CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211349Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA Multidisciplinary Review and Evaluation

Application Number	**NDA 211349**
Application Type	Original Type 1
Priority or Standard	Priority
Submit Date	3/29/2018
Received Date	3/29/2018
PDUFA Goal Date	11/29/2018
Division/Office	DHP/OHOP
Review Completion Date	11/26/2018
Applicant	Astellas Pharma US, Inc.
Proposed Trade Name	Xospata®
Established Name	Gilteritinib
Pharmacologic Class	Kinase inhibitor
Formulations	Tablet (40 mg)
Dosing Regimen	120 mg daily
Applicant Proposed Indication/Population	For the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test.
Recommendation on Regulatory Action	Regular approval
Recommended Indication/Population	For the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test

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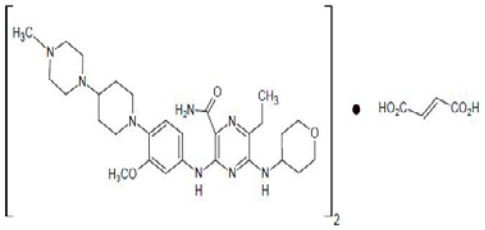
Glossary

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AML	acute myeloid leukemia
APL	acute promyelocytic leukemia
AXL	AXL tyrosine kinase
CFR	Code of Federal Regulations
CYP3A4	cytochrome P450 enzyme
DDI	drug-drug interaction
DHOT	Division of Hematology Oncology Toxicology
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
FDA	Food and Drug Administration
FLT3	FMS-like tyrosine kinase-3
GCP	good clinical practice
GMR	geometric least squares mean ratio
HSCT	hematopoietic stem cell transplantation
HU	hydroxyurea
ICH	International Conference on Harmonization
ITT	intent to treat
LFS	Leukemia free survival
MATE1	multidrug and toxin extrusion 1
MTD	maximum tolerated dose
NDA	new drug application
OPQ	Office of Pharmaceutical Quality
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PK	pharmacokinetics
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SOC	System Organ Class
TEAE	treatment emergent adverse event

1 Executive Summary

1.1 Product Introduction

Proposed Trade Name:	Xospata®
Established Name:	Gilteritinib
Also Known As:	ASP2215 (b) (4)
Chemical Name:	2-Pyrazinecarboxamide, 6-ethyl-3-[[3-methoxy-4-[4-(4-methyl-1-piperazinyl)-1-piperidinyl] phenyl] amino]-5-[(tetrahydro-2H-pyran-4-yl) amino]-, (2E)-2-butenedioate (2:1)
Molecular Formula:	$(C_{29}H_{44}N_8O_3)_2 \bullet C_4H_4O_4$
Chemical Structure:	
Molecular Weight:	1221.5 g/mol
Dosage Forms:	Tablet, 40 mg
Therapeutic Class:	Antineoplastic
Chemical Class:	Small molecule
Pharmacologic Class:	Kinase inhibitor
Mechanism of Action:	Inhibits multiple receptor tyrosine kinases, including FMS-like tyrosine kinase 3 (FLT3). The mutant forms of FLT3 inhibited include the FLT3 internal tandem duplication (FLT2-ITD), the tyrosine kinase domain mutation (TKD) FLT3-D835Y, and the combined FLT3-ITD-D835Y.

Gilteritinib is a new molecular entity. NDA 211349 was submitted for the proposed indication of treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test using a dose of 120 mg daily.

1.2 Conclusions on the Substantial Evidence of Effectiveness

The review team recommends regular approval of gilteritinib under 21 CFR 314.105 for the indication "Treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test" using a dose of 120 mg daily. The recommendation is based on the finding of durable complete remission with complete or partial hematopoietic recovery (CR/CRh) and conversion to transfusion independence in Study 2215-CL-0301 (NCT02421939).

Safety during long-term use, characterization of gilteritinib-induced differentiation syndrome and confirmation that risks are outweighed by the benefit for patients with TKD mutations remain to be determined in postmarketing studies.

Study 2215-CL-0301 was a multicenter, randomized, open-label study comparing outcomes for patients with relapsed or refractory (R/R) FLT3-positive AML treated with gilteritinib versus chemotherapy. Gilteritinib was given orally at a dose of 120 mg daily until unacceptable toxicity or lack of clinical benefit. The design included an interim single-arm analysis of CR/CRh to be performed when approximately 141 patients on the gilteritinib arm had completed at least 112 days (4 cycles) or discontinued (RAS population). There was no basis provided for the sample size, which is a major deficiency of the design, but the Applicant prespecified that the lower limit of the confidence interval was required to exclude 12%. At the time of the first interim analysis, there were 142 patients in the RAS population. The CR/CRh rate was 21.8% (95% CI: 15.3%, 29.5%), so the primary objective was met.

For the purposes of establishing efficacy in the intended population, FDA' s analysis included only patients in Study 2215-CL-0301 with documented relapsed or refractory AML at study entry, with a confirmed FLT3 mutation using the proposed companion diagnostic (the LeukoStrat CDx FLT3 Mutation Assay), and who were treated at the recommended dose. The FDA Efficacy Analysis Population (EAP) included 138 patients of median 60 years (range, 20 to 84 years); 38% were $\geq$ 65 years old, 46% were male, and 60% were white. The disease was an untreated relapse in 59%, primary refractory in 41% and refractory relapse in none. The median number of relapses was 1 (range, 0 to 2).

The CR/CRh rate as adjudicated by the FDA clinical reviewer was 21.0% (95% CI: 14.5, 28.8). The median time to response was 3.6 months (range, 0.9 to 9.6 months), and the median duration of response was 4.6 months (range, 0.1 to 15.8 months). Among the 106 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 33 (31.1%) became independent of RBC and platelet transfusions during any 56-day postbaseline period. Of the 32 patients who were independent of both RBC and platelet transfusions at baseline, 17 (53.1%) remained transfusion independent during any 56-day postbaseline period.

Supporting evidence came from Study 2215-CL-0101, an exploratory single-arm trial of gilteritinib which did accrue patients with refractory relapse. In this study, the CR/CRh rate in 49 patients as adjudicated by the FDA clinical reviewer was 18.4% (95% CI: 8.8, 32.0), the median duration of response was 12.3 months (range, 0.5 to 36.0+ months), and 23.4% of 47 transfusion-dependent patients became transfusion-independent for at least 56 days.

In a pooled subgroup analysis, CR/CRh responses were seen across various demographic and disease status subgroups, except for black patients and patients with a TKD mutation. However, the numbers of patients in these subgroups were small (12 and 19 patients, respectively), and the upper 95% confidence interval bound still included the possibility of CR/CRh rates similar to that in the rest of the EAP.

It is concluded that the durable CR or CRh associated with transfusion-independence induced by gilteritinib constitutes substantial evidence of effectiveness.

1.3 Benefit-Risk Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• With supportive care alone, patients with relapsed or refractory (R/R) AML survive only weeks.	R/R AML is a fatal disease.
Current Treatment Options	• For R/R AML with FLT3 mutations, the reported remission rates are < 40% using intensive chemotherapy, with median survival 3-12 months.	There is a need for an effective agent to treat R/R AML with FLT3 mutations.
Benefit	• In Study 2215-CL-0301, 138 adults with FLT3-mutated R/R AML were treated with gilteritinib 120 mg orally daily. Median follow-up was 4.6 months. • CR or CRh was achieved by 21% (95% CI: 14.5%, 28.8%). Median DOR was 4.6 months. There were no responses in the small subgroup of patients with TKD mutations. • Conversion to transfusion independence was achieved by 31%, and 53% maintained transfusion independence. • Median OS was 9 months • Outcomes were similar in a supporting exploratory trial that included 49 patients.	There is substantial evidence that gilteritinib is active in patients with FLT3-mutant R/R AML based on CR/CRh rate and conversion to transfusion independence while on therapy.
Risks and Risk Management	• The main safety population included 292 patients with R/R AML treated with gilteritinib 120 mg daily. • The most common adverse reactions (≥20%) included myalgia/arthralgia, transaminase increase, fatigue/ malaise, fever, noninfectious diarrhea, dyspnea, edema, rash, pneumonia, nausea, stomatitis, cough, headache, hypotension, dizziness and vomiting • PRES, QT interval prolongation, and pancreatitis that was life-threatening or fatal occurred. • Several patients showed signs consistent with differentiation syndrome (DS). • The protocol included monitoring for risks and instructions for intervention. Adverse reaction led to discontinuation for 8%. • The safety of long-term use is unclear.	The overall short-term safety profile of gilteritinib is acceptable for patients with R/R AML. Monitoring, including ECG and laboratory monitoring. is needed to minimize the risks. Studies of long-term use and DS are needed to confirm safety.

Patients with FLT3-mutated AML that has relapsed or that is refractory to induction therapy have a poor prognosis. In Study 2215-CL-0301, 21.0% (95% CI: 14.5, 28.8) of the study subjects treated with gilteritinib achieved a CR or CRh, conversion to transfusion independence was achieved by 31%, and 53% maintained transfusion independence. Follow-up is too short to determine whether there is a long-term benefit or substantial effect on survival. Instead, FDA chose to base the finding of effectiveness on durable CR/CRh and transfusion independence, which even in the short-term provides a meaningful benefit for patients.

In general, the safety profile of gilteritinib was similar to that of other kinase inhibitors. The major safety issues identified were prolonged QT interval (1.4% had a QTc interval greater than 500 msec and 7% had an increase from baseline QTc greater than 60 msec), posterior reversible

encephalopathy (rare cases), pancreatitis (rare cases), and the potential for embryofetal toxicity (based on nonclinical data). With procedures in place for early detection and intervention, fatal toxicities in the pivotal population were limited. The seriousness of these risks warrants warnings in labeling. However, only 8% of patients discontinued treatment due to an adverse reaction, so the dose is considered tolerable. There was also a signal that differentiation syndrome might occur. Additional study is needed to assess safety during long-term use, and to characterize the risk of gilteritinib-induced differentiation syndrome

Given the potential to avoid transfusions short-term using gilteritinib and the tolerability of this drug, and with the safety mitigation plan in place, the clinical benefit appears to outweigh the risks of gilteritinib for adult patients with R/R AML with FLT3 mutations.

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application

				Section of review where discussed, if applicable
□	**The patient experience data that were submitted as part of the application include:**			
	□	Clinical outcome assessment (COA) data, such as		
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

Donna Przepiorka, MD, PhD
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1 Analysis of Condition

Acute myeloid leukemia is a relatively common form of leukemia, with 19,520 cases expected in 2018.[1] Although AML can occur at any age, it is most common in older patients. Furthermore, while it is treatable and sometimes curable, long term survival is relatively rare, especially in older patients who constitute the majority of new patients.[2] A total of 10,670 deaths due to AML are expected in 2018.

Mutations in the FLT3 gene on chromosome 13q12 are seen in about 30% of patients with AML.[3] Mutations may result in either internal tandem duplication of amino acids in the juxtamembrane region of the FLT3 protein or a point mutation in the activation loop of the tyrosine kinase domain. Either mutation results in constitutive activation of FLT3 kinase. FLT3-ITD mutations are associated with a higher likelihood of relapse and decreased overall survival. The effect of FLT3-TKD mutations is debatable and may be dependent on other mutations in the individual's leukemia.

2.2 Analysis of Current Treatment Options

With the exception of acute promyelocytic leukemia (APL), which is frequently curable with retinoic acid and arsenic trioxide and is excluded from further discussion in this review, combination chemotherapy regimens with or without allogeneic hematopoietic stem cell transplantation (HSCT) are the mainstay of therapy for patients with AML. The standard regimen used first-line induction in patients with AML who can tolerate intensive chemotherapy is the "7+3 regimen" consisting of an anthracycline and cytarabine for induction of remission followed by high dose cytarabine for consolidation. Midostaurin is approved in combination with induction and consolidation chemotherapy for first-line treatment of AML with a FLT3 mutation.

There are numerous drugs approved for treatment of R/R AML (Table 1). None has substantial activity as a single-agent, so combinations of cytotoxic drugs have been the mainstay for treatment of R/R AML. Patients treated in first relapse after a long remission have CR rates of 40-60%. For patients treated for relapse after a short first remission and those with later

[1] SEER Cancer Stat Facts: Leukemia-Acute Myeloid Leukemia Accessed 6/18 https://seer.cancer.gov/statfacts/html/amyl.html
[2] Pulte D, L Jansen, FA Castro, et al., 2016, Survival in patients with acute myeloblastic leukemia in Germany and the United States: Major differences in survival in young adults. Intl J Cancer, 139:1289–1296.
[3] Stone RM, SJ Mandrekar, BL Sanford, et al., 2017, Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. New Engl J Med, 377:454–464.

relapses, the CR rates are less than 40%, median survival 3-12 months, and 5-year survival less than 10%. Gemtuzumab ozagamicin (GO) is the only targeted therapy with an approved indication that would encompass patients with R/R FLT3-mutated AML. With GO, the CR rate was 26% for patients in first relapse, and the median duration of relapse-free survival was 11.6 months.

There are seven kinase inhibitors with activity against FLT3 marketed in the US (brigatinib, cabozantinib, midostaurin, nintedanib, sorafenib and sunitinib). None has an indication for treatment of R/R FLT3-mutated AML, and midostaurin carries a limitation of use due to its established lack of efficacy as monotherapy in this setting.

Table 1: Drugs Approved in the US for Acute Myelogenous Leukemia (Excluding APL)

Drug	Indication
Cyclophosphamide	For treatment of acute myelogenous and monocytic leukemia, most frequently concurrently or sequentially with other antineoplastic drugs
Cytarabine	In combination with other approved anticancer drugs for remission induction in acute non-lymphocytic leukemia of adults and children.
Daunorubicin	In combination with other approved anticancer drugs for remission induction in acute non-lymphocytic leukemia of adults
Doxorubicin	For treatment of acute myeloblastic leukemia
Enasidenib	For treatment of adult patients with relapsed or refractory AML with an IDH2 mutation as detected by an FDA-approved test.
Gemtuzumab	For treatment of newly-diagnosed or R/R CD33+ AML
Glasdegib	In combination with low-dose cytarabine, for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adult patients who are ≥ 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy
Idarubicin	In combination with other approved anti-leukemic drugs for treatment of AML in adults
Ivosidenib	For treatment of adult patients with relapsed or refractory AML with a susceptible IDH1 mutation as detected by an FDA-approved test.
Midostaurin	In combination with cytarabine and daunorubicin induction and cytarabine consolidation in adults with newly-diagnosed AML that is FLT3 mutation-positive as detected by an FDA approved test.
Mitoxantrone	In combination with other approved drugs in the initial therapy of acute non-lymphocytic leukemia in adults
Thioguanine	For remission induction and consolidation treatment of acute non-lymphocytic leukemia.
Venetoclax	In combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed acute myeloid leukemia (AML) in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.
Vincristine	In acute leukemia
Vyxeos	For treatment of adults with a diagnosis of therapy-related AML or AML with myelodysplasia-related changes

3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

Gilteritinib is not currently marketed in the United States.

3.2 Summary of Presubmission/Submission Regulatory Activity

25 Feb 2015: End of phase 1 meeting
13 Nov 2015: Type B pre-phase 3 meeting
8 Apr 2016: End of phase 2/pre-phase 3 meeting
31 May 2017: Type C guidance
5 Dec 2017: Pre-NDA meeting

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

The Office of Scientific Investigations conducted inspections for studies 2215-CL-0101 and 2215-CL-0301 at clinical sites in New York, NY (Weill Cornell Medical College), Baltimore, MD (University of Maryland Greenbaum Cancer Center), and Philadelphia, PA (University of Pennsylvania Abramson Cancer Center). These sites had the highest accrual and greatest center-level impact on the primary endpoint. Inspection review of the Philadelphia site identified minor regulatory deficiencies (failure to report serious adverse events (SAEs) within the mandatory reporting period). A Form 483 was issued to the Investigator, and the classification was Voluntary Action Indicated. The classification of the other sites was No Action Indicated. The Applicant (Astellas) was also audited. The preliminary classification for the Applicant inspection was No Action Indicated. Based on these inspection results, the study data derived from the inspected clinical sites were considered reliable in support of the requested indication.

4.2. Product Quality

Gilteritinib drug product (Xospata) is presented as a light yellow, round, film-coated tablet containing 40 mg gilteritinib active ingredient as free base (corresponding to 44.2 mg gilteritinib fumarate) for oral use. The tablets are debossed with the Astellas logo and '235' on the same side. The inactive ingredients are mannitol, hydroxypropyl cellulose, low-substituted hydroxy-propyl cellulose, magnesium stearate, hypromellose, talc, polyethylene glycol, titanium dioxide and ferric oxide. All excipients are compendial-compliant. The drug product is supplied in bottles of 90 tablets with an expiry of 36 months when stored at USP controlled room temperature.

The to-be-marketed formulation was utilized in the pivotal trial, Study 2215-CL-0301. During clinical development, changes were made in the size, excipient content, and manufacturing of the drug product. Based on the data submitted, including a relative bioavailability study (Study 2215-CL-110), no clinically meaningful differences between the early clinical trial formulations and the to-be-marketed formulation were identified, and it was concluded that data from the early clinical trials were acceptable for use in the assessment of safety and clinical activity.

There were no outstanding safety issues identified for the manufacturing process or from the facilities inspections. The Applicant claimed a categorical exclusion from the requirement for an environmental assessment, and the claim was accepted under U.S. Code of Federal Regulations (CFR) Title 21 Part 25.31(b). Approval of the NDA was recommended by the Product Quality review team.

4.3 Devices and Companion Diagnostic Issues

The Applicant is seeking an indication for patients with relapsed or refractory AML limited to those who have an FLT3 mutation, which is a target of gilteritinib. It was determined that a device to select patients for therapy would be required for safe use of gilteritinib when marketed. The Applicant cross-referenced PMA P160040 for the LeukoStrat® CDx FLT3 Mutation Assay. This device detects FLT3-ITDs and the TKD mutations D835 and I836.

The LeukoStrat® CDx FLT3 Mutation Assay was used to select patients for Study 2215-CL-0301, and to confirm retrospectively the eligibility of patients on Study 2215-CL-0101 and 2215-CL-0102. Since the samples tested retrospectively for Study 2215-CL-0102 were outside of the sample stability window at the time of testing, the Applicant did not consider the central test results for this study to be valid, so results from Study 2215-CL-0102 would not be acceptable for the integrated assessment of efficacy.

At the time of completion of this review, the Center for Devices and Radiologic Health had not yet made a final regulatory determination for PMA P160040.

5 Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

Gilteritinib (ASP2215) is an orally-available small molecule drug to treat adult patients with R/R AML with an FLT3 mutation. Gilteritinib has in vitro activity (>50% inhibition at 1 nM) against FLT3, nucleophosmin 1-anaplastic lymphoma kinase (NPM1-ALK), leukocyte tyrosine kinase (LTK), ALK, and AXL tyrosine kinase (AXL). At 5 nM, gilteritinib also produces greater than half maximal inhibition of tropomyosin receptor kinase A (TRKA) and proto-oncogene tyrosine-protein kinases (ROS, RET, and MER).

In studies to elucidate its mechanism of action, gilteritinib demonstrated the ability to inhibit FLT3 receptor signaling, e.g., decreasing phosphorylation of signal transducer and activator of transcription 5 (STAT5), protein kinase B (AKT), and extracellular signal-regulated kinase (ERK). Gilteritinib also decreased proliferation in cells exogenously expressing FLT3-wild type and FLT3 mutants, including FLT3-internal tandem duplication (FLT3-ITD) and tyrosine kinase domain mutations (TKD) FLT3-D835Y and FLT3-ITD-D835Y, and it induced apoptosis in leukemic MV4-11 cells expressing FLT3-ITD. The established pharmacologic class of gilteritinib is kinase inhibitor.

The results of the gilteritinib safety pharmacology testing were not remarkable. There were no toxicologically significant effects at doses of gilteritinib up to 100 mg/kg in the central nervous system (CNS) of rats or in the cardiovascular or respiratory systems of dogs. Gilteritinib also has low in vitro potency at blocking hERG currents.

Gilteritinib is highly bound to plasma protein in a variety of species (90% in humans). In non-pigmented rats [^{14}C]-gilteritinib was widely distributed, with the highest radioactivity observed in the liver. In pigmented rats, [^{14}C]-gilteritinib distributed to the eyeball in the melanin-rich tissues such as ciliary body, retina, and choroid. Radioactivity levels in eyeballs of pigmented rats were approximately 30-fold higher than in the non-pigmented rats.

The cytochrome P450 enzyme (CYP3A4) is involved in the metabolism of gilteritinib by N-dealkylation and oxidation, allowing for glutathione conjugation. The majority of gilteritinib is eliminated from the body unchanged. None of the main M10, M16, or M17 metabolites are human specific or exceed 10% of overall parent exposure. Elimination studies showed that gilteritinib was mainly excreted through the fecal route in both rats (90%) and dogs (88%) with some elimination through the urine (1.4% in rats and 9.5% in dogs).

In the 13-week study in rats, gilteritinib was administered by oral gavage at 0 (vehicle), 2.5, 5, 10, or 20 mg/kg/day once daily with a 4-week recovery period. Mortality was observed in 2 animals (1 male and 1 female) treated with 20 mg/kg/day. In rats surviving until the end of the 13-week study, body weights were decreased >10%, compared to controls, in males at ≥5 mg/kg/day and in females at 20 mg/kg/day. Clinical pathology changes included decreases in lymphocytes, white blood cells, and basophils; and increases in aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and albumin/globulin (A/G) ratio. Target organs of toxicity included the spleen, thymus, lymph follicles, gastrointestinal (GI) tract, bone marrow, lung, kidney, and eye. The histopathological changes were mostly very slight to slight from normal grade with some exceptions. Toxicities included microgranuloma (lymph nodes), necrosis and/or atrophy (thymus, spleen), microvacuolation of the mucosal epithelia in the GI tract, hypocellularity in the bone marrow, accumulation of foam cells in the lung, vacuolation of the renal medulla as well as increased mesangial matrix, tubular basophilia, hyaline droplets in the renal tubule, hyaline casts, and edematous change in the papilla, and inflammatory cell infiltration in the choroid, ciliary body, iris, and/or conjunctiva in the eye. Electron microscopy revealed test article-related

phospholipidosis in the lung and kidney at 20 mg/kg/day. All changes noted in the dosing period recovered or tended to recover by the end of a 4-week recovery period.

In the 13-week study in dogs, gilteritinib was administered orally at doses of 0 (vehicle), 1, 2.5 or 5 mg/kg/day once daily with a 4-week recovery period. Mortality was observed in 2 males treated with 5 mg/kg/day. In dogs surviving until the end of the 13-week study, changes in clinical pathology included: decreases in erythrocytes and lymphocytes; increases in AST, ALP, and gamma-globulin; and decreased albumin and A/G ratio. The target organs of toxicity included the spleen, thymus, lymph nodes, Peyer's patch, lung, liver, gall bladder, kidney, GI, and eye. The histopathological changes were mostly very slight to slight from normal grade with some exceptions. The toxicities included atrophy (thymus), congestion (spleen), and lymphocyte necrosis of the lymph nodes and Payer's patch, accumulation of foam cells, edema, focal alveolar hemorrhage, inflammatory cell infiltration, alveolar epithelial hypertrophy/ hyperplasia in the lung, vacuolation and atrophy, perivascular mononuclear cell infiltration, and brown pigment deposition in the Kupffer cell in the liver, mucosal hypertrophy/mucus hypersecretion in the gallbladder, tubular vacuolation at the cortico-medullary junction, inflammatory cell infiltration in the medulla and pelvis, renal tubular regeneration, and focal congestion in the renal medulla in the kidney, inflammation in molar and incisor alveoli and gingiva, and vacuolation in the rod-cone layer/outer nuclear layer of the retina. Electron microscopy revealed test article-related liver injury, dilated endoplasmic reticulum/ inflammation of the kidney, and effects on photoreceptor cells of the eye. In the 4-week repeated oral dose toxicity study of gilteritinib in dogs, degeneration/necrosis of the germ cells in the testes and spermatid giant cell formation was observed at 10 mg/kg/day and the incidence and severity were greater than those in the control group.

Based on findings in animals and its mechanism of action, gilteritinib can cause embryo-fetal harm when administered to a pregnant woman. In an embryo-fetal development (EFD) study in rats, pregnant animals were administered gilteritinib once daily during the period of organogenesis on gestation days (GD) 7-17, at doses of 0 (vehicle), 0.3, 3, 10, or 30 mg/kg/day. The dose levels were justified based on the results from a dose range-finding EFD study in pregnant rats. Signs of maternal toxicity were limited to decreased body weight and food consumption at 30 mg/kg/day (resulting in exposures approximately 0.4 times the area under the curve (AUC) in patients receiving the recommended dose). Gilteritinib at 30 mg/kg/day resulted in embryo-fetal death (postimplantation loss) and increased incidence of fetal gross external, visceral, and skeletal abnormalities. Findings in the EFD studies support the inclusion of a warning for embryo-fetal toxicity in the gilteritinib label.

Single oral administration of [^{14}C]-gilteritinib to pregnant rats resulted in transfer of radioactivity through the blood-placental barrier into the fetus. Radioactivity from [^{14}C]-gilteritinib also distributed from milk into infant tissues. Because of the potential for serious adverse reactions in a breastfed child, lactating women will be advised not to breastfeed during treatment and for 2 months after the last dose. Pregnancy testing will be recommended for

females of reproductive potential within seven days prior to initiating treatment. Females of reproductive potential will be advised to use effective contraception during treatment and for at least 6 months after the last dose. Males of reproductive potential will be advised to use effective contraception during treatment and for at least 4 months after the last dose.

Gilteritinib was not mutagenic in the in vitro bacterial reverse mutation test or clastogenic in the in vitro chromosomal aberrations assay in Chinese hamster lung cells. Gilteritinib was positive for the induction of micronuclei in the in vivo bone marrow micronucleus assay in mice. No carcinogenicity studies have been conducted or are required to support marketing of gilteritinib for the current indication.

The nonclinical pharmacology and toxicology data submitted to this NDA are adequate to support the approval of gilteritinib for the proposed indication.

5.2 Referenced NDAs, BLAs, DMFs

None.

5.3 Pharmacology

Primary Pharmacology

In Vitro Pharmacology
Gilteritinib concentrations of 1 and 5 nmol/L were evaluated for inhibitory effects against 79 human tyrosine kinases (Study 2215-PH-0006). At these concentrations, gilteritinib produced half maximal inhibition of several kinases (**Table 2)**.

Table 2: Inhibitory Effect of Gilteritinib on Various Tyrosine Kinases

Kinase	% inhibition	
	Gilteritinib fumarate (nmol/L)	
	1	5
FLT3	86.8	96.4
NPM1-ALK	82.2	99.5
LTK	81.8	97.5
ALK	76.1	97.6
AXL	54.3	85.5
TRKA	38.3	74.9
ROS	35.0	71.7
RET	26.0	65.5
MER	21.5	55.7

(Table excerpted from NDA 211349)

Gilteritinib was tested for the ability to inhibit proliferation of both, Ba/F3 cells exogenously expressing wild type FLT3 or FLT3 mutants (FLT3-ITD, FLT3-D835Y, and FLT3-ITD-D835Y), as well

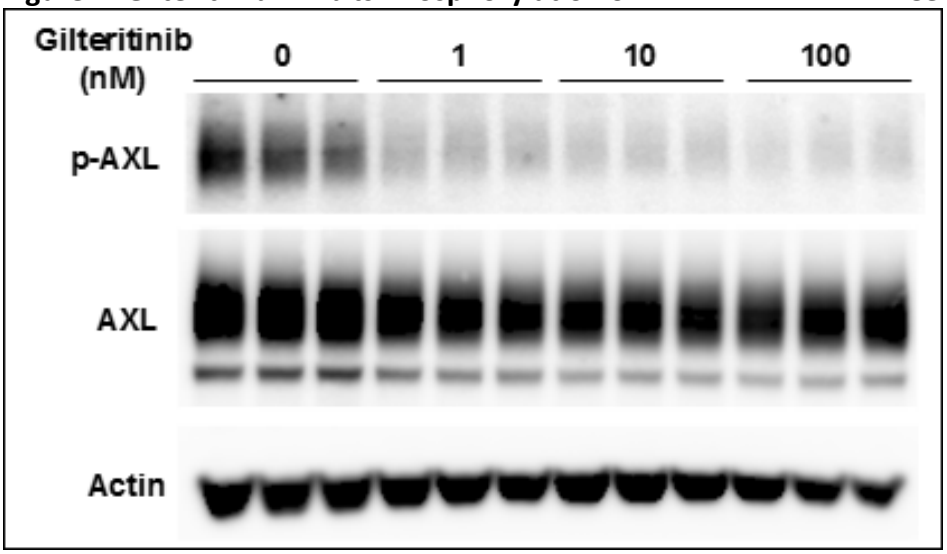
as of MV4-11 cells, human AML cells endogenously expressing FLT3-ITD (Study 2215-PH-0009 Ba/F3 cells and 2215-PH-0008 with MV4-11 cells). The Ba/F3 cells and the MV4-11 were treated with gilteritinib at concentrations of 0-12.8 nmol/L for 2 or 0-30 mol/L for 5 days, respectively. Cell viability was determined using a CellTiter-Glo® Luminescent Cell Viability Assay (**Table 3**).

Table 3: Antiproliferative Activity of Gilteritinib in Cells Expressing FLT3

	IC_{50} (nmol/L)				
Test System	FLT3-WT Ba/F3	FLT3-ITD-Ba/F3	FLT3-D835Y Ba/F3	FLT3-ITD-D835Y	FLT3-ITD (MV4-11)
Gilteritinib fumarate	0.92	1.8	1.6	2.1	0.92

Gilteritinib was also tested for its ability to inhibit phosphorylation of MV4–11-AXL cells (**Figure 1**), which exogenously express AXL tyrosine kinase.[4] At concentrations of 1nM, 10nM, and 100nM for 4 hours, gilteritinib treatment decreased phosphorylated AXL levels by 38%, 29%, and 22%, respectively, relative to that of vehicle-treated cells.

Figure 1: Gilteritinib Inhibits Phosphorylation of AXL in MV4-11-AXL Cells

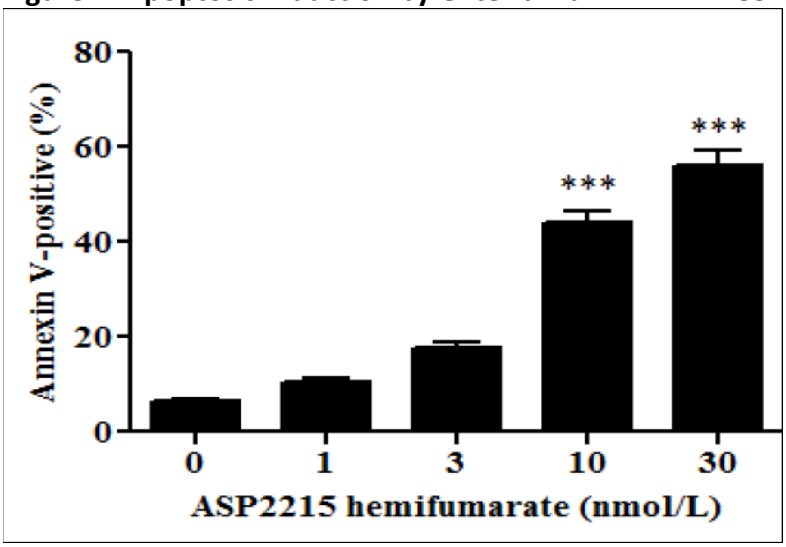


(Excerpted from Mori et al 2017 reference provided by the Applicant)

Gilteritinib was tested for its ability to induce apoptosis in MV4-11 cells (AML cells endogenously expressing FLT3-ITD) exposed for 48 hours (**Figure 2**). Cells were harvested and incubated with Guava® Nexin Reagent to determine annexin-V-positivity as an index of cellular apoptosis (Study No. 2215-PH-9005).

[4] Mori et al., Invest New Drugs, 2017, Gilteritinib, a FLT3/AXL inhibitor, shows antileukemic activity in mouse models of FLT3 mutated acute myeloid leukemia, 35:556–565

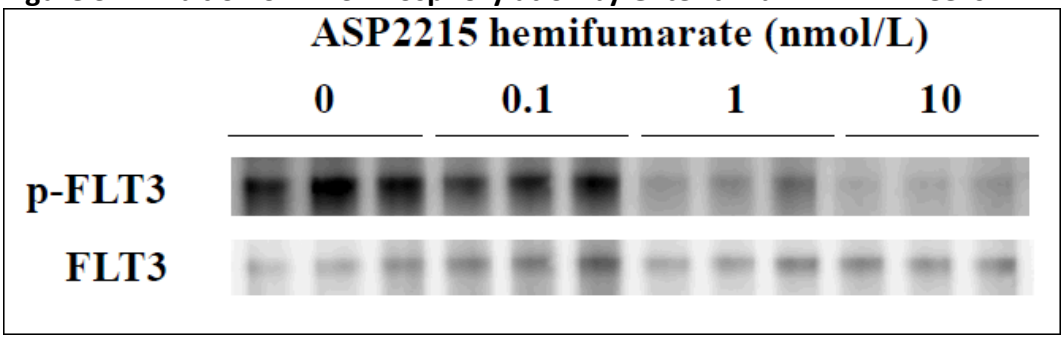
Figure 2: Apoptosis Induction by Gilteritinib in MV4-11 Cells



(Figure excerpted from NDA 211349)

The inhibitory effect of gilteritinib on phosphorylation of FLT3 (**Figure 3**) was examined in MV4-11 cells exposed for 2 hours (Study No. 2215-PH-0010). Protein lysates were subjected to immunoprecipitation with anti-FLT3 antibody, resolution by SDS-PAGE, and immunoblotting for phosphorylated FLT3 (p-FLT3), and FLT3. Gilteritinib inhibited phosphorylation of FLT3 by up to 86% compared to the control in MV4-11 cells (AML cells endogenously expressing FLT3-ITD).

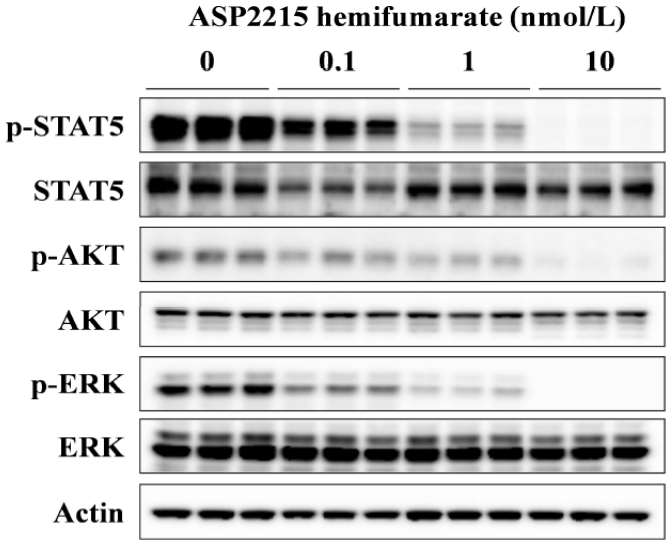
Figure 3: Inhibition of FLT3 Phosphorylation by Gilteritinib in MV4-11 Cells



(Figure excerpted from NDA 211349)

Phosphorylation of proteins downstream of FLT3, such as STAT5, AKT, and ERK, was also inhibited by gilteritinib treatment (**Figure 4**).

Figure 4: Inhibition of STAT5, AKT, and ERK Phosphorylation by Gilteritinib



MV4-11 cells were treated with 0 (vehicle), 0.1, 1, and 10 nmol/L of ASP2215 hemifumarate for 2 h. Protein lysates were subjected to immunoblotting for indicated proteins. As for the ERK protein, upper and lower band represent ERK1 and ERK2, respectively.

(Figure excerpted from NDA 211349)

In Vivo Pharmacology

The antitumor activity of gilteritinib was studied in a xenograft model using MV4-11 cells (Study No. 2212-PH-0011). MV4-11 cells (AML cells endogenously expressing FLT3-ITD) were subcutaneously inoculated into the flank of 50 male nude (CAnN.Cg-Foxn1nu/CrlCrlj[nu/nu]) mice. Gilteritinib was administered orally daily for 28 days at 1, 3, 6, or 10 mg/kg/day. Body weights and tumor diameters were measured on Days −1, 2, 6, 10, 14, 17, 21, 24, and 28. Administration of gilteritinib significantly inhibited tumor growth.

The body weights of the mice treated with gilteritinib fumarate were not affected at any doses tested. The phosphorylation of FLT3 and STAT5 in MV4-11 tumors was inhibited by administration of gilteritinib fumarate following single oral administration at 1, 3, 6 or 10 mg/kg to mice xenografted subcutaneously with MV4-11 cells (2215-PH-9006).

Table 4: Antitumor Activity of Gilteritinib in MV4-11 Cell Xenografts

		Percent inhibition of tumor growth (%)	Percent regression of tumor (%)	Animal number with complete regressions
ASP2215 hemifumarate	1 mg/kg	63	-	-
	3 mg/kg	80	-	-
	6 mg/kg	>100	93	4/6
	10 mg/kg	>100	100	6/6

(Table excerpted from NDA 211349)

Secondary Pharmacology

Gilteritinib was evaluated in radioligand binding assays across a diverse set of 46 receptors, 5 ion channels, and 3 transporters. Notably, gilteritinib at 10 µmol/L resulted in 100% inhibition of agonist-specific ligand binding to the $5HT_{2B}$ (human) serotonin receptor; IC_{50}=0.190 nmol/L. In a functional assay, gilteritinib showed no agonistic activity at the human $5HT_{2B}$ receptor. Gilteritinib is not expected to have off-target activity at other human receptors, enzymes, or ion channels at clinically relevant concentrations.

Safety Pharmacology

The potential for gilteritinib to affect the CNS (general activity and behaviors) was assessed using a modified Irwin's method in Sprague Dawley (SD) rats given single oral doses of 10, 30 and 100 mg/kg. The findings were limited to decreased numbers of rats urinating at ≥30 mg/kg, and decreased numbers of rats defecating at 100 mg/kg. These findings were confirmed to be reversible in an additional study.

Gilteritinib was tested at 1-30 µmol/L for its potential to inhibit hERG channel potassium currents in HEK293 cells; IC_{50}=16 µmol/L (8.84 µg/mL) (Study No. 2215-PT-0001). The effects of gilteritinib (0.1-10 µmol/L) on cardiac ion channels were investigated using HEK293 cells or Chinese hamster ovary cells expressing various human cardiac ion channels (sodium channel, calcium channel, potassium channel). Gilteritinib increased calcium and potassium currents at concentrations ≥1 µmol/L.

In a telemetry study in conscious Beagle dogs given single oral doses of gilteritinib at 1, 3, 10, 30, and 100 mg/kg, there were no effects on body temperature, blood pressure, heart rate, electrocardiogram (ECG), respiratory rate, or blood gas concentrations (Study No. 2215-PT-0002). Findings of retching at 3 mg/kg, vomiting and a positive fecal occult blood reaction at ≥10 mg/kg, decreased blood calcium concentration at 30 mg/kg, and salivation and altered (increased and decreased) blood calcium concentrations were noted at 100 mg/kg.

5.4 ADME/PK

Type of Study	Major Findings
Absorption	
Pharmacokinetics of ASP2215 in Rats after Single Intravenous and Oral Administration of ASP2215 Hemifumarate/2215-ME-0007 Pharmacokinetics of ASP2215 in Dogs after Single Intravenous and Oral Administration of ASP2215 Hemifumarate/ 2215-ME-0008	**Gilteritinib Pharmacokinetics – Single Oral Dose** (Table excerpted from NDA 211349) Following repeat dosing (13 weeks), exposure (C_{max} and AUC_{24h}) increased more than dose proportionally in rats and dogs.
Distribution	
In Vitro Plasma Protein Binding of ASP2215 in Mice, Rats, Rabbits, Dogs, Monkeys, and Humans/2215-ME-0010	**Plasma Protein Binding of Gilteritinib** (Table excerpted from NDA 211349)
Tissue Distribution after Single Oral Administration of [^{14}C]ASP2215 Hemifumarate to Non-Pigmented Rats/2215-ME-0009 Tissue Distribution of Radioactivity in Pigmented Rats after Single Oral Administration of [^{14}C]ASP2215	<u>Non-pigmented and pigmented rats</u> Tissue distribution following single oral 1 mg/kg doses of [^{14}C]-gilteritinib was investigated in non-pigmented and pigmented rats. In non-pigmented rats, tissue radioactivity concentrations peaked at 4 h postdose in almost all tissues. Concentrations were highest in the liver, then spleen, kidneys, adrenal glands and lung; and lowest in the plasma, followed by the testes, brain and blood. In pigmented Long-Evans rats, the radioactivity concentrations reached maximum levels at 4 h postdose in most tissues. The maximum concentrations of radioactivity (in the eyeballs) were approximately 30-fold higher than in the eyeballs of non-pigmented rats by Day 3. The quantitative whole body autoradioluminogram (QWBA) study showed that the radioactivity in the eyeballs was distributed in the melanin-rich tissues, such as ciliary body, retina, and choroid.

Species	Dose (mg/kg)	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	AUC_t (ng·h/mL)	AUC_{inf} (ng·h/mL)	BA [a] (%)
Rat	1	5.36	6.00	NC	63.6 [b]	69.0 [e]	26.8
	3	23.29	6.00	6.64	274 [c]	276	35.8
	10	125.47	4.00	6.41	1750 [c]	1760	68.6
Dog	0.3	5.61 ± 1.21	6.50 ± 1.00	27.73 ± 4.57	177 ± 50 [d]	213 ± 72	88.2 ± 16.5
	1	22.11 ± 4.45	6.50 ± 1.00	27.67 ± 1.80	601 ± 112 [d]	704 ± 132	88.7 ± 9.6
	3	88.28 ± 15.91	6.00 ± 0.00	47.95 ± 12.92	2070 ± 528 [d]	2860 ± 910	118.4 ± 19.8

NC: Not calculated

a: BA (%) = ([Dose (iv) × AUC_{inf} (po)]/[Dose (po) × AUC_{inf} (iv)]) × 100
b: AUC_{24h}; c: AUC_{48h}; d: AUC_{72h} e: AUC_{48h} was assumed to be AUC_{inf}.
Rat values were calculated from the mean plasma concentrations of three rats/time point.
Dog values represent the mean ± standard deviation of parameters calculated from the individual plasma concentrations of four dogs.

Species	Plasma protein binding ratio (%) Tested concentration (µg/mL) 0.1	1	10
Normal mouse	89.6 ± 0.2	87.7 ± 0.4	85.1 ± 0.5
Pharmacological model mouse [a]	84.2 ± 0.5	78.7 ± 0.5	75.4 ± 0.6
Rat	78.8 ± 0.7	79.2 ± 1.1	77.7 ± 0.9
Rabbit	78.7 ± 2.4	78.7 ± 2.7	75.5 ± 2.4
Dog	79.1 ± 3.0	80.7 ± 3.1	78.0 ± 3.5
Cynomolgus monkey	81.3 ± 0.7	82.4 ± 0.9	81.4 ± 0.7
Human	90.4 ± 0.1	90.5 ± 1.2	90.2 ± 0.5

Values of mice represent the mean ± standard deviations of three determinations for pooled plasma. Values of rats, rabbits, dogs, cynomolgus monkeys, and humans represent the means ± standard deviations of three individual plasma samples.
a: NOD.CB17-Prkdc SCID/J mouse xenografted NCI-H2228 cells

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Hemifumarate/2215-ME-0025/2215-ME-0017

Transfer of Radioactivity into Fetuses and Breast Milk in Rats after a Single Oral Administration of [14C]ASP2215 Hemifumarate/ 2215-ME-0022</td><td><u>Gilteritinib transfer into fetuses and breast milk</u>
Radioactivity was detected in the placentas and fetuses, indicating that gilteritinib-derived components passed through the blood-placental barrier and transferred to the fetus.

After a single oral administration of [14C]-gilteritinib to rats during organogenesis (Day 14) or to lactating rats (Day 14 postpartum), radioactivity was detected in maternal and fetal/infant tissues, indicating that gilteritinib and/or its metabolite(s) are transferred to the fetus via the placenta, and infants can be exposed via milk.
Gilteritinib Maternal Transfer and Infant Distribution
<table>
<tr><th rowspan="2">Tissue</th><th colspan="4">Tissue concentration (ng eq./mL or ng eq./g)</th></tr>
<tr><th>4 h</th><th>24 h</th><th>48 h</th><th>72 h</th></tr>
<tr><td>Blood of maternal animal</td><td>3.62 ± 0.76</td><td>ND</td><td>ND</td><td>ND</td></tr>
<tr><td>Plasma of maternal animal</td><td>1.24 ± 1.11</td><td>ND</td><td>ND</td><td>ND</td></tr>
<tr><td>Milk</td><td>41.3 ± 12.4</td><td>6.72 ± 1.49</td><td>ND</td><td>ND</td></tr>
<tr><td>Blood of infant</td><td>ND</td><td>ND</td><td>ND</td><td>ND</td></tr>
<tr><td>Plasma of infant</td><td>ND</td><td>ND</td><td>ND</td><td>ND</td></tr>
<tr><td>Brain of infant</td><td>ND</td><td>ND</td><td>ND</td><td>ND</td></tr>
<tr><td>Lung of infant</td><td>ND</td><td>9.19 ± 3.24</td><td>4.71 ± 2.19</td><td>4.85 ± 1.25</td></tr>
<tr><td>Heart of infant</td><td>ND</td><td>3.17 ± 0.82</td><td>ND</td><td>1.35 ± 1.23</td></tr>
<tr><td>Liver of infant</td><td>ND</td><td>15.6 ± 4.4</td><td>6.76 ± 4.48</td><td>7.40 ± 1.95</td></tr>
<tr><td>Kidney of infant</td><td>ND</td><td>14.3 ± 3.9</td><td>8.87 ± 6.36</td><td>8.07 ± 0.80</td></tr>
<tr><td>Milk lump in stomach of infant</td><td>22.3 ± 5.0</td><td>15.9 ± 5.9</td><td>1.80 ± 0.41</td><td>6.79 ± 10.4</td></tr>
</table>
ND: Not detected. Each value represents the mean ± standard deviation of three rats. Radioactivity concentrations are expressed as equivalent amounts of gilteritinib.
(Table excerpted from NDA 211349)</td></tr>
<tr><td>Metabolism</td><td></td></tr>
<tr><td>In Vitro Metabolic Profile/2215-ME-0002/2215-ME-0001/2215-ME-0004

Quantitative Metabolite Profiling after a Single Oral Administration of [14C]ASP2215 Hemifumarate to Rats, Dogs, and Humans/2215-ME-0028</td><td>The in vitro metabolic profiles of gilteritinib in pooled liver microsomes and in pooled cryopreserved hepatocytes were investigated using [14C]-gilteritinib at a substrate concentration of 10 µmol/L. The species investigated were mice, rats, rabbits, dogs, monkeys, and humans. Except for two minor metabolites, all human metabolites were also detected in at least one animal species. The results suggest that no major human-specific liver metabolites were formed. CYP3A4 is involved in the metabolism of gilteritinib by N-demethylation, N-dealkylation, and oxidation, allowing for glutathione conjugation.

[14C]-gilteritinib metabolite profiles were assessed in plasma, urine, feces from male rats (1 mg/kg oral, 3/time point), male dogs (1 mg/kg oral, 3 males), and humans (120 to 240 mg, N=5, from Protocol No. 2215-CL-0105). Gilteritinib was extensively metabolized, with at least 17 drug-related peaks measured by LC-MS. Gilteritinib was the most abundant peak in all 3 analytes across the species. Metabolic pathways of gilteritinib in humans involve oxidation, N-dealkylation and glutathione conjugation followed by hydrolysis and glucuronidation.</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td>Species Comparison of Gilteritinib Exposure – Single Oral Dose
<table>
<tr><th rowspan="2">Species, Sex</th><th rowspan="2">Dose mg/kg</th><th colspan="2">Gilteritinib (Parent)</th></tr>
<tr><th>C_{max} (ng/mL)</th><th>AUC_{0-t} (ng·h/mL)</th></tr>
<tr><td>Rat</td><td>1</td><td>5</td><td>69</td></tr>
<tr><td>Rat</td><td>3</td><td>23</td><td>276</td></tr>
<tr><td>Rat</td><td>10</td><td>125</td><td>1,761</td></tr>
<tr><td>Dog</td><td>0.3</td><td>6</td><td>72</td></tr>
<tr><td>Dog</td><td>1</td><td>22</td><td>703</td></tr>
<tr><td>Dog</td><td>3</td><td>88</td><td>2,862</td></tr>
<tr><td>Human</td><td>120*</td><td>680</td><td>13464</td></tr>
<tr><td colspan="4">*Recommended human dose 120 mg/day</td></tr>
</table></td></tr>
<tr><td>Blood and Plasma Concentrations and Excretion of Radioactivity After a single Oral Administration of [14C]ASP2215 Hemifumarate to Dogs/2215-ME-0027</td><td>A single dose of 1 mg/kg of [^{14}C]-gilteritinib was administered orally to Beagle dogs (3/sex).
Elimination of Radioactivity in Dogs
<table>
<tr><th rowspan="2">Sample</th><th>% of Radioactive Dose (Mean)</th></tr>
<tr><th>Males</th></tr>
<tr><td>Urine</td><td>9.5%</td></tr>
<tr><td>Feces</td><td>88.1%</td></tr>
</table></td></tr>
</table>

5.5 Toxicology

5.5.1 General Toxicology

Study title/ number: A 13-week Repeated Oral Dose Toxicity Study of ASP2215 Hemifumerate in Rats Followed by a 4-Week Reversibility Study/ 2215-TX-0002

Key Study Findings

- Rats tolerated up to 10 mg/mg/day.
- Target organs of toxicity included lymphohematopoietic system (thymus, spleen lymph follicles), GI tract, bone marrow, lung, kidney, and eye.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 2.5, 5, 10, and 20 mg/kg/day and daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Crl:CD(SD) rats
Number/Sex/Group:	10/sex/group in the main study; 5/sex in control group, 10 and 20 mg/kg in the recovery study
Age:	7 weeks at the time of study initiation

Satellite groups/ unique design: 3/sex in control group and 9/sex in each test article group for TK

Deviation from study protocol affecting interpretation of results: No

Toxicology Observations and Results: Changes Compared to Control

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Mortality</td><td>20 mg/kg: 1/15 females (main study, Day-47) and 1/5 male (TK group, Day-58); Bacterial infection due to deterioration of general condition was the potential cause of death.</td></tr>
<tr><td>Clinical Signs</td><td>Unscheduled deaths: Hypothermia, pale skin, bradypnea, lacrimation, and reddish urine.</td></tr>
<tr><td>Body Weights/food consumption</td><td>Percent change in body weights compared to vehicle control
<table><tr><th>Dose mg/kg/day</th><th>Males</th><th>Females</th></tr><tr><td>2.5</td><td>-7%</td><td>+2%</td></tr><tr><td>5.0</td><td>-11%</td><td>-4%</td></tr><tr><td>10</td><td>-20%</td><td>-8%</td></tr><tr><td>20</td><td>-37%</td><td>-20%</td></tr></table>Body weights tend recover in the recovery period.
Lower food consumption was observed at all doses in during treatment period that recovered in the recovery period and partially at 20 mg/kg/day.</td></tr>
<tr><td>Ophthalmoscopy</td><td>20 mg/kg/day: Corneal opacity during the treatment and the recovery period</td></tr>
<tr><td>Hematology</td><td>≥5 mg/kg/day: ≤-35% WBC, ≤-7% MCV, ≤-9% MCH
20 mg/kg/day: ≤-26% lymphocytes, ≤-59% basophils</td></tr>
<tr><td>Clinical Chemistry</td><td>≥10 mg/kg/day: ≤101% AST, ≤ALT 160%
20 mg/kg/day: ≤74% ALP (recovery group)
≥2.5 mg/kg/day: ≤-31% serum gamma-globulin fraction
≥5 mg/kg/day: ≤-20% serum A/G ratio</td></tr>
<tr><td>Urinalysis</td><td>≥10 mg/kg/day: ↓excretion of electrolytes
20 mg/kg/day: ↓pH, ↓specific gravity, ↓ketone bodies, erythrocytes in sediment</td></tr>
<tr><td>Gross Pathology</td><td>20 mg/kg/day: white focus in the lung in one male rat</td></tr>
<tr><td>Organ Weights (Relative organ weights based on 100 g body weight on the day of gross pathology)</td><td>≥2.5 mg/kg/day: ≤-43% spleen
≥5 mg/kg/day: pituitary ≤-32%, ≤+62% brain, ≤+31% ovary
≥10 mg/kg/day: ≤-49% thymus, ≤-17% lung, ≤-21% kidney, ≤-21% liver, ≤-23% heart, ≤+21% seminal vesicle, ≤+51% testis
20 mg/kg/day: ≤-26% submandibular, ≤-28% prostate</td></tr>
<tr><td colspan="2">- : indicates reduction in parameters compared to control
+ or ↑: indicates increase in parameters compared to control</td></tr>
<tr><td>Histopathology

Adequate battery</td><td>Unscheduled deaths: Bacterial colonies in kidney, heart and cecum accompanied by necrosis, cellular infiltration, and/or inflammation. Inhibitory effects on the immune system (atrophy of the thymus, atrophy of the white pulp in the spleen, and/or lymphocyte necrosis in the submandibular lymph nodes and Peyer's patch). Changes in lung, adrenal, liver and duodenum were noted.

Yes.
Scheduled necropsy: Target organs of toxicity - GI, liver, kidney,</td></tr>
</table>

	lung, bone marrow, eye, lymphohematopoietic system (spleen, thymus, lymph follicles). **2.5 mg/kg/day:** No test article-related changes were observed in either sex.

Histopathology Changes in Surviving Rats in 13-week Toxicology Study

Treatment-Related Microscopic Findings			No. of Animals Affected (Main/Recovery)									
			Males					Females				
Dose (mg/kg/day)			0	2.5	5	10	20	0	2.5	5	10	20
Number of animals			10/5	9/0	10/0	10/5	10/5	10/5	10/0	10/0	10/5	9/5
Organ	Finding											
Sternal bone marrow	Hypocellularity	Slight	-	-	-	8/0	-	-	-	-	-	2/0
Femoral bone marrow	Hypocellularity	Slight	-	-	-	5/0		-	-	-	-	2/0
Thymus	Atrophy	Very slight	1/0			3/0	9/0	-	-	-	-	1/0
		slight	-	-	-	-		-	-	-	-	1/0
	Necrosis, lymphocyte	Very slight	-	-	-	-	2/0	-	-	-	-	2/0
		slight	-	-	-	-	3/0	-	-	-	-	
Spleen	Atrophy, white pulp	Very slight	-	-	-	-	5/0	-	-	-	-	1/0
	Dilatation, splenic sinusoid	Very slight	-	-	1	7/0	10/0	-	-	1	5/0	5/0
	Extramedullary hematopoiesis	Very slight	3/5	5	7	7/5	6/5	6/4	5	6	2/4	3/5
	Microgranuloma	Slight	-	-	-	-	1/0	-	-	-	-	-
Submandibular lymph node	Microgranuloma	Very slight	-	-	-	-	1/0	-	-	-	-	-
Mesenteric lymph node	Atrophy, lymph follicle	Very slight	-	-	-	-	4/0	-	-	-	-	-
	Microgranuloma	Very slight	-	-	-	2/0	3/3	-	-	2	2/1	2/0
		Slight	-	-	-	-	3/0	-	-	-	-	-
Peyer's patch	Necrosis, lymphocyte	Very slight			1	4/0	7/0			2	3/0	5/0
Lung	Accumulation, foam cell	Very Slight	0/2	2	2	3/3	2/1	2/2	1	1	3/3	5/0
		Slight	-	-	-	1/0	5/0	-	-	-	-	3/1
Ileum	Microvacuolation mucosal epithelium	Very slight	-	-	-	6/0	9/0	-	-	-	-	9/0
		Slight	-	-	-		1/0	-	-	-	-	-
Cecum	Microvacuolation mucosal epithelium	Very slight	-	-	-	4/0	5/0	-	-	-	-	4/0
Kidney	Basophilic	Very	4/0	1	2	6/2	8/2	1/1	1	1	1/0	5/2

Treatment-Related Microscopic Findings			No. of Animals Affected (Main/Recovery)									
			Males					Females				
Dose (mg/kg/day)			0	2.5	5	10	20	0	2.5	5	10	20
Number of animals			10/5	9/0	10/0	10/5	10/5	10/5	10/0	10/0	10/5	9/5
Organ	Finding											
	change, renal tubule	slight										
		Slight	-	-	-	-	1/0	-	-	-	-	1
	Cast, hyaline	Very slight	-	1	-	-	7/1	-	-	-	1/0	3/2
		Slight	-	-	-	-		-	-	-	-	-
	Edematous change, renal papilla	Very slight	-	-	-	-	4/0	-	-	-	-	-
	Hyaline droplet, renal tubule	Very slight	-	-	-	-	2/0	-	-	-	-	-
	Increase, mesangial matrix	Very slight	-	-	-	-	2/0	-	-	-	-	-
	Vacuolation renal tubule, medullary	Mode rate	-	-	-	-	10/0	-	-	-	-	-
Eyeball	Cellular infiltration, inflammatory cell choroid	Very slight	-	-	-	-	1/0	-	-	-	-	-
		Slight	-	-	-	-	1/0	-	-	-	-	-
	Cellular infiltration, inflammatory cell, ciliary body/iris	Very slight	-	-	-	-	2/0	-	-	-	-	-
		Slight	-	-	-	-	1/0	-	-	-	-	-
	Cellular infiltration, inflammatory cell, conjunctiva	Slight	-	-	-	-	1/0	-	-	-	-	-

- = no test-article related histopathology

Electron microscopy	20 mg/kg/day: Marked lamellar bodies in the lung (corresponding to microscopic accumulation of foam cells) in 2 males and 2 females. Marked increase of vacuolar structure in the thick limb at the Henle's loop in males and slight lamellar bodies in the collecting duct (corresponding to microscopic vacuolation of the medullary renal tubules) in the kidney in 2 males were noted, suggesting that the test article caused phospholipidosis. Slight fragmented organelles in the vacuolar structure in the ileac mucosal epithelium (corresponding to microscopic microvacuolation) were observed in both sexes.
Recovery	All changes noted in the dosing period recovered or tended to recover by the end of a 4-week recovery period.

Table 5: Gilteritinib Toxicokinetics – 13-Week Rat Study

Daily Dose mg/kg		2.5		5		10		20	
		3M	3F	9M	9F	9M	9F	9M	9F
t_{max} (h)	Day 1	6	6	6	8	8	6	6	10
	Day 91	6	6	8	4	6	6	4	4
C_{max} (ng/mL)	Day 1	9	11	28	22	63	60	228	212
	Day 91	33	32	85	69	190	138	304	258
AUC_{24h} (ng·h/mL)	Day 1	121	119	360	280	830	858	3091	3050
	Day 91	440	423	1103	875	2925	1995	5702*	4136*

* Gilteritinib exposure on Day 91 of dosing was approximately 0.4 and 0.3 times in male and females respectively, the AUC_{24h} (13463.35 ng·h/mL) [Study 2215-CL-0102] at the recommended clinical dose (120 mg/day)

Study title/ number: A 13-Week Repeated Oral Dose Toxicity Study of ASP2215 Hemifumarate in Beagle Dogs Followed by a 4-Week Reversibility Study/2215-TX-0009

Key Study Findings

- Tolerated up to 2.5 mg/mg/day.
- Target organs of toxicity included lymphohematopoietic system, lung, liver, gall bladder, kidney, GI, and eye.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 (vehicle), 1, 2.5, and 5 mg/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Dog/Beagle
Number/Sex/Group:	4/sex/group in the main study; 3/sex at 2.5 and 5 mg/kg in the recovery study
Age:	6-7 months old at the time of study initiation
Deviation from study protocol affecting interpretation of results:	No

Toxicology Observations and Results: Changes Compared to Control

Parameters	**Major findings**
Mortality	5 mg/kg: 2/7 males (Day-42 and Day-77). Findings included decreased activity, decreased food consumption, erosion in foot pads or oral mucosa, abnormal ocular findings, nasal bleeding, positive occult blood reaction, and moribund condition.

	Histopathology findings included hypocellularity in the sternal and femoral bone marrow, abnormal eye findings, multiorgan inflammation, inflammatory cell infiltration, haemorrhage, and necrosis.
Clinical Signs	2.5 and 5 mg/kg/day: Erosion in foot pads 5 mg/kg/day: Erosion in the skin (face, hind limbs, oral mucosa) Persistent in recovery period, some of the erosions changed to crust.
Body Weights/Food Consumption	5 mg/kg/day: Decreased body weights and food consumption was noted during the treatment period. No effects in the recovery period.
Fecal Occult Blood Examination	2.5 and 5 mg/kg/day: Positive reaction in 1 female at 2.5 mg/kg/day and in 4 males and all females at 5 mg/kg/day; partially recovered in 5 mg/kg/day in the recovery group.
Ophthalmoscopy	5 mg/kg/day: Abnormal ocular fundus color (dark). These changes partially recovered in the recovery group.
Electrocardiography	Unremarkable
Hematology	5 mg/kg/day: ≤+300% reticulocytes, ≤+85% leukocyte, ≤+87% PLT, ≤+99% monocyte, ≤+120% large unstained cell counts, and ≤+45% neutrophil count, and ≤-13% erythrocytes, ≤-23% lymphocyte count.
Clinical Chemistry	5 mg/kg/day: ≤+223% AST, ≤+120% ALP, and ≤+61%beta- and ≤+124% gamma-globulin ratios, and ≤-96% total bilirubin, altered total protein, ≤-43% albumin concentration, ≤-63% albumin/globulin ratio, ≤-23% glucose, ≤-10% calcium.
Urinalysis	5 mg/kg/day: positive occult blood reaction, erythrocytes in sediment, ↑proteins, ↑glucose, ↑ketone bodies, and ↑increased sodium excretion.
Gross Pathology	5 mg/kg/day: Red focus in the lungs and kidneys, ulcer in the foot pads, ulcer and foci in oral cavity, and crusty skin.
Organ Weights (Relative organ weights based on 100 g body weight on the day of gross pathology)	5 mg/kg/day: ↑12% Kidney, ↑29% liver Recovery: High lever weights were noted
- : indicates reduction in parameters compared to control **+ or ↑: indicates increase in parameters compared to control**	
Histopathology **Adequate Battery:**	Yes. 1 mg/kg/day: No test article-related changes were noted in this group. Target organs of toxicity included GI, skin, lung, liver, gall bladder, kidney, eye, and lymphohematopoietic system at higher gilteritinib dose groups.

Histopathology Changes in Surviving Dogs in 13-week Toxicology Study

Treatment-Related Microscopic Findings			**No. of Animals Affected (Main/Recovery)**							
			Males				**Females**			
Dose (mg/kg/day)			**0**	**1**	**2.5**	**5**	**0**	**1**	**2.5**	**5**
Number of animals			**4/0**	**4/0**	**4/3**	**3/2**	**4/0**	**4/0**	**4/3**	**4/3**
Organ	Finding									
Thymus	Atrophy	Very slight	1	2	2/0	1/1	2	1	3/2	0/1
		Slight	2		1/0	1/0	1	1		1/0

Treatment-Related Microscopic Findings			No. of Animals Affected (Main/Recovery)							
			Males				Females			
Dose (mg/kg/day)			0	1	2.5	5	0	1	2.5	5
Number of animals			4/0	4/0	4/3	3/2	4/0	4/0	4/3	4/3
Organ	Finding									
		Moderate	-	-	-	1/0	-	-	-	1/0
Spleen	Congestion	Very slight	-	-	-	3/0	-	-	-	1/0
		Slight	-	-	-	-	-	-	-	1/0
		Moderate	-	-	-	-	-	-	-	1/0
Submandibular lymph node	Necrosis, lymphocyte	Slight	-	-	-	2/0	-	-	-	-
Peyer's patch	Necrosis, lymphocyte	Very slight	-	-	-	1/0	-	-	-	2/0
		Slight	-	-	-	1/0	-	-	-	-
Lung	Accumulation, foam cell	Very slight	1	-	1/0	-	-	-	-	2/2
		Slight	-	-	1/0	-	-	-	-	-
	Cellular infiltration, inflammatory cell	Slight	-	-	2/0	1/0	1	2	-	-
		Moderate	-	-	-	1/0	-	-	-	-
	Deposit, fibrin like material, alveolus	Very slight	-	-	1/0	-	-	-	1/0	-
		Slight	-	-	1/0	-	-	-	-	-
	Dysplasia, bronchial tube	Slight	-	1	-	-	-	-	-	-
	Edema	Very slight	-	-	1/0	1/0	-	-	-	-
		Slight	-	-	1/0	-	-	-	-	-
	Haemorrhage, alveolus, focal	Very slight	-	-	-	1/0	-	1	-	-
		Slight	-	-	2/0	-	1	-	1/0	-
	Hypertrophy/hyperplasia, alveolar epithelium	Very slight	-	-	-	-	-	-	1/0	-
		Slight	-	-	1/0	1/0	-	-	1/0	
		Moderate	-	-	1/0	-	-	-	-	-
Liver	Atrophy, hepatocyte	Slight	-	-	-	1/0	-	-	-	-
	Cellular infiltration, mononuclear cell, perivascular	Very slight	-	-	-	1/0	-	-	-	1/0
		Slight	-	-	-	1/0	-	-	-	-
	Deposit, pigment, brown, Kupffer cell	Very slight	-	-	-	1/1	-	-	-	3/2
		Slight	-	-	-	2/0	-	-	-	1/0
	Vacuolation, hepatocyte	Very slight	-	-	-	1/0	-	-	-	-
Gallbladder	Cellular infiltration, mononuclear cell	Very slight	2	1	½	0/1	1	1	2/0	1/0
	Hypertrophy, mucosa/hypersecretion, mucus	Very slight	-	-	-	3/0	-	-	-	1/0
Pancreas	Decrease, Zymogen granules	Very slight	-	-	-	1/0	-	-	-	-
Kidney	Cast, hyaline	Very slight	1		1/0	0/1		2		2/0
	Cellular infiltration, inflammatory cell,	Slight	-	-		1/0	-	-	-	-

Treatment-Related Microscopic Findings			No. of Animals Affected (Main/Recovery)							
			Males				Females			
Dose (mg/kg/day)			**0**	**1**	**2.5**	**5**	**0**	**1**	**2.5**	**5**
Number of animals			**4/0**	**4/0**	**4/3**	**3/2**	**4/0**	**4/0**	**4/3**	**4/3**
Organ	Finding									
	medulla/pelvis									
	Cellular infiltration, mononuclear cell, cortex	Very slight	-	-	-	1/0	-	-	1/0	-
	Congestion, medulla, focal	Very slight	-	-	-	1/0	-	-	-	-
	Regeneration, renal tubule	Very slight	-	-	-	1/0	-	-	-	-
	Vacuolation, cortico-medullary junctional tubule	Very slight	-	-	-	3/0	-	-	-	1/0
		Slight	-	-	-	-	-	-	-	1/0
Urinary bladder	Vacuolation, transitional cell	Very slight	-	-	-	1/0	-	-	-	-
Eyeball	Vacuolation, rods and cones layer/outer nuclear layer	Slight	-	-	-	2/0	-	-	-	-
Lacrimal gland	Atrophy	Very slight	-	-	-	1/0	-	-	-	-
	Cellular infiltration, mononuclear cell	Very slight	-	-	1/0	1/0	-	-	-	-
Skin	Ulcer/inflammation	Moderate	-	-	-	1/0	-	-	-	-
	Acanthosis	Very slight	-	-	-	0/1	-	-	-	1/0
		Slight	-	-	-	-	-	-	-	0/1
	Scab	Very slight	-	-	-	0/1	-	-	-	1/0
Molar tooth	Inflammation, alveolus/gingiva	Very slight	-	-	0/1	2/1	-	-	-	4/3
		Slight	-	-	-	1/0	-	-	-	
Incisor tooth	Inflammation, alveolus/gingiva	Very slight	-	-	-	3/2	-	-	1/0	4/2
Forelimb	Ulcer/inflammation	Slight	-	-	-	1/0	-	-	-	1/0
Hindlimb	Ulcer/inflammation	Slight	-	-	-	1/0	-	-	-	3/0
		Moderate	-	-	-	1/0	-	-	-	1/0
Oral mucosa	Ulcer/inflammation	Slight	-	-	-	-	-	-	-	-
	Acanthosis	Very slight	-	-	-	0/1	-	-	-	-
	Cellular infiltration, mononuclear cell	Very slight	-	-	-	0/1	-	-	-	-

- = no test-article related histopathology

Electron microscopy	5 mg/kg/day Liver: Slight increase single-membrane-bounded electron-dense bodies in the Kupffer cells corresponding to the pigmentation, and Swelling of the hepatocellular mitochondria was observed suggesting liver injury. Kidney: Slight vacuolation, single-membrane-bounded vacuoles in the renal collecting tubules suggesting dilated endoplasmic reticulum/inflammation. Eyeball: Slight to moderate Swelling, mitochondria, rods/cones

	layer; slight to moderate vacuole, single-membrane-bound, rods/cones layer suggesting test article effect on photoreceptor cells.
Recovery	All changes noted in the dosing period recovered or tended to recover by the end of a 4-week recovery period except for increased urinary glucose and large unstained cell count, and decreased lymphocyte count and serum glucose.

- : indicates reduction in parameters compared to control
+ or ↑: indicates increase in parameters compared to control

Table 6: Gilteritinib Toxicokinetics – 13-Week Dog Study

Daily dose (mg/kg)		1		2.5		5	
No. of animals		4M	4F	7M	7F	7M	7F
t_{max} (h)	Day 1	5	6	6	6	7	7
	Day 91	5	6	6	7	5	7
C_{max} (ng/mL)	Day 1	15	14	43	35	98	85
	Day 91	24	24	79	82	329	305
AUC_{24h} (ng·h/mL)	Day 1	216	227	619	574	1606	1427
	Day 91	389	400	1355	1392	6470*	6001*

***** The gilteritinib exposure on Day 91 of dosing was 0.45 and 0.36 times in males and females, respectively the AUC_{24} (13463.35 ng·h/mL) [Study 2215-CL-0102] at the recommended clinical dose (120 mg/day)

General Toxicology: Additional Studies

A Preliminary 1-Week Repeated Oral Dose Toxicity Study of AS2582215-FM in Rats/2215-tx-3004

ASP2215 fumarate (gilteritinib fumarate) was administered once daily for a week by oral gavage at doses of 0 (vehicle), 1, 3, 10, and 30 mg/kg per day to 5 male and 5 female Sprague-Dawley rats per group. At 10 mg/kg/day test article-related toxicities included hypocellularity in the bone marrow, and alveolar foam cells in the lungs (males). At 30 mg/kg/day additional toxicities included mild interstitial pneumonia, and minimal vacuolation of the rod-cone layer of the retina.

Study title/ number: A 4-Week Repeated Oral Dose Toxicity Study of ASP2215 Hemifumarate in Beagle Dogs Followed by a 4-Week Reversibility Study/2215-TX-0003

ASP2215 fumarate (gilteritinib fumarate) was administered once daily for 4 weeks by oral gavage at doses of 1 and 10 mg/kg per day to 4 male Beagle dogs per group and at 100 and 1000 mg/kg per day to 7 male Beagle dogs per group. Dosing was terminated early at 100 and 1000 mg/kg/day due to mortality. Necropsies were conducted on Day 12 for the 10 mg/kg/day group due to moribundity. Additional findings at 10 mg/kg/day after 12 days of dosing included

degeneration/necrosis of the germ cells in the testes in 2 males. Spermatid giant cell formation was observed in all animals including the moribund animal and the incidence and severity were greater than those in the control group. Additional dogs (4/sex/group) were administered gilteritinib at 0 (vehicle), 1, 2.5, and 5 mg/kg/day. Clinical pathology and histopathology findings were comparable to 13-week study.

5.5.2 Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: A Bacterial Reverse Mutation Test of ASP2215 Hemifumarate/2215-TX-0004

Key Study Findings:

- ASP2215 was cytotoxic (growth inhibition) at ≥2500 µg/plate in TA 1535 without metabolic activation.
- ASP2215 was negative in bacterial reverse mutation test with or without metabolic activation up to 5000 µg/plate.

GLP compliance: Yes
Test system: *Salmonella typhimurium* (TA100, TA1535, TA98, and TA1537) and *Escherichia coli (WP2uvrA)*; up to 5000 µg/plate; +/- S9.
Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study title/ number: A Chromosomal Aberration Test of ASP2215 Hemifumarate in Cultured Mammalian Cells/2215-TX-0005

Key Study Findings:

- ASP2215 was cytotoxic (≥50% cell proliferation ratio) to CHL cells at ≥2.16 µg/mL and ≥3.89 µg/mL in short-term treatments without and with metabolic activation, respectively, and at ≥0.5 µg/mL in continuous treatment for 24 hours without S9.
- ASP2215 was negative in the CHL chromosome aberration test up to at least 50% cytotoxic dose levels without and with metabolic activation.

GLP compliance: Yes
Test system: Cultured mammalian (CHL/IU) cells; up to 3.89 µg/mL; +/-S9
Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: A Micronucleus Test of ASP2215 Hemifumarate in Mice/2215-TX-0007

Key Study Findings:

- ASP2215 statistically significantly increased the number of micronucleated polychromatic erythrocytes (MNPCE) in males and females in the 65 and 200 mg/kg/day groups when compared with the negative control group.
- ASP2215 was positive for the induction of MNPCE in mouse bone marrow cells.

GLP compliance: Yes

Test system: Crlj:CD1(ICR) mice
Study is valid: Yes
Data: The %MNPCE in males were 0%, 0.01%, 0.54%, and 1.43% in the 0, 20, 65, and 200 mg/kg/day groups, respectively. The %MNPCE in females were 0.02%, 0.09%, 0.65%, and 2.21% in the 0, 20, 65, and 200 mg/kg/day groups, respectively.

Other Genetic Toxicity Studies

Genetic Toxicology Studies with AS3320130-00
AS3320130-00 was tested in bacterial reverse mutation test and in vitro chromosome aberration test in CHL cells.

Bacterial reverse mutation test
The test was conducted with 5 test strains of bacteria (S. typhimurium TA100, TA1535, TA98, and TA1537, and E. coli WP2uvrA) using the preincubation method, in the presence or absence of rat liver S9.

- AS3320130-00 was cytotoxic (growth inhibition) without S9 and no cytotoxicity was observed with S9.
- AS3320130-00 was negative in bacterial reverse mutation test with or without metabolic activation up to 5000 µg/plate.

In vitro chromosome aberration test in CHL cells

- AS3320130-00 was cytotoxic (≥50% cell proliferation ratio) to CHL cells at 4 µg/mL in short-term treatments without and with metabolic activation, and at 3.5 µg/mL in continuous treatment for 24 hours without S9.
- AS3320130-00 was negative in the CHL chromosome aberration test up to at least 50% cytotoxic dose levels without and with metabolic activation.

5.5.3 Carcinogenicity

Not needed or conducted at this time per International Conference on Harmonisation (ICH) S9.

5.5.4 Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development
Studies of gilteritinib effects on fertility and early embryonic development to implantation and for effects on pre and postnatal development (including maternal function) were not needed or conducted for the proposed indication.

Embryo-Fetal Development

Study title/ number: Study for Effects of ASP2215 Hemifumarate on Embryo-Fetal Development by Oral Administration in Rats/ 2215-TX-0011

Key Study Findings

- Maternal effects at 30 mg/kg/day were limited to decreased body weight gain and decreased food consumption.
- Gilteritinib caused fetal toxicity characterized by teratogenicity, embryo-fetal lethality, and suppressed fetal growth at 30 mg/kg per day.
- Maternal exposures at the 30 mg/kg/day dose were approximately 0.4 times the human clinical exposure based on AUC at the recommended human dose.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 0.3, 3, 10, and 30 mg/kg/day and daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5 w/v% methylcellulose solution
Species/Strain:	Crl:CD(SD) rats
Number/Sex/Group:	20 females/group
Satellite groups:	Toxicokinetics: 4 females/group in control and 12 females /group in gilteritinib dose groups
Study design:	Pregnant rats were administered gilteritinib once daily on GD 7-17, scheduled necropsy/cesarean section conducted on GD 20
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Mortality</td><td>None</td></tr>
<tr><td>Clinical Signs</td><td>Unremarkable</td></tr>
<tr><td>Body Weights and food consumption</td><td>30 mg/kg/day: BW gain ↓51% and food consumption ↓31.8%, compared to control</td></tr>
<tr><td>Necropsy findings Cesarean</td><td>No changes were noted in numbers of corpora lutea or implantations at any dose level.</td></tr>
<tr><td>Necropsy findings Offspring</td><td>30 mg/kg/day: Live fetal body weights ↓32% for males and females

HD: clearly fetotoxic
Summary of Malformations in Fetuses
<table>
<tr><th>Dose: mg/kg/day</th><th>0</th><th>0.3</th><th>3</th><th>10</th><th>30</th></tr>
<tr><td colspan="6">Placental Findings</td></tr>
<tr><td>Abnormalities‡</td><td>2 (1.75)[1]</td><td>2 (5.00)</td><td>0 (0.00)</td><td>0 (0.00)</td><td>0 (0.00)</td></tr>
<tr><td>Enlargement</td><td>2 (1.75)</td><td>2 (5.00)</td><td>0 (0.00)</td><td>0 (0.00)</td><td>0 (0.00)</td></tr>
<tr><td colspan="6">Mean Placental Weight (g):</td></tr>
</table></td></tr>
</table>

	Males	0.53	0.52	0.5	0.51	0.44
	Females	0.5	0.47	0.48	0.48	0.38**¶
	Number of Live Fetuses	260	276	282	252	179
	Mean Number of Live Fetuses	13.7	13.8	14.1	13.3	9.4**¶
	Postimplantation Loss (%)	5	4.6	5.3	7.6	40.2**††
	Placental Remnant (%)	5	4.6	5.3	7.3	36.5**††
	Dead Fetus Rate (%)	0	0	0	0.4	3.6*††
	Sex Ratio (Male/Total)	0.466	0.542	0.505	0.516	0.564
	External Findings	0 (0.00)	1 (0.34)	0 (0.00)	0 (0.00)	20 (13.53**††)
	Abnormalities‡	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	2 (1.51)
	Anasarca	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	5 (2.26)
	Local edema	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.75)
	Exencephaly	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	6 (2.46)
	Cleft lip	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	1 (0.41)
	Cleft palate	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	8 (6.74*††)
	Short tail	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
	Thread-like tail	0 (0.00)	1 (0.34)	0 (0.00)	0 (0.00)	0 (0.00)
	Anal atresia	0 (0.00)	1 (0.34)	0 (0.00)	0 (0.00)	2 (0.81)
	Umbilical hernia	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	20 (13.53**††)
	Abnormalities‡	0 (0.00)	NE	NE	0 (0.00)	27 (32.74**††)
	Microphthalmia	0 (0.00)	NE	NE	0 (0.00)	3 (4.38)
	Enlarged atrial chamber	0 (0.00)	NE	NE	0 (0.00)	1 (0.88)
	Enlarged ventricular chamber	0 (0.00)	NE	NE	0 (0.00)	1 (1.75)
	Membranous ventricular septum defect	0 (0.00)	NE	NE	0 (0.00)	1 (1.75)
	Hypoplastic right ventricle	0 (0.00)	NE	NE	0 (0.00)	1 (1.75)
	Absent kidney	0 (0.00)	NE	NE	0 (0.00)	11 (11.01**††)
	Fused kidney	0 (0.00)	NE	NE	0 (0.00)	1 (0.75)
	Abnormal revolution kidney	0 (0.00)	NE	NE	0 (0.00)	6 (6.19*††)
	Malpositioned kidney	0 (0.00)	NE	NE	0 (0.00)	6 (10.57*††)
	Misshapen kidney	0 (0.00)	NE	NE	0 (0.00)	1 (1.05)
	Small kidney	0 (0.00)	NE	NE	0 (0.00)	7 (12.21*††)
	Malpositioned adrenal	0 (0.00)	NE	NE	0 (0.00)	3 (3.68)
	Malpositioned ovary	0 (0.00)	NE	NE	0 (0.00)	8 (7.90*††)
	Variations‡	8 (5.55)	NE	NE	0 (0.00)	6 (5.14)

Thymic remnant in neck	3 (1.97)	NE	NE	0 (0.00)	1 (0.66)
Dilated renal pelvis	0 (0.00)	NE	NE	0 (0.00)	3 (2.07)
Convoluted ureter	0 (0.00)	NE	NE	0 (0.00)	0 (0.00)
Dilated ureter	5 (3.57)	NE	NE	0 (0.00)	5 (4.48)
Skeletal Findings					
Abnormalities‡	0 (0.00)	NE	NE	0 (0.00)	4 (3.69*††)
Sternoschisis	0 (0.00)	NE	NE	0 (0.00)	1 (0.88)
Absent rib	0 (0.00)	NE	NE	0 (0.00)	1 (0.88)
Fused rib	0 (0.00)	NE	NE	0 (0.00)	1 (0.88)
Fused cervical arch	0 (0.00)	NE	NE	0 (0.00)	1 (0.88)
Misaligned cervical vertebra	0 (0.00)	NE	NE	0 (0.00)	1 (1.05)
Absent thoracic vertebra	0 (0.00)	NE	NE	0 (0.00)	1 (0.88)
Variations‡	22 (16.28)	NE	NE	16 (10.63)	81 (85.58**††)
Full supernumerary rib	0 (0.00)	NE	NE	1 (0.58)	6 (6.32*††)
Short supernumerary rib	15 (11.02)	NE	NE	8 (5.06)	35 (41.73**††)
Dumbbell ossification of thoracic centrum	4 (2.97)	NE	NE	4 (2.82)	35 (33.17**††)
Splitting of thoracic centrum	1 (0.75)	NE	NE	4 (2.82)	64 (65.39**††)
Dumbbell ossification of lumbar centrum	1 (0.66)	NE	NE	0 (0.00)	2 (2.37)
Supernumerary lumbar vertebra	1 (0.66)	NE	NE	0 (0.00)	28 (29.99**††)
Number Ossified					
Sternebrae	5.04	NE	NE	5.21	3.06**§
Sacral and caudal vertebrae	7.56	NE	NE	7.98*¶	4.87**¶

---: no noteworthy findings; GD: gestation day; NC: not calculated; NE: not examined; SD: Sprague Dawley
[1] No. of fetuses with findings and (Type and frequency (%))
Numerical data are expressed as mean values, unless otherwise specified.
*, **: P<0.05, P<0.01 (statistically significant)
†: Calculation of toxicokinetic parameters was based on data for 3 animals/group/time point.
‡: total number (mean %); §: Dunnett's test; ¶: Dunnett's test after rank-transformation; ††: Wilcoxon's rank sum test

Table 7: Toxicokinetics of Gilteritinib in the Definitive EFD Study in Rats

Daily dose (mg/kg)		0.3	3	10	30
No. of animals		9	9	9	9
T_{max} (h)	GD 7	10	8	6	10
	GD 17	4	8	6	8
C_{max} (ng/mL)	GD 7	0.821	25.8	119	432
	GD 17	0.847	32.1	148	394
AUC_{24} (ng·h/mL)	GD 7	11.3	266	1610	6750
	GD 17	11.7	307	1930	5880

At the dose of 10 and 30 mg/kg per day, the gilteritinib exposure (AUC_{24}) was approximately 0.1 and 0.4 times the AUC_{24} (13463.35 ng·h/mL) [Study 2215-CL-0102], respectively at the recommended clinical dose (120 mg/day)

5.5.5 Other Toxicology Studies

Studies with Impurity:

A 4-Week Repeated Oral Dose Toxicity Study (b) (4)
To qualify (b) (4) a related substance impurity contained in gilteritinib, (b) (4) was evaluated in a 4-week repeated dose toxicology study at 0 (0.5 w/v% methylcellulose solution/suspension), 0.05, 0.15, and 0.4 mg/kg/day in male and female Crl:CD (SD) strain rats. The high dose level was set at (b) (4) mg/kg/day, based on the estimated maximum clinical dose, (b) (4) mg/day with a specification set at (b) (4) %. The dose in rats corresponds to (b) (4) mg/kg/day with the body surface area conversion factor for rats (b) (4). All animals survived during the treatment period. There were no toxicologically significant (b) (4) -related changes at any dose in either sex.

Primary Reviewer
Ramadevi Gudi, PhD

Team Leader
Christopher M. Sheth, PhD

6 Clinical Pharmacology

6.1 Executive Summary

The proposed starting dose of gilteritinib is 120 mg (three 40-mg tablets) orally once-daily with or without food. The efficacy and safety of gilteritinib in R/R FLT3+ AML patients was evaluated in 3 studies, including 1 multinational active controlled phase 3 Study (2215-CL-0301) and 2 supportive dose-escalation studies (2215-CL-0101 and 2215-CL-0102).

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 211349. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized in **Table 8**.

Table 8: Key Review Issues and Recommendations, NDA 211349

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The efficacy of gilteritinib in R/R FLT3+ AML patients was evaluated in 3 studies, including 1 multinational active controlled phase 3 study (2215-CL-0301) and 2 supportive dose-escalation studies (2215-CL-0101 and 2215-CL-0102).
General dosing instructions	The proposed starting of gilteritinib is 120 mg orally once-daily with or without food.
Dosing in patient subgroups (intrinsic and extrinsic factors)	▪ Interrupt and reduce the dose of gilteritinib in patients who have a QTcF >500 msec. ▪ Avoid concomitant use with combined P-gp and strong CYP3A Inducers. ▪ Avoid concomitant use with strong CYP3A Inhibitors. If the concomitant use of strong CYP3A inhibitors cannot be avoided, monitor patients for increased risk of gilteritinib adverse reactions. ▪ Avoid the concomitant use of drugs that target 5HT2B receptor or sigma nonspecific receptor, unless the use is considered essential for the care of the patient. ▪ No dose adjustment is required based on age, weight, race, or sex. ▪ No dose adjustment is recommended for patients with mild and moderate hepatic or renal impairments.
Labeling	Generally acceptable. The review team has specific content and formatting change recommendations. Labeling language reviewed, corrected, and updated according to the guidance of clinical pharmacology section of labeling for human prescription drug and biological products - content and format (published December 2016).
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed formulation was used in the phase 3 Study 2215-CL-0301.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

6.2.1.1 Mechanism of Action

Gilteritinib inhibits FMS-like tyrosine kinase 3, leukocyte tyrosine kinase, AXL tyrosine kinase, echinoderm microtubule-associated protein-like 4 (EML4)-ALK variant 1 (ALK) and KIT tyrosine

kinase (KIT) kinase activities with IC_{50} of 0.291, 0.350, 0.726, 1.2 and 229nM, respectively. Gilteritinib demonstrated efficacy following repeated oral doses in a nonclinical AML model, with complete regression of tumors in the xenograft model of mice transplanted with MV4-11, a human AML cell line expressing FLT3 internal tandem duplication (ITD). In addition, gilteritinib showed similar activities inhibiting the growth of Ba/F3 cells expressing FLT3-ITD, FLT3-D835Y or FLT3-ITD-D835Y.

6.2.1.2 Clinical Pharmacokinetics

In R/R AML patients, gilteritinib exhibited linear, dose-proportional pharmacokinetics at doses ranging from 20 to 450 mg administered once daily. Steady-state gilteritinib concentrations were achieved by day 15 after once daily dosing. After single dose administration of gilteritinib at 120-mg dose, the median C_{max} was 85.7 ng/mL (78.9 – 246) and AUC_{24} was 1390 ng•mL/h (1290 – 4760). After multiple dose administration of gilteritinib at daily dose of 120 mg, median steady state C_{max} was 282 ng/mL (248 – 593) and AUC_{24} was 6180 ng•mL /h (4170 – 10500). Gilteritinib had mean (SD) accumulation index (Rac) of 6.83 (2.8) with range from 3.29 – 9.64 across dose range of 20 mg to 300 mg once daily.

Absorption: Following oral administration of gilteritinib tablet, peak concentrations were observed at a median T_{max} of ~4 to 6 hours in healthy volunteers and patients with R/R AML. Absolute bioavailability of gilteritinib was not determined. Gilteritinib absorption slightly decreased by high fat meal as evidenced by a <10% decrease in AUC_{inf} and AUC_{last}, indicating gilteritinib exposure is comparable when administered with and without food. There was a 26% decrease in gilteritinib C_{max} and a 2-hour delay in gilteritinib median T_{max} when gilteritinib was coadministered with a high fat meal.

Distribution: The population estimates of central (Vc/F) and peripheral (Vp/F) volume of distribution are 1092 L and 1100 L, respectively. Average total blood-to-plasma ratios of [^{14}C]-radioactivity in human ranged from 0.85 to 1.36, indicating low association of gilteritinib with blood cellular components. Gilteritinib is mainly bound to human serum albumin with mean (%CV) fraction of unbound (fu) in healthy subjects of 0.057.

Elimination: Gilteritinib plasma concentrations declined in a biexponential manner with a calculated half-life ($T_{1/2}$) of 113 hours. It has an estimated CL/F of 14.85 L/h based on the population pharmacokinetic model. After a single dose of [^{14}C]-gilteritinib, 64.5% of the total administered dose recovered in feces and 16.4% recovered in urine with ≤10% excreted unchanged in urine. Results from in vitro studies using recombinant human CYP microsomes indicate gilteritinib is metabolized via CYP3A4. The quantified metabolites in human include M17 (formed via N-dealkylation and oxidation), M16, and M10 (both formed via N dealkylation) and were also observed in animals. None of these 3 metabolites exceeded 10% of overall parent exposure and their pharmacological activity has not been evaluated.

6.2.2 General Dosing and Therapeutic Individualization

General Dosing

For the proposed indication of R/R FLT3+ AML, the Applicant proposes a dosing regimen of 120 mg (three 40-mg tablets) to be taken orally once daily with or without food. The proposed gilteritinib dosing regimen is based on the results of phase 1/2 dose-escalation clinical studies 2215-CL-0101 and 2215-CL-0102 (n=265 and 24, respectively), and a phase 3 controlled clinical study, 2215-CL-0301 (n=168).

Therapeutic Individualization

Dose adjustment schema

Dose escalation schema: In the original NDA submission, the applicant proposed dose escalation to 200 mg gilteritinib once daily in patients who do not achieve response after 28-day treatment with 120 mg gilteritinib once daily. However, based on the available data, there is no strong evidence to support the clinical benefit that would outweigh the risk of dose increase to 200 mg. Accordingly, the applicant removed dose increase recommendation from the label.

Reviewer assessment: assessment for the efficacy and safety of dose increase to 200 mg once daily has been conducted as following:

Efficacy: In the original NDA submission, the Applicant provided a dose modification analysis to justify the dose increase and stated that dose escalations to 200 mg daily can have value in increasing the likelihood of a CR/CRh response (complete remission/complete remission with partial hematologic recovery rate) in patients that have not achieved remission at 120 mg daily. However, the clinical team at FDA has adjudicated the efficacy results to exclude patients who achieved response after HSCT. In the adjudicated analysis, the number of responders after dose increase decreased from 8 responders to 3 responders, and the CR/CRh rate dropped from 10.8% (95% CI; 4.8%, 20.2%) to 4.1% (95% CI, 0.84%-11.4%) in the pooled population of 2215-CL-0101 and 2215-CL-0301 studies (**Table 9**). Moreover, there is no apparent exposure-response relationship for CR/CRh from the currently available data (14.4.2 Clinical PK and/or PD Assessments).

Table 9: CR/CRh Rate by Dose Increase-Pooled Response Analysis-FDA Adjudicated

Dose adjustment	2215-CL-0101 (N=55)	2215-CL-0301 (n=141)	Total (N=196)
Overall			
Increased n/N (%) (95% CI)	5/28 (17.9%) (6.1%, 36.9%)	2/46 (4.4%) (0.53%, 14.8%)	7/74 (9.5%) (3.9%, 18.5%)

Dose adjustment	2215-CL-0101 (N=55)	2215-CL-0301 (n=141)	Total (N=196)
Unchanged n/N (%) (95% CI)	3/21 (14.3%) (3%, 36.3%)	22/68 (32.4%) (21.5%, 44.8%)	25/89 (28.1%) (19.1%, 38.6%)
Before dose adjustment			
Increased n/N (%) (95% CI)	4/28 (14.3%) (4%, 32.7%)	0/46 (0%) (0.01%, 7.7%)	4/74 (5.4%) (1.5%, 13.3%)
After dose adjustment			
Increased n/N (%) (95% CI)	1/28 (3.6%) (0.09%, 18.4%)	2/46 (4.4%) (0.53%, 14.8%)	3/74 (4.1%) (0.84%, 11.4%)

Source: Clinical pharmacology review team analysis

Safety: Analysis of gilteritinib safety showed that treatment discontinuation due to adverse reaction in Study 0101 was more common in dose 200 mg cohort (20.9%) compared to dose 120 mg dose cohort (6.8%). Consistent with this high rate of discontinuation at dose 200 mg, E-R relationship between overall grade 3 or higher treatment-related adverse reactions and gilteritinib exposure in the pooled population of 2215-CL-0101 and 2215-CL-0301 studies were marginally significant. Analysis of the E-R relationship has been conducted by the applicant for the hematological and nonhematological AEs. There was no statistically significant E-R relationship between neutropenia, thrombocytopenia or anemia and gilteritinib exposure. However, this analysis was confounded by the high rate of hematologic AEs in this patient population due to the underlying malignancy (refer review of safety, section 8.3.8). Gilteritinib exposure appears to influence nonhematological TEAEs (AST, ALT and CK elevations, ALB reduction). Although, this effect was not clinically meaningful based on the E-R analyses, safety analysis in patients who underwent a dose increase from 120 mg to 200 mg showed increased rates of drug-related grade 3 or higher AST, ALT and CK elevations (0%, 2.2% and 0% before dose increase vs. 10.9%, 6.5% and 6.5% after dose increase, respectively). The QTc prolongation at the proposed therapeutic dose did not reach the 10 msec threshold for regulatory significance, however, patients taking 200 mg were more likely to have values >500 msec while receiving gilteritinib. Two patients developed drug-related grade 3 or higher cardiac failure after dose increase, one of them died from the complications of grade 5 drug-related congestive cardiac failure after dose increase to 200 mg.

Accordingly, there is no strong evidence to support the clinical benefit of increasing gilteritinib dose to 200 mg QD in nonresponders that would outweigh the risk associated with dose increase.

Dose reduction schema: The applicant recommends dose reduction from 120 mg to 80 mg gilteritinib for patients who develop grade 3 or greater toxicity.

Specific Populations

Organ impairments: Dose adjustment is not recommended for patients with mild or moderate hepatic or renal impairments. Non-cancer subjects with mild or moderate hepatic impairment had no clinically meaningful changes in their safety profiles following exposure to gilteritinib, and there was no clinically significant correlation between gilteritinib exposure and serum creatinine level in patients with renal impairment. Exposure of gilteritinib in patients with severe hepatic or severe renal impairment is unknown.

Drug-Drug Interactions

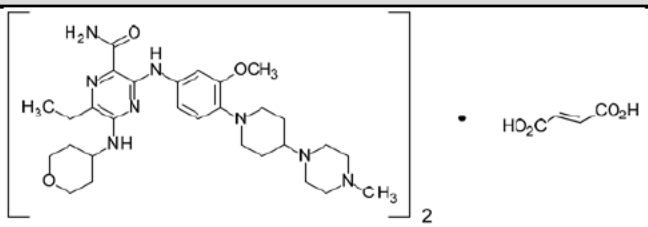
Combined P-gp and strong CYP3A Inducers: Concomitant use of gilteritinib with combined P-gp and strong CYP3A Inducers should be avoided. This recommendation is based on the significant reduction (by approximately 70%) in gilteritinib exposure with combined P-gp and strong CYP3A Inducers.

Strong CYP3A inhibitors: Consider alternative therapies that do not strongly inhibit CYP3A activity. If the concomitant of strong CYP3A inhibitors is considered essential for the care of the patient, monitor patients for increased risk of XOSPOTA adverse reactions. Combined P-gp and strong CYP3A inhibitor, itraconazole, increased the exposure of gilteritinib by 2.2-fold. Safety analysis from Study 2215-CL-0101 showed that increase by less than 2-fold in gilteritinib exposure due to concomitant use of moderate or strong CYP3A inhibitors was not associated with clinically significant safety issues.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

Summary of Clinical Pharmacology and Pharmacokinetics Information

Physicochemical characteristics	
Chemical structure	 Molecular formula: (C29H44N8O3)2 • C4H4O4 Molecular weight: 1221.50
Physical properties	Gilteritinib fumarate appears as a light yellow to yellow powder or crystals that is sparingly soluble in water and very slightly soluble in anhydrous ethanol.

Pharmacology	
Mechanism of Action	Gilteritinib inhibits FMS-like tyrosine kinase 3 (FLT3) with IC50 of 0.291nM. It also has inhibitory effects on LTK, AXL, ALK, and KIT kinase activities. It showed similar activities inhibiting the growth of Ba/F3 cells expressing FLT3-ITD, FLT3-D835Y or FLT3-ITD-D835Y.
Active Moieties	Gilteritinib
QT Prolongation	No large QTc prolongation effect (i.e. >20 ms) of gilteritinib (120 mg QD – therapeutic dose) was observed. Of 241 patients treated with gilteritinib at 120 mg in clinical trials, 4 patients (<2%) experienced a QTcF >500 msec. Additionally, across all doses, 2.7% of relapse/refractory subjects had a maximum post baseline QTcF interval >500 msec.
General Information	
Bioanalysis	Plasma and urine concentrations of gilteritinib and its metabolite in clinical studies were measured by validated LC-MS/MS following supported liquid extraction. A summary of the method validation report is included in the Appendix 14.4.1.
Healthy volunteers vs. patients	Population PK modeling showed that gilteritinib CL/F is 46% greater in healthy volunteers compared to AML patients and apparent central volume of distribution is 63% greater in healthy volunteers than that for patients with R/R AML. However, the estimated increases in CL/F and Vc/F did not result in clinically meaningful differences in gilteritinib exposure in healthy volunteers and patients.
Drug exposure at steady state following the therapeutic dosing regimen	Based on the results of the phase 1/2 dose escalation study (2215-CL-0101), the median C_{max} and $AUC_{0\text{-}24,\,ss}$ values for gilteritinib at steady state (Day 15) were 282 ng/mL (248 – 593) and 6180 ng·h/mL (4170 – 10500), respectively, for 120 mg once daily doses.
Minimal effective dose or exposure	80 mg once daily. The efficacy of gilteritinib was evaluated at doses 20, 40, 80, 120, 200, and 300 mg once daily in R/R AML patients in the phase 1/2 dose escalation study, 2215-CL-0101. 20 and 40-mg dose levels were closed early due to the lack of efficacy.
Maximal tolerated dose or exposure	300 mg once daily.
Dose Proportionality	The exposure of gilteritinib was approximately dose proportional following oral administration at single and multiple doses ranging from 20 to 450 mg once daily.
Accumulation	Mean (SD) Accumulation index (Rac) is 6.83 (2.8) and ranges from 3.29 – 9.64 across dose range of 20 – 300 mg once daily.
Absorption	
Oral Bioavailability	Absolute oral bioavailability of gilteritinib is unknown.
T_{max} [Oral]	4 to 6 hours in fasted state.
Food effect	In healthy adults, gilteritinib C_{max} decreased by 26% and AUC decreased by less than 10% when coadministered with a high-fat meal (~800-1000 kcal with 500-600 kcal from fat compared to a fasted state. Median T_{max} delayed by 2 hours with food.

<table>
<tr><td>Bioequivalent (BE) under Fasted Conditions</td><td>Gilteritinib tablet formulation used in phase 3 clinical trials is the to-be-marketed formulation. A different formulation was used in early clinical development studies. However, a relative bioavailability study showed no clinically meaningful difference in exposure (AUC ratio 89.4% and C_{max} ratio 93.2%) following the administration of the clinical formulation used during the early clinical development studies and the to-be-marketed formulation used in phase 3 (2215-CL-301).</td></tr>
<tr><td colspan="2">Distribution</td></tr>
<tr><td>Volume of distribution</td><td>The population estimates of apparent central (Vc/F) and peripheral (Vp/F) volume of distribution were 1092 L and 1100 L, respectively.</td></tr>
<tr><td>Plasma protein binding</td><td>~90% gilteritinib bound to plasma proteins, mainly albumin.</td></tr>
<tr><td>Blood to plasma ratio</td><td>0.85 to 1.36</td></tr>
<tr><td>Substrate of transporter systems</td><td>Gilteritinib is a substrate of P-gp.</td></tr>
<tr><td colspan="2">Elimination</td></tr>
<tr><td>Half-life ($T_{1/2}$)</td><td>Gilteritinib has a median $T_{1/2}$ of 113 hours.</td></tr>
<tr><td>Metabolism</td><td>In vitro studies: gilteritinib is primarily metabolized via CYP3A4.</td></tr>
<tr><td>Excretion</td><td>After a single dose of [^{14}C]-gilteritinib, 64.5% of the total administered dose recovered in feces and 16.4% recovered in urine with ≤10% excreted unchanged in urine.</td></tr>
<tr><td colspan="2">Drug-Drug interactions</td></tr>
<tr><td>In vitro studies</td><td>Gilteritinib is a substrate of CYP3A and P-gp.
Gilteritinib is a strong inhibitor of MATE1 (IC_{50}=0.054μM), BCRP1 (IC_{50}=1.4μM), and OCT1 (IC_{50}=2.9μM), and a weak inhibitor of CYP3A (IC_{50}=63μM), CYP2C19 (IC_{50}=62μM), OATP1B1 (IC_{50}=29μM), OCT2 (IC_{50}=35μM), MATE2-K (IC_{50}=48μM).</td></tr>
<tr><td>Clinical studies (Gilteritinib as a victim)</td><td><u>Strong CYP3A inducer:</u> coadministration of rifampicin significantly decreased gilteritinib systemic exposure by approximately 70%.
<table>
<tr><th>Comparison</th><th>Dose Normalized Parameter</th><th>Geometric LS Mean for the Numerator</th><th>Geometric LS Mean for the Denominator</th><th>Geometric LS Mean Ratio (%)</th><th>90 % CI of the Ratio (%)</th></tr>
<tr><td rowspan="3">RIF + ASP2215/ ASP2215 alone §</td><td>AUC_{inf} (ng•h/mL)</td><td>8.71</td><td>30.6</td><td>28.47</td><td>(24.21, 33.48)</td></tr>
<tr><td>AUC_{last} (ng•h/mL)</td><td>8.42</td><td>28.8</td><td>29.21</td><td>(24.71, 34.54)</td></tr>
<tr><td>C_{max} (ng/mL)</td><td>0.364</td><td>0.495</td><td>73.44</td><td>(61.36, 87.91)</td></tr>
</table></td></tr>
</table>

Strong CYP3A inhibitor: co-administration of itraconazole, a strong CYP3A and P-gp inhibitor, increased gilteritinib systemic exposure by approximately 2.2-fold.

Comparison	Dose Normalized Parameter	Geometric LS Mean for the Numerator	Geometric LS Mean for the Denominator	Geometric LS Mean Ratio (%)	90 % CI of the Ratio (%)
ITZ + ASP2215/ ASP2215 alone †	AUC_{inf} (ng•h/mL)	67.7	30.6	221.39	(188.26, 260.36)
	AUC_{last} (ng•h/mL)	61.5	28.8	213.51	(180.58, 252.44)
	C_{max} (ng/mL)	0.593	0.495	119.80	(100.09, 143.39)

Moderate CYP3A inhibitor: coadministration of fluconazole, a moderate CYP3A inhibitor, increased gilteritinib systemic exposure by approximately 1.4-fold.

Comparison	Dose Normalized Parameter	Geometric LS Mean for the Numerator	Geometric LS Mean for the Denominator	Geometric LS Mean Ratio (%)	90 % CI of the Ratio (%)
FLZ + ASP2215/ ASP2215 alone ‡	AUC_{inf} (ng•h/mL)	43.9	30.6	143.46	(121.99, 168.71)
	AUC_{last} (ng•h/mL)	41.5	28.8	144.02	(121.81, 170.28)
	C_{max} (ng/mL)	0.573	0.495	115.73	(96.69, 138.52)

Clinical studies (Gilteritinib as a perpetrator)

Effect of gilteritinib on CYP3A4: Midazolam, a CYP3A4 substrate, mean C_{max} and AUC_{inf} increased approximately 10% when coadministered with gilteritinib.

Analyte	Parameter	N	Geometric LS Mean for Reference Treatment	Geometric LS Mean for Test Treatment	Geometric LS Mean Ratio (%)† (Test/Reference)	90% CI of Mean Ratio (%)†
Midazolam	AUC_{24} (ng•h/mL)	8	54.28	59.42	109.46	(49.82, 240.48)
	C_{max} (ng/mL)	9	14.33	16.00	111.64	(69.54, 179.25)
1-hydroxymidazolam	AUC_{24} (ng•h/mL)	8	11.31	16.95	149.90	(74.88, 300.06)
	C_{max} (ng/mL)	9	3.489	4.308	123.47	(72.41, 210.52)

Effect of gilteritinib on MATE1: cephalexin, a MATE1 transporter substrate, systemic exposure was comparable when gilteritinib was coadministered with cephalexin as reflected by an approximate minimal decrease (3% to 9%) in cephalexin mean C_{max}, AUC_{last} and AUC_{inf}.

Parameter	N	Geometric LS Mean for Reference Treatment	Geometric LS Mean for Test Treatment	Geometric LS Mean Ratio (%)† (Test/Reference)	90% CI of Mean Ratio (%)†
AUC_{last} (ng•h/mL)	16	50808	49647	97.71	(74.19, 128.70)
AUC_{inf} (ng•h/mL)	12	54066	50802	93.96	(75.29, 117.26)
C_{max} (ng/mL)	16	16946	15498	91.46	(74.60, 112.12)

6.3.2 Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. Study 2215-CL-0101, a phase 1/2 dose escalation study investigated the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of gilteritinib in R/R AML patients. The

results from this study, along with the clinical pharmacology program collectively provide adequate evidence for the effectiveness of gilteritinib at a dose of 120 mg QD in R/R AML patients. This study had two cohorts of patients; Cohort 1 comprised the initial dose-escalation cohort with dose range of 20 mg to 450 mg and Cohort 2 was the dose expansion cohort. Cohort 1 enrolled R/R AML patient. At least 10 patients with FLT3 mutations (ITD or activating point mutations) were to be enrolled to each expanded dose level. In this study, gilteritinib exhibited linear, dose-proportional pharmacokinetics in R/R AML patients at doses ranging from 20 mg to 450 mg administered once daily and the maximum tolerated dose (MTD), based on dose-limiting toxicities, was 300 mg daily. The Applicant presented the following results from Study 2215-CL-0101 to support the effectiveness of gilteritinib at the recommended dose of 120 mg:

1. PD analysis: Ex vivo FLT3 plasma inhibitory assay showed that by day 8 of cycle 1 of gilteritinib dosing, greater than 90% inhibition of FLT3 phosphorylation was observed at doses of ≥80 mg which indicates a rapid and sustained inhibition of FLT3 phosphorylation at doses ≥80 mg.

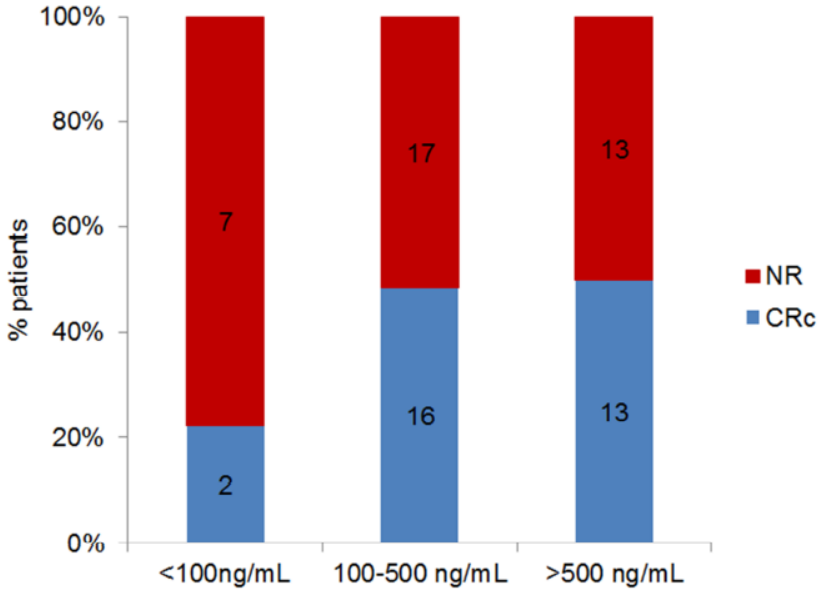
2. Exposure-response analysis: No substantial differences in steady state C_{trough} values between responders and nonresponders were observed (**Figure 5)**. These data suggest adequate drug exposure in the majority of patients who were likely to respond. Moreover, this analysis indicates a potential threshold at 100 ng/mL with 22%, 48%, and 50% CRc rates at steady-state C_{trough} values of <100, 100 to 500, and >500 ng/mL respectively (**Figure 6)**. Monte Carlo analysis of distribution of steady-state C_{trough} for each dose group estimated the percentages of patients with steady-state C_{trough} below 100 ng/mL threshold with values of 38.3%, 0.6%, and 0% at doses of 80, 120, and 200 mg, respectively.

3. Antileukemic activity: CR/CRh rates in FLT3+ patients were 25.0%, 23.2%, 19.1%, and 30% for the 80, 120, 200, and 300-mg dose levels, respectively.

This assessment supported dose selection of 120 mg and higher to ensure adequate efficacy in most patients. However, preliminary safety analysis of Study 2215-CL-0101 results showed that 46% of the FLT3+ R/R AML patients at dose 200 mg required dose interruption compared to 19% at dose 120 mg. These results are supported by additional analysis of the integrated safety population (2215-CL-0101 and 2215-CL-0301) in which gilteritinib treatment was discontinued in 97.8% of the patients treated with doses >120 mg compared to 73.4% in patients treated with 120 mg.

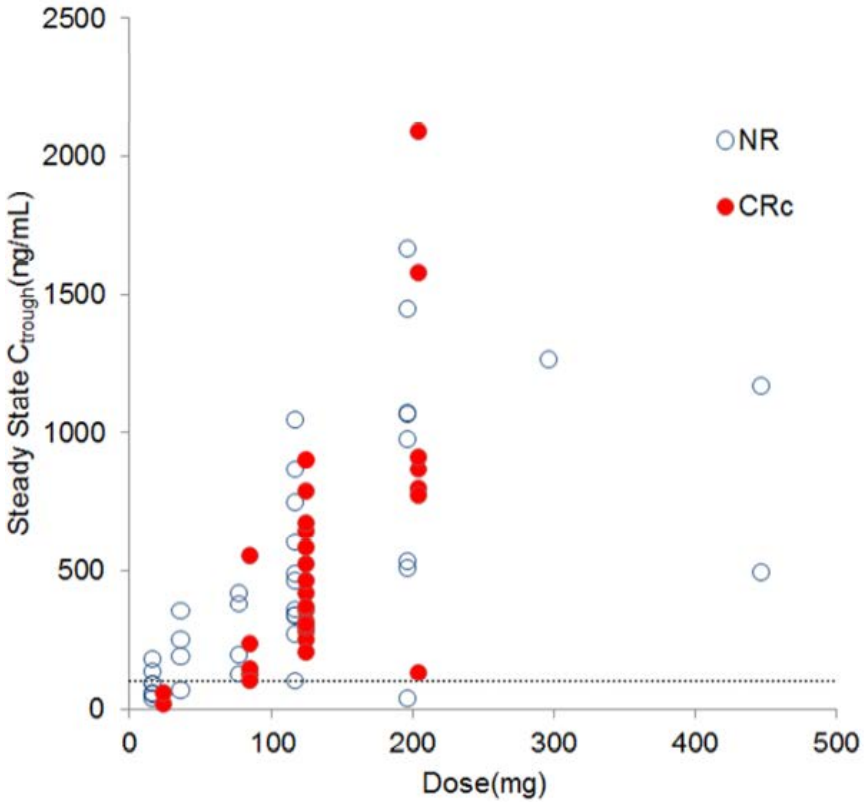
Overall, the efficacy and safety analyses of 2215-CL-0101 and 2215-CL-0301 along with other clinical pharmacology studies provide evidence for the effectiveness of gilteritinib at a dose of 120 mg.

Figure 5: Response (CRc or NR) by Gilteritinib Steady-State C_{trough} Values, FLT3+ Population



Source: Summary of clinical efficacy, Figure 18, Section 4.1.2

Figure 6: Response (CRc or NR) by Gilteritinib Steady-State C_{trough} Values, FLT3+ Population



Source: Summary of clinical efficacy, Figure 19, Section 4.1.2

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed gilteritinib dosing regimen of 120 mg QD for R/R FLT3+ AML patient population appears appropriate based on the available efficacy and safety data.

Efficacy: Analysis of gilteritinib exposure and CR/CRh response was conducted for the most recently available data for studies 2215-CL-0101 and 2215-CL-0301. In Study 2215-CL-0101, 97% (37/38) of the FLT3+ patients who achieved a best overall response of CR/CRh had gilteritinib plasma C_{trough} ≥100 ng/mL, the established gilteritinib threshold concentration for response. In comparison, 21% (37/174) of patients that achieved gilteritinib plasma C_{trough} ≥100 ng/mL achieved CR/CRh, while only 6% (1/17) achieved CR/CRh among the patients that had a gilteritinib plasma concentration of <100 ng/mL. In 2215-CL-0301, all patients were FLT3+ and dosed with 120 mg QD gilteritinib. At steady state, all patients in the 2215-CL-0301 pharmacokinetic analysis set achieved a C_{trough} >100 ng/mL (median plasma concentration of gilteritinib ranged from 257 to 354 ng/mL for cycles 2 through 6). Results of these two studies support the dosing of 120 mg QD to keep the gilteritinib plasma C_{trough} above the predetermined threshold of 100 ng/mL.

Safety: The safety profile of gilteritinib was similar for the overall integrated R/R AML safety population (FLT3 positive and negative patients from studies 2215-CL-0101, 2215-CL-0102 and 2215-CL-0301) and the subset of the integrated R/R AML safety population that was positive for FLT3 mutation. In the integrated R/R AML safety population, at the 120-mg dose level, 57.3% of patients had at least one grade 3 or higher drug-related TEAE. The most frequently reported drug-related adverse reactions included ALT increased (22.4%), AST increased (20.7%), and anemia (15.4%). In the gilteritinib 120 mg group, the percentage of patients experiencing a maximum postbaseline QTcF value >450 to ≤480 msec was 28.8%, with 5.0% and 1.7% of patients experiencing a maximum postbaseline QTcF value of >480 to ≤500 msec or >500 msec, respectively. In Study 2215-CL-0301, only one patient (0.6%) had a postbaseline QTcF value of >500 msec, and no patients discontinued the study due to QT prolongation. The safety profiles of gilteritinib at doses 80, 120, and 200 mg support the selected dose of 120 for general FLT3 R/R AML patient population.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No. Based on the results from a dedicated hepatic impairment study, a mass balance study and population PK analyses, no dose adjustment is recommended for R/R AML patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment and mild (creatinine clearance (CLCr 50-80 mL/min) or moderate (CLCr 30-50 mL/min) renal impairment. The effect of severe hepatic (Child-Pugh Class C) or severe renal impairment (CLCr ≤29 mL/min) on gilteritinib pharmacokinetics is unknown. Population PK analysis and safety and efficacy

assessments indicated that age (20-87 years), weight (40-157 kg), sex (male vs. female), and race (Caucasian, African American, or Asian) do not have clinically meaningful effects on the pharmacokinetics of gilteritinib.

Hepatic Impairment:
Gilteritinib is mainly eliminated by hepatic metabolism and an increase in its exposure is possible due to hepatic impairment. Therefore, the Applicant conducted a dedicated hepatic impairment clinical study (Study 2215-CL-0106) in non-cancer patients to assess the effect of mild and moderate hepatic impairments on gilteritinib pharmacokinetics and safety. Study 2215-CL-0106 is an open-label single dose study designed to compare the single-dose (10 mg) pharmacokinetics and safety of gilteritinib in subjects with mild (Class A: Child-Pugh classification score of 5 – 6, group 1) and moderate hepatic impairment (Class B: Child-Pugh classification score of 7 – 9, groups 2) to matched healthy subjects with normal hepatic function (group 3). Results of this study suggested that total gilteritinib exposure decreased with increasing degree of hepatic impairment (**Table 10)**. However, unbound gilteritinib exposure in subjects in the mild or moderate hepatic impairment groups is comparable to that observed in subjects in the normal hepatic function group (**Table 11)**. The Applicant attributed reduction in total gilteritinib exposure to increase in unbound fraction of gilteritinib, an approximate 51% increase in mean gilteritinib fraction unbound (fu) was observed in subjects in the moderate hepatic impairment group compared to subjects in the normal hepatic function group.

The Applicant did not conduct clinical study to assess the effect of severe hepatic impairment on pharmacokinetics and safety of gilteritinib. Real world data (RWD) based on health insurance claims data filed between 2006 to 2015 suggest a low prevalence (8/2378; 0.3%) of patients with R/R AML who have moderate/severe liver disease at the time of diagnosis of relapsed or refractory to treatment.

Table 10: Summary of Total Gilteritinib Plasma Pharmacokinetic Parameters in Subjects in the Mild Impairment, Moderate Impairment, and Normal Hepatic Function Groups

Parameter	Statistic	10 mg ASP2215		
		Mild (Group 1) (n = 8)	Moderate (Group 2) (n = 8)	Normal (Group 3) (n = 8)
AUC_{inf} (ng•h/mL)	Mean	425	351	542
	SD	108	152	167
	%CV	25.5	43.2	30.9
	Median	431	355	513
	Min - Max	231 - 560	155 - 577	364 - 866
C_{max} (ng/mL)	Mean	8.1	6.40	7.48
	SD	2.67	2.47	2.23
	%CV	32.9	38.6	29.8
	Median	8.17	6.30	6.97
	Min - Max	4.14 – 11.5	2.25 – 9.88	4.67 – 10.7
CL/F (L/h)	Mean	25.3	34.5	19.9
	SD	8.19	16.9	5.51
	%CV	32.4	48.9	27.7
	Median	23.2	28.4	19.6
	Min - Max	17.9 – 43.4	17.3 – 64.6	11.6 – 27.5
t_{max} (h)	Mean	3.75	2.88	4.63
	SD	2.54	2.22	2.07
	%CV	NA	NA	NA
	Median	4.50	2.00	6.00
	Min - Max	0.50 – 6.00	0.50 – 6.00	1.00 – 6.00
$t_{½}$ (h)	Mean	126	112	116
	SD	19.2	31.9	12.3
	%CV†	15.2	28.5	10.6
	Median	126	116	115
	Min - Max	105 - 159	69.3 - 161	98.0 - 136
V_z/F (L)	Mean	4520	5090	3340
	SD	1310	1680	977
	%CV	29.0	33.0	29.2
	Median	3960	4850	3470
	Min - Max	3520 - 7300	3350 - 7910	1910 - 4700

Source: Study 2215-CL-0106, Clinical study report, Table 3, Section 8.1.1

Table 11: Statistical Analysis of Hepatic Impairment on Total and Unbound Gilteritinib PKs

Parameter	Statistic	10 mg ASP2215		
		Mild (Group 1) (n = 8)	Moderate (Group 2) (n = 8)	Normal (Group 3) (n = 8)
f_u	Mean	0.0640	0.0865	0.0572
	SD	0.00546	0.0297	0.00610
	%CV	8.5	34.4	10.7
	Median	0.0626	0.0874	0.0562
	Min - Max	0.0583 – 0.0737	0.0476 – 0.135	0.0489 – 0.0670
$AUC_{inf,u}$ (ng•h/mL)	Mean	27.2	29.8	31.0
	SD	7.49	17.6	10.8
	%CV	27.5	59.1	34.8
	Median	28.5	21.6	27.5
	Min - Max	15.0 – 35.4	15.3 – 66.5	21.8 – 55.3
$C_{max,u}$ (ng/mL)	Mean	0.518	0.520	0.429
	SD	0.177	0.198	0.138
	%CV	34.1	38.2	32.2
	Median	0.488	0.531	0.409
	Min - Max	0.269 – 0.715	0.223 – 0.806	0.228 – 0.668
CL_u/F (L/h)	Mean	398	423	349
	SD	132	185	90.4
	%CV	33.1	43.7	25.9
	Median	358	463	363
	Min - Max	283 - 666	150 - 652	181 - 458
$V_{z,u}/F$ (L)	Mean	70900	61500	58500
	SD	20500	16500	15500
	%CV	28.9	26.8	26.4
	Median	67000	60400	62400
	Min - Max	47800 - 112000	35000 - 80900	29900 - 74900

Source: Study 2215-CL-0106, Clinical study report, Table 5, Section 8.1.3

Renal Impairment:
Clinical data from mass balance study (2215-CL-0105) indicated that renal excretion contributes to ~10% of the elimination of unchanged gilteritinib. The population pharmacokinetic model included serum creatinine, a marker of renal function, as a statistically significant covariate but the impact on gilteritinib exposure was less than 2-fold in non-Japanese patients with R/R AML and less than 1.5-fold in Japanese patients with R/R AML. Therefore, impaired renal function is not expected to significantly affect gilteritinib exposure, indicating dose adjustment is not warranted in patients with mild or moderate renal impairment.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Yes. In vitro, gilteritinib is primarily metabolized by CYP3A4, therefore, inhibitors and inducers of CYP3A4 could clinically affect its exposure. The Applicant conducted a clinical study (2215-CL-0108) to assess the effect of concomitant use of combined P-gp and strong CYP3A4 inhibitor (itraconazole), moderate CYP3A inhibitor (fluconazole), and combined P-gp and strong CYP3A4 inducer (rifampin) on gilteritinib exposure. Based on the results of this study, the Applicant recommended that the concomitant use of CYP3A4 inducers with gilteritinib should be avoided. Similarly, the use of strong CYP3A4 inhibitors should be avoided unless it is deemed necessary

to the clinical care of the patient, in this case patient should be monitored for increased risk of gilteritinib adverse reactions.

In vitro, gilteritinib is a weak inhibitor of CYP3A4 and strong inhibitor of MATE1, BCRP, and OCT2 transporters. To assess the effect of gilteritinib on the exposure of CYP3A4 and MATE1 substrates, the Applicant opened cohorts in the expansion phase of Study 2215-CL-0101 at dose cohort of 300 mg to investigate the effect of gilteritinib on CYP3A substrate (midazolam), and at dose cohort of 200 mg, to investigate the effect of gilteritinib on MATE1 substrate (cephalexin). From these sub-studies, the Applicant concluded that gilteritinib is unlikely to clinically affect pharmacokinetics of CYP3A and MATE1 substrates. No specific recommendations were included in the label for CYP3A and MATE1 substrates, but the clinical pharmacology team added the results of these studies to section 12.3. in the label.

No clinically relevant food effect was observed with gilteritinib. In vitro, gilteritinib is soluble in aqueous medium at pH up to 6.8. Therefore, gilteritinib is expected to be soluble in physiologically relevant pH conditions, and acid-lowering agents (e.g., proton pump inhibitor, H2-receptor antagonist, antacid) are not expected to affect its oral bioavailability.

Study 2215-CL-0108: Effect of CYP3A and P-gp modulators on gilteritinib pharmacokinetics:

This is a dedicated open-label, phase 1, drug-drug interaction study that assessed the effect of combined P-gp and strong CYP3A4 inhibitor (itraconazole), moderate CYP3A inhibitor (fluconazole) and combined P-gp and strong CYP3A4 inducer (rifampin) on gilteritinib exposure. In this study, 81 healthy adult male and female subjects were randomly assigned 1:1:1:1 to four treatment arms shown in **Table 12**.

Table 12: Study 2215-CL-0108 Study Arms

Arm	Treatment
1	10-mg ASP2215 on day 1
2	200-mg ITZ twice daily on day 1, 200-mg ITZ once daily on days 2 to 28 and 10-mg ASP2215 on day 6
3	400-mg FLZ on day 1, 200-mg FLZ once daily on days 2 to 28 and 10-mg ASP2215 on day 6
4	600-mg RIF once daily on days 1 to 21 and 20-mg ASP2215 on day 8

FLZ: fluconazole; ITZ: itraconazole; RIF: rifampin
Source: Study 2215-CL-0106, Clinical study report, Table 1, Section 5.1.1

Coadministration of itraconazole (a combined P-gp and strong CYP3A4 inhibitor) with gilteritinib resulted in a small increase (~20%) in mean gilteritinib C_{max} (5.2 ng/mL for gilteritinib alone vs. 6.1 ng/mL for gilteritinib with itraconazole). Mean AUC_{last} and AUC_{inf} were increased by ~2.2-fold (303 vs. 632 ng•h/mL and 320 vs. 696 ng•h/mL, respectively). Corresponding decreases in mean CL/F (33.9 vs. 15.2 L/h) and longer $T_{1/2}$ (88.9 vs. 161 h) were observed. The geometric least squares mean ratios comparing gilteritinib exposure with and without

itraconazole suggest a significant increase (~120%) in gilteritinib systemic exposure with concomitant use of a combined P-gp and strong CYP3A4 inhibitor (**Table 13)**.

Table 13: Statistical Assessment of the Interaction Effect of Itraconazole, Fluconazole, and Rifampin on the Pharmacokinetics of ASP2215

Comparison	Dose Normalized Parameter	Geometric LS Mean for the Numerator	Geometric LS Mean for the Denominator	Geometric LS Mean Ratio (%)	90 % CI of the Ratio (%)
ITZ + ASP2215/ ASP2215 alone †	AUC_{inf} (ng•h/mL)	67.7	30.6	221.39	(188.26, 260.36)
	AUC_{last} (ng•h/mL)	61.5	28.8	213.51	(180.58, 252.44)
	C_{max} (ng/mL)	0.593	0.495	119.80	(100.09, 143.39)
FLZ + ASP2215/ ASP2215 alone ‡	AUC_{inf} (ng•h/mL)	43.9	30.6	143.46	(121.99, 168.71)
	AUC_{last} (ng•h/mL)	41.5	28.8	144.02	(121.81, 170.28)
	C_{max} (ng/mL)	0.573	0.495	115.73	(96.69, 138.52)
RIF + ASP2215/ ASP2215 alone §	AUC_{inf} (ng•h/mL)	8.71	30.6	28.47	(24.21, 33.48)
	AUC_{last} (ng•h/mL)	8.42	28.8	29.21	(24.71, 34.54)
	C_{max} (ng/mL)	0.364	0.495	73.44	(61.36, 87.91)

Source: Study 2215-CL-0108, Clinical study report, Table 5, Section 8.1

In comparison with the administration of gilteritinib alone, coadministration of fluconazole (a moderate CYP3A4 inhibitor) resulted in a small increase (~16%) in mean gilteritinib C_{max} (5.2 vs. 6.4 ng/mL). Mean AUC_{last} and AUC_{inf} increased by ~1.5-fold with fluconazole (303 vs. 444 ng•h/mL and 320 vs. 466 ng•h/mL, respectively). Corresponding decreases in mean CL/F (33.9 vs. 24.7 L/h) and longer $T_{1/2}$ (88.9 vs. 113 h) were observed. The geometric least squares mean ratios for AUC_{inf}, AUC_{last} and C_{max} suggest a significant increase (~45%) in gilteritinib systemic exposure with concomitant use of moderate CYP3A4 inhibitors (**Table 13)**.

Dose-normalized pharmacokinetic parameters were calculated to compare gilteritinib systemic exposure after a single 10-mg dose of gilteritinib administered alone relative to a 20 mg dose of gilteritinib coadministered with rifampin, a combined P-gp and strong CYP3A4 inducer. Coadministration of rifampin with gilteritinib resulted in a ~17% decrease in mean gilteritinib C_{max} (0.52 vs. 0.38 ng/mL/mg), and ~80% reduction in its total exposure (mean AUC_{last} of 30.3 vs. 8.8 ng•h/mL/mg and AUC_{inf} of 32 vs. 9.1 ng•h/mL/mg). A corresponding decrease in mean $T_{1/2}$ of gilteritinib (88.9 vs. 33.2 h) was also reported. The dose-normalized geometric least squares mean ratios for AUC_{inf}, AUC_{last}, and C_{max} suggest a significant decrease in gilteritinib systemic exposure with concomitant use of a combined P-gp and strong CYP3A4 inducer (**Table 13).**

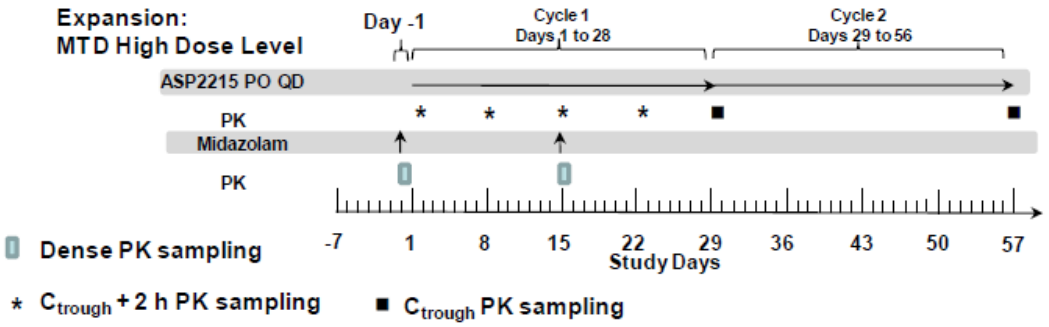
Based on the results of this study, adjustment in the starting dose is not recommended. However, concomitant use of combined P-gp and strong CYP3A4 inhibitor with gilteritinib should be avoided because it might decrease the clinical benefits of gilteritinib. Due to the potential for increase in gilteritinib exposure, drugs that do not strongly inhibit CYP3A activity should be considered. If the use of strong CYP3A4 inhibitors deemed necessary for the care of the patients, caution should be exercised with the coadministration of gilteritinib with strong CYP3A inhibitors and gilteritinib adverse reactions should be closely monitored.

Study 2215-CL-0101: Effect of gilteritinib on CYP3A and MATE1 substrates:

Although Study 2215-CL-0101 was designed to assess the safety and tolerability of oral gilteritinib, the potential induction of CYP3A4 by gilteritinib and the effect of gilteritinib on multidrug and toxin extrusion 1 (MATE1) were assessed in R/R AML patients in the expansion phase of this study. Study 2215-CL-0101 had two cohorts of patients: Cohort 1 (dose escalation) and Cohort 2 (dose expansion). In Cohort 2, at the highest dose level of gilteritinib (MTD=300 mg), the effect of gilteritinib on midazolam pharmacokinetics was evaluated. To further evaluate drug-drug interaction (DDI), a sub-study with a MATE1 substrate was conducted at gilteritinib dose of 200 mg.

Expansion Cohort with Induction Study (Cohort 2, 300-mg dose, CYP3A Sub-study):
The effect of gilteritinib on the pharmacokinetics of midazolam, a CYP3A substrate, was investigated in patients with R/R AML. Midazolam (2 mg) was administered as a single oral dose on day -1 and day 15 of cycle 1. Gilteritinib was administered once daily starting on day 1 of cycle 1, **Figure 7**. Plasma concentrations of midazolam and its metabolite, 1-hydroxy midazolam were evaluated.

Figure 7: Study Scheme for the Assessment of Gilteritinib Effect on Midazolam Exposure



Source: Study 2215-CL-0101, Clinical study report, Section 5.3.1.2.3

Relative to administration of midazolam alone, midazolam C_{max} and AUC_{24} increased by approximately 10% when gilteritinib was coadministered with midazolam (C_{max} 14.7±8.9 vs. 18.5±9.5 ng/mL and AUC_{24} 66.6±57.7 vs. 81.6±65.8 ng•h/mL, for midazolam alone [n=16] and midazolam + gilteritinib [n=9], respectively). For 1-hydroxymidazolam, C_{max} and AUC_{24} increased

by approximately 23% and 50%, respectively (C_{max} 4.6±2.9 vs. 5.1±3.2 ng/mL and AUC_{24} 20.4±24.8 vs. 23.1±21.6 ng•h/mL, for midazolam alone [n=16] and midazolam + gilteritinib [n=9], respectively). The geometric least squares mean ratios (GMRs) for midazolam C_{max} and AUC_{24} were 111.64 and 109.46, respectively, **Table 14**. The GMRs for 1-hydroxymidazolam C_{max} and AUC_{24} were 123.47 and 149.90, respectively, **Table 14**. These results suggest coadministration of midazolam with gilteritinib did not result in a significant difference in midazolam exposure relative to administration of midazolam alone.

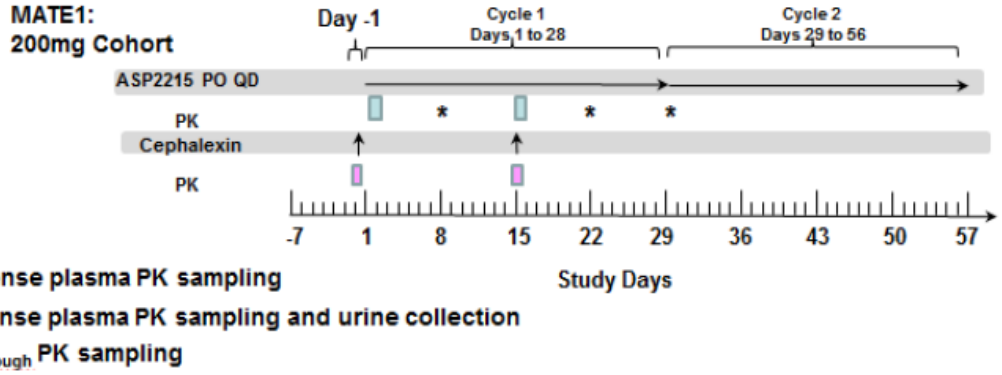
Table 14: Statistical Comparison of Midazolam Exposure after Administration of Midazolam Alone or Coadministered with Gilteritinib

Analyte	Parameter	N	Geometric LS Mean for Reference Treatment	Geometric LS Mean for Test Treatment	Geometric LS Mean Ratio (%)† (Test/Reference)	90% CI of Mean Ratio (%)†
Midazolam	AUC_{24} (ng•h/mL)	8	54.28	59.42	109.46	(49.82, 240.48)
	C_{max} (ng/mL)	9	14.33	16.00	111.64	(69.54, 179.25)
1-hydroxymidazolam	AUC_{24} (ng•h/mL)	8	11.31	16.95	149.90	(74.88, 300.06)
	C_{max} (ng/mL)	9	3.489	4.308	123.47	(72.41, 210.52)

Source: Study 2215-CL-0101, Clinical study report, Table 26, Section 8.3.2.2

Expansion Cohort with MATE1 Substrate Study (Cohort 2, 200-mg dose, MATE1 Sub-study):
The effect of gilteritinib on the pharmacokinetics of cephalexin, a MATE1 substrate, was investigated in patients with R/R AML. Cephalexin (500 mg) was administered as a single oral dose on day -1 and day 15 of cycle 1. Gilteritinib 200 mg was administered once a day starting on day 1 of cycle 1, **Figure 8**. Plasma and urine concentrations of cephalexin were evaluated.

Figure 8: Study Scheme for the Assessment of Gilteritinib Effect on Cephalexin Exposure



Source: Study 2215-CL-0101, Clinical study report, Section 5.3.1.2.4

GMRs and 90% CI for cephalexin C_{max}, AUC_{last}, and AUC_{inf} are summarized in **Table 15**. Relative to administration of cephalexin alone, cephalexin systemic exposure was comparable when

gilteritinib was coadministered with cephalexin as reflected by an approximate minimal decrease (3% to 9%) in C_{max}, AUC_{last}, and AUC_{inf}. Additionally, cephalexin urinary excretion decreased approximately 17% when cephalexin was coadministered with gilteritinib relative to cephalexin administered alone. These results suggest coadministration of gilteritinib and a MATE1 substrate is not expected to result in a clinically-relevant DDI.

Table 15: Statistical Assessment of the Effect of Gilteritinib on Cephalexin Pharmacokinetics after Administration of Cephalexin Alone or Coadministered with Gilteritinib

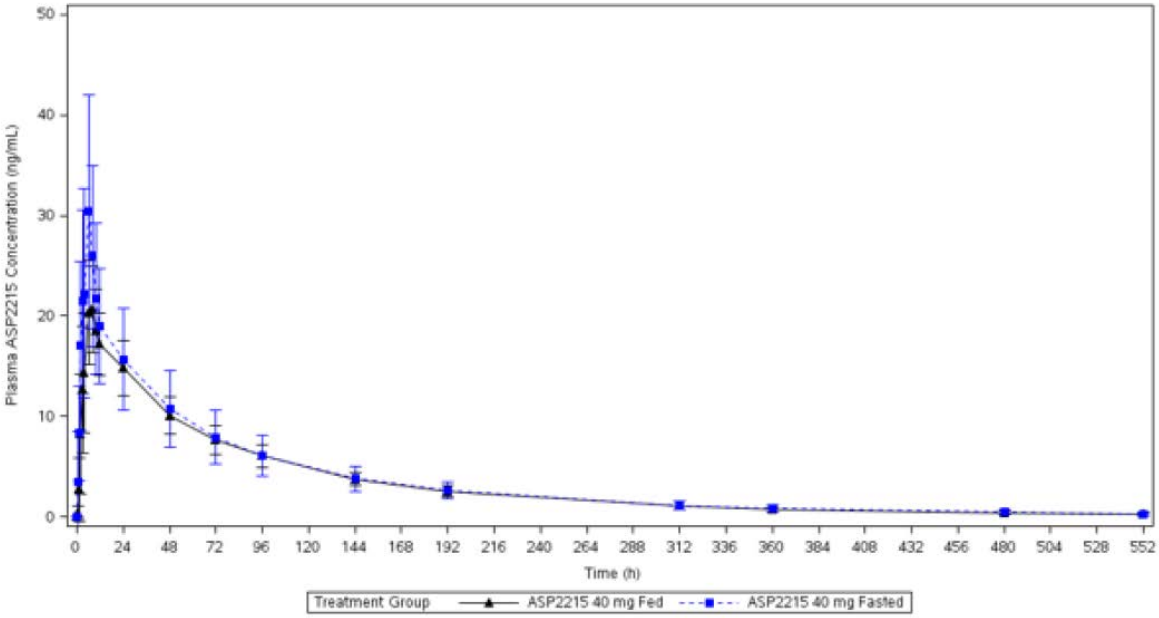
Parameter	N	Geometric LS Mean for Reference Treatment	Geometric LS Mean for Test Treatment	Geometric LS Mean Ratio (%)† (Test/Reference)	90% CI of Mean Ratio (%)†
AUC_{last} (ng•h/mL)	16	50808	49647	97.71	(74.19, 128.70)
AUC_{inf} (ng•h/mL)	12	54066	50802	93.96	(75.29, 117.26)
C_{max} (ng/mL)	16	16946	15498	91.46	(74.60, 112.12)
Ae (mg)	10	436.9	366.7	83.93	(46.53, 151.39)
CLr (L/h)	6	10.67	8.842	82.84	(40.25, 170.48)

Source: Study 2215-CL-0101, Clinical study report, Table 28, Section 8.3.2.3

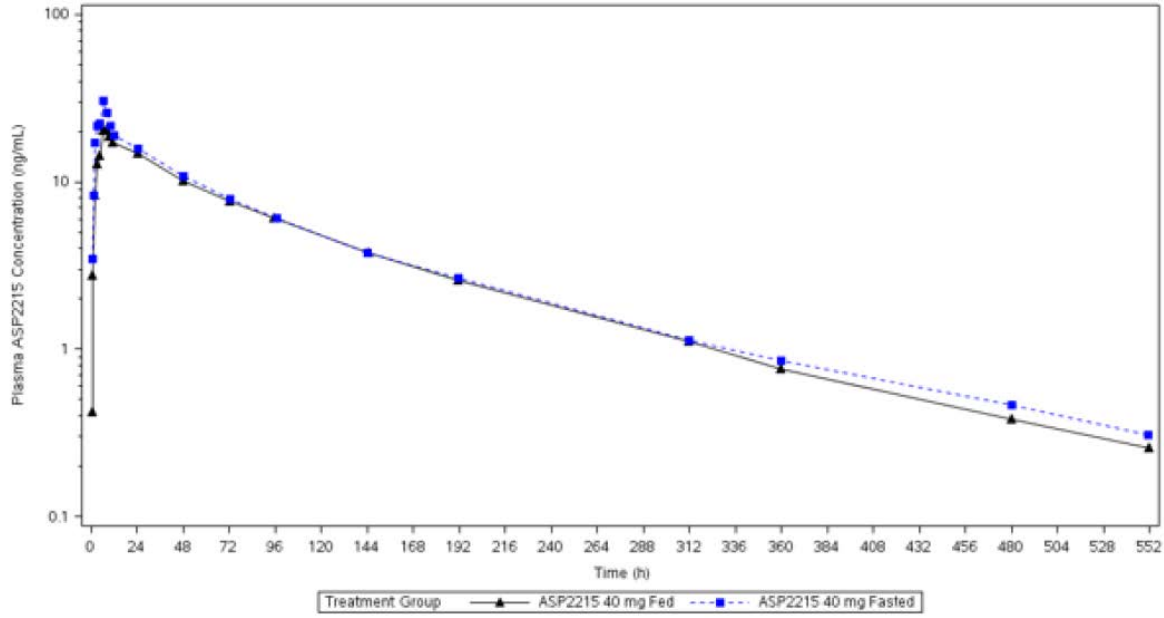
Food Effect: The exposure of gilteritinib was not altered following co-administration with a high fat meal. In a pivotal open-label study (2215-CL-0113), a single 40 mg gilteritinib tablet of the to-be-marketed formulation was administered to healthy subjects under fasting condition (≥10 hours) (n=20) and with a high-fat meal (approximately 800-1000 kcal with 500-600 kcal from fat) (n=20). There was no clinically relevant exposure difference in fed and fasted conditions. The mean gilteritinib C_{max} decreased after gilteritinib was administered under fed conditions (21.6 ng/mL) relative to fasted conditions (30.4 ng/mL). Gilteritinib exposure decreased slightly (AUC_{inf} 1970 ng•h/mL vs. 1800 ng•h/mL, AUC_{last} 1920 ng•h/mL vs. 1760 ng•h/mL, and AUC_{72} 997 ng•h/mL vs. 878 ng•h/mL) and absorption was delayed (2-hour increase in median T_{max}) when gilteritinib was administered with a high-fat meal relative to fasted conditions (**Figure 9** and **Table 16)**. Gilteritinib $T_{1/2}$, CL/F, and Vz/F were comparable in the fasted and fed treatment groups. Overall, although C_{max} decreased approximately 26% under fed conditions, the overall exposure of gilteritinib was comparable under fasted and fed conditions as evidenced by the less than 10% difference in AUC **(Table 17)**. Based on the efficacy and safety analysis, these changes are not expected to have clinically meaningful effects on the efficacy and safety of gilteritinib. Thus, the Applicant's proposal to administer gilteritinib without regard to food is acceptable.

Figure 9: Mean ASP2215 Plasma Concentration Time Profiles in Fed and Fasted Treatment Groups- A. Linear Scale Plot and B. Semi-log Scale Plot

A. Linear Scale



B. Semi-log Scale



Source: Study 2215-CL-0113, Clinical study report, Figures 1 and 2, Section 8.1.1

Table 16: Gilteritinib Plasma Pharmacokinetic Parameters in Healthy Adult Subjects Administered Gilteritinib Under Fasted or Fed Conditions

Parameter Statistic	Fasted (n = 16)	Fed (n = 16)
AUC_{inf} (ng•h/mL)		
Mean (SD)	1970 (609)	1800 (311)
%CV	30.8	17.3
Median	1880	1740
Min – Max	1190 – 3320	1330 – 2280
AUC_{last} (ng•h/mL)		
Mean (SD)	1920 (597)	1760 (300)
%CV	31.1	17.0
Median	1820	1700
Min – Max	1140 – 3190	1310 – 2230
AUC_{72} (ng•h/mL)		
Mean (SD)	997 (332)	878 (158)
%CV	33.3	18.0
Median	907	859
Min – Max	581 – 1850	666 – 1180
C_{max} (ng/mL)		
Mean (SD)	30.4 (11.6)	21.6 (4.63)
%CV	38.1	21.4
Median	28.7	19.8
Min – Max	13.8 – 62.9	15.8 – 31.6
t_{max} (h)		
Median	6.00	7.98
Min – Max	5.98 – 7.97	5.97 – 10.0

Source: Study 2215-CL-0113, Clinical study report, Table 3, Section 8.1.2

Table 17: Statistical Assessment of Gilteritinib Absorption Parameters in Healthy Subjects Administered Gilteritinib Under Fasted or Fed Conditions

	Fasted		Fed		Geometric LS Mean Ratio (%)†	90% CI of Ratio†
Parameter	n	Geometric LS Mean	n	Geometric LS Mean		
AUC_{inf} (ng•h/mL)	16	1900	16	1780	93.8	(81.2, 108.4)
AUC_{last} (ng•h/mL)	16	1840	16	1740	94.6	(81.8, 109.3)
AUC_{72} (ng•h/mL)	16	951	16	865	91.0	(78.2, 105.9)
C_{max} (ng/mL)	16	28.6	16	21.2	74.0	(62.2, 88.1)

Source: Study 2215-CL-0113, Clinical study report, Table 4, Section 8.1.3

Effect of acid-reducing agents on gilteritinib pharmacokinetics:

Based on the gilteritinib dissolution data **Table 18** and food effect study results discussed above, it is unlikely for acid-reducing agent to affect gilteritinib pharmacokinetics.

Table 18: In Vitro Gilteritinib Solubility at Different pHs

Attribute	Results	
Solubility Profile at 20 ± 5°C	Water	29 mg/mL (Sparingly soluble)
	Aqueous solution (pH 1) † (After dissolution: pH 5.8)	190 mg/mL (Freely soluble)
	Aqueous solution (pH 3) ‡ (After dissolution: pH 5.2)	130 mg/mL (Freely soluble)
	Aqueous solution (pH 5) ‡ (After dissolution: pH 5.3)	82 mg/mL (Soluble)
	Aqueous solution (pH 7) ‡ (After dissolution: pH 6.6)	0.087 mg/mL (Practically insoluble)

†0.1 mol/L hydrochloric acid was used. This pH value was measured before sample dissolution.

‡Carmody's buffer solutions (mixtures of 0.2 mol/L boric acid, 0.05 mol/L citric acid and 0.1 mol/L trisodium phosphate) were used. This pH value was measured before dissolution.

Source: Summary of biopharmaceutic studies and analytical methods, Table 8, Section 2.1

Primary Reviewer
Hisham Qosa, PhD.

Team Leader
Wentao Fu, PhD.

7 Sources of Clinical Data and Review Strategy

7.1 Table of Clinical Studies

Table 19: Clinical Studies of Gilteritinib

Study	Study Design	Regimen/ schedule/route	Endpoints	No. of patients enrolled (treated)	Study Population
Controlled Studies to Support Efficacy and Safety					
2215-CL-0301	Randomized phase 3	120-200 mg PO/day	OS, CR/CRh, EFS, CR	255 (242)	R/R FLT3+ AML
2215-CL-0101	Single arm dose finding	20-450 mg PO/day	MTD, PK	265 (252)	R/R FLT3+ AML
2215-CL-0102	Single arm dose finding	20-300 mg PO/day	MTD, PK	27 (24)	R/R FLT3+ AML
Studies to Support Safety					
2215-CL-0106	PK in hepatic impairment	10 mg x 1	PK, safety	24	Healthy and hepatic impaired
2215-CL-0108	Drug-drug interaction	10-20 mg x 1 on d 1, 6, or 8	PK, safety	81	Healthy subjects
2215-CL-0113	Evaluation of effect of food	40 mg	PK, safety	32	Healthy subjects
2215-CL-0110	PK evaluation	40 mg x 1	PK, safety	42	Healthy subjects
2215-CL-5101	Phase 1b/2 single arm	80 or 120 mg PO/day (with 150 mg erlotinib)	Safety, efficacy	10	EGFR+ advanced NSCLC
2215-CL-0105	Phase 1 single arm	120 mg daily	PK, safety	6	Solid tumors

7.2 Review Strategy

7.2.1 Efficacy Analysis

The review of efficacy is based primarily on data from three protocols: 2215-0101, -0102, and 0301. Studies 0101 and 0102 are single-arm dose-finding trials of different doses of gilteritinib in patients with R/R AML, including some patients with FLT3-negative disease. For the efficacy evaluation, all patients with FLT3-positive AML who were treated with 120 mg of gilteritinib will be evaluated. Study 0301 is a randomized trial comparing gilteritinib to chemotherapy in patients with relapsed or refractory FLT3 positive AML. in the final analysis, response rates and survival will be compared for patients receiving gilteritinib versus chemotherapy. This review is based on the prespecified first interim analysis of CR/CRh rates in the gilteritinib arm. At the time of submission of the NDA, the sponsor was blinded to the results in the control arm of Study 0301.

7.2.2 Safety Analysis

The analysis of safety included the above efficacy trials and additional studies in subjects with or without cancer.

Studies 2215-CL-0110, 00106, -0108, and -0113 assessed the pharmacokinetics and safety of doses of gilteritinib ranging from 10 mg to 40 mg given x1 in healthy subjects or subjects with mild to moderate hepatic impairment (Study 0106). Study 0108 was a DDI study examining the effect of coadministration of gilteritinib with fluconazole, itraconazole, and rifampin and Study 0113 examined the effect of food on the absorption of gilteritinib.

Two studies, 2215-CL-0105 and -0501, examined gilteritinib in solid tumors. Study 0105, examined its pharmacokinetics in patients with advanced solid malignancies, and Study 0501 evaluated its use with erlotinib in patients with advanced non-small cell lung cancer. Each study used repeated doses of 80 mg to 120 mg gilteritinib. The small number of patients in these trials (16) limits the conclusions that can be derived from them. However, they present the opportunity to examine the effect of repeated therapeutic doses of gilteritinib on hematologic parameters without the confounding effect of leukemia.

Lastly, two rollover/expanded access studies, 2215-CL-0109 and -9100, were opened to provide continued access to participants in previous studies who continue to benefit from treatment. These on-going studies have recruited only 2 and 6 participants, respectively, and thus are not substantial sources of data.

8 Statistical and Clinical Evaluation – Efficacy

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 2215-CL-0301

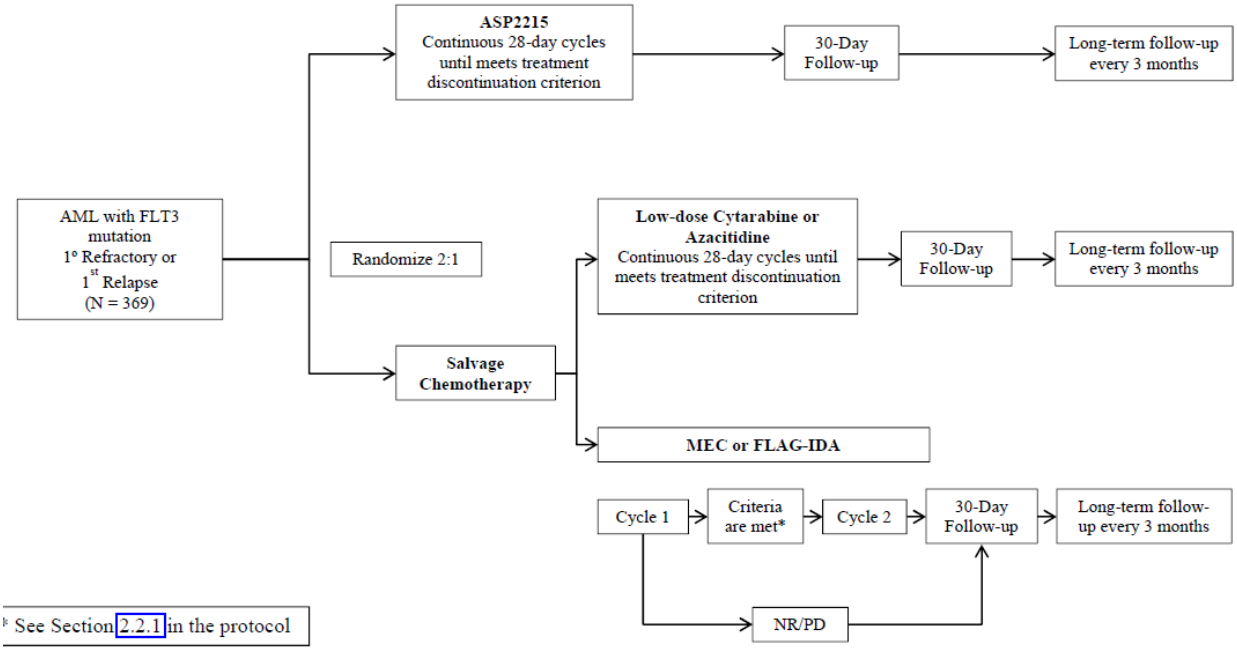
A Phase 3 Open-label, Multicenter, Randomized Study of ASP2215 versus Salvage Chemotherapy in Patients with Relapsed or Refractory Acute Myeloid Leukemia (AML) with FLT3 Mutation

INVESTIGATIONAL PLAN

Trial Design and Endpoints

This is a phase 3, randomized, open-label study comparing outcomes for patients with R/R FLT3-positive AML who are treated with gilteritinib versus chemotherapy. The randomization is stratified by response to first-line AML therapy and preselected salvage chemotherapy. The design of the trial is summarized in **Figure 10**.

Figure 10: Design of Study 2215-CL-0301 (Gilteritinib Versus Chemotherapy)



Source: Study 2215-CL-0301

Key patient eligibility criteria include:

- Adults with R/R AML (primary or secondary to MDS) after first-line treatment (with or without consolidation or HSCT)
- FLT3-activating mutation identified in marrow or whole blood as determined by central lab
- Patients with BCR-ABL-positive AML, acute promyelocytic leukemia, AML secondary to prior chemotherapy, CNS involvement, and patients who are relapsed or refractory to more than one line of therapy are excluded
- Adequate performance status and organ function
- No uncontrolled infection, HIV viral infection, or active hepatitis B or C

Study endpoints include:

Primary Efficacy Endpoints:

- Complete Remission and Complete Remission with Partial Hematologic Recovery Rate (CR/CRh): defined as the number of patients who achieved either CR or CRh at any of the postbaseline visits divided by the number of patients in the analysis population.
- Overall survival (OS): defined as the time from the date of randomization until the date of death from any cause.
- Duration of CR/CRh: included duration of CR and CRh

Key Secondary Efficacy Endpoints:

- Event-free survival (EFS): defined as the time from the date of randomization until the date of documented relapse (excluding relapse after PR. PR isn't generally considered to be a response in the setting of AML so it is not included for EFS in general), treatment failure or death, whichever occurred first.
- CR: defined as the number of patients who achieved the best response of CR divided by the number of patients in the analysis population.

Other Endpoints:

- LFS, duration of remission, CRc (CR+CRi+CRp), transplantation, brief fatigue inventory (BFI) (secondary efficacy endpoints)
- AEs, laboratory values, vital signs, ophthalmologic assessments, EKGs, and Eastern Cooperative Oncology Group (ECOG) scores (safety endpoints).

Clinical Reviewer Comment:
Patient reported outcomes (i.e. BFI) were not provided in the interim analyses.

Statistical Reviewer Comments:

- ***After communication with the sponsor, the following criteria was added to the definition of CR/CRh:***
- ***If the response occurred after HSCT, the subject should not be considered a responder.***
- ***In the calculation of Duration of Remission, deaths among patients who died without report of relapse should be treated as events.***

Statistical Analysis Plan

Definitions of Analysis Sets:

Response Analysis Set (RAS, Interim Analysis 1 Only): consisted of data from patients who were at least 112 days past the first dose of gilteritinib or randomization. The data from patients were analyzed based on the randomized treatments. For Interim Analysis 1, the RAS was used for the primary analyses of efficacy data (i.e., CR+CRh rate).

Intention to Treatment Set (ITT, Interim 2 and Final Analysis): consisted of all patients who were randomized. The data from patients will be analyzed based on the randomized treatments. The ITT was used for the primary analyses of OS and EFS.

Safety Analysis Set (SAF, All Data Analyses): consisted of data from all patients who received at least 1 dose of study drug (gilteritinib or salvage chemotherapy). The data from patients were analyzed based on the actual treatment received.

Full Analysis Set (FAS, Interim 2 and Final Analysis): consisted of data from all randomized patients with FLT3 mutation based on central testing by FLT3 CDx. The data from patients were analyzed based on the randomized treatments.

Analysis of Efficacy Endpoints:
The significance levels at each interim and final analyses for each of co-primary and secondary endpoints are specified in **Table 20**.

Table 20: Study 0301 - Summary of Timing, Sample Size and Decision Guidance at the Planned Analyses

Analysis	Criteria for conduct of analysis (Projected timing)	Endpoint /Analysis Set	Efficacy Boundary*		Futility Boundary*	
			p-value (1-sided) at the Boundary	Approx. Observed HR at Boundary	p-value (1-sided) at the Boundary	Approx. Observed HR at Boundary
First Interim Analysis: CR/CRh rate	When 141 subjects are randomized into ASP2215 arm and at least 112 days (4 treatment cycles) post first dose or randomization (for subjects who received no study drug)	CR/CRh rate /2215 subjects in RAS	NA (0.0005 nominal)	NA	NA	NA
Second Interim Analysis: OS; EFS when null hypothesis of OS is rejected; CR rate when null hypotheses of both EFS and OS are rejected	Approx. 129 OS events were observed	OS/ITT	0.00147	0.57	0.38674	0.95
		EFS/ITT	0.01519	0.67	0.30218	0.91
		CR rate/ITT	0.01519	NA	0.30218	NA
Final Analysis: OS; EFS when null hypothesis of OS is rejected; CR rate when null hypotheses of both EFS and OS are rejected	Approx. 258 OS events were observed	OS/ITT	0.02402	0.77	NA	NA
		EFS/ITT	0.01357	0.75	NA	NA
		CR rate/ITT	0.01357	NA	NA	NA

*: P-value at both efficacy and futility boundaries(except the first interim) are based on 50% information fraction for OS, EFS and CR rate, and need update based on observed information fraction at the second interim.

Statistical Reviewer Comment:
The overall 0.025 one-sided type I error rate is allocated by 0.0005 and 0.0245 for the two co-primary efficacy endpoints of CR/CRh and OS, respectively. The one-sided type I error of 0.0005 in the first interim analysis is a nominal alpha which is arbitrarily selected for acknowledgement of the CR/CRh rate evaluation and will not be recycled.

Analysis of Primary Efficacy Endpoints:

The co-primary efficacy endpoint of CR/CRh rate will be evaluated at the first interim analysis only. The two-sided 95% exact CI of CR/CRh rate will be calculated for approximately 141 subjects who are randomized into gilteritinib arm in the RAS set. The lower limit will be used to compare with the benchmark of CR/CRh rate of 12%.

The co-primary endpoint of the OS will be tested only at second interim and final analyses. The p-value will be calculated using the stratified log-rank test (primary test) with strata to control for response to first-line AML therapy and preselected salvage chemotherapy. The hazard ratio (HR) of the treatment effect along with 95% CI will be calculated by the stratified Cox proportional hazard model. The same stratification factors will be applied to both the stratified log-rank test and the stratified Cox proportional hazard model. Kaplan-Meier survival plots will be used to describe the OS in each treatment group.

Statistical Reviewer Comment:
At the first interim analysis for the co-primary efficacy endpoint CR/CRh, data from only 142 patients in the gilteritinib arm were submitted, and Astellas stayed blinded to the randomized portion of the data to maintain integrity of trial and prevent from any unforeseen change of the study conduct.

Subgroup Analysis: The co-primary efficacy endpoints (CR/CRh rate and OS) and key secondary endpoints (EFS and CR rate) will be assessed for each of the subgroups listed below:

- Age group (<65 years and ≥65 years)
- Sex (Female and Male)
- Race (White, Black or African American, Asian, Other)
- Baseline ECOG (0-1, ≥2)
- Region (North America, Europe (including Turkey and Israel), Asia)
- Central FLT3 Mutation Type (FLT3-ITD alone, FLT3-TKD alone, FLT3-ITD & TKD, Others (Unknown/Missing/Negative))
- Response to First-line Therapy (Relapse within 6 months after allogeneic HSCT, Relapse after 6 months after allogeneic HSCT, Primary refractory without HSCT, Relapse within 6 months after composite complete remission (CRc) and no HSCT, Relapse after 6 months after CRc and no HSCT)
- Salvage Chemotherapy (High intensity chemotherapy (FLAG-IDA, MEC), Low intensity chemotherapy (LoDAC or azacitidine))

Statistical Reviewer Comment:
These are exploratory analyses, not controlled for multiplicity, and will not be used to make inferential statements.

Analysis of Secondary Efficacy Endpoints:
The key secondary efficacy endpoint of EFS will be analyzed in the same manner as the co-primary endpoint of OS. To maintain the overall 1-sided Type I error rate at the 0.0245 significance level, the EFS will be tested only at second interim and final analyses, only if the null hypothesis on OS is rejected.

The key secondary efficacy endpoint of CR rate will be analyzed using the Cochran-Mantel-Haenszel (CMH) test to control for response to first-line AML therapy and preselected salvage chemotherapy (Per IRT) on ITT. To maintain the overall 1-sided Type I error rate at the 0.0245 significance level, the CR rate will be tested only at second interim and final analyses and only if the null hypothesis on OS and EFS are rejected hierarchically.

Other Secondary Efficacy Analyses:
Duration of CR/CRh will be summarized descriptively by median, corresponding 95%CI and range as estimated from the Kaplan-Meier curve.

Determination of Sample Size*:*
This group sequential design is based on the co-primary endpoint of OS using the O'Brien-Fleming boundaries (non-binding) as implemented by Lan-DeMets alpha/beta spending method. Two interim analyses and one final analysis are planned. The first interim analysis is planned when approximately 141 subjects are randomized into gilteritinib arm and at least 112 days (4 treatment cycles) post first dose or randomization. The second interim analysis is planned when approximately 129 death events have occurred, and the final analysis is planned when approximately 258 death events have occurred.

CR/CRh rate:
According to the reviewer's calculation, 141 patients are necessary to provide 80% power to exclude a CR/CRh rate lower than 12% using a 95% exact confidence interval, assuming the CR/CRh rate is 21%

OS:
For the final OS analysis, the planned 258 death events will provide about 90% power to detect a hazard ratio of 0.65 in OS, (median survival time: 7.7 vs. 5 months), at the overall one-sided 0.0245 significance level.

Protocol Amendments

Key changes from substantial amendments are listed below. Nonsubstantial or non-US country specific amendments are not included.
Amendment 1 key changes include:

- Clarification of inclusion criteria
- Exclusion of patients who require treatment with strong inducers of CYP3A

- Exclusion of patients with active GVHD or are on steroids for GVHD
- Modification of language concerning concomitant medication restrictions and requirements to clarify exclusion of patients requiring treatment with strong CYP3A inhibitors, remove hydroxyurea (HU) daily dose limit, clarify that IT chemotherapy should be prophylactic, and add cranial radiation as an allowed therapy.
- Modified discontinuation criteria to define lack of efficacy in patients receiving low dose chemotherapy or gilteritinib and clarify that HU use does not require discontinuation.
- Added monitoring for hyperuricemia
- Reduced number of patient reported outcome measures at 30-day assessment.
- Updated clinical information
- Changes in guidelines for dose interruption or reduction.
- Changed definition of transfusion independence from 4 weeks to one week.
- Removed subgroup analyses not planned to be used in filing (baseline marrow aspirate, platelet count, and WBC count.)

Amendment 2:

- Exclusion of patients with a QTcF of >450 msec at screening based on central reading or long QT syndrome at screening
- Exclusion of patients with hypokalemia or hypomagnesemia at screening
- Removal of HSCT as reason for discontinuation in gilteritinib arm
- Added 12-lead ECG and PK sampling at day 8 and confirmatory ECG added on day 9 and dose reduction assessment to be performed if QTc increases >30 msec with no known etiology
- Clarified that mean QTc will be used for treatment decisions and added dose modification for elevated QTc

Amendment 4:

- Provided clarification that if bone cellularity was between 5% and 20% after treatment with MEC or FLAG-IDA chemotherapy, then the investigator should determine whether a subject should receive another treatment cycle
- Changes in acceptable contraception methods made
- Exclusion criteria with respect prolonged QTc and long QT syndrome
- Clarified discontinuation criteria for MEC or FLAG-IDA

Amendment 7:

- Long-term follow-up schedule changed to every 3 months up to 3 years from the subject's end of treatment visit (addition of 3 years as the maximum follow-up).
- Inclusion of midostaurin as permitted prior treatment
- Clarified FLT3 mutation types included in the protocol
- Deleted MATE1 substrates as exclusion and added donor lymphocyte infusion as an allowed concomitant treatment for AML
- Clarified discontinuation criteria to state that subject eligible to continue until a discontinuation criterion is met or gilteritinib becomes commercially available
- Inclusion of hazard ratio in interim analysis

- Clarified bone marrow samples are required on cycle 1, day 15 or later only for MEC or FLAG-IDA
- Updated PK data
- Clarified dose interruption and reduction guidelines
- Updated methods of assessing drug exposure and compliance, laboratory tests administered, and PRx substudy participation

STUDY RESULTS

Data Quality and Integrity

Data from Study 2215-CL-0301 was provided electronically with ADaM and STDM formats. Data quality appeared to be acceptable in general. The result of this review is based on the Data Cutoff Date of 08/04/2017.

Compliance with Good Clinical Practices

The study was conducted under a U.S. Investigational New Drug application, in accordance with ICH guidelines for good clinical practice (GCP), the principles expressed in the Declaration of Helsinki, and consistent with the CFR, Title 21. The study protocols and informed consent documents were reviewed by local IRB/IEC as required by regulations prior to implementation at practicing institutions.

Financial Disclosure

The Applicant states that one investigator, Dr. Yoshinobu Kanda, had disclosable financial interests, specifically research grants, equipment, retainer for ongoing consultation, or honoraria. No further specifics were provided. Two patients were randomized at the site where Dr. Kanda practices.

Patient Disposition

At the time of data cut-off, 169 patients had been randomized to gilteritinib and 168 had received at least one dose of therapy. Of these, 109 had discontinued treatment, most commonly for disease progression (39), death (17), disease relapse (15), and lack of efficacy (12). In addition, 14 patients discontinued due to adverse events (AEs). Fifty-nine patients were actively receiving treatment with gilteritinib at the time of data cut-off.

Of those patients receiving chemotherapy for whom disposition information was available, lack of efficacy (19), withdrawal by subject (15), and physician decision (10) were the most common reasons for treatment discontinuation while death (13) and withdrawal by subject (11) were the most common reasons for study discontinuation. Four patients withdrew due to AEs. Of those patients who withdrew consent, refusal to participate in the standard of care arm was documented as part of the reason for withdrawal for five patients. In addition, at least one withdrew due to AEs that the patient found intolerable. Of note, all but two treatment

discontinuations due to withdrawal of consent occurred within one month of randomization, including 7 that occurred within 24 hours of randomization.

Protocol Violations/Deviations

Protocol deviations reported included patients entered into the study despite not satisfying all entry criteria and received excluded concomitant treatment. One patient in Japan entered despite fulfilling exclusion criterion #12 (use of a CYP3A4 inducer or inhibitor other than an anti-infective medication). In the non-Japan group, 15 subjects were entered into the study despite not fulfilling entry criteria and 6 received excluded concomitant treatment. No other protocol violations were reported. Inclusion criteria not fulfilled included 5 subjects who did not have FLT3 mutations in marrow or whole blood by central lab (inclusion criterion #5), 2 not R/R to first-line therapy (inclusion criterion #4), and one with labs not meeting criteria described in inclusion criterion #8. Exclusion criteria violated included one subject each with another malignancy in the past 5 years and prior treatment with FLT3 inhibitor (exclusion criteria 6 and 7), 4 with QTc of >450 ms on central read (exclusion criterion #12), and 4 with hypokalemia or hypomagnesemia at screening (exclusion criterion #14). Some subjects had more than one violation. No patient discontinued the study due to protocol deviations.

Demographic Characteristics

A total of 429 patients were screened for study 0301. Of these, 174 were screen failures, with the most common reason for screen failure being no FLT3 mutation detected at screening per central testing (114 patients). Three patients were considered screen failures because of withdrawal of consent. Overall, 255 subjects were randomized 2:1 to gilteritinib and chemotherapy. At the time of data cut-off, 169 patients had been randomized to gilteritinib and 168 had received at least one dose.

Table 21: Study 0301 - Demographic Characteristics of the Primary Efficacy Analysis

Demographic Parameters	Gilteritinib (N=169)	Chemotherapy (N=86)	Total (N=255)
Sex			
Male	83 (49%)	38 (44%)	121 (47%)
Female	86 (51%)	48 (56%)	134 (53%)
Age			
Mean years (SD)	58.5 (14.9)	55.8 (15.8)	57.6 (15.2)
Median (years)	60	58	60
Min, max (years)	20, 84	19, 79	19,84
Age Group			
<65 years	102 (60%)	54 (63%)	156 (61%)
≥65 years	67 (40%)	32 (37%)	99 (39%)

Demographic Parameters	Gilteritinib (N=169)	Chemotherapy (N=86)	Total (N=255)
Race			
White	95 (56%)	57 (66%)	152 (60%)
Black or African American	12 (7%)	3 (3%)	15 (6%)
Asian	51 (30%)	19 (22%)	70 (27%)
Other[1]	11 (7%)	7 (8%)	18 (7%)
Ethnicity			
Hispanic or Latino	8 (5%)	1 (1%)	9 (4%)
Not Hispanic or Latino[2]	161 (95%)	85 (99%)	246 (96%)
Region			
United States	85 (50%)	37 (43%)	122 (48%)
Rest of the World	6 (4%)	4 (5%)	10 (4%)
Europe	30 (18%)	28 (33%)	58 (23%)
Asia	48 (28%)	17 (20%)	65 (25%)

[1] Includes Native Hawaiian or other Pacific Islander, Native American/Alaskan Native and patients listed as other, unknown, or with no race listed
[2] Includes patients listed as not Hispanic or Latino, unknown, or with no ethnicity listed
Source FDA analysis

Other Baseline Characteristics (e.g. disease characteristics, important concomitant drugs)

Of patients in the safety population and receiving gilteritinib, 147 had a FLT3-ITD mutation only, 13 had FLT3-TKD only, and five patients had both FLT3-ITD and FLT3-TKD. Four patients in the RAS were negative for FLT3 mutational status by central diagnosis but positive per local lab and were started on treatment prior to central testing due to rapidly progressive disease. One of these four patients was later identified as FLT3 negative on local testing after reassessment. One patient with negative central FLT3 was discontinued prior to starting treatment and was not included in the safety data set. Of those planned for chemotherapy, FLT3-ITD alone was detected in 78, FLT3-TKD in 7, and one was unknown/missing.

Prior to randomization, the chemotherapy that would be given to the patient if they were in the chemotherapy arm was chosen by the investigator. Actual chemotherapy given to those in the chemotherapy arm was azacitidine (22), low dose ARA-C (8), FLAG-IDA (33), and MEC (23).

In the gilteritinib arm, two patients had prior exposure to midostaurin and none had prior exposure to quizartinib. Of the patients who received gilteritinib, 103 (73%) had received some form of 7+3 regimen and 47 had received high dose ARA-C, with or without anthracyclines. Seventy (49%) patients randomized to gilteritinib had CR after prior therapy and 57 (40%) had treatment failure.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment details are available only for the gilteritinib cohort at this time. The relative dose intensity for patients receiving gilteritinib was near to 100%, with a range of 39% to 159%. Dose interruptions were observed in 146 (87%) of patients and 40 (24%) required dose decreases.

Efficacy Results – Primary Endpoint

In this review, the determination of efficacy was based on the co-primary endpoint of the CR/CRh rate, and the duration of CR/CRh (DOR), and the rate of conversion from transfusion dependence to transfusion independence in the pivotal study of 0301. The median follow-up was 4.7 months (range: 2.9 to 16.1 months). The efficacy results are shown in **Table 22**.

CR/CRh Rate
Of the 142 patients included in the RAS, 31 patients (21.8%; 95% CI: 15.3%, 29.5%) achieved a CR/CRh prior to HSCT. The lower bound of the 95% exact CI exceeded the prespecified threshold of 12%.

Table 22: Study 0301 - Summary of CR/CRh and Duration of CR/CRh in the Gilteritinib Arm

Parameter	Gilteritinib, 120 mg, (N=142)
CR/CRh	
n (%); (95%CI)	31 (21.8%); (15.3%, 29.5%)
Duration of Response: Median (range); months	4.4; (0+, 15.8+)
CR	
n (%); (95%CI)	18 (12.7%); (7.7%, 19.3%)
Duration of Response: Median (range); months	8.6; (0.6,+ 13.8+)
CRh	
n (%); (95%CI)	13 (9.2%); (5.0%, 15.1%)
Duration of Response: Median (range); months	4; (0+, 15.8+)

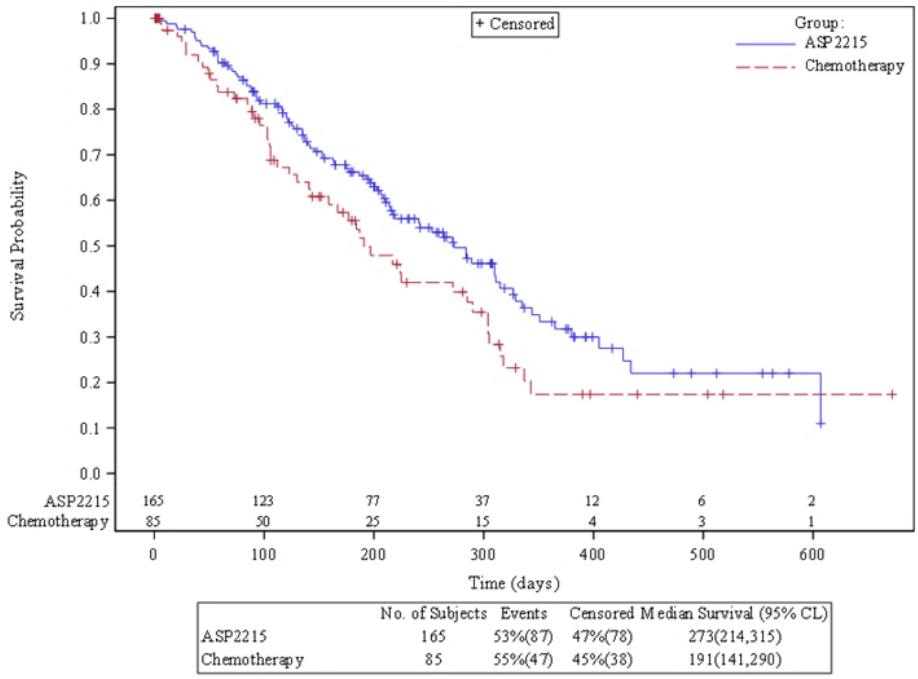
+ indicates censoring

For patients who achieved a CR/CRh, the median time to first response was 3.8 months (range: 0.9 to 9.7 months). The CR/CRh rate was 29 of 126 in patients with FLT3-ITD and 0 of 12 in patients with FLT3-TKD. Five patients with both ITD and TKD were included in the ITD group. Three patients with both ITD and TKD had responses, including two with CR. Among the 107 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 34 (31.8%) became independent of RBC and platelet transfusions during any 56-day postbaseline period. For the 34 patients who were independent of both RBC and platelet transfusions at baseline, 18 (52.9%) remained transfusion-independent during any 56-day postbaseline period.

After removal of the requirement that patients need be on study for at least 112 days past the first dose of gilteritinib or randomization, 33 of the 169 ITT patients achieved a CR/CRh in the gilteritinib arm, which is 19.53% with 95%CI (13.6%, 25.5%). The result is consistent with the result based on RAS dataset.

Overall Survival
Even though no analysis was planned for the co-primary endpoint of OS at the first interim analysis, the Kaplan-Meier plot in **Figure 11** demonstrates patients in the gilteritinib arm also had a higher median OS compared with patients in chemotherapy arm based on the unplanned interim look of the data. The hazard ratio is 0.75 with 95% CI (0.50, 1.03), which is for informational purpose only.

Figure 11: KM Plot for OS in Study 0301 (unplanned interim look)



Source: reviewer's analyses

For the primary endpoint of CR/CRh rate, only responses prior to HSCT are counted. In the calculation of Duration of Remission, deaths among patients who died without report of relapse are treated as events.

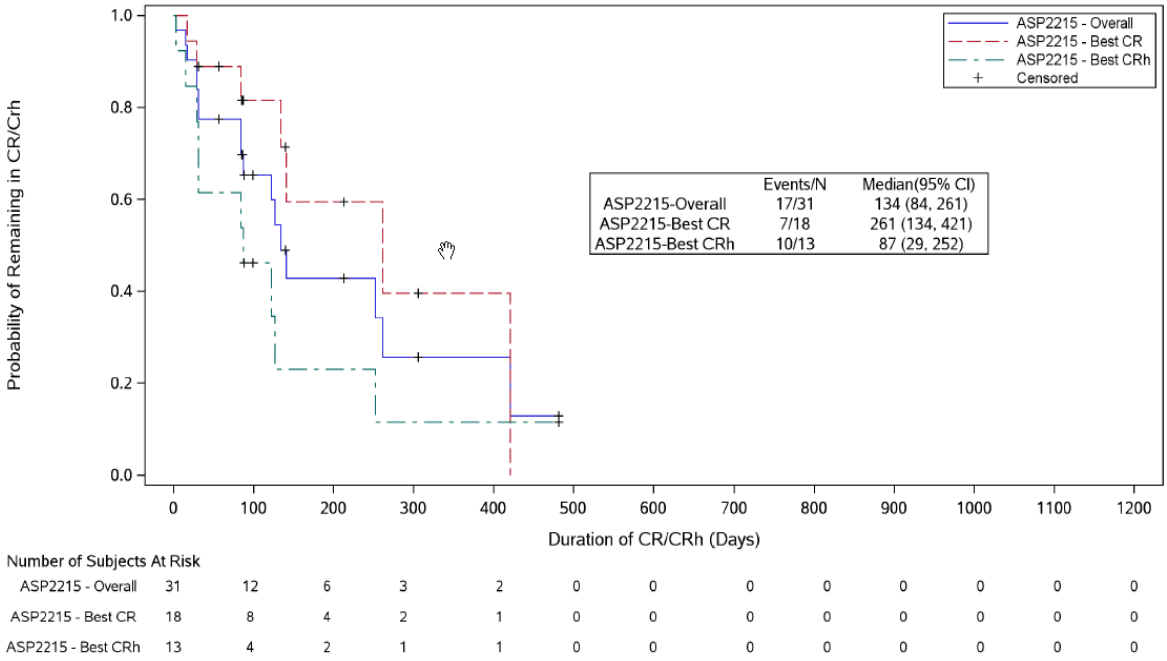
Statistical Reviewer Comment:
The presentation of OS curves is based on unplanned interim look, since the number of events for the OS analysis has not been met yet. The data was submitted by a third party.

Efficacy Results – Secondary and Other Relevant Endpoints

Duration of CR/CRh

As shown in **Figure 12**, among the 31 patients (21.8%) who achieved CR/CRh, the estimated median duration of remission was 4.4 months (95% CI: 2.8, 8.6). Among the 18 patients who achieved CR and the 13 patients who achieved CRh, the estimated median duration of response was 8.6 months (95% CI: 4.4, 13.8) and 2.9 months (95% CI: 1, 8.3), respectively.

Figure 12: Kaplan-Meier Plot of Duration of CR/CRh in Gilteritinib Arm of Study 0301



Source: reviewer's analyses

Statistical Reviewer Comment:

The KM-plots based on the responder only (CR or CRh) show that patients with a best response of CR appear to demonstrate longer DOR, as compared with patients who had either CR or CRh or CRh only.

Subpopulations

Subgroup Analysis of CR/CRh Rate

The CR/CRh rate results by age, gender, race, and geographic regions are presented in the forest plot shown in **Table 23**. All results from the subgroups appear consistent, except in the Black subgroup, but it may be due to the small sample size. Due to the nature of subgroup analyses and small sample sizes, interpretation of subgroup results should be interpreted with caution.

Table 23: Study 0301 - Response Rate by Age, Gender, Race and Geographic Region

Subgroup	CR/CRh (%)	95% CI
Age		
<65 (n=88)	17 (19.3)	(11.7, 29.1)
≥65 (n=54)	14 (25.9)	(15.0, 39.7)
Gender		
Male (n=66)	11 (16.7)	(8.6, 27.9)
Female (n=76)	20 (26.3)	(16.9, 37.7)
Race		
White (n=85)	23 (27.1)	(18.0, 37.8)
Black (n=11)	1 (9.1)	(0.2, 41.3)
Asian (n=37)	7 (18.9)	(8.0, 35.2)
Other (n=9)	0 (0)	(NA, NA)
Region		
North America (n=78)	17 (21.8)	(13.2, 32.6)
Europe (n=28)	8 (28.6)	(13.2, 48.7)
Asia (n =36)	6 (16.7)	(6.4, 32.8)

Source: reviewer's analyses

Efficacy Results – Secondary or Exploratory Clinical Outcome Assessment Endpoints

No patient-reported outcome (PRO) data were submitted.

8.1.2 2215-CL-0101

A Phase 1/2 Open-Label, Dose Escalation Study Investigating the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ASP2215 in Patients with Relapsed or Refractory Acute Myeloid Leukemia

INVESTIGATIONAL PLAN

Trial Design and Endpoints

This trial was a phase 1 dose escalation and dose expansion study of gilteritinib in patients with R/R AML consisting of two dosing cohorts. In Cohort 1 an accelerated titration design was used, starting at 20 mg and doubling the dose (increasing by 2 dose levels) until a DLT or a second grade 2 AE (observed in 2 subjects) judged at least possibly related was observed. At that time, the study moved to a modified 3+3 design. After dose level 5, subsequent dose levels were to be tested using the 3+3 design. A dose level was expanded in Cohort 2 if at least one subject in Cohort 1 achieved CR, CRp, or CRi, with a minimum of three patients to be enrolled in the dose expansion at this dose level. In the absence of a CRc, if the median decrease in FLT3 phosphorylation was ≥90%, in at least three subjects on a dose level, that dose level was to be expanded. After a decision was made to dose escalate or stop, up to 17 further patients were enrolled on the given dose level. Further dose expansion cohorts of up to 40 patients were

planned for 120 mg and above cohorts, once safety was determined in the dose escalation cohort. For the latter dose expansion cohorts, only patients with FLT3-positive AML were enrolled.

Primary endpoints:

- Safety and tolerability (MTD)
- Pharmacokinetics

Secondary endpoints:

- Efficacy in AML
    - CR rate
    - CRc rate (CR+CRp+CRi)
    - Best response rate (CRc + partial response)
    - Duration of response
    - OS
    - EFS
    - Leukemia-free survival
- Pharmacokinetics of gilteritinib and the effect of CYP3A4 inhibitors
- Pharmacokinetics of midazolam, potential induction of CYP3A4 by gilteritinib
- Pharmacokinetics of cephalexin, MATE1 inhibition by gilteritinib

Study Population

Key inclusion criteria:

- Age 18 or older
- Morphologically documented primary or secondary AML which fulfills one of the following:
    - Refractory to at least one cycle of induction chemotherapy
    - Relapsed after achieving remission with a prior therapy
- ECOG PS ≤2
- Adequate organ function
- For MATE sub-study documented FLT3 mutation positive AML

Key exclusion criteria:

- Acute promyelocytic leukemia or chronic myelogenous leukemia in blast crisis
- Active tumors other than AML or MDS
- Nonhematologic toxicity ≥grade 2
- HSCT and meets any of the following:
    - Within 2 months of transplant
    - Clinically significant GVHD
    - Grade 2 or greater toxicity from transplant
- Any of the following cardiac issues:
    - NYHA class III or IV heart failure

- QTc>450 based on Fridericia correction
- Long QT syndrome

Statistical Analysis Plan

Definitions of Analysis Sets:
Full Analysis Set (FAS): consisted of all patients who were enrolled and received at least one dose of study drug and who have at least one post-treatment data point. Efficacy analysis is based on the 56 patients in FAS, who are in the 120 mg dose group and FLT3 mutation positive.

Safety Analysis Set (SAF): consisted of all patients who received at least one dose of study drug. The SAF will be used for summaries of demographic and baseline characteristics and all safety and tolerability related variables.

Analysis of Efficacy Endpoints:

Efficacy endpoints of ASP2215 in AML are secondary endpoints of the study.

CR rate: Defined as the number of subjects with CR divided by the number of subjects in the analysis population. Subjects with unknown or missing response, or who provide no information on response at the end of study will be treated as nonresponders and will be included in the denominator when calculating rates.

Complete remission with partial hematologic recovery (CRh) rate: Defined as the number of subjects who achieve CRh at any of the postbaseline visits and do not achieve best response of CR divided by the number of subjects in the analysis population.

Complete remission and complete remission with partial hematologic recovery (CR/CRh) rate: Defined as the number of subjects who achieve either CR or CRh at any of the postbaseline visits divided by the number of subjects in the analysis population.

Overall survival (OS): The time from the date of first dose of study drug until the date of death from any cause (death date – first dose date +1). For a subject who is not known to have died by the end of study follow-up, OS is censored at the date of last contact (date of last contact – first dose date +1).

Determination of Sample Size*:*
The sample size is not based on a statistical power calculation. The total number of subjects estimated for enrollment is between 2 and 270 subjects.

Protocol Amendments

Substantial amendment 1:

- Primary objective changed to determination of MTD rather than determining DLTs
- Clarifications to the description of the dose escalation and dose expansion cohorts
- Updates to the inclusion and exclusion criteria
- Added text prohibiting AML treatment during therapy with gilteritinib except for HU to keep blast count below 50K
- Added grade 3 nonhematologic toxicity, grade 3 nausea, and hematologic toxicity related to prolonged myelosuppression to DLTs
- Clarified description of "no clinical benefit" to indicate that subjects should be taken off treatment if no response after 2 cycles
- Removed subject dosing diary for cycle 1
- Updated continual reassessment method to Bayesian logistic regression modeling
- Updated primary endpoint to reflect tolerability as endpoint
- Updated schedule of assessments and flow chart
- Updated packaging and labeling
- Updated dose modification guidelines
- Added thyroid function to chemistry panel
- Updated list of prohibited medication

Substantial amendment 2:

- Pharmacodynamic parameters moved from secondary to exploratory endpoints.
- Removal of STAT5 and addition of S6 phosphorylation to PD parameters
- Addition of EFS to secondary endpoints
- Updating of study design to a modified 3+3 design to allow testing all dose levels based on assessment of PK data
- Subject replacement guidelines added
- Allowable collection window for PK, PD, and PIA samples and ophthalmologic assessment added
- Bone marrow biopsy changed from optional to required
- Clarified that voriconazole is a CYP3A4 inhibitor to be used in the Cohort 2 schedule of assessments 2B
- Clarified midazolam usage in DDI study Cohort 2D
- Schedule of assessments and footnotes updated
- Introduction with literature information updated
- Updated assignment and allocation instructions
- Moved and updated missed dose instructions
- Clarified treatment compliance deviations and treatment schedule after dose escalation
- Updated laboratory assessment table
- Allowed use of Snellen charts for visual acuity
- Updated section 5.8, total blood volume
- Updated FAS definition to include all patients who have at least one post-treatment data point
- Added ophthalmologic assessment to safety analysis

- Clarified safety monitoring review

Substantial amendment 3:

- Concomitant medication restrictions and requirements updated (higher dose of HU to reduce blast count allowed)

Substantial amendment 4:

- Updated study design for Cohort 2 to allow participation without DDI component for patients with contraindication to voriconazole or midazolam and to allow voriconazole DDI study to be conducted at the next lowest dose level if original level is closed before 12 patients participate
- Allowable collection window for screening CT/CXR added
- Updated table 2E: post treatment schedule of assessments
- Clarified CYP3A4 inhibitor use in Cohort 2 to restrict use only in cohorts 2B and 2D
- Updated test drug dosage forms and specifications
- Limit DDI study participation to U.S.

Substantial amendment 5:

- Updated number of subjects
- Updated study design for Cohort 2
- Added allowable collection window for screening marrow
- Modified rescreening restrictions
- Removed waiting period for immunosuppressive therapies

Substantial amendment 6:

- Modified discontinuation criteria to allow subjects experiencing clinical benefit but not response to continue treatment
- Updated study design to allow re-enrollment of subjects who discontinued for reasons other than toxicity or disease progression

Substantial amendment 7:

- Updated number of subjects
- Updated post-treatment contraception timelines
- Updated restrictions for drugs that inhibit or induce P-gp and substrates of MATE1 and added precautions for medications metabolized by other CYP enzymes, P-gp, and BCRP
- Updated to allow treatment with gilteritinib after HSCT
- Added safety data from prior experience to protocol
- Allowed multiple dose escalations for Cohort 2 subjects
- Clarified allowable dose interruptions
- Added aldolase to chemistry panel for central lab
- Added language that additional testing for metabolites of gilteritinib may be performed

Substantial amendment 9 (amendment 8 country specific for DE and FR)

- MATE1 substrate drug-drug interaction sub-study added for U.S. only
- Removal of ERG examination
- Clinical safety update

- Bone marrow required after CRc every 3 cycles x1 year then as needed clinically and at end of study
- Changed transfusion independence from 4 weeks to one week without transfusion

Substantial amendment 10:

- Removal of requirement for 15 evaluable patients in the MATE1 study
- Modify exclusion criteria to exclude patients with QTcF>450 msec and exclude patients with long QT syndrome
- Added day 9 ECG
- Clarified that mean QTc is based on central reading
- Added dose modifications for QT prolongation
- Revised dose reduction language to withhold drug for any grade 3 AE that is not a constitutional symptom irrespective of length of event

Substantial amendment 11:

- Revised study design to allow participants to continue to receive treatment in rollover study if eligible
- Updated concomitant medication guidelines to forbid use of strong CYP3A inducers, strong inducers or inhibitors of P-gp, and drugs that target 5HT1R and 5HT2BR receptors; drugs known to prolong QT should be used with caution only

STUDY RESULTS

Compliance with Good Clinical Practices

The study was conducted under a U.S. IND application, in accordance with ICH guidelines for GCP, the principles expressed in the Declaration of Helsinki, and consistent with the CFR, Title 21. The study protocols and informed consent documents were reviewed by local IRB/IEC as required by regulations prior to implementation at practicing institutions.

Financial Disclosure

A summary of the financial disclosures for Study 0101 is provided in the appendix (section 14.2). The Applicant reported that no investigators involved in this study had disclosable financial interests with the sponsor.

Data Quality and Integrity

Data from Study 2215-CL-0101 was provided electronically with ADaM and STDM formats. Data quality appeared to be acceptable in general. The result of this review is based on the Data Cutoff Date of 08/04/2017.

Patient Disposition

A total of 347 patients were consented for the study. Of these, 25 were treated in the dose escalation phase and 240 in the dose expansion phase, including 5 who were re-enrolled onto

the study, with a total of 252 unique patients receiving at least one dose of the study drug and eight who were registered but never received drug. At the time of data cut-off, eight patients continued to receive treatment with the study drug (5 at the 120-mg dose level, 3 at the 200-mg dose level) and an additional 20 were in long-term follow up. The most common reason for treatment discontinuation was progressive disease (85 patients), lack of efficacy (44), death (37), and AEs (35). Discontinuation due to AE was noted in 23 (20.9%) of patients at 200 mg and 5 (6.8%) of patients at 120 mg. Fifty-six of the patients, who are in 120 mg and FLT3 mutation positive, will be included in the efficacy analysis.

Protocol Violations/Deviations

Protocol deviations were noted in 23/265 (8.7%) patients registered. Protocol violations included two patients who did not satisfy entry criteria, one due to recent use of an experimental drug, the other due to poor performance status. Seven patients were initially reported to have received at least one incorrect dose of the study drug. However, review of the data showed that one report was in error and that this patient, enrolled at the 20-mg dose, had received all doses according to the protocol. Fourteen patients received excluded concomitant medications, including methotrexate and hydroxyurea (in a dose or time period that exceeds exclusion criteria.)

Demographic Characteristics

Demographic characteristics are described in **Table 24**. Of note, FLT3-negative patients were more likely to be male, slightly older on average, more likely to be over 65, and more likely to be of nonwhite racial origin.

The trial was conducted in the United States, Germany, and Italy, with the majority of patients coming from the United States.

Table 24: Study 0101 - Demographic Characteristics of the Primary Efficacy Analysis

	Safety analysis set		**Total**
Demographic Parameters	**FLT3+ (N=194) (77%)**	**FLT3- (N=58) (23%)**	**(N=252) (100%)**
Sex			
Male	92 (47%)	37 (64%)	129 (51%)
Female	102 (53%)	21 (36%)	123 (49%)
Age			
Mean years (SD)	57.8 (15.2)	63.4 (14.0)	59.0 (15.1)
Median (years)	60.0	66.5	62.0
Min, max (years)	21-87	29-90	21-90

Demographic Parameters	Safety analysis set		Total (N=252) (100%)
	FLT3+ (N=194) (77%)	FLT3- (N=58) (23%)	
Age Group			
<65 years	121 (62%)	20 (34%)	141 (56%)
≥65 years	73 (38%)	38 (66%)	111 (44%)
Race			
White	171 (88%)	42 (72%)	213 (85%)
Black or African American	9 (5%)	7 (12%)	16 (6%)
Asian	7 (4%)	0	7 (3%)
Other	7 (4%)	9 (16%)	16 (6%)
Ethnicity			
Hispanic or Latino	9 (5%)	2 (3%)	11 (4%)
Not Hispanic or Latino	185 (95%)	56 (97%)	241 (96%)

Source: reviewer's analysis

Other Baseline Characteristics

Of the subjects who were FLT3 mutation positive, 178 were FLT3-ITD mutation positive by local testing and 33 were FLT3-TKD positive (including those with both mutations). Central testing showed 160 FLT3-ITD positive and 36 FLT3-TKD positive, with 4 samples not available for central testing. Samples were considered FLT3 positive if any testing result was positive.

All patients had prior AML therapy, with 150 receiving some form of 7+3 regimen, 23 receiving an anthracycline plus high-dose cytarabine, 34 MEC, 26 FLAG-IDA, and 220 other regimens. A total of 153 patients (60.7%) had previously achieved a CR to therapy, with a median duration of 180 days. One hundred and eleven (44%) of patients had received at least three prior lines of therapy, including 65 (25.8%) who had received prior TKI therapy, including therapy with quizartinib in seven patients.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was high for the majority of patients for which it was documented, with 111 patients having >80% compliance and no patients with <50% compliance documented. However, compliance data were missing for 134 patients.

Efficacy Results – Primary Endpoint

CR/CRh Rate

Of the 56 patients, whose disease was positive for the FLT3 mutation by central testing by FLT3 CDx, 10 patients (17.9%; 95% CI: 8.9%, 30.4%) achieved a CR/CRh prior to HSCT.

Table 25: Summary of CR/CRh and Duration of CR/CRh in the Gilteritinib Arm of Study 0101

Parameter	Gilteritinib, 120 mg, (N=56)
CR/CRh	
n (%); (95%CI)	10 (17.9%); (8.9%, 30.4%)
Duration of Response: Median (range); months	12.3; (0.5, 36.0+)
CR	
n (%); (95%CI)	4 (7.1%); (2.0%, 17.3%)
Duration of Response: Median (range); months	NE; (12.3, 36.0+)
CRh	
n (%); (95%CI)	6 (10.7%); (4.0%, 21.9%)
Duration of Response: Median (range); months	1.8; (0.5, 27.9+)

+ indicates censoring
Source: reviewer's analysis

The efficacy results of the Study 0101 are shown in **Table 25**. Among the 52 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 11 (21.2%) became independent of RBC and platelet transfusions during any 56-day postbaseline period. For the four patients who were independent of both RBC and platelet transfusions at baseline, three (75%) remained transfusion-independent during any 56-day postbaseline period. The CR/CRh rate was 10 of 50 in patients with FLT3-ITD and 0 of 6 in patients with FLT3-TKD. Patients with both ITD and TKD are included in the ITD population. All patients with CR/CRh were ITD alone.

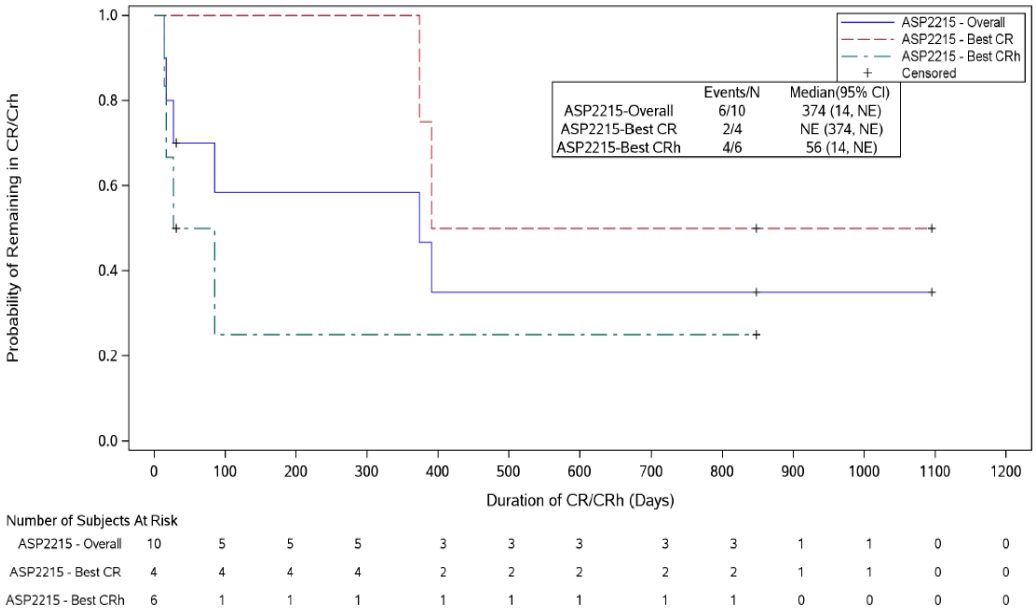
For the primary endpoint of CR/CRh rate, only responses prior to HSCT are counted. In the calculation of Duration of Remission, deaths among patients who died without report of relapse are treated as events.

Efficacy Results – Secondary and Other Relevant Endpoints

Duration of CR/CRh

As shown in **Figure 13**, of the 10 patients (17.9%) who achieved CR/CRh, the estimated median duration of remission was 374 days (95% CI: 14, NE). For the four patients who achieved CR and the six patients who achieved CRh, the estimated median duration of response was NE days (95% CI: 374, NE) and 56 days (95% CI: 14, NE), respectively.

Figure 13: Kaplan-Meier Plot of Duration of CR/CRh in Study 0101



Source: reviewer's analysis

Statistical Reviewer Comment:
It is noted that the plots are based on responders only. See comments for the Kaplan-Meier Plot of Duration of CR/CRh in gilteritinib arm of Study 0301.

Efficacy Results – Secondary or Exploratory Clinical Outcome Assessment Endpoints

No PRO data were submitted.

Additional Analyses Conducted on the Individual Trial

Study 010 included 174 patients who had a FLT3 mutation retrospectively using the proposed companion diagnostic, received at least one dose of study drug, and had at least one postbaseline assessment (FAS population). Patients in this group had a median age of 59 years (range: 21 to 87 years), and 36% were at least 65 years old. Among the 174 patients, 45% were male and 55% were female; 89% were white, 5% were black, 4% were "other" race, and 3% were Asian; and 4% were Hispanic or Latino. The CR/CRh by dose cohort is shown in **Table 26**.

Table 26: Study 0101 – CR/CRh by Dose Group

Dose Group		**CR/CRh Achieved[a]**	
	N	n (%)	[95% CI]
<120 mg/day	33	3 (9.1%)	[3.1, 23.6]
120 mg/day	54	10 (18.5%)	[10.3, 30.8]
>120 mg/day	87	13 (14.9%)	[8.9, 23.9]

[a] Using FDA-adjudicated responses
Source: reviewer's analysis

Clinical TL Review Comment:
The results suggest that there is no efficacy benefit with use of doses higher than 120 mg.

8.1.3 2215-CL-0102

A Phase 1 Open-Label, Dose-Escalation Study Investigating the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ASP2215 in Japanese Patients with Relapsed or Refractory Acute Myeloid Leukemia

INVESTIGATIONAL PLAN

Trial Design and Endpoints

Trial 2215-CL-0102 was a dose escalation and dose expansion study of the tolerability of gilteritinib in the Japanese population. A Bayesian continual reassessment method was used for dose escalation, with a minimum of one subject in the first cohort (20 mg) and three subjects in all subsequent cohorts.

Study objectives
Primary objectives:

- Assess safety and tolerability of gilteritinib
- Determine MTD based on the onset of DLT and/or determine the recommended dose for the next phase

Secondary objectives:

- Assess the antileukemic activity of various doses of gilteritinib
- Determine the pharmacokinetic parameters of gilteritinib

Key inclusion criteria:

- Age 18 or older
- Documented AML which is refractory to prior induction chemotherapy or relapsed after achieving remission with a prior therapy
- At least 14 days since last antineoplastic agent except for HU to control blast count
- ECOG PS of 0 to 2
- Adequate organ function and ability to swallow pills

Key exclusion criteria:

- Acute promyelocytic leukemia or BCR-ABL positive leukemia
- Active malignancy other than AML
- Symptomatic CNS leukemia
- Cardiac impairment including:
    - Complete LBBB
    - Cardiac pacemaker
    - Long QT syndrome
    - Mean QTcF of >450 on screening ECG

  - RBB with left anterior hemiblock
  - Angina or MI within 3 months of study drug administration
  - CHF of NYHA class 3 or 4 or LVEF <45%
  - Low potassium or magnesium
- HSCT within 2 months or clinically significant GVHD or persistent nonhematologic toxicities of grade 2+ from transplant
- Persistent grade 2+ toxicities from prior treatment
- Requirement for use of concomitant drugs that were strong inhibitors or inducers of CYP3A4 or P-gp or substrates of MATE1 or drugs that target 5HT1R, 5HT2BR or sigma nonspecific receptors; exceptions would be considered for drugs considered absolutely essential for which no interchangeable drugs were available (MATE1 restriction removed by later amendment)

Statistical Reviewer Comment:
Because the study was not studied based on the intended dose level, the efficacy analysis results will not be considered for labeling purposes.

Protocol Amendments

Amendment 1:
- Acceptable time ranges for urine sampling for PK analysis updated

Amendment 2:
- Addition of the statement that a marrow does not need to be performed at screening if one was performed within 12 days prior to the start of treatment
- Clarification of definition of SAE
- Removal of diarrhea as one of the common SAE listed in appendix 7

Amendment 3:
- Removal of treatment with MATE1 substrates from exclusion criteria

Amendment 4:
- Extension of planned study period

STUDY RESULTS

Compliance with Good Clinical Practices

The study was conducted in accordance with ICH guidelines for GCP, the principles expressed in the Declaration of Helsinki. The study protocols and informed consent documents were reviewed by local IRB/IEC as required by regulations prior to implementation at practicing institutions.

Financial Disclosure

A summary of the financial disclosures for Study 0102 is provided in the appendix. The Applicant reports no investigators involved in the study had disclosable interests.

Data Quality and Integrity

Data from Study 2215-CL-0102 was provided electronically with ADaM and STDM formats. Data quality appeared to be acceptable in general. The result of this review is based on the Data Cutoff Date of 06/27/16.

Patient Disposition

Twenty-seven patients were enrolled in the study, of whom 24 received study drug. All patients had discontinued treatment by the time of data cut-off. The reasons for treatment discontinuation were PD (15), AE (6), withdrawal by patient (2), and lack of efficacy (1). Eleven patients had completed the 28-day follow-up period and 13 discontinued the study before completing the follow-up. The most common reason for study discontinuation was PD. One patient death was reported. Treatment discontinuation due to AE was more common in the higher doses, with two patients each withdrawing for AE in the 200-mg and 300-mg dose levels.

Protocol Violations/Deviations

A single protocol deviation was reported, with the patient in question having received an excluded concomitant medication (haloperidol). The patient was in the 200 mg dosing group.

Demographic Characteristics

The study was conducted at five sites in Japan. All patients involved were Asian. The age range for patients was much smaller compared to 0101, with all patients being at least 60 at time of enrollment.

Table 27: Demographic characteristics of the primary efficacy analysis

Characteristic	FLT3 status		Total (N=24*)
	FLT3+ (N=5) (21%)	FLT3- (N=16) (79%)	
Sex			
Male	3 (60%)	10 (63%)	15 (63%)
Female	2 (40%)	6 (38%)	9 (38%)
Age			
Mean years (SD)	72.0 (7.0)	71.4 (5.6)	70.7 (6.3)
Median (years)	71	70	71
Min, max (years)	64, 81	63, 81	60, 81
Age Group			
<65 years	1 (20%)	1 (6%)	4 (17%)
≥65 years	4 (80%)	15 (94%)	20 83%)

* Includes three patients with missing or invalid tests
Source: reviewer's analysis

Other Baseline Characteristics

ECOG PS was 0 for 12 patients, 1 for 11 patients, and 2 for one patient.

FLT3 mutational status was negative for 16 patients, positive for 5, and missing or invalid for 3. Of those with FLT3 mutations, three were FLT3-ITD and two FLT3-TKD positive.

AML with myelodysplastic changes was the most common genetic abnormality, recorded in five patients. AML with t(8;21)(q22;q22) was noted in two patients, and AML with inv(16)or t(16;16) in one each. Information on genetic abnormalities was missing for 15 patients.

All patients had received prior chemotherapy. Of these, 15 had a prior CR, 1 PR, and 8 PD or NR. Fifteen patients had received some variant of 7+3 regimen, 4 high dose cytarabine, one gemtuzumab ozogamicin, 4 MEC, and 23 another form of chemotherapy. Two had undergone HSCT.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance in the first cycle was mixed, with three patients receiving <50% of planned dose, 6 receiving 50% to 80%, and the remainder (15) receiving >80%. Both patients assigned to the 300-mg dose had a compliance of 50% to 80% for the first cycle. Treatment compliance for the whole study (i.e., all exposure from the date of first dosing to day of last dosing) was 100% in all but one patient, in whom the compliance was unknown. Thus, the majority of the low receipt in the first cycle was due to early termination of treatment.

8.2 Integrated Review of Effectiveness

8.2.1 Assessment of Efficacy Across Trials

Methods

The Applicant proposed the indication "for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test." The clinical development program included three single-arm trials with efficacy data for patients with R/R AML (Study 0101, 0102 and 0301), one of which (Study 0101) included a dose-escalation portion. These three studies are described in Section 8.1.

The primary efficacy endpoint for the first interim analysis of Study 0301 was the CR/CRh rate. Transfusion independence was an additional secondary endpoint to be reported only descriptively. Evaluation for response, including marrow examination, was required on C2D1, C3D1, D1 of every two subsequent cycles, at the end-of-treatment visit, and as indicated clinically. For subjects who achieved a response, the evaluation was to be repeated 1 month after the date of response, every three subsequent cycles, and when there was suspicion of relapse by blood examination. Complete blood counts were required on D1 of each cycle. The

schedule of efficacy assessments was similar in Studies 0101 and 0102. This frequency of efficacy assessments was considered adequate.

Clinical TL Review Comment:
For regulatory decision-making, FDA usually uses CR as an endpoint reasonably likely to predict clinical benefit. In acute leukemia settings without intent to cure, and especially when the new therapeutic has little toxicity, FDA has also considered using durable CR and CRh. The basis for this has been the observed treatment-induced transition to blood counts adequate to protect against infection and avoid transfusions for the short-term. Corroborating evidence, such as persistent transfusion-independence, provides support for durable CR and CRh. The intended population proposed by the Applicant is consistent with this setting, so durable CR/CRh and transfusion independence may reflect clinical benefit here, but the results will need to outweigh the risks.

Studies 0101 and 0102 did not include hypothesis testing for efficacy or justification for the sample size, so these studies are considered descriptive and provide only supportive information about the activity of gilteritinib. As described in Section 8.1.1, Study 0301 has a prespecified interim analysis to assess the CR/CRh rate in the first 141 patients in the gilteritinib arm after at least four cycles of therapy. The Applicant conducted the analysis in the first 142 patients (RAS population). The observed CR/CRh rate reported was 28.2% (95% CI: 20.9, 36.3), which met the prespecified objective of excluding a 12% CR/CRh rate, so the study outcome was considered positive. FDA calculated a CR/CRh rate of 21.8% (95% CI:15.3, 29.5).

Statistical Reviewer Comments: For Study 0301, the lower 95% CIs of the CR/CRh rates, both based on the applicant RAS population and the FDA adjudicated population, appear to rule out 12%. The median DORs were 4.9 and 4.6 months for applicant RAS population and the FDA adjudicated population, respectively.

Clinical TL Review Comment: Since Studies 0101 and 0102 were descriptive only, the results should not be included in labeling.

For FDA's analysis of efficacy, patients who did not fit the intended population based on FDA's adjudication were excluded. Specifically, the FDA Efficacy Analysis Population (EAP) consisted only of patients a) with AML that was relapsed or refractory, b) with confirmed FLT3 mutation using the proposed companion diagnostic (or bridged to the proposed companion diagnostic), and c) who were treated with gilteritinib 120 mg daily. FDA identified 138 patients in Study 0301 and 49 patients in Study 0101 who met these criteria. As described in Section 4.3, the FLT3 mutation eligibility criterion could not be confirmed for Study 0102, so this study is not considered further with regard to efficacy. The median age of the patients in the EAP was 60 years (range: 20 to 84 years) in Study 0301 and 59 years (range: 23 to 87 years). The median relapse number was 1 (range: 0 to 2) in Study 0301 and 1 (range: 0 to 3) in Study 0201. The remainder of the demographics of the EAP for Studies 0301 and 0101 are shown in **Table 28**.

Table 28: Efficacy Analysis Population – Demographics

Characteristic	Study 2215-CL-0301 (n=138)		Study 2215-CL-0101 (n=49)	
	N		N	
Age Category				
<65 years	85	62%	33	67%
≥65 years	53	38%	16	33%
≥75 years	19	14%	8	16%
Sex				
Male	64	46%	22	45%
Female	74	54%	27	55%
Race				
White	82	60%	43	88%
Asian	37	27%	1	2%
Black	10	7%	2	4%
Other or missing	7	5%	3	6%
Ethnicity				
Not Hispanic or Latino	127	94%	46	94%
Hispanic or Latino	6	4%	3	6%
Unknown or missing	2	1%	0	0%
ECOG Performance Status				
≥2	25	18%	13	27%
Region				
North America	74	54%	47	96%
Asia	36	26%	0	0%
Europe	28	20%	2	4%
FLT3 Mutation				
ITD	120	87%	41	84%
TKD	12	9%	4	8%
Both	5	4%	4	8%
Missing	1	1%	0	0%
Disease Status				
Primary refractory	56	41%	18	37%
Refractory relapse	0	0%	14	29%
Untreated relapse	82	59%	17	35%
Prior Relapses				
0	56	41%	18	37%
1	80	58%	22	45%
2 or more	2	1%	9	18%
Prior HSCT				
Yes	27	20%	16	33%

Source: FDA analysis

Clinical TL Review Comment:
It is noted that the FLT3 mutations identified by the proposed companion diagnostic are limited to FLT3-ITDs and the D835 and I836 TKD mutations. Moreover, as discussed in Section 5.3, the Applicant tested only the FLT3-ITD and D835Y TKD mutations for sensitivity in

nonclinical studies. As a result of these limitations, little can be said about expected efficacy for patients with other FLT3 mutations. In accordance with guidance, the intended population will be broad, based on the mechanism of action. With regards to patient selection in practice, it would likely be of interest to practitioners to have a greater understanding of the mutations that are activating and sensitive to gilteritinib. This can be accomplished as a post-marketing commitment.

Primary Endpoint

CR/CRh: The FDA clinical reviewer adjudicated all responses and identified subjects with a CR or CRh using only gilteritinib and no additional follow-on therapies. The final FDA-adjudicated responses are listed in the variable FDACRCH in the ISE data file adresp.xpt submitted 8/24/2018. The results for the EAP are show in **Table 29**.

Table 29: Efficacy Analysis Population – Primary Endpoint Results

Response	Study 2215-CL-0301 (n=138)	Study 2215-CL-0101 (n=49)
CR/CRh (n, %)	29 (21.0%)	9 (18.4%)
[95%CI]	(14.5%, 28.8%)	(8.8%, 32.0%)
Median DOR [95%CI]	4.6 mos [0.1, 15.8)	12.3 mos [0.5, 36.0+)
CR (n, %)	16 (11.6%)	3 (6.1%)
[95%CI]	(6.8%, 18.1%)	(1.3%, 16.9%)
Median DOR [95%CI]	8.6 mos [1.0, 13.8)	NE [12.3, 36.0+]
CRh (n, %)	13 (9.4%)	6 (12.2%)
[95%CI]	(5.1%, 15.6%)	(4.6%, 24.8%)
Median DOR [95%CI]	2.9 mos [0.1, 15.8]	1.8 mos [0.5, 27.9+]

Source: FDA analysis

The median time to first response was 3.6 mos (range: 0.9 to 9.6 mos) on Study 0301 and 1.0 mos (range: 1.0 to 9.2 mos) on Study 0101.

Clinical TL Review Comment:
The time to response apparently can be delayed. In view of this observation, labeling should reflect a minimum duration of treatment before concluding failure in patients whose condition does not require urgent cytoreduction.

The median follow-up times were 4.6 mos for Study 0301 and 7.3 mos for Study 0101. Thirty-seven (26.8%) patients on Study 0301 and 12 (24.5%) on Study 0101 went on to HSCT. The DOR using Kaplan-Meier estimates are shown in **Table 29.** Based on observed data, median DOR was 2.9+ mos (range, 0.1-15.8+ mos) for Study 0301 and 2.8 mos (range, 0.5-35.9+ mos) for Study 0101.

Clinical TL Review Comment:
Although the 95% CI lower bound for CR/CRh in the EAP for Study 0301 still excludes the prespecified null rate, the point estimate is rather modest, and both the Kaplan-Meier estimated and observed DORs are somewhat short. However, the minimum follow-up on Study 0301 was only 112 days, so the point estimates may not include late responders, and DOR may be longer with more follow-up.

Secondary and Other Endpoints

Transfusion Independence: Most patients on Studies 0301 and 0101 were dependent on red blood cell or platelet transfusions at baseline as a consequence of AML. **Table 30** shows that 23% to 31% of such patients became transfusion-independent for at least 56 days while on treatment with gilteritinib. Additionally, 50 to 53% of patients who were transfusion-independent at study baseline maintained transfusion independence for at least 56 days.

Table 30: Efficacy Analysis Population – Transfusion Independence

Baseline Status	**Study 2215-CL-0301**		**Study 2215-CL-0101**	
	N	**Transfusion Independent Postbaseline n (%)**	**N**	**Transfusion Independent Postbaseline n (%)**
Any Transfusions				
Dependent	106	33 (31.1%)	47	11 (23.4%)
Independent	32	17 (53.1%)	2	1 (50.0%)
RBC Transfusions				
Dependent	100	30 (30.0%)	47	13 (27.7%)
Independent	38	21 (55.3%)	2	2 (100%)
Platelet Transfusions				
Dependent	91	30 (33.0%)	41	12 (29.3%)
Independent	47	31 (66.0%)	8	4 (50.0%)

Source: FDA analysis

Clinical TL Review Comment:
Achieving independence of transfusions represents a notable palliative effect of gilteritinib for patients with R/R FLT3-mutated AML who seek only quality of life in the short term.

FDA also assessed consistency between CR/CRh and transfusion-independence as described above. As displayed in **Table 31**, patients who achieve CR or CRh have a numerically higher rate of transfusion-independence, confirming internal consistency.

Table 31: Assessment for Consistency Between Response and Clinical Outcomes

Outcome	Response Achieved[a]		
	CR (n=19)	CRh (n=19)	Less than CR/CRh (n=149)
Transfusion-independence	17 (89%)	13 (68%)	32 (21%)

[a] Using pooled population from Studies 0101 and 0301
Source: FDA analysis

Subpopulations

Table 32 shows the subgroup analysis of CR/CRh rate for the EAPs pooled from Studies 0301 and 0101. The CR/CRh rates were consistent across all subgroups, with the exception of race and FLT3 mutation type.

Table 32: Efficacy Analysis Population – Efficacy by Subpopulation

Characteristic	N[a]	CR/CRh n (%)
Age		
<65 years	118	21 (17.8%)
≥65 years	69	17 (24.6%)
≥75 years	27	5 (18.5%)
Sex		
Male	86	11 (12.8%)
Female	101	27 (26.7%)
Race		
White	125	31 (24.8%)
Asian	38	7 (18.4%)
Black	12	0
Other or missing	12	0
Ethnicity		
Not Hispanic or Latino	173	37 (21.4%)
Hispanic or Latino	9	1 (11.1%)
Unknown or missing	5	0
ECOG Performance Status		
0-1	149	28 (18.7%)
≥2	38	10 (26.3%)
Region		
North America	121	24 (19.8%)
Asia	36	6 (16.7%)
Europe	30	8 (26.7%)
FLT3 Mutation		
ITD	161	35 (21.7%)
TKD	18	0
Both	8	3 (37.5%)

Characteristic	N[a]	CR/CRh n (%)
Disease Status		
Primary refractory	74	14 (18.9%)
Refractory relapse	14	2 (14.3%)
Untreated relapse	99	22 (22.2%)
Prior Relapses		
0	74	14 (18.9%)
1	102	21 (20.6%)
2 or more	11	3 (27.3%)
Prior HSCT		
No	144	26 (18.1%)
Yes	43	12 (27.9%)

[a] Using pooled FLT3+ population from Studies 0101 and 0301
Source: FDA analysis

Clinical TL Review Comment:
The lack of any response in black patients (0/12) or in patients with a TKD mutation (0/18) does not necessarily indicate a lack of efficacy, since the numbers of patients in these groups are small. In both cases, the upper 95% confidence interval bound (24% and 19%, respectively) still includes the possibility of CR/CRh rates similar to the rest of the EAP. The uncertainty can be addressed with subgroup analyses after additional accrual as planned.

Persistence of Effect

The duration of response is discussed above.

Additional Efficacy Considerations

Dose Selection

The effect of gilteritinib starting dose on achievement of CR/CRh was assessed in the Study 0101, which included dose escalation and dose expansion phases. As shown in Section 8.1.2 above, the starting dose of 120 mg was associated with a higher response rate than with lower doses, and the response rate was not improved with higher starting doses.

Proposed Optional Dose Increase for Lack of Efficacy

Study 0301 allowed for an increase in the gilteritinib dose from 120 mg to 200 mg if no CR, CRp or CRi was achieved with at least one cycle of therapy, and the Applicant proposed to include this instruction in labeling. FDA identified 75 patients from Studies 0101 and 0301 who had a FLT3 mutation using the proposed companion diagnostic and who had a dose increase to 200 mg/day after failure of treatment with gilteritinib 120 mg/day. The median time to start 200 mg/day was 39 days (range: 28 to 237 days) on study, and the patients were treated with the higher dose for a median of 57 days (range: 5 to 923 days). Only 2 (2.7%) of the 75 patients

(subject No. 2215-CL-0301-3400550123 and 2215-CL-0301-4901050212) achieved a CR/CRh after multiple doses of gilteritinib at the higher dose.

Clinical TL Review Comment:
The proposed dose of 120 mg is supported by the dose-response analysis. For patients who failed to achieve a rapid response at this dose and were then treated with 200 mg, a later achievement of CR/CRh was rare. The optional dose increase would not be acceptable if there is toxicity with the higher dose.

8.2.2 Integrated Assessment of Effectiveness

The data provided from the pivotal trial, Study 0301, indicate that gilteritinib 120 mg daily is active for treatment of patients with R/R AML having a FLT3 mutation as detected by the proposed companion diagnostic.

8.3 Review of Safety

8.3.1 Safety Review Approach

Table 33: Safety Database – Description

STUDYID	Pop	10 mg	20 mg	40 mg	80 mg	120 mg	200 mg	300 mg	450 mg	All
2215-CL-0101	R/R AML		17	16	24	69	103	20	3	252
2215-CL-0102	R/R AML		1	4	4	4	9	2	0	24
2215-CL-0301	R/R AML		0	0	0	219	0	0	0	219
Total - R/R AML			**18**	**20**	**28**	**292[a]**	**112**	**22**	**3**	**495**
2215-CL-0106	Volunteers	24	0	0						24
2215-CL-0108	Volunteers	61	20	0						81
2215-CL-0110	Volunteers	0	0	42						42
2215-CL-0113	Volunteers	0	0	32						32
Total - Volunteers		**85**	**20**	**74**						**179**
2215-CL-0105	Solid Tumors					6				6
2215-CL-5101	Solid Tumors				7	3				10
Total - Solid Tumors					**7**	**9**				**16**
Total Treated		***85***	***38***	***94***	***35***	***301***	***112***	***22***	***3***	***690***

[a] Main safety population (AML Safety Population)
Source: FDA analysis

Safety data through the safety update submission were available for 690 individuals treated with at least one dose of gilteritinib (**Table 33)**. These included 495 patients with R/R AML, 179 volunteers in PK studies, and 16 patients with solid tumors. The designs of the nine studies included in the safety database are described in Section 7.1. All nine studies listed in **Table 33** were reviewed for major safety events.

The proposed dose of gilteritinib is 120 mg daily. There were 301 patients treated with that dose, but the subgroup of nine patients with solid tumors was considered disparate, since the primary malignancy was quite different from AML, and some of these patients may have

received other antineoplastic drugs in combination with gilteritinib. Therefore, only the group of 292 patients with R/R AML treated with gilteritinib at a dose of 120 mg daily (AML Safety Population) was considered the main safety population. Detailed safety analyses were undertaken only in the AML Safety Population. Where relevant, additional observations in the solid tumor or volunteer populations are reported separately.

8.3.2 Review of the Safety Database

Relevant characteristics of the safety population

The demographics of the patients with R/R AML and the volunteers are shown in **Table 34**. Of the 16 patients with solid tumors, the median age was 64.5 years (49-80), 8 were ≥ 65 years (1 ≥75 years), 7 were male and 9 female, 10 were Asian and 6 white, none were Hispanic, and 6 were from North America.

Table 34: Safety Database – Demographics

Characteristic	R/R AML 120 mg* (N=292)		R/R AML Other Doses (N=203)		Volunteers (N=179)	
	n		n		n	
Age						
<65 years	173	59%	102	50%	177	99%
≥65 years	119	41%	101	50%	2	1%
≥75 years	39	13%	30	15%	0	0%
Sex						
Male	138	47%	111	55%	159	89%
Female	154	53%	92	45%	20	11%
Race						
White	180	62%	154	76%	106	59%
Asian	71	24%	26	13%	8	4%
Black	16	5%	13	6%	60	34%
Other or missing	25	9%	10	5%	5	3%
Ethnicity						
Hispanic or Latino	13	5%	7	4%	54	30%
Region						
North America	167	57%	167	82%	179	100%
Asia	67	23%	20	10%		
Europe	58	20%	16	8%		

*AML Safety Population
Source: FDA analysis

Overall Exposure

An exposure data file was not submitted with the Safety Update, but the Applicant provided derived exposure summaries in adsl.xpt. For the 292 patients in the AML Safety Population, the

Median exposure was 92 days (range: 4 to 1285 days). Exposure was greater than 6 months for 69 (24%) patients (**Table 35)**.

Table 35: AML Safety Population – Exposure

Duration	**(N=292)**	
	n	
≤28 days	24	8%
29 to ≤84 days	111	38%
85 to ≤168 days	77	26%
≥169 days	80	27%

Source: FDA analysis

Adequacy of the Safety Database

The size of the safety database is adequate to provide an estimate of adverse reactions that may be observed with use of gilteritinib. The demographics of patients included in the trials do not reflect the higher proportion of elderly patients with AML in the general population, but it is not clear what proportion of elderly patients would have FLT3 mutations specifically. Additionally, the number of patients of minority race or ethnicity is lower than that in the U.S. population with AML. Consequently, it will be of interest to determine whether there are discernible differences in safety by age, race and ethnicity.

The duration of treatment in the AML Safety Population is adequate to provide assessment of adverse reactions in the short term. However, data are lacking regarding long-term toxicities.

Clinical TL Review Comment:
Additional information will be needed to confirm safety of long-term use of gilteritinib, especially in the older population.

8.3.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data sets were provided in standardized format. Narratives were provided for patients who experienced AEs of interest including death, other SAEs, AE leading to discontinuation, potential for drug-induced liver injury, and other AEs of special interest.

Categorization of Adverse Events

AEs and SAEs were defined according to ICH E2A guidelines. AEs were reported using the investigator's verbatim term and coded by the Applicant using Medical Dictionary for Regulatory Activities version 19.0 and 20.0 terms. The events were graded using the NCI-CTCAE version 4.03.

FDA compared verbatim terms to Medical Dictionary for Regulatory Activities preferred terms for AEs, and no irregularities were identified. In order to improve the accuracy of estimating the risk of adverse reactions, grouped terms were used by FDA for some analyses. The grouped terms are defined in Section 14.5.1. FDA excluded the System Organ Class (SOC) "Neoplasms benign, malignant and unspecified" from the general analyses, since most of the preferred terms were related to primary AML. An assessment of secondary malignancies is provided in Section 8.3.9.

On the basis of mechanism of action, nonclinical toxicology, and safety signals observed during clinical development, the Applicant identified 12 AEs of special interest (AESI) for detailed analysis. The Applicant's search criteria for the AESI are listed in **Table 36.**

Table 36: Applicant's Search Strategy for AESI

Risk	**Search Strategy**
PRES	Noninfectious encephalopathy/delirium (SMQ Narrow)
Cardiac failure	Cardiac failure (SMQ Narrow)
Pericarditis/pericardial effusion	HLT Noninfectious pericarditis PT Pericardial effusion
Arrhythmia due to QT prolongation	Torsade de pointes/QT prolongation (SMQ Broad)
Teratogenicity and embryo-fetal deaths	Any pregnancy cases
Creatine phosphokinase increased and myopathy	Blood creatine phosphokinase abnormal, ≥grade 3 Blood creatine phosphokinase increased, ≥grade 3 Blood creatine phosphokinase MM increased, ≥grade 3 Rhabdomyolysis/myopathy (SMQ narrow) Preferred terms of myalgia, myositis, and muscular weakness
Liver transaminase increased	Liver related investigations, signs, and symptoms (SMQ narrow)
Differentiation syndrome	PT Acute promyelocytic leukemia differentiation syndrome
Squamous cell carcinoma of the skin	Based on individual case review†
Gastrointestinal haemorrhage	Gastrointestinal haemorrhage (SMQ Broad)
Gastrointestinal obstruction	Gastrointestinal obstruction (SMQ Narrow)
Gastrointestinal perforation	Gastrointestinal perforation (SMQ Narrow)

Source: Module 5.3.5.3 Safety Update Table 2

Routine Clinical Tests

The schedules of testing for the AML Safety Population (Studies 0301, 0101 and 0102) are described in Section 8.1 above. The schedule of testing was adequate to assess the risks of serious safety events as discussed below.

8.3.4 Safety Results

Deaths

A total of 216 deaths were reported for patients on Study 0101 and 87 deaths for patients on Study 0301 who received gilteritinib. A single patient death due to AML was reported for Study 0102.

Of the deaths reported for patients on Study 0101, 111 died more than 30 days after terminating participation in the study and no cause of death (COD) is available for these patients. It is unlikely that any of these deaths were related to the study treatment given the length of time between treatment and death. Of the 105 remaining patients, death was assessed as due to AML or other causes in 101 cases. The remaining cases included two patients who died of cardiac events, including sudden death and cardiac arrest. Another patient died of sepsis following bowel perforation. The final patient died of pulmonary edema. This patient had a prolonged QT interval after starting gilteritinib.

Eighty-seven deaths were reported among the patients receiving gilteritinib on protocol 0301. Of these, 81 were attributed to AML and four to causes other than AML or the study drug. The two remaining cases were considered potentially related to drug toxicity. These included one patient death due to congestive heart failure and one due to pancreatitis, **Table 37**.

Table 37: Deaths, Studies 2215-CL-0101 and 2215-CL-0301

Subject ID	Proximate cause of death	Brief narrative
(b) (6)	Sepsis/multi-organ failure	64 y/o WF died of sepsis occurring shortly after bowel perforation and respiratory failure. Initial event of bowel perforation considered possibly related to gilteritinib due to timing of the event.
	Sudden death	43 y/o WF with normal baseline QTc interval of 348 msec at baseline, increased to 437 msec on predose reading day 8 (with individual readings exceeding 450 msec) died suddenly with no preceding symptoms on day 13-14 of treatment. Underlying COD likely Torsade de pointe related to increased QT interval due to study drug.
	Cardiac arrest	64 y/o WM with h/o hypertension and COPD died of cardiac arrest while on active treatment with 200 mg gilteritinib, increased to 300 mg due to inadequate response. Patient died of a sudden cardiac arrest, hypothesized to be due to ischemic disease but no data to support this are available. The timing suggests that gilteritinib may have played a role in the cardiac dysfunction.

Subject ID	Proximate cause of death	Brief narrative
(b) (6)	Pulmonary edema	71 y/o WM experienced prolonged QT on day 15 of study (grade 2), He continued on the study with no worsening of QT but developed worsening dyspnea and was transferred to hospice for terminal care. Last labs and bone marrow prior to end of study showed response and no evidence of relapse. Of note, the patient had a prior HSCT and residual GVHD. Gilteritinib may have contributed to cardiac dysfunction, dyspnea, and death.
Study ID: 2215-CL-0301		
(b) (6)	CHF	62 WF with h/o anthracycline use died of CHF. The patient had a LVEF of 58% at start of study, which decreased to 25% after 2-3 months of treatment with gilteritinib. The gilteritinib was stopped due to transaminase elevation and the patient was started on chemotherapy. Within a week of starting second line chemotherapy, the patient's LVEF decreased to 20% and she became symptomatic, eventually dying of CHF.
(b) (6)	Pancreatitis	72 y/o AM with h/o CHF, liver failure, and pulmonary fungal infection while receiving gilteritinib developed pancreatitis on day 47 of treatment. Dose was interrupted at the time of diagnosis, but it is unclear when the initial symptoms onset (i.e. delirium considered potentially related to pancreatitis was diagnosed on day 31).
(b) (6)	Differentiation syndrome	44 y/o BM hospitalized day 29 of treatment with chest and back pain, found to have left pleural effusion and pericardial effusion. He was treated with antibiotics but deteriorated and died of cardiac arrest. No trial of steroids given.

No deaths were reported in the studies of healthy volunteers or trial 0501, gilteritinib in NSCLC. One death was reported in Study 0105, a 75-year-old male with chondrosarcoma. The patient developed a pleural effusion, progressive lung metastases, and severe hypoxia shortly prior to death and his death was attributed to progressive disease.

Serious Adverse Events

SAEs were common among patients treated on the AML treatment studies, with grade 3 or greater treatment emergent events being reported in 443 (89%) patients in the AML Safety Population, including 260 (89%) of those receiving the recommended dose of 120 mg. SAEs are summarized by SOC in **Table 38**.

Table 38: R/R AML – Serious Adverse Events by SOC

SOC	R/R AML 120 mg* (N=292)		R/R AML Other Doses (N=203)	
	n	(%)	n	(%)
Infections and infestations	116	40	96	47
Blood and lymphatic system disorders	104	36	77	38
General disorders and administration site conditions	46	16	23	11
Gastrointestinal disorders	37	13	31	15
Respiratory, thoracic and mediastinal disorders	33	11	34	17
Cardiac disorders	29	10	22	11
Nervous system disorders	29	10	26	13
Hepatobiliary disorders	21	7	12	6
Musculoskeletal and connective tissue disorders	21	7	12	6
Vascular disorders	19	7	13	6
Renal and urinary disorders	18	6	27	13
Injury, poisoning and procedural complications	13	4	8	4
Metabolism and nutrition disorders	13	4	9	4
Skin and subcutaneous tissue disorders	8	3	4	2
Immune system disorders	7	2	6	3
Investigations	6	2	3	1
Eye disorders	2	1	1	0
Psychiatric disorders	2	1	2	1
Endocrine disorders	1	0	0	0
Reproductive system and breast disorders	1	0	0	0

*AML Safety Population
Source: FDA analysis

Table 39 lists the SAEs by Preferred Term (PT) that occurred in at least 2% of the AML Safety Population.

Table 39: R/R AML – Serious Adverse Events by PT

PT[a]	R/R AML 120 mg* (N=292)		R/R AML Other Doses (N=203)	
	n	(%)	n	(%)
Neutropenia	89	30	63	31
Pneumonia	55	19	34	17
Pyrexia	37	13	12	6
Sepsis	37	13	44	22
Dyspnoea	21	7	27	13

	R/R AML 120 mg* (N=292)		R/R AML Other Doses (N=203)	
PT[a]	**n**	**(%)**	**n**	**(%)**
Diarrhea	18	6	10	5
Renal impairment	16	5	27	13
Hypertransaminasaemia	14	5	8	4
Arrhythmia	10	3	6	3
Cellulitis	10	3	4	2
Hypotension	9	3	8	4
Anemia	8	3	7	3
Fall	8	3	2	1
Haemorrhage intracranial	8	3	10	5
Pericarditis	8	3	2	1
Thrombocytopenia	8	3	4	2
Fatigue	7	2	2	1
Gastrointestinal haemorrhage	7	2	8	4
Cardiac arrest	6	2	4	2
Cardiac failure	6	2	7	3
Fungal infection	6	2	8	4
Encephalopathy	5	2	4	2
Haematoma	5	2	1	0
Headache	5	2	1	0
Hyperbilirubinaemia	5	2	4	2
Myositis	5	2	6	3
Syncope	5	2	6	3
Upper respiratory tract infection	5	2	1	0
Urinary tract infection	5	2	5	2

*AML Safety Population
[a] Includes grouped terms (see Appendix 14.5)
Source: FDA analysis

Cytopenias were the most common SAEs observed. However, further evidence from labs and comparisons to AE among patients with solid tumors suggested that the cytopenias observed were related to the underlying AML rather than the medication (see table below). Among nonhematologic SAEs, cardiac and potentially cardiac events (QT prolongation, syncope, hypotension) were common as were liver abnormalities, most notably increased transaminases. Among patients treated with gilteritinib for solid tumors, there was one grade 5 event (chondrosarcoma progression) and 32 grade 3 to 4 events, of which, 17 were transaminase abnormalities occurring in seven individual patients. In addition, two events each of grade 3 to 4 diarrhea and dyspnea were seen. All other grade 3 to 4 AEs occurred only once. No SAEs were observed among subjects on the healthy volunteer studies.

Dropouts and/or Discontinuations Due to Adverse Effects

A total of 54 patients withdrew from treatment due to AEs in any of the AML treatment studies on 120 mg of gilteritinib. Treatment discontinuation due to AE was more common among patients assigned to the 200-mg dose compared to the 120-mg dose for studies 0101 and 0102. Common reasons for discontinuation included transaminase elevation, cardiac arrest, ventricular arrhythmias, respiratory failure/dyspnea, elevated bilirubin. This figure does not include those patients who discontinued due to disease progression, infection, or bleeding as these were considered related to the disease rather than the drug.

Significant Adverse Events

Table 40 shows the incidence of AESI as reported by the Applicant.

Table 40: AML Safety Population – AESI Incidence per Applicant

AESI	R/R AML 120 mg* (N=292)	
Liver transaminase increased	131	45%
Creatine phosphokinase increased and myopathy	67	23%
Arrhythmia due to QT prolongation	42	14%
Cardiac failure	21	7%
Gastrointestinal haemorrhage	20	7%
Pericarditis/pericardial effusion	14	5%
PRES	9	3%
Gastrointestinal perforation	4	1%
Differentiation syndrome	2	<1%
Squamous cell carcinoma of the skin	2	<1%
Gastrointestinal obstruction	2	<1%
Teratogenicity and embryo-fetal deaths	0	0%

* AML Safety Population
Source: Module 5.3.5.3 Safety Update Section 4.5

Tyrosine kinase inhibitors as a class have a broad range of toxicities.[5] **Table 41** shows the incidence of any-grade SMQs (Narrow) occurring in at least 20% of the AML Safety Population or established as a tyrosine kinase inhibitor toxicity. Also listed are the incidences for each limited to grades 3-5, noted as serious adverse reactions or resulting in withdrawal of therapy.

[5] Shah DR, et al. Tyrosine kinase inhibitors: Their on-target toxicities as potential indicators of efficacy. Drug Saf 2013: 36:413-426.

Table 41: AML Safety Population – SMQ Analysis

	R/R AML 120 mg* (N=292)			
SMQ(N)	**Any Grade**	**Grade 3-5**	**SAE**	**Withdrawal**
Hepatic disorders (Drug related)	49%	22%	7%	1%
Haemorrhage terms (excl laboratory terms)	48%	9%	8%	1%
Haemodynamic oedema, effusions and fluid overload	42%	5%	3%	1%
Oropharyngeal disorders[1]	40%	4%	2%	0
Hypersensitivity	37%	6%	3%	<1%
Noninfectious diarrhea	35%	5%	6%	0
Cardiac arrhythmias (terms)	22%	7%	4%	<1%
Acute renal failure	20%	4%	5%	1%
Noninfectious encephalopathy	13%	3%	2%	0
Hypertension	10%	6%	<1%	0
Peripheral neuropathy	8%	1%	<1%	0
Torsades pointe/QT Prolongation	8%	2%	1%	0
Cardiac failure	5%	4%	2%	0

* AML Safety Population
Source: FDA analysis
[1](excluding neoplasms, infections and allergies)

Table 42: AML Safety Population – HLT Analysis

	R/R AML 120 mg* (N=292)			
HLT	**Any Grade**	**Grade 3-5**	**SAE**	**Withdrawal**
Hepatic enzymes and function abnormalities	42%	16%	5%	1%
Asthenic conditions	40%	5%	2%	0
Diarrhoea (excl infective)	35%	5%	6%	0
Febrile disorders	35%	4%	13%	0
Breathing abnormalities	34%	13%	7%	1%
Nausea and vomiting symptoms	34%	2%	2%	0
Oedema NEC	34%	2%	1%	0
Rashes, eruptions and exanthems NEC	30%	3%	1%	<1%
Gastrointestinal atonic and hypomotility disorders NEC	29%	<1%	<1%	0
Coughing and associated symptoms	28%	<1%	1%	0
Potassium imbalance	27%	10%	0	0
Musculoskeletal/connective tissue pain and discomfort	26%	1%	1%	0
Stomatitis and ulceration	26%	4%	1%	0
Tissue enzyme analyses NEC	23%	3%	<1%	0
Neurological signs and symptoms NEC	22%	<1%	<1%	0
Headaches NEC	21%	1%	2%	0
Muscle infections and inflammations	21%	5%	2%	<1%
Vascular hypotensive disorders	21%	7%	3%	<1%
Renal failure and impairment	18%	4%	5%	1%

* AML Safety Population
Source: FDA analysis

Table 42 shows the incidence of any-grade High Level Terms (HLTs) occurring in at least 20% of the AML Safety Population or established as a tyrosine kinase inhibitor toxicity. Also listed are

the incidences for each limited to grades 3-5, noted as serious adverse reactions or resulting in withdrawal of therapy.

Clinical TL Review Comment:
The SMQ and HLT analyses demonstrate that patients treated with gilteritinib exhibited the broad range of toxicities known to occur with kinase inhibitors. The neurological toxicity is some what unique. However, most events were low-grade; only hepatic disorder and breathing abnormalities occurred at grades 3-5 in a substantial proportion of patients. Few events were identified as serious and rarely resulted in withdrawal of therapy.

Further FDA analysis of AESI focused on transaminase elevation, bilirubin elevation, QT prolongation and ventricular arrhythmias (see QT/cardiac section of the review for further details), other cardiac issues, differentiation syndrome, and creatine phosphokinase (CPK) elevation/rhabdomyolysis. The incidence of second primary malignancies (SPM) was briefly examined as well.

Liver issues: Elevation of transaminases and bilirubin were identified in clinical and nonclinical trials as potential safety issues for patients receiving gilteritinib for AML. Increased transaminases, including grade 3 and 4 increased were common among patients treated with gilteritinib (see SAE, above) and increased bilirubin was reported as an adverse event in 41 patients with 23 grade 3 to 4 events in 16 patients reported. Ninety-nine events in 59 patients were reported in the hepatobiliary SOC, with the majority of these events being Hyperbilirubinaemia (33) and hepatic function abnormal (31). Other common hepatobiliary disorders included cholecystitis (7), cholelithiasis (7), jaundice (3), and hepatic failure, hepatic lesion, hepatic steatosis, and hepatomegaly (2 each). No fatal events were reported.

Differentiation syndrome: Prior publications have suggested that FLT3 inhibiting agents may lead to differentiation syndrome in some patients. Investigators involved in the included studies identified three cases of probable differentiation syndrome (DS) in patients on trial 0101. Afte4r review, two of these were felt to be possible or probable DS and one unlikely to be DS based on the available information. In addition, patients on trials 0101 and 0301 were screened for possible differentiation syndrome using a program that identified patients in whom at least two of the Montesinos criteria occurred within seven days of each other. Using this algorithm, an additional six possible or probable cases were identified. One case of possible fatal DS was identified. In addition, deaths due to cardiopulmonary disease of uncertain origin occurred in several patients (see table above) and a component of DS cannot be ruled out in these patients.

Brief narratives for cases of possible or probable differentiation syndrome are described below:
Study 0101:

- (b) (6): 33 y/o woman receiving 200 mg daily gilteritinib presented on day 12 with fever. She was initially diagnosed with sepsis, but no organism was identified. A CXR showed bilateral pleural effusions but no infiltrates, suggestive of volume overload. On

day 14 her condition worsened and she was admitted to the ICU for hypoxemic respiratory failure, volume overload, acute kidney injury, and a pericardial effusion. She was treated initially with antibiotics, supportive care, and diuresis. Pleural fluid demonstrated both blasts and maturing myeloid cells. Prednisone was started on day 28 with improvement in aeration but continued increase in WBC. She was started on hydroxyurea on day 36 and improved on a combination of steroids, hydroxyurea, and the study drug. Her ANC peaked at day 30 at 7500.

- (b) (6): 51 y/o man receiving 80 mg daily gilteritinib experienced orthostatic hypotension and tachycardia on day 14 and admitted for differentiation syndrome. A pericardial rub and leukocytosis with a left shift were noted at that time. He was treated with dexamethasone with rapid resolution of pleurisy but developed avascular necrosis of the hips. The dexamethasone was stopped on day 28.
- (b) (6): 65 y/o woman on 200 mg gilteritinib admitted to the hospital on day 2 with pleural effusion and prolonged QT interval. On day 7, leukocytosis with increased ANC and decreased blasts was reported and dexamethasone was started. Gilteritinib was held on day 9. She developed hypoxemia and was treated with steroids, bipap, diuresis, and antibiotics. She improved symptomatically and hypoxia resolved on day 14. However, she developed a pericardial effusion shortly thereafter and opted for hospice treatment at that time.
- (b) (6): 79 y/o woman treated initially with 120 mg then increased to 200 mg on day 36. On day 75, the patient developed dyspnoea, increased AST/ALT, bilateral infiltrates, and hyponatremia. She was treated with antibiotics with initial improvement and was discharged but presented on day 89 with increased dyspnoea and diagnosed with DS versus infection versus pneumonitis. She was treated with steroids and antibiotics with resolution.
- (b) (6) 42 y/o woman treated with 200-mg dose admitted day 53 with fever, cough, chest pain, and neutropenia. She was treated initially with antibiotics, but steroids were added on day 57 for possible DS and cytokine release. Cultures were negative and pulmonary symptoms improved with treatment.
- (b) (6): 57 y/o woman treated with 120 mg gilteritinib who was hospitalized on day 11 with hypoxic respiratory failure versus pneumonia. Her ANC rose from 0 to 1320 during this period. She was treated with antibiotics and steroids.

Trial 0301:

- (b) (6): 49 y/o woman admitted on day 16 with neutropenic fever and headache. Started initially on antibiotics but developed pericardial effusion and hypotension and was transferred to the ICU where she was treated with fluids, supportive care, and antibiotics. She had some improvement with this treatment, but her fevers continued despite an increasing ANC. She was given prednisone starting on day 58 for DS and her symptoms began to improve. It should be noted that gilteritinib was stopped at about this time as well.

- [redacted] (b) (6): 44 y/o man admitted on day 29 for chest pain and back pain, found to have a left pleural effusion and pericardial effusion. He was treated with antibiotics alone. No steroid treatment was provided (except for doses given as premedication). He progressed and died of cardiac arrest shortly thereafter.

Reviewer's Comment:
Although few of the cases above were classic differentiation syndrome, all were considered suspicious by the standard criteria for DS and some patients showed improvement with steroid treatment. Due to the combination of multiple possible or probable cases of DS, the presence of at least one probable death due to DS, and a plausible biological mechanism of action for DS in FLT3 inhibitors, a warning in the label is justified to alert clinicians to the risk.

CPK elevations/rhabdomyolysis: Elevations in CPK were identified in healthy volunteers exposed to low doses of gilteritinib, with increases of 500 U/L or more seen in 11 patients. In addition, one subject experienced grade 2 rhabdomyolysis. Two subjects with solid tumors receiving gilteritinib experienced CPK elevations of 500 U/L or more during the study. In the AML studies, a total of 261 patients experienced any CPK elevation, including one who had a grade 1 elevation at baseline. Eight patients experienced grade 4 toxicity and 28 experienced grade 3 toxicity. In addition, mean CPK increased as dose increased (see labs section for details). Rhabdomyolysis was reported as an AE only once in the AE dataset. However, myopathy, myositis, necrotizing myositis, and soft tissue necrosis were reported in 12 patients and musculoskeletal chest pain, musculoskeletal discomfort or pain, myalgia, and pain in the extremity were reported in 110 patients.

Pancreatitis was reported in five patients (six events), including one fatality. Amylase and lipase were not routinely monitored during the included trials, thus, it is not possible to determine the risk of asymptomatic elevations of amylase and lipase. Hyperbilirubinaemia or increased blood bilirubin were reported in three out of five patients with pancreatitis and liver failure in another. No clear associated risks were reported in the final patient.

Among patients receiving 120 mg of gilteritinib, the incidence of any event other than a leukemia-related event under the SOC neoplasms, was 14 events occurring in 12 patients. The majority of these were a combination of benign and malignant skin cancers, including one basal cell skin cancer and two squamous cell skin cancers, as well as seven cases of benign skin growths. In addition, one case each was observed of uterine fibroids, gastric adenocarcinoma, carcinoma of the esophagus, and choroidal nevus.

Treatment Emergent Adverse Events and Adverse Reactions

TEAEs are summarized by SOC in **Table 43.** The SOC most commonly affected include blood and lymphatic systems, gastrointestinal, investigations, and metabolism and nutrition disorders.

Table 43: R/R AML – TEAEs by SOC

SOC	R/R AML 120 mg* (N=292)		R/R AML Other Doses (N=203)	
	n	%	n	%
Blood and lymphatic system disorders	223	76	140	69
Gastrointestinal disorders	219	75	151	74
General disorders and administration site conditions	208	71	137	67
Infections and infestations	205	70	136	67
Respiratory, thoracic and mediastinal disorders	178	61	123	61
Metabolism and nutrition disorders	169	58	113	56
Musculoskeletal and connective tissue disorders	157	54	90	44
Nervous system disorders	156	53	113	56
Skin and subcutaneous tissue disorders	140	48	102	50
Hepatobiliary disorders	137	47	88	43
Investigations	132	45	78	38
Vascular disorders	109	37	76	37
Eye disorders	103	35	44	22
Renal and urinary disorders	97	33	76	37
Injury, poisoning and procedural complications	86	29	60	30
Psychiatric disorders	74	25	56	28
Cardiac disorders	71	24	65	32
Immune system disorders	48	16	19	9
Reproductive system and breast disorders	27	9	14	7
Ear and labyrinth disorders	15	5	12	6
Endocrine disorders	9	3	5	2
Surgical and medical procedures	0	0	1	0

*AML Safety Population
Source: FDA analysis

The TEAE that occurred in at least 5% of the AML Safety Population are listed by PT in **Table 44**. Cytopenias were common, as expected in patients with AML. In addition, transaminase increases, diarrhea, nausea, vomiting, fever, fatigue, decreased electrolytes, edema, increased creatinine, and increased CK were observed.

Table 44: R/R AML – TEAEs by PT

PT[a]	R/R AML 120 mg* (N=292)		R/R AML Other Doses (N=203)	
	n	%	n	%
Neutropenia	159	54	97	48
Hypertransaminasaemia	121	41	66	33
Anemia	119	41	65	32
Thrombocytopenia	119	41	60	30
Fatigue	116	40	78	38

PT[a]	R/R AML 120 mg* (N=292)		R/R AML Other Doses (N=203)	
	n	%	n	%
Diarrhea	103	35	76	37
Pyrexia	103	35	49	24
Oedema	100	34	72	35
Dyspnoea	98	34	73	36
Pneumonia	89	30	53	26
Rash	87	30	41	20
Constipation	80	27	49	24
Nausea	78	27	47	23
Stomatitis	77	26	55	27
Cough	74	25	44	22
Hypokalaemia	67	23	39	19
Myositis	62	21	40	20
Headache	60	21	26	13
Hypotension	60	21	46	23
Dizziness	57	20	37	18
Vomiting	56	19	37	18
Renal impairment	54	18	58	29
Blood alkaline phosphatase increased	53	18	23	11
Abdominal pain	49	17	27	13
Epistaxis	48	16	39	19
Hypocalcaemia	47	16	33	16
Decreased appetite	44	15	28	14
Hypomagnesaemia	43	15	24	12
Sepsis	43	15	48	24
Insomnia	42	14	23	11
Arrhythmia	41	14	41	20
Hyperglycaemia	39	13	20	10
Pain in extremity	39	13	18	9
Acute myeloid leukemia	37	13	38	19
Hypophosphataemia	37	13	17	8
Leukopenia	37	13	15	7
Hyponatraemia	35	12	26	13
Arthralgia	33	11	24	12
Hypoalbuminaemia	33	11	27	13
Back pain	32	11	14	7
Dysgeusia	31	11	20	10
Fungal infection	31	11	20	10
Hyperbilirubinaemia	31	11	30	15
Fall	30	10	24	12
Hypertension	30	10	28	14
Dry eye	26	9	8	4
Blood lactate dehydrogenase increased	25	9	15	7

PT[a]	R/R AML 120 mg* (N=292)		R/R AML Other Doses (N=203)	
	n	%	n	%
Cellulitis	25	9	7	3
Delirium	25	9	24	12
Muscular weakness	25	9	8	4
Paraesthesia	25	9	10	5
Chills	24	8	16	8
Electrocardiogram QT prolonged	24	8	12	6
Visual impairment	24	8	11	5
Pain	23	8	6	3
Pruritus	23	8	13	6
Upper respiratory tract infection	23	8	11	5
Hypersensitivity	22	8	10	5
Oropharyngeal pain	22	8	13	6
Dry mouth	21	7	16	8
Graft versus host disease	21	7	8	4
Transfusion reaction	21	7	4	2
Urinary tract infection	21	7	12	6
Gastrointestinal haemorrhage	20	7	20	10
Hyperkalaemia	20	7	13	6
Pleural effusion	20	7	17	8
Anxiety	19	7	9	4
Nasal congestion	19	7	13	6
Neuropathy peripheral	18	6	12	6
Retinal haemorrhage	18	6	2	1
Dyspepsia	17	6	4	2
Hyperuricaemia	17	6	14	7
Encephalopathy	16	5	28	14
Haematuria	16	5	7	3
Productive cough	16	5	4	2
Dry skin	15	5	8	4
Haematoma	15	5	11	5
Pericarditis	15	5	8	4
Weight decreased	15	5	8	4
Depression	14	5	8	4
Leukocytosis	14	5	17	8
Sinusitis	14	5	5	2

*AML Safety Population
[a] Includes grouped terms (see Appendix 14.5)
Source: FDA analysis

Patients with solid tumors had a distinct TEAE profile, with the most notable difference being that there were only four events in the blood and lymphatic system disorders SOC, all of which were anemia. However, a case of lymphocyte count decreased was noted in the investigations

SOC as well. The most common AE reported for solid tumors were in the investigations, gastrointestinal, skin and subcutaneous tissues, and metabolism and nutrition SOCs. The most common events by PT included ALT increased (32 events), drug eruption (31), AST increased (25), diarrhea (17), and hypoalbuminemia (11). Blood CPK was increased for eight patients.

A total of 99 TEAEs were reported for in 61 individuals from the gilteritinib cycles in the volunteer studies. Almost all were grade 1. The most common TEAE in the volunteers were headache (8%), constipation (6%), back pain (2%), blister (2%), diarrhea (2%), dyspepsia (2%), flatulence (2%) and insomnia (2%). The moderate intensity events included muscle strain, gastroenteritis, dysmenorrhea, elevated liver function tests, rhabdomyolysis and headache (n=1 each).

Grade 3 to 5 TEAEs occurred most commonly in the SOCs Blood and lymphatic system disorders (70%), Infections and infestations (46%), Metabolism and nutrition disorders (28%), and Hepatobiliary disorders (21%). The grade 3 to 5 TEAEs that occurred in at least 2% of the AML Safety Population are listed by PT in **Table 45**.

Table 45: R/R AML – Grade 3 to 5 TEAEs by PT

	R/R AML 120 mg* (N=292)		R/R AML Other Doses (N=203)	
PT[a]	n	%	n	%
Neutropenia	156	53	92	45
Thrombocytopenia	105	36	55	27
Anemia	92	32	52	26
Pneumonia	66	23	41	20
Hypertransaminasaemia	47	16	23	11
Sepsis	41	14	45	22
Dyspnoea	36	12	39	19
Leukopenia	35	12	14	7
Hypokalaemia	26	9	9	4
Hypophosphataemia	21	7	14	7
Hypotension	21	7	17	8
Hypertension	17	6	6	3
Hyperglycaemia	16	5	9	4
Hyponatraemia	16	5	9	4
Diarrhea	15	5	15	7
Myositis	15	5	14	7
Arrhythmia	14	5	8	4
Fatigue	14	5	13	6
Hyperbilirubinaemia	14	5	10	5
Pyrexia	13	4	8	4

	R/R AML 120 mg* (N=292)		R/R AML Other Doses (N=203)	
PT[a]	**n**	**%**	**n**	**%**
Cellulitis	12	4	5	2
Hypocalcaemia	12	4	12	6
Renal impairment	11	4	16	8
Stomatitis	11	4	9	4
Cardiac failure	10	3	8	4
Syncope	10	3	14	7
Fungal infection	9	3	10	5
Fall	8	3	5	2
Hypersensitivity	8	3	2	1
Rash	8	3	2	1
Urinary tract infection	8	3	7	3
Cytopenia	7	2	2	1
Device related infection	7	2	3	1
Electrocardiogram QT prolonged	7	2	6	3
Haemorrhage intracranial	7	2	9	4
Sinusitis	7	2	4	2
Skin infection	7	2	3	1
Blood alkaline phosphatase increased	6	2	1	0
Cardiac arrest	6	2	4	2
Decreased appetite	6	2	3	1
Gastrointestinal haemorrhage	6	2	8	4
Leukocytosis	6	2	10	5
Staphylococcal bacteraemia	6	2	2	1
Thrombosis	6	2	2	1
Abdominal pain	5	2	2	1
Blood lactate dehydrogenase increased	5	2	3	1
Encephalopathy	5	2	6	3
Gamma-glutamyltransferase increased	5	2	1	0
Hypoalbuminaemia	5	2	5	2
Oedema	5	2	7	3
Pancreatitis	5	2	4	2
Pleural effusion	5	2	3	1
Upper respiratory tract infection	5	2	1	0
Urinary tract infection bacterial	5	2	0	0
Urinary tract infection enterococcal	5	2	2	1

*AML Safety Population
[a] Includes grouped terms (see Appendix 14.5)
Source: FDA analysis

The TEAEs that were considered by investigators to be related and that occurred in at least 5% of the AML Safety Population are listed by PT in **Table 46**.

Table 46: R/R AML – Related TEAEs by PT

	R/R AML 120 mg* (N=292)		R/R AML Other Doses (N=203)	
PT[a]	n	%	n	%
Hypertransaminasaemia	83	28	43	21
Thrombocytopenia	72	25	27	13
Neutropenia	66	23	25	12
Anemia	47	16	20	10
Fatigue	44	15	32	16
Myositis	38	13	31	15
Diarrhea	36	12	36	18
Leukopenia	30	10	9	4
Rash	30	10	8	4
Nausea	29	10	20	10
Blood alkaline phosphatase increased	28	10	7	3
Constipation	23	8	17	8
Oedema	21	7	19	9
Pyrexia	21	7	8	4
Stomatitis	21	7	13	6
Electrocardiogram QT prolonged	19	7	9	4
Dysgeusia	18	6	16	8
Headache	17	6	6	3
Hyperbilirubinaemia	17	6	7	3
Vomiting	17	6	12	6
Decreased appetite	16	5	10	5
Dyspnoea	16	5	10	5
Dizziness	15	5	15	7
Pneumonia	14	5	3	1

*AML Safety Population
[a] Includes grouped terms (see Appendix 14.5)
Source: FDA analysis

Laboratory Findings

Although hematologic AE and abnormal CBC values were common among patients in the studies examining gilteritinib in AML, they were rarely observed for patients in the studies of healthy volunteers or patients receiving gilteritinib for nonhematologic malignancies.

Table 47: Hematologic Values for Subjects on Trials Involving Gilteritinib

Period	Labs (Mean value)	AML	Healthy volunteers*	Solid tumors
Baseline	Hemoglobin (g/dl)	93 (55-146)	142 (112-170)	122 (109-135)
	ANC (10^6/L)	1585 (0-54,600)	3544 (1100-8400)	4076 (2662-7770)
	Platelets (10^9/L)	59 (0-602)	233 (50-487)	243 (150-365)
End of cycle 1 (day 29)	Hemoglobin (g/dl)	91 (52-143)	149 (125-165)	119 (79-138)
	ANC (10^6/L)	1293 (0-19,649)	3285 (1300-6100)	4406 (2156-0372)
	Platelets (10^9/L)	51 (1-440)	219 (136-324)	218 (17-308)
End of treatment	Hemoglobin (g/dl)	89 (59-166)	139 (105-167)	107 (10.4-143)
	ANC (10^6/L)	3504 (0-65,290)	3374 (1000-8800)	4369 (1940-9150)
	Platelets (10^9/L)	43 (2-431)	224 (34-375)	231 (144-394)

* Data for end of cycle 1 (day 29) available only for study 0108

Table 48: AML Safety Population – Common Laboratory Abnormalities

	R/R AML 120 mg* (N=292)	
Parameter	**Any Grade n (%)**	**Grade ≥3* n (%)**
Creatinine increased	273 (94)	10 (3)
Hyperglycemia	252 (86)	26 (9)
Hypertriglyceridemia	237 (81)	18 (6)
Alanine aminotransferase increased	229 (78)	35 (12)
Aspartate aminotransferase increased	228 (78)	28 (10)
Alkaline phosphatase increased	189 (65)	3 (1)
Hypocalcemia	179 (61)	15 (5)
Hypoalbuminemia	169 (58)	10 (3)
Creatine kinase increased	157 (54)	14 (5)
Hypophosphatemia	141 (48)	36 (12)
Hypokalemia	103 (35)	25 (9)
Hyponatremia	93 (32)	36 (12)

*AML Safety Population

Table 48 above shows the most common laboratory abnormalities in the AML Safety Population. The most common grade 3-4 abnormalities were hypophosphatemia, hyponatremia, and elevated transaminases.

CPK elevations from normal or low baseline to grade 3 to 4 toxicity were observed at any time during treatment in 34 patients in the integrated summary of safety database, including 14 patients treated at the 120-mg dose. All patients with grade 3 or 4 elevations had normal baselines. An additional 91 patients experienced grade 2 elevations from a normal or low baseline. In addition, there was an increase in mean value of CPK from 42 U/L (5-298) at baseline to 230 (17-11816) at cycle 2 day 1 and 244 (8-3443) at end of treatment. When dose was considered, patients exposed to <120 mg per day had a mean CPK on day 1 of cycle 2 of 98 (17-537), 120 mg of 178 (17-1932), and >120 of 416 U/L (18-11816).

Low potassium or magnesium levels are of particular interest due to the risk of QT prolongation associated with the use of gilteritinib. Therefore, changes in these electrolytes with treatment were examined. Overall, neither potassium nor magnesium levels changed. However, occasional low values were observed for potassium, suggesting the need for monitoring and replacement during treatment with gilteritinib to avoid hypokalemia. A single patient had persistently high magnesium levels which worsened during treatment.

Vital Signs

Mean change in weight for patients participating in the study was an increase of 2.1 kg with a range of -24.5 to +36.6 kg. Weight loss of 10 kg or more was observed in 26 patients and weight gain of 10 kg or more in 56 patients. Weight was measured at baseline and end of study in the healthy volunteers studies and these showed a mean decrease of 1.5 kg in weight with a range of -6.9 to +2.7 kg in these subjects.

Both fever and hypothermia were common in patients on the primary studies, with changes in temperature ranging from -3.1°C to +3.2°C during the study. However, these data are difficult to interpret given the frequent occurrence of infections in patients with AML, regardless of treatment. Subjects on the healthy volunteer studies had a mean change of 0.1°C, with a range of -1.9°C to +1.9°C in temperature. No subject had a temperature above 37.5°C during the studies, with 3 subjects having temperatures of 37.5°C at any time after exposure to gilteritinib. In addition, 3 subjects had temperatures of 35°C or less after exposure.

Considerable variation in pulse was observed as well, with values ranging from 43 to 196 beats per minute (BPM) and changes from baseline varying from -113 to +77 BPM. Fifty-seven patients experienced pulse rates of >120 BPM with an increase of 15 or more BPM during the study. Again, due to the high incidence of infection, these values are difficult to interpret. Healthy volunteers had pulses of 36-115 with changes of -58 to +49 bpm (mean +1.6) observed.

Systolic blood pressure (SBP) varied from 79-165 for subjects in the volunteer studies. Changes in SBP ranged from -56 to +61 (mean change 2.3). SBP varied more significantly for patients on the AML studies, with values ranging from 63 to 208 and changes ranging from -75 to +89. Increases in SBP of ≥20 and to ≥180 occurred in 25 patients. The mean increase was about 5 mmHg. No clear dose/response pattern was observed, with mean changes in SBP of 6 mmHg

for those receiving 120 mg and 4 mmHg for those receiving 200 mg. Again, infection and other causes of multiorgan dysfunction may confound the measurements. It should be noted that headache and dizziness/syncope were both reported as AEs in patients on the AML studies, although neither was prominent in the healthy volunteer studies.

Diastolic blood pressure varied from 42 to 99 mmHg and changes ranged from -35 to +28 (mean -4 mmHg) for subjects on the volunteer studies. For patients on the AML studies, values varied from 35 to 125 mmHg and changes from -57 to +51 mmHg (mean change 3.6).

QT/Electrocardiograms (ECGs)

ECGs were performed on patients enrolled in the included studies. Three individual ECGs were performed at each timepoint and the average was used to calculate QT interval. Fridericia's correction was used for determining QTc. Data from at least one ECG were available for 444 patients.

Overall, there was relatively little change in the mean value of the QTcF for patients receiving gilteritinib. However, the value of the highest values increased over the first cycle for patients receiving gilteritinib, i.e. the maximum value went from 485 msec at baseline to 508 msec at day 15 of cycle 1. A greater increase in the mean value and highest values was observed for patients with normal baseline QTc, with the mean value decreasing slightly for patients with high initial QTc, although the maximum value increased for these patients as well.

In addition, patients who received the 200-mg dose had higher maximum ranges and slightly higher medians compared to those who received 120 mg. The highest averaged values for patients receiving 200 mg reached over 500 msec and individual ECG measurements went as high as 520 msec by day 1 of cycle 2. Individual increases in QTc could be high, i.e. subject (b) (6) had an increase in mean QTcF from 429 at baseline to 501 at day 8 of cycle 1.

Table 49: Mean Value and Range of Values for Patients with AML Treated with Gilteritinib

	Time point (predose)			
Subgroup	**Baseline**	**C1D8**	**C1D15**	**C2D1**
All patients (N=444)	419 353-485	422 343-501	426 (336-508)	426 (347-507)
Baseline ≤450 (N=413)	415 353-450	420 (343-501)	424 (336-487)	424 (347-507)
Baseline >450 (N=31)	463 450*-485	450 (415-486)	455 (422-508)	455 (426-504)
Dose=120 mg (N=241)	417 (353-485)	421 (343-484)	425 (336-487)	425 (347-494)
Dose=200 mg (N=112)	421 (363-476)	424 (375-500)	428 (346-508)	431 (379-507)

* Lowest value included is equal to 450 due to rounding

Reviewer's Comment:
Although the mean value of QTc shows little change with use of gilteritinib, more patients had abnormally high values while taking gilteritinib than at baseline. In addition, patients taking 200 mg were more likely to have values >500 msec while receiving gilteritinib. In addition, several deaths suspicious for ventricular fibrillation/torsade occurred on the study. Thus, there appears to be a significant risk of increased QT interval in some patients receiving gilteritinib and a boxed warning for this event is recommended. The higher risk at 200 mg precludes the use of this dose unless clear evidence of increased efficacy becomes available.

Immunogenicity

No specific clinical studies on immunogenicity were performed. TEAEs in the SOC of immune system disorders occurred in 44 patients in Study 0101. The majority of these events were related to graft versus host disease. However, two anaphylactic reactions, one drug hypersensitivity, and four cases of hypersensitivity were identified. The case of drug sensitivity was identified in the investigator's term as an allergic reaction to paracetamol. Of the two events of anaphylaxis or angioedema, one occurred shortly after the patient had started a new antibiotic and resolved after discontinuation. Gilteritinib was interrupted but restarted with no dose change and no recurrence. No specific inciting agent was provided in the narrative. However, the patient was able to continue taking gilteritinib without interruption or dose reduction. Of the four cases coded as hypersensitivity, one was listed as a skin reaction and one seasonal allergies in the investigator's terms. Both were considered grade 1. The other two were listed as allergic reactions in the investigator's terms section with no further information provided. Both were listed as grade 2 and no dose interruption or change occurred for either.

An additional 36 TEAEs in the immune system disorders SOC were observed in Study 0301. Again, the majority were GVHD, but two anaphylactic reactions, one cytokine release syndrome, and six drug hypersensitivity reactions were reported. The event of CRS occurred during preparative treatment for HSCT after discontinuation of gilteritinib for this procedure. Five of the drug hypersensitivity reactions were identified as being due to drugs other than gilteritinib. The remaining case was identified as related to gilteritinib and occurred in one of the patients reported to have anaphylaxis as well (see below). One case of hypersensitivity occurred in a 62 y/o woman who experienced facial swelling and upper airway edema on day 4 of the study which was thought to be likely related to gilteritinib. After resolution of the event, she successfully completed a gilteritinib challenge and was able to tolerate treatment with 80 mg of the medication. The second patient was a 27 y/o woman who experienced anaphylaxis on day 73 of the study. She had recently started meropenem for sinusitis and the reaction was initially attributed to the antibiotic. Gilteritinib was stopped at this time as well. The initial event resolved but the patient had a second reaction attributed to a new antibiotic (azotreonam). This antibiotic was discontinued and she was treated for anaphylaxis successfully. Gilteritinib was restarted, although the timing is unclear. On day 86, the patient took the last planned dose of gilteritinib prior to HSCT and had an allergic reaction with tongue

swelling, difficulty swallowing, and breathing difficulty. She responded partially to treatment and event resolved completely by day 89. She was able to tolerate restarting on a lower dose of gilteritinib after transplant.

A single immune system disorder, described as a seasonal allergy, was observed in trial 0102.

Reviewer's Comment:
At least one definite event of anaphylaxis to gilteritinib was observed. Although this patient was later able to tolerate a lower dose, her treatment was restarted only after HSCT and thus it is uncertain whether she would have been able to tolerate continued treatment under other circumstances. Allergic reactions, including anaphylaxis, are a risk for patients receiving gilteritinib.

8.3.5 Analysis of Submission-Specific Safety Issues

See review of AESI above. There were no additional submission-specific safety issues.

8.3.6 Safety Analyses by Demographic Subgroups

FDA evaluated TEAEs by subgroup only in the 292 patients in the AML Safety Population.

Age
TEAE incidence was assessed using an age cutpoint of 65 years. **Table 50** shows the TEAEs with a risk difference between age groups of at least 5%.

Table 50: AML Safety Population – Common TEAEs by Age Group

PT[a]	Age <65 Years (N=173)		Age ≥65 Years (N=119)		Risk Difference
	n	%	n	%	
Sepsis	18	10	25	21	-11
Hyponatraemia	14	8	21	18	-10
Fall	12	7	18	15	-8
Epistaxis	23	13	25	21	-8
Muscular weakness	10	6	15	13	-7
Pneumonia	48	28	41	34	-7
Leukocytosis	4	2	10	8	-6
Hyperglycaemia	19	11	20	17	-6
Diarrhea	57	33	46	39	-6
Anemia	67	39	52	44	-5
Pancreatitis	2	1	7	6	-5
Oedema	56	32	44	37	-5
Retinal haemorrhage	14	8	4	3	5
Mouth haemorrhage	10	6	1	1	5
Hypocalcaemia	32	19	15	13	6
Dizziness	38	22	19	16	6

PT[a]	Age <65 Years (N=173)		Age ≥65 Years (N=119)		Risk Difference
	n	%	n	%	
Hypokalaemia	44	25	23	19	6
Rash	56	32	31	26	6
Hyperbilirubinaemia	23	13	8	7	7
Leukopenia	27	16	10	8	7
Paraesthesia	20	12	5	4	7
Hypertransaminasaemia	77	45	44	37	8
Pain	19	11	4	3	8
Pruritus	19	11	4	3	8
Electrocardiogram QT prolonged	20	12	4	3	8
Nausea	52	30	26	22	8
Headache	42	24	18	15	9
Hypomagnesaemia	32	19	11	9	9
Neutropenia	101	58	58	49	10
Vomiting	43	25	13	11	14

Source: FDA analysis
[a] Includes grouped terms (see Appendix 14.5)

Gender

Table 51 shows the TEAEs with a risk difference between males and females of at least 5%.

Table 51: AML Safety Population – Common TEAEs by Gender

PT[a]	Males (N=138)		Females (N=154)		Risk Difference
	n	%	n	%	
Urinary tract infection	0	0	21	14	-14
Stomatitis	27	20	50	32	-13
Hypertransaminasaemia	49	36	72	47	-11
Blood alkaline phosphatase increased	17	12	36	23	-11
Hypokalaemia	24	17	43	28	-11
Oedema	40	29	60	39	-10
Epistaxis	31	22	17	11	11

Source: FDA analysis
[a] Includes grouped terms (see Appendix 14.5)

Race and Ethnicity

Table 52 shows the TEAEs with a risk difference of at least 15% between Black and White subgroups. The comparisons are confounded by the small number of patients in the Black subgroup. Similarly, the small number of Hispanic patients (n=13) did not allow for a meaningful comparison. There were no clinically meaningful differences in TEAEs between the White and Asian subgroups.

Table 52: AML Safety Population – Common TEAEs by Race

PT[a]	White (N=180)		Asian (N=71)		Black (N=16)		Risk Difference*
	n	%	n	%	n	%	
Dizziness	34	19	11	15	7	44	-25
Pneumonia	59	33	17	24	9	56	-23
Hypomagnesaemia	26	14	8	11	6	38	-23
Pericarditis	6	3	3	4	4	25	-22
Encephalopathy	9	5	3	4	4	25	-20
Cough	43	24	20	28	7	44	-20
Haematoma	10	6	1	1	4	25	-19
Nausea	46	26	19	27	7	44	-18
Decreased appetite	24	13	14	20	5	31	-18
Vomiting	36	20	11	15	6	38	-18
Urinary retention	4	2	0	0	3	19	-17
Arrhythmia	27	15	7	10	5	31	-16
Constipation	52	29	21	30	2	13	16
Anemia	83	46	28	39	4	25	21

*Risk difference for Black and White subgroups
[a] Includes grouped terms (see Appendix 14.5)
Source: FDA analysis

Clinical TL Review Comment:
Although there are some differences in the incidences of some TEAEs by age, gender or race, there is no obvious pattern that is biologically plausible, and the observed differences may be spurious. These differences should be investigated further as more safety data are accrued in this population.

Weight

Table 53 shows the TEAEs with a risk difference of at least 15% between the highest and lowest weight subgroups. A number of TEAEs had incidences that increased with weight across all three weight subgroups.

Table 53: AML Safety Population – Common TEAEs by Weight Group

PT[a]	<55 kg (N=52)		55-99 kg (N=209)		≥100 kg (N=26)		Risk Difference*
	n	%	n	%	n	%	
Dyspnoea	14	27	67	32	15	58	-31
Renal impairment	4	8	41	20	9	35	-27
Fatigue	14	27	90	43	12	46	-19
Diarrhea	15	29	75	36	12	46	-17
Dysgeusia	6	12	18	9	7	27	-15
Hypotension	6	12	47	22	7	27	-15
Pain in extremity	2	4	31	15	5	19	-15

PT[a]	<55 kg (N=52)		55-99 kg (N=209)		≥100 kg (N=26)		Risk Difference*
	n	%	n	%	n	%	
Pneumonia	14	27	62	30	11	42	-15
Hypokalaemia	16	31	47	22	4	15	15

*Risk difference for <55 kg vs. ≥100 kg subgroups
[a] Includes grouped terms (see Appendix 14.5)
Source: FDA analysis

Clinical TL Review Comment:
Since gilteritinib is given at a flat rather than weight-based dose, the pattern of increased incidence of toxicities in patients with a higher weight is not consistent with the effect being drug-related. The results do not suggest that the flat dose is too high for patients of low weight or too low for patients with a high weight.

Creatinine Clearance
The TEAE incidence was grouped by creatinine clearance >90 mL/min (N=167), 60 to <90 mL/min (N=83) and <60 mL/min (N=41). The TEAE renal impairment was the only TEAE with a substantial difference in incidence across subgroups (13% vs. 22% vs. 37%).

Baseline ECOG Performance Status (PS)
The only TEAEs with a risk difference of at least 15% between patients with baseline ECOG PS 0-1 (N=239) vs. PS 2 or more (N=52) were dyspnoea (31% vs. 48%) and pneumonia (27% vs. 44%).

FLT3 Mutation Status
For the purposes of the safety analysis, the pooled results included patients independent of presence or absence of the FLT3 mutation. The only TEAEs with a risk difference of at least 15% between patients with (N=267) vs. without (N=21) the FLT3 mutation were Renal impairment (18% vs. 33%) and Elevated transaminases (43% vs. 24%).

8.3.7 Clinical Outcomes Assessments Informing Tolerability/Safety

There were no PRO data submitted.

8.3.8 Specific Safety Studies/Clinical Trials (including dose-related safety)

Dose Selection

In addition, a comparison of AE rate for patients assigned to 120 mg versus 200 mg was performed as part of the subset analysis. Severe nonhematologic AEs were more common in the 200 mg group, with the exception of transaminase increase which was slightly more common in the 120 mg group (**Table 54**). Of particular note, SAE in the SMQ Torsade occurred in 8% of patients in the 120 mg group and 20% in the 200 mg group.

Table 54: Rate of Grade 3 or Higher Nonhematologic TEAEs by Assigned Dose Group

AE	120 mg	200 mg	Risk difference
Torsade de pointe	20 (8%)	22 (20%)	12%
Sepsis	52 (22%)	34 (30%)	8%
Syncope/falls	13 (5%)	14 (13%)	8%
Musculoskeletal pain	11 (5%)	11 (10%)	5%
Pneumonia	51 (21%)	28 (25%)	4%
Hypotension	19 (8%)	13 (12%)	4%
Haemorrhage	29 (12%)	17 (15%)	3%
Transaminase increase	38 (16%)	14 (13%)	-3%

Proposed Optional Dose Increase for Lack of Efficacy

The safety of the 120-mg dose versus the 200-mg dose of gilteritinib was examined in order to inform recommendations concerning the issue of whether a dose increase would be included in the label. Eighty-six patients in Study 0301 who underwent a dose increase from 120 to 200 mg were examined with respect to their risk of AE before and after dose increase. Hematologic AEs were not included due to the high rate of hematologic AEs related to the underlying malignancy and potential for confounding.

Table 55: Rate of Nonhematologic TEAEs by Dose of Gilteritinib

AE	120 mg	200 mg	Risk difference
Pyrexia	10%	27%	16%
Fatigue	12%	26%	14%
Diarrhea	14%	28%	14%
Hypokalemia	9%	22%	13%
Pneumonia	7%	20%	13%
Decreased appetite	3%	15%	12%

Table 56: Rate of Grade 3 or Higher Nonhematologic TEAEs by Dose of Gilteritinib

AE	120 mg	200 mg	Risk difference
Pneumonia	7%	16%	9%
ALT increased	1%	9%	8%
Febrile neutropenia	22%	29%	7%
Hypokalemia	1%	8%	7%
Hypophosphatemia	1%	7%	6%
Fatigue	1%	6%	5%
CPK increased	1%	5%	4%
QT prolonged	0%	3%	3%

When nonhematologic issues were considered, the rate of TEAE was higher for several common AEs. In addition, there was an increase risk in SAEs, including QT prolongation and grade 3 or higher pneumonia, ALT increase, febrile neutropenia, and hypokalemia.

Clinical TL Review Comment:
The increased toxicities at the higher dose of gilteritinib outweighs the rare response seen with dose increase. The proposed optional dose increase is not in the patient's best interest.

8.3.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No formal clinical studies of carcinogenicity were performed. Occasional second primary malignancies were observed (see AESI, above), but no pattern of specific tumor types suggesting an increased risk was observed. However, longer term studies are needed to fully assess the potential for carcinogenicity.

Pediatrics and Assessment of Effects on Growth

No data from trials in children were submitted with this application.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The abuse potential for gilteritinib is considered very low. No withdrawal or rebound effects have been identified.

8.3.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Gilteritinib has not yet been marketed in any country and therefore no postmarket experience is available.

Expectations on Safety in the Postmarket Setting

Safety in the postmarket setting is expected to be similar to that observed in clinical trials, although rare events may be identified in the postmarketing setting that have not yet been observed in the trials.

8.3.11 Integrated Assessment of Safety

In general, all adverse events were considered adverse reactions with the exception of cytopenias. At the present time, the available evidence indicates that gilteritinib does not cause cytopenias. The safety profile of gilteritinib is otherwise similar to that of other kinase inhibitors. The most common adverse reactions (≥20%) were myalgia/ arthralgia (42%), transaminase increased (41%), fatigue/malaise (40%), fever (35%), noninfectious diarrhea

(34%), dyspnea (34%), edema (34%), rash (30%), pneumonia (30%), nausea (27%), stomatitis (26%), cough (25%), headache (21%), hypotension (21%), dizziness (20%) and vomiting (20%). Other clinically significant adverse reactions occurring in ≤10% of patients included: electrocardiogram QT prolonged (7%), cardiac failure (4%), pericardial effusion (3%), pericarditis (2%), differentiation syndrome (1%), anaphylactic reaction (1%) and posterior reversible encephalopathy syndrome (1%).

The most frequent nonhematological serious adverse reactions (≥5%) reported in patients were pneumonia (19%), sepsis (13%), fever (13%), dyspnea (7%) and renal impairment (5%). Overall, 22 of 292 patients (8%) discontinued XOSPATA treatment permanently due to an adverse reaction. The most common adverse reactions (>1%) leading to discontinuation were pneumonia (2%), sepsis (2%) and dyspnea (1%).

Overall, gilteritinib is tolerable at a dose of 120 mg daily. However, there are several specific safety issues that warrant monitoring and intervention to avoid high-grade toxicities.

First, QT prolongation can occur with some patients receiving gilteritinib. Monitoring of QT interval by ECG appears to reduce this risk. Close monitoring of ECG such as was used in trial 0301 may identify patients at risk for torsades early in the course of treatment and prevent sudden death. Although gilteritinib was not clearly associated with electrolyte abnormalities, diarrhea, which can deplete electrolytes, was a common TEAE and close monitoring of electrolytes is recommended to reduce the risk of torsades.

Second, a risk of differentiation syndrome was identified in patients receiving gilteritinib, including a suspected fatal case. Although the risk appears to be small compared to that associated with all trans retinoic acid or differentiating agents such as enasidenib, differentiation syndrome is treatable but potentially fatal without treatment and therefore it is important that clinicians be aware of this potential diagnosis so that treatment can be started promptly.

Third, gilteritinib use is associated with transaminase increases, bilirubin increases, and some symptomatic liver disease. Therefore, close monitoring of liver function tests is needed during treatment.

Fourth, CPK elevations were common among patients receiving gilteritinib. Although rhabdomyolysis was identified in only a single patient, other musculoskeletal events which may suggest an undiagnosed or subclinical rhabdomyolysis, including fatigue/malaise and musculoskeletal pain or soreness, were commonly observed. Thus, monitoring of CPK during treatment and clinical awareness of the risk are recommended.

Fifth, pancreatitis was observed as a rare but potentially fatal event. Clinicians should have a high index of suspicion for pancreatitis in patients with abdominal pain.

SUMMARY AND CONCLUSIONS

8.4 Statistical Issues

While the lower bound of the 95% CI of the CR/CRh rates appear to rule out 12% based on both of Applicant's prespecified analysis population and FDA's adjudicated population. Whether the median DOR can be estimated accurately in Study 301 may be a concern due to the short duration of follow-up.

8.5 Conclusions and Recommendations

The results of the clinical trials submitted for consideration show a positive benefit/risk ratio for the use of gilteritinib in patients with FLT3-positive R/R AML. Approval is based on the CR/CRh rate, and evaluation of toxicity. There are serious risks associated with the use of gilteritinib, including QT prolongation, differentiation syndrome and pancreatitis. Study of long-term outcomes and characterization of the risk of differentiation syndrome is needed postmarketing. Risks can be mitigated by appropriate labeling. In view of the clinical benefit demonstrated, the review team recommends regular approval of gilteritinib.

Primary Statistical Reviewer Yaping Wang, PhD	Statistical Team Leader Yuan Li Shen, DrPH
Primary Clinical Reviewer E. Dianne Pulte, MD	Clinical Team Leader Donna Przepiorka, MD, PhD

9 Advisory Committee Meeting and Other External Consultations

This application was not discussed at an advisory committee.

10 Pediatrics

(b) (4) has Orphan Designation for the treatment of AML and is therefore exempt from the requirement for pediatric studies under the Pediatric Research Equity Act (PREA). No pediatric data were submitted with this NDA.

11 Labeling Recommendations

11.1 Prescribing Information

Summary of Significant Labeling Changes	
Section	**Approved Labeling**
2.3	Recommended dose modifications added
5.3	Pancreatitis added as a warning
6.1	Safety population increased to all 292 patients treated with 120 mg gilteritinib using grouped terms for adverse reactions. Laboratory abnormalities added.
14.1	Efficacy outcomes limited to the 138 patients confirm to have a FLT3 mutation by the proposed companion diagnostic. (b) (4)

12 Risk Evaluation and Mitigation Strategies

It was concluded that a REMS is not needed to ensure that the benefits of gilteritinib outweigh its risks in the intended population. Healthcare providers who will prescribe and administer (b) (4) are likely to be able to monitor for and manage the gilteritinib-related adverse reactions without additional risk mitigation measures beyond labeling.

13 Postmarketing Requirements and Commitments

PMR-1

Demonstrate safety of long-term treatment with gilteritinib. Submit an integrated report and the supporting data files to summarize the safety outcomes when all patients on 2215-CL-0101, 22215-CL-0102 and 2215-CL-0301 have completed at least three years of treatment with gilteritinib or withdrew earlier.

PMR-2

Characterize the risk of differentiation syndrome in patients receiving gilteritinib for treatment of acute myeloid leukemia with a FLT3 mutation. Conduct a pooled analysis to characterize gilteritinib-related differentiation syndrome, specifically, incidence, observed signs and symptoms, duration, and response to intervention, based on patient-level data from on-going trials in patients with acute myeloid leukemia. Submit the study report and analysis data set.

PMR-3

Provide data to establish that the risks of gilteritinib are outweighed by the potential benefit for patients with AML having a mutation in the FLT3 tyrosine kinase domain (TKD). Submit a summary report and a supporting data set that includes outcomes for at least 30 patients with a FLT3-TKD mutation.

PMC-1

Clarify the sensitivity of various FLT3 mutations other than internal tandem duplications (ITDs) and the D835Y tyrosine kinase domain mutation by in vitro testing. Include testing of I836 mutations, other D835 mutations, and other mutations reported to occur in AML. Submit a summary report.

14 Appendices

14.1 References

See footnotes in text.

14.2 Financial Disclosure

The Sponsor identified only a single investigator for trials 0101 or 0301 who had financial interests to disclose. He was stated to have received "significant payments of other sorts…related to his research and development service grants." His site randomized two patients to the study. Attachments for disclosure of financial information are not applicable to Study 0101. In addition, financial disclosure was not available for four sub-investigators on protocol 0301, two at Massachusetts General Hospital and two at Mount Sinai Medical Center. In each case, the Sponsor states that the CRO is following up with the site to obtain the necessary information. Five patients were enrolled at MGH and 3 at MSMC.

Covered Clinical Study (Name and/or Number): 0101

Was a list of clinical investigators provided:	Yes X ☐	No ☐
Total number of investigators identified: 261 at sites which enrolled subjects plus 7 which were initiated but did not enroll patients		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: NA Significant payments of other sorts: NA Proprietary interest in the product tested held by investigator: NA Significant equity interest held by investigator in S Sponsor of covered study: NA		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes	No
Is a description of the steps taken to minimize potential bias provided:	Yes X	No
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes	No

Study 0103:

Was a list of clinical investigators provided:	Yes X	No (Request list from Applicant)
Total number of investigators identified: 358		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	No (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes X	No (Request explanation from Applicant)

14.3 Nonclinical Pharmacology/Toxicology Appendices

None.

14.4 OCP Appendices

14.4.1 Summary of Bioanalytical Method Validation and Performance

Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Yes. Plasma and urine concentrations of the active parent, gilteritinib was measured in the clinical pharmacology and biopharmaceutics studies. From preclinical studies and clinical mass balance study (2215-CL-0105), none of the metabolite has exposure exceeded 10% of the parent gilteritinib exposure. Therefore, for the phase 1/2 dose escalation (2215-CL-0101) and phase 3 (2215-CL-0301) clinical studies and clinical pharmacology studies (2215-CL-0106, 2215-CL-0108, 2215-CL-0110, and 2215-CL-0113), the Applicant measured only the plasma concentration of gilteritinib.

For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total plasma concentration of gilteritinib was measured in all studies, except for clinical pharmacology study that assessed the effect of hepatic impairment on gilteritinib pharmacokinetics (2215-CL-0106), where both total and free forms of gilteritinib were measured. For this study, a validated analytical method for measuring the concentration of the free form of gilteritinib in human plasma dialysate containing K_2EDTA by tandem mass spectrometry (LC-MS/MS) was used to evaluate protein binding. The average fraction unbound (f_u) values of gilteritinib ranged from 0.0572±0.0061 in subjects with normal hepatic function to 0.0865±0.0297 in subjects with moderate hepatic impairment as measured by LC/MS/MS methods for total and free forms of gilteritinib.

What bioanalytical methods are used to assess concentrations?

The concentration of gilteritinib and its metabolites were quantified in human plasma and urine using liquid chromatography with LC-MS/MS detection methods. Summary of the methods used for the measurement of plasma and urine concentrations of gilteritinib in clinical studies are listed in **Table 57**. Sample analysis conducted in two laboratories, Astellas Research Institute of America (ARIA) (b) (4) Cross validation of the methods used to measure human plasma concentrations of gilteritinib at ARIA (b) (4) was performed and demonstrated that both laboratories provided comparable results. A summary of these results is provided in **Table 58**. In all methods, the gilteritinib concentrations was measured using the least-squares linear regression with $1/X^2$ weighting of the ratio of peak areas (analyte/internal standard). Across all methods used in the clinical studies, the quantification range was 0.1 to 5000 ng/mL and 0.5 to 250 ng/mL for analyzing gilteritinib in plasma and urine, respectively, after supported liquid extraction. Overall, the precision, accuracy, selectivity and performance of the methods used to analyze gilteritinib in plasma and

urine were acceptable and within the FDA guidance recommended criteria. Gilteritinib was stable up to 54 hours at room temperature and at 4°C, 843 days at -20 and -80°C and after up to 10 freeze and thaw cycles in the plasma and urine samples. Incurred sample reanalysis met the acceptance criteria for all studies which requires that at least 2/3 of the reanalyzed samples to fall within 20% of the original concentration.

Table 57: Methods for Measurement of Plasma and Urine Concentrations of Gilteritinib in Clinical Studies

Method Validation Study	ME-0015	ME-0032	ME-0033	ME-0016	ME-0036	ME-0035
Matrix	Plasma	Plasma	Plasma	Urine	Plasma	Urine
Analyte	Gilteritinib	Gilteritinib	Gilteritinib	Gilteritinib	Gilteritinib	Gilteritinib
Analytical instrument and detection method	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS	LC-MS/MS
Sample preparation technique	SLE	SLE	SLE	SLE	SLE	SLE
Validation results						
Lower limit of quantitation [ng/mL]	0.5	0.1	10.0	0.5	0.100	0.5
Amount of matrix used [mL]	0.05	0.05	0.05	0.055 of IPA treated (1:10) urine	0.05	0.05 of IPA treated (1:10) urine
Concentration range [ng/mL]	0.5 to 250	0.1 to 50	10.0 to 5000	0.5 to 250	0.100 to 50.0	0.500 to 250
Within-run accuracy [%RE]	−5.2 to 8.7	−5.9 to 20	−6.3 to 2.0	−14.0 to 4.9	−8.7 to 20.0	−3.0 to 4.4
Between-run accuracy [%RE]	−3.8 to 6.4	−1.4 to 10	−5.0 to −0.3	−6.4 to −0.9	−1.5 to 13.0	−2.0 to 2.6
Within-run precision [%CV]	1.8 to 6.9	3.0 to 10.0	1.2 to 6.1	1.7 to 8.1	1.5 to 17.7	1.2 to 13.3
Between-run precision [%CV]	2.7 to 5.7	3.7 to 9.1	2.0 to 5.0	4.9 to 7.8	5.4 to 13.5	1.6 to 8.5
Dilution integrity Accuracy [%RE] Precision [%CV]	100-fold −9.0 1.6	100-fold 2.4 3.7	100-fold −7.0 2.5	100-fold −8.6 2.0	10-fold −11.5 2.4	100-fold −2.5 3.4
Short-term stability	26 h at RT and ambient light	24 h at RT	54 h at RT and 4°C	27 h at RT	69 h at RT and 4°C	67 h at RT and 4°C
Long-term stability	843 days at −20°C and −80°C	304 days at −20°C and −80°C	750 days at −20°C 735 days at −80°C	580 days at −20°C and −80°C	Not Applicable	Not Applicable
Freeze-thaw stability	4 cycles at −20°C and −80°C	4 cycles at −20°C and −80°C	10 cycles at −80°C, 5 cycles at −20°C	3 cycles at −20°C and −80°C	4 cycles at −20°C and −80°C	5 cycles at −20°C and −80°C
Whole blood stability	2 h at RT and on ice	2 h at RT	2 h at RT and 4°C	Not Applicable	Not Applicable	Not Applicable
Test facility	ARIA	ARIA	inVentiv Health	ARIA	inVentiv Health	inVentiv Health
Clinical study in which the method was used	CL-0101 CL-0102 CL-0103 CL-5101	CL-0106 CL-0108 CL-0110	CL-0101 CL-0103 CL-0105 CL-0301	CL-0102	CL-0113	CL-0105

ARIA: Astellas Research Institute of America LLC; CV: coefficient of variation; IPA: isopropyl alcohol; LC-MS/MS: liquid chromatography-tandem mass spectrometry; RE: relative error; RT: room temperature; SLE: supported liquid extraction.

Source: Summary of biopharmaceutic studies and analytical methods, Table 4, Section 1.2.1.2

Table 58: Interlaboratory Cross Validation Summary for Measurement of Plasma Concentrations of Gilteritinib

Study No.	2215-ME-0037			
Sample Origin	ARIA			
Sample Storage Temperature (nominal)	-20°C			
Linearity - Correlation Coefficient, r	0.9973			
Spiked Cross Validation Sample Results	Nominal Concentration [ng/mL]	Mean Concentration [ng/mL]	Accuracy [%RE]	Precision [%CV]
ARIA				
LQC	40.0	39.8	-0.5	2.3
MQC	400	418	4.5	3.5
HQC	4000	4100	2.5	1.6
(b) (4)				
LQC	40.0	38.0	-4.8	11.6
MQC	400	408	2.1	4.1
HQC	4000	3920	-2.0	2.9
Blanks	<LLOQ	<10.0	NA	NA
Incurred Samples	91.7% (11 out of 12) of incurred samples met acceptance criteria			

ARIA: Astellas Research Institute of America LLC; CV: coefficient of variation; HQC: high quality control; LLOQ: lower limit of quantitation; LQC: low quality control; MQC: middle quality control; NA: not applicable; RE: relative error
Source: Summary of biopharmaceutic studies and analytical methods, Table 5, Section 1.2.1.2

14.4.2 Clinical PK and/or PD Assessments

Gilteritinib Pharmacokinetics:
The clinical pharmacokinetics of gilteritinib was evaluated in two phase 1/2 dose escalation studies (2215-CL-0101 and 2215-CL-0102). The result of these studies showed that gilteritinib disposition in AML patients can be adequately described by a two-compartment model with first order absorption and first order elimination. Gilteritinib has extensive accumulation (up to 10-fold) in AML patients after multiple dose administration. This accumulation explained by long $T_{1/2}$ of gilteritinib (median of 113 hours). A summary of gilteritinib pharmacokinetic parameters after single and multiple (cycle 1 day 28) dose administration is presented in **Table 59** and **Table 60** for Study 2215-CL-0101 and **Table 61** and **Table 62** for Study 2215-CL-0102. Comparison of gilteritinib pharmacokinetics in Japanese and non-Japanese R/R AML patients demonstrated that the exposure of gilteritinib in Japanese patients was comparable to that of non-Japanese patients. The estimated geometric mean ratios (GMRs) of dose-normalized exposure, DN-AUC_{24} and DN-C_{max} after multiple-dose administration in Japanese compared with non-Japanese patients were 1.02 and 1.04, respectively, suggesting no ethnic difference in exposure, **Table 63**. Population pharmacokinetic modeling estimated 46% greater gilteritinib CL/F in healthy volunteers compared to AML patients and 63% greater central volume of distribution in healthy volunteers than that for patients with R/R AML. However, the estimated increases in CL/F and Vc did not result in clinically meaningful differences in gilteritinib exposure in healthy volunteers and patients.

Table 59: Plasma Pharmacokinetic Parameters of Gilteritinib by Dose Level in R/R AML Patients after Single Dose Administration – Study 2215-CL-0101

Parameter Statistic	20 mg (N = 5)	40 mg (N = 3)	80 mg (N = 3)	120 mg (N = 3)	200 mg (N = 3)	300 mg (N = 3)	450 mg (N = 3) †
C_{max} (ng/mL)							
Mean (SD)	28.13 (21.49)	24.98 (14.58)	75.29 (25.22)	136.7 (94.37)	168.2 (45.34)	204.3 (136.4)	207.6 (51.81)
%CV	76.4	58.3	33.5	69.0	27.0	66.8	25.0
Median	23.70	16.89	71.46	85.66	149.0	136.5	215.7
Min – Max	7.46 - 64.5	16.3 - 41.8	52.2 - 102	78.9 - 246	136 - 220	115 - 361	152 - 255
t_{max} (h)							
Median	2.00	5.983	4.000	2.083	5.233	6.067	5.783
Min – Max	0.500 - 4.03)	3.97 - 24.0	4.00 - 4.08	2.00 - 3.83	4.00 - 5.97	4.08 - 24.1	4.08 - 5.92
AUC_{24} (ng·h/mL)							
Mean (SD)	302.1 (207.0)	360.0 (223.5)	1216 (472.6)	2480 (1972)	3022 (843.6)	4163 (3178)	3324 (221.1)
%CV	68.5	62.1	38.9	79.5	27.9	76.3	6.7
Median	262.2	314.9	995.3	1393	2538	2446	3324
Min – Max	98.5 - 642	163 - 603	895 - 1759	1291 - 4756	2533 - 3997	2214 - 7830	3168 - 3480

Source: Study 2215-CL-0101, Clinical study report, Table 21, Section 8.3.1.2

Table 60: Plasma Pharmacokinetic Parameters of Gilteritinib by Dose Level in R/R AML Patients after Multiple Dose Administration (Cycle 1 Day 15) – Study 2215-CL-0101

Parameter Statistic	20 mg (N = 4)†	40 mg (N = 3)‡	80 mg (N = 3)	120 mg (N = 3)	200 mg (N = 2)	300 mg (N = 3)	450 mg (N = 1)
C_{max} (ng/mL)							
Mean (SD)	64.64 (48.77)	107.6 (31.92)	376.4 (150.5)	374.2 (190.1)	1462 (815.1)	1525 (664.6)	1528
%CV	75.5	29.7	40.0	50.8	55.8	43.6	
Median	45.57	105.6	396.3	282.0	1462	1257	
Min – Max	30.5 - 137	76.7 - 140	217 - 516	248 - 593	886 - 2038	1036 - 2282	
t_{max} (h)							
Median	4.008	3.867	4.333	2.167	6.033	6.050	5.933
Min – Max	4.00 - 6.00	0.50 - 6.00	4.00 - 4.42	1.95 - 5.75	6.00 - 6.07	4.08 - 6.07	
AUC_{24} (ng·h/mL)							
Mean (SD)	1299 (1006)	2482 (33.28)	6958 (3273)	6943 (3221)	31428 (21412)	31005 (10068)	34768
%CV	77.4	1.3	47.0	46.4	68.1	32.5	
Median	917.0	2482	6234	6180	31428	28711	
Min – Max	540 - 2440	2458 - 2505)	4108 - 10532	4171 - 10477	16288 - 46568	22282 - 42022	
$t_{1/2}$ (h)							
Mean (SD)	62.14 (17.88)	151.8 (129.2)	86.11 (24.08)	45.85 (18.83)	141.9 (61.51)	142.2 (55.04)	NC
%CV	28.8	85.1	28.0	41.1	43.3	38.7	
Median	54.46	151.8	91.03	44.93	141.9	159.0	
Min – Max	49.4 - 82.6	60.5 - 243)	60.0 - 107	27.5 - 65.1	98.4 - 185	80.7 - 187	
R_{ac}							
Mean (SD)	4.259 (1.069)	9.640 (7.754)	5.693 (1.442)	3.290 (1.118)	9.041 (3.693)	9.057 (3.303)	NC
%CV	25.1	80.4	25.3	34.0	40.8	36.5	
Median	3.799	9.640	5.987	3.232	9.041	10.07	
Min – Max	3.50 - 5.48	4.16 - 15.1	4.13 - 6.97	2.20 - 4.44	6.43 - 11.7	5.37 - 11.7	

Source: Study 2215-CL-0101, Clinical study report, Table 22, Section 8.3.1.2

Table 61: Plasma Pharmacokinetic Parameters of Gilteritinib by Dose Level in R/R AML Japanese Patients after Single Dose Administration – Study 2215-CL-0102

Parameter Statistic	20 mg (n = 1)	40 mg (n = 4)	80 mg (n = 4)	120 mg (n = 4)	200 mg (n = 9)	300 mg (n = 2)
C_{max} (ng/mL)						
Mean	15.32	29.81	67.07	216.38	221.22	292.49
(SD)	(NA)	(13.56)	(26.02)	(167.00)	(97.05)	(NA)
%CV	NA	45.5	38.8	77.2	43.9	NA
Median	NA	31.17	65.58	165.83	209.94	292.49
Min,	NA,	12.34,	44.47,	75.44,	91.62,	170.40,
Max	NA	44.56	92.64	458.44	403.11	414.58
AUC_{24} (ng·h/mL)						
Mean	241.65	435.59	1047.54	3340.23	3595.61	5367.62
(SD)	(NA)	(167.16)	(574.97)	(2353.76)	(1463.99)	(NA)
%CV	NA	38.4	54.9	70.5	40.7	NA
Median	NA	492.41	1036.55	2742.81	3616.03	5367.62
Min,	NA,	192.64,	438.43,	1183.55,	1776.16,	2810.75,
Max	NA	564.89	1678.61	6691.76	6701.00	7924.49
t_{max} (h)						
Median	NA	4.01	4.03	3.03	5.92	6.93
Min,	NA,	3.88,	2.00,	1.93,	3.85,	3.88,
Max	NA	4.08	9.93	6.17	10.00	9.98

Source: Study 2215-CL-0102, Clinical study report, Table 15, Section 8.3.1.2

Table 62: Plasma Pharmacokinetic Parameters of Gilteritinib by Dose Level in R/R AML Japanese Patients after Multiple Dose Administration (Cycle 1 Day 28) – Study 2215-CL-0101

Parameter Statistic	20 mg (n = 1)	40 mg (n = 3)	80 mg (n = 3)	120 mg (n = 2)	200 mg (n = 5)
C_{max} (ng/mL)					
Mean	70.53	122.96	205.90	680.23	1016.28
(SD)	(NA)	(66.06)	(36.78)	(NA)	(295.23)
%CV	NA	53.7	17.9	NA	29.0
Median	NA	158.24	215.76	680.23	886.50
Min,	NA,	46.75,	165.20,	668.89,	837.54,
Max	NA	163.88	236.75	691.57	1538.03
AUC_{tau} (ng·h/mL)					
Mean	1345.53	2411.97	4142.27	13463.35	21573.86
(SD)	(NA)	(1181.65)	(738.07)	(NA)	(6230.86)
%CV	NA	49.0	17.8	NA	28.9
Median	NA	3092.77	4510.94	13463.35	19400.24
Min,	NA,	1047.52,	3292.50,	13151.21,	16968.79,
Max	NA	3095.63	4623.37	13775.49	32181.53
t_{max} (h)					
Median	NA	3.92	6.08	5.06	6.00
Min,	NA,	2.05,	1.93,	4.03,	3.98,
Max	NA	3.95	6.12	6.08	10.00
R_{ac} (AUC)					
Mean	5.57	5.86	5.97	7.97	8.10
(SD)	(NA)	(0.70)	(4.08)	(NA)	(3.69)
%CV	NA	11.9	68.4	NA	45.6
Median	NA	5.48	4.68	7.97	8.83
Min,	NA,	5.44,	2.69,	4.83,	3.89,
Max	NA	6.67	10.55	11.11	12.18

Source: Study 2215-CL-0102, Clinical study report, Table 16, Section 8.3.1.2

Table 63: Statistical Comparison of Mean Dose-Normalized Plasma Gilteritinib Exposure Parameters Between Japanese and Non-Japanese Patients After Multiple Dose Administration

Parameter	Comparison	Japanese (2215-CL-0102)		non-Japanese (2215-CL-0101)		GMR	90% CI
		N	LS Mean	N†	LS Mean		
DN- AUC_{24} (ng.h/mL/mg)	Japanese/ non-Japanese	14	76.3	17	74.7	1.02	0.75-1.39
DN- C_{max} (ng/mL/mg)	Japanese/ non-Japanese	14	3.7	19	3.6	1.04	0.77-1.41

CI: confidence interval; LS: least squares; GMR: geometric LS mean ratio.

Standard deviation was not calculated nor displayed in case that the number of individuals per time point is less than three.

†Cohort 1 in 2215-CL-0101

Source: Summary of clinical pharmacology studies, Table 15, Section 3.5.1

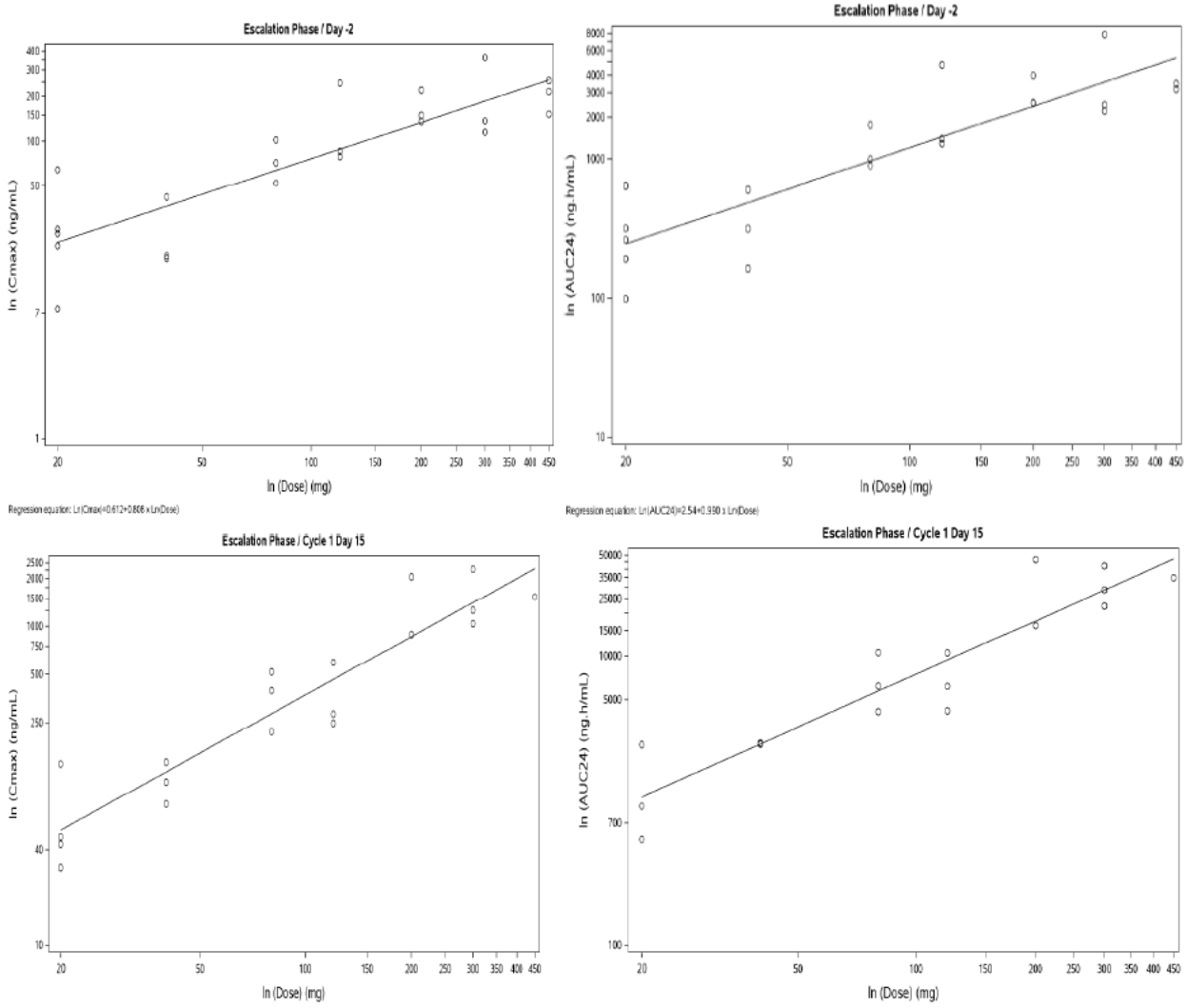
Dose Proportionality:
Dose proportionality of gilteritinib exposure was evaluated in two phase1/2 dose escalation studies (2215-CL-0101 and 2215-CL-0102). In Study 2215-CL-0101, gilteritinib exhibited approximate dose proportional pharmacokinetics following once daily administration of gilteritinib over the dose range of 20 mg to 450 mg. The power model suggested dose proportionality of C_{max} and AUC_{24} after single- and multiple-dose (**Table 64** and **Figure 14**) administration with positive slope estimates at or near unity. Similarly, results from Study 2215-CL-0102 in Japanese patients, demonstrated dose proportional exposure of gilteritinib after single and multiple administration with power model analysis supporting this conclusion, **Table 64**.

Table 64: Statistical Assessment Using Power Model of Gilteritinib Dose Proportionality in R/R AML Patients – Studies 2115-CL-0101 and 2115-CL-0102

Study	Visit	Parameter	Slope Estimate	90% CI
2215-CL-0101	Day -2 (single dose)	AUC_{24} (ng•h/mL)	0.990	(0.788, 1.19)
		C_{max} (ng/mL)	0.808	(0.629, 0.988)
	Cycle 1 Day 15 (multiple dose)	AUC_{24} (ng•h/mL)	1.22	(1.00, 1.43)
		C_{max} (ng/mL)	1.21	(1.02, 1.41)
2215-CL-0102 Japanese Patients	Day -2 20 mg to 300 mg	AUC_{last} (ng·h/mL)	1.28	(0.978, 1.57)
		C_{max} (ng/mL)	1.19	(0.881, 1.49)
	Day -2 20 mg to 200 mg	AUC_{last} (ng·h/mL)	1.30	(0.974, 1.63)
		C_{max} (ng/mL)	1.24	(0.900, 1.57)
	Cycle 1 Day 28 20 mg to 200 mg	AUC_{tau} (ng·h/mL)	1.35	(1.04, 1.66)
		C_{max} (ng/mL)	1.31	(0.983, 1.65)

Source: Summary of clinical pharmacology studies, Tables 7 and 8, Sections 2.3.1.1 and 2.3.1.2

Figure 14: Dose Proportionality of C_{max} and AUC_{24} for Gilteritinib in R/R AML Patients after Single (Day -2) and Multiple (Cycle 1 Day 15) Dose Administration – Study 2115-CL-0101

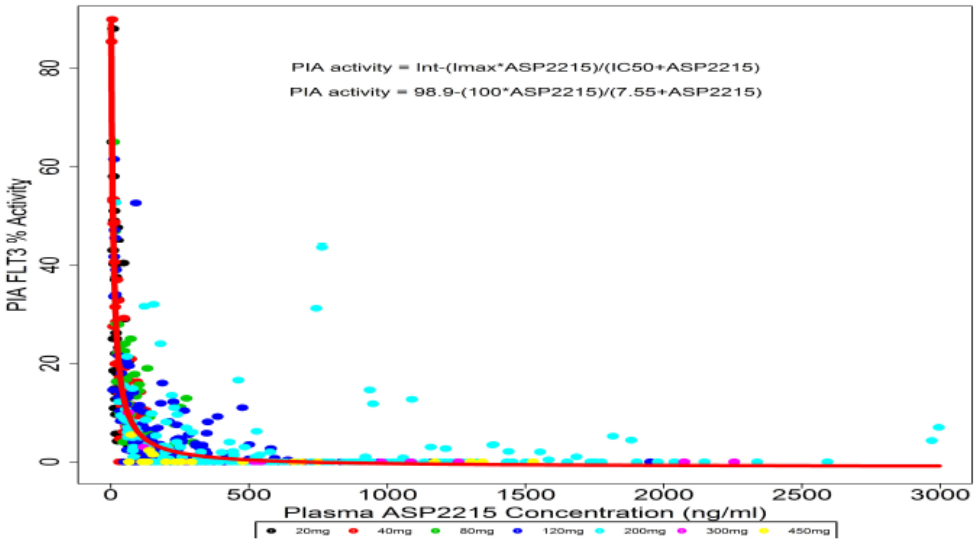


Source: Study 2215-CL-0101, Clinical study report, Figure 9, Section 8.3.1.3

Gilteritinib Pharmacodynamics:

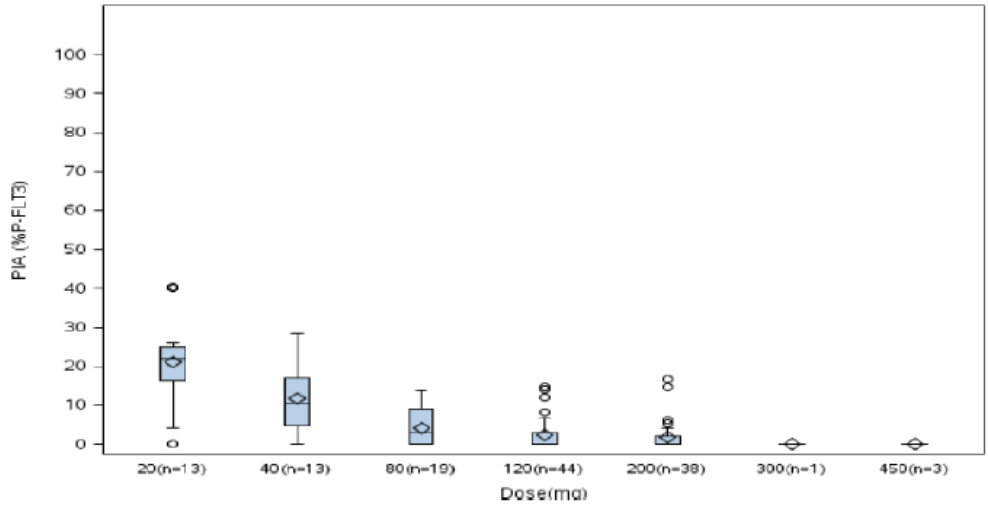
The Applicant conducted ex-vivo assays to assess the pharmacodynamic of gilteritinib. Plasma inhibitory assay (PIA) was performed on blood samples collected from patients enrolled in Study 2215-CL-0101 at predose (0.5 hours before drug administration) and postdose (2, 6 and 24 hours following drug administration) time points. Inhibition of FLT3 phosphorylation for plasma samples at each time point was using the PIA assay described in Levis et al, 2006. Assessment of the relationship between gilteritinib concentration and inhibition of FLT3 phosphorylation showed a strong correlation, **Figure 15**. This assay showed that greater than 90% inhibition of FLT3 phosphorylation was observed by day 8 of cycle 1 at gilteritinib doses of ≥80 mg, **Figure 16**.

Figure 15: Relationship between Gilteritinib Exposure and PIA Activity



Source: Summary of clinical pharmacology studies, Figure 11, Section 2.7.1

Figure 16: Inhibition of pFLT3 by Dose Level at Cycle 1 Day 8 (Predose)



Source: Summary of clinical pharmacology studies, Figure 12, Section 2.7.1

Relative Bioavailability Study:
Although the to-be-marketed formulation used in the phase 3 clinical study, different tablet formulation has been used in the early clinical development studies that assessed the clinical pharmacokinetics characteristics of gilteritinib **Table 65**. The Applicant performed relative bioavailability study to compare gilteritinib exposure between two formulations. The results of relative bioavailability study showed similar gilteritinib exposure between the two formulations, in 40 healthy adult subjects. The GMR (90% CI) values were reported for the to-be-market tablet formulation (n=20) over the reference formulation (n=20) after a single dose of 40 mg under fasted conditions (**Table 66** and **Figure 17**): C_{max} 93.21 (80.75, 107.6); AUC_{last} 89.4 (78.23, 102.16); AUC_{inf} 89.33 (78.2, 102). The study was not powered for testing the bioequivalence, however, the two formulations are without clinically relevant exposure difference. Inter-subject variability in exposure parameters, AUC and C_{max}, was less after administration with the new tablet formulation (CV=18.2% - 23.0%) compared to the reference tablet formulation (CV=33.1% - 35.0%).

Table 65: Summary of Gilteritinib Tablet Formulations Used in Clinical Studies

	OLD FORMULATION			NEW FORMULATION
Strength	10 mg	40 mg	100 mg	40 mg
Formulation code	(b) (4)			
Formulation name	ASP2215 Tablets 10 mg	ASP2215 Tablets 40 mg	ASP2215 Tablets 100 mg	Gilteritinib Tablets 40 mg
Clinical Study				
	[2215-CL-0101] Phase 1/2 Dose Escalation Study	[2215-CL-0101] Phase 1/2 Dose Escalation Study	[2215-CL-0101] Phase 1/2 Dose Escalation Study	[2215-CL-0301] Phase 3 Study
	[2215-CL-0102] Phase 1/2 Dose Escalation Study Japanese Pts.	[2215-CL-0105] Mass Balance Study	[2215-CL-0102] Phase 1/2 Dose Escalation Study Japanese Pts.	[2215-CL-0113] Food Effect Study
	[2215-CL-0106] Hepatic Impairment Study	[2215-CL-0110] Relative Bioavailability Study		[2215-CL-0110] Relative Bioavailability Study
	[2215-CL-0108] DDI Study			

Source: Summary of biopharmaceutic studies and analytical methods, Table 2, Section 1.1

Table 66: Statistical Assessment of the Relative Bioavailability Between 40-mg gilteritinib New (Treatment A) and 40-mg Gilteritinib Reference (Treatment B) Tablet Formulations

Comparison	Parameter	Geometric LS Mean for Numerator	Geometric LS Mean for Denominator	Geometric LS Mean Ratio (%) †	90 % CI of the Ratio (%) †
Treatment A / Treatment B	AUC_{inf} (ng•h/mL)	1620	1810	89.33	(78.20, 102.04)
	AUC_{last} (ng•h/mL)	1580	1760	89.40	(78.23, 102.16)
	C_{max} (ng/mL)	29.5	31.7	93.21	(80.75, 107.60)

The pharmacokinetic analysis set consisted of the subset of subjects from the safety analysis set population for whom sufficient plasma concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter and for whom the time of dosing on the day of sampling was known.

ANCOVA: Analysis of Covariance; LS: Least squares

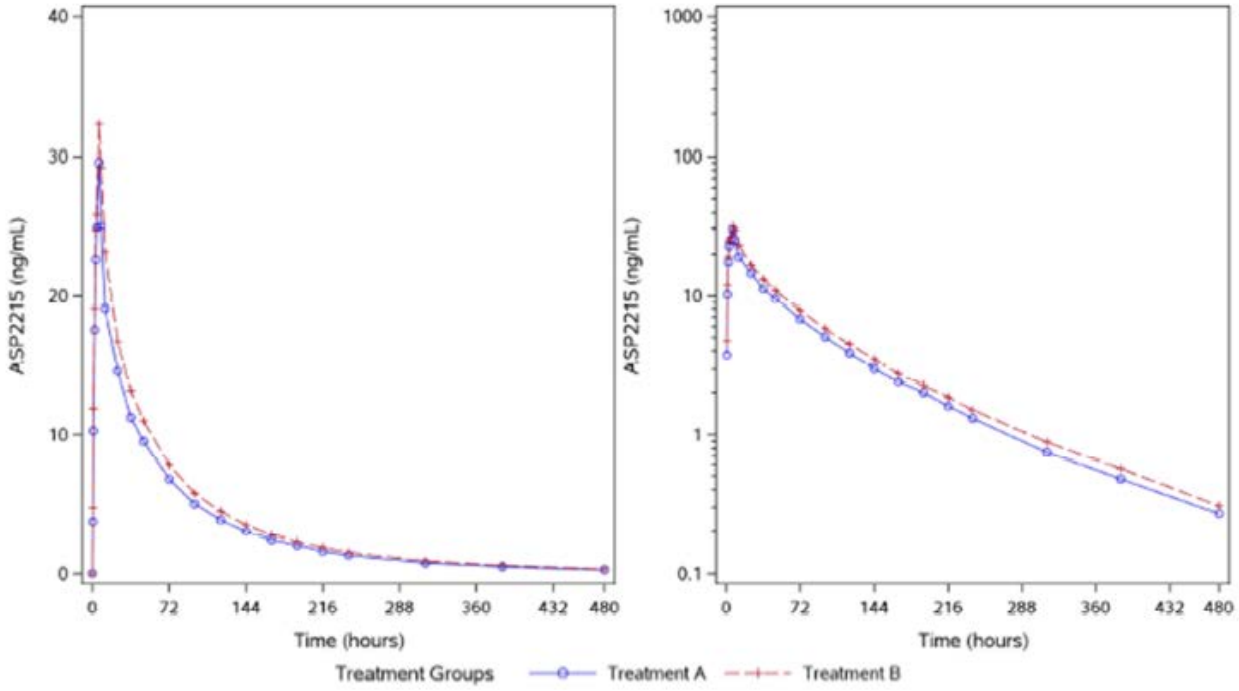
The analysis was performed using an ANCOVA model using natural logarithmic-transformed pharmacokinetic parameters (AUC_{inf}, AUC_{last} and C_{max}) after single dose administration of ASP2215 with weight, treatment as a fixed effect.

† The difference of LS means of log-transformed pharmacokinetic parameters between test and reference formulations and its 90% CI are back-transformed to the raw scale and are expressed as percent.

Treatment A: 40-mg ASP2215 new tablet; treatment B: 40-mg ASP2215 reference tablet.

Source: Study 2215-CL-0110, Clinical study report, Table 4, Section 8.1

Figure 17: Mean Plasma Concentration vs. Time Profiles of 40-mg Gilteritinib New (Treatment A) and 40-mg Gilteritinib Reference (Treatment B) Tablets (Linear and Semi-Logarithmic Scales)



Source: Study 2215-CL-0110, Clinical study report, Figure 1, Section 8.1

Population PK:
A population PK model for gilteritinib was developed using data from 5 Phase 1 studies, 1 Phase 1/2 study and 1 Phase 3 study, a total of 7,529 measurements from 618 subjects. Subject distribution in the analysis dataset by study is summarized in **Table 67** and by key continuous and dichotomous covariates in the dataset are summarized in **Table 68** and **Table 69** .

Table 67: Number of Patients and Concentration Records in Population PK Analysis

Protocol number	Number of patients with available plasma concentrations	Original number of patients	Total number of gilteritinib plasma concentrations valid for analysis	Original number of plasma concentrations
2215-CL-0101	256	257	2738	3012
2215-CL-0102	24	24	391	418
2215-CL-0106	24	24	583	656
2215-CL-0108	81	81	1502	1766
2215-CL-0110	42	42	896	943
2215-CL-0113	32	32	597	640
2215-CL-0301	159	168	822	1116
Total	618	628	7529	8551

Source: Population PK Report, Table 1, page 18

Table 68: Statistical Summary of Key Continuous Covariate Distribution (N=618)

Variable	Definition	Mean	SD	Med	Min	Max
AGE	Age (y)	53.53	16.7	55	20	90
WT	Body weight (kg)	75.5	17.9	74.7	36	157.1
LBM	Lean body mass(kg)	54.51	10.36	54.68	30.90	79.15
BSA	Body surface area (m^2)	1.95	0.26	1.96	1.29	2.96
BMI	Body mass index (kg/m^2)	26.02	5.45	25.46	14.81	57.63
ALB	Albumin (g/L)	39.1	5.9	40	20	58
TBL	Total bilirubin (mg/dL)	0.49	0.33	0.41	0.034	3.4
SCR	Serum creatinine (mg/dL)	0.88	0.29	0.82	0.23	2.1
LAST	Log transformed Aspartate aminotransferase (IU/L)	3.19	0.57	3.14	1.79	6.39
LALP	Log transformed Alkaline phosphatase (IU/L)	4.50	0.54	4.42	3.30	6.50
LCK	Log transformed Creatine phosphokinase (IU/L)	4.09	0.87	4.11	1.61	6.40
LALT	Log transformed Alanine aminotransferase (IU/L)	3.22	0.67	3.14	1.61	6.64

Source: Population PK Report, Table 2, page 21

Table 69: Statistical Summary of Key Dichotomous Covariate Distribution (N=618)

Variable	Definition	n	%(n/N*100)
RACE	Caucasian	412	67
	Black	88	14
	Asian	86	14
	Other	32	5
SEX	Male	382	62
	Female	236	38
FORM	Phase 1 tablet	406	66
	Phase 3 tablet	212	34
C3HS	Non-CYP3A strong inhibitor	430	70
	CYP3A strong inhibitor	188	30
C3HM	Non-CYP3A moderate inhibitor	416	67
	CYP3A moderate inhibitor	202	33
C3D	Non-CYP3A inducer	537	87
	CYP3A inducer	81	13
LF	Normal	525	85
	Mild	93	15
FAST	Fasted	602	97
	Fed	16	3
ECOG	ECOG 0	293	47
	ECOG 1	234	38
	ECOG 2 & above	91	15
FLT3M	(-)	79	13
	(+)	360	58
	non-AML	179	29
STAT	AML	439	71
	non-AML	179	29

Source: Population PK Report, Table 3, page 22

The observed data were well described by a 2-compartment model with first-order absorption. The parameter estimates from the final population PK model are summarized in **Table 70**.

Table 70: PK Parameter Estimates of the Final Full Covariate Model

Parameters (units)	Description	Mean estimate	%Relative Standard Error[a]	Bootstrap 95% Confidence Interval[b] (n=300)
Primary parameters				
θ1: TVCL (L/hr)	Typical value of apparent clearance	14.85	5.04	(12.97,16.26)
θ2: TVV2 (L)	Typical value of apparent central volume of distribution	1092.05	9.22	(912.29,1245.66)
θ3: TVQ(L/hr)	Typical value of inter-compartment clearance	45.34	14.11	(33.07,60.1)
θ4: TVV3 (L)	Typical value of apparent peripheral volume of distribution	1100.21	4.99	(988.74,1218.69)

θ5: TVKA(hr^{-1})	Typical value of absorption rate constant	0.43	13.17	(0.33,0.57)
θ7: ALAG1 (hr)	Typical value of lag time	0.34	5.34	(0.31,0.37)
θ8: F1 (%)	Typical value of relative bioavailability	1.01	3.96	(0.93,1.1)
θ9	Scaling parameter[d]	2.63	29.9	(1.24,3.97)
θ10: AGE exponent	Exponent for effect of AGE on CL	-0.27	27.23	(-0.42,-0.11)
θ11:ALB exponent	Exponent for effect of ALB on CL	0.53	27.91	(0.2,0.83)
θ12:C3D intercept	Intercept for effect of C3D on CL	0.15	65.91	(-0.03,0.39)
θ13:C3HM intercept	Intercept for effect of C3HM on CL	-0.21	23.16	(-0.3,-0.1)
θ14:C3HS intercept	Intercept for effect of C3HS on CL	-0.25	26.3	(-0.38,-0.11)
θ15:STAT intercept	Intercept for effect of STAT on CL	0.46	20.42	(0.3,0.66)
θ16:ALT exponent	Exponent for effect of ALT on CL	-0.21	45.78	(-0.42,-0.02)
θ17:WT exponent	Exponent for effect of WT on CL	0.76	25.57	(0.35,1.11)
θ18:PGPH intercept	Intercept for effect of PGPH on CL	-0.11	60.72	(-0.23,0.04)
θ19:SCR exponent	Exponent for effect of SCR on CL	-0.3	29.85	(-0.48,-0.12)
θ20:FAST intercept	Intercept for effect of FAST on KA	-0.73	5.92	(-0.8,-0.62)
θ21:STAT intercept	Intercept for effect of STAT on KA	1.43	24.67	(0.84,2.19)
θ22:LF intercept	Intercept for effect of LF on KA	0.82	41.7	(0.31,1.64)
θ23:C3D intercept	Intercept for effect of C3D on Q	2.03	23.55	(1.05,3.05)

θ24:STAT intercept	Intercept for effect of STAT on Q	-0.67	8.61	(-0.74,-0.5)
θ25:TBL exponent	Exponent for effect of TBL on Q	0.33	39.2	(0.04,0.62)
θ26:WT exponent	Exponent for effect of WT on V2	0.81	17.6	(0.5,1.07)
θ27:STAT intercept	Intercept for effect of STAT on V2	0.63	25.82	(0.42,0.92)
θ28:ECOG intercept	Intercept for effect of ECOG on V2	-0.25	29.07	(-0.37,-0.12)
θ29:ECOG intercept	Intercept for effect of ECOG on V2	-0.44	18.63	(-0.6,-0.25)
θ30:ALB exponent	Exponent for effect of ALB on V3	1.26	19.52	(0.84,1.81)
θ31:WT exponent	Exponent for effect of WT on V3	0.63	28.56	(0.25,0.94)
θ32: CLI Intercept	intercept for effect of STAT and C3D on CL	1.91	17.16	(1.3,2.6)
Random inter-individual variability (%IIV)				
ω1,1: BCL	IIV in CL	47.61	5.22	(43.59,53.85)
ω2,2: BV2	IIV in V2	46.02	5.44	(38.73,50)
ω3,3: BQ	IIV in Q	28.01	27.56	(20,57.45)
ω5,5: BKA	IIV in KA	96.81	5.92	(84.26,108.17)
Residual variability (%RV)[c]				
θ6: PERR	Proportional error of RV	27	3.07	(25,28)

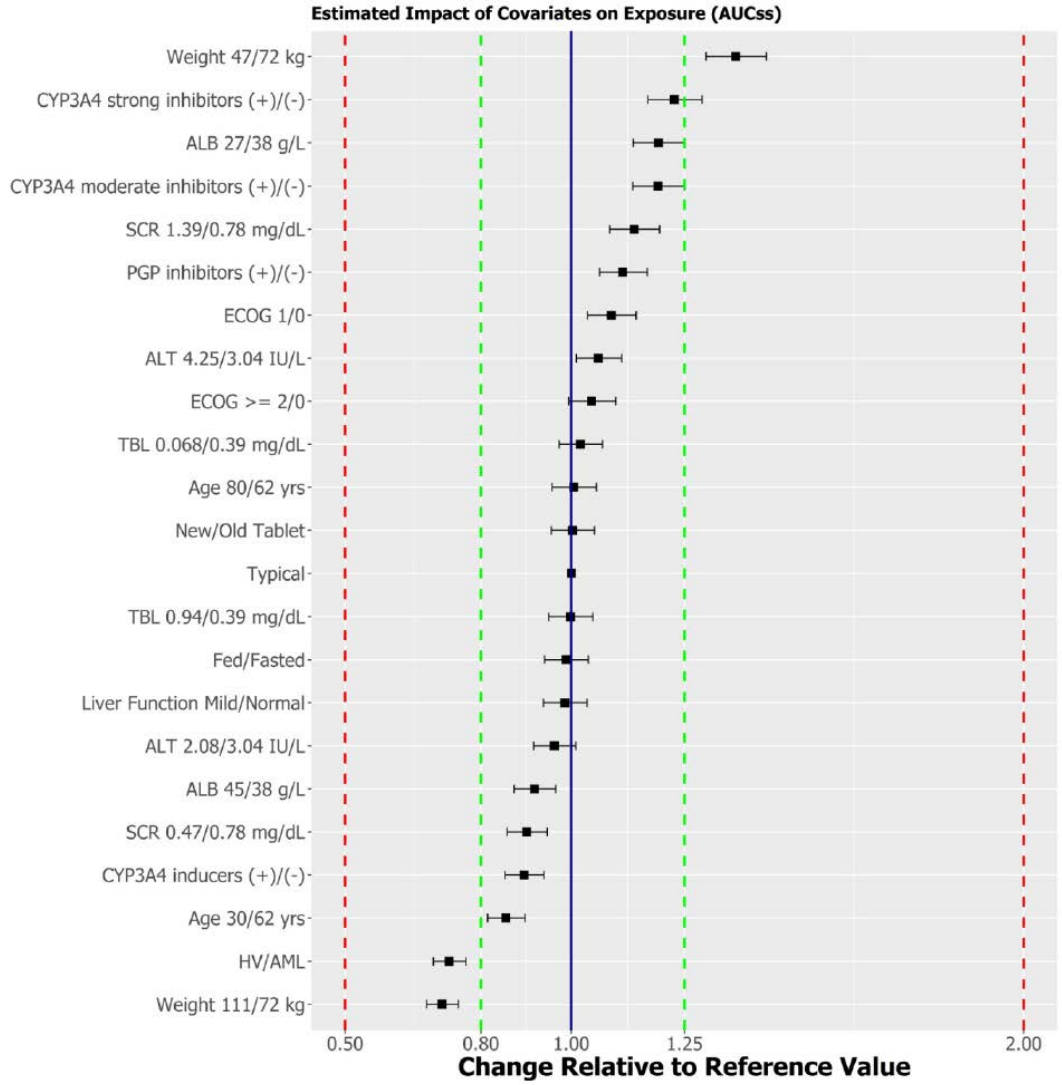
Source: Population PK Report, Table 7, page 32

The apparent clearance (CL/F) of gilteritinib decreased with increasing age and ALT levels. It increased with increasing body weight and albumin levels. Clearance also decreased with a strong/moderate CYP3A4 inhibitors and a p-gp inhibitor. It increased with a CYP3A inducer. Gilteritinib clearance and central volume of distribution was 46% and 63% higher, respectively, in healthy volunteers compared to AML patients. Healthy volunteers had a 143% greater absorption rate constant compared to AML patients under fasted state. Body weight, ECOG were also covariates on central volume of distribution and body weight and albumin were covariates on peripheral volume of distribution. CYP3A inducers and bilirubin were covariates on distributional clearance and food decreased the absorption rate constant by approximately 73% relative to the fasted state. Subjects with mild hepatic function had 82% greater absorption rate constant compared to subjects with normal hepatic function.

Although these covariates were identified to be statistically significant, none of them appear to have clinically meaningful effect on gilteritinib exposures. As shown in **Figure 18**, $AUC_{24,ss}$ at 120 mg once daily dose for a typical patient (AML patient, age 62, 72 kg, SCR=0.78 mg/dL, ALB=38 g/L, TBL=0.39 mg/dL, LALT=3.04 IU/L, ECOG=0, without any CYP3A4 inhibitors/inducers taken, Phase 1 table taken under fasted conditions) and $AUC_{ss,24}$ at 120 mg once daily dose for patients whose exposures were then calculated at the 5^{th} and 95^{th} percentiles of all continuous covariates of AML patients, or at the alternate values of the categorical covariates, are

comparable. Although exposures for patients with 111 kg or 47 kg appear to be outside 0.8-1.25 range, the reviewer's analysis confirmed that the effect of body weight on exposure-response relationship for efficacy is not significant.

Figure 18: Estimated Impact of Covariates on Exposure (AUC_{ss}) of Gilteritinib

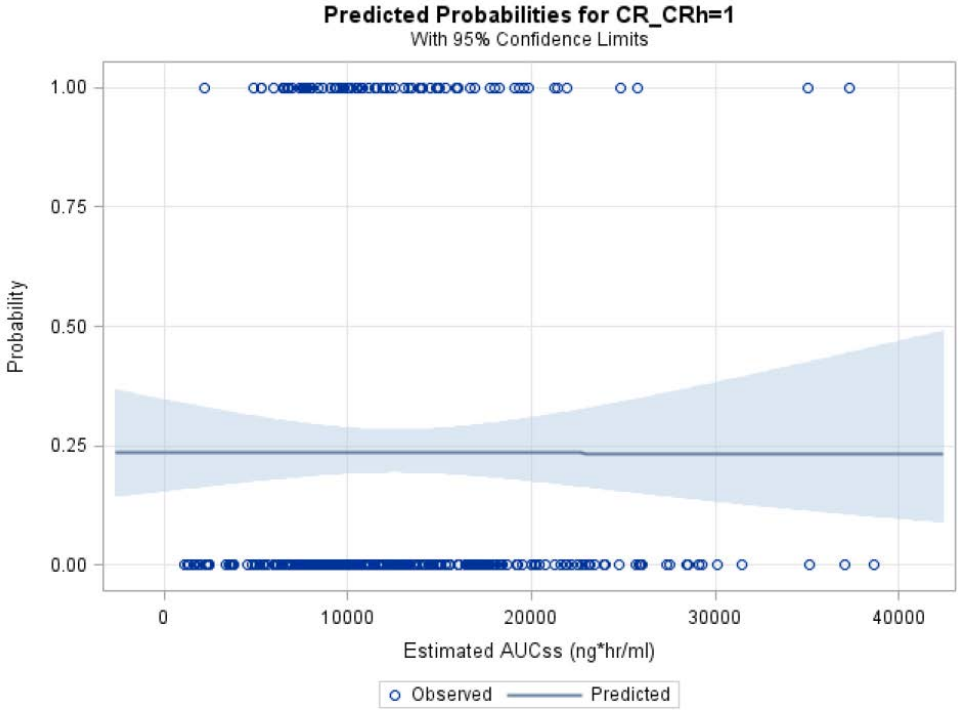


Source: Population PK Report, Figure 7, page 38

Exposure-Response for Efficacy:

These estimated $AUC_{ss,24}$ (similarly $C_{min,ss}$) were utilized for exposure-response analysis for efficacy and safety. Mean $AUC_{ss,24}$ in 78 responders and 254 nonresponders for CR/CRh were 12,634 ng*hr/mL and 12,650 ng*hr/mL, respectively. Mean $C_{min,ss}$ in those responders and non-responders were 456 ng/mL and 456 ng/mL. As visually confirmed from **Figure 19**, there is no apparent exposure-response relationship for CR/CRh from the currently available data.

Figure 19: Predicted Probability for CR/CRh with 95% CI vs. $AUC_{24,ss}$



Source: Applicant's exposure-efficacy analysis report, Figure 1, page 13

Exposure-Response for Safety:

The Applicant also conducted exposure-safety analysis for creatine kinase (CK), AST, ALT, and QTcF using data from a total of 332 subjects (334 for QTcF) in 2215-CL-0101, 2215-CL-0102 and 2215-CL-0301. The summary of dataset is provided in **Table 71**.

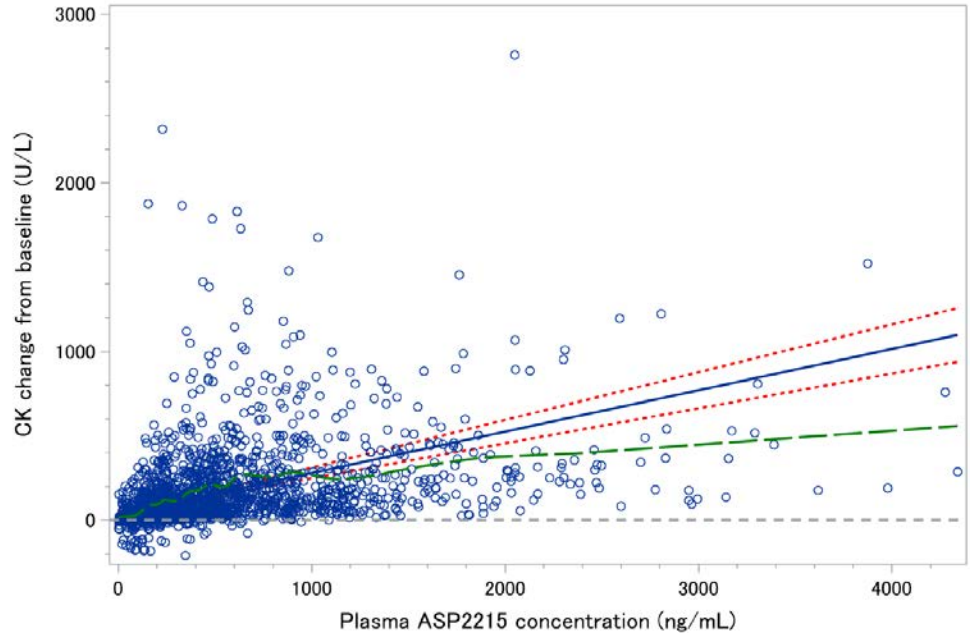
Table 71: Numbers of Patients and Observations in Exposure-Safety Analysis Dataset

Data	Clinical study	Number of Patients	Number of observations (pair of ECG/ laboratory data and ASP2215 concentration)
CK	2215-CL-0101	248	1629*
	2215-CL-0102	23	57
	2215-CL-0301	61	306
	Total	332	1992
AST	2215-CL-0101	248	1624
	2215-CL-0102	23	59
	2215-CL-0301	61	303
	Total	332	1986
ALT	2215-CL-0101	248	1624
	2215-CL-0102	23	59
	2215-CL-0301	61	306
	Total	332	1989
ALB	2215-CL-0101	248	1630
	2215-CL-0102	23	57
	2215-CL-0301	61	311
	Total	332	1998
QTcF	2215-CL-0101	251	1885
	2215-CL-0102	24	159
	2215-CL-0301	59	239
	Total	334	2283

Source: Applicant's exposure-safety analysis report, Table 2, page 11

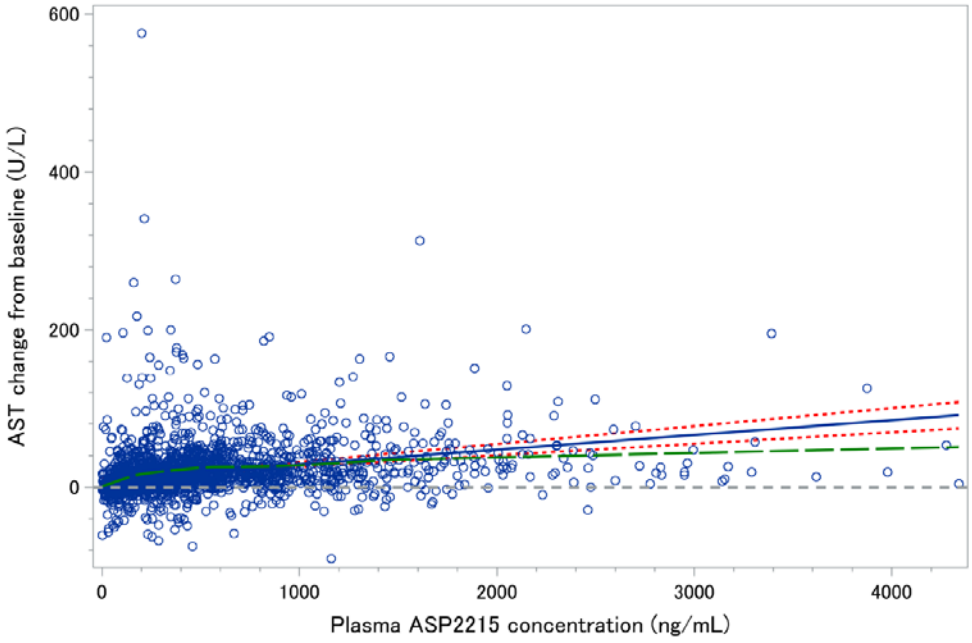
The safety endpoints utilized for the analysis were creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin (ALB), and Fridericia's corrected QT interval (QTcF). Regression plots for these endpoints are depicted in **Figures 20-24**.

Figure 20: Regression Plot of dCK and Concentration of Gilteritinib



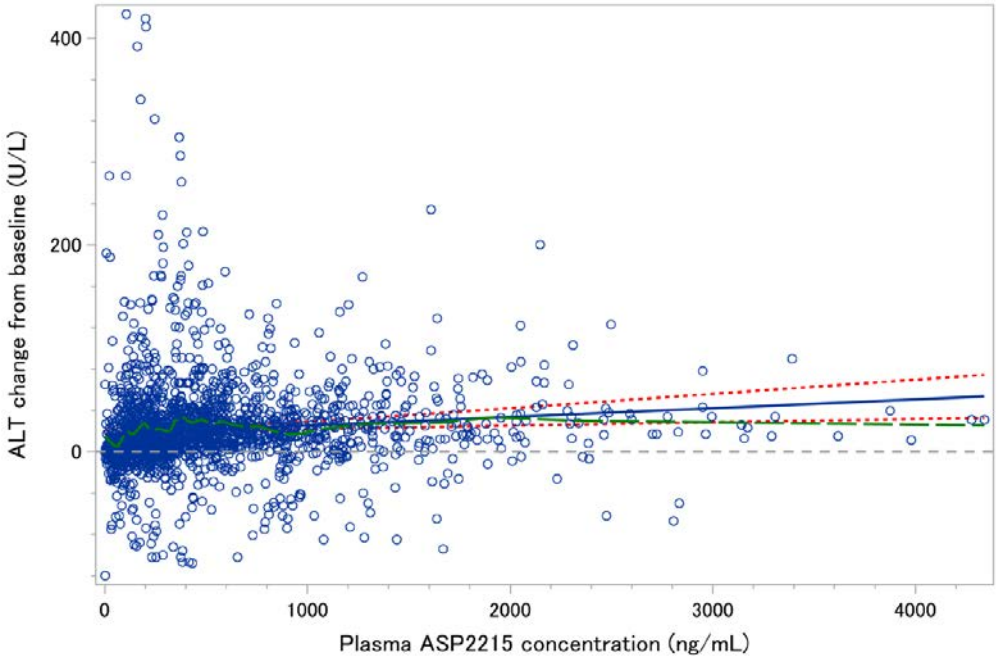
Source: Applicant's exposure-safety analysis report, Figure 2, page 14

Figure 21: Regression Plot of dAST and Concentration of Gilteritinib



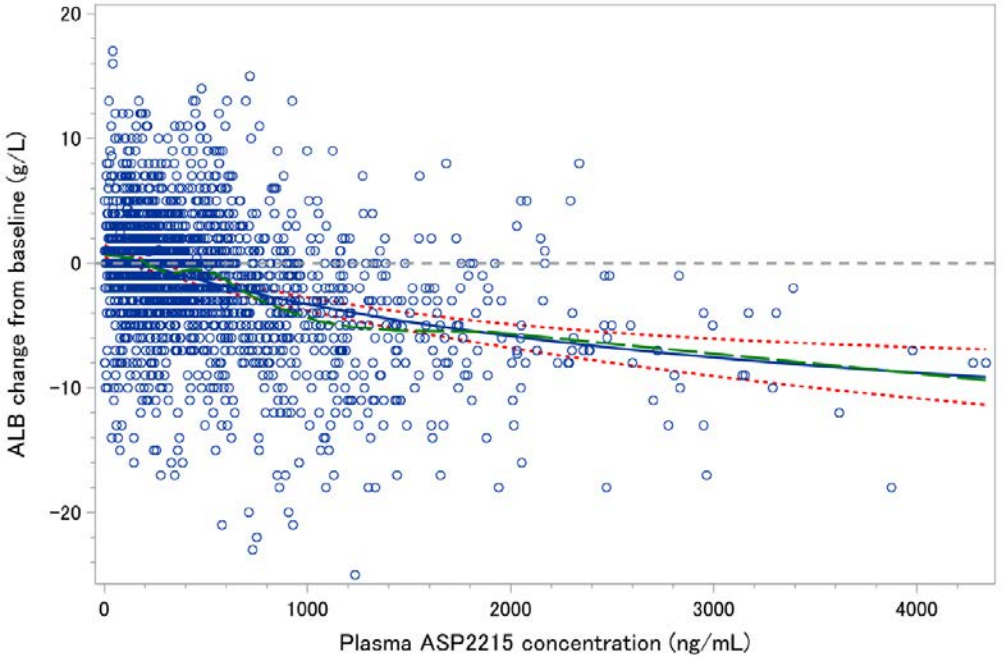
Source: Applicant's exposure-safety analysis report, Figure 4, page 17

Figure 22: Regression Plot of dALT and Concentration of Gilteritinib



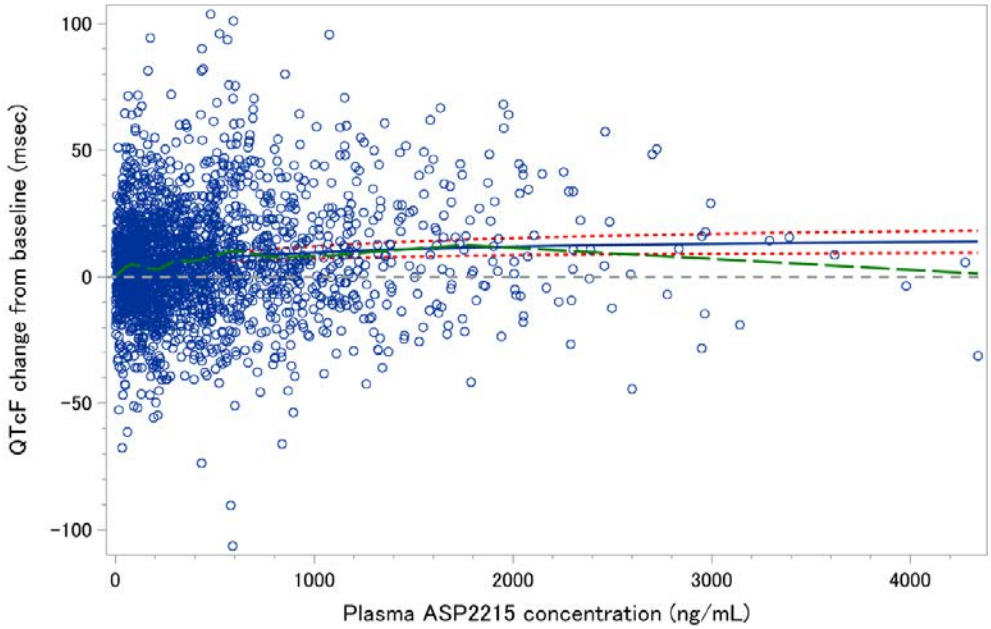
Source: Applicant's exposure-safety analysis report, Figure 6, page 20

Figure 23: Regression Plot of dALB and Concentration of Gilteritinib



Source: Applicant's exposure-safety analysis report, Figure 8, page 23

Figure 24: Regression Plot of dQTcF Intervals and Concentration of Gilteritinib



Source: Applicant's exposure-safety analysis report, Figure 10, page 26

The exposures of gilteritinib appear to have influence on CK, AST, ALT, and ALB levels. The prediction at 120-mg dose, which corresponds to a median C_{max} of 282.0 ng/mL, was 104 U/L (upper 1-sided 95% CI:116 U/L) in dCK, 14.9 U/L (upper 1-sided 95% CI: 16.8 U/L) in dAST and 191. U/L (lower 1-sided 95% CI: 22.0 U/L) in dALT, respectively. The prediction of dALB at 120-mg dose was -0.470 g/L (lower 1-sided 95% CI: -0.830 g/L). The prolongation at 120-mg dose was 5.50 msec (upper 1-sided 95% CI: 6.98 msec), which was lower than the critical cutoff of 10 msec.

Additionally, the Applicant submitted dose-safety analysis for grade 3 or higher anemia, thrombocytopenia, neutropenia and all grade 3 or higher AEs upon the agency's information request. As shown in **Table 72**, any significant dose-response relationships for these endpoints were not observed.

Table 72: Grade 3 or Higher Selected Treatment Emergent Adverse Events

Preferred Term	<120 mg (N=66)	120 mg (N=241)	>120 mg (N=137)	Total (N=444)	CL-0301 120 mg (N=168)
Overall	54 (81.8%)	218 (90.5%)	129 (94.2%)	401 (90.3%)	156 (92.9%)
Anemia	13 (19.7%)	73 (30.3%)	38 (27.7%)	124 (27.9%)	58 (34.5%)
Thrombocytopenia	3 (4.5%)	41 (17.0%)	20 (14.6%)	64 (14.4%)	31 (18.5%)
Neutropenia	0	22 (9.1%)	15 (10.9%)	37 (8.3%)	16 (9.5%)

Source: Response to Information Request dated July 19, 2018, Table 1, page 2

Reviewer's Comment:
The population PK analysis and exposure-response analyses for efficacy and safety were acceptable. Since dose was adjusted based on lack of efficacy (nonresponders for CRc) or tolerability, exposure-response analysis using steady state exposure metrics would not be able to detect the true exposure-response relationships. However, reviewer's exposure-response analysis using exposures prior to dose adjustment also showed an insignificant relationship for efficacy. The Applicant's exposure- and dose-safety analyses are acceptable.

14.5 Description of Grouped Terms

Table 73: Grouped Terms

Grouped term	Included terms
Abdominal pain	Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Gastrointestinal pain
Adrenal insufficiency	Adrenal insufficiency, Secondary adrenocortical insufficiency
Amnesia	Amnesia, Memory impairment
Anaemia	Anaemia, Aplasia pure red cell, Autoimmune haemolytic anaemia, Haematocrit decreased, Haemoglobin decreased, Haemolysis, Haemolytic anaemia, Red blood cell count decreased
Anxiety	Adjustment disorder with anxiety, Anxiety
Aphasia	Aphasia, Dysphasia
Arrhythmia	Arrhythmia, Atrial fibrillation, Atrial flutter, Atrial tachycardia, Bradycardia, Heart rate irregular, Sinus bradycardia, Sinus node dysfunction, Sinus tachycardia, Supraventricular tachycardia, Tachycardia, Ventricular arrhythmia, Ventricular fibrillation, Ventricular tachycardia
Cardiac arrest	Cardiac arrest, Death, Sudden death
Cardiac failure	Cardiac failure, Cardiac failure congestive, Cardiomegaly, Cardiomyopathy, Chronic left ventricular failure, Diastolic dysfunction, Ejection fraction decreased
Cataract	Cataract, Cataract nuclear, Lenticular opacities
Cushing's syndrome	Cushingoid, Cushing's syndrome
Cytopenia,	Bone marrow failure, Cytopenia, Pancytopenia
Delirium	Agitation, Confusional state, Delirium, Delusion, Disorientation, Hallucination, Hallucination, visual, Restlessness
Depression	Adjustment disorder with depressed mood, Depressed mood, Depression
Diarrhoea	Colitis, Diarrhoea, Diarrhoea haemorrhagic, Diarrhoea infectious, Enteritis, Enterocolitis, Gastroenteritis, Gastroenteritis viral, Neutropenic colitis
Dizziness	Dizziness, Dizziness postural, Vertigo
Dyspepsia	Dyspepsia, Epigastric discomfort
Dyspnoeaa	Acute respiratory distress syndrome, Acute respiratory failure, Dyspnoea, Dyspnoea exertional, Hypoxia, Pulmonary oedema, Respiratory distress, Respiratory failure, Tachypnoea, Wheezing
Ear pain	Ear pain, External ear pain
Encephalopathy	Cognitive disorder, Depressed level of consciousness, Disturbance in attention, Encephalopathy, Lethargy, Mental status changes, Posterior reversible encephalopathy syndrome, Somnolence
Eosinophilia	Eosinophil count increased, Eosinophilia
Fatigue	Asthenia, Fatigue, Malaise
Flushing	Flushing, Hot flush

Grouped term	Included terms
Fungal infection	Bronchitis fungal, Bronchopulmonary aspergillosis, Candida infection, Coccidioidomycosis, Eye infection fungal, Fungaemia, Fungal infection, Fungal rhinitis, Fungal skin infection, Laryngitis fungal, Lower respiratory tract infection fungal, Oral candidiasis, Oral fungal infection, Pulmonary mycosis, Respiratory moniliasis, Respiratory tract infection fungal, Sinusitis fungal, Skin candida, Systemic candida, Systemic mycosis, Vulvovaginal candidiasis
Gastrointestinal haemorrhagee	Gastric haemorrhage, Gastrointestinal haemorrhage, Haematemesis, Haematochezia, Haemorrhoidal haemorrhage, Lower gastrointestinal haemorrhage, Melaena, Occult blood positive, Rectal haemorrhage, Small intestinal haemorrhage, Upper gastrointestinal haemorrhage
Gastrointestinal ulcer	Gastric ulcer, Gastrointestinal ulcer, Large intestinal ulcer
Graft versus host disease	Acute graft versus host disease, Acute graft versus host disease in intestine, Acute graft versus host disease in skin, Chronic graft versus host disease, Chronic graft versus host disease in skin, Graft versus host disease, Graft versus host disease in eye, Graft versus host disease in gastrointestinal tract, Graft versus host disease in liver, Graft versus host disease in skin
Haematuria	Cystitis haemorrhagic, Haematuria
Haemorrhage	Haemorrhage, Post procedural haematoma, Post procedural haemorrhage, Renal haematoma, Renal haemorrhage
Haemorrhage intracranial	Cerebral haematoma, Cerebral haemorrhage, Haemorrhage intracranial, Subarachnoid haemorrhage, Subdural haematoma, Subdural haemorrhage
Headache	Headache, Sinus headache, Tension headache
Hyperammonaemia	Ammonia increased, Hyperammonaemia
Hyperbilirubinaemia	Bilirubin conjugated increased, Blood bilirubin increased, Hyperbilirubinaemia, Jaundice
Hyperglycaemia	Diabetes mellitus, Diabetes mellitus inadequate control, Glucose tolerance impaired, Hyperglycaemia, Type 2 diabetes mellitus, Dyslipidaemia, Hypercholesterolaemia, Hyperlipidaemia, Hypertriglyceridaemia, Lipid metabolism disorder
Hypersensitivity	Anaphylactic reaction, Angioedema, Dermatitis allergic, Drug hypersensitivity, Erythema multiforme, Hypersensitivity, Urticaria
Hypertension	Blood pressure increased, Hypertension
Hypertransaminasaemia	Alanine aminotransferase increased, Aspartate aminotransferase increased, Hepatic failure, Hepatocellular injury, Hepatotoxicity, Liver function test increased, Transaminases increased
Hypoacusis	Deafness, Hypoacusis
Hyponatraemia	Hyponatraemia, Hyponatraemic syndrome
Hypotension	Blood pressure decreased, Blood pressure orthostatic, Circulatory collapse, Hypotension, Orthostatic hypotension, Shock
Injection site reaction	Injection site extravasation, Injection site reaction
Intestinal obstruction	Ileus, Intestinal obstruction, Small intestinal obstruction
Intestinal perforation	Duodenal perforation, Intestinal perforation, Large intestine perforation
Leukocytosis,	Leukocytosis, White blood cell count increased
Leukopenia	Leukopenia, White blood cell count decreased
Muscular weakness	Muscular weakness, Myopathy
Myocardial infarction	Acute coronary syndrome, Acute myocardial infarction, Myocardial infarction, Myocardial necrosis marker increased, Troponin I increased, Troponin increased, Troponin T increased

Grouped term	Included terms
Myositis	Aldolase increased, Blood creatine phosphokinase decreased, Blood creatine phosphokinase increased, Myalgia, Myositis, Necrotising myositis, Rhabdomyolysis
Neuropathy peripheral	Axonal neuropathy, Carpal tunnel syndrome, Neuromyopathy, Neuropathy peripheral, Peripheral sensory neuropathy
Neutropenia	Febrile neutropenia, Neutropenia, Neutrophil count decreased
Oedema,	Face oedema, Fluid retention, Generalised oedema, Localised oedema, Oedema, Oedema peripheral, Peripheral swelling, Swelling face
Pancreatitis	Amylase increased, Lipase increased, Pancreatitis, Pancreatitis acute, Pericardial effusion, Pericardial fibrosis, Pericardial haemorrhage, Pericardial rub, Pericarditis
Phlebitis	Phlebitis, Thrombophlebitis
Pneumonia	Interstitial lung disease, Lower respiratory tract infection, Lower respiratory tract infection bacterial, Lung infection, Lung infiltration, Organising pneumonia, Pneumonia, Pneumonia aspiration, Pneumonia bacterial, Pneumonia fungal, Pneumonia viral, Pneumonitis, Respiratory syncytial virus infection, Respiratory tract infection
Pruritus	Pruritus, Pruritus allergic, Pruritus generalised
Rash	Dermatitis, Dermatitis bullous, Dermatitis contact, Dermatitis exfoliative, Drug eruption, Eczema, Eczema asteatotic, Epidermolysis, Erythema, Lichen planus, Palmar-plantar erythrodysaesthesia syndrome, Perivascular dermatitis, Photosensitivity reaction, Psoriasis, Rash, Rash erythematous, Rash follicular, Rash generalised, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Seborrhoeic dermatitis, Skin exfoliation, Toxic skin eruption
Renal impairment	Acute kidney injury, Acute prerenal failure, Blood creatinine increased, Chronic kidney disease, Glomerular filtration rate decreased, Oliguria, Renal disorder, Renal failure, Renal impairment, Renal injury, Renal tubular necrosis
Seizure	Epilepsy, Seizure, Seizure like phenomena
Sepsis	Bacteraemia, Bacterial sepsis, Enterobacter sepsis, Neutropenic sepsis, Sepsis, Septic shock, Urosepsis
Stomatitis	Aphthous ulcer, Mouth haemorrhage, Mouth ulceration, Mucosal inflammation, Oral mucosal blistering, Oral mucosal erythema, Stomatitis, Tongue ulceration
Syncope	Loss of consciousness, Syncope
Thrombocytopenia	Platelet count decreased, Thrombocytopenia
Thrombosis	Deep vein thrombosis, Embolism, Embolism venous, Jugular vein thrombosis, Pulmonary embolism
Transfusion reaction	Allergic transfusion reaction, Anaphylactic transfusion reaction, Febrile nonhaemolytic transfusion reaction, Transfusion reaction
Tremor	Essential tremor, Tremor
Visual impairment	Vision blurred, Visual acuity reduced, Visual impairment

15 Division Director (DHOT)

John Leighton, PhD
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Nam Atiqur Rahman, PhD
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(This review was based in part on the reviews of Dr. Diane Pulte, Dr. Donna Przepiorka and Dr. Yaping Wang)

Background: On March 29, 2018, Astellas Pharma US, Inc. submitted NDA 211349 in which they requested approval of gilteritinib (Xospata) for the treatment of relapsed refractory acute myeloid leukemia (AML) with a FMS like tyrosine kinase 3 (FLT3) mutation as detected by an FDA approved test. Priority review was requested. Accelerated approval was also requested as the Sponsor claimed that gilteritinib demonstrates an advantage over the available therapies, as measured by complete remission (CR)/complete remission with incomplete hematopoietic recovery (CRh), the duration of CR/CRh (DOR), and the rate of conversion from transfusion dependence to transfusion independence.

The request for accelerated approval relied upon one phase 3 trial (the Admiral trial-NCT02421939) which was an open-label study (2215-CL-0301) in which 369 patients with relapsed refractory AML with a FLT3 mutation as detected by an FDA approved test were randomized 2:1 to gilteritinib (120 mg daily) or to one of four salvage regimens: Low dose cytosine arabinoside (LDAC), the combination of 5-azacitidine, mitoxantrone, etoposide and intermediate-dose cytarabine (MEC) or the combination of fludarabine, cytarabine, and granulocyte colony-stimulating factor with idarubicin (FLAG-IDA).

Two interim analyses (IA) were pre-specified. The first interim analysis was IA1, which was planned to occur when 141 patients were randomized into the gilteritinib arm and were at least 112 days (4 treatment cycles) past the first dose of gilteritinib. This IA was designed to evaluate the co-primary endpoint of CR/CRh rate in the gilteritinib arm only which is the primary focus of NDA 211349. The second interim analysis is IA2, which is scheduled to take place when 50% of the total planned death events (N=129) have occurred. The final analysis is to be based on overall survival (OS) which will occur after 100% of the planned death events (N=258) have been observed.

Efficacy Results: The 2-sided exact 95% CI of CR/CRh rate for patients randomized into the gilteritinib arm, was 21% or 29/138 (95% CI: 14.5%, 28.8%). The CR rate was 11.6% or 16/138 (95 % CI: 6.8%, 18.1%) and the CRh rate was 9.4% or 13/138 (95% CI: 5.1%, 15.6%), respectively. For the 29 patients who achieved CR/CRh, the median duration of the CR/CRh was 4.6 months (range in months: 0.1 to 15.8). For the 16 patients who achieved CR, the median duration of response was 8.6 months (range in months: 1 to 13.8). For the 13 patients who achieved CRh, the median duration of response was 2.9 months (range in months: 0.1 to 15.8).

Of the 106 patients who were RBC and/or platelet transfusion dependent at baseline, 33/106 (31.1%) became independent of RBC and platelet transfusions during any 56-day post baseline period.

Safety Results: The main safety population is all patients with relapsed refractory AML who received a dose of 120 mg/day of gilteritinib (N=292) in the following 3 studies which were pooled to generate the safety population: 2215-CL-0101, 2215-CL-0102, and 2215-CL-0301. An analysis was also performed of all of the 292 patients with relapsed refractory AML who were given a daily dose of gilteritinib at 120mg per day on Study 2215-CL-0301 (N=219).

Deaths: Of the 87 deaths which occurred among the 219 patients on protocol 2215-CD-0301, 81 were attributed to AML. Four were attributed to causes other than AML or the study drug. The two remaining cases were considered potentially related to drug toxicity: one due to congestive heart failure and the other due to pancreatitis.

The rate of patients who permanently discontinued gilteritinib due to an adverse reaction among the 292 that were given 120 mg was 10%. Common adverse reactions leading to discontinuation were: transaminase elevation, cardiac arrest, ventricular arrhythmias, respiratory failure, dyspnea, and elevated bilirubin (this list does not include discontinuations due to disease progression, infections and bleeding which are causes for discontinuation that are disease related rather than drug related).

The adverse reactions (>20%) most commonly encountered were: myalgia/arthralgia, transaminase elevations, fever, non-infectious diarrhea, dyspnea, edema, rash, nausea, stomatitis, pneumonia, cough, sepsis, headache, hypotension, dizziness, and vomiting.

Adverse reactions that are potentially life threatening included QT prolongation, pancreatitis and differentiation syndrome.

Benefit Risk Discussion: The safety profile is mostly that associated with patients with relapse/refractory AML with the exception of QT prolongation and differentiation syndrome for which close monitoring measures are required. These toxicities were more than offset by the substantial CR rate which were clinically meaningful. The benefit risk profile is favorable**.**

Recommended Regulatory Action: This Supervisory Associate Division Director reviewer agrees with the recommendation of the review teams that the NDA 211349 be approved for the following indication: for the treatment of adult patients who have relapsed or refractory AML with a FMS-like tyrosine kinase 3 (FLT3) mutation as detected by an FDA-approved test.

Albert Deisseroth, MD, PhD
Supervisory Associate Division Director
Division of Hematology Products (DHP

19 Office Director (or designee)

This application was reviewed under the auspices of the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. The risk-benefit of gilteritinib was also assessed by Drs. Przepiorka and Pulte, and I concur with their recommendation to approve this drug. My signature below also represents an approval recommendation for the clinical portion of this application under CDER.

Richard Pazdur, MD
Director
Office of Hematology and Oncology Products (OHOP)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ROSA J LEE-ALONZO
11/26/2018

ELIZABETH D PULTE
11/26/2018

CHRISTOPHER M SHETH on behalf of RAMADEVI GUDI
11/26/2018

CHRISTOPHER M SHETH
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JOHN K LEIGHTON
11/26/2018

HISHAM H QOSA
11/26/2018

JEE E LEE
11/26/2018

LIAN MA
11/26/2018

WENTAO FU
11/26/2018

NAM ATIQUR RAHMAN
11/26/2018
I concur with the recommendation.

YAPING WANG
11/26/2018

YUAN L SHEN
11/26/2018

RAJESHWARI SRIDHARA
11/26/2018

RAJESHWARI SRIDHARA
11/26/2018

DONNA PRZEPIORKA
11/26/2018

ALBERT B DEISSEROTH
11/26/2018

ANN T FARRELL
11/26/2018
Dr. Farrell signing for Dr. Richard Pazdur