alpha$, respectively, where $L_n=\prod_i^n f(x_i;\theta_1)/f(x_i;\theta_0)$ is the likelihood ratio, and c_α is determined to have the size α. When the sample size is not fixed in advance, further improvement is possible by using Wald's Sequential Probability Ratio Test (SPRT). The SPRT continues to sample as long as $B<L_n<A$ for some constant $B<1<A$, stops sampling and decides in favor of H_1 as soon as $L_n>A$, and stops sampling and decides in favor of H_0 as soon as $L_n<B$.

The usual measures of performance of such a procedure are the error probabilities α and β of rejecting H_0 when $\theta=\theta_0$, and of accepting H_0 when $\theta=\theta_1$, respectively, and the expected sample size $E(N|\theta_j)\equiv E_j(N)$. Wald and Wolfowitz showed that among all tests, sequential or not, for which $\Pr_0(\text{reject}H_0)\le\alpha$ and $\Pr_1(\text{reject}H_0)\le\beta$, and for which $E_j(N)$ are finite, j=0,1, the SPRT with error probabilities α and β minimizes $E_0(N)$ and $E_1(N)$. If, in addition, the $x1,x2,..$ are independent and identically distributed (i.i.d.) with density function $f(x,\theta)$, with monotone likelihood ratio in $\tau(x)$, then any SPRT for testing θ_0 against $\theta_1(>\theta_0)$ has non-decreasing power function.

For the SPRT with error probabilities α and β, the SPRT boundaries are given approximately by $A=(1-\beta)/\alpha$ and $B=\beta/(1-\alpha)$. The operating characteristics of the SPRT are given by $O(\theta,\alpha,\beta,\theta_0,\theta_1)=(A^{h(\theta)}-1)/(A^{h(\theta)}-B^{h(\theta)})$ where $h(\theta)$ is the non-trivial solution to the equation $\int(f(x;\theta_1)/f(x,\theta_2))^{h(\theta)}f(x;\theta)dx=1$.

The formula $E(N;\theta)=[[(1-O(\theta)]\log A+O(\theta)\log B]/E(z;\theta)$ provides the average sample number for an arbitrary θ. The sample size distribution is very highly skewed, $Var(N)\approx[E(N)]^2$. Thus we will consider a truncated test with maximum sample size of N_0 and simulate to obtain the operating characteristics of the test.

Derivation of the SPRT for Censored Exponential Survival Times

Suppose that we wish to construct a sequential test for the composite null hypothesis that the rate of overall mortality at an early time point t is less than or equal to p_0 versus the alternative hypothesis that it is greater than or equal to p_0. Let us assume that the survival times, $T_1, T_2, ..., T_n$, are i.i.d. with exponential density function $f(T,\theta) = \theta e^{-\theta T}$. Although an exponential model may not fit well for overall mortality, it usually provides a reasonable model over a short time frame for modeling toxicity, so in all discussion below we assume that exponential survival times are censored at time point t. In the exponential parameterization, a t-day survival rate of p_0 translates into a mean survival of μ_0=-t/ln(1-p_0) (rate parameter θ_0 =-ln(1-p_0)/t).

The SPRT is derived with reference to a simple null and alternative hypothesis for the rate parameter, in this case, $H_0 : \theta = \theta_o$ versus $H_1 : \theta = \theta_1$. The log-likelihood ratio for the exponential in the presence of censoring is $\log \prod_i^n f(x_i;\theta_1) - \log \prod_i^n f(x_i,\theta_0) = d(\log(\theta_1) - \log(\theta_0)) - (\theta_1 - \theta_0)\sum_i^n T_i$, where d is the number of events. The SPRT can be represented graphically when plotting the number of deaths (d) on the y axis against the total time on study $\sum_i^n T_i$ on the x axis. The continuation region in terms of d is bounded by two parallel lines given by

$$\left[\frac{\log(B)}{(\log\theta_1 - \log\theta_0)}\right] + \left[\frac{(\theta_1 - \theta_0)}{(\log\theta_1 - \log\theta_0)}\right]\sum_i^n T_i < d < \left[\frac{\log(A)}{(\log\theta_1 - \log\theta_0)}\right] + \left[\frac{(\theta_1 - \theta_0)}{(\log\theta_1 - \log\theta_0)}\right]\sum_i^n T_i$$

with common slope $(\theta_1 - \theta_0)/(\log\theta_1 - \log\theta_0)$, and intercepts $\log A/(\ln\theta_1 - \ln\theta_0)$ and $\log B/(\ln\theta_1 - \ln\theta_0)$, for the upper and lower bounds, respectively. For monitoring purposes, at an interim analysis calendar time point s, suppose that d(s) events have occurred and that the total time on study is $\sum_i^n T_i(s)$.The cumulative number of events d(s) is plotted on the y axis against the total time on study, $\sum_i^n T_i(s)$. When this graph crosses the upper boundary, the null hypothesis is rejected. In practice, monitoring will be scheduled monthly after the start of enrollment to the study.

A truncated version of the SPRT can be obtained by specifying a maximum sample size. We truncate the SPRT by declaring that if the test has failed to terminate after the maximum sample size, that the null hypothesis will be accepted. Since the probability that the untruncated SPRT would reject the null at the maximum sample size is negligible, it makes little difference how the final boundary value is selected, and this rule is chosen for simplicity. The operating characteristics of this proposed truncated SPRT for censored exponential data can be estimated by simulation.

APPENDIX F
KARNOFSKY PERFORMANCE STATUS SCALE

APPENDIX F

KARNOFSKY PERFORMANCE STATUS SCALE

Index	Specific Criteria	General
100	Normal, no complaints, no evidence of disease.	Able to carry on normal activity and to work. No special care needed.
90	Able to carry on normal activity, minor signs or symptoms of disease.	
80	Normal activity with effort, some signs or symptoms of disease.	
70	Care for self, unable to carry on normal activity or to do work.	Unable to work. Able to live at home, care for most personal needs. A varying amount of assistance needed.
60	Requires occasional assistance but is able to care for most of his needs.	
50	Requires considerable assistance and frequent medical care	
40	Disabled, requires special care and assistance.	Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be rapidly progressing.
30	Severely disabled, hospitalization indicated, although death not imminent.	
20	Very sick, hospitalization necessary, active supportive treatment necessary.	
10	Moribund; fatal processes progressing rapidly.	
0	Dead	

Source: Karnofsky DA, Abelman WH, Craver LF, Burchenal JH. The use of the nitrogen mustards in the palliative treatment of carcinoma. Cancer. 1948;1(4):634-56.

APPENDIX G
HCT – SPECIFIC COMORBIDITY INDEX SCORE

APPENDIX G

HCT-SPECIFIC COMORBIDITY INDEX SCORE

Comorbidities	Definition	Score
Migraine/headache		**0**
Osteoporosis		**0**
Osteoarthritis		**0**
Hypertension		**0**
Gastrointestinal	Including inflammatory bowel disease	**0**
Mild pulmonary	DLCO and/or FEV1 > 80% or Dyspnea on moderate activity	**0**
Mild renal	Serum creatinine 1.2-2 mg/dL	**0**
Endocrine		**0**
Bleeding		**0**
Coagulopathy	Deep venous thrombosis or pulmonary embolism	**0**
Asthma		**0**
Arrhythmia		**1**
Myocardial	Coronary artery disease, congestive heart failure, history of medically documented myocardial infarction, EF ≤ 50%	**1**
Mild hepatic	Chronic hepatitis, bilirubin > ULN to 1.5 x ULN, or AST/ALT > ULN to 2.5 x ULN	**1**
Cerebro-vascular accident	History of transient ischemic attack or cerebro-vascular accident	**1**
Morbid obesity		**1**
Diabetes	Requiring treatment	**1**
Depression/anxiety		**1**
Infection	Requiring continuation of treatment after day 0	**1**
Rheumatologic	SLE, RA, polymyositis, mixed CTD, polymyalgia rheumatica	**2**
Moderate pulmonary	DLCO and/or FEV1 66% - 80% or Dyspnea on slight activity	**2**
Peptic ulcer	Patients who have required treatment	**2**
Moderate-severe renal	Serum creatinine > 2 mg/dl, on dialysis, or prior renal transplantation	**2**
Valvular heart disease	Except mitral valve prolapse	**3**
Prior solid tumor	Requiring treatment with chemotherapy	**3**
Moderate-severe hepatic	Liver cirrhosis, Bilirubin > 1.5 x ULN, or AST/ALT > 2.5 x ULN	**3**
Severe pulmonary	DLCO and/or FEV1 ≤ 65% or Dyspnea at rest or requiring oxygen	**3**

Total score is the sum of all comorbidities present at time of transplantation.

AST: aspartate aminotransferase; ALT; alanine aminotransferase; CTD: connective tissue disease; DLCO: diffusing capacity of the lung for carbon monoxide; EF: ejection fraction; FEV1: forced expiratory volume in 1 second; HCT: hematopoietic cell transplantation; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; ULN: upper limit of normal.

Source: Sorror ML, Maris MB, Storb R, et al: Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2015:106(8):2912-9.

APPENDIX H

LIST OF EXCLUDED AND PRECAUTIONARY MEDICATIONS

APPENDIX H

LIST OF EXCLUDED AND PRECAUTIONARY MEDICATIONS

The following list describes medications and foods that are common strong inhibitors of CYP3A and these drugs should be avoided unless the drugs are considered absolutely essential for the care of the participant. This list should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity to inhibit CYP3A. If there are concerns or questions about concomitant use of any drugs listed below, discussion with the co-chairs and protocol officer is strongly encouraged.

Strong CYP3A Inhibitors

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

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

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
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/mood stabilizer	Thioridazine Mesoridazine Chlorpromazine Prochlorperazine Trifluoperazine Fluphenazine Perphenazine Pimozide Risperidone Ziprasidone Lithium Haloperidol
Tricyclic/tetracyclic antidepressants	Amitriptyline Desipramine Doxepin Dosulepin hydrochloride Imipramine Maprotiline
Selective serotonin and norepinephrine reuptake inhibitors (SSNRIs) antidepressants	Venlafaxine
Macrolide antibiotics	Azithromycin Erythromycin Clarithromycin Dirithromycin Roxithromycin Tulathromycin
Fluoroquinolone antibiotics	Moxifloxacin Gatifloxacin
Table continued on next page	

Drug Type	**Generic Drug Name**
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

APPENDIX I
DIAGNOSIS AND SEVERITY SCORING FOR ACUTE AND CHRONIC GRAFT-VERSUS-HOST DISEASE

APPENDIX I

DIAGNOSIS AND SEVERITY SCORING FOR ACUTE AND CHRONIC GRAFT-VERSUS-HOST DISEASE

1. Acute graft-versus-host disease (GVHD) organ staging

Stage	Skin	Liver (bilirubin)	GI (stool output per day)
0	No rash	< 2 mg/dL (< 34.2 µmol/L)	< 500 ml/day
1	Maculopapular rash < 25% BSA	2 to 3 mg/dL (34.2 to 51.3 µmol/L)	500 to < 1000 ml/day or persistent nausea
2	Maculopapular rash 25 – 50% BSA	> 3 to 6 mg/dL (> 51.3 to 102.6 µmol/L)	1000 to 1500 ml/day
3	Maculopapular rash > 50% BSA	> 6 to15 mg/dL (> 102.6 to 256.5 µmol/L)	>1500 ml/day
4	Generalized erythroderma plus bullous formation	> 15 mg/dL (> 256.5 µmol/L)	Severe abdominal pain with or without ileus

BSA: body surface area; GI: gastrointestinal; GVHD: graft-versus-host disease

Grade	Skin	Liver (bilirubin)	GI (Stool output/day)
I	Stage 1–2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III	-	Stage 2–3 or	Stage 2–4
IV	Stage 4 or	Stage 4	-

GI: gastrointestinal

Source: modified from Jacobsohn DA, Vogelsang GB. Acute graft versus host disease. Orphanet J Rare Dis. 2007;2:35. doi:10.1186/1750-1172-2-35

2. Grading of Chronic Graft-Versus-Host Disease (National Institutes of Health Criteria)

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
PERFORMANCE SCORE: ☐ **KPS ECOG LPS**	☐ Asymptomatic and fully active (ECOG 0; KPS or LPS 100%)	☐ Symptomatic, fully ambulatory, restricted only in physically strenuous activity (ECOG 1, KPS or LPS 80-90%)	☐ Symptomatic, ambulatory, capabl of self-care, >50% of waking hours ou of bed (ECOG 2, KPS or LPS 60-70%)	☐ Symptomatic, limited self-care, >50% of waking hours in bed (ECOG 3-4, KPS or LPS <60%)
SKIN† ☐ **SCORE % BSA**				
GVHD features to be scored by BSA: **Check all that apply:** ☐ Maculopapular rash/erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like GVHD	☐ No BSA involved	☐ 1-18% BSA	☐ 19-50% BSA	☐ >50% BSA
SKIN FEATURES SCORE:	☐ No sclerotic features		☐ Superficial sclerotic features "not hidebound" (able to pinch)	**Check all that apply:** ☐ Deep sclerotic features ☐ "Hidebound" (unable to pinch) ☐ Impaired mobility ☐ Ulceration
Other skin GVHD features (NOT scored by BSA) **Check all that apply:** ☐ Hyperpigmentation ☐ Hypopigmentation ☐ Poikiloderma ☐ Severe or generalized pruritus ☐ Hair involvement ☐ Nail involvement ☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
MOUTH *Lichen planus-like features present:* ☐ **Yes** ☐ **No**	☐ No symptoms	☐ Mild symptoms **with** disease signs but not limiting oral intake significantly	☐ Moderate symptoms with disease signs **with** partial limitation of oral intake	☐ Severe symptoms with disease signs on examination **with** major limitation of oral intake
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				

	SCORE 0	SCORE 1	SCORE 2	SCORE 3
EYES *Keratoconjunctivitis sicca (KCS) confirmed by ophthalmologist:* ☐ **Yes** ☐ **No** ☐ **Not examined**	☐ No symptoms	☐ Mild dry eye symptoms not affecting ADL (requirement of lubricant eye drops ≤ 3 x per day)	☐ Moderate dry eye symptoms partially affecting ADL (requiring lubricant eye drops > 3 x per day or punctal plugs), **WITHOUT** new vision impairment due to KCS	☐ Severe dry eye symptoms significantly affecting ADL (special eyeware to relieve pain) **OR** unable to work because of ocular symptoms **OR** loss of vision due to KCS
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
GI Tract ***Check all that apply:*** ☐ Esophageal web/ proximal stricture or ring ☐ Dysphagia ☐ Anorexia ☐ Nausea ☐ Vomiting ☐ Diarrhea ☐ Weight loss ≥5%* ☐ Failure to thrive	☐ No symptoms	☐ Symptoms without significant weight loss* (<5%)	☐ Symptoms associated with mild to moderate weight loss* (5-15%) **OR** moderate diarrhea without significant interference with daily living	☐ Symptoms associated with significant weight loss* >15%, requires nutritional supplement for most caloric needs **OR** esophageal dilation **OR** severe diarrhea with significant interference with daily living
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____				
LIVER	☐ Normal total bilirubin and ALT or AP < 3 x ULN	☐ Normal total bilirubin with ALT ≥3 to 5 x ULN or AP ≥ 3 x ULN	☐ Elevated total bilirubin but ≤3 mg/dL or ALT > 5 ULN	☐ Elevated total bilirubin > 3 mg/dL
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*				
LUNGS**				
Symptom score:	☐ No symptoms	☐ Mild symptoms (shortness of breath after climbing one flight of steps)	☐ Moderate symptoms (shortness of breath after walking on flat ground)	☐ Severe symptoms (shortness of breath at rest; requiring 0_2)
Lung score: **%** FEV1 ☐	☐ FEV1≥80%	☐ FEV1 60-79%	☐ FEV1 40-59%	☐ FEV1 ≤39%
Pulmonary function tests ☐ Not performed				
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):* _____				

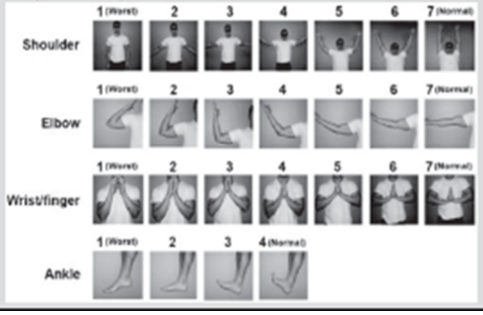
	SCORE 0	SCORE 1	SCORE 2	SCORE 3
JOINTS AND FASCIA P-ROM score *(see below)* Shoulder (1-7):___ Elbow (1-7): ____ Wrist/finger (1-7):___ Ankle (1-4):___	☐ No symptoms	☐ Mild tightness of arms or legs, normal or mild decreased range of motion (ROM) **AND** not affecting ADL	☐ Tightness of arms or legs **OR** joint contractures, erythema thought due to fasciitis, moderate decrease ROM **AND** mild to moderate limitation of ADL	☐ Contractures **WITH** significant decrease of ROM ***AND*** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				
GENITAL TRACT (*See Supplemental figure*‡) ☐ Not examined *Currently sexually active* ☐ Yes ☐ No	☐ No signs	☐ Mild signs‡ and females with or without discomfort on exam	☐ Moderate signs‡ and may have symptoms with discomfort on exam	☐ Severe signs‡ with or without symptoms
☐ *Abnormality present but explained entirely by non-GVHD documented cause (specify):*_____				

Other indicators, clinical features or complications related to chronic GVHD (check all that apply and assign a score to severity (0-3) based on functional impact where applicable none – 0,mild -1, moderate -2, severe – 3)

☐ Ascites (serositis)___	☐ Myasthenia Gravis___	
☐ Pericardial Effusion___	☐ Peripheral Neuropathy___	☐ Eosinophilia > 500/µl___
☐ Pleural Effusion(s)___	☐ Polymyositis___	☐ Platelets <100,000/µl ___
☐ Nephrotic syndrome___	☐ Weight loss>5%* without GI symptoms ___	☐ Others (specify):_____

Overall GVHD Severity *(Opinion of the evaluator)* ☐ **No GVHD** ☐ **Mild** ☐ **Moderate** ☐ **Severe**

Photographic Range of Motion (P-ROM)



Source: Jagasia MH, Hildegard TG, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. The 2014 Diagnosis and Staging Working Group Report. Biology of blood and marrow transplantation. Biol Blood Marrow Transplant. 2015 March;21(3): 389–401.e1. doi:10.1016/j.bbmt.2014.12.001.

3. Categories of Acute and Chronic Graft-Versus-Host Disease

Categories of Acute and Chronic Graft-Versus-Host Disease			
Category	**Time of Symptoms after HCT**	**Presence of Acute GVHD Features**	**Presence of Chronic GVHD Features***
Acute GVHD			
Classic acute GVHD	≤ 100 d	Yes	No
Persistent, recurrent or late-onset acute GVHD	>100 d	Yes	No
Chronic GVHD			
Classic chronic GVHD	No time limit	No	Yes
Overlap syndrome	No time limit	Yes	Yes

D: day; GVHD: graft-versus-host disease; HCT: hematopoietic cell transplant

*As defined in Section 4 (below)

Source: Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant. 2005;11:945–56. [PubMed: 16338616]

4. Signs and Symptoms of Chronic Graft-Versus-Host Disease

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)	Distinctive (Seen in Chronic GVHD, but Insufficient Alone to Establish a Diagnosis of Chronic GVHD)	Other Features*	Common (Seen with Both Acute and Chronic GVHD)
Skin	Poikiloderma	Depigmentation	Sweat impairment	Erythema
	Lichen planus-like features		Ichthyosis	Maculopapular rash
	Sclerotic features		Keratosis pilaris	Pruritus
	Morphea-like features		Hypopigmentation	
	Lichen sclerosis-like features		Hyperpigmentation	
Nails		Dystrophy		
		Longitudinal ridging, splitting, or brittle features		
		Onycholysis		
		Pterygium unguis		
		Nail loss (usually symmetric; affects most nails)†		
Scalp and body hair		New onset of scarring or nonscarring scalp alopecia (after recovery from chemoradiotherapy) Scaling, papulosquamous lesions	Thinning scalp hair, typically patchy, coarse, or dull (not explained by endocrine or other causes)	
			Premature gray hair	
Mouth	Lichen-type features	Xerostomia		Gingivitis
	Hyperkeratotic plaques	Mucocele		Mucositis
	Restriction of mouth opening from sclerosis	Mucosal atrophy Pseudomembranes† Ulcers†		Erythema Pain
Eyes		New onset dry, gritty, or painful eyes‡	Photophobia	
		Cicatricial conjunctivitis ‡Keratoconjunctivitis sicca‡ Confluent areas of punctate keratopathy	Periorbital hyperpigmentation	

Table continued on next page

Organ or Site	**Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)**	**Distinctive (Seen in Chronic GVHD, but Insufficient Alone to Establish a Diagnosis of Chronic GVHD)**	**Other Features***	**Common (Seen with Both Acute and Chronic GVHD)**
			Blepharitis (erythema of the eyelids with edema)	
Genitalia	Lichen planus-like features	Erosions†		
	Vaginal scarring or stenosis	Fissures†		
		Ulcers†		
GI tract	Esophageal web Strictures or stenosis in the upper to mid third of the esophagus†		Exocrine pancreatic insufficiency	Anorexia Nausea Vomiting Diarrhea
				Weight loss
				Failure to thrive (infants and children)
Liver				Total bilirubin, alkaline phosphatase > 2 × ULN†
				ALT or AST > 2 × ULN†
Lung	Bronchiolitis obliterans diagnosed with lung biopsy	Bronchiolitis obliterans diagnosed with PFTs and radiology‡		BOOP
Muscles, fascia, joints	Fasciitis Joint stiffness or contractures secondary to sclerosis	Myositis or polymyositis‡ Myositis or polymyositis‡	Edema Muscle cramps Arthralgia or arthritis	
Hematopoietic and immune			Thrombocytopenia	
			Eosinophilia	
			Lymphopenia	
			Hypo- or hypergammaglobulinemia	
			Autoantibodies (AIHA and ITP)	

Table continued on next page

Organ or Site	Diagnostic (Sufficient to Establish the Diagnosis of Chronic GVHD)	Distinctive (Seen in Chronic GVHD, but Insufficient Alone to Establish a Diagnosis of Chronic GVHD)	Other Features*	Common (Seen with Both Acute and Chronic GVHD)
Other			Pericardial or pleural effusions	
			Ascites	
			Peripheral neuropathy	
			Nephrotic syndrome	
			Myasthenia gravis	
			Cardiac conduction abnormality or cardiomyopathy	

Abbreviations: AIHA: autoimmune hemolytic anemia; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BOOP: bronchiolitis obliterans-organizing pneumonia; GVHD: graft-versus-host disease; ITP: idiopathic thrombocytopenic purpura; PFTs: pulmonary function tests; ULN: upper limit of normal.

* Can be acknowledged as part of the chronic GVHD symptomatology if the diagnosis is confirmed.

† In all cases, infection, drug effects, malignancy, or other causes must be excluded.

‡ Diagnosis of chronic GVHD requires biopsy or radiology confirmation (or Schirmer test for eyes).

Source: Filipovich AH, Weisdorf D, Pavletic S, Socie G, Wingard JR, Lee SJ, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant. 2005;11:945–56. [PubMed: 16338616]

APPENDIX J
LIVER SAFETY MONITORING AND ASSESSMENT

APPENDIX J

LIVER SAFETY MONITORING AND ASSESSMENT

Any participant enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases to > 3 × upper limit of normal (ULN; to > 5 × ULN in participants with liver metastases) or total bilirubin (TBL) > 2 × ULN, should undergo detailed testing for liver enzymes (including at least alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP] and TBL). Testing should be repeated within 48-72 hours of notification of the test results. Participants should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

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

	ALT or AST		**TBL**
Moderate	> 3 x ULN (in participants without liver metastases), > 5 x ULN (in participants with liver metastases)	or	> 2 x ULN
Severe†	> 3 x ULN	and	> 2 x ULN

In addition, the participant 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 (in the absence of liver metastases)
- ALT or AST > 3 × ULN and International normalization 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-CRF (LA-CRF) or appropriate document. Participants 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 participant 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 an SAE. The Sponsor should be contacted and informed of all participants 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. New-onset diseases should be recorded as "AEs" in Advantage eClinical. Symptoms are recorded on the LA-CRF. Illnesses and conditions such as hypotensive events and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis is seen in obese hyperlipoproteinemic and/or diabetic participants and may be associated with fluctuating aminotransferase levels. The investigator should ensure that the medical history form captures any illness that predates study enrollment that may be relevant in assessing hepatic function.
    - Obtain a history of concomitant drug use (including nonprescription medication, complementary and alternative medications), alcohol use, recreational drug use and special diets. Medications, 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 participant'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 PT or 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 LFTs, such as viral hepatitis, preexisting or acute liver disease, presence of liver metastases or exposure to other agents associated with liver injury, the participant may be discontinued from the study. The investigator may determine that it is not in the participant'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 (in participants without liver metastases)
- ALT or AST > 3 × ULN and TBL > 2 × ULN or INR > 1.5 (If INR testing is applicable/evaluated)
- ALT or AST > 5 × ULN and TBL > 2 × ULN (in participants with liver metastases)
- 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 participant with moderate or severe hepatic laboratory tests is not possible, drug should be discontinued.

† Hy's Law Definition: drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10% - 50% mortality (or transplant). The 3 "requirements" for Hy's Law are the following:

1. Evidence that a drug can cause hepatocellular-type injury, generally shown by an increase in transaminase elevations higher than 3 × ULN (2 × ULN elevations are too common in treated and untreated participants to be discriminating)
2. Cases of increased TBL (at least 2 × ULN) with concurrent transaminase elevations at least 3 × ULN and no evidence of intra- or extra-hepatic bilirubin obstruction (elevated ALP) or Gilbert's syndrome
3. No other reason can be found to explain the combination of increased transaminases and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

Source: Temple R. Hy's law: predicting serious hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006;15:241-3; FDA. Guidance for industry-drug-induced liver injury: premarketing clinical evaluation. 2009.

APPENDIX K
COMMON SERIOUS ADVERSE EVENTS

APPENDIX K

COMMON SERIOUS ADVERSE EVENTS

The purpose of this appendix is to outline those serious AEs that commonly occur in the study population. The events listed below require reporting through the expedited AE reporting system via Advantage eClinical.

The following is a list of SAEs that the Sponsor considers to be associated with the disease state being studied. **The list does NOT change the reporting obligations or prevent the need to report an AE meeting the definition of an SAE.** The purpose of this list is to identify some events reported as SAEs which may not require expedited reporting to the regulatory authorities based on the classification of "common SAEs."

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

Serious Adverse Events Caused by Active AML/Transplant	Grades Usually Observed with Active AML/Transplant
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
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
Table continued on next page	

Serious Adverse Events Caused by Active AML/Transplant	Grades Usually Observed with Active AML/Transplant
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 - 4
Hypertrophied gums	0 - 1
Hyperuricemia	0 - 1
Hypokalemia	0 - 2
Hypotension	0 - 2
Hypoxia	0 - 3
INR increased	0 - 1
Lactate dehydrogenase increased	0 - 2
Malaise	0 - 2
Multiorgan failure	0 - 5
Nausea	0 - 2
Oral dysesthesia	0 - 2
Petichiae	0 - 2
Pruritus	0 - 3
Skin and subcutaneous tissue disorders	0 - 3
Transient ischemic attacks	0 - 2
Tumor lysis syndrome	3 - 5
Vasculitis	0 - 5
Vomiting	0 - 2
Weight loss	0 - 2

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

APPENDIX L
CHARACTERIZATION OF CONDITIONING REGIMENS

APPENDIX L

CHARACTERIZATION OF CONDITIONING REGIMENS

Myeloablative Conditioning (MAC)*	**Reduced Intensity/Non-Myeloablative Conditioning (RIC/NMA)**
MAC regimens are defined as regimens containing: • Total body irradiation (TBI) ≥ 5 Gy single dose or ≥ 8 Gy fractionated, or • Busulfan > 8 mg/kg PO or 6.4 mg/kg IV (total dose), or • Treosulfan > 30000 mg/m^2 (or > 30 g/m^2), or • Melphalan > 150 mg/m^2, or • Thiotepa ≥ 10 mg/kg.	Any regimen that does not meet criteria to be defined as MAC regimen will be characterized as RIC/NMA

MAC: myeloablative conditioning; NMA: non-myeloablative; RIC: reduced intensity conditioning; TBI: total body irradiation

*New agents, dosing or regimens that are developed during the study that may be considered myeloablative and are not documented in the protocol will be documented in the conditioning regimen adjudication charter and will be included in the next available protocol amendment.

APPENDIX M
CORRELATIVE LABORATORY STUDIES

APPENDIX M

CORRELATIVE LABORATORY STUDIES

The correlative laboratory studies for this clinical trial are directed at several goals. The first goal is to re-test the diagnostic specimens with a FLT3-ITD to-be-marketed companion diagnostic test, in the event a companion diagnostic is essential for the safe and effective use of ASP2215. A related, second goal will be to determine the diagnostic FLT3 mutant-to-wild type allelic ratio in as many participants as possible and correlate that result with trial endpoints. A third goal is to assess the correlation of a standardized assay for minimal residual disease (MRD) with survival and relapse. These results could inform future study designs of FLT3 inhibitors. A fourth goal will be to correlate the presence or absence (at diagnosis or during therapy) of AML-associated mutations (such as NPM1) with trial endpoints. A fifth goal will be to assess FLT3 mutation status at the time of relapse.

As detailed in the Informed Consent document, all participants in this study will have the opportunity to give consent to allow the trial investigators and their designated affiliates access to any diagnostic material (BM aspirate or blood, or DNA or RNA derived therefrom) available. It is recognized that diagnostic material may be available for only a subset of participants. The diagnostic material will be used to 1) compare with the results of local testing for a FLT3/ITD mutation; 2) estimate the FLT3/ITD mutant-to-wild type allelic ratio present at diagnosis; and 3) assay for the presence of AML-associated mutations (for example, DNMT3a, NPM1). Those diagnostic samples that are already stored at Invivoscribe will not be available for central banking with the BMT CTN as they are the property of Invivoscribe (which maintains a policy of keeping such samples for a 15 year period).

Bone marrow aspirates will be collected prior to allogeneic transplant and at designated time points following transplant as detailed in the protocol (Table 4, Schedule of Assessments). During the BM aspirate procedure, the first pull (approximately 2 mL) of the marrow aspirate will be specifically collected and shipped to the Reference Laboratory (Invivoscribe). The aspirate material will be used to assay for MRD using a next-generation sequencing (NGS)-based test. The results of this MRD assay represent a key secondary endpoint of this trial, and will be correlated with relapse and survival endpoints.

Specimens collected for MRD will be stored at the reference laboratory until completion of the study (and all designated correlative lab studies or bridging studies if required by regulatory authorities), and then samples from North American participants will be transferred to the BMT CTN for storage and possible future use by designated investigators.

APPENDIX N
REFERENCES

APPENDIX N

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