A Phase 1/2 Open-label Rollover Study for Subjects Who Have Participated in an Astellas Sponsored ASP2215 Trial

Protocol for Phase 1/2 Study of ASP2215

ISN/Protocol 2215-CL-0109

Version 2.1

Incorporating Non-Substantial Amendment 1 [See Attachment 1]

19 July 2018

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Sponsor:

Astellas Pharma Global Development, Inc. (APGD)
1 Astellas Way
Northbrook, IL 60062

Protocol History:
Version 1.0 [22Jun2015]
Version 2.0 [17May2018] Incorporating Substantial Amendment 1

Investigator: Investigator information is on file at Astellas

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I. SIGNATURES

1. SPONSOR'S SIGNATURE

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

Specific to Japan:

AGREEMENT BETWEEN THE SPONSOR'S RESPONSIBLE PERSON AND THE INVESTIGATOR

This clinical study will be conducted in adherence to GCP, ICH Guidelines and applicable laws and regulatory requirements, as well as this study protocol. As the evidence of the agreement, the investigator (CHIKEN SEKININ ISHI) and responsible person of the Sponsor (CHIKEN IRAI SEKININSHA) inscribe in the bipartite agreement.

2. INVESTIGATOR'S SIGNATURE

A Phase 1/2 Open-label Rollover Study for Subjects Who Have Participated in an Astellas Sponsored ASP2215 Trial

ISN/Protocol 2215-CL-0109

Version 2.1 Incorporating Non-Substantial Amendment 1

19 Jul 2018

I have read all pages of this clinical study protocol for which Astellas is the Sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines and applicable local regulations. I will also ensure that sub-Investigator(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: ----------

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

24 h-Contact for Serious Adverse Events (SAEs) **See Section 5.5.5**	PPD PPD **Global Medical Oncology Science** **Astellas Pharma Global Development, Inc.** PPD **Please fax or email the SAE Worksheet to:** **Astellas Pharma Global Development, Inc.** **Global Pharmacovigilance** **North America Fax Number: 888-396-3750** **(North America Alternate Fax: 847-317-1241)** **International Fax Number: +44-800-471-5263** **Email: safety-us@astellas.com**
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III. LIST OF ABBREVIATIONS AND DEFINITION OF KEY TERMS

List of Abbreviations

Abbreviations	Description of Abbreviations
$5HT_1R$	5-hydroxytryptamine receptor 1
$5HT_{2B}R$	5-hydroxytryptamine receptor 2B
ΔQTcF	Fridericia-corrected QT interval corrected relative to baseline
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
APGD	Astellas Pharma Global Development, Inc.
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUST	Astellas United States Technologies
AXL	AXL tyrosine kinase
BCRP	Breast cancer resistance protein
Ca^{+2}	Calcium
CK	Creatine kinase
CR	Complete remission
CRc	Composite complete remission
CRF	Case report form
CRi	Complete remission with incomplete hematologic recovery
CRO	Contract Research Organization
CRp	Complete remission with incomplete platelet recovery
CTCAE	Common Terminology Criterion for Adverse Events
C_{trough}	Observed trough concentration
CYP	Cytochrome P450
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EGFR	Epidermal growth factor receptor
FLT3	FMS-like tyrosine kinase
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IC_{50}	Half maximal inhibitory concentration
ICF	Informed Consent Form

Abbreviations	Description of Abbreviations
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IND	Investigational new drug
INR	International normalization ratio
IRB	Institutional Review Board
IRT	Interactive response technology
ITD	Internal tandem duplication
LA-CRF	Liver Abnormality-Case Report Form
LFT	Liver function test
LTK	Leukocyte receptor tyrosine kinase
MATE1	Multidrug and toxin extrusion protein 1
NCI	National Cancer Institute
NDA	New Drug Application
NOAEL	No observed adverse effect level
OATP	Organic anion transporting polypeptide
PD	Protocol deviation
P-gp	P-glycoprotein
PR	Partial remission
PT	Preferred term
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TLFs	Tables, listings and figures
ULN	Upper limit of normal
WHO	World Health Organization

Definition of Key Study Terms

Terms	Definition of Terms
Baseline	Observed values/findings which are regarded as the starting point for comparison.
Enroll	To register or enter into a clinical trial. NOTE: Once a subject has been enrolled, the clinical trial protocol applies to the subject.
Intervention	The drug, therapy or process under investigation in a clinical study that is believed to have an effect on outcomes of interest in a study (e.g., health-related quality of life, efficacy, safety and pharmacoeconomics).
Investigational period	Period of time where major interests of protocol objectives are observed and where the test drug or comparative drug (sometimes without randomization) is usually given to a subject and continues until the last assessment after completing administration of the test drug or comparative drug.
Screen failure	Potential subject who signed consent but did not meet 1 or more criteria required for participation in a trial and did not randomize to the trial.
Screening	A process of active consideration of potential subjects for enrollment in a trial.
Screening period	Period of time before entering the investigational period, usually from the time of starting a subject signing consent until just before the registration.
Study period	Period of time from the first site initiation date to the last site completing the study.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values.

IV. SYNOPSIS

Date and Version # of Protocol Synopsis:	19 Jul 2018, Version 2.1
Sponsor: Astellas Pharma Global Development Inc. (APGD)	**Protocol Number:** 2215-CL-0109
Name of Study Drug: ASP2215	**Phase of Development:** Phase 1/2
Title of Study: A Phase 1/2 Open-label Rollover Study for Subjects Who Have Participated in an Astellas Sponsored ASP2215 Trial	
Planned Study Period: From 3Q2015 to 3Q2023 Study period implies the period from the first screened subject at the first site until the last scheduled visit of the last subject in the study.	
Study Objective(s): The purpose of the study is to provide access to continued treatment for subjects who participated in other Astellas sponsored ASP2215 (single agent) trials and for whom the Investigator feels the subject may benefit from continued treatment.	
Planned Total Number of Study Centers and Location(s): Sites that currently have subjects actively participating in an Astellas sponsored ASP2215 trial. North America, Europe, Asia	
Study Population: Subjects who are actively participating in an Astellas sponsored ASP2215 trial that has completed the primary analysis, whom the investigator feels may have potential to continue to derive clinical benefit from the treatment with ASP2215, and who did not meet any of the study discontinuation criteria in the present study.	
Number of Subjects to be Enrolled / Randomized: Dependent on the number of subjects enrolled in the protocols rolling over into this trial.	
Study Design Overview: This is a multi-center, open-label, rollover protocol for Astellas sponsored, single agent ASP2215 trials in AML and advanced solid tumors. Subjects must have completed the protocol requirements of the previous ASP2215 trial and be actively participating in the previous ASP2215 trial. In addition, subjects must be continuing to derive clinical benefit from treatment with ASP2215 without any persistent intolerable toxicity from ASP2215, in the opinion of the investigator and must meet the entry criteria for this rollover study prior to being enrolled. Subjects should sign the informed consent at their cycle 1 day 1 visit. The assessments from the last treatment visit from the parent study can be utilized for the cycle 1 day 1 visit. The subject will then receive ASP2215 study drug for the rollover study and return all ASP2215 study drug from the parent study.	

Inclusion/Exclusion Criteria:

Inclusion:

1. Institutional Review Board (IRB)-/Independent Ethics Committee (IEC)-approved written Informed Consent and privacy language as per national regulations [e.g., Health Insurance Portability and Accountability Act (HIPAA) Authorization for US sites] must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject must currently be participating in an Astellas sponsored ASP2215 trial, receiving ASP2215 and have not met any discontinuation criteria of the parent study and can enroll into this rollover study without interruption of study drug, or with no more than 2 weeks interruption in study drug.
3. Subject must be deriving benefit from continued treatment without any persistent intolerable toxicity from continued treatment of ASP2215, as determined by the investigator.
4. Female subject must either:
    - Be of non-childbearing potential:
        - post-menopausal (defined as at least 1 year without any menses) prior to Screening, or
        - documented surgically sterile or post-hysterectomy (at least one 1 month prior to Screening)
    - Or, if of childbearing potential,
        - Agree not to try to become pregnant during the study and for 180 days after the final study drug administration
        - And have a negative urine pregnancy test at screening
        - And, if heterosexually active, agree to consistently use two forms of highly effective birth control* (at least one of which must be a barrier method) starting at Screening and throughout the study period and for 180 days after the final study drug administration.
5. Female subject must agree not to breastfeed starting at Screening and throughout the study period, and for 60 days after the final study drug administration.
6. Female subject must not donate ova starting at Screening and throughout the study period, and for 180 days after the final study drug administration.
7. Male subject and their female spouse/partners who are of childbearing potential must be using highly effective contraception consisting of two forms of birth control* (at least one of which must be a barrier method) starting at Screening and continue throughout the study period, and for 120 days after the final study drug administration.
8. Male subject must not donate sperm starting at Screening and throughout the study period and, for 120 days after the final study drug administration.
9. Subject agrees not to participate in another interventional study while on treatment.

*Highly effective forms of birth control include:

- Consistent and correct usage of established oral contraception.
- Established intrauterine device (IUD) or intrauterine system (IUS).
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository (for regions where spermicidal foam/gel/film/cream/suppository is not available e.g., Japan)
- Calendar-based contraceptive methods (Knaus-Ogino or rhythm method applicable to subjects enrolled at sites in Japan).

Waivers to the inclusion criteria will NOT be allowed.

Exclusion:

1. Subject requires treatment with concomitant drugs that are strong inducers of cytochrome P450 (CYP)3A.
2. Subject requires treatment with concomitant drugs that target serotonin 5-hydroxytryptamine receptor 1 ($5HT_1R$) or 5-hydroxytryptamine receptor 2B ($5HT_{2B}R$) or sigma nonspecific receptor with the exception of drugs that are considered absolutely essential for the care of the subject.
3. Subject requires treatment with concomitant drugs that are strong inhibitors or inducers of P-glycoprotein (P-gp) with the exception of drugs that are considered absolutely essential for the care of the subject.

Waivers to the exclusion criteria will NOT be allowed.

Investigational Product(s):

ASP2215 tablets containing 40 mg of active ingredient.

Dose(s):

Subject will continue dosing at the dose received in original study with ASP2215, dose not to exceed 280 mg. If the original subject dose is over 280 mg, the subject will begin dosing in this protocol at 280 mg.

Mode of Administration:

ASP2215 will be administered orally.

Comparative Drug(s):

Not applicable

Concomitant Medication Restrictions or Requirements:

Treatment with concomitant drugs that are strong inducers of CYP3A are prohibited. Treatment with concomitant drugs that are strong inhibitors or inducers of P-gp and concomitant drugs that target serotonin $5HT_1R$ or $5HT_{2B}R$ or sigma nonspecific receptor are to be avoided with the exception of drugs that are considered absolutely essential for the care of the subject. Treatment with concomitant drugs that are strong inhibitors of CYP3A should be avoided with the exception of antibiotics, antifungals and antivirals that are used as standard of care to prevent or treat infections. If CYP3A inhibitors are used concomitantly, subjects should be closely monitored for AEs.

Precaution should be used in treatment of ASP2215 with concomitant drugs that are known to prolong QT or QTc intervals.

Duration of Treatment:

Subject may continue on study drug until any of the criteria for study drug discontinuation have been met.

Discontinuation Criteria:

- Subject declines further study participation (i.e. withdrawal of consent).
- Subject develops an intolerable or unacceptable toxicity.
- Investigator/sub-Investigator determines the subject is no longer receiving clinical benefit from study treatment.
- Investigator/sub-Investigator determines that the continuation of the study treatment will be detrimental to the subject.

- Female subject becomes pregnant.
- Subject is lost to follow-up despite reasonable efforts by the Investigator to locate the subject.
- Death.

If an Investigator intends to discontinue participation in the study, the Investigator must immediately inform the Sponsor.

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

Endpoints for Evaluation:

Primary

Safety, as measured by AEs and safety laboratory evaluations.

Secondary

No formal secondary analysis is planned.

Statistical Methods:

Sample Size Justification:

The sample size for this protocol is based on the number of subjects who are continuing to derive benefit from treatment with ASP2215 as assessed by their Investigator at the completion of the original study they enrolled under.

Efficacy:

Not applicable

Pharmacokinetics:

Not applicable

Pharmacodynamics:

Not applicable

Safety:

Safety measures will be summarized and listed for all subjects.

Interim Analysis:

Not applicable

V. SCHEDULE OF ASSESSMENTS

Table 1 Schedule of Assessments

Assessments	**Screening** [a] (Day -28 to 1)	**Treatment Cycle 1 Day 1** [a]	**Day 1 of Treatment Cycle 3 and Every Other Cycle (i.e., Cycles 5, 7, 9, etc.)** [b] (+/- 5 days)	**End of Treatment** [c]
Informed Consent	X			
Verify Inclusion/Exclusion	X	X		
Subject Enrollment		X		
Demographics [d]		X		
Medical History [e]		X		
Physical Examination		X		X
Vital Signs		X		X
ECOG Performance Status		X		X
Clinical Laboratory Tests (chemistry, hematology, coagulation, urinalysis)		X	X	X
Pregnancy Test for Women of Childbearing Potential (WOCBP)		X	X	X
Prior and Concomitant Medications	←	—	—	→
Adverse Event Assessment [g]	←	—	—	→
ASP2215 Administration [h]		← Daily →		

ECOG: Eastern Cooperative Oncology Group

a. Subject should sign the informed consent at the final visit of the original study they enrolled in. The Screening and Treatment Cycle 1 Day 1 visits may be combined. A subject's procedures performed during their final visit for the original study will be used for Treatment Cycle 1 Day 1 if the final visit occurred within 7 days prior to visit.
b. Each treatment cycle is 28 days. Subject to be seen on Day 1 of every 2 treatment periods (every 8 weeks).
c. End of treatment visit to be conducted within 30 days of last dose, prior to starting a new anticancer therapy or upon marketing authorization and commercial availability of ASP2215 in the country of residence. Subjects discontinuing due to commercial availability will be notified by the site and an end of treatment visit scheduled within 3 months.
d. Demographic data will be obtained from the original study.
e. Medical history will be obtained from the original study.
f. Adverse events from the original study that are ongoing at the time of Screening will continue to be followed as adverse events during this protocol and should not be captured as medical history. Adverse events will be captured until the End of Treatment visit, 30 days after last dose, or until start of a new anticancer therapy, whichever is sooner.
g. Subject will continue dosing at the dose received in original study with ASP2215 dose not to exceed 280 mg. If the original subject dose is over 280 mg, the subject will begin dosing in this protocol at 280 mg.

1 INTRODUCTION

1.1 Background

ASP2215 hemifumarate (gilteritinib), is a new chemical entity discovered by Astellas Pharma Inc. in collaboration with Kotobuki Pharmaceutical Co., Ltd. It is a FMS-like tyrosine kinase 3 (FLT3) inhibitor under development for the treatment of acute myeloid leukemia (AML). ASP2215 also has inhibitory activities for AXL tyrosine kinase (AXL), leukocyte receptor tyrosine kinase (LTK) and anaplastic lymphoma kinase (ALK).

FLT3 is a member of the class III receptor tyrosine kinase family that is normally expressed on the surface of hematopoietic progenitor cells. FLT3 and its ligand play an important role in proliferation, survival and differentiation of multipotent stem cells. FLT3 is overexpressed in the majority of AML cases. In addition, activated FLT3 with an internal tandem duplication (ITD) in and around the juxtamembrane domain and tyrosine kinase domain (TKD) mutations at around D835 in the activation loop are present in 28% to 34% and 11% to 14% of AML cases, respectively [Schlenk & Döhner, 2009]. These activated mutations in FLT3 are oncogenic and show transforming activity in cells [Yamamoto et al, 2001]. Furthermore, patients with activated FLT3 show poor prognosis, with a higher relapse rate, more rapid relapse, reduced disease-free survival and overall survival [Patel et al, 2012; Gale et al, 2008; Yanada et al, 2005; Moreno et al, 2003].

ALK is another receptor tyrosine kinase; this molecule appears to play a role in the development of the nervous system, although the mechanisms remain poorly understood [Camidge & Doebele, 2012]. Non-small cell lung cancer (NSCLC) with ALK gene arrangements represents approximately 4% to 5% of all NSCLC patients in both Caucasians and Asians. In absence of treatment with a targeted agent, ALK gene arrangements are associated with a poorer clinical outcome [Chia et al, 2014]. Over 20 ALK fusion partners have been identified in NSCLC. The most common ALK fusion is echinoderm microtubule associated protein like 4 (EML4)-ALK, representing 29% to 33% of gene fusions identified [Chia et al, 2014]. EML4-ALK demonstrated transforming activities in vitro and in vivo, confirming its oncogenic properties [Soda et al, 2007].

Nonclinical data suggest that AXL overexpression mediates resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in NSCLC with an EGFR activating mutation and that AXL inhibition can restore sensitivity to EGFR tyrosine kinase inhibitors. Nonclinical data also suggest that in some cases, overexpression of growth arrest-specific 6 (GAS6; the ligand for AXL) can promote AXL activation in the setting of acquired resistance in the absence of AXL overexpression [Zhang et al, 2012]. The incidence of AXL or GAS6 overexpression in advanced NSCLC has not been extensively characterized. In 35 matched EGFR-mutant NSCLC specimens obtained from patients both before treatment with erlotinib or gefitinib and after the development of resistance, increased (2-fold or greater) expression of AXL was observed in 7 of 35 (20%) specimens and GAS6 in 7 of 28 (25%) specimens [Zhang et al, 2012].

1.2 Nonclinical and Clinical Data

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

1.2.1 Nonclinical Data

ASP2215 inhibited activities of FLT3, nucleophosmin-1 gene-ALK, LTK, ALK and AXL kinases at 1 and 5 nmol/L and tropomyosin receptor kinase A, ROS, RET and MER kinases at 5 nmol/L by over 50%. ASP2215 inhibited FLT3, echinoderm microtubule-associated protein-like 4-ALK variant 1 and KIT kinase activities with the half maximal inhibitory concentration (IC_{50}) values of 0.291, 1.2 and 229 nmol/L, respectively.

ASP2215 inhibited each radioligand binding to adenosine A1 receptor (rat), serotonin 5-hydroxytryptamine receptor 1 ($5HT_1R$) (nonselective, rat), serotonin 5-hydroxytryptamine receptor 2B ($5HT_{2B}R$) (human) and sigma receptor (nonselective, guinea pig) with IC_{50} values of 4.57, 4.90, 0.190 and 0.615 μmol/L, respectively.

ASP2215 inhibited human $5HT_{2B}R$ function in a cell function assay with an IC_{50} value of 5.82 μmol/L without showing agonistic activity.

ASP2215 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 inhibited the growth of MV4-11 cells with IC_{50} value of 0.92 nmol/L. In MV4-11 cells, treatment of ASP2215 at 0, 0.1, 1 and 10 nmol/L resulted in FLT3 phosphorylation of 100%, 86%, 19% and 7%, respectively.

ASP2215 induced significant growth inhibition of MV4-11 tumors and tumor regression in vivo. Further, ASP2215 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 was not affected at any tested doses.

These results indicate ASP2215 should show the antitumor efficacy against AML subjects with FLT3-ITD and FLT3 mutation at D835.

The IC_{50} value of ASP2215 against FLT3 kinase was about 800-fold lower than that against KIT kinase, and neutropenia was not observed in the toxicity studies in rats and dogs.

In Caco-2 cells, the permeability of ASP2215 was between that of known low and high permeability markers. ASP2215 was a substrate for P-glycoprotein (P-gp), but not a substrate for breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP)1B1, OATP1B3 or organic cation transporter (OCT) 1. ASP2215 demonstrated a potential to inhibit BCRP and MATE1 at clinically relevant concentrations of ASP2215.

No major human-specific ASP2215 metabolites were formed by liver microsomes or hepatocytes. The main enzyme involved in the metabolism of ASP2215 was estimated to be cytochrome P450 (CYP) 3A4. ASP2215 has a potential to induce CYP enzyme activities (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4/5) and mRNA levels

(CYP2B6, CYP2C8, CYP2C9 and CYP3A4). However, these results should be interpreted with caution because these effects were not uniformly observed in all donor samples and the concentration-dependency of these effects could not be evaluated. For CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP2D6 inhibition, IC_{50} values were > 100 µmol/L. Very weak direct inhibition of CYP2C19 and CYP3A was observed. Overall, ASP2215 showed minimal direct inhibition of CYP enzymes at clinically relevant concentrations.

1.2.2 Clinical Data

1.2.2.1 Studies Using Human Biomaterials

No human-specific ASP2215 metabolites were formed by liver microsomes or hepatocytes, with the exception of 1 minor metabolite detected in human hepatocytes. ASP2215 is a substrate for CYP3A4 and P-gp but not a substrate for human BCRP, OATP1B1, OATP1B3 or OCT1. The IC_{50} values of inhibition to drug transport by P-gp, BCRP, OATP1B1, OCT1, OCT2, MATE1 and MATE2-K inhibition are > 30, 1.41, 29.4, 2.92, 34.9, 0.0543 and 47.7 µmol/L, respectively.

1.2.2.2 Clinical Pharmacokinetics and Pharmacodynamics

The pharmacokinetic parameters of unchanged drug after single and multiple dosing of ASP2215 to AML subjects were investigated in the dose escalation cohort of Study 2215-CL-0101. Assessment of observed trough concentration (C_{trough}) over time for individual subjects (both dose escalation and dose expansion cohorts) showed that in most subjects, the trough concentration of ASP2215 appeared to reach steady state by day 15 of multiple administrations of ASP2215 from 20 to 120 mg once daily.

Since ASP2215 is mainly metabolized by CYP3A4, the effect of a strong CYP3A4 inhibitor (voriconazole) on the pharmacokinetics of ASP2215 was investigated as a part of Study 2215-CL-0101. Since a substantial number of subjects in Study 2215-CL-0101 required coadministration of strong (voriconazole and posaconazole) or moderate (fluconazole) CYP3A4 inhibitors during the course of treatment, C_{trough}/dose values of these subjects were compared with subjects that did not receive CYP3A4 inhibitors. Overall, these data suggest a low probability for increased exposure of ASP2215 by strong or moderate CYP3A4 inhibitors.

Plasma inhibitory assay (PIA) from the samples collected predose and postdose on days 1, 8, 15 and 29 demonstrated sustained inhibition of phospho-FLT3 at doses 80 mg and higher.

Evaluation of time matched ASP2215 plasma concentrations Fridericia-corrected QT interval corrected relative to baseline (ΔQTcF) was performed. Comparison of time matched ASP2215 plasma concentrations with ΔQTcF values showed no substantial relationship, although a positive trend was observed. Overall these data indicate a low probability of a substantial increase in ΔQTcF over the range of ASP2215 plasma concentrations evaluated (20 to 300 mg).

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

1.2.2.3 Clinical Efficacy

In Study 2215-CL-0101, as of 02Feb2015, 154 subjects were evaluable for response. The response assessments were done based on central laboratory evaluation of bone marrow samples supplemented with local results when the central results were not available (derived response).

Based on the derived response at end of treatment in the 154 subjects (both FLT3-mutation positive and negative) who received at least 1 dose of ASP2215, 41 (26.6%) subjects achieved composite complete remission (CRc), and the best overall response rate (CRc + PR) was 35.7%.

Nearly all subjects that achieved a derived response of partial remission (PR) or CRc at the end of treatment were FLT3-mutation positive. Based on the derived response in the 98 FLT3-mutation positive subjects at the end of treatment, 36 (36.7%) subjects achieved CRc, and the best overall response rate was 49.0%. Five (5.1%) subjects achieved complete remission (CR), 3 (3.1%) subjects achieved complete remission with incomplete platelet recovery (CRp), 28 (28.6%) subjects achieved complete remission with incomplete hematologic recovery (CRi) and 12 (12.2%) subjects achieved PR.

CRc rates for 80, 120 and 200 mg dose groups were 41.7%, 48.6% and 45.8% respectively. Among the 77 FLT3-mutation positive subjects in the 80 mg, 120 mg, 200 mg, 300 mg and 450 mg dose groups, 34 (44.2%) had achieved CRc as the derived response at the end of treatment and the overall response rate was 55.8%. Four (5.2%) subjects achieved CR, 3 (3.9%) subjects achieved CRp, 27 (35.1%) subjects achieved CRi and 9 (11.7%) subjects achieved PR

Based on the derived response in the 47 FLT3-mutation negative subjects at the end of treatment, 2 (4.3%) subjects achieved CRc, and the best overall response rate was 8.5%. Two (4.3%) subjects each achieved CRi and PR.

1.3 Summary of Key Safety Information for Study Drugs

1.3.1 Nonclinical Data

ASP2215 showed a concentration-dependent suppression effect on the human ether-a-go-go-related gene current in HEK293 cells at concentrations of 3×10^{-6}, 1×10^{-5} and 3×10^{-5} mol/L with compensated suppression rates of 18.1%, 32.8% and 70.7%, respectively; no suppression was observed at 1×10^{-6} mol/L. The IC_{50} was 1.6×10^{-5} mol/L.

ASP2215 showed no effects on the central nervous system in rats at 10 mg/kg. At 30 mg/kg and higher, decreased urination was noted. In addition, at 100 mg/kg, decreased defecation was noted. The changes in urination and defecation resolved in the recovery period.

ASP2215 did not show any effect on the cardiovascular or respiratory system in dogs up to 100 mg/kg or on the central nervous system at 1 mg/kg. At 3 mg/kg and higher, the following signs were noted: retching at 3 mg/kg, vomiting and positive fecal occult blood at 10 mg/kg and higher, a decrease in the blood calcium (Ca^{+2}) concentration at 30 mg/kg and salivation and an increase followed by a decrease in the blood Ca^{+2} concentration at 100 mg/kg. All of the findings recovered.

In the single oral dose toxicity study in rats, the approximate lethal dose level was 300 mg/kg for males and females. The major change was a gastrointestinal hemorrhagic disorder at 100 and 300 mg/kg. Reversibility of the changes noted in the surviving animals was seen. No definitive single oral dose toxicity study in dogs was conducted. In the 4-week toxicity study in dogs, a dose of 1000 mg/kg per day caused deaths and moribund sacrifices on day 2. The cause of death and moribundity was considered to be deterioration of general condition caused by gastrointestinal hemorrhage.

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

ASP2215 did not induce gene mutation in the definitive in vitro reversion test in bacteria. Similarly, ASP2215 did not induce chromosomal aberrations in the definitive in vitro chromosomal aberration test in mammalian cells. The definitive in vivo micronucleus test showed that ASP2215 has a potential to induce micronuclei in mice. Based on the results of the battery of genotoxicity studies above, it was concluded that ASP2215 has a potential to induce genotoxicity in vivo.

ASP2215 showed teratogenic potential and embryo-fetal deaths in the embryo-fetal development study in rats. The NOAEL of ASP2215 for dams and embryo-fetal development was 10 mg/kg per day.

ASP2215 showed no potential to induce phototoxicity to cultured mammalian cells.

1.3.2 ASP2215 Clinical Data

Of the first 154 subjects that received ASP2215, 147 (95.5%) developed at least one Treatment Emergent Adverse Event (TEAE) during the study. Overall, the most frequently reported TEAEs (occurring in at least 10% of subjects) include febrile neutropenia (34.4%), anemia (27.9%), fatigue (26.6%), diarrhea (26.0%), peripheral edema (20.8%), increased aspartate aminotransferase (AST) (19.5%), dyspnea (18.2%), dizziness (16.9%), epistaxis (16.2%), constipation (15.6%), pyrexia, increased alanine aminotransferase (ALT) and cough (14.9% each), nausea, sepsis and hypotension (14.3% each), vomiting (13.6%), increased blood creatinine and hypokalemia (13.0% each), decreased platelet count and hypocalcemia (12.3% each), hypomagnesemia (11.7%), hyponatremia (11.0%), thrombocytopenia, pneumonia and increased blood alkaline phosphatase (10.4% each). A total of 102 (66.2%) subjects experienced at least 1 TEAE considered by the Investigator to be at least possibly related to study drug. Common drug-related TEAEs (occurring in at least 5% of subjects) include fatigue (13.6%), diarrhea (10.4%), anemia, constipation (9.1% each), increased AST (8.4%), nausea, peripheral edema, decreased platelet count (7.8% each), dizziness (7.1%), thrombocytopenia, vomiting (6.5% each) and increased ALT (5.8%).

A total of 112 (72.7%) of the subjects developed at least one serious TEAE. The most commonly reported serious TEAE (occurring in at least 5% of subjects) include febrile neutropenia (27.3%), sepsis (13.0%), AML (9.7%), pneumonia (6.5%), hypotension (5.8%), and diarrhea (5.2%). Of the serious TEAEs, 31 (20.1%) subjects had serious TEAEs that were considered by the Investigators to be at least possibly related to ASP2215. Drug-related serious TEAEs that occurred in 2 more subjects include febrile neutropenia (1.9%), diarrhea and abnormal liver function test (1.3% each).

Forty subjects experienced a TEAE that resulted in death. One event of intracranial hemorrhage, 1 event of septic shock, and the event of hemoptysis were considered possibly related to ASP2215 by the Investigator. One event of respiratory failure and the event of febrile neutropenia were considered probably related to ASP2215 by the Investigator. One event of bacteremia was recorded as grade 3 with a fatal outcome and was considered possibly related to ASP2215 by the Investigator.

The majority of patients (92 [79.3%]) experienced at least 1 grade 3 or higher TEAE. Common grade 3 or higher TEAEs (occurring in at least 2% of patients) include febrile neutropenia (30.2%), anemia (21.6%), pneumonia and sepsis (10.3%), decreased platelet count (9.5%), disease progression (7.8%) thrombocytopenia and hypoxia (6.9%), bacteremia, acute renal failure and hypotension (5.2%), leukocytosis, decreased neutrophil count and respiratory failure (4.3%), asthenia, multi-organ failure and acute myeloid leukemia (3.4%), fatigue,

pyrexia, cellulitis, septic shock, urinary tract infection, hypokalemia, hypophosphatemia, intracranial hemorrhage, dyspnea and epistaxis (2.6%).

After the data cutoff, 1 subject in the 200 mg dose group developed altered mental status and 1 episode of seizure with MRI results consistent with posterior reversible encephalopathy syndrome (PRES). ASP2215 was discontinued and the subject's symptoms resolved. Additionally, 1 case of rhabdomyolysis with associated CK elevations was reported in a subject in the 300 mg dose group. Both SAEs were considered DLTs.

For CK, 21 (13.7%) subjects experienced a shift of 2 grades or higher, and these shifts appeared to increase with increasing dose. For ALT, 19 (12.4%) subjects experienced a shift of 2 grades or higher. For AST, 19 (12.4%) subjects experienced a shift of 2 grades or higher.

Sixteen subjects experienced dose-limiting toxicities (DLTs); 14 subjects in the dose expansion cohort (1 in 20 mg dose group, 1 in 40 mg dose group, 2 in 80 mg dose group, 3 in 120 mg dose group, 4 in 200 mg dose group, and 3 in the 300 mg dose group) and 2 subjects in the dose escalation cohort (both in the 450 mg dose group). None of the doses below 450 mg met the criteria for pausing enrollment. Thus, the maximum tolerated dose (MTD) in Study 2215-CL-0101 is considered to be 300 mg.

1.4 Risk-Benefit Assessment

In Study 2215-CL-0101, ASP2215 has resulted in CRc in over 40% of subjects receiving 80 mg or higher dose. The median survival was over 7 months in the 120 mg dose level. The majority of subjects in the trial received multiple treatments prior to receiving ASP2215.

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

ASP2215 has a potential to induce genotoxicity in vivo. ASP2215 showed teratogenic potential and embryo-fetal deaths in the embryo-fetal development toxicity study in rats.

This study is designed to only include subjects who are currently enrolled in an ASP2215 trial and is intended to provide continued access to ASP2215 for subjects who have derived benefit in the opinion of the Investigator from their administered treatment on the original study in which they are currently participating.

2 STUDY OBJECTIVES, DESIGN AND ENDPOINTS

2.1 Study Objectives

The objective of the study is to provide access to continued treatment for subjects who participated in other previous Astellas sponsored ASP2215 (single agent) trials and for whom the Investigator feels the subject may benefit from continued treatment.

2.2 Study Design and Dose Rationale

2.2.1 Study Design

This is a multi-center, open-label, rollover protocol for Astellas sponsored, single agent ASP2215 trials in AML and advanced solid tumors. Subjects must have completed the protocol requirements of the previous ASP2215 trial and be actively participating in the previous ASP2215 trial to be eligible for participation in this study. The number of subjects and number of centers will be dependent on the number of subjects and centers that enroll into the protocols rolling over into this trial. Centers in North America, Europe and Asia may rollover subjects into this trial. It is estimated that up to approximately 130 subjects across 40 centers will enroll into this trial. Subjects will be eligible to continue receiving treatment in this study until they meet a discontinuation criterion as outlined in Section 6.1 or upon marketing authorization and commercial availability of ASP2215 in the country of residence.

2.2.2 Dose Rationale

2.2.2.1 ASP2215

Subjects will continue ASP2215 at the dose they were on at the time of their end of study visit in the previous ASP2215 study.

2.3 Endpoints

2.3.1 Primary Endpoint

Safety, as measured by adverse events (AEs) and safety laboratory evaluations.

3 STUDY POPULATION

3.1 Selection of Study Population

Subjects who are actively participating in an Astellas sponsored ASP2215 trial that has completed the primary analysis, whom the investigator feels may have potential to continue to derive clinical benefit from the treatment with ASP2215, and who did not meet any of the study discontinuation criteria in the present study.

3.2 Inclusion Criteria

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

1. Institutional Review Board (IRB)-/Independent Ethics Committee (IEC)-approved written Informed Consent and privacy language as per national regulations [e.g., Health Insurance Portability and Accountability Act (HIPAA) Authorization for US sites] must be obtained from the subject or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Subject must currently be participating in an Astellas sponsored ASP2215 trial, receiving ASP2215 and is able to enroll into this rollover study without interruption of study drug, or with no more than 2 weeks interruption in study drug.
3. Subject must be deriving benefit from continued treatment as determined by the Investigator.
4. Female subject must either:
   - Be of non-childbearing potential:
     - post-menopausal (defined as at least 1 year without any menses) prior to Screening, or
     - documented surgically sterile or post-hysterectomy (at least one 1 month prior to Screening)
   - Or, if of childbearing potential,
     - Agree not to try to become pregnant during the study and for 180 days after the final study drug administration
     - And have a negative urine pregnancy test at screening
     - And, if heterosexually active, agree to consistently use two forms of highly effective birth control* (at least one of which must be a barrier method) starting at Screening and throughout the study period and for 180 days after the final study drug administration.
5. Female subject must agree not to breastfeed starting at Screening and throughout the study period, and for 60 days after the final study drug administration.
6. Female subject must not donate ova starting at Screening and throughout the study period, and for 180 days after the final study drug administration.
7. Male subject and their female spouse/partners who are of childbearing potential must be using highly effective contraception consisting of two forms of birth control* (at least one of which must be a barrier method) starting at Screening and continue throughout the study period, and for 120 days after the final study drug administration.
8. Male subject must not donate sperm starting at Screening and throughout the study period and, for 120 days after the final study drug administration.
9. Subject agrees not to participate in another interventional study while on treatment.

*Highly effective forms of birth control include:

- Consistent and correct usage of established oral contraception.
- Established intrauterine device (IUD) or intrauterine system (IUS).
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository (for regions where spermicidal foam/gel/film/cream/suppository is not available, e.g., Japan)
- Calendar-based contraceptive methods (Knaus-Ogino or rhythm method applicable to subjects enrolled at sites in Japan).

Waivers to the inclusion criteria will NOT be allowed.

3.3 Exclusion Criteria

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

1. Subject requires treatment with concomitant drugs that are strong inducers of cytochrome P450 (CYP)3A.
2. Subject requires treatment with concomitant drugs that target serotonin 5-hydroxytryptamine receptor 1 ($5HT_1R$) or 5-hydroxytryptamine receptor 2B ($5HT_{2B}R$) or sigma nonspecific receptor with the exception of drugs that are considered absolutely essential for the care of the subject.
3. Subject requires treatment with concomitant drugs that are strong inhibitors or inducers of P-glycoprotein (P-gp) with the exception of drugs that are considered absolutely essential for the care of the subject.

Waivers to the exclusion criteria will NOT be allowed.

4 TREATMENT(S)

4.1 Identification of Investigational Products

4.1.1 Test Drug

ASP2215 tablets contain 40 mg of active ingredient. The tablets are contained within the high-density polyethylene bottle.

There will be a total of 30 tablets per bottle. The study centers will be provided bottles of ASP2215 each containing 30 tablets. The study site personnel will fill out the label to indicate the dispensing date, subject's ASP2215 dose and the corresponding number of tablets that need to be taken each day. The ASP2215 40 mg tablet product information is listed in [Table 2].

Table 2 Test Drug (ASP2215 Tablets 40 mg)

Test drug	**ASP2215 Tablets 40 mg**
Code name	ASP2215
Active ingredient	Chemical name: $C_{29}H_{44}N_8O_3 \cdot 1/2\ C_4H_4O_4$
Composition and dosage form	One tablet contains 40 mg of ASP2215 in free form. ASP2215 Tablets are round light-yellow film-coated tablets.
Lot No.	Described in separately prepared "Study Drug Handling Procedures"
Storage	Bottled ASP2215 should be stored at a temperature between 20°C and 25°C (68°F and 77°F) and protected from light in a tight container, with excursions in temperature permitted between 15°C and 30°C (59°F and 86°F). Store in original container.

4.2 Packaging and Labeling

ASP2215 used in this study will be prepared, packaged and labeled under the responsibility of qualified staff at Astellas Pharma Global Development, Inc. (APGD)-Astellas United States Technologies (AUST) or Sponsor's designee in accordance with APGD-AUST or Sponsor's designee Standard Operating Procedures (SOPs), Good Manufacturing Practice guidelines, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local laws/regulations.

Each bottle will bear a label conforming to regulatory guidelines, Good Manufacturing Practice and local laws and regulations which identifies the contents as investigational drug.

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

4.3 Study Drug Handling

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

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

Drug inventory and accountability records for the study drugs will be kept by the investigator, head of study site (specific to Japan), or designee. Study drug accountability throughout the study must be documented and reconciled.

The following guidelines are therefore pertinent:

- The investigator, or designee agrees not to supply study drug(s) to any persons except the eligible subjects in this study in accordance with the protocol.
- The investigator, head of study site (specific to Japan) or designee will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these study drugs.
- A study drug inventory will be maintained by the investigator or designee. The inventory will include details of material received and a clear record of when they were dispensed and to which subject.
- At the conclusion or termination of this study, the investigator, head of study site (specific to Japan) or designee agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record. It must be possible to reconcile delivery records with those of used and/or returned medication. Any discrepancies must be accounted for and documented. Appropriate forms of deliveries and returns must be signed by the site staff delegated this responsibility.
- The site must return unused study drug ASP2215 supplied by Sponsor back to the Sponsor or designee at the end of the study or upon expiration.

Specific to Japan

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

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

4.4 Blinding

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

4.5 Assignment and Allocation

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

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drugs and Other Medications

5.1.1 Dose/Dose Regimen and Administration Period

ASP2215 is an oral tablet that subjects will take once daily without food in continuous 28-day cycles. Subjects will be instructed to take the assigned daily dose with water as close to the same time each morning as possible. ASP2215 can be taken at least 2 hours after or 1 hour before food. ASP2215 will be self-administered at home when subjects are not scheduled for clinic visits. If a subject forgets to take a dose in the morning and within 6 hours of the planned dosing time, they should be instructed to take their dose. If the subject forgets to take their daily dose and more than 6 hours has passed the planned dosing time, they should be instructed to wait for the next morning to dose. If vomiting occurs after dosing, the subject should not receive another dose, but just wait until the next morning to dose.

ASP2215 will be given daily in continuous 28-day cycles. A subject will receive the corresponding number of bottles to cover 2 cycles of dosing (plus allowable window) at their dose level. For example, a subject taking 120 mg per day would be dispensed 7 bottles of ASP2215.

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

5.1.2 Escalation or Reduction in Dose of the Study Drug

Guidelines for ASP2215 dose reduction for nonhematological events are provided in Table 4. The Investigator may also dose reduce ASP2215 based on clinical assessment.

ASP2215 dose reduction is to follow a step-wise manner, as outlined in Table 3. After the initial dose reduction, one additional dose reduction may occur. If no further dose reductions are available, study treatment will be discontinued.

Table 3 Dose Levels

Subject Dose level	Dose Reduction Dose Level
280 mg	200 mg
200 mg	120 mg
120 mg	80 mg
80 mg	40 mg
40 mg	Study treatment discontinued

Table 4 Guidelines for ASP2215 Dose Reduction Event

ASP2215 Dosing Instructions	
Event	**Action**
Nonhematological Events	
Grade 3 at least possibly related to ASP2215	Dosing will be interrupted for up to 14 days. If the AE resolves to ≤ grade 1 within 14 days, the subject may resume dosing at the reduced dose.
Grade 4 toxicity at least possibly related to ASP2215	Treatment will be discontinued.

AE: adverse event

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

All medications and concomitant treatments administered from 28 days prior to cycle 1 day 1 through the end of treatment visit must be recorded in the electronic case report form (eCRF). Treatment with concomitant drugs that are strong inducers of CYP3A are prohibited. Treatment with concomitant drugs that are strong inhibitors or inducers of P−gp and concomitant drugs that target serotonin $5HT_1R$ or $5HT_{2B}R$ or sigma nonspecific receptor are to be avoided, with the exception of drugs that are considered absolutely essential for the care of the subject. Treatment with concomitant drugs that are strong inhibitors of CYP3A should be avoided, with the exception of antibiotics, antifungals and antivirals that are used as standard of care to prevent or treat infections. If CYP3A inhibitors are used concomitantly, subjects should be closely monitored for AEs.

Precaution should be used in use of ASP2215 with concomitant drugs that are known to prolong QT or QTc intervals.

Precaution should be used in use of ASP2215 with concomitant drugs that are substrates of BCRP, since the transporter has been shown to be inhibited by ASP2215 in in vitro studies.

Common CYP3A inhibitors, CYP3A inducers, drugs targeting the serotonin receptor, P-gp inhibitors or inducers and drugs known to prolong QT or QTc intervals are listed in [Appendix 12.1]. The investigator should consult individual labels for all drugs that the subject is taking to evaluate if they fall into any of the above named categories. For concomitant drugs that have the potential to prolong QT or QTc intervals, a cardiology consult should be obtained as medically indicated. Any other treatments of AML (including but not limited to chemotherapy, radiotherapy, surgery, immunotherapy or cellular therapy) are prohibited during therapy with ASP2215, with the exception of hydroxyurea up to 5 g daily for up to 2 weeks to keep the absolute blast count below 50 x 10^9/L, prophylactic intrathecal chemotherapy or cranial irradiation. Participation in another interventional study while on treatment is prohibited.

Refer to [Appendix 12.1 List of Excluded and Cautionary Concomitant Medications].

5.1.4 Treatment Compliance

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

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

The dose and schedule of ASP2215 administered to each subject will be recorded at every visit. Reasons for dose delay, reduction or omission will also be recorded. This information, plus tablet accountability for ASP2215 at every visit will be used to assess compliance with the treatment.

Treatment compliance should be monitored closely and deviations in compliance should be reported to the Sponsor except in cases where directed by protocol or Principal Investigator (e.g., account for dose interruptions, adjustments, etc.).

Any subjects that have been off treatment for more than 15 days other than for study drug related AE can only resume treatment after discussion with the medical monitor.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

Demographic information for the subject will be obtained from the original study.

5.2.2 Medical History

Medical history data for the subject will be obtained from the original study.

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

Medical history of the target disease for the subject that was studied in the original protocol will be obtained from the original study.

5.2.4 Performance Status

The ECOG Scale [Oken et al, 1982] will be used to assess performance status [Table 5].

Table 5 ECOG Performance Status

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

ECOG: Eastern Cooperative Oncology Group

5.3 Efficacy Assessment

Not applicable

5.4 Safety Assessment

5.4.1 Vital Signs

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

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

5.4.2 Adverse Events

AE collection continues from the original study until the End of Treatment visit, 30 days after last dose or until start of a new anticancer therapy, whichever is sooner. AEs occurring during the original study will continued to be followed as AEs in the current study. AEs will be documented at each clinic visit, but can be collected at any time. Any AE that meets the definition of a serious adverse event (SAE will also be reported on a separate form to the Sponsor. See [Section 5.5, Adverse Events and Other Safety Aspects] for information regarding AE collection and data handling.

5.4.2.1 Adverse Events of Possible Hepatic Origin

See Appendix 12.2 Liver Safety Monitoring and Assessment for detailed information on liver abnormalities, monitoring and assessment, if the AE for a subject enrolled in a study and

receiving study drug is accompanied by increases in liver function tests (LFTs) [e.g., AST, ALT, total bilirubin (TBL), etc.] or is suspected to be due to hepatic dysfunction.

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

5.4.3 Laboratory Assessments

The below table contains the laboratory tests that will be performed locally during the conduct of the study. Refer to the Schedule of Assessments for study visit collection days. Additional laboratory tests should be performed according to institutional standard of care. Clinical significance of out-of-range laboratory findings is to be determined and documented by the Investigator/or delegated sub-Investigator who is a qualified physician.

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

Panel/ Assessment	**Parameters to be Analyzed**	
Hematology	White Blood Cell Count White Blood Cell Differential Red Blood Cell Count Hemoglobin Hematocrit	Mean Corpuscular Volume Platelet Count Mean Corpuscular Hemoglobin Concentration Mean Corpuscular Hemoglobin
Chemistry	Sodium Potassium Chloride Bicarbonate Blood Urea Nitrogen Creatinine Glucose Calcium Phosphate Magnesium Albumin Total Protein	Alkaline Phosphatase Lactate Dehydrogenase Creatine Phosphokinase Liver Function Tests including: Total Bilirubin Alanine Aminotransferase Aspartate Aminotransferase
Serum Pregnancy Test	Human Chorionic Gonadotropin	
Coagulation Profile (PT/INR)	INR (with PT if reported) aPTT	
Table continued on next page		

Panel/ Assessment	Parameters to be Analyzed	
Urinalysis	Color	Glucose
	Appearance	Ketones
	Specific Gravity	Leukocyte Esterase
	pH	Nitrite
	Bilirubin	Protein
	Blood	Urobilinogen

aPTT: activated partial thromboplastin time; INR: international normalization ratio; PT: prothrombin time

5.4.4 Physical Examination

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

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events

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

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

An abnormality identified during a medical test [e.g., laboratory parameter, vital sign, electrocardiogram (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

5.5.2 Definition of Serious Adverse Events

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

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

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent 1 of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are intensive treatment in an 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.

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

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

All of the events of interest noted above should be recorded on the (e)CRF. Any situation involving these events of interest that also meets the criteria for an SAE should be recorded on the AE page of the (e)CRF and marked 'serious' and the SAE worksheet.

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

5.5.3 Criteria for Causal Relationship to the Study Drug

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

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

5.5.4 Criteria for Defining the Severity of an Adverse Event

AEs, including abnormal clinical laboratory values, will be graded using the National Cancer Institute (NCI)-CTCAE guidelines (version 4.03). The items that are not stipulated in the NCI-CTCAE version 4.03 will be assessed according to the criteria below and entered into the eCRF.

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

5.5.5 Reporting of Serious Adverse Events

SAE collection will continue in the original study through the End of Treatment visit, 30 days after last dose of study medication, or until start of a new anticancer therapy, whichever is sooner. Any ongoing SAE will be captured in the 2215-CL-0109 study. In the case of an SAE, the Investigator must contact the Sponsor by telephone or fax immediately (within 24 hours of awareness).

The Investigator should complete and submit an SAE Worksheet containing all information that is required by the Regulatory Authorities to the Sponsor/delegated Contract Research Organization (CRO) by fax immediately (within 24 hours of awareness). If the faxing of an

SAE Worksheet is not possible or is not possible within 24 hours, the local drug safety contact should be informed by phone.

SPECIFIC to Investigational sites in Japan:

In the case of a SAE, the Investigator or sub-Investigator must report to the head of the study site and must contact the Sponsor 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 Sponsor 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 Sponsor should be informed by phone.

For contact details, see Section II Contact Details of Key Sponsor's Personnel. Please fax or email the SAE Worksheet to:

Astellas Pharma Global Development
Global Pharmacovigilance
North American Fax: 888-396-3750
(North America Alternate Fax: 847-317-1241)
International Fax: +44-800-471-5263
Email: safety-us@astellas.com

SPECIFIC to Investigational sites in Japan:

JUTOKUNA YUUGAIJISHOU HOUKOKUSHO the SAE Worksheet to:

Astellas Pharma Inc.-Japan
APGD-JP Clinical Development,
Fax: +81-0-3243-5737

If there are any questions or if clarification is needed regarding the SAE, please contact the Sponsor's Medical Monitor/Expert or his/her designee (see Section II Contact Details of Key Sponsor’s Personnel).

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

Full details of the SAE should be recorded on the medical records and on the (e)CRF.

The following minimum information is required:

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

The Sponsor or Sponsor's designee will submit expedited safety reports (i.e., investigational new drug [IND] Safety Reports) to the regulatory agencies (i.e., FDA) as necessary and will inform the Investigators of such regulatory reports. Investigators must submit safety reports as required by their IRB/IEC within timelines set by regional regulations (i.e., European Union, (e)Common Technical Document, FDA). Documentation of the submission to and receipt by the IRB/IEC of expedited safety reports should be retained by the site.

The Sponsor/delegated CRO will notify all Investigators responsible for ongoing clinical studies with the study drug of all SAEs which require submission per local requirements IRB/IEC/head of the study site.

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

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

5.5.6 Follow-up of Adverse Events

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

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

Please refer to Appendix 12.2 Liver Safety Monitoring and Assessment for detailed instructions on drug induced liver injury.

5.5.7 Monitoring of Common Serious Adverse Events

Common SAEs are SAEs commonly anticipated to occur in the study population independent of drug exposure. SAEs classified as “common” are provided in Appendix 12.3 Common Serious Adverse Events for your reference. The list does NOT change your reporting obligations or prevent the need to report an AE meeting the definition of an SAE as detailed above. The purpose of this list is to alert you that some events reported as SAEs may not require expedited reporting to the regulatory authorities based on the classification of “common serious adverse events” as specified in Appendix 12.3 Common Serious Adverse Events. The Sponsor will monitor these events throughout the course of the study for any change in frequency. Any changes to this list will be communicated to the participating investigational sites. Investigators must report individual occurrences of these events as stated in Section 5.5.5 Reporting of Serious Adverse Events.

5.5.8 Procedure in Case of Pregnancy

If a female subject or partner of a male subject becomes pregnant during the study dosing period or within 180 days from the discontinuation of dosing, the Investigator should report the information to the Sponsor/delegated CRO as if it is an SAE. The expected date of delivery or

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

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

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

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

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

5.5.9 Emergency Procedures and Management of Overdose

In the event of suspected ASP2215 overdose, the subject should receive supportive care and monitoring. The Medical Monitor/Expert should be contacted as applicable.

5.5.10 Supply of New Information Affecting the Conduct of the Study

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

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 Section 8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of Written Information.

2. In addition to the above item (1), when the head of the study site receives the revisions of the Investigator's Brochure, protocol or written information, information on the matters covering the quality of the study drug, efficacy and safety, information necessary for conducting the clinical study properly or documents to be examined by the IRB should be sent to the IRB.

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

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

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

5.6 Test Drug Concentration

Not applicable.

5.7 Other Measurements, Assessments or Methods

Not applicable.

5.8 Total Amount of Blood

The total amount of blood collected for study assessments for each subject will vary depending on how long they stay on treatment. The amount of blood collected at each clinic visit is approximately 15 mL.

At any time during the study, if any laboratory abnormalities are found for a subject additional blood may be drawn for monitoring.

6 DISCONTINUATION

6.1 Discontinuation of Individual Subject(s)

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

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

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

Discontinuation Criteria from Treatment for Individual Subjects:

- Subject declines further study participation (i.e., withdrawal of consent).
- Subject develops an intolerable or unacceptable toxicity.
- Investigator/sub-Investigator determines the subject is no longer receiving clinical benefit from study treatment.
- Investigator/sub-Investigator determines that the continuation of the study treatment will be detrimental to the subject.
- Female subject becomes pregnant.
- Subject is lost to follow-up despite reasonable efforts by the Investigator to locate the subject.
- Death.

6.2 Discontinuation of the Site

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

6.3 Discontinuation of the Study

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

7 STATISTICAL METHODOLOGY

The statistical analysis will be coordinated by the responsible biostatistician of APGD-United States. A Statistical Analysis Plan (SAP) will be written to provide details of the analysis, along with specifications for tables, listings and figures (TLFs) to be produced. The SAP will be finalized before the database soft lock at the latest. Any changes from the analyses planned in SAP will be justified in the Clinical Study Report.

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

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

7.1 Sample Size

The sample size for this study is based on the number of subjects who are continuing to derive benefit from treatment with ASP2215 as assessed by their Investigator at the completion of the original study they enrolled under.

7.2 Analysis Sets

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

7.2.1 Full Analysis Set

No efficacy analysis is planned for this study.

7.2.2 Per Protocol Set

No efficacy analysis is planned for this study.

7.2.3 Safety Analysis Set

For the statistical summary of the safety data, the SAF will be used. The SAF consists of all subjects who took at least 1 dose of study medication (ASP2215) and will be used for safety analyses.

7.2.4 Pharmacokinetic Analysis Set

No pharmacokinetic analysis is planned for this study.

7.3 Demographics and Other Baseline Characteristics

7.3.1 Demographics

Descriptive summary statistics will be produced for all parameters.

7.3.2 Medical History

A detailed medical history for each subject will be obtained during Screening of the prior study and will be summarized by treatment group for the SAF.

7.3.3 Disease History

Each subject's complete cancer history will be listed.

7.3.4 Previous and Concomitant Medications

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

7.3.5 Subject Disposition

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

7.3.6 Treatment Compliance

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

7.3.7 Extent of Exposure

Exposure to treatment, measured by the duration of treatment in number of days will be summarized by treatment group on SAF. Duration of exposure to a study drug is defined as: (the last date that subject took study drug – the first dose date + 1 – number of days without drug administration in between). The total dose administered, number and proportion of subjects with dose reduction, dose escalation and dose interruption will be tabulated.

7.4 Analysis of Efficacy

No efficacy analysis is planned for this study.

7.5 Analysis of Safety

The safety evaluation will be based on AEs and clinical laboratory assessments. Descriptive statistics will be used to summarize safety data. All safety data will be performed on the SAF.

7.5.1 Adverse Events

All AEs recorded on treatment including within 30 days from the last study treatment will be summarized. AEs will be coded to SOC and PT using MedDRA and will be graded according to the NCI-CTCAE version 4.03.

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

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

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

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

7.5.2 Laboratory Assessments

Clinical laboratory evaluations (including hematology, urinalysis, chemistry and coagulation) 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 NCI-CTCAE grade and lab reference range indicator. Frequency of subjects with laboratory values outside normal range will be generated in addition to tabulation of worst toxicity grade.

7.5.3 Vital Signs

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

7.5.4 Physical Examination

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

7.5.5 Ophthalmologic Assessment

Ophthalmologic variables will be summarized by treatment group at the end of treatment for each eye.

7.5.6 ECOG Performance Scores

ECOG performance scores will be summarized by treatment group and visit.

7.5.7 Pregnancy Test

Pregnancy test result for women of childbearing potential will be displayed in a listing.

7.6 Analysis of Pharmacokinetics

No pharmacokinetic analysis is planned for this study.

7.7 Protocol Deviations

Protocol deviations (PDs) as defined in Section 8.1.6 Protocol Deviations will be summarized for all registered subjects by treatment group and total as well as by site. A data listing will be provided by site and subject.

The PD criteria will be uniquely identified in the summary table and listing. The unique identifiers will be as follows:

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

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

PD3-Received wrong treatment or incorrect dose

PD4-Received excluded concomitant treatment

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

No formal interim analysis is planned.

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

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

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

The Investigator or site designee will enter data collected using an Electronic Data Capture system. In the interest of collecting data in the most efficient manner, the Investigator or site designee should record data (including laboratory values, if applicable) in the eCRF within 10 days after the subject visit.

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

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

For screen failures, the minimum demographic data (i.e., sex, age, informed consent date) and reason for screen failure will be collected in the eCRF and screen failure log if applicable.

8.1.2 Specification of Source Documents

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

The following information should be included in the source medical records:

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

8.1.3 Clinical Study Monitoring

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

8.1.4 Direct Access to Source Data/Documents

The Investigator and the study site must accept monitoring and auditing by the Sponsor or delegated CRO as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents (refer to Section 8.1.2 Specification of Source Documents) when they are requested by the Sponsor monitors and auditors, the IRB/IEC or regulatory authorities. The confidentiality of the subject's identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

8.1.5 Data Management

Data Management will be coordinated by the Global Data Science department of the Sponsor in accordance with the SOPs for data management. All study specific processes and definitions will be documented by Data Management. (e)CRF completion will be described in the (e)CRF instructions. Coding of medical terms and medications will be performed using MedDRA and WHO Drug Dictionary respectively.

8.1.6 Protocol Deviations

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

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

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

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

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

If a deviation impacts the safety of a subject, the Investigator must contact the Sponsor immediately.

The Investigator will also assure that deviations meeting IRB/IEC and applicable regulatory authorities' criteria are documented and communicated appropriately. All documentation and communications to the IRB/IEC and applicable regulatory authorities will be provided to the Sponsor and maintained within the Trial Master File.

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

8.1.7 End of Trial in All Participating Countries

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

8.2 Ethics and Protection of Subject Confidentiality

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

Any substantial amendments to the protocol will require IEC/IRB approval prior to implementation of the changes made to the study design at the site. The Investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

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

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

8.2.2 Ethical Conduct of the Study

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

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

The Investigator or his/her representative will explain the nature of the study to the subject or his/her guardian or legal representative and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed (*specific to sites in Japan*, place a personal seal) and dated by the subject or his/her guardian or legal representative, the person who administered the informed consent and any other signatories according to local requirements. A copy of the signed (*specific to sites in Japan*, or sealed) ICF will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in

the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

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

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

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

8.2.4 Subject Confidentiality

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

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

All individuals and organizations involved in the study must pay very careful attention to protect subjects' privacy with appropriate measures, for example, by prohibiting the use of any private information that may identify a subject (e.g., name or address). These details shall be processed in accordance with the applicable local and regional laws.

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

The Sponsor affirms the subject's right to protection against invasion of privacy. Only a subject identification number and/or initials will identify subject data retrieved by the

Sponsor. However, the Sponsor requires the Investigator to permit the Sponsor, Sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The Sponsor will ensure that the use and disclosure of protected health information obtained during a research study complies with the federal and/or regional legislation related to the privacy and protection of personal information (i.e., HIPAA).

8.3 Administrative Matters

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

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

Publication of the study results is discussed in the Clinical Study Agreement.

8.3.2 Documents and Records Related to the Clinical Study

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

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

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

Financial disclosure in compliance with federal regulation 21CFR Part 54

- Signed and dated FDA form 1572, if conducted under a U.S. IND
- Signed Investigator's Statement in this protocol and CRF
- Current Curricula Vitae of all investigators
- List of sub-investigators and collaborators
- IRB approval of the protocol, protocol amendments (if applicable) including a membership list with names and qualification (COPY)
- Instruction and decision of the head of the study site (specific to sites in Japan)

- Study contract
- Laboratory normal reference ranges (if applicable, signed and dated by the responsible laboratory employee)

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

- Unused CRFs and other study documentation,
- Unused study drug

The Investigator will archive all study data (e.g., Subject Identification Code List, source data, CRFs and Investigator's File) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation (for United States sites, 2 years after approval of the New Drug Application (NDA) or discontinuation of the IND). The Sponsor will notify the site/Investigator if the NDA/Marketing 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.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. All data will be entered on the CRFs supplied for each subject.

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

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 3 years after the decision to discontinue development is notified)
2. Until 3 years after discontinuation or termination of the study.

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

1. Source documents (clinical data, documents and records for preparing the CRF) hospital records, medical records, test records, memoranda, administration records, data recorded by automatic measuring instruments, reproductions or transcripts verified as precise copies, microfiche, negative films, microfilms/magnetic media, X-ray films, subject files and study-related records kept at either a pharmacy, a laboratory or medical technical

office, as well as subject registration forms, laboratory test slips including central measurement, worksheets specified by the Sponsor, records of clinical coordinators and records related to the clinical study selected from those verified in other departments or hospitals.

2. Contracts, written ICFs, written information and other documents or their copies prepared by the study personnel. A letter of request for clinical study (including a request for continuation/amendment), letter of request for review, notice of clinical study contract, clinical study contract, notification of discontinuation or completion of clinical study, written information for informed consent (including revisions), signed and dated written informed consent (including revisions), Curriculum Vitaes of Investigators, list of sub-Investigators, list of signatures and print of seals (copy) and CRFs (copy), etc.
3. The protocol, documents obtained from the IRB related to the adequacy of conducting the clinical study by the head of the study sites (Article 32-1, MHW Ordinance No. 28), documents obtained from the IRB related to the adequacy of conducting a clinical study whose period exceeds 1 year or the adequacy of continuously conducting the clinical study from which information on adverse drug reactions is obtained and other documents obtained. An agreed-upon protocol (including revisions), Investigator's Brochure (including revisions), operational procedures for the Investigator, materials and information supplied by the Sponsor (e.g., AE report), matters reported by the Investigator (revisions of the protocol, AE reports, etc.), operational procedures for the IRB, the list of names of the IRB members, materials for IRB review (including continuous deliberation), IRB review records (including continuous deliberation) and the review result report of the IRB (including continuous deliberation), etc.
4. Records of control for study drugs and other duties related to the clinical study. Procedure for controlling the study drugs, drug inventory and accountability record, vouchers for the receipt and return of the study drugs and the prescriptions for concomitant medications

8.3.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments: substantial amendments and/or nonsubstantial 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) followed by the approval of the head of the study site (specific to sites in Japan).

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

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

8.3.4 Insurance of Subjects and Others

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

SPECIFIC to 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.

8.3.5 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and European Union Directive 2001/83/EC requires that a final study report which forms part of a Marketing Authorization Application be signed by the representative for the Coordinating Investigator(s) or the Principal Investigator(s). The representative for the Coordinating Investigator (s) or the Principal Investigator(s) will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. The representative for Coordinating Investigator(s) or the Principal Investigator(s) will be selected from the participating Investigators by the Sponsor prior to database lock.

9 QUALITY ASSURANCE

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

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

10 STUDY ORGANIZATION

10.1 Independent Data Monitoring Committee

Not applicable.

10.2 Other Study Organization

Not applicable.

10.3 Registration of Subjects (Specific to Japan)

The Investigator will fill in the subject registration forms to reconfirm whether the candidate subjects are eligible. The Sponsor should obtain the information on candidate subjects to be included in the clinical study from subject registration forms before administration to confirm their eligibility, and to inform the Investigator of the results.

In the situation of rapidly proliferative disease which is acute or requires immediate-treatment, it is difficult for the Sponsor to confirm the eligibility of the candidate subjects prior to starting the study. Confirmation should be made instantly for the eligibility of the candidates by referring to the subject’s registration forms obtained after the start of administration.

Prevention system in IRT will be constructed to check duplicative registration from minimum information (each birth date and gender of subjects).

In case IRT system points out a possibility as duplicative registration, clinical research monitor must check whether or not the registration is duplicative.

Investigators and Clinical Research Coordinators in each site can check directly with subjects whether or not the registration is duplicative.

11 REFERENCES

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12 APPENDICES

12.1 List of Excluded and Cautionary Concomitant Medications

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

Strong CYP3A Inhibitors

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

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

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.

CYP3A Inducers

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

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

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

Drugs Targeting Serotonin Receptors

Drug Type	Generic Drug Name
Affinity or function to $5HT_{2B}R$	eletriptan hydrobromide
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 haloperidol decanoate lesopitron methylergonovine maleate methylergotamine methysergide maleate naratriptan hydrochloride pizotifen quetiapine fumarate rizatriptan benzoate sumatriptan succinate tegaserod maleate thioridazine 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 Targeting Sigma (nonspecific) Receptor (sigma R)

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

Drugs That May Prolong QT or QTc

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

Drug Type	Generic Drug Name
Class IA antiarrhythmics	Quinidine Procainamide Disopyramide
Class IC antiarrhythmics	Flecainide Propafenone Moricizine
Class III antiarrhythmics	Amiodarone Sotalol Bretylium Ibutilide Dofetilide
Table continued on next page	

Drug Type	Generic Drug Name
Antipsychotics	Thioridazine Mesoridazine Chlorpromazine Prochlorperazine Trifluoperazine Fluphenazine Perphenazine Pimozide Risperidone Ziprasadone Lithium Haloperidol
Tricyclic/tetracyclic antidepressants	Amitriptyline Desipramine Doxepin Dosulepin hydrochloride Imipramine Maprotiline
Selective serotonin and norepinephrine reuptake inhibitors (SSNRIs) antidepressants	Venlafaxine
Macrolide antibiotics	Azithromycin Erythromycin Clarithromycin Dirithromycin Roxithromycin Tulathromycin
Fluoroquinolone antibiotics	Moxifloxacin Gatifloxacin
Azole antifungals	Ketoconazole Fluconazole Itraconazole Posaconazole Voriconazole
Antimalarials	Amodiaquine Atovaquone Chloroquine Doxycycline Halofantrine Mefloquine Proguanil Primaquine Pyrimethamine Quinine Sulphadoxine

Table continued on next page

Drug Type	Generic Drug Name
Antiprotozoals	Pentamidine
Antiemetics	Droperidol Dolasetron Granisetron Ondansetron
Antiestrogens	Tamoxifen
Immunosuppressants	Tacrolimus

Source: Yap 2003

Reference

Yap Y. Drug induced QT prolongation and torsades de pointes. Heart. 2003;89(11):1363-1372.

12.2 Liver Safety Monitoring and Assessment

Any subject enrolled in a clinical study with active drug therapy and reveals an increase of serum aminotransferases to > 3 × upper limit of normal (ULN) (to > 5 × ULN in subjects with liver metastases) or TBL > 2 × ULN, should undergo detailed testing for liver enzymes (including at least ALT, AST, alkaline phosphatase [ALP] and TBL). Testing should be repeated within 48 - 72 hours of notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central lab regarding moderate and severe liver abnormality to inform the Investigator, study monitor and study team. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction.

Definition of Liver Abnormalities

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

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

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

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks (in the absence of liver metasteses)
- 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-Case Report Form (LA-CRF) or appropriate document. Subjects with confirmed abnormal liver function testing should be followed as described below.

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

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

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

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new onset-diseases should be recorded as 'AEs' on the AE page of (e)CRF. Illnesses and conditions such as hypotensive events and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Nonalcoholic steatohepatitis is seen in obese hyperlipoproteinemic and/or diabetic subjects and may be associated with fluctuating 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 (e)CRF. Information on alcohol, other substance use and diet should be entered on the LA-CRF or an appropriate document.
    - Obtain a history of exposure to environmental chemical agents.
    - Based on the subject's history, other testing may be appropriate including:
        - acute viral hepatitis (A,B, C, D, E or other infectious agents)
        - ultrasound or other imaging to assess biliary tract disease
        - other laboratory tests including INR, direct bilirubin
    - Consider gastroenterology or hepatology consultations.
    - Submit results for any additional testing and possible etiology on the LA-CRF or an appropriate document.

Study 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 subject may be discontinued from the study. The Investigator may determine that it is not in the subject's best interest to continue study enrollment. Discontinuation of treatment should be considered if:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks (in subjects without liver metasteses)
- 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 subjects with liver metasteses)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%).

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

† Hy's Law Definition: drug-induced jaundice caused by hepatocellular injury, without a significant obstructive component, has a high rate of bad outcomes, from 10% - 50% mortality (or transplant). The 2 "requirements" for Hy's Law are 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 subjects 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

Source: Temple R. Hy's law: predicting serious hepatotoxicity. Pharmacoepidemiol Drug Saf. 2006;15:241-3.

Reference

FDA. Guidance for industry-drug-induced liver injury: premarketing clinical evaluation. 2009.

12.3 Common Serious Adverse Events

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

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

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

Serious Adverse Events Caused by AML	Grades Usually Observed with AML
Psychiatric and Nervous System Related AE	
Anxiety	0 - 2
Cognitive disturbance	0 - 3
Confusion	0 - 5
Depressed level of consciousness	0 - 5
Depression	0 - 3
Libido decreased	0 - 2
Meningismus	0 - 5
Seizure	0 - 5
Somnolence	0 - 5
Syncope	3
Other AE	
Activated partial thromboplastin time prolonged	0 - 2
Alanine aminotransferase increased	0 - 2
Alkaline phosphatase increased	0 - 2
Anorexia	0 - 2
Aspartate aminotransferase increased	0 - 2
Blood bilirubin increased	0 - 2
Bone and/or joint pain	0 - 2
Bruising	0 - 2
Bleeding/hemorrhage	0 - 5
Diarrhea	0 - 2
Dyspnea	0 - 5
Fatigue	0 - 3
Flushing	0 - 2
Gamma-glutamyltransferase increased	0 - 1
GVHD-acute and chronic	0 - 2
Hypertrophied gums	0 - 1
Hyperuricemia	0 - 1
Hypokalemia	0 - 2
Hypotension	0 - 2
Hypoxia	0 - 3
INR increased	0 - 1
Lactate dehydrogenase increased	0 - 2
Malaise	0 - 2
Multi-organ 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
Table continued on next page	

Serious Adverse Events Caused by AML	Grades Usually Observed with AML
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

Serious Adverse Events from Advanced Solid Tumors	Grades
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
Diarrhea	0-2
Dyspnea	0-5
Fatigue	0-3
Flushing	0-2
Gamma-glutamyltransferase increased	0-1
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
Multi-organ failure	0-5
Nausea	0-2
Oral dysesthesia	0-2
Pruritus	0-3
Tumor Lysis Syndrome	3-5
Vasculitis	0-5
Vomiting	0-2
Weight loss	0-2

13 ATTACHMENT 1: NON-SUBSTANTIAL AMENDMENT 1

I. The purpose of this amendment is:

Non-Substantial Changes
1. Extend Planned Study Period
DESCRIPTION OF CHANGE:
The planned study period is extended to 3Q2023.
RATIONALE:
This study is a rollover study. Timelines for rollover is contingent on feeder study completion. The study timeline is being extended to accommodate potential future feeder studies.
2. Update Laboratory Assessments
DESCRIPTION OF CHANGE:
Five chemistry parameters are removed from the list of required laboratory assessments.
RATIONALE:
Aldolase, triglycerides, total cholesterol, phospholipid and globulin laboratory assessments are not routinely performed at local laboratories. Removal of these laboratory parameters will not compromise subject safety monitoring and will streamline laboratory assessments that sites are able to complete through their local laboratory.
3. Minor Administrative-type Changes
DESCRIPTION OF CHANGE:
Include minor administrative-type changes (e.g., typos, format, numbering and consistency throughout the protocol).
RATIONALE:
To provide clarifications to the protocol and to ensure complete understanding of study procedures.

II. Amendment Summary of Changes:

IV Synopsis, Planned Study Period
WAS:
From 3Q2015 to 1Q2019
IS AMENDED TO:
From 3Q2015 to ~~1Q2019~~**3Q2023**

5 Treatments and Evaluation

5.4.3 Laboratory Assessments

WAS:

Panel/ Assessment	Parameters to be Analyzed	
Chemistry	Sodium	Alkaline Phosphatase
	Potassium	Lactate Dehydrogenase
	Chloride	Creatine Phosphokinase
	Bicarbonate	Aldolase
	Blood Urea Nitrogen	Triglycerides
	Creatinine	Total Cholesterol
	Glucose	Phospholipid
	Calcium	Globulin
	Phosphate	Liver Function Tests including:
	Magnesium	Total Bilirubin
	Albumin	Alanine Aminotransferase
	Total Protein	Aspartate Aminotransferase

IS AMENDED TO:

Panel/ Assessment	Parameters to be Analyzed	
Chemistry	Sodium	Alkaline Phosphatase
	Potassium	Lactate Dehydrogenase
	Chloride	Creatine Phosphokinase
	Bicarbonate	~~Aldolase~~
	Blood Urea Nitrogen	~~Triglycerides~~
	Creatinine	~~Total Cholesterol~~
	Glucose	~~Phospholipid~~
	Calcium	~~Globulin~~
	Phosphate	Liver Function Tests including:
	Magnesium	Total Bilirubin
	Albumin	Alanine Aminotransferase
	Total Protein	Aspartate Aminotransferase

III. Non-Substantial Amendment Rationale:

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

14 SPONSOR'S SIGNATURES