CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

211349Orig1s001

Trade Name:	Xospata® tablets, 40 mg
Generic or Proper Name:	gilteritinib
Sponsor:	Astellas Pharma US, Inc.
Approval Date:	May 29, 2019
Indication:	This Prior Approval supplemental new drug application provides for the following updates to the United States Prescribing Information: addition of a boxed warning for differentiation syndrome; addition of dosage odifications for XOSPATA-related toxicities (Section 2.3); addition of differentiation syndrome in warnings and precautions (Section 5.1), revisions to the warnings and precautions for posterior reversible encephalopathy syndrome, prolonged QT interval and pancreatitis (Sections 5.2, 5.3, 5.4); updates in adverse reactions (Section 6.1); updates based on the final analysis of Study 2215-CL-0301 (Section 14), and addition of patient counseling information about differentiation syndrome (Section 17). Also, the Patient Package Insert was converted to a Medication Guide.

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

NDA 211349/S-001

SUPPLEMENT APPROVAL

Astellas Pharma US, Inc.
Attention: Tim Farber
Director, Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Mr. Farber:

Please refer to your supplemental new drug application (sNDA) dated February 22, 2019, received February 22, 2019, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Xospata® (gilteritinib) tablets, 40 mg.

This Prior Approval supplemental new drug application provides for the following updates to the United States Prescribing Information: addition of a boxed warning for differentiation syndrome; addition of dosage modifications for XOSPATA-related toxicities (Section 2.3); addition of differentiation syndrome in warnings and precautions (Section 5.1), revisions to the warnings and precautions for posterior reversible encephalopathy syndrome, prolonged QT interval and pancreatitis (Sections 5.2, 5.3, 5.4); updates in adverse reactions (Section 6.1); updates based on the final analysis of Study 2215-CL-0301 (Section 14), and addition of patient counseling information about differentiation syndrome (Section 17). Also, the Patient Package Insert was converted to a Medication Guide.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

The Medication Guide statement shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed and shall state how the Medication Guide is provided. Your proposed statement does not appear to state to whom the Medication Guide is dispensed. Consider if the statement "Dispense enclosed Medication Guide to each patient." is appropriate and satisfies the regulation 21 CFR 208.24(d).

Submit final printed carton and container labeling that are identical to the submitted carton and container labeling from May 1, 2019, except with the revisions listed above, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 211349/S-001**." Approval of this submission by FDA is not required before the labeling is used.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

All promotional materials that include representations about your drug product must be promptly revised to be consistent with the labeling changes approved in this supplement, including any new safety information [21 CFR 314.70(a)(4)]. The revisions in your promotional materials should include prominent disclosure of the important new safety information that appears in the revised labeling. Within 7 days of receipt of this

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

letter, submit your statement of intent to comply with 21 CFR 314.70(a)(4) to the address above, by fax to 301-847-8444, or electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Rosa Lee-Alonzo, Regulatory Project Manager, at (301) 348-3004.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Supervisory Associate Division Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide

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/

ALBERT B DEISSEROTH
05/29/2019 06:03:49 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211349Orig1s001

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use XOSPATA safely and effectively. See full prescribing information for XOSPATA.

XOSPATA® (gilteritinib) tablets, for oral use
Initial U.S. Approval: 2018

WARNING: DIFFERENTIATION SYNDROME
See full prescribing information for complete boxed warning.

Patients treated with XOSPATA have experienced symptoms of differentiation syndrome, which can be fatal if not treated. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution. (5.1, 6.1)

----------RECENT MAJOR CHANGES----------

Boxed Warning	5/2019
Dosage and Administration (2.3)	5/2019
Warnings and Precautions (5.1, 5.2, 5.3)	5/2019

---------- INDICATIONS AND USAGE ----------

XOSPATA is a kinase inhibitor indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukemia (AML) with a FLT3 mutation as detected by an FDA-approved test. (1.1)

---------- DOSAGE AND ADMINISTRATION ----------

120 mg orally once daily. (2.2)

---------- DOSAGE FORMS AND STRENGTHS ----------

Tablets: 40 mg. (3)

---------- CONTRAINDICATIONS ----------

Hypersensitivity to gilteritinib or any of the excipients. Anaphylactic reactions have been observed in clinical trials. (4, 6.1)

---------- WARNINGS AND PRECAUTIONS ----------

- Posterior reversible encephalopathy syndrome (PRES): Discontinue XOSPATA in patients who develop PRES. (2.3, 5.2, 6.1)
- Prolonged QT Interval: Interrupt and reduce XOSPATA dosage in patients who have a QTcF >500 msec. Correct hypokalemia or hypomagnesemia prior to and during XOSPATA administration. (2.3, 5.3, 12.2, 6.1)
- Pancreatitis: Interrupt and reduce the dose in patients who develop pancreatitis. (2.3, 5.4)
- Embryo-Fetal Toxicity: XOSPATA can cause fetal harm when administered to a pregnant woman. Advise of the potential risk to a fetus and to use effective contraception. (5.5, 8.1, 8.3)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions (≥20%) were transaminase increased, myalgia/arthralgia, fatigue/malaise, fever, mucositis, edema, rash, noninfectious diarrhea, dyspnea, nausea, cough, constipation, eye disorders, headache, dizziness, hypotension, vomiting, and renal impairment. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Astellas Pharma US, Inc. at 1-800-727-7003 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

- Combined P-gp and Strong CYP3A Inducers: Avoid concomitant use. (7.1)
- Strong CYP3A Inhibitors: Consider alternative therapies. If the concomitant use of strong CYP3A inhibitors cannot be avoided, monitor patients more frequently for XOSPATA adverse reactions. (2.3, 7.1)

---------- USE IN SPECIFIC POPULATIONS ----------

Lactation: Advise women not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: DIFFERENTIATION SYNDROME

Patients treated with XOSPATA have experienced symptoms of differentiation syndrome, which can be fatal or life-threatening if not treated. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, or renal dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

1 INDICATIONS AND USAGE

1.1 Relapsed or Refractory Acute Myeloid Leukemia

XOSPATA is indicated 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.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients for the treatment of AML with XOSPATA based on the presence of FLT3 mutations in the blood or bone marrow *[see Clinical Studies (14)]*. Information on FDA-approved tests for the detection of a FLT3 mutation in AML is available at http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage

The recommended starting dose of XOSPATA is 120 mg orally once daily with or without food. Response may be delayed. In the absence of disease progression or unacceptable toxicity, treatment for a minimum of 6 months is recommended to allow time for a clinical response.

Do not break or crush XOSPATA tablets. Administer XOSPATA tablets orally about the same time each day. If a dose of XOSPATA is missed or not taken at the usual time, administer the dose as soon as possible on the same day, and at least 12 hours prior to the next scheduled dose. Return to the normal schedule the following day. Do not administer 2 doses within 12 hours.

2.3 Dose Modification

Assess blood counts and blood chemistries, including creatine phosphokinase, prior to the initiation of XOSPATA, at least once weekly for the first month, once every other week for the second month, and once monthly for the duration of therapy. Perform electrocardiogram (ECG) prior to initiation of treatment with gilteritinib, on days 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles.

Interrupt dosing or reduce dose for toxicities as per Table 1.

Table 1: Dosage Modifications for XOSPATA-Related Toxicities*

Adverse Reaction	Recommended Action
Differentiation Syndrome	• If differentiation syndrome is suspected, administer systemic corticosteroids and initiate hemodynamic monitoring until symptom resolution and for a minimum of 3 days *[see Warnings and Precautions (5.1)]*.

	• Interrupt XOSPATA if severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids *[see Warnings and Precautions (5.1)]*. • Resume XOSPATA when signs and symptoms improve to Grade 2* or lower.
Posterior Reversible Encephalopathy Syndrome	• Discontinue XOSPATA.
QTc interval greater than 500 msec	• Interrupt XOSPATA. • Resume XOSPATA at 80 mg when QTc interval returns to within 30 msec of baseline or less than or equal to 480 msec.
QTc interval increased by >30 msec on ECG on day 8 of cycle 1	• Confirm with ECG on day 9. • If confirmed, consider dose reduction to 80 mg.
Pancreatitis	• Interrupt XOSPATA until pancreatitis is resolved. • Resume XOSPATA at 80 mg.
Other Grade 3* or higher toxicity considered related to treatment.	• Interrupt XOSPATA until toxicity resolves or improves to Grade 1*. • Resume XOSPATA at 80 mg.

*Grade 1 is mild, Grade 2 is moderate, Grade 3 is serious, Grade 4 is life-threatening.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 40 mg as light yellow, round-shaped, film-coated tablets debossed with the Astellas logo and '235' on the same side.

4 CONTRAINDICATIONS

XOSPATA is contraindicated in patients with hypersensitivity to gilteritinib or any of the excipients. Anaphylactic reactions have been observed in clinical trials *[see Adverse Reactions (6) and Description (11)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Differentiation Syndrome

Of 319 patients treated with XOSPATA in the clinical trials, 3% experienced differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms of differentiation syndrome in patients treated with XOSPATA included fever, dyspnea, pleural effusion, pericardial effusion, pulmonary edema, hypotension, rapid weight gain, peripheral edema, rash, and renal dysfunction. Some cases had concomitant acute febrile neutrophilic dermatosis. Differentiation syndrome occurred as early as 2 days and up to 75 days after XOSPATA initiation and has been observed with or without concomitant leukocytosis. Of the 11 patients who experienced differentiation syndrome, 9 (82%) recovered after treatment or after dose interruption of XOSPATA.

If differentiation syndrome is suspected, initiate dexamethasone 10 mg IV every 12 hours (or an equivalent dose of an alternative oral or IV corticosteroid) and hemodynamic monitoring until improvement. Taper corticosteroids after resolution of symptoms and administer corticosteroids for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt XOSPATA until signs and symptoms are no longer severe *[see Dosage and Administration (2.3)]*.

5.2 Posterior Reversible Encephalopathy Syndrome

Of 319 patients treated with XOSPATA in the clinical trials, 1% experienced posterior reversible encephalopathy syndrome (PRES) with symptoms including seizure and altered mental status. Symptoms have resolved after

discontinuation of XOSPATA. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinue XOSPATA in patients who develop PRES *[see Dosage and Administration (2.3) and Adverse Reactions (6.1)]*.

5.3 Prolonged QT Interval

XOSPATA has been associated with prolonged cardiac ventricular repolarization (QT interval). Of the 317 patients with a post-baseline QTc measurement on treatment with XOSPATA in the clinical trial, 1% were found to have a QTc interval greater than 500 msec and 7% of patients had an increase from baseline QTc greater than 60 msec. Perform electrocardiogram (ECG) prior to initiation of treatment with gilteritinib, on days 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles. Interrupt and reduce XOSPATA dosage in patients who have a QTcF >500 msec *[see Dosage and Administration (2.3), Adverse Reactions (6.1) and Clinical Pharmacology (12.2)]*.

Hypokalemia or hypomagnesemia may increase the QT prolongation risk. Correct hypokalemia or hypomagnesemia prior to and during XOSPATA administration.

5.4 Pancreatitis

Of 319 patients treated with XOSPATA in the clinical trials, 4% experienced pancreatitis. Evaluate patients who develop signs and symptoms of pancreatitis. Interrupt and reduce the dose of XOSPATA in patients who develop pancreatitis *[see Dosage and Administration (2.3)]*.

5.5 Embryo-Fetal Toxicity

Based on findings in animals and its mechanism of action, XOSPATA can cause embryo-fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of gilteritinib to pregnant rats during organogenesis caused embryo-fetal lethality, suppressed fetal growth and teratogenicity at maternal exposures (AUC_{24}) approximately 0.4 times the AUC_{24} in patients receiving the recommended dose. Advise females of reproductive potential to use effective contraception during treatment with XOSPATA and for at least 6 months after the last dose of XOSPATA. Advise males with female partners of reproductive potential to use effective contraception during treatment with XOSPATA and for at least 4 months after the last dose of XOSPATA. Pregnant women, patients becoming pregnant while receiving XOSPATA or male patients with pregnant female partners should be apprised of the potential risk to the fetus *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Differentiation syndrome *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Posterior reversible encephalopathy syndrome *[see Warnings and Precautions (5.2)]*
- Prolonged QT interval *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety profile of XOSPATA is based on 319 patients with relapsed or refractory AML treated with gilteritinib 120 mg daily in three clinical trials. The median duration of exposure to XOSPATA was 3.6 months (range 0.1 to 43.4 months).

Fatal adverse reactions occurred in 2% of patients receiving XOSPATA. These included cardiac arrest (1%) and one case each of differentiation syndrome and pancreatitis. The most frequent (≥5%) nonhematological serious adverse reactions reported in patients were fever (13%), dyspnea (9%), renal impairment (8%), transaminase increased (6%) and noninfectious diarrhea (5%).

Of the 319 patients, 91 (29%) required a dose interruption due to an adverse reaction; the most common adverse reactions leading to dose interruption were aspartate aminotransferase increased (6%), alanine aminotransferase increased (6%) and fever (4%). Twenty patients (6%) required a dose reduction due to an adverse reaction. Twenty-two (7%) discontinued XOSPATA treatment permanently due to an adverse reaction. The most common (>1%) adverse reactions leading to discontinuation were aspartate aminotransferase increased (2%) and alanine aminotransferase increased (2%).

Overall, for the 319 patients, the most frequent (≥10%) all-grade nonhematological adverse reactions reported in patients were transaminase increased (51%), myalgia/arthralgia (50%), fatigue/malaise (44%), fever (41%), mucositis (41%), edema (40%), rash (36%), noninfectious diarrhea (35%), dyspnea (35%), nausea (30%), cough (28%), constipation (28%), eye disorders (25%), headache (24%), dizziness (22%), hypotension (22%), vomiting (21%), renal impairment (21%), abdominal pain (18%), neuropathy (18%), insomnia (15%) and dysgeusia (11%). The most frequent (≥5%) grade ≥3 nonhematological adverse reactions reported in patients were transaminase increased (21%), dyspnea (12%), hypotension (7%), mucositis (7%), myalgia/arthralgia (7%), and fatigue/malaise (6%). Shifts to grades 3-4 nonhematologic laboratory abnormalities included phosphate decreased 42/309 (14%), alanine aminotransferase increased 41/317 (13%), sodium decreased 37/314 (12%), aspartate aminotransferase increased 33/317 (10%), calcium decreased 19/312 (6%), creatine kinase increased 20/317 (6%), triglycerides increased 18/310 (6%), creatinine increased 10/316 (3%), and alkaline phosphatase increased 5/317 (2%).

Adverse reactions reported in the first 30 days of therapy on the ADMIRAL Study *[see Clinical Studies (14)]* are shown in Tables 2 and 3, according to whether patients were preselected for high intensity or low intensity chemotherapy.

Table 2: Adverse Reactions Reported in ≥10% (Any Grade) or ≥5% (Grade 3-5)* of Patients with Relapsed or Refractory AML in the Pre-selected High Intensity Chemotherapy Subgroup in the First 30 Days of the ADMIRAL Trial

	Any Grade n (%)		Grade ≥3 n (%)	
Adverse Reaction	**XOSPATA (120 mg daily) n=149**	**Chemotherapy n=68**	**XOSPATA (120 mg daily) n=149**	**Chemotherapy n=68**
Musculoskeletal and connective tissue disorders				
Myalgia/arthralgia†	56 (38)	20 (29)	1 (1)	3 (4)
Investigations				
Transaminase increased‡	46 (31)	11 (16)	15 (10)	5 (7)
General disorders and administration site conditions				
Fatigue/malaise§	36 (24)	9 (13)	1 (1)	2 (3)
Fever	25 (17)	21 (31)	2 (1)	4 (6)
Edema¶	20 (13)	13 (19)	0	0
Gastrointestinal disorders				
Constipation	29 (20)	10 (15)	0	0
Mucositis#	18 (12)	30 (44)	0	5 (7)
Nausea	23 (15)	26 (38)	0	0
Abdominal pain♭	16 (11)	16 (24)	0	0
Blood and lymphatic system disorder				
Febrile neutropenia	26 (17)	30 (44)	26 (17)	30 (44)
Skin and subcutaneous tissue disorders				
Rashß	23 (15)	21 (31)	1 (1)	2 (3)

Respiratory, thoracic and mediastinal disorders				
Dyspnea[à]	20 (13)	9 (13)	1 (1)	6 (9)
Cough	18 (12)	5 (7)	1 (1)	0
Nervous system disorders				
Neuropathy[è]	19 (13)	0	0	0
Dizziness[ð]	17 (11)	2 (3)	0	0
Headache	17 (11)	12 (18)	0	0

*Grade 3-5 includes serious, life-threatening and fatal adverse reactions

[†]Grouped terms: arthralgia, back pain, bone pain, flank pain, limb discomfort, medial tibial stress syndrome, myalgia, muscle twitching, musculoskeletal discomfort, musculoskeletal pain, muscle spasms, neck pain, non-cardiac chest pain, pain and pain in extremity

[‡]Grouped terms: aspartate aminotransferase increased, alanine aminotransferase increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, hepatic enzyme increased, hepatic function abnormal, hepatoxicity, liver function test increased and transaminases increased

[§]Grouped terms: asthenia, fatigue, lethargy and malaise

[¶]Grouped terms: edema, edema peripheral, face edema, fluid overload, generalized edema, hypervolemia, localized edema, periorbital edema and swelling face

[#]Grouped terms: aphthous ulcer, colitis, enteritis, esophageal pain, gingival pain, large intestinal ulcer, laryngeal inflammation, lip blister, lip ulceration, mouth hemorrhage, mouth ulceration, mucosal inflammation, oral discomfort, oral pain, oropharyngeal pain, proctalgia, stomatitis, swollen tongue, tongue discomfort and tongue ulceration

[þ]Grouped terms: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper and gastrointestinal pain

[ß]Grouped terms: acne, dermatitis bullous, dermatitis contact, drug eruption, eczema asteatotic, erythema, hyperkeratosis, lichenoid keratosis, palmar-plantar erythrodysesthesia syndrome, rash, rash maculo-papular, rash papular, skin exfoliation, skin lesion and skin hyperpigmentation

[à]Grouped terms: acute respiratory distress syndrome, dyspnea, dyspnea exertional, hypoxia, pulmonary edema, respiratory failure, tachypnea and wheezing

[è]Grouped terms: hyperesthesia, hypoesthesia, neuralgia, neuropathy peripheral, peripheral sensory neuropathy and paresthesia

[ð]Grouped terms: coordination abnormal and dizziness

Table 3: Adverse Reactions Reported in ≥10% (Any Grade) or ≥5% (Grade 3-5)* of Patients with Relapsed or Refractory AML in the Pre-selected Low Intensity Chemotherapy Subgroup in the First 30 Days of the ADMIRAL Trial

	Any Grade n (%)		**Grade ≥3 n (%)**	
Adverse Reaction	**XOSPATA (120 mg daily) n=97**	**Chemotherapy n=41**	**XOSPATA (120 mg daily) n=97**	**Chemotherapy n=41**
Investigations				
Transaminase increased[†]	35 (36)	6 (15)	9 (9)	1 (2)
Blood and lymphatic system disorder				
Febrile neutropenia	26 (27)	5 (12)	25 (26)	5 (12)
Musculoskeletal and connective tissue disorders				
Myalgia/arthralgia[‡]	21 (22)	7 (17)	2 (2)	0
General disorders and administration site conditions				
Fatigue/malaise[§]	20 (21)	9 (22)	4 (4)	1 (2)
Edema[¶]	19 (20)	5 (12)	1 (1)	0
Fever	11 (11)	7 (17)	0	0
Gastrointestinal disorders				
Mucositis[#]	19 (20)	7 (17)	1 (1)	1 (2)
Constipation	13 (13)	5 (12)	1 (1)	0
Diarrhea	12 (12)	2 (5)	0	0
Nausea	10 (10)	7 (17)	0	0
Respiratory, thoracic and mediastinal disorders				
Dyspnea[þ]	11 (11)	2 (5)	3 (3)	2 (5)
Skin and subcutaneous tissue disorders				
Rash[ß]	10 (10)	2 (5)	2 (2)	0

[*]Grade 3-5 includes serious, life-threatening and fatal adverse reactions

[†]Grouped terms: aspartate aminotransferase increased, alanine aminotransferase increased, blood alkaline phosphatase increased and transaminases increased

[‡]Grouped terms: arthralgia, arthritis, back pain, limb discomfort, myalgia, muscle contracture, muscle spasms, myositis, non-cardiac chest pain, pain, pain in extremity and polyarthritis

[§]Grouped terms: asthenia, fatigue and malaise

[¶]Grouped terms: edema, face edema, localized edema, edema peripheral, peripheral swelling, periorbital edema, scrotal edema and swelling face

[#]Grouped terms: colitis, mouth hemorrhage, mouth ulceration, mucosal inflammation, oropharyngeal pain, proctalgia, stomatitis, tongue discomfort and tongue ulceration

[þ]Grouped terms: acute respiratory failure, dyspnea, hypoxia and respiratory failure

[ß]Grouped terms: dermatitis acneiform, dermatitis bullous, dermatitis exfoliative, erythema, rash, rash maculo-papular, rash papular, rosacea and skin ulcer

Other clinically significant adverse reactions occurring in ≤10% of patients included: electrocardiogram QT prolonged (9%), hypersensitivity (8%), pancreatitis* (5%), cardiac failure* (4%), pericardial effusion (4%), acute febrile neutrophilic dermatosis (3%), differentiation syndrome (3%), pericarditis/myocarditis* (2%), large intestine perforation (1%), and posterior reversible encephalopathy syndrome (1%).

*Grouped terms: cardiac failure (cardiac failure, cardiac failure congestive, cardiomegaly, cardiomyopathy, chronic left ventricular failure, and ejection fraction decreased), hypersensitivity (anaphylactic reaction, angioedema, dermatitis allergic, drug hypersensitivity, erythema multiforme, hypersensitivity, and urticaria), pancreatitis (amylase increased, lipase increased, pancreatitis, pancreatitis acute), pericarditis/myocarditis (myocarditis, pericardial hemorrhage, pericardial rub, and pericarditis).

Selected post-baseline laboratory values that were observed in patients with relapsed or refractory AML are shown in Table 4.

Table 4: Shifts to Grade 3-4 Laboratory Abnormalities in Patients with Relapsed or Refractory AML by Pre-selected High Intensity and Low Intensity Chemotherapy in the First 30 Days of the ADMIRAL Trial

	Pre-selected High Intensity Chemotherapy Subgroup		Pre-selected Low Intensity Chemotherapy Subgroup	
	XOSPATA (120 mg daily)	Chemotherapy	XOSPATA (120 mg daily)	Chemotherapy
Alanine aminotransferase increased	7/149 (5%)	1/66 (2%)	7/95 (7%)	1/41 (2%)
Alkaline phosphatase increased	1/149 (1%)	0	0	0
Aspartate aminotransferase increased	8/149 (5%)	2/65 (3%)	5/95 (5%)	0
Calcium decreased	2/149 (1%)	3/65 (5%)	3/94 (3%)	0
Creatine kinase increased	1/149 (1%)	0	1/95 (1%)	0
Phosphatase decreased	4/144 (3%)	6/65 (9%)	4/93 (4%)	3/38 (8%)
Sodium decreased	7/148 (5%)	5/65 (8%)	6/93 (6%)	2/41 (5%)
Triglycerides increased	1/146 (1%)	0	2/94 (2%)	0

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on XOSPATA

Combined P-gp and Strong CYP3A Inducers

Concomitant use of XOSPATA with a combined P-gp and strong CYP3A inducer decreases gilteritinib exposure which may decrease XOSPATA efficacy *[see Clinical Pharmacology (12.3)]*. Avoid concomitant use of XOSPATA with combined P-gp and strong CYP3A inducers.

Strong CYP3A Inhibitors

Concomitant use of XOSPATA with a strong CYP3A inhibitor increases gilteritinib exposure *[see Clinical Pharmacology (12.3)]*. Consider alternative therapies that are not strong CYP3A inhibitors. If the concomitant use of these inhibitors is considered essential for the care of the patient, monitor patient more frequently for XOSPATA adverse reactions. Interrupt and reduce XOSPATA dosage in patients with serious or life-threatening toxicity *[see Dosage and Administration (2.3)]*.

7.2 Effect of XOSPATA on Other Drugs

Drugs that Target 5HT2B Receptor or Sigma Nonspecific Receptor

Concomitant use of gilteritinib may reduce the effects of drugs that target the $5HT_{2B}$ receptor or the sigma nonspecific receptor (e.g., escitalopram, fluoxetine, sertraline). Avoid concomitant use of these drugs with XOSPATA unless their use is considered essential for the care of the patient *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies *(see Data)* and its mechanism of action, XOSPATA can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*.

There are no available data on XOSPATA use in pregnant women to inform a drug-associated risk of adverse developmental outcomes. In animal reproduction studies, administration of gilteritinib to pregnant rats during organogenesis caused adverse developmental outcomes including embryo-fetal lethality, suppressed fetal growth, and teratogenicity at maternal exposures (AUC_{24}) approximately 0.4 times the AUC_{24} in patients receiving the recommended dose (*see Data*). Advise pregnant women of the potential risk to a fetus.

Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

Animal Data

In an embryo-fetal development study in rats, pregnant animals received oral doses of gilteritinib of 0, 0.3, 3, 10, and 30 mg/kg/day during the period of organogenesis. Maternal findings at 30 mg/kg/day (resulting in exposures approximately 0.4 times the AUC_{24} in patients receiving the recommended dose) included decreased body weight and food consumption. Administration of gilteritinib at the dose of 30 mg/kg/day also resulted in embryo-fetal death (postimplantation loss), decreased fetal body and placental weight, and decreased numbers of ossified sternebrae and sacral and caudal vertebrae, and increased incidence of fetal gross external (anasarca, local edema, exencephaly, cleft lip, cleft palate, short tail, and umbilical hernia), visceral (microphthalmia; atrial and/or ventricular defects; and malformed/absent kidney, and malpositioned adrenal, and ovary), and skeletal (sternoschisis, absent rib, fused rib, fused cervical arch, misaligned cervical vertebra, and absent thoracic vertebra) abnormalities.

Single oral administration of [^{14}C] gilteritinib to pregnant rats resulted in transfer of radioactivity to the fetus similar to that observed in maternal plasma on day 14 of gestation. In addition, distribution profiles of radioactivity in most maternal tissues and the fetus on day 18 of gestation were similar to that on day 14 of gestation.

8.2 Lactation

Risk Summary

There are no data on the presence of gilteritinib and/or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Following administration of radiolabeled gilteritinib to lactating rats, milk concentrations of radioactivity were higher than radioactivity in maternal plasma at 4 and 24 hours post-dose. In animal studies, gilteritinib and/or its metabolite(s) were distributed to the tissues in infant rats via the milk. Because of the potential for serious adverse reactions in a breastfed child, advise a lactating woman not to breastfeed during treatment with XOSPATA and for at least 2 months after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy testing

Pregnancy testing is recommended for females of reproductive potential within seven days prior to initiating XOSPATA treatment *[see Use in Specific Populations (8.1)]*.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment and for at least 6 months after the last dose of XOSPATA.

Males

Advise males of reproductive potential to use effective contraception during treatment and for at least 4 months after the last dose of XOSPATA.

8.4 Pediatric Use

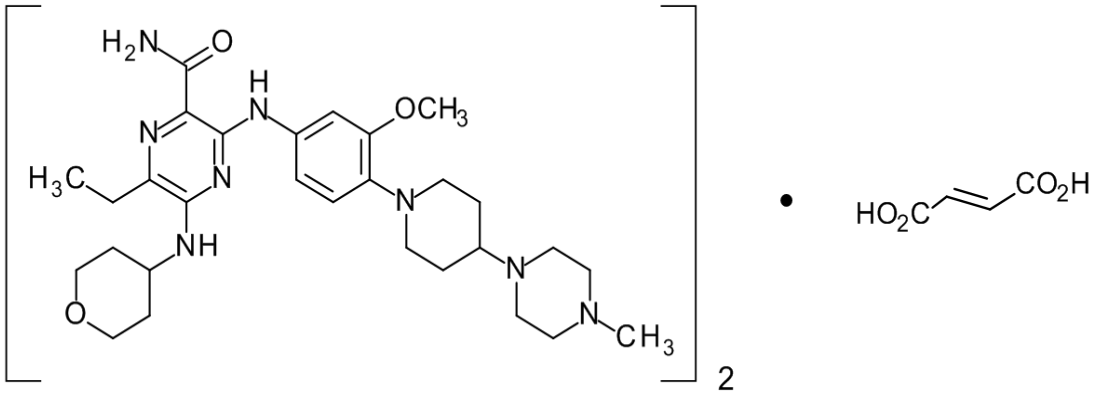
Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the 319 patients in clinical studies of XOSPATA, 43% were age 65 years or older, and 13% were 75 years or older. No overall differences in effectiveness or safety were observed between patients age 65 years or older and younger patients.

11 DESCRIPTION

Gilteritinib is a tyrosine kinase inhibitor. The chemical name is 2-Pyrazinecarboxamide, 6-ethyl-3-[[3-methoxy-4-[4-(4-methyl-1-piperazinyl)-1-piperidinyl] phenyl] amino]-5-[(tetrahydro-2*H*-pyran-4-yl) amino]-, (2*E*)-2-butenedioate (2:1). The molecular weight is 1221.50 and the molecular formula is $(C_{29}H_{44}N_8O_3)_2 \cdot C_4H_4O_4$. The structural formula is:



Gilteritinib fumarate is a light yellow to yellow powder or crystals that is sparingly soluble in water and very slightly soluble in anhydrous ethanol.

XOSPATA (gilteritinib) is provided as a tablet for oral administration. Each tablet contains 40 mg of gilteritinib active ingredient as free base (corresponding to 44.2 mg gilteritinib fumarate). The inactive ingredients are ferric

oxide, hydroxypropyl cellulose, hypromellose, low-substituted hydroxypropyl cellulose, mannitol, magnesium stearate, talc, polyethylene glycol and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Gilteritinib is a small molecule that inhibits multiple receptor tyrosine kinases, including FMS-like tyrosine kinase 3 (FLT3). Gilteritinib demonstrated the ability to inhibit FLT3 receptor signaling and proliferation in cells exogenously expressing FLT3 including FLT3-ITD, tyrosine kinase domain mutations (TKD) FLT3-D835Y and FLT3-ITD-D835Y, and it induced apoptosis in leukemic cells expressing FLT3-ITD.

12.2 Pharmacodynamics

In patients with relapsed or refractory AML administered gilteritinib 120 mg, substantial (>90%) inhibition of FLT3 phosphorylation was rapid (within 24 hours after first dose) and sustained, as characterized by an *ex vivo* plasma inhibitory activity (PIA) assay.

Cardiac Electrophysiology

The effect of XOSPATA 120 mg once a day on the QTc interval has been evaluated in patients, which showed an absence of large mean increases (i.e., 20 msec) in the QTc interval.

Of 317 patients with a post-baseline QTc measurement on treatment with gilteritinib at 120 mg in clinical trials, 4 patients (1.3%) experienced a QTcF >500 msec. Additionally, across all doses 2.3% of patients with relapse/refractory AML had a maximum post-baseline QTcF interval >500 msec *[see Warnings and Precautions (5.3)]*.

12.3 Pharmacokinetics

The following pharmacokinetic parameters were observed following administration of gilteritinib 120 mg once daily, unless otherwise specified.

Gilteritinib exposure (C_{max} and AUC_{24}) increases proportionally with once daily doses ranging from 20 mg to 450 mg (0.17 to 3.75 times the recommended dosage) in patients with relapsed or refractory AML. Gilteritinib mean (±SD) steady-state C_{max} is 374 ng/mL (±190) and AUC_{24} is 6943 ng•hr/mL (±3221). Steady-state plasma levels are reached within 15 days of dosing with an approximate 10-fold accumulation.

Absorption

The time to maximum gilteritinib concentration (t_{max}) observed is approximately between 4 and 6 hours postdose in the fasted state.

Effect of Food

In healthy adults administered a single gilteritinib 40 mg dose (0.3 times the recommended dosage), gilteritinib C_{max} decreased by 26% and AUC decreased by less than 10% when co-administered with a high-fat meal (approximately 800 to 1,000 total calories with 500 to 600 fat calories, 250 carbohydrate calories, 150 protein calories) compared to a fasted state. Median t_{max} was delayed 2 hours when gilteritinib was administered with a high-fat meal.

Distribution

The population mean (%CV) estimates of apparent central and peripheral volume of distribution were 1092 L (9.22%) and 1100 L (4.99%), respectively, which may indicate extensive tissue distribution. *In vivo*, gilteritinib is approximately 94% bound to human plasma proteins. *In vitro*, gilteritinib is primarily bound to human serum albumin.

Elimination

The estimated half-life of gilteritinib is 113 hours, and the estimated apparent clearance is 14.85 L/h.

Metabolism

Gilteritinib is primarily metabolized via CYP3A4 *in vitro*. At steady state, the primary metabolites in humans include M17 (formed via N-dealkylation and oxidation), M16 and M10 (both formed via N-dealkylation). None of these 3 metabolites exceeded 10% of overall parent exposure.

Excretion

After a single radiolabeled dose, gilteritinib is excreted in feces with 64.5% of the total administered dose recovered in feces. Of the total radiolabeled dose of gilteritinib, 16.4% was recovered in urine as unchanged drug and metabolites.

Specific Populations

Age (20-87 years), sex, race, 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 do not have clinically meaningful effects on the pharmacokinetics of gilteritinib.

The effect of severe hepatic (Child-Pugh Class C) or severe renal impairment (CLCr $\leq$ 29 mL/min) on gilteritinib pharmacokinetics is unknown.

Drug Interaction Studies

Clinical Studies

Combined P-gp and Strong CYP3A Inducers:

Gilteritinib C_{max} decreased approximately 30% and AUC decreased approximately 70% when co-administered with rifampin (a combined P-gp and strong CYP3A inducer).

Strong CYP3A Inhibitors:

Gilteritinib C_{max} increased approximately 20% and AUC increased approximately 120% when co-administered with itraconazole (a strong CYP3A inhibitor).

Moderate CYP3A Inhibitors:

Gilteritinib C_{max} increased approximately 16% and AUC increased approximately 40% when co-administered with fluconazole (a moderate CYP3A inhibitor).

CYP3A Substrates:

Midazolam (a CYP3A substrate) C_{max} and AUC increased approximately 10% when co-administered with gilteritinib.

MATE1 Substrates:

Cephalexin (a MATE1 substrate) C_{max} and AUC decreased by less than 10% when co-administered with gilteritinib.

In Vitro Studies

Gilteritinib inhibits human $5HT_{2B}$ receptor or sigma nonspecific receptors, which may reduce the effects of drugs that target these receptors such as escitalopram, fluoxetine and sertraline.

Gilteritinib is a substrate of P-gp transporter and has the potential to inhibit breast cancer resistance protein (BCRP) and organic cation transporter 1 (OCT1) transporters.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with gilteritinib.

Gilteritinib was not mutagenic in a bacterial mutagenesis (Ames) assay and was not clastogenic in a chromosome aberration test assay in Chinese hamster lung cells. Gilteritinib was positive for the induction of micronuclei in mouse bone marrow cells from 65 mg/kg (195 mg/m^2) the mid dose tested (approximately 2.6 times the recommended human dose of 120 mg).

The effect of XOSPATA on human fertility is unknown. Administration of 10 mg/kg/day gilteritinib in the 4-week study in dogs (12 days of dosing) resulted in degeneration and necrosis of germ cells and spermatid giant cell formation in the testis as well as single cell necrosis of the epididymal duct epithelia of the epididymal head.

13.2 Animal Toxicology and/or Pharmacology

In the 13-week oral repeated dose toxicity studies in rats and dogs, target organs of toxicity included the eye and kidney.

14 CLINICAL STUDIES

14.1 Relapsed or Refractory Acute Myeloid Leukemia

The efficacy of XOSPATA was assessed in the ADMIRAL Trial (NCT02421939**)**, which included adult patients with relapsed or refractory AML having a FLT3 ITD, D835, or I836 mutation by the LeukoStrat® CDx *FLT3* Mutation Assay. XOSPATA was given orally at a starting dose of 120 mg daily until unacceptable toxicity or lack of clinical benefit.

First Interim Analysis

The efficacy of XOSPATA was established on the basis of the rate of complete remission (CR)/CR with partial hematological recovery (CRh), the duration of CR/CRh (DOR), and the rate of conversion from transfusion dependence to transfusion independence at the first interim analysis in the ADMIRAL trial (n=138). The median follow-up was 4.6 months (95% CI: 2.8, 15.8). Fourteen patients were still in remission at the time of the first interim DOR analysis. The efficacy results are shown in Table 5. For patients who achieved a CR/CRh, the median time to first response was 3.6 months (range, 0.9 to 9.6 months). The CR/CRh rate was 29 of 126 in patients with FLT3-ITD or FLT3-ITD/TKD and 0 of 12 in patients with FLT3-TKD only.

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 post-baseline period. For the 32 patients who were independent of both RBC and platelet transfusions at baseline, 17 (53.1%) remained transfusion-independent during any 56-day post-baseline period.

Table 5: Efficacy Results in Patients with Relapsed or Refractory AML Treated with XOSPATA in the First Interim Analysis (ADMIRAL Trial)

Remission Rate	**XOSPATA N=138**
CR*/CRh† n/N (%)	29/138 (21)
95% CI‡	14.5, 28.8
Median DOR§ (months)	4.6
Range (months)	0.1 to 15.8¶
CR* n/N (%)	16/138 (11.6)
95% CI‡	6.8, 18.1
Median DOR§ (months)	8.6
Range (months)	1 to 13.8
CRh† n/N (%)	13/138 (9.4)
95% CI‡	5.1, 15.6
Median DOR§ (months)	2.9
Range (months)	0.1 to 15.8¶

CI: confidence interval; NE: not estimable; NR: not reached; Only responses prior to HSCT were included in response rate.

*CR was defined as an absolute neutrophil count ≥1.0 x 109/L, platelets ≥100 x 109/L, normal marrow differential with <5% blasts, must have been red blood cells, platelet transfusion independent and no evidence of extramedullary leukemia.

†CRh was defined as marrow blasts <5%, partial hematologic recovery absolute neutrophil count ≥0.5 x 109/L and platelets ≥50 x 109/L, no evidence of extramedullary leukemia and could not have been classified as CR.

‡The 95% CI rate was calculated using the exact method based on binomial distribution.

§DOR was defined as the time from the date of either first CR or CRh until the date of a documented relapse of any type. Deaths were counted as events.

¶Response was ongoing.

Final Analysis

The final analysis of the ADMIRAL trial included 371 adult patients randomized 2:1 to receive XOSPATA 120 mg once daily (n=247) over continuous 28-day cycles or a prespecified chemotherapy regimen (n=124). Randomization was stratified by response to first-line AML therapy and prespecified chemotherapy. The prespecified chemotherapy regimens included high intensity combinations (MEC and FLAG-IDA) and low intensity regimens (LDAC and AZA).

The demographic and disease characteristics of the randomized patients are shown in Table 6.

Table 6: Baseline Demographic and Disease Characteristics in Patients with Relapsed or Refractory AML in the Final Analysis (ADMIRAL Trial)

Demographic and Disease Characteristics	Xospata (120 mg daily) N=247	Chemotherapy N=124
Demographics		
Median Age (Years) (Range)	62 (20, 84)	62 (19, 85)
Age Categories, n (%)		
<65 years	141 (57)	75 (60)
≥65 years	106 (43)	49 (40)
Sex, n (%)		
Male	116 (47)	54 (44)
Female	131 (53)	70 (57)
Race, n (%)		
White	145 (59)	75 (60)
Asian	69 (28)	33 (27)
Black or African American	14 (6)	7 (6)
Native Hawaiian or Other Pacific Islander	1 (0.4)	0
Other	5 (2)	1 (0.8)
Unknown/Missing	13 (5)	8 (6)
Baseline ECOG, n (%)		
0-1	206 (83)	105 (85)
≥2	41 (17)	19 (15)
Disease Characteristics		
Untreated relapse AML, n (%)	151 (61)	74 (60)
Primary refractory AML, n (%)	96 (39)	49 (40)
Refractory relapse AML, n (%)	0	1 (0.8)
Number of Relapses, n (%)		
0	96 (39)	49 (40)
1	149 (60)	74 (60)
2 or more	2 (0.8)	1 (0.8)
Median number of relapses (Range)	1 (0, 2)	1 (0, 2)
Transfusion Dependent at Baseline, n (%)[*]	197 (80)	97 (89)
FLT3 Mutation Status, n (%)		
ITD alone	215 (87)	113 (91)
TKD alone	21 (9)	10 (8)
ITD and TKD	7 (3)	0
Prior Use of FLT3 Inhibitor[†]**, n (%)**		
No	215 (87)	110 (89)
Yes	32 (13)	14 (11)
Prespecified Chemotherapy		
High Intensity	149 (60)	75 (60)
MEC[‡]	-	33 (27)
FLAG-IDA[§]	-	42 (34)
Low Intensity	98 (40)	49 (40)
LDAC[¶]	-	17 (14)
AZA[#]	-	32 (26)

AML: acute myeloid leukemia; FLT3: FMS-related tyrosine kinase 3; ITD: internal tandem duplication; TKD: D835/I836 tyrosine kinase domain point mutation; ECOG PS: Eastern Cooperative Oncology Group performance status; CRc: Composite complete remission (complete remission [CR] + complete remission with incomplete hematologic recovery [CRi] + complete remission with incomplete platelet recovery [CRp]); HSCT: Hematopoietic stem cell transplantation

*Patients were defined as transfusion dependent at baseline if they were dosed and received any red blood cell or platelet transfusions within the 56-day baseline period.

†Prior use of FLT3 inhibitor is defined as "Yes" if patients received prior AML therapy of midostaurin, sorafenib or quizartinib; otherwise, prior use of FLT3 inhibitor was assigned as "No."

‡MEC: mitoxantrone 8 mg/m^2, etoposide 100 mg/m^2 and cytarabine 1000 mg/m^2 once daily by IV for 5 days

§FLAG-IDA: granulocyte colony-stimulating factor 300 mcg/m^2 once daily by SC days 1 to 5, fludarabine 30 mg/m^2 once daily by IV days 2 through 6, cytarabine 2000 mg/m^2 once daily by IV for days 2 through 6, idarubicin 10 mg/m^2 once daily by IV days 2 through 4

¶LDAC: cytarabine 20 mg twice daily by subcutaneous (SC) or intravenous (IV) for 10 days

#AZA: azacitidine 75 mg/m^2 once daily by SC or IV for 7 days

The final analysis included an assessment of OS, measured from the date of randomization until death by any cause. At the time of analysis, median follow-up was 17.8 months (range, 14.9 to 19.1). Patients randomized to the XOSPATA arm had significantly longer survival compared to the chemotherapy arm (HR 0.64; 95% CI: 0.49 – 0.83; 1-sided p-value: 0.0004). Figure 1 and Table 7 show the results of the OS analysis.

Exploratory subgroup analyses demonstrated that the hazard ratio for survival was 0.66 (95% CI: 0.47 –0.93) for patients in the high intensity chemotherapy stratum and 0.56 (95% CI: 0.38 – 0.84) for patients in the low intensity chemotherapy stratum. The CR rates are shown in Table 7. For patients on XOSPATA and chemotherapy arms, the CR rates were 15.4% (95% CI: 10% – 22.3%) and 16% (95% CI: 8.6% – 26.3%), respectively, for patients in the high intensity chemotherapy stratum, and 12.2% (95% CI: 6.5% – 20.4%) and 2% (95% CI 0.1% – 10.9%), respectively, for patients in the low intensity chemotherapy stratum.

Table 7: OS and CR* in Patients with Relapsed or Refractory AML in the Final Analysis (ADMIRAL Trial)

	XOSPATA N=247	**Chemotherapy N=124**
Overall Survival		
Deaths, n (%)	171 (69.2%)	90 (72.6%)
Median in months (95% CI)	9.3 (7.7, 10.7)	5.6 (4.7, 7.3)
Hazard Ratio (95% CI)	0.64 (0.49, 0.83)	
p-value (1-sided)	0.0004	
Complete Remission		
CR, n (%)	35 (14.2%)	13 (10.5%)
(95% CI†)	(10.1, 19.2)	(5.7, 17.3)
Median DOR‡ (range) (months)	14.8 (0.6 to 23.1+)	1.8 (<0.1+ to 1.8)

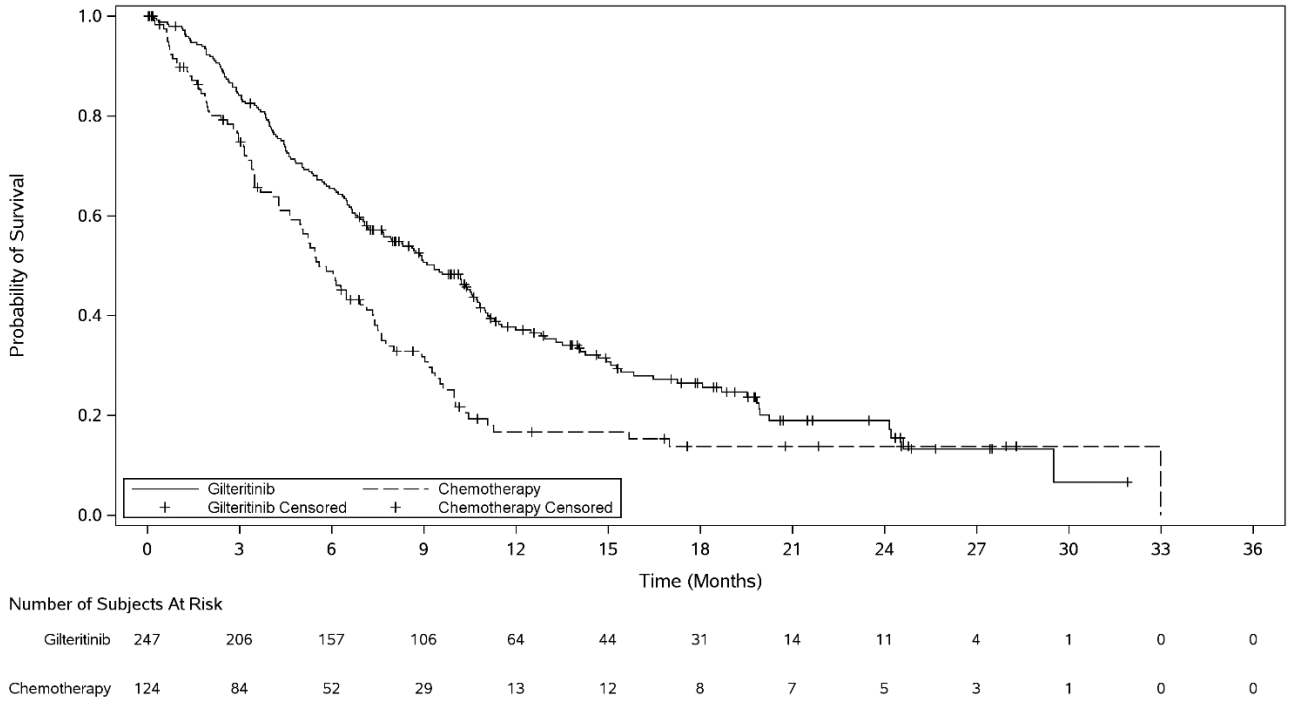
CI: confidence interval; Only responses prior to HSCT were included in response rate.

*CR was defined as an absolute neutrophil count ≥1.0 x 10^9/L, platelets ≥100 x 10^9/L, normal marrow differential with <5% blasts, must have been red blood cells, platelet transfusion independent and no evidence of extramedullary leukemia.

†The 95% CI rate was calculated using the exact method based on binomial distribution.

‡DOR was defined as the time from the date of first remission until the date of a documented relapse.

Figure 1: Kaplan-Meier Plot of Overall Survival in ADMIRAL Trial



In the final analysis, the CR/CRh rate in the gilteritinib arm was 22.6% (55/243) and the DOR was 7.4 months (range, <0.1+ to 23.1+). For patients who achieved a CR/CRh, the median time to first response was 2 months (range, 0.9 to 9.6 months). The CR/CRh rate was 49 of 215 in patients with FLT3-ITD only, 3 of 7 in patients with FLT3-ITD/TKD and 3 of 21 in patients with FLT3-TKD only.

Among the 197 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 68 (34.5%) became independent of RBC and platelet transfusions during any 56-day post-baseline period. For the 49 patients who were independent of both RBC and platelet transfusions at baseline, 29 (59.2%) remained transfusion-independent during any 56-day post-baseline period.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

XOSPATA (gilteritinib) 40 mg tablets are supplied as light yellow, round-shaped, film-coated tablets debossed with the Astellas logo and ‘235’ on the same side. XOSPATA tablets are available in the following package size:

- Bottles of 90 tablets with Child Resistant Closure, (NDC 0469-1425-90)

16.2 Storage

Store XOSPATA tablets at 20ºC to 25ºC (68°F to 77°F); excursions permitted between 15ºC to 30ºC (59°F to 86°F) [See USP Controlled Room Temperature]. Keep in original container until dispensed. Protect from light, moisture and humidity.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Differentiation Syndrome

Advise patients of the risks of developing differentiation syndrome as early as 2 days after the start of therapy and during the first 3 months on treatment. Ask patients to immediately report any symptoms suggestive of differentiation syndrome, such as fever, cough or difficulty breathing, rash, low blood pressure, rapid weight gain, swelling of their arms or legs, or decreased urinary output, to their healthcare provider for further evaluation *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Posterior Reversible Encephalopathy Syndrome

Advise patients of the risk of developing posterior reversible encephalopathy syndrome (PRES). Ask patients to immediately report any symptoms suggestive of PRES, such as seizure and altered mental status, to their healthcare provider for further evaluation *[see Warnings and Precautions (5.2)]*.

Prolonged QT Interval

Advise patients to consult their healthcare provider immediately if they feel faint, lose consciousness, or have signs or symptoms suggestive of arrhythmia. Advise patients with a history of hypokalemia or hypomagnesemia of the importance of monitoring their electrolytes *[see Warnings and Precautions (5.3)]*.

Pancreatitis

Advise patients of the risk of pancreatitis and to contact their healthcare provider for signs or symptoms of pancreatitis, which include severe and persistent stomach pain, with or without nausea and vomiting *[see Warnings and Precautions (5.4)]*.

Use of Contraceptives

- Advise female patients with reproductive potential to use effective contraceptive methods while receiving XOSPATA and to avoid pregnancy while on treatment and for 6 months after completion of treatment.
- Advise patients to notify their healthcare provider immediately in the event of a pregnancy or if pregnancy is suspected during XOSPATA treatment.
- Advise males with female partners of reproductive potential to use effective contraception during treatment with XOSPATA and for at least 4 months after the last dose of XOSPATA *[see Use in Specific Populations (8.3)]*.

Lactation

Advise women not to breastfeed during treatment with XOSPATA for at least 2 months after the final dose *[see Use in Specific Populations (8.2)]*.

Dosing Instructions

- Advise patients not to break, crush or chew the tablets but to swallow them whole with a cup of water.
- Instruct patients that, if they miss a dose of XOSPATA, to take it as soon as possible on the same day, and at least 12 hours prior to the next scheduled dose, and return to the normal schedule the following day. Instruct patients to not take 2 doses within 12 hours *[see Dosage and Administration (2.2)]*.

Distributed by:
Astellas Pharma US, Inc.
Northbrook, Illinois 60062

222317-GLT

MEDICATION GUIDE
XOSPATA® (Zoh spah' tah)
(gilteritinib)
tablets

What is the most important information I should know about XOSPATA?
XOSPATA may cause serious side effects, including:
Differentiation Syndrome. Differentiation syndrome is a condition that affects your blood cells and may be life-threatening or lead to death if not treated. Differentiation syndrome can happen as early as 2 days after starting XOSPATA and during the first 3 months of treatment. Call your healthcare provider or go to the nearest hospital emergency room right away if you develop any of the following symptoms of differentiation syndrome while taking XOSPATA:

- fever
- cough
- trouble breathing
- rash
- dizziness or lightheadedness
- rapid weight gain
- swelling of your arms or legs
- decreased urination

If you develop any of these symptoms of differentiation syndrome, your healthcare provider may treat you with a corticosteroid medicine and may monitor you in the hospital.

See **"What are the possible side effects of XOSPATA?"** for more information about side effects.

What is XOSPATA?
XOSPATA is a prescription medicine used to treat adults with acute myeloid leukemia (AML) who have a FMS-like tyrosine kinase 3 (FLT3) mutation:

- when the disease has come back, or
- has not improved after previous treatment(s).

Your healthcare provider will perform a test to make sure that XOSPATA is right for you.

It is not known if XOSPATA is safe and effective in children.

Who should not take XOSPATA?
Do not take XOSPATA if you are allergic to gilteritinib or any of the ingredients in XOSPATA. See the end of this Medication Guide for a complete list of ingredients in XOSPATA.

Before taking XOSPATA, tell your healthcare provider about all of your medical conditions, including if you:

- have any heart problems, including a condition called long QT syndrome.
- have problems with abnormal electrolytes such as sodium, potassium, or magnesium levels.
- are pregnant or plan to become pregnant. XOSPATA can cause harm to your unborn baby. You should avoid becoming pregnant during treatment with XOSPATA. Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with XOSPATA.
  - If you are able to become pregnant, your healthcare provider may perform a pregnancy test 7 days before you start treatment with XOSPATA.
  - **Females** who are able to become pregnant should use effective birth control (contraception) during treatment with XOSPATA and for at least 6 months after the last dose of XOSPATA.
  - **Males** who have female partners that are able to become pregnant should use effective birth control (contraception) during treatment with XOSPATA and for at least 4 months after the last dose of XOSPATA.
- are breastfeeding or plan to breastfeed. It is not known if XOSPATA passes into your breast milk. Do not breastfeed during treatment with XOSPATA and for at least 2 months after the last dose of XOSPATA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How should I take XOSPATA?

- Take XOSPATA exactly as your healthcare provider tells you to. Do not change your dose or stop taking XOSPATA without talking to your healthcare provider.
- Take XOSPATA 1 time a day at about the same time each day.
- Swallow XOSPATA tablets whole. Do not break, crush, or chew the tablet.
- XOSPATA can be taken with or without food.
- If you miss a dose of XOSPATA, or did not take it at the usual time, take your dose as soon as possible and at least 12 hours before your next dose. Return to your normal schedule the following day. Do not take 2 doses of XOSPATA within 12 hours.

What are the possible side effects of XOSPATA?
XOSPATA may cause serious side effects, including:

- **See "What is the most important information I should know about XOSPATA?"**
- **Posterior Reversible Encephalopathy Syndrome (PRES)**. If you take XOSPATA, you may be at risk of developing a condition involving the brain called PRES. Tell your healthcare provider right away if you have a seizure or quickly worsening symptoms such as headache, decreased alertness, confusion, reduced eyesight, blurred vision, or other visual problems. Your healthcare provider will do a test to check for PRES. Your healthcare provider will stop XOSPATA if you develop PRES.
- **Changes in the electrical activity of your heart called QTc prolongation. QTc prolongation can cause irregular heartbeats that can be life-threatening.** Your healthcare provider will check the electrical activity of your heart with a test called an electrocardiogram (ECG) before you start taking XOSPATA and during your treatment with XOSPATA. Tell your healthcare provider right away if you feel dizzy, lightheaded, or faint. The risk of QT prolongation is higher in people with low blood magnesium or low blood potassium levels. Your healthcare provider will do blood tests to check your potassium and magnesium levels before and during your treatment with XOSPATA.
- **Inflammation of the pancreas (pancreatitis)**. Tell your healthcare provider right away if you have severe stomach (abdomen) pain that does not go away. This pain may happen with or without nausea and vomiting.

The most common side effects of XOSPATA include:

- changes in liver function tests
- joint or muscle pain
- tiredness
- fever
- pain or sores in mouth or throat
- swelling of arms or legs
- rash
- diarrhea
- shortness of breath
- nausea
- cough
- constipation
- eye problems
- headache
- dizziness
- low blood pressure
- vomiting
- decreased urination

Your healthcare provider may tell you to decrease your dose, temporarily stop, or completely stop taking XOSPATA if you develop certain side effects during treatment with XOSPATA.

These are not all of the possible side effects of XOSPATA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XOSPATA?

- XOSPATA comes in a child-resistant package.
- Store XOSPATA at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep XOSPATA in the original container provided by your pharmacist to protect it from light, moisture and humidity.
- **Keep XOSPATA and all medicines out of the reach of children.**

General information about the safe and effective use of XOSPATA.
Medicines are sometimes prescribed for conditions not listed in a Medication Guide. Do not use XOSPATA for a condition for which it was not prescribed. Do not give XOSPATA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about XOSPATA that is written for healthcare professionals.

What are the ingredients in XOSPATA?
Active ingredient: gilteritinib
Inactive ingredients: ferric oxide, hydroxypropyl cellulose, hypromellose, low-substituted hydroxypropyl cellulose, mannitol, magnesium stearate, talc, polyethylene glycol and titanium dioxide.

Distributed by: Astellas Pharma US, Inc., Northbrook, Illinois 60062

For more informa ion about XOSPATA, call 1-800-727-7003, or visit www.XOSPATA.com.

222317-GLT

This Medication Guide has been approved by the U.S. Food and Drug Administration. Issued: May 2019

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/

ALBERT B DEISSEROTH
05/29/2019 06:03:49 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211349Orig1s001

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 S-001**
Application Type	SE 8
Priority or Standard	Priority - RTOR
Received Date	2/22/2019
PDUFA Goal Date	8/22/2019
Division/Office	DHP/OHOP
Review Completion Date	5/29/2019
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
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	Approval

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Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA

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Clinical Team Leader	Donna Przepiorka, MD, PhD
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Glossary

ADMIRAL	Study 2215-CL-0301
ADR	adverse drug reactions
AE	adverse event
AML	acute myeloid leukemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
$AUC_{24,ss}$	area under the curve for 24 hours at steady-state
BFI	Brief Fatigue Inventory
CFR	Code of Federal Regulations
CHRYSALIS	Study 2215-CL-0101
CI	confidence interval
CK	creatine kinase
C_{max}	maximum plasma drug concentration
$C_{max,ss}$	maximum plasma drug concentration at steady-state
CMC	chemistry, manufacturing, and controls
$C_{min,ss}$	minimum concentration at steady-state
COA	clinical outcome assessment
CR	complete remission
CRc	composite complete remission
CRh	complete remission with partial hematological recovery
CRi	complete remission with incomplete hematologic recovery
CRp	complete remission with incomplete platelet recovery
C_{trough}	trough plasma drug concentration
$C_{trough,ss}$	trough plasma drug concentration at steady-state
CSR	Clinical Study Report
CYP	cytochrome P450
ΔALT	change in alanine aminotransferase
ΔAST	change in aspartate aminotransferase
ΔCK	change in creatine kinase
DBP	diastolic blood pressure
DFS	disease-free surviv al
DNMT3A	DNA Methyltransferase 3 Alpha
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
FACIT-Dys-SF	Functional Assessment of Chronic Illness Therapy-Dyspnea-Short Form
FACT-Leu	Functional Assessment of Cancer Therapy-Leukemia

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FAS	Full Analysis Set
FLAG-IDA	fludarabine, cytarabine and granulocyte colony-stimulating factor with idarubicin
FLT3	FMS-like tyrosine kinase
FLT3 CDx	LeukoStrat CDx FLT3 Mutation Assay
GCP	Good Clinical Practice
HR	hazard ratio
HSCT	hematopoietic stem cell transplant
IAP	interim analysis plan
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IND	investigational new drug application
IRT	interactive response technology
ISS	Integrated Summary of Safety
ITD	internal tandem duplication
ITT	Intention to Treatment Set
LFS	leukemia-free survival
LoDAC	low-dose cytarabine
MAS	Multigene Analysis Set
MEC	mitoxantrone, etoposide and intermediate-dose cytarabine
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
N/A	not applicable
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NE	not estimable
NPM1	Nucleophosmin 1
NR	no response
NSCLC	non-small cell lung cancer
OS	overall survival
PADER	Periodic Adverse Drug Experience Report
PCS	potentially clinically significant
PKAS	Pharmacokinetic Analysis Set
PPS	Per Protocol Set
PR	partial remission
PRES	posterior reversible encephalopathy syndrome
PT	preferred term
Q1	first quartile
Q3	third quartile
QTc	corrected QT interval
QTcF	Fridericia-corrected QT interval

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RAS	Response Analysis Set
RBC	red blood cell
RTOR	Real-time Oncology Review
R/R	relapsed or refractory
SAE	serious adverse event
SAF	Safety Analysis Set
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SMQs	standardized MedDRA queries
sNDA	supplemental new drug application
SOC	system organ class
TEAE	treatment-emergent adverse event
TKD	tyrosine kinase domain
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
WT1	Wilms Tumor 1

1 Executive Summary

1.1. Product Introduction

Trade Name:	Xospata®
Established Name:	Gilteritinib
Also Known As:	ASP2215, (b) (6)
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 was approved 11/26/2018 for 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 on the basis of CR/CRh in the first interim analysis of Study 2215-CL-0301 (Study 0301; ADMIRAL; NCT02421939). The Applicant now submits a labeling revision (b) (4) to update the safety and efficacy data with the results from Study 0301.

1.2. Recommended Regulatory Action

The review team recommends approval of the revised label with addition of a boxed warning for differentiation syndrome; addition of dosage modifications for toxicities (Section 2.3); addition of differentiation syndrome in warnings and precautions (Section 5.1), revisions to the warnings and precautions for posterior reversible encephalopathy syndrome, prolonged QT interval and pancreatitis (Sections 5.2, 5.3, 5.4); updates in adverse reactions (Section 6.1); updates based on the final efficacy analysis of Study 0301 (Section 14), addition of patient counseling information about differentiation syndrome (Section 17), and conversion of the Patient Package Insert was converted to a Medication Guide.

1.3. Basis for the Regulatory Recommendation

The final analysis of the Study 0301 included 371 adult patients randomized 2:1 to receive gilteritinib (n=247) or a prespecified chemotherapy regimen (n=124). Randomization was stratified by response to first-line AML therapy and prespecified chemotherapy (intensive chemotherapy vs low-intensity chemotherapy). The demographic and disease characteristics of

the randomized patients were balanced between arms.

The final analysis included a prespecified assessment of OS, measured from the date of randomization until death by any cause. At the time of analysis, median follow-up was 17.8 months (range, 14.9 to 19.1). Patients randomized to the gilteritinib arm had significantly longer survival compared to the chemotherapy arm (HR 0.64; 95% CI: 0.49 – 0.83; 1-sided p-value: 0.0004).

The strata of intensive chemotherapy and low-intensity chemotherapy represent distinct controls that may be associated with different treatment effects. To confirm that a treatment effect was independent of the control used and to determine if the treatment effect was consistent across strata, FDA assessed OS by stratum intensity. The hazard ratio for survival was 0.66 (95% CI: 0.47 –0.93) for patients in the high intensity chemotherapy stratum and 0.56 (95% CI: 0.38 – 0.84) for patients in the low intensity chemotherapy stratum. An imbalance between arms was observed in the use of various poststudy therapies, including HSCT, but additional analyses demonstrated that the effect of gilteritinib on OS was independent of poststudy therapy. The OS results were considered credible and appropriate for inclusion in labeling.

As gilteritinib may be considered as an alternative to intensive chemotherapy, CR is an additional endpoint of interest. FDA-adjudicated CR was achieved by 35 (14.2%) patients on gilteritinib and 13 (10.5%) patients on the chemotherapy arm. For patients on gilteritinib and chemotherapy arms, the CR rates were 15.4% (95% CI: 10% – 22.3%) and 16% (95% CI: 8.6% – 26.3%), respectively, for patients in the high intensity chemotherapy stratum, and 12.2% (95% CI: 6.5% – 20.4%) and 2% (95% CI 0.1% – 10.9%), respectively, for patients in the low intensity chemotherapy stratum. Although this analysis did not fall within the alpha-controlled hierarchy, these additional CR results are appropriate to display descriptively in labeling to assist healthcare providers and patients in treatment decision-making.

The original approval of gilteritinib was based on CR/CRh rate and conversion to transfusion independence in the patients treated with gilteritinib. In the final analysis, the CR/CRh rate in the gilteritinib arm was 22.6% (55/243), and the DOR was 7.4 months (range, < 0.1+ to 23.1+). For patients who achieved a CR/CRh, the median time to first response was 2 months (range, 0.9 to 9.6 months). CR/CRh occurred in 49 of 215 patients with FLT3-ITD only, 3 of 7 with FLT3-ITD/TKD, and 3 of 21 with FLT3-TKD only. Among the 197 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 68 (34.5%) became independent of RBC and platelet transfusions during any 56-day post-baseline period. For the 49 patients who were independent of both RBC and platelet transfusions at baseline, 29 (59.2%) remained transfusion-independent during any 56-day post-baseline period. Labeling should be updated to include these results.

(b) (4)

The safety profile was updated to include results from 319 patients with relapsed or refractory AML treated with gilteritinib 120 mg daily in three clinical trials. The median duration of exposure was 3.6 months (range 0.1 to 43.4 months). Fatal adverse reactions occurred in 2%. These included cardiac arrest (1%) and one case each of differentiation syndrome and pancreatitis. Of the 319 patients, 91 (29%) required a dose interruption due to an adverse reaction; the most common adverse reactions leading to dose interruption were aspartate aminotransferase increased (6%), alanine aminotransferase increased (6%) and fever (4%). Twenty patients (6%) required a dose reduction due to an adverse reaction. Twenty-two (7%) discontinued treatment permanently due to an adverse reaction. The most common (>1%) adverse reactions leading to discontinuation were aspartate aminotransferase increased (2%) and alanine aminotransferase increased (2%).

Overall, for the 319 patients, the most frequent (≥10%) all-grade nonhematological adverse reactions reported in patients were transaminase increased (51%), myalgia/arthralgia (50%), fatigue/malaise (44%), fever (41%), mucositis (41%), edema (40%), rash (36%), noninfectious diarrhea (35%), dyspnea (35%), nausea (30%), cough (28%), constipation (28%), eye disorders (25%), headache (24%), dizziness (22%), hypotension (22%), vomiting (21%), renal impairment (21%), abdominal pain (18%), neuropathy (18%), insomnia (15%) and dysgeusia (11%). The most frequent (≥5%) grade ≥3 nonhematological adverse reactions reported in patients were transaminase increased (21%), dyspnea (12%), hypotension (7%), mucositis (7%), myalgia/ arthralgia (7%), and fatigue/malaise (6%). Shifts to grades 3-4 nonhematologic laboratory abnormalities included phosphate decreased 42/309 (14%), alanine aminotransferase increased 41/317 (13%), sodium decreased 37/314 (12%), aspartate aminotransferase increased 33/317 (10%), calcium decreased 19/312 (6%), creatine kinase increased 20/317 (6%), triglycerides increased 18/310 (6%), creatinine increased 10/316 (3%), and alkaline phosphatase increased 5/317 (2%).

Review of the data for these 319 patients confirmed the occurrence of differentiation syndrome with an incidence of 3%. Since the experience included fatal cases, a boxed warning is warranted. Since most treatment with gilteritinib occurs in the outpatient setting, additional patient counseling instructions and a Medication Guide to inform patient are also warranted.

Since selection of intensive vs low-intensity chemotherapy may vary by patient characteristics,

healthcare providers may need to understand comparative safety for the different populations. To this end, the comparisons of adverse events for gilteritinib vs the control arm for Study 0301 would be most suitable if displayed separately by stratum of chemotherapy intensity. Additionally, since the control arm treatment was relatively short, limiting the results to the first 30 days would provide the most fair comparison.

Donna Przepiorka, MD, PhD
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Acute myeloid leukemia (AML) is a life-threatening cancer of the blood, generally characterized by aberrant differentiation and proliferation of malignantly transformed myeloid progenitor cells. When untreated or refractory to available treatments, AML results in the accumulation of these transformed cells within the bone marrow, suppression of the production of normal blood cells (resulting in severe neutropenia and/or thrombocytopenia), as well as infiltration of these cells into other organs and tissues, and can be rapidly fatal. It has been estimated that 19950 people were diagnosed with AML in the US in 2018, with a similar incidence in Europe (Siegel et al, 2016) and 5524 people diagnosed in Japan in 2016 (Kantar Health, 2017). First-line treatment for AML includes induction and consolidation chemotherapy, with treatment goals of remission followed by stem cell transplant, where possible (O'Donnell et al, 2017). Approximately 30% of adult AML patients are refractory to induction therapy, and of those who achieve complete remission (CR), approximately 75% will relapse. Five-year survival after first relapse is approximately 10%, demonstrating the lack of an effective cure for patients in relapsed AML (Rowe et al, 2010).

Certain genetic factors appear to predispose AML patients to poorer outcomes. Mutational status of FMS-like tyrosine kinase (FLT3), a member of the class III receptor tyrosine kinase, is now well recognized as delineating a subtype of leukemia with poor prognosis. There are known mutations in FLT3 that appear to be self-activating. Two of these mutations are well described in the literature: an internal tandem duplication (ITD) in the juxtamembrane domain of FLT3 which is present in 28% to 34% of AML cases and a tyrosine kinase domain (TKD) mutation at around D835 in the activation loop of FLT3, which is present in 11% to 14% of AML cases (Schlenk & Döhner, 2009). Each of these activating mutations in FLT3 is oncogenic and shows transforming activity in cells (Yamamoto et al, 2001). Patients with FLT3-ITD mutation

show poor prognosis in clinical studies, with a higher relapse rate, a shorter duration of remission from initial therapy (6 months versus 11.5 months for those without FLT3-ITD mutations), as well as reduced disease-free survival (DFS) (16% to 27% versus 41% at 5 years) and overall survival (OS) (15% to 31% versus 42% at 5 years) (Patel et al, 2012; Gale et al, 2008; Yanada et al, 2005; Tiesmeier et al, 2004; Moreno et al, 2003). Similar to their prognosis for first-line therapy, patients with relapsed or refractory (R/R) FLT3 mutation positive AML have lower remission rates with salvage chemotherapy, shorter durations of remission to second relapse and decreased OS relative to FLT3 mutation negative patients (Konig & Levis, 2015; Chevallier et al, 2011; Levis et al, 2011). There is currently a substantial unmet medical need for patients with FLT3 mutation positive R/R AML (O'Donnell et al, 2017).

The FDA's Assessment:

FDA agrees that AML with a FLT3 mutation is a serious disease with a substantial risk of mortality.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

XOSPATA® (gilteritinib) is a multikinase inhibitor approved by the FDA on 28 Nov 2018 for the treatment of adult patients who have R/R AML with a FLT3 mutation as detected by an FDA-approved test [Table 1]. Prior to this, there were no approved targeted therapies for patients with R/R FLT3-mutated AML, and the National Comprehensive Cancer Network (NCCN) guideline for AML strongly recommended clinical trial as the first option for these patients. The guideline also provided a list of commonly used chemotherapy regimens for R/R AML. The choice of specific regimen was based on factors such as prior treatment, eligibility for allogeneic hematopoietic stem cell transplant (HSCT) and institutional preference. Additionally, there were no definitive studies that demonstrated superiority of any single regimen. For this submission, in the phase 3 Study 2215-CL-0301 (ADMIRAL), a limited list of regimens, which were included in the NCCN guideline, were provided as comparator chemotherapy regimens for the investigators to choose from. Similar to the guidelines, both aggressive (mitoxantrone, etoposide and intermediate-dose cytarabine [MEC] and fludarabine, cytarabine and granulocyte colony-stimulating factor with idarubicin [FLAG-IDA]) and less-aggressive (low-dose cytarabine [LoDAC] and azacitidine) regimens were included in the study.

Table 1 Approved Treatment Options for Relapsed or Refractory Acute Myeloid Leukemia with a FLT3 Mutation

Product (s) Name	Relevant Indication	Year of Approval And Type of Approval	Dosing/ Admini-stration	Efficacy Information	Important Safety and Tolerability Issues
XOSPATA (Gilteritinib, ASP2215)	Adult patients who have R/R acute myeloid leukemia with a FLT3 mutation	2018 full approval	120 mg orally once daily/ 40-mg tablets	The determination of efficacy was established on the basis of the rate of CR/ CRh, the DOR and the rate of conversion from transfusion dependence to transfusion independence in the ADMIRAL trial. The median follow-up was 4.6 months (95% CI: 2.8, 15.8). 14 patients were still in remission at the time of the first interim DOR analysis. For patients who achieved a CR/CRh, the median time to first response was 3.6 months (range, 0.9 to 9.6 months). The CR/CRh rate was 29 of 126 in patients with FLT3-ITD or FLT3-ITD/TKD and 0 of 12 in patients with FLT3-TKD only. Among the 106 patients who were dependent on RBC and/or platelet transfusions at baseline, 33 (31.1%) became independent of RBC and platelet transfusions during any 56-day postbaseline period. For 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.	PRES; prolonged QT Interval; pancreatitis

CI: confidence interval; CR: complete remission; CRh: complete remission with partial hematologic recovery; DOR: the duration of CR/CRh; FLT3: FMS-like tyrosine kinase; ITD: internal tandem duplication; PRES: posterior reversible encephalopathy syndrome; RBC: red blood cell; R/R: relapsed or refractory; TKD: tyrosine kinase domain. Source: XOSPATA (Gilteritinib, ASP2215) Prescribing Information

The FDA's Assessment:

Gilteritinib is currently approved only for R/R AML with a FLT3 mutation. Approval was based on the finding of durable complete remission with complete or partial hematopoietic recovery (CR/CRh) and conversion to transfusion independence, which even in the short-term provides a meaningful benefit for patients with relapsed AML. This largely palliative clinical benefit negated the need to demonstrate a survival advantage.

There are numerous drugs with FDA approval for the treatment of AML (see Table below). For patients in first relapse who are fit for intensive therapy, the standard of care is treatment with a combination chemotherapy regimen followed by HSCT. About half will achieve a second CR, and the 5-year survival of patients who achieve a second remission and undergo HSCT is about 40% (Dohner et al. 2017).

FDA-Approved Treatments for Acute Myeloid Leukemia

Agent	Excerpted Indication
Cyclophosphamide	Indicated for the treatment of leukemias
Cytarabine	Indicated in combination with other approved anticancer drugs for induction in acute non-lymphocytic leukemia of adults and children
Daunorubicin	Indicated in combination with other approved anticancer drugs for remission induction in acute non-lymphocytic leukemia of adults
Daunorubicin and cytarabine liposome injection	Indicated for the treatment of adults with newly-diagnosed therapy-related AML or AML with myelodysplasia-related changes
Dexamethasone	For the palliative management of leukemias and lymphomas
Doxorubicin	Doxorubicin has been used successfully to produce regression in disseminated neoplastic conditions, including acute myeloblastic leukemia
Enasidenib	Indicated for the treatment of adults with relapsed or refractory AML with an IDH2 mutation
Gemtuzumab ozogamicin	Indicated for the treatment of newly-diagnosed CD33-positive AML in adults and indicated for the treatment of relapsed or refractory CD33-positive AML in adults and pediatric patients 2 years and older.
Gilteritinib	Indicated for the treatment of adult patients who have relapsed or refractory AML with a FLT3 mutation as detected by an FDA-approved test.
Glasdegib	Indicated in combination with low-dose cytarabine, for the treatment of newly-diagnosed AML in adult patients who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy.
Hydrocortisone	For palliative management of leukemias and lymphomas in adults, acute leukemia of childhood.
Idarubicin	Indicated in combination with other approved anti-leukemic drugs for the treatment of AML in adults
Ivosidenib	Indicated for the treatment of adults with relapsed or refractory AML with an IDH1 mutation
Methylprednisolone	For palliative management of leukemias and lymphomas in adults, acute leukemia of childhood
Midostaurin	Indicated for newly diagnosed, FLT3+ AML in combination with standard cytarabine and Daunorubicin induction and cytarabine consolidation.
Mitoxantrone	Indicated in combination with other approved drug(s) in the initial therapy of acute non-lymphocytic leukemia in adults
Prednisone	For palliative management of leukemias and lymphomas in adults, acute leukemia of childhood
Thioguanine	Indicated for remission induction and remission consolidation treatment of acute non-lymphocytic leukemias, with higher remission rates in combination with other chemotherapy agents
Venetoclax	Indicated in combination with azacitidine or decitabine or low-dose cytarabine for the treatment of newly-diagnosed AML in adults age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.
Vincristine	Indicated in acute leukemia

Source: FDA analysis

Patients with refractory or multiply-relapsed disease have worse prognosis. In large phase 3 studies in primary refractory AML or AML relapsed after 1 or more prior regimens, the rate of CR

ranged from 12 to 18%, and median OS ranged from 3.3 to 6.3 months in control arms of high-dose cytarabine or investigator's choice (e.g., hypomethylating agents, multi-agent chemo-therapy, cytarabine, hydroxyurea, or supportive care) (Faderl et al. 2012; Roboz et al. 2014). Even in first relapse, patients with FLT3-AML fare poorly. In a randomized study of patients with first relapse of FLT3-mutated AML, the control arm of MEC or high-dose cytarabine resulted in a CR rate of 12% and median OS of roughly 4 months (Levis et al, 2011). A novel treatment with a benefit on OS would be of value to patients with R/R FLT3-mutated AML.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

XOSPATA (gilteritinib) is a multikinase inhibitor approved 28 Nov 2018, under NDA 211349, for the treatment of adult patients who have R/R AML with a FLT3 mutation as detected by an FDA approved test. The approval was based on an interim analysis of response in the gilteritinib arm of the phase 3 Study 2215-CL-0301 (ADMIRAL).

The FDA's Assessment:

The Applicant's description of the regulatory action and approved indication is confirmed. It should be noted that at the time of approval, postmarketing requirements were issued to obtain data on safety of long-term administration of gilteritinib, characterization of gilteritinib-induced differentiation syndrome and a risk-benefit assessment for the subgroup of patients with a FLT3 tyrosine kinase domain (TKD) mutation.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

A summary of the key activities and Agency advice are provided in [Table 2].

Table 2 Key Regulatory Activities

Date	Meeting Type	Description
08 May 2012	N/A	Initial IND 117548 submitted for the treatment of AML
07 Jun 2012	N/A	Study May Proceed letter for IND 117548 received and first in human Study 2215-CL-0101 was initiated in the US
25 Feb 2015	Type B, End of Phase 1	Discussion of the design of 2 phase 3 studies: 2215-CL-0301 (ADMIRAL) and 2215-CL-0201

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Date	Meeting Type	Description
05 May 2015	Type C Guidance: Written Responses	Agreement on the recommended dose of ASP2215 for the proposed phase 3 studies
18 May 2015	Type C, CMC (cancelled following preliminary comments)	Agreement on the designation of starting materials for (b) (4) drug substance.
17 Feb 2017	Type C Guidance: Written Responses	The potential for accelerated approval for gilteritinib for the treatment of patients with relapsed or refractory FLT3 mutated AML was proposed to the Agency.
31 May 2017	Type C Guidance: Teleconference	Discussed the Agency's Written Response letter dated February 17, 2017; specifically the Agency's response to Question 1.b recommending that the Sponsor revise Study 2215-CL-0301 to support an accelerated approval. The 2215-CL-0301 was subsequently revised to include an interim analysis based on CR/CRh.
Table continued on next page.		
19 Dec 2017	Type B, Pre-NDA	FDA agreed that CR/CRh may be an appropriate endpoint to assess clinical benefit for a treatment of patients with AML without curative intent, but additional information about transfusion independence and corroborating results from other protocols would improve the strength of evidence.
29 Mar 2018	N/A	Original NDA 211349 submitted for the treatment of adult patients who have R/R AML with an FLT3 mutation.
18 May 2018	Application Orientation	Presented NDA 211349 XOSPATA (gilteritinib)
25 May 2018	N/A	Filing Communication Letter received. Priority review granted with a user fee goal date of November 29, 2018.
23 Jul 2018	Mid-Cycle teleconference	Update from FDA on the status of the review of the application
26 Sep 2018	Late-Cycle	Discuss late cycle review issues for the NDA submitted on March 29, 2018 for ASP2215 for the treatment of adult patients with R/R AML with FLT3 mutation.
28 Nov 2018	N/A	Approval of NDA 211349
12 Dec 2018	Type B, pre-sNDA	Agreement on content and submission plan for the supplemental NDA submission based on the final analysis from study 2215-CL-0301. FDA indicated that the sNDA would be managed under the RTOR pilot program. Meeting was scheduled for 17 Dec 2018 but was cancelled following receipt of Preliminary Comments.

AML: acute myeloid leukemia; CR: complete response; CMC: chemistry, manufacturing, and controls; CRh: complete remission with partial hematological recovery; FLT3: FMS-like tyrosine kinase; IND: investigational new drug application; ITD: internal tandem duplication; N/A: not applicable; R/R: relapsed or refractory; RTOR: Real-time Oncology Review; sNDA: supplemental new drug application.

Real-time Oncology Review (RTOR):
In the presupplemental new drug application (sNDA) meeting preliminary comments dated 12 Dec 2018, the Agency indicated that this sNDA will be managed under the RTOR pilot program.

The FDA's Assessment:

FDA confirms the regulatory history milestones described above.

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

4.1. Office of Scientific Investigations (OSI)

Since the study data came from the same trial as in the original application, no new inspections of clinical trial sites were requested for this labeling supplement.

4.2. Product Quality

There are no new product quality data for review in this labeling supplement.

4.3. Devices and Companion Diagnostic Issues

The trial population was selected based on results of the LeukoStrat® CDx FLT3 Mutation Assay. This device is approved as an aid in identifying patients with AML having a FLT3 mutation for treatment with gilteritinib (PMA P160040 S004). This supplement does not contain any new information concerning this device.

5 Nonclinical Pharmacology/Toxicology

There are no new nonclinical data for review in this supplement.

Donna Przepiorka, MD, PhD
Cross-Discipline Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

The proposed starting dose of gilteritinib in the current supplement is 120 mg (three 40-mg tablets) orally once-daily with or without food. The efficacy and safety of gilteritinib 120 mg dose in R/R FLT3+ AML patients was supported by the results of 3 clinical studies which include one phase 3 Study (2215-CL-0301) and two supportive dose-escalation studies (2215-CL-0101 and 2215-CL-0102). (b) (4)

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(b) (4)

The updated exposure-response analysis for efficacy and safety using data from study 2215-CL-0301, were generally consistent with the previous analysis.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 211349, Supplement 01. This NDA supplement is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

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 which include 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)	No revisions
Labeling	Generally acceptable. The review team has specific content change recommendations (b) (4)
Bridge between the to-be-marketed and clinical trial	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

The Applicant's Position:

No new information is provided in the current submission.

The FDA's Assessment:

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FDA has no revisions for this section in the current submission.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant's Position:

The recommended starting dose of XOSPATA is 120 mg orally once daily with or without food. A comprehensive assessment review supports the dose selection of 120 mg (b) (4) to ensure adequate efficacy in most patients [see supportive data in Section 0]. Exposure-efficacy analyses of gilteritinib concentrations and efficacy endpoints, OS or CR/CR with partial hematologic recovery (CRh), based on the final analysis data cutoff of 17 Sep 2018, are summarized herein.

Exposure-efficacy analyses of gilteritinib concentrations and efficacy endpoints, OS or CR/CRh, were not strongly correlated (Report 2215-PK-0008). However, an analysis of steady-state C_{trough} and composite complete remission (CRc) rates reflected a trend to greater clinical response in patients with FLT3-mutation positive R/R AML who had steady-state gilteritinib C_{trough} >100 ng/mL, which can be achieved at gilteritinib doses 80 mg and greater. Of the 191 patients from Study 2215-CL-0101 who were included in the exposure-efficacy dataset, 16 patients had steady-state C_{trough} (i.e., $C_{min,ss}$, <100 ng/mL and only 6% [1/16] of these patients achieved CR/CRh while 94% [15/16] were nonresponders). Comparatively, of the 175 patients who had $C_{min,ss}$ ≥ 100 ng/mL, 21% (37/175) achieved CR/CRh and 79% (138/175) were nonresponders.

The FDA's Assessment:

FDA agrees with the Applicant's proposed starting dose of 120 mg orally once daily, which is the same as previously approved in the original submission. (b) (4)

Therapeutic Individualization

The Applicant's Position:

No new information is provided in the current submission.

The FDA's Assessment:

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FDA has no revisions for this section in the current submission.

Outstanding Issues

The Applicant's Position:

No outstanding issues for the current submission.

The FDA's Assessment:

FDA agrees with the Applicant that there is no outstanding clinical pharmacology related issues in the current submission.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

Gilteritinib has demonstrated biological activity and efficacy at doses 80 mg and greater. The therapeutic 120 mg dose of gilteritinib is well supported by evidence of biological activity and efficacy. Dose reduction or increase are supported by linear, dose-proportional kinetics. Exposure-efficacy analyses did not suggest correlation between efficacy endpoints, OS or CR/CRh, and gilteritinib concentration.

The FDA's Assessment:

FDA agrees with 120 mg QD starting dose and dose reduction to 80 mg QD due to TEAEs.

(b) (4)

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

Gilteritinib effectiveness was demonstrated based on substantial and sustained inhibition of FLT3 phosphorylation. An exposure-response analysis indicated a strong correlation between gilteritinib concentration and inhibition of FLT3 phosphorylation. At doses of 80 mg and greater, FLT3 phosphorylation was inhibited by more than 90% by cycle 1 day 8. Additionally, clinical response is improved at doses that achieve steady-state trough levels of 100 ng/mL or greater.

The FDA's Assessment:

FDA generally agrees with the Applicant's position on the supportive evidence of gilteritinib effectiveness. It should be noted that the correlation between gilteritinib concentration and inhibition of FLT3 phosphorylation was observed ex-vivo at dose range of 20-450 mg.

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

The Applicant's Position:

Generally, gilteritinib is well tolerated with a safety profile that is acceptable for the treatment of patients with R/R FLT3 mutation positive AML at the proposed 120 mg therapeutic dose taken once daily.

The FDA's Assessment:

FDA agrees with the Applicant's position on the selection of 120 mg dose taken once daily.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?
The Applicant's Position:

No new information is provided in the current submission.

The FDA's Assessment:

FDA has no revisions for this section in the current submission.

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

The Applicant's Position:

No new information is provided in the current submission.

The FDA's Assessment:

FDA has no revisions for this section in the current submission.

Hisham Qosa, PhD
Primary Reviewer

Olanrewaju Okusanya, PharmD, MSc
Team Leader

Liang Li, PhD
Primary Pharmacometrics Reviewer

Lian Ma, PhD
Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

The Applicant's Position:

Study 2215-CL-0301 (ADMIRAL) is the focus of this supplemental submission to NDA 211349. This study is a phase 3, open-label, multicenter, randomized study that compared the efficacy and safety of gilteritinib therapy to salvage chemotherapy in FLT3-mutated AML patients who were refractory to or had relapsed after first-line AML therapy. For the original NDA 211349 submission, results pertaining to the first interim analysis (data cutoff date, 04 Aug 2017), which included the coprimary endpoint CR/CRh rate results, were provided for Study 2215-CL-0301. For this supplemental submission, the final analysis (data cutoff date, 17 Sep 2018), which includes the results for the coprimary endpoint of OS, is provided for this phase 3 study.

Two phase 1 studies (Studies 2215-CL-0101 and 2215-CL-0102) in R/R AML patients are also included in this submission to provide integrated data on the safety and tolerability of gilteritinib. A listing of clinical trials related to this submission is presented in [Table 3].

Table 3 Listing of Clinical Trials Relevant to this NDA

Trial Identity	National Clinical Trial No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow-up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety								
2215-CL-0301	NCT02421939	Phase 3, open-label, multicenter, randomized study	Gilteritinib: 120 mg qd po or comparative chemotherapy administered as 28-day cycles and per institutional guidelines (LoDAC, Azacitidine, MEC induction chemotherapy, or FLAG-IDA induction chemotherapy).	Primary: Clinical benefit of gilteritinib therapy in patients with FLT3 mutated AML who are R/R after first-line AML therapy as shown with OS compared to salvage chemotherapy; efficacy of gilteritinib therapy as assessed by the rate of CR/CRh in patients with FLT3 mutated AML who are refractory to or have relapsed after first-line AML therapy (this coprimary objective was only assessed in the first interim analysis) Key Secondary: Overall efficacy in EFS of gilteritinib compared to salvage chemotherapy; overall efficacy in CR rate of gilteritinib compared to salvage chemotherapy	For gilteritinib, treatment will continue until the patient meets a treatment discontinuation criterion	371 enrolled: 247 gilteritinib (246 dosed); 124 salvage chemotherapy (109 dosed)	FLT3-mutated AML patients who are R/R after first-line AML therapy	As of the final analysis data cutoff date of 17 Sep 2018, 107 sites in a total of 14 countries, including North America, Europe, Asia and rest of the world, have participated in this study.
Other Studies Pertinent to the Review of Efficacy or Safety (e.g., Clinical Pharmacological Studies)								
2215-CL-0101	NCT02014558	Phase 1/2, uncontrolled, open-label multicenter, dose escalation monotherapy study	Gilteritinib: 20, 40, 80, 120, 200, 300, 450 mg qd po	Primary: Safety, tolerability and MTD of gilteritinib; pharmacokinetics of gilteritinib Secondary: Antileukemic activity of gilteritinib, effects of CYP3A4 inhibitors on pharmacokinetics of gilteritinib, potential induction of CYP3A4 by gilteritinib	Until discontinuation criteria is met (including DLT or SAE requiring discontinuation during cycle 1 or no PR or CRc and no clinical benefit after 2 cycles)	265 enrolled (252 dosed): 25 dose-escalation (23 dosed), 240 expansion (229 dosed, 5 re-enrolled and dosed)†	Patients with R/R AML	27 sites in the US, Germany and Italy

Table continued on next page

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Trial Identity	National Clinical Trial No.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow-up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
2215-CL-0102	NCT 02181660	Phase 1, uncontrolled, open-label, multicenter, dose-escalation monotherapy study	Gilteritinib: 20, 40, 80, 120, 200, 300 mg qd po	Primary: Safety and tolerability of gilteritinib; MTD of gilteritinib Secondary: Antileukemic activity of gilteritinib; pharmacokinetics of gilteritinib	Until discontinuation criteria is met (including AE requiring discontinuation or no PR, CR, CRp or CRi after 2 cycles)	27 enrolled (24 dosed)	Japanese patients with R/R AML	5 sites in Japan

AE: adverse event; AML: acute myeloid leukemia; CR: complete remission; CRc: composite complete remission; CRh: complete remission with partial hematologic recovery; CRi: complete remission with incomplete hematologic recovery; CRp: complete remission with incomplete platelet recovery; CYP: cytochrome P450; DLT: dose-limiting toxicity; EFS: event-free survival; FLAG-IDA: fludarabine, cytarabine and granulocyte colony-stimulating factor with idarubicin; FLT3: FMS-like tyrosine kinase; LoDAC: low-dose cytarabine; MEC: mitoxantrone, etoposide and intermediate-dose cytarabine; MTD: maximum tolerated dose; NDA: new drug application; OS: overall survival; PR: partial remission; R/R: relapsed or refractory; SAE: serious adverse event.
†Includes 5 patients who were re-enrolled into the study.

7.2. Review Strategy

The FDA's Assessment:

FDA agrees with the summary of Studies 2215-CL-0301, 2215-CL-0101, and 2215-CL-0102 presented in Table 3 above. It is notable that Study 2215-CL-0301 allowed for dose escalation of gilteritinib to 200 mg qday in selected patients beyond cycle 1.

The FDA review was based on data from NDA-211349 S-001, relevant published literature, and relevant information in the public domain.

The final analysis of Study 2215-CL-0301 was used for the primary analysis of efficacy and safety. The final analysis was triggered by reaching the prespecified criterion of 258 death events for the evaluation of OS. The actual number of death events that were included was 261. Correspondingly, the efficacy boundary for OS of the final analysis was also adjusted as <0.0238. The Applicant submitted a complete dataset for this study, using a data cut date of September 17, 2018, on November 19, 2018, ahead of the sNDA submission as part of the RTOR pilot. Data from the single-arm studies 2215-CL-0101 and 2215-CL-0102 were considered as supportive.

The primary efficacy endpoint review was conducted by Dr. Qing Xu. Items reviewed included the primary dataset submitted by applicant, Clinical Study Report of Study 2215-CL-0301, review of FDA databases regarding the regulatory history for the gilteritinib IND/NDA, and a literature review regarding the role of gilteritinib therapy in patients with FLT3 mutated AML who are R/R after first-line AML therapy.

Summaries of the data and statistical analyses by the reviewer were performed using JMP 12.0, SAS Version 9.4 (both SAS Institute, Inc., Cary, NC) and Excel 2010 (Microsoft, Redmond, WA). MedDRA Adverse Events Diagnostic 1.9.1 (MAED) (FDA, Silver Spring, MD) was used to look for safety signals. Where possible, confidence intervals are provided to assist in the interpretation of the efficacy data. For additional statistical methodologies, see Section 8.1.1.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. 2215-CL-0301 (ADMIRAL)

The Applicant's Position [Clinical study report 2215-CL-0301 v2.0]:

TRIAL DESIGN

Study 2215-CL-0301 is a phase 3, open-label, multicenter, randomized study to compare the efficacy and safety of gilteritinib therapy to salvage chemotherapy in FLT3-mutated AML patients who are refractory to or have relapsed after first-line AML therapy.
The primary study objectives were 1) determine the clinical benefit of gilteritinib therapy in patients with FLT3-mutated AML who were refractory to or have relapsed after first-line AML therapy as shown with OS compared to salvage chemotherapy and 2) to determine the efficacy of gilteritinib therapy as assessed by the rate of CR/CRh in patients with FLT3-mutated AML who were refractory to or have relapsed after first-line AML therapy.

The key secondary study objectives were 1) determine the overall efficacy in event-free survival (EFS) of gilteritinib compared to salvage chemotherapy and 2) to determine the overall efficacy in CR rate of gilteritinib compared to salvage chemotherapy.

Three hundred sixty-nine patients were to be randomized in a 2:1 ratio to receive gilteritinib or salvage chemotherapy. Patients were to be recruited from approximately 140 centers in North America, Europe, Asia and rest of the world. Patients were to enter the screening period up to 14 days prior to the start of treatment. Prior to randomization, the investigator was to preselect

a salvage chemotherapy regimen for each patient; options were to include LoDAC, azacitidine, MEC or FLAG-IDA. The randomization was to be stratified by response to first-line therapy and preselected salvage chemotherapy. Patients were to be administered treatment over continuous 28-day cycles and per institutional guidelines for chemotherapy product preparation and administration.

Study Endpoints

- Primary Efficacy Endpoints: OS (second interim and final only) and CR/CRh rate (first interim only)
- Key Secondary Efficacy Endpoints: EFS and CR rate
- Other Secondary Efficacy Endpoints: Leukemia-free survival (LFS), CRh rate, CRc rate, duration of remission, transfusion conversion rate and transfusion maintenance rate, transplantation rate and Brief Fatigue Inventory (BFI)
    - Response definition: CR, complete remission with incomplete platelet recovery (CRp), complete remission with incomplete hematological recovery (CRi), CRc, CRh, partial remission (PR), not evaluable/no response (NR), relapse and best response
- Exploratory Endpoints: pharmacogenomics, FLT3 gene mutation status, exploratory (predictive) biomarkers of gilteritinib activity; resource utilization, including hospitalization, blood transfusion, antibiotic intravenous infusions, medication for AEs and opioid usage; Functional Assessment of Chronic Illness Therapy-Dyspnea-Short Form (FACIT-Dys-SF), Functional Assessment of Cancer Therapy-Leukemia (FACT-Leu), EuroQol Group-5 Dimension-5 Level, dizziness and mouth sore items

Statistical Analysis Plan and Amendments

The statistical analysis plan (SAP) and interim analysis plan (IAP) were finalized and signed prior to the database hard lock and interim database snapshot to minimize bias. Based on the coprimary endpoint of OS, a group sequential design was implemented using the O'Brien-Fleming boundaries (nonbinding) as implemented by Lan-DeMets alpha/beta spending method (East®).

The overall 0.025 one-sided type I error rate was allocated by 0.0005 and 0.0245 (corresponding to 0.001 and 0.049 for 2-sided type I error rates) for the 2 coprimary efficacy endpoints of CR/CRh and OS, respectively. The type I error (alpha) in interim analysis 1 was a nominal alpha that was arbitrarily selected for acknowledgement of the CR/CRh rate evaluation at interim analysis 1 and was not recycled in interim analysis 2 and the final analysis.
Two interim analyses and 1 final analysis were planned. At the first interim analysis, only the coprimary endpoint of CR/CRh rate was evaluated for patients in the gilteritinib arm. The descriptive statistics, including 2-sided 95% exact CI of CR/CRh rate, were provided to an

Independent Data Monitoring Committee (IDMC). A nominal 1-sided P-value of 0.0005 (i.e., 2-sided P-value of 0.001), which was arbitrarily selected, was utilized to acknowledge the single-arm CR/CRh rate evaluation at the first interim analysis. The lower limit was used to compare with the benchmark of CR/CRh rate of 12%. The first interim analysis was performed with a data cutoff date of 04 Aug 2017 (database lock, 06 Oct 2017); 255 patients were randomized with 142 patients randomized into the gilteritinib arm and at least 112 days (4 treatment cycles) past the first dose of gilteritinib or randomization (for patients who did not receive gilteritinib). The predetermined criterion that the lower limit of 95% exact CI of CR/CRh rate was higher than 12% was met. The first interim analysis results were reported in the original NDA 211349.

The second interim analysis was performed when approximately 50% of the planned total number of deaths (death events =129 of planned 258 death events) by any cause have occurred. The second interim analysis was utilized to determine whether the study should be terminated earlier than planned if gilteritinib had more favorable or harmful outcome than the salvage chemotherapy arm. The second interim analysis was performed with a data cutoff date of 18 Sep 2017 (database snapshot, 30 Oct 2017); the actual number of death events that were included was 139. Correspondingly, the boundaries for OS for interim analysis 2 and the final analysis were adjusted. For interim analysis 2, the P-value boundary was < 0.00218 for efficacy and > 0.31416 for futility. Based on interim analysis 2, the IDMC recommended that the study continue with no changes.

The final analysis was triggered by reaching the prespecified criterion of 258 death events (data cutoff date of 17 Sep 2018) for the evaluation of OS. The actual number of death events that were included was 261. Correspondingly, the efficacy boundary for OS of the final analysis was also adjusted as < 0.0238.

EFS was planned to be tested at interim analysis 2 and the final analysis only when the OS null hypothesis was rejected. During interim analysis 2 and the final analysis, only death, relapse and treatment failure occurring on or prior to the cutoff date were counted as EFS events. Patients without these events before the cutoff date were censored at the last relapse-free disease assessment date postbaseline on or before the cutoff date. CR rate was planned to be tested at interim analysis 2 and the final analysis and only when both the OS and EFS null hypotheses were rejected.

Definition of Key Analysis Sets

- The Intention to Treatment Set (ITT) consisted of all patients who were randomized. The ITT was used for the primary analyses of efficacy data, as well as selected demographic and baseline characteristics, PRO measures and resource utilization in the final analysis.

- The Multigene Analysis Set (MAS) consisted of all randomized patients with FLT3 mutation by either local testing or testing by the companion diagnostic and has nonmissing multigene assessment at screening. The MAS included the derived mutation status for each gene with at least 10% mutation positive status of all MAS patients. The MAS was used to assess the relationship of efficacy of gilteritinib and mutational status of a panel of AML related genes (multigene panel) in patients with R/R AML with FLT3 mutation.
- The Safety Analysis Set (SAF) consisted of all patients who received at least 1 dose of study treatment. The patients were analyzed based on the actual treatment received. The SAF was used for summaries of demographic and baseline characteristics and all safety variables.
- Other analyses sets were analyzed including: Response Analysis Set (RAS), modified RAS, Full Analysis Set (FAS), Per Protocol Set (PPS), and Pharmacokinetic Analysis Set (PKAS).

Adhoc Analyses: The following analyses were performed ad hoc (not prespecified in the SAP): (1) sensitivity analysis of OS on ITT patients who received at least 1 dose of study drug, (2) sensitivity analysis of EFS using the long-term follow-up data of death and new AML therapies.

Protocol Amendments

The original study protocol was dated 24 Mar 2015. No patients were enrolled under the original version of the protocol. As of the final analysis data cutoff date of 17 Sep 2018, there were 8 substantial amendments and 3 nonsubstantial amendments to the protocol. No protocol amendments were implemented following the original NDA approval.

The FDA's Assessment:

The applicant described the protocol and SAP for Study 2215-CL-0301, focusing on the key design elements relevant to this sNDA application. The SAP specified the co-primary efficacy endpoint at the time of the second interim and final analyses to be OS. CR/CRh rate was the co-primary efficacy endpoint at the first interim analysis only and served as the basis of the initial approval of gilteritinib. The final analysis of the co-primary OS endpoint was analyzed and reported when approximately 258 OS events were observed, which is acceptable to FDA. Furthermore, FDA agrees that the secondary endpoints of CR rate, duration of CR, CRh rate, duration of CRh, duration of CR/CRh, transfusion conversion, and transfusion maintenance rate are relevant supportive efficacy endpoints. FDA does not agree that the secondary endpoints of EFS, LFS, or CRc are relevant supportive endpoints due to inclusion of responses less than CRh. FDA wishes to clarify the stratification factors, as follows.
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 CRc and no HSCT
- Relapse after 6 months after CRc and no HSCT

Preselected chemotherapy:

- High intensity chemotherapy (FLAG-IDA or MEC)
- Low intensity chemotherapy (LDAC or azacitidine)

Shorter duration of first CR and prior HSCT correlate with worse OS in patients with AML in first relapse (Breems et al, 2005). Relapse within 6 months is associated with the highest risk. Therefore, FDA agrees with the first stratification factor, which takes the first remission duration and prior HSCT into account.

Of note, the PPS excluded patients for the following reasons:

- Entered into the study even though the subject violated the inclusion or exclusion criteria which may affect the assessment of the efficacy of the study drug
- Received wrong treatment or incorrect dose
- Administration of excluded concomitant treatment prohibited by protocol or antileukemia treatment prohibited by protocol
- No evaluable post-baseline assessment
- Randomized but received no drug
- Developed withdrawal criteria during the study and was not withdrawn
- Neither central FLT3 mutation nor local FLT3 mutation with rapidly progressing disease at baseline
- No active relapse at baseline

The FAS consisted of all randomized subjects with FLT3 mutation based on central test.
The RAS consisted of subjects who are at least 112 days post first dose or randomization (for subjects who didn't take any dose). The RAS was to be used only at the interim analyses and for primary analyses of response related efficacy data.

The statistical analysis plan (SAP) and interim analysis plan (IAP) were finalized and signed prior to the database hard lock and interim database snapshot to minimize bias. During the study design overview, the sponsor clarified that the chemotherapy was pre-chosen before randomization to avoid bias, and there was no cross-over for the chemotherapy as it could confound the analysis of OS. There were 140 sites distributed globally. The DMC raised a question of how to deal with the heterogeneity of the various standard care in the control group in different geographic similar balance by region in the treatment arms. The DMC also was concerned about patients being randomized into control group who quickly choose to leave the trial. The sponsor clarified the protocol defined long term follow up after the subjects come off study treatment, but stay in the study, and still were included in the ITT population.

The sponsor mentioned that patient can undergo hematopoietic stem cell transplant (HSCT) on the ASP2215 arm without leaving the study, but ASP2215 dose was stopped. Patient who were in the chemotherapy arm would be discontinued from the study treatment.

STUDY RESULTS

Data Quality and Integrity

(as of the final analysis data cutoff date of 17 Sep 2018)
The sponsor implemented and maintained quality assurance and quality control systems with written standard operating procedures to ensure that trials were conducted and data were generated, documented, recorded and reported in compliance with the protocol, GCP and applicable regulatory requirement(s). Furthermore, Astellas Northbrook and 3 clinical trial sites were inspected by the FDA during the original review of NDA 211349.

The FDA's Assessment:

No issues were identified with the data quality or integrity from the pivotal study which could affect the efficacy results. The submitted data sets are generally consistent and variables are clearly labeled and/or explained.

Upon further clarification from the applicants per FDA's information requests (IRs), the reviewers were able to:

- Reproduce the applicant's analysis and analysis results for the primary and secondary efficacy endpoints

- Conduct FDA's sensitivity analyses for the primary efficacy endpoint and subgroup analysis for the primary and secondary efficacy endpoints.

Compliance with Good Clinical Practices

The Applicant's Position:

Study 2215-CL-0301 was conducted under a U.S. Investigational New Drug application, in accordance with International Council for Harmonisation (ICH) guidelines for Good Clinical Practice (GCP), the principles expressed in the Declaration of Helsinki, and consistent with the Code of Federal Regulations (CFR), Title 21. The study protocols and informed consent documents were reviewed by a local Institutional Review Board/Independent Ethics Committee as required by regulations prior to implementation at practicing institutions.

The FDA's Assessment:

FDA confirms the Applicant's position.

Financial Disclosure

The Applicant's Position:

Appropriate financial disclosure was collected during the course of Study 2215-CL-0301, and no financial arrangements with the Investigator impacted the validity of the study. Additional information regarding financial disclosures can be found in Section 12.2.

The FDA's Assessment:

FDA confirms the Applicant's position.

Patient Disposition

The Applicant's Position:

A total of 625 patients had consented for the study. A total of 371 patients were randomized to treatment; of these, 247 were randomized to the gilteritinib 120 mg group and included in the ITT, and 124 were randomized to salvage chemotherapy and included in the ITT. Of the patients receiving salvage chemotherapy, 16 patients received LoDAC, 25 patients received azacitidine, 28 patients received a MEC regimen (that included the components of mitoxantrone, etoposide and cytarabine) and 40 patients received a FLAG-IDA regimen (that included the components of granulocyte-colony stimulating factor, fludarabine, cytarabine and idarubicin). A total of 254 patients (40.6%) were considered screen failures.

In the gilteritinib arm, of the 247 patients in the ITT, 217 were included in the PPS and 243 had a FLT3 mutation based on central testing by LeukoStrat CDx FLT3 Mutation Assay (FLT3 CDx) and were included in the FAS. The SAF consisted of all patients who received at least 1 dose of gilteritinib. Of the 246 patients in the SAF, 236 patients had at least 1 plasma concentration data point available with the time of sampling and time of dosing on the day of sampling available and were included in the PKAS.

In the salvage chemotherapy arm, of the 124 patients in the ITT, 70 were included in the PPS and 123 had a FLT3 mutation based on central testing by FLT3 CDx and were included in the FAS. The SAF consisted of all patients who received at least 1 dose of salvage chemotherapy and excluded 15 patients.

In the gilteritinib arm, 84.6% (209/247) patients in the ITT discontinued treatment as of the final analysis data cutoff date. The most frequent primary end of treatment reasons were progressive disease (28.3% [70/247]), death (14.6% [36/247]), disease relapse (13.4% [33/247]) and AE (11.3% [28/247]).

In the salvage chemotherapy arm, all patients in the ITT discontinued treatment as of the final analysis data cutoff date. The most frequent primary end-of-treatment reasons were lack of efficacy (25.0% [31/124]), withdrawal by patient (19.4% [24/124]), study completion (defined as patients on high-dose chemotherapy who either completed 1 cycle of treatment with a CRc and were taken off treatment), or completed 2 cycles of treatment, (15.3% [19/124)] and progressive disease (12.9% [16/124]).

Between treatment groups, fewer patients withdrew from treatment in the gilteritinib arm compared with the salvage chemotherapy arm (2.0% [5/247] versus 19.4% [24/124]).
As of the final analysis data cutoff date of 17 Sep 2018, 38 patients remained on gilteritinib treatment.

The FDA's Assessment:

For the purposes of determining reasons for treatment discontinuation, FDA considers death under the primary reason for discontinuation (i.e., either primary disease or adverse event). Thus, the reason "adverse event" included 8 deaths due to an adverse reaction on the gilteritinib arm and 4 deaths due to an adverse reaction on the chemotherapy arm, in addition to the disposition events coded as adverse event. The reason "primary disease" included 21 deaths due to primary disease on the gilteritinib arm and 6 deaths due to primary disease on the chemotherapy arm, in addition to the disposition events coded as progressive disease, disease relapse, or lack of efficacy.

Table 4 Reasons for Treatment Discontinuation in ITT Population

	Gilteritinib (N=247) n (%)	Chemotherapy (N=124) n (%)
Therapy ongoing	38 (15%)	0
Discontinued therapy		
Primary disease	145 (59%)	55 (44%)
Adverse event	36 (15%)	9 (7%)
Other	12 (5%)	25 (20%)
Physician decision	11 (4%)	11 (9%)
Withdrawal by subject	5 (2%)	24 (19%)

Source: FDA analysis

It is notable to point out that only 1 patient on the gilteritinib arm was randomized but not

treated, compared to 15 patients on the chemotherapy arm. It will be important to assess efficacy in the treated population (SAF) to ensure consistency of results (See reviewer's OS sensitivity analysis section)

Protocol Violations/Deviations

The Applicant's Position:

There were no meaningful differences in protocol deviations between the treatment arms. In the gilteritinib arm, 11.7 % (29/247) of patients in the ITT had a protocol deviation: 21 patients entered into the study even though they did not satisfy entry criteria, 6 patients received excluded concomitant treatment and 2 patients developed withdrawal criteria during the study and were not withdrawn.

In the salvage chemotherapy arm, 11.3 % (14/124) of patients in the ITT had a protocol deviation: 11 patients entered into the study even though they did not satisfy entry criteria and 3 patients received excluded concomitant treatment.

One patient in each treatment arm discontinued treatment due to a protocol deviation.

The FDA's Assessment:

Note that all protocol deviations mentioned by the applicant are major protocol violations.

Major violations regarding eligibility criteria on the gilteritinib arm included not FLT3 positive by central lab (n=10), QTcF > 450 ms at screening (n=7), hypokalemia and hypomagnesemia below the lower limit of normal at screening (n=6), AST or ALT not within the required range (n=2), second relapse (n=2), diagnosed with another malignancy (n=2), required treatment with strong inducer of CYP3A (n=1), has a condition which in the investigator's opinion makes the subject unsuitable for study participation (n=1), received prior gilteritinib or other FLT3 inhibition with the exception of sorafenib (n=1), eligible for preselected salvage chemotherapy (n=1), and major surgery within 4 weeks (n=1). On the chemotherapy arm, violations regarding eligibility included QTcF > 450 ms at screening (n=4), FLT3 positive by central lab (n=3), hypokalemia and hypomagnesemia (n=3), AST or ALT not within the required range (n=1), diagnosed with another malignancy (n=1), and relapsed or refractory to first-line AML therapy (n=1).

As none of the deviations were likely to bias the study in favor of the gilteritinib arm, all patients, including those with major protocol deviations were included in the FDA's analysis of efficacy endpoints.

Table of Demographic Characteristics

The Applicant's Position:

The demographic and baseline characteristics were similar between treatment arms [Table 5]. Overall, for the ITT, the median age was 62.0 years, with 41.8% (155/371) of patients aged ≥ 65 years, the population was 54.2% (201/371) female, 61.5% (220/371) of patients were White, and 28.5% (102/371) of patients were Asian and 5.9% (21/371) of patients were Black or African American. A total of 83.8% (311/371) of patients had a baseline Eastern Cooperative Oncology Group (ECOG) status of 0 to 1 and the median weight and height were 70.0 kg and 166.5 cm, respectively.

Overall, a majority of patients (73.0% [271/371]) was characterized with intermediate cytogenetic risk, 10.0% (37/371) of patients were characterized with unfavorable risk and only 1.3% (5/371) of patients were characterized with favorable cytogenetic risk.

Overall, 88.4% (328/371) of patients had only a FLT3-ITD mutation, 8.4% (31/371) of patients had only a FLT3-TKD mutation and 1.9% (7/371) of patients had both a FLT3-ITD and a FLT3-TKD mutation per central testing by FLT3 CDx. At screening, 1.3% (5/371) of patients were negative for a FLT3 mutation by central testing.

Table 5 Demographic and Baseline Characteristics – Intention to Treatment Set

Parameter Category/Statistic	Gilteritinib 120 mg (N = 247)	Chemotherapy (N = 124)	Total (N = 371)
Sex, n (%)			
Female	131 (53.0)	70 (56.5)	201 (54.2)
Male	116 (47.0)	54 (43.5)	170 (45.8)
Ethnicity, n (%)			
Not Hispanic or Latino	221 (93.6)	116 (96.7)	337 (94.7)
Hispanic or Latino	12 (5.1)	2 (1.7)	14 (3.9)
Unknown	3 (1.3)	2 (1.7)	5 (1.4)
Missing	11	4	15
Race, n (%)			
White	145 (60.9)	75 (62.5)	220 (61.5)
Asian	69 (29.0)	33 (27.5)	102 (28.5)
Black or African American	14 (5.9)	7 (5.8)	21 (5.9)
Native Hawaiian or Other Pacific Islander	1 (0.4)	0	1 (0.3)
Unknown	4 (1.7)	4 (3.3)	8 (2.2)
Other	5 (2.1)	1 (0.8)	6 (1.7)
Missing	9	4	13
Age (Years)			
Mean (SD)	59.0 (14.6)	57.6 (14.8)	58.5 (14.7)
Median (min, max)	62.0 (20, 84)	61.5 (19, 85)	62.0 (19, 85)
Age Group (Years), n (%)			
< 65	141 (57.1)	75 (60.5)	216 (58.2)
≥ 65	106 (42.9)	49 (39.5)	155 (41.8)

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Parameter Category/Statistic	Gilteritinib 120 mg (N = 247)	Chemotherapy (N = 124)	Total (N = 371)
Region, n (%)			
North America	114 (46.2)	52 (41.9)	166 (44.7)
Europe (including Turkey and Israel)	68 (27.5)	43 (34.7)	111 (29.9)
Asia	65 (26.3)	29 (23.4)	94 (25.3)
Baseline ECOG, n (%)			
0-1	206 (83.4)	105 (84.7)	311 (83.8)
≥ 2	41 (16.6)	19 (15.3)	60 (16.2)
Table continued on next page			
Weight (kg)			
N	243	124	367
Mean (SD)	72.79 (20.47)	69.91 (19.73)	71.82 (20.25)
Median (min, max)	71.00 (39.0, 157.1)	67.00 (36.5, 157.9)	70.00 (36.5, 157.9)
Height (cm)			
N	234	123	357
Mean	167.25 (10.31)	166.39 (10.63)	166.95 (10.41)
Median (min, max)	167.00 (140.0, 193.0)	166.00 (137.5, 191.0)	166.50 (137.5, 193.0)
FLT3 Mutation Status by Central Testing by FLT3 CDx, n (%)			
FLT3-ITD alone	215 (87.0)	113 (91.1)	328 (88.4)
FLT3-TKD alone	21 (8.5)	10 (8.1)	31 (8.4)
FLT3-ITD and FLT3-TKD	7 (2.8)	0	7 (1.9)
Others (unknown/missing/negative)	4 (1.6)	1 (0.8)	5 (1.3)
Prior Use of FLT3 Inhibitor, n (%)†			
No	215 (87.0)	110 (88.7)	325 (87.6)
Yes	32 (13.0)	14 (11.3)	46 (12.4)
Cytogenetic Risk Status, n (%)			
Intermediate	182 (73.7)	89 (71.8)	271 (73.0)
Unfavorable	26 (10.5)	11 (8.9)	37 (10.0)
Favorable	4 (1.6)	1 (0.8)	5 (1.3)
Other‡	35 (14.2)	23 (18.5)	58 (15.6)

All patients who were randomized (Intention to Treatment Set).
AML: acute myeloid leukemia; ECOG: Eastern Cooperative Oncology Group; FLT3: FMS-like tyrosine kinase 3; FLT3 CDx: LeukoStrat CDx FLT3 Mutation Assay; ITD: internal tandem duplication; max: maximum; min: minimum; TKD: tyrosine kinase domain.
†Prior use of FLT3 inhibitor was defined as "Yes" if patients received prior AML therapy of Midostaurin, Sorafenib or Quizartinib; otherwise, prior use of FLT3 inhibitor was assigned as "No." ‡The category of "Other" includes those with cytogenetic risk status that cannot be categorized as favorable, intermediate or unfavorable.
Source: Study 2215-CL-0301, ADSL Table 12.1.2.1.1

The FDA's Assessment:

The percentages in Table 4 above do not include missing values in the denominator (e.g. ethnicity and race). Therefore, the applicant's statement that 61.5% of the population were White, 28.5% were Asian, and 5.9% were Black or African American is incorrect. The correct percentages are 59.3% (220/371) White, 27.5% (102/371) Asian, and 5.7% (21/371) Black or African American.

Of the 5 patients who were CDx-negative, 4 were on gilteritinib arm and 1 was on the chemo-therapy arm. Only 1 patient on the gilteritinib arm was negative for FLT3 on local testing.

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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

The Applicant's Position:

Overall, for the ITT, 60.9% (226/371) of patients had untreated relapse AML, 39.1% (145/371) of patients had primary refractory AML and no patients had refractory relapse AML. Th median number of relapses was 1 (range, 0 to 2). A total of 39.1% (145/371) of patients had no relapses, 59.0% (219/371) of patients had 1 relapse and 1.9% (7/371) of patients had 2 or more relapses.

There were no meaningful differences in prior AML chemotherapies between treatment arms. All patients in the ITT (in both treatment groups) previously received induction chemotherapy for AML, which included known and investigational anticancer agents. Overall, the most common predefined chemotherapy combinations were standard dose cytarabine + idarubicin (39.4% [146/371]) and standard dose cytarabine + daunorubicin (26.1% [97/371]) and the most common predefined chemotherapy monotherapy was high-dose cytarabine (27.0% [100/371]). For patients who did have prior use of FLT3 inhibitor, the most commonly used FLT3 inhibitor was Sorafenib (6.5% [24/371]) followed by Midostaurin (5.7% [21/371]). Based on the best response to any prior therapy for AML (if a patient had multiple prior AML therapies, the patient was summarized under the best response), CR was seen in 53.6% (199/371) of patients, CRi in 5.9% (22/371) of patients, CRp in 1.1% (4/371) of patients and 39.4% (146/371) of patients experienced prior treatment failure. For patients who had a response of CR, CRp and CRi, the median duration of response was 182 days, with a range of 10 to 1826 days.
There were no meaningful differences in prior transplant characteristics between treatment arms. In the gilteritinib arm, 19.4% (48/247) of patients had received at least 1 prior HSCT and the majority had received an allogeneic HSCT (95.8% [46/48]). Of the patients who had received prior HSCT, 68.8% (33/48) of patients experienced relapse and 29.2% (14/48) of patients experienced continued CR. In the salvage chemotherapy arm, 21.0% (26/124) of patients had received at least 1 prior HSCT and all 26 patients had received an allogeneic HSCT. Of the patients who had received prior HSCT, 73.1% (19/26) of patients experienced relapse and 26.9% (7/26) of patients experienced continued CR.

The FDA's Assessment:

In response to an information request, the applicant clarified that the 7/371 (1.9%) patients with 2 or more relapses was an overestimation as it was derived based on an algorithm using the information from the prior AML chemotherapy and prior HSCT CRF pages. Of the seven patients noted to have 2 or more relapses, two patients on the gilteritinib am had 2 relapses (untreated relapse) which were noted as protocol deviations, one patient on the chemotherapy arm had 2 relapses (refractory relapse) but was taken off study prior to initiating treatment for ineligibility due to other criteria, three patients (2 on gilteritinib arm and 1 on chemotherapy

arm) were incorrectly identified as 2 relapses by the algorithm (received 2 induction cycles) and should have been noted as 1 relapse, and one patient on the chemotherapy arm had conflicting information in a CRF page resulting in the algorithm identifying 2 relapses (received 2 induction regimens to achieve response, relapsed and received HSCT 63 days prior to enrollment).

FDA notes that the median duration of first response to first-line chemotherapy in patients who achieved a prior CRc was 182 days or roughly 6 months (range 0.3-60 months). Duration of first CR correlates with OS in patients with AML in first relapse (Breems et al, 2005), and a relapse within 6 months is associated with the highest risk.

Note that FDA clarified with the applicant the meaning of the statement "Of the patients who had received prior HSCT, 68.8% (33/48) of patients experienced relapse and 29.2% (14/48) of patients experienced continued CR." In the CRF, some sites entered the patient's status immediately after HSCT (i.e. patients were in CR prior to and after HSCT). Thus, "continued CR" represents the patients' status directly after HSCT. All patients who previously underwent HSCT were relapsed when they enrolled on the current trial.

FDA wishes to summarize additional baseline characteristics in the Table below.

Table 6 Additional baseline characteristics on Study 2215-CL-0301

Variable		Gilteritinib (N=247)	Chemotherapy (N=124)
ECOG PS	Median (range)	1 (0-3)	1 (0-3)
Pre-selected chemotherapy	High dose Low dose	149 (60%) 98 (40%)	75 (60%) 49 (40%)
Relapse Type	Untreated relapse AML, n (%) Primary refractory AML, n (%) Refractory relapse AML, n (%)	151 (61%) 96 (39%) 0	74 (60%) 49 (40%) 1 (0.8%)
Prior Relapses	Median (range)	1 (0, 2)	1 (0, 2)
Secondary AML	Yes	39 (16%)	11 (9%)
Response to first-line therapy	Primary refractory without HSCT Relapse > 6 months after HSCT Relapse > 6 months and no HSCT Relapse ≤ 6 months after HSCT Relapse ≤ 6 months and no HSCT	96 (39%) 17 (7%) 37 (15%) 30 (12%) 67 (27%)	49 (40%) 8 (6%) 18 (15%) 17 (14%) 32 (26%)
Prior FLT3i	Yes	32 (13%)	14 (11%)

FDA analysis

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Of the 75 patients preselected for high-intensity therapy on the control arm, 42 (56%) were preselected to receive FLAG-IDA and 33 (44%) were preselected to receive MEC. Of the 49 patients preselected for low-intensity therapy on the control arm, 32 (65%) were preselected to receive azacitidine and 17 (35%) were preselected to receive LDAC.

Of note, 39 (16%) of patients on the gilteritinib arm had secondary AML following MDS (n=34), CMML (n=4), or other myeloproliferative disorder (n=1). A total of 11 (9%) of patients on the chemotherapy arm had secondary AML following MDS (n=9) or CMML (n=2).

Of the 32 patients on the gilteritinib arm who received a prior FLT3 inhibitor, 13 (41%) received midostaurin, 18 received sorafenib (56%), and 1 (3%) received quizartinib. Of the 14 patients on the chemotherapy arm who received a prior FLT3 inhibitor, 8 (57%) received midostaurin, 6 (43%) received sorafenib, and none received quizartinib.

Treatment Compliance, Concomitant Medications and Rescue Medication Use

The Applicant's Position:

Treatment Compliance

The dose and schedule of gilteritinib or salvage chemotherapy administered to each patient were recorded on the appropriate form at every cycle. Reasons for dose increase, reduction or omission were also recorded. This information, plus dispensing and return for gilteritinib at every cycle was listed for all patients in the SAF. Treatment compliance was not summarized for this analysis.

Study Exposure

As expected in this study, because the majority of salvage chemotherapy patients finished the study by cycle 2 of treatment, the duration of exposure (median [min, max]) was longer in the gilteritinib arm compared with the salvage chemotherapy arm (126.00 [4.0, 885.0] days versus 28.0 [5.0, 217.0] days). Longer exposure durations were experienced by more patients in the gilteritinib arm compared with the salvage chemotherapy arm in the range of ≥ 84 to < 168 days (27.6% versus 5.5%) and ≥ 168 days (37.4% versus 3.7%) and, consistent with this difference in exposure duration, the number of treatment cycles (median [min, max]) was higher in the gilteritinib arm compared with the salvage chemotherapy arm (5.00 [1.0, 33.0] cycles versus 1.00 [1.0, 7.0] cycles).

In Study 2215-CL-0301, all patients randomized to the gilteritinib arm began at a starting dose of 120 mg but had the option of receiving an escalated dose of 200 mg based on lack of efficacy, as assessed by the investigator. However, the majority of patients in the gilteritinib arm (168/246) did not experience a dose escalation and generally had similar exposure to study drug as the overall 2215-CL-0301 gilteritinib arm. For patients in the study who were administered an escalated dose of gilteritinib 200 mg based on lack of efficacy at the starting

dose of gilteritinib 120 mg, the median number of dosing days for patients before dose escalation was 42.0 days, ranging from 26 to 531 days. The median number of dosing days for patients after dose escalation was 48.0 days, ranging from 1 to 756 days.

Concomitant Therapies
Between treatment arms, there were no meaningful differences in use of concomitant and nonmedication therapies, as well as for previous and concomitant transfusions.

The FDA's Assessment:

The reviewer's exposure analysis results agree with the results presented in this section by applicant. The distributions of treatment duration were imbalanced between gilteritinib arm and salvage chemotherapy arm.

Of note, the protocol specified dose escalation from 120 mg to 200 mg gilteritinib if patients had no CRc (CR, CRp or CRi) after cycle 1. Although the median number of dosing days before dose escalation was 42 days, some patients dose escalated much later in the course of therapy.

The concomitant medication file included a poststudy leukemia therapy for 86 (35%) patients on gilteritinib and 54 (44%) patients on the chemotherapy arm. FDA coded the poststudy therapies as being HSCT, intensive cytotoxic chemotherapy, other FLT3 inhibitor, or other. Table 7 shows the numbers of patients who received treatments that might affect their survival outcome.

HSCT was used in a higher proportion of patients in the gilteritinib arm (26% vs 15%). For patients who achieved CR, HSCT was used less frequently in the gilteritinib arm (23% vs 46%), and for those who did not achieve CR, HSCT was used more frequently in the gilteritinib arm (26% vs 12%). Additionally, the use of poststudy intensive chemotherapy was similar between arms (26% vs 23%), but fewer patients in the gilteritinib arm with treated with an alternative FLT3 inhibitor (12% vs 23%).

Table 7 Study 0301 - Poststudy Therapies

	High Intensity Stratum				Low Intensity Stratum				All Patients			
Therapy Type	Gilteritinib n=149		Chemotherapy n=75		Gilteritinib n=98		Chemotherapy n=49		Gilteritinib n=247		Chemotherapy n=124	
HSCT	54	36%	17	23%	9	9%	2	4%	63	26%	19	15%
in CR	7/23	30%	5/12	42%	1/12	8%	1/1	100%	8/35	23%	6/13	46%
not in CR	47/126	37%	12/63	19%	8/86	9%	1/48	2%	55/212	26%	13/111	12%
Intensive Chemotherapy	54	36%	16	21%	11	11%	13	27%	65	26%	29	23%
Other FLT3 Inhibitor	20	13%	22	29%	9	9%	6	12%	29	12%	28	23%

Source: FDA Analysis

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Efficacy Results – Primary Endpoint for Final Analysis (Including Sensitivity Analyses)

Overall Survival (ITT)

The Applicant's Position:

OS was significantly longer in the gilteritinib arm (median, 9.3 months) compared with the salvage chemotherapy arm (median, 5.6 months) using a Kaplan-Meier estimate (hazard ratio [HR]: 0.637; 95% CI: 0.490, 0.830; 1-sided P-value 0.0004). The survival probability was higher in the gilteritinib arm compared with the salvage chemotherapy arm at 6 months (65.5% versus 48.9%) and 12 months (37.1% versus 16.7%) [Table 8].

A sensitivity analysis of OS was conducted by censoring patients at the time of HSCT. In this sensitivity analysis, the OS was significantly longer in the gilteritinib arm compared with the salvage chemotherapy arm (median OS: 8.3 months versus 5.3 months) using a Kaplan-Meier estimate (HR: 0.575; 95% CI: 0.434, 0.762; 1-sided P value: < 0.0001). The survival probability was higher in the gilteritinib arm compared with the salvage chemotherapy arm at 12 months (30.5% versus 8.7%) [Table 8].

Median OS was also longer in the gilteritinib arm compared with the salvage chemotherapy arm for the sensitivity analyses conducted by censoring patients at the time of new antileukemia therapy .

Median OS by CR/CRh status was higher for patients in the gilteritinib arm compared with salvage chemotherapy who achieved either CR; CRh but not CR; and CR or CRh (HR < 1.0). The restricted mean survival time by a prespecified cutoff time at 18 months was significantly longer in the gilteritinib arm (10 months) compared with the salvage chemotherapy arm (7.2 months) based on weighted differences of Kaplan-Meier curves (treatment difference: 2.8 months; 95% CI: 1.5, 4.1; 1-sided P-value: < 0.0001).

Table 8 Overall Survival – Intention to Treatment Set

Parameter Category/ Statistics	Gilteritinib 120 mg (N = 247)	Chemotherapy (N = 124)
Patient Status, n (%)		
Death events	171 (69.2)	90 (72.6)
Censored events	76 (30.8)	34 (27.4)
Duration of Overall Survival, Month†		
Q1 (95% CI)	4.4 (3.8, 5.1)	3.0 (1.9, 3.5)
Median (95% CI)	9.3 (7.7, 10.7)	5.6 (4.7, 7.3)
Q3 (95% CI)	18.7 (14.9, 24.1)	10.0 (8.0, 15.7)
Range‡	(0.2, 31.9+)††	(<0.1+, 33.0)
Stratified Analysis (Primary)§		
Log-ranked Test: P-value [1-sided P-value]	0.0007 [1-sided P-value: 0.0004]	

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Parameter Category/ Statistics	Gilteritinib 120 mg (N = 247)	Chemotherapy (N = 124)
Wald Test: P-Value¶	0.0008	
Hazard ratio (95% CI)¶	0.637 (0.490, 0.830)	
Unstratified Analysis		
Log-rank test (P-value)	0.0005	
Wald test: P-Value¶	0.0006	
Hazard ratio (95% CI)¶	0.636 (0.491, 0.823)	
Overall Survival Rate % (95% CI)††		
6 months	65.5 (59.2, 71.1)	48.9 (39.3, 57.8)
12 months	37.1 (30.7, 43.6)	16.7 (9.9, 25)
24 months	19.0 (12.8, 26.0)	13.8 (7.5, 22.0)
36 months	NE (NE, NE)	0 (NE, NE)
OS Sensitivity Analysis with Patients Censored at HSCT		
Patient status, n (%)		
Death events	142 (57.5)	84 (67.7)
Censored events	105 (42.5)	80 (32.3)
Duration of Overall Survival, Months†		
Q1 (95% CI)	4.1 (3.6, 4.6)	3.0 (1.9, 3.5)
Median (95% CI)	8.3 (6.7, 10.2)	5.3 (4.3, 6.1)
Q3 (95% CI)	14.9 (11.1, 18.7)	8.9 (7.3, 9.6)
Range‡	0.2, 27.4+	<0.1+, 33.0
Stratified Analysis§		
Log-ranked test: P-value [1-sided P-value]	0.0001 [1-sided P-value: <0.0001]	
Wald test: P-Value¶	0.0001	
Hazard ratio (95% CI)¶	0.575 (0.434, 0.762)	
Overall Survival Rate % (95% CI)§§		
6 months	62.1 (55.1, 68.4)	43.5 (33.2, 53.4)
12 months	30.5 (23.2, 38.0)	8.7 (3.6, 16.5)
24 months	13.2 (7.3, 20.9)	5.4 (1.6, 12.6)
36 months	NE (NE, NE)	0 (NE, NE)

All patients who were randomized (Intention to Treatment Set).
AML: acute myeloid leukemia; CI: confidence interval; HSCT: hematopoietic stem cell transplantation; IRT: interactive response technology; NE: not estimable; Q1: first quartile; Q3: third quartile.
†Based on Kaplan-Meier estimates. ‡A "+" indicates censoring. §Stratification factors were response to first-line AML therapy and preselected salvage chemotherapy per IRT. ¶Based on Cox proportional hazards model. Assuming proportional hazards, a hazard ratio of < 1 indicates a reduction in the hazard rate in favor of the gilteritinib arm. ††Survival rate and 95% CI were estimated using the Kaplan-Meier method and the Greenwood formula.
Sources: Study 2215-CL-0301, Adhoc Tables 12.3.1.1M and 12.3.1.4M; ADTTE Tables 12.3.1.1 and 12.3.1.4

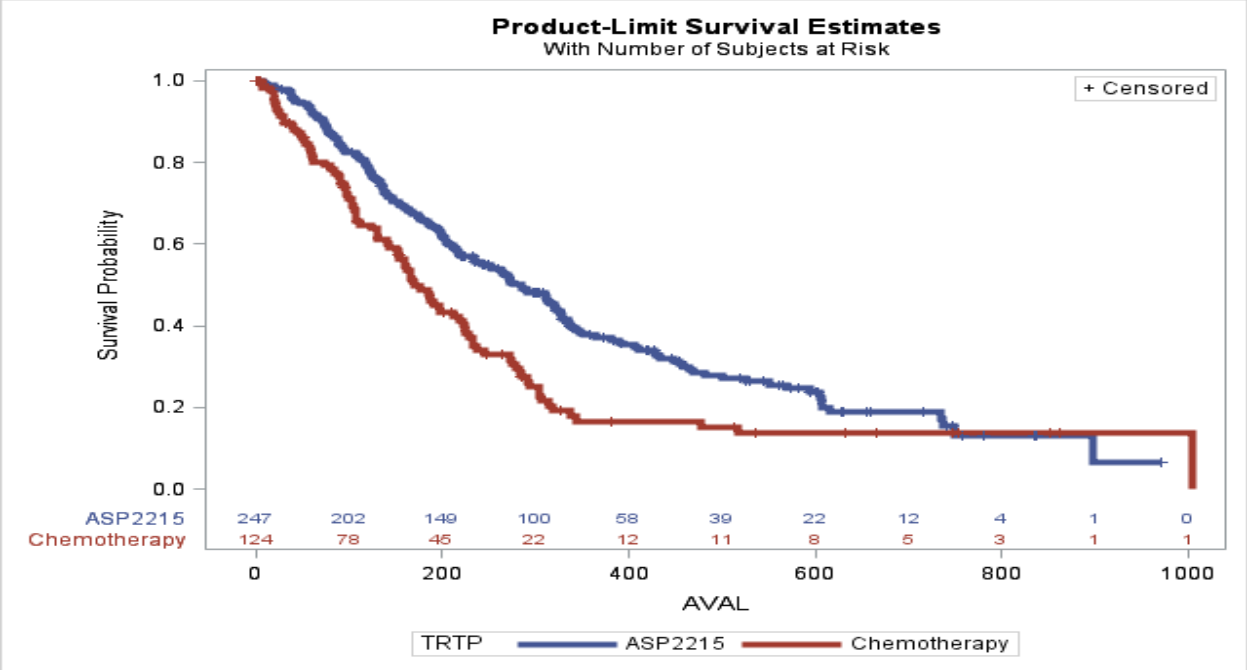
The FDA's Assessment:

The reviewer's primary analysis results of overall survival agree with the results presented in this section by applicant. The estimate hazard ratio was 0.64 (95% CI:0.49-0.83. one sided p-value 0.0004) based on pre-specified primary stratified analysis.

A central assumption of Cox regression is that covariate effects on the hazard rate, namely hazard ratio, are constant over time. Violations of the proportional hazard assumption may cause bias in the estimated coefficients as well as incorrect inference regarding significance of effects. If the assumption of proportional hazards holds, the graphs of the survival function

should look parallel, in the sense that they should have basically the same shape, should not cross and should not close in earlier period and then diverge slowly through follow up time. In this study, Kaplan-Meier estimates of the survival function plotted for OS using ITT population crossed after 25 months, indicating a violation of the assumption of proportional hazard. The Restricted Mean Survival (RMST) is an assumption free method. The analysis of RMST showed that gilteritinib demonstrated a statistically significant improvement in the OS primary efficacy endpoint compared to the salvage chemotherapy with 1-sided p-value <0.0001. The mean survival time in gilteritinib arm was 10 months while the mean survival time in salvage chemotherapy arm was 7.2 month.

Reviewer's Kaplan-Meier Plot for Overall Survival (ITT)



Source: FDA analysis

In all the sensitivity analyses conducted by reviewer, the hazard ratio point estimates were below 1, supportive of the primary analysis for OS endpoint. The reviewer's sensitivity analysis using the PPS demonstrated that the HR was 0.84 with 95% CI of (0.60,1.18) using stratified Cox PH model. P-value was 0.31 using stratified log-rank test. The median OS was numerically higher in the gilteritinib arm compared with salvage chemotherapy arm. The nonsignificant result may be due to the small sample size in PPS (only 87.9% patients in gilteritinib arm and 56.5% patients in chemotherapy arm are included in the PPS). The reviewer's sensitivity analysis using Safety Analysis Set demonstrated that the HR was 0.68 with 95% CI of (0.52, 0.89), supportive of the primary analysis for OS endpoint. Even though the post baseline

transplant distributions are different between two arms (11.7% in the gilteritinib arm, 37.1% in salvage chemotherapy arm), such difference does not appear to have impact on the OS results.

Subgroup Analysis

The Applicant's Position:

Median OS was similar in the gilteritinib arm for patients whose dose was increased (200-mg dose; 8.9 months), decreased (80-mg dose; 10.8 months) or remained at 120 mg (8.9 months). The survival probability was also similar in the gilteritinib arm for patients whose dose was increased, decreased or remained at 120 mg at 6 months (69.9%, 69.0% and 61.3%, respectively) and 12 months (33.3 %, 44.4% and 36.2%, respectively) [Table 9]. Of note, the dose adjustment groups were not randomized and, therefore, the effect of dose adjustment should be interpreted with caution.

The OS treatment effect was consistent across most analyzed subgroups [Figure 1]. Median OS was numerically higher for patients in the gilteritinib arm compared with salvage chemotherapy across all subgroups (HR < 1.0), with the exception of patients who had an unfavorable cytogenetic risk status at baseline (HR: 1.630; 95% CI: 0.690, 3.848) [Figure 1]. This result should be interpreted with caution due to small patient numbers.

For patients with no prior use of a FLT3 inhibitor, the HR was 0.620 (95% CI: 0.470, 0.818). For patients with prior use of a FLT3 inhibitor, the HR was 0.705 (95% CI: 0.346, 1.438).
For patients with high-intensity preselected chemotherapy, the HR was 0.663 (95% CI: 0.471, 0.932). For patients with low-intensity preselected chemotherapy, the HR was 0.563 (95% CI: 0.378, 0.839).

Table 9 Summary of Overall Survival by Dose Adjustment in the Gilteritinib 120-mg Arm – Intention to Treatment Set

Parameter Category/ Statistics	Gilteritinib Increase ¶ (n = 78)	Gilteritinib Decrease †† (n = 58)	Gilteritinib No Change (n = 110)
Patient Status, n (%)			
Death events	59 (75.6)	37 (63.8)	74 (67.3)
Censored events	19 (24.4)	21 (36.2)	36 (32.7)
Duration of Overall Survival, Months†			
Q1 (95% CI)	4.8 (4.0, 6.6)	5.3 (4.0, 8.3)	3.1 (2.4, 4.2)
Median (95% CI)	8.9 (6.8, 10.8)	10.8 (8.3, 14.3)	8.9 (6.1, 11.0)
Q3 (95% CI)	14.7 (11.0, 16.5)	19.8 (14.3, NE)	19.9 (14.1, NE)
Range‡	1.9, 29.5	0.7, 25.7+	0.2, 31.9+
Overall Survival Rate % (95% CI)§			
6 months	69.9 (58.2, 78.9)	69.0 (55.4, 79.2)	61.3 (51.4, 69.7)
12 months	33.3 (22.2, 44.8)	44.4 (30.5, 57.4)	36.2 (26.8, 45.6)
24 months	8.4 (2.6, 18.8)	23.2 (10.1, 39.5)	23.6 (13.9, 34.8)
36 months	0 (NE, NE)	NE (NE, NE)	NE (NE, NE)

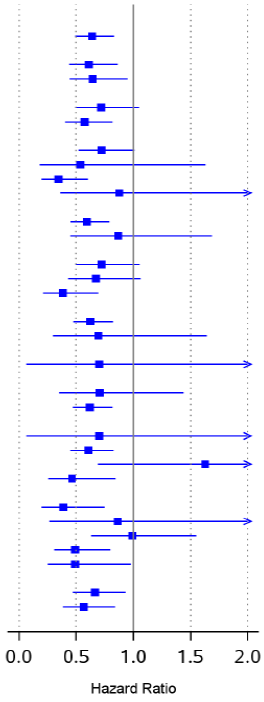
All patients who were randomized (Intention to Treatment Set).
In this table, only patients who received at least 1 dose are included in the analysis and dose adjustment was categorized by the first dose adjustment of the patient.

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

CI: confidence interval; NE: not estimable; Q1: first quartile; Q3: third quartile.
†Based on Kaplan-Meier estimates. ‡A "+" indicates censoring. §Survival rate and 95% CI were estimated using the Kaplan-Meier method and the Greenwood formula. ¶Increased to gilteritinib 200 mg from gilteritinib 120 mg. ††Decreased to gilteritinib 80 mg from gilteritinib 120 mg.
Sources: Study 2215-CL-0301, ADTTE Adhoc Table 12.3.1.9M

Figure 1 Forest Plot for Subgroup Analysis of Overall Survival – Intention to Treatment Set

Subgroup	ASP2215 Event/N	Chemotherapy Event/N	HR[95%CI]
All	171/247	90/124	0.637 (0.490, 0.830)
Age			
< 65 years	91/141	52/75	0.610 (0.432, 0.863)
>=65 years	80/106	38/49	0.643 (0.436, 0.948)
Sex			
Male	86/116	40/54	0.717 (0.491, 1.048)
Female	85/131	50/70	0.573 (0.402, 0.816)
Race			
White	102/145	56/75	0.723 (0.520, 1.005)
Black or African American	13/14	6/7	0.538 (0.178, 1.627)
Asian	42/69	20/33	0.342 (0.195, 0.602)
Other/Missing	14/19	8/9	0.872 (0.359, 2.121)
Baseline ECOG			
0-1	138/206	78/105	0.595 (0.449, 0.788)
>=2	33/41	12/19	0.868 (0.446, 1.690)
Region			
North America	88/114	42/52	0.722 (0.497, 1.050)
Europe(including Turkey and Israel)	43/68	32/43	0.674 (0.426, 1.066)
Asia	40/65	16/29	0.378 (0.206, 0.693)
Central FLT3 Mutation Type			
FLT3-ITD Alone	145/215	81/113	0.623 (0.473, 0.820)
FLT3-TKD Alone	16/21	8/10	0.693 (0.293, 1.643)
FLT3-ITD and FLT3-TKD	6/7	0	NE (NE, NE)
Others (Unknown/Missing/Negative)	4/4	1/1	0.702 (0.062, 7.918)
Prior use of FLT3 inhibitor			
Yes	26/32	11/14	0.705 (0.346, 1.438)
No	145/215	79/110	0.620 (0.470, 0.818)
Cytogenetic Risk status			
Favorable	3/4	1/1	0.702 (0.062, 7.918)
Intermediate	119/182	63/89	0.605 (0.444, 0.824)
Unfavorable	22/26	7/11	1.630 (0.690, 3.848)
Other	27/35	19/23	0.462 (0.254, 0.843)
Response to First-line Therapy per IRT			
Relapse within 6 months after allogeneic HSCT	24/31	16/17	0.382 (0.195, 0.747)
Relapse after 6 months after allogeneic HSCT	10/17	4/8	0.860 (0.264, 2.803)
Primary refractory without HSCT	70/98	28/48	0.990 (0.632, 1.550)
Relapse within 6 months after CRc and no HSCT	47/67	28/34	0.492 (0.304, 0.795)
Relapse after 6 months after CRc and no HSCT	20/34	14/17	0.492 (0.247, 0.978)
Pre-selected Chemotherapy per IRT			
High intensity	96/149	52/75	0.663 (0.471, 0.932)
Low intensity	75/98	38/49	0.563 (0.378, 0.839)



All patients who were randomized (Intention to Treatment Set).
An arrow is displayed for the 95% CI of the HR if the upper bound is greater than 2.
A HR and 95% CI for all patients were based on a stratified Cox proportional hazard model with response to first-line AML therapy and preselected salvage chemotherapy per IRT as stratification factors. In each subgroup, the HR and 95% CI were estimated using an unstratified Cox proportional hazard model. Assuming proportional hazards, an HR of less than 1 indicates a reduction in the HR, in favor of the gilteritinib arm.
AML: acute myeloid leukemia; ASP2215: gilteritinib; CI: confidence interval; CRc: composite complete remission; ECOG: Eastern Cooperative Oncology Group; FLT3: FMS-like tyrosine kinase 3; HSCT: hematopoietic stem cell transplant; HR: hazard ratio; IRT: interactive response technology; ITD: internal tandem duplication; N: total number of patients; NE: not estimable; TKD: tyrosine kinase domain.
Source: Study 2215-CL-0301, ADTTE Figure 12.3.5.1

The FDA's Assessment:

The reviewer's subgroup analysis results of overall survival agree with the results presented in this section by applicant. Hazard ratio for the patients who had an unfavorable cytogenetic risk

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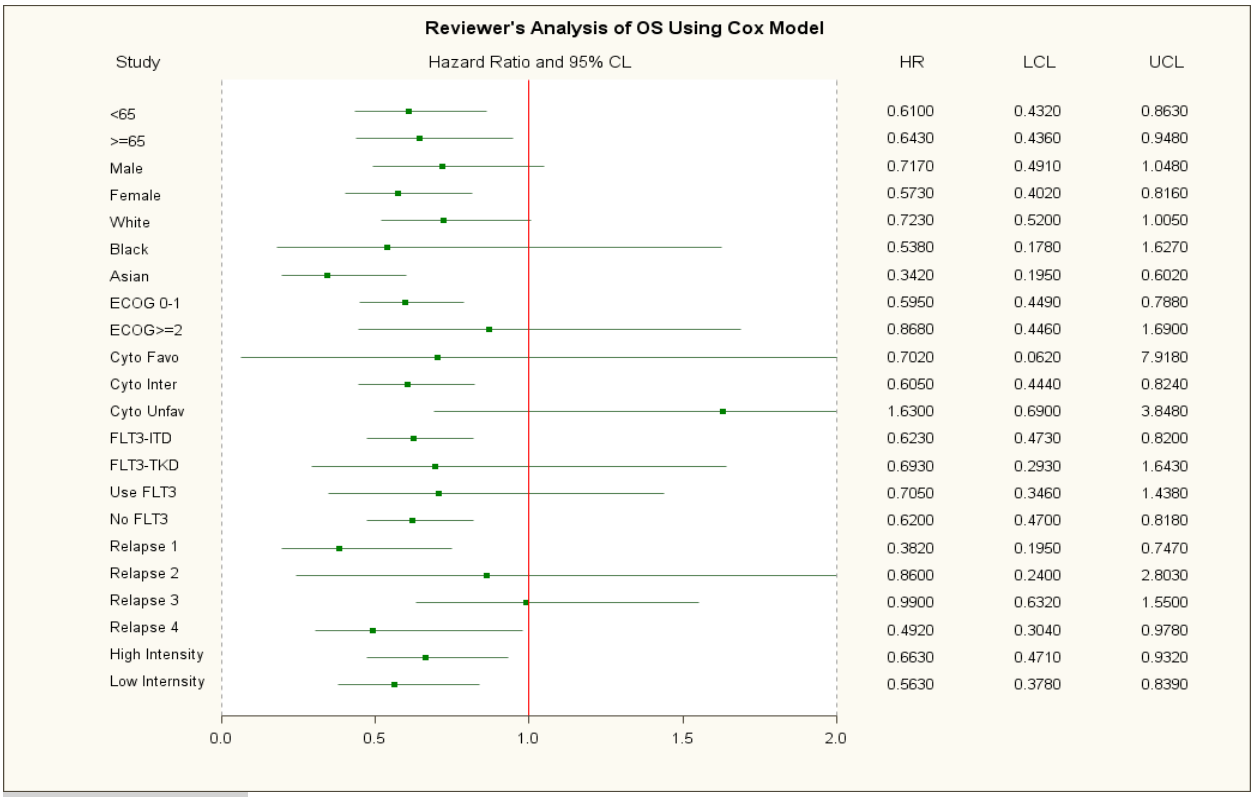
status at baseline was 1.63 with 95% CI of 0.69 to 3.84. This result was in favor in the salvage chemotherapy arm. Due to the small sample size for each of the subgroups, the results should be interpreted with caution.

Reviewer's Subgroup Analysis in Overall Survival-ITT



Source: FDA analysis

To better understand the apparent detriment in OS seen in the unfavorable-risk cytogenetic subgroup, FDA performed an exploratory analysis of OS by preselected chemotherapy in subjects with unfavorable cytogenetic risk. The Table below demonstrates that the detriment in OS was consistent regardless of whether patients were selected for low versus high-intensity chemotherapy.

Table 10 OS by Preselected Chemotherapy for Unfavorable Cytogenetic Risk Group

Unfavorable Cytogenetic Risk Group	Gilteritinib deaths, n (%)	Chemotherapy deaths, n (%)
High Dose Chemotherapy	11/14 (78.57%)	4/7 (57.14%)
Low Dose Chemotherapy	11/12 (91.67%)	3/4 (75.00%)

Source: FDA analysis

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Reviewer comments: Although the sample size of the subgroup is small, the HR 1.63 (95% CI 0.69-3.85) in patients with unfavorable risk cytogenetics is concerning. It is biologically rational that patients with unfavorable-risk cytogenetics may not respond to a single agent targeted therapy. Although, it is difficult to draw firm conclusions based on a small subgroup analysis from a single clinical trial.

Efficacy Results – Secondary and other relevant endpoints

Key Secondary Endpoint (ITT) – EFS

The Applicant's Position:
EFS trended toward increasing duration in the gilteritinib arm (median, 2.8 months) compared with the salvage chemotherapy arm (median, 0.7 months); however, the EFS endpoint did not meet the prespecified criteria for statistical significance (HR: 0.793; 95% CI: 0.577, 1.089; 1-sided P-value: 0.0415) [Table 11].

Median EFS also trended towards increasing duration in the gilteritinib arm compared with the salvage chemotherapy arm for the sensitivity analyses conducted using the FAS, the PPS, with treatment failure event date at the first antileukemia therapy, including lost to follow-up as events, with only best response of NR considered as treatment failure and with best response of not evaluable also considered as treatment failure.

Because the majority of salvage chemotherapy patients finished the study by cycle 2 of treatment, the duration of exposure was short in the salvage chemotherapy arm, which led to the high censoring of EFS (50.0% [62/124]). Therefore, a sensitivity analysis of EFS was performed that also considered subsequent AML therapies during the long-term follow-up and all death data. The modified analysis of EFS, defined as a failure to obtain a CRc with failures assigned as an event on study day 1, relapse, or death from any cause, including events and initiation of new antileukemia treatments reported in long-term follow up, showed an improvement with a median of 2.3 months for gilteritinib versus 0.7 months for salvage chemotherapy with an HR of 0.499 (95% CI: 0.387, 0.643; 1-sided P-value: < 0.0001). For this sensitivity analysis, the EFS probability was higher in the gilteritinib arm compared with the salvage chemotherapy arm at 6 months (30.5% versus 5.8%) [Table 11]. The EFS treatment effect was consistent across most analyzed subgroups.

Table 11 Event-free Survival – Intention to Treatment Set

Parameter Category/Statistics	Gilteritinib (n = 247)	Chemotherapy (n = 124)
EFS Events, n (%)†	189 (76.5)	62 (50.0)
Relapse	75 (30.4)	1 (0.8)
Treatment failure	97 (39.3)	48 (38.7)
Death	17 (6.9)	13 (10.5)

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Parameter Category/Statistics	Gilteritinib (n = 247)	Chemotherapy (n = 124)
Censored events	58 (23.5)	62 (50.0)
Table continued on next page.		
Duration of EFS, Months‡		
Q1 (95% CI)	< 0.1 (NE, NE)	< 0.1 (NE, NE)
Median (95% CI)	2.8 (1.4, 3.7)	0.7 (0.2, NE)
Q3 (95% CI)	8.3 (6.5, 12.1)	NE (3.4, NE)
Range§	< 0.1, 31.2+	< 0.1, 6.6+
Stratified Analysis (Primary)¶		
Log-rank test (primary) (P-value [1-sided P-value])	0.0830 [1-sided P-value: 0.0415]	
Wald test: P-value	0.1521	
Hazard ratio (95% CI)††	0.793 (0.577, 1.089)	
Unstratified Analysis		
Log-rank test (P-value)	0.1364	
Wald test: P-value	0.2287	
Hazard ratio (95% CI)††	0.825 (0.604, 1.128)	
EFS Rate % (95% CI)‡‡		
6 months	33.2 (27.2, 39.3)	27.1 (8.2, 50.6)
12 months	19.8 (14.6, 25.7)	NE (NE, NE)
24 months	12.2 (6.7, 19.6)	NE (NE, NE)
36 months	NE (NE, NE)	NE (NE, NE)
EFS Using the Long-Term Follow-Up Data of Death and new AML Therapies		
EFS Events, n (%)†	207 (83.8)	111 (89.5)
Relapse	75 (30.4)	1 (0.8)
Relapse-off Treatment	6 (2.4)	8 (6.5)
New AML Therapy	3 (1.2)	26 (21.0)
Treatment failure	97 (39.3)	48 (38.7)
Death	26 (10.5)	28 (22.6)
Censored events	40 (16.2)	13 (10.5)
Duration of EFS, Months‡		
Q1 (95% CI)	<0.1 (NE, NE)	<0.1 (NE, NE)
Median (95% CI)	2.3 (1.4, 3.6)	0.7 (0.1, 1.3)
Q3 (95% CI)	7.4 (5.7, 10.0)	2.0 (1.7, 2.6)
Range§	<0.1, 31.2+	<0.1, 10.0
Stratified Analysis (Primary)¶		
Log-rank test (primary) (P-value [1-sided P-value])	<0.0001 (1-sided P-value: <0.0001)	
Wald test: P-value††	<0.0001	
Hazard ratio (95% CI)††	0.499 (0.387, 0.643)	
Unstratified Analysis		
Log-rank test (P-value)	<0.0001	
Wald test: P-value††	<0.0001	
Hazard ratio (95% CI)††	0.508 (0.397, 0.651)	
EFS Rate % (95% CI)‡‡		
6 months	30.5 (24.8, 36.3)	5.8 (2.2, 11.8)
12 months	16.3 (11.7, 21.5)	0 (NE, NE)
24 months	9.4 (5.0, 15.5)	0 (NE, NE)
36 months	NE (NE, NE)	0 (NE, NE)

All patients who were randomized (Intention to Treatment Set).
Percentages were calculated based on the total number of patients with nonmissing event/censored value.

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

AML: acute myeloid leukemia; CI: confidence interval; EFS: event-free survival; IRT: interactive response technology; NE: not estimable; Q1: first quartile; Q3: third quartile.
Footnotes continued on next page.

†Patients were summarized under the categories that occurred first. If treatment failure and death occurred on the same day, patients were summarized under death. ‡Based on Kaplan-Meier estimates. §Note: A "+" indicates censoring. ¶Stratification factors were response to first-line AML therapy and preselected salvage chemotherapy per IRT. ††Based on the Cox proportional hazards model. Assuming proportional hazards, a hazard ratio of < 1 indicates a reduction in the hazard rate in favor of the gilteritinib arm. ‡‡EFS rate and 95% CI were estimated using the Kaplan-Meier method and the Greenwood formula.
Source: Study 2215-CL-0301, ADTTE Adhoc Tables 12.3.2.1M and 12.3.2.9M

The FDA's Assessment:

The reviewer's primary analysis on the key efficacy endpoint of EFS results agree with the results presented in this section by applicant. The EFS endpoint did not meet the prespecified criteria for statistical significance (HR: 0.793; 95% CI: 0.577, 1.089; 1-sided P-value: 0.0415).The median duration of follow up time is imbalanced. The EFS estimates maybe biased due to more early study discontinuation in the chemotherapy arm.

In addition, the Agency does not agree with the applicant definition of EFS. It was defined as the time from the date of randomization until the date of documented relapse (excluding relapse after PR), treatment failure or death from any cause within 30 days after the last dose of study drug, which ever occurred first. If the subject failed to achieve CR, CRp, CRi, or PR during the treatment period, the patient was defined as having an EFS event related to treatment failure, and the event date was the randomization date. This definition of EFS is not acceptable since it includes responses less than a CR.

Key Secondary Endpoint (ITT) – CR Rate

The Applicant's Position:

For the ITT, the CR rate was higher in the gilteritinib arm (21.1% [52/247]) compared with the salvage chemotherapy arm (10.5% [13/124]). The treatment difference in CR rate between the gilteritinib and salvage chemotherapy arms was 10.6% (95% CI: 2.8, 18.4; 1-sided nominal P-value: 0.0053) [Table 12].

For the ITT, the CR rate prior to HSCT was higher in the gilteritinib arm (13.8% [34/247]) compared with the salvage chemotherapy arm (10.5% [13/124]). The treatment difference in CR rate between the gilteritinib and salvage chemotherapy arms was 3.3% (95% CI: -4.0, 10.5; 1-sided nominal P-value: 0.3639)

Due to the statistical nonsignificance of EFS and the preplanned hierarchical testing method, statistical significance of CR rate was not achieved.

CR rate was consistent across most analyzed subgroups. The CR rate was higher in the gilteritinib arm compared with the salvage chemotherapy arm across all subgroups (risk difference > 0), with the exception of patients who were categorized as other for race (risk difference: -0.6; 95% CI: -33.5, 32.3), patients who had a baseline ECOG status of ≥ 2 (risk difference: -4.0; 95% CI: -29.5, 21.5), patients who had a FLT3 mutation type of FLT3-TKD alone (risk difference: -1.0; 95% CI: -38.3, 36.4) and patients who had an unfavorable cytogenetic risk status at baseline (risk difference: -23.4; 95% CI: -57.2, 10.4).

Table 12 Summary of CR Rate

Parameter **Category/Statistics**	**Gilteritinib** **(n = 247)**	**Chemotherapy** **(n = 124)**
Primary Analysis, ITT		
CR Rate, n/N (%) [95% CI]†	52/247 (21.1) [16.1, 26.7]	13/124 (10.5) [5.7, 17.3]
Adjusted treatment difference % [95% CI]‡	10.6 [2.8, 18.4]	
Stratified P-value (primary) [1-sided P-value]‡	0.0106 [1-sided P-value: 0.0053]	
Unstratified P-value [1-sided P-value]§	0.0134 [1-sided P-value: 0.0067]	
Sensitivity Analysis, ITT and Received at Least 1 Dose of Study Drug		
CR Rate, n/N (%) [95% CI]†	52/246 (21.1) [16.2, 26.8]	13/109 (11.9) [6.5, 19.5]
Adjusted treatment difference % [95% CI]‡	9.3 [1.0, 17.6]	
P-value‡	0.0348	
Sensitivity Analysis, ITT With at Least 1 Postbaseline Bone Marrow Assessment		
CR Rate, n/N (%) [95% CI]†	52/232 (22.4) [17.2, 28.3]	13/65 (20.0) [11.1, 31.8]
Adjusted treatment difference % [95% CI]‡	3.3 [-8.1, 14.7]	
P-value‡	0.5693	
Sensitivity Analysis, ITT, Achieving CR prior to HSCT¶		
CR Rate, n/N (%) [95% CI]†	34/247 (13.8) [9.7, 18.7]	13/124 (10.5) [5.7, 17.3]
Adjusted treatment difference % [95% CI]‡	3.3 [-4.0, 10.5]	
P-value‡	0.3639	

Footnotes appear on next page.
All patients who were randomized (Intention to Treatment Set).
AML: acute myeloid leukemia; CI: confidence interval; CR: complete remission; HSCT: hematopoietic stem cell transplant; IRT: Interactive Response Technology.
†Using exact method based on binomial distribution. ‡Based on stratified Cochran-Mantel-Haenszel test. Stratification factors were response to first-line AML therapy and preselected salvage chemotherapy per IRT. Pooled strata were used as shown in Table 12.3.3.2. Treatment differences were adjusted based on pooled strata. Treatment difference = gilteritinib – chemotherapy. §Based on 2-sided Fisher's exact test. ¶The CR rate prior to HSCT was defined as the number of patients who achieved CR at any postbaseline visit prior to HSCT divided by the number of patients in the analysis population.
Source: Study 2215-CL-0301, ADTTE Table 12.3.3.1

The median duration of CR was 14.8 months in the gilteritinib arm [Table 13]. Because the majority of salvage chemotherapy patients finished the study by cycle 2 of treatment, the duration of exposure was short in the salvage chemotherapy arm, which led to limited follow-up of response and high censoring of the duration of CR. Therefore, the median duration of CR could not be reliably estimated in the salvage chemotherapy arm.

Table 13 Duration of CR – Intention to Treatment Set

Parameter Category/Statistics	Gilteritinib (n = 247)	Chemotherapy (n = 124)
Patients with CR, n†	52	13
Events, n (%)	18 (34.6)	1 (7.7)
Censored events, n (%)	34 (65.4)	12 (92.3)
Duration of CR, Months‡		
Q1 (95% CI)	4.6 (2.8, 12.9)	1.8 (NE, NE)
Median (95% CI)	14.8 (11.0, NE)	1.8 (NE, NE)
Q3 (95% CI)	NE (NE, NE)	1.8 (NE, NE)
Range§	0.6, 23.1+	< 0.1+, 1.8
Unstratified Analysis		
Log-rank test (P-value)	0.1189	
Wald test: P-value¶	0.1619	
Hazard ratio (95% CI)¶	0.206 (0.022, 1.886)	

All patients who were randomized (Intention to Treatment Set). Stratified analyses were not conducted.
CI: confidence interval; CR: complete remission; NE: not estimable; Q1: first quartile; Q3: third quartile.
†Duration of CR was only applicable to patients with best overall response of CR. ‡Based on Kaplan-Meier estimates. §Note: A "+" indicates censoring. ¶Based on the Cox proportional hazards model. Assuming proportional hazards, a hazard ratio of < 1 indicates a reduction in the hazard rate in favor of the gilteritinib arm.
Source: Study 2215-CL-0301, ADTTE Adhoc Table 12.3.5.1M

The FDA's Assessment:

The Agency does not agree with the applicant derived CR endpoint. First, FDA does not consider CR responses that were only reached following HSCT. The applicant initially found that CR rate prior to HSCT on the gilteritinib arm was 13.8% (34/247). However, based on FDA's review, subject (b) (6) had full neutrophil and platelet recovery on day 42 before HSCT. This patient was recorded as a CRh by the applicant, but FDA considered this patient to have a response of CR. The applicant agreed with FDA's assessment.

The summary of FDA's adjudicated of CR endpoint is given in the table below. The CR rate per FDA's adjudication was 14.2% with 95% CI of (10.1%, 19.2%) in the gilteritinib arm compared with 10.5% with 95% CI of (5.7%, 17.3%) in salvage chemotherapy arm. The rate difference between two arms was not statistically significant with p-value of 0.15 using stratified CMH test.

Table 14 Reviewer's Analysis Results of CR bye FDA's Adjudication-ITT

Parameter Category/Statistics	Gilteritinib (n = 247)	Chemotherapy (n = 124)
CR rate n (%) 95% CI	35 (14.2%) (10.1%, 19.2%)	13 (10.5) (5.7%, 17.3%)
Median DOR (Month) (Range)	14.8 (0.6-23.1)	1.8 (<0.1-1.8)
Nominal p-value	0.15 using stratified CMH test	

Source: FDA analysis

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Table below shows FDA's descriptive analysis of CR rate by cytogenetic risk status and preselected chemotherapy status. Among patients preselected for high dose intensity at baseline, the CR rate is numerically slightly lower in the giteritinib arm (15.44%) compared with those in salvage chemotherapy arm (16.00%). Among patients who had an unfavorable cytogenetic risk status at baseline, the CR rate was lower in the gilteritinib arm (3.85%) compared with those in salvage chemotherapy arm (27.27%).

Table 15 FDA's Summary of CR rate by preselected chemotherapy and cytogenetic risk status

	Gilteritinib	Chemotherapy
Preselected Chemotherapy		
High Dose Intensity	23/149 (15.44%)	12/75 (16.00%)
Low Dose Intensity	12/98 (12.24%)	1/49 (2.04%)
Cytogenetic Risk Status		
Intermediate	33/182 (18.13%)	9/89 (10.11%)
Unfavorable	1/26 (3.85%)	3/11 (27.27%)

Reviewer comments: The CR rate on the gilteritinib arm was not significantly higher than that on the control arm. While considering the limitations of these post-hoc subgroup analyses, the CR rate data by treatment intensity indicates that gilteritinib has roughly the same CR rate as high-intensity chemotherapy in patients with first relapse or primary refractory FLT3-mutated AML, whereas the CR rate appears higher with gilteritinib than low-intensity chemotherapy. Given that survival was improved in both the low- and high-intensity subgroups, the benefit of gilteritinib in patients eligible for high-intensity chemotherapy may be due to less acute toxic effects of the therapy. This will be evaluated in FDA's safety review.

Again, the efficacy of gilteritinib appears less in patients with high-risk cytogenetics when compared to the chemotherapy control arm. However, no firm conclusions can be derived from this small subgroup analysis.

Other Relevant Endpoints

CR/CRh

The Applicant's Position:
The coprimary endpoint of CR/CRh rate was analyzed in interim analysis 1 for only the gilteritinib arm, and the results were reported in NDA 211349. The CR/CRh rate was summarized for the gilteritinib arm and the salvage chemotherapy arm for the final analysis.

For the ITT, the CR/CRh rate was higher in the gilteritinib arm (34.0% [84/247]) compared with the salvage chemotherapy arm (15.3% [19/124]). The treatment difference in CR/CRh rate between the gilteritinib and salvage chemotherapy arms was 18.6% (95% CI: 9.8,27.4; 1-sided nominal P-value: 0.0001). For the ITT, the CR/CRh rate prior to HSCT was higher in the gilteritinib arm (26.3% [65/247]) compared with the salvage chemotherapy arm (15.3% [19/124]). The treatment difference in CR/CRh rate between the gilteritinib and salvage chemotherapy arms was 10.9% (95% CI: 2.4,19.5; 1-sided nominal P-value: 0.0171).

A sensitivity analysis was conducted based on the adjudicated CR/CRh by FDA (FDA information request on 18 Dec 18 and Astellas Response Sequence 0034, 07 Jan 19). Based on this sensitivity analysis, CR/CRh rate was higher in the gilteritinib arm (23.1% [57/247]) compared with the salvage chemotherapy arm (12.9% [16/124]), and median duration of CR/CRh was 7.4 months for the gilteritinib arm [Table 16]. For patients who achieved a CR/CRh, the median time to first response was 1.9 months (range, 0.9 to 9.6 months) based on this sensitivity analysis. The CR/CRh rate was 49 of 215 in patients with FLT3-ITD, 3 of 7 in patients with FLT3-ITD/TKD and 3 of 21 in patients with FLT3-TKD only.

The CR/CRh rate for the other sensitivity analyses (patients in the ITT who received at least 1 dose of study drug, patients in the ITT with at least 1 postbaseline bone marrow assessment, patients in the FAS and patients in the PPS) was similar to the primary analysis and was higher in the gilteritinib arm compared with the salvage chemotherapy arm.

The median duration of CR/CRh was 11 months in the gilteritinib arm. The median follow-up of response was 10.1 months in the gilteritinib arm.

The median duration of CR/CRh with death as an event was 7.4 months in the gilteritinib arm. For patients who did not have transplantation, the median duration of CR/CRh was 4.4 months in the gilteritinib arm.

Because the majority of salvage chemotherapy patients finished the study by cycle 2 of treatment, the duration of exposure was short in the salvage chemotherapy arm, which led to limited follow-up of response and high censoring of the duration of CR/CRh. Therefore, the median duration of CR/CRh could not be reliably estimated in the salvage chemotherapy arm.

Table 16 Summary of CR/CRh by FDA Adjudication

Remission Rate	**Gilteritinib** (n = 247)	**Chemotherapy** (n = 124)
CR†/CRh§ n/N (%)	57/247 (23.1)	16/124 (12.9)
95% CI§	18, 28.8	7.6, 20.1
Median DOR¶ (months)	7.4	1.8
Range (months)	<0.1+ to 23.1+	<0.1+ to 1.8
CR† n/N (%)	35/247 (14.2)	13/124 (10.5)

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95% CI§	10.1. 19.2	5.7, 17.3
Median DOR¶ (months)	14.8	1.8
Range (months)	0.6 to 23.1+	<0.1+ to 1.8
CRh‡ n/N (%)	22/247 (8.9)	3/124 (2.4)
95% C§	5.7, 13.2	0.5, 6.9
Median DOR¶ (months)	2.9	NE
Range (months)	<0.1+, 9.5+	<0.1+, <0.1+

All patients who were randomized (Intention to Treatment Set).
CI: confidence interval; CR: complete remission; CRh: complete remission with incomplete hematological recovery; DOR: duration of response; NE: not estimable.
Footnotes continued on next page.
Only responses prior to HSCT were included in response rate.
† CR was defined as an absolute neutrophil count ≥1.0 x 10^9/L, platelets ≥100 x 10^9/L, normal marrow differential with <5% blasts, must have been red blood cells, platelet transfusion independent and no evidence of extramedullary leukemia.
‡ CRh was defined as marrow blasts <5%, partial hematologic recovery absolute neutrophil count ≥0.5 x 10^9/L and platelets ≥50 x 10^9/L, no evidence of extramedullary leukemia and could not have been classified as CR.
§ The 95% CI rate was calculated using the exact method based on binomial distribution.
¶ DOR was defined as the time from the date of either first CR or CRh until the date of a documented relapse of any type.
Source: Adhoc Label ADRESP Table 12.3.3.4.1 and Adhoc Label ADTTE Tables 12.3.5.4M; FDA information request on 18 Dec 18 and Astellas Response Sequence 0034, 07 Jan 19

The FDA's Assessment:

The reviewer's analysis results based on the adjudicated CR/CRh by FDA agree with the results presented in this section by applicant. Time to event analysis based on response endpoint should be considered as exploratory.

Reviewer comments: While FDA-adjudicated responses for CR+CRh are presented in Table 10 above, it is worth mentioning that CRh responses do not apply to patients treated with cytotoxic therapies, like those on the control arm of Study 2215-CL-0301. Therefore, FDA only considers the CR+CRh responses on the gilteritinib arm to be valid in describing a palliative benefit to patients.

Best Response Rate

The Applicant's Position:

Overall response rate was numerically higher in the gilteritinib arm compared with the salvage chemotherapy arm (67.6% [167/247] versus 25.8% [32/124]). Best response rates were as follows: CR (21.1% [52/247] versus 10.5% [13/124]), CRp (7.7% [19/247] versus no patients), CRi (25.5% [63/247] versus 11.3% [14/124]) and PR (13.4% [33/247] versus 4.0% [5/124]).

The CRc rate during the study was numerically higher in the gilteritinib arm compared with the salvage chemotherapy arm (54.3% [134/247] versus 21.8% [27/124]).

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

For patients with prior use of FLT3 inhibitor, overall response rate was numerically higher in the gilteritinib arm compared with the salvage chemotherapy arm (62.5% [20/32 versus 28.6% [4/14]). Best response rates were as follows: CR (18.8% [6/32] versus no patients), PR (15.6% [5/32] versus 7.1% [1/14]), CRp (12.5% [4/32] versus no patients) and CRi (15.6% [5/32] versus 21.4% [3/14]).

CR/CRh response rates were numerically higher in the gilteritinib arm compared with the salvage chemotherapy arm (31.3% [10/32] versus 7.1% [1/14]), as were the response rates for CRh (12.5% [4/32] versus 7.1% [1/14]).

The CRc rate during the study was numerically higher in the gilteritinib arm compared with the salvage chemotherapy arm (46.9% [15/32] versus 21.4% [3/14]).

For patients with no prior use of FLT3 inhibitor, overall response rate was numerically higher in the gilteritinib arm compared with the salvage chemotherapy arm (68.4% [147/215] versus 25.5% [28/110]). Best response rates were as follows: CRi (27.0% [58/215] versus 10.0% [11/110]), CR (21.4% [46/215] versus 11.8% [13/110]), PR (13.0% [28/215] versus 3.6% [4/110]) and CRp (7.0% [15/215] versus no patients).

In the gilteritinib arm, best overall response rates were similar for patients with prior use of FLT3 inhibitor compared with patients with no prior use of FLT3 inhibitor.

The FDA's Assessment:
FDA does not consider best response rate as measure of clinical benefit to patients with AML. Furthermore, the CR rate results listed in this section are incorrect as they consider CR responses that only occurred following HSCT.

Reviewer comments: FDA did not adjudicate responses less than a CRh. While responses less than a CRh (i.e., CRp, CRi, PR) may represent a biological effect of gilteritinib, they do not represent true clinical benefit to patients given inadequate blood count recovery.

Response Rate by Dose Adjustment

The Applicant's Position:
In the gilteritinib arm, 78 patients had a dose increase to 200 mg from 120 mg. Among those patient with a dose increase, 12 patients (15.4%) experienced CR/CRh after the dose adjustment. Fifty-eight patients had a dose decrease to 80 mg from 120 mg. Among those patients with a dose decrease, 24 patients (41.4%) achieved CR/CRh after the dose adjustment, suggesting that a dose reduction did not adversely affect response rate. Of note, the dose adjustment groups were not randomized groups and, therefore, the effect of dose adjustment should be interpreted with caution.

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Leukemia-free Survival
The gilteritinib arm had a median LFS of 4.4 months. The salvage chemotherapy arm had a high percentage of patients who were censored early, which made the survival curve estimate (median LFS) unreliable for this treatment arm. The HR was not reliable for the same aforementioned reason.

The FDA's Assessment:
FDA disagrees with the applicant's assessment of CR+CRh rates following dose adjustments of gilteritinib.

The data on achievement of CR+CRh following dose escalation of gilteritinib to 200 mg daily does not support dose escalation in patients without a CRc response (CR+CRi+CRp) following cycle 1. While the sample sizes are small, preventing clear conclusions, only a minority of patients achieved CR+CRh response following dose escalation (6.4%), whereas patients with dose decrease had an even higher chance of achieving CR+CRh (22.5%).

The patients with dose escalation may possess higher-risk disease given that they did not achieve CRc as quickly and the physicians made the decision to dose escalate. However, of the 93 patients who did not achieve a response at or before 4 weeks, more patients in the subgroup that remained on the same dose responded (29/67, 43%) than in the subgroup of patients who dose-escalated (2/26, 8%).

The median time to response suggests that dose escalation after only 1 month would not allow patients adequate time to respond to the therapy. Furthermore, PK and PD data support gilteritinib 120 mg qday as sufficient to achieve adequate exposure and to reach the target of FLT3 inhibition (b) (4)

The reviewer's analysis on the leukemia-free survival results agree with the results presented in this section by applicant.

Time to Remission

The Applicant's Position:
The median time to CRc and CR was higher in the gilteritinib arm (1.8 months [range: 0.9, 9.5 months] and 4.4 months [range: 0.9, 16.0 months], respectively) compared with the salvage chemotherapy arm (1.1 months [range: 0.8, 2.9 months] and 1.2 months [range: 1.0, 2.6 months], respectively). The median time to response (only evaluated for patients who achieved CRc or PR) was similar between the gilteritinib arm (1.1 months) and the salvage chemotherapy arm (1.2 months).

The median time to first CR/CRh (for patients with a response of CR/CRh) was higher in the gilteritinib arm (3.7 months [range: 0.9, 10.6 months]) compared with the salvage chemotherapy arm (1.2 months [range: 1.0, 2.6 months]). The median time to best CR/CRh (for patients with a response of CR/CRh) was also higher in the gilteritinib arm (3.8 months [range: 0.9, 16.0 months]) compared with the salvage chemotherapy arm (1.2 months [range: 1.0, 2.6 months]).

The FDA's Assessment:
The reviewer's analysis on the time to remission results agree with the results presented in this section by applicant.

CRc

The Applicant's Position:
The CRc rate was higher in the gilteritinib arm (54.3% [134/247]) compared with the salvage chemotherapy arm (21.8% [27/124]). The treatment difference in CRc rate between the gilteritinib and salvage chemotherapy arms was 32.5% (95% CI: 22.3, 42.6; P < 0.0001). The median duration of CRc for the gilteritinib arm was 4.6 months. Because the majority of salvage chemotherapy patients finished the study by cycle 2 of treatment, the duration of exposure was short in the salvage chemotherapy arm, which led to limited follow-up of response and high censoring of the duration of CRc. Therefore, the median duration of CRc could not be estimated for the salvage chemotherapy arm.

The FDA's Assessment:
FDA does not agree that the secondary endpoint of CRc is relevant supportive endpoint due to inclusion of response less than CRh.

Reviewer comments: Responses less than CRh are not considered clinically meaningful. Therefore, FDA did not adjudicate responses less than CRh.

Transplantation Rate

The Applicant's Position:
The transplantation rate was 25.5% (63/247) in the gilteritinib arm and 15.3% (19/124) in the salvage chemotherapy arm. The treatment difference in transplantation rate between the gilteritinib and salvage chemotherapy arms was 10.2% (95% CI: 1.2, 19.1; P-value: 0.0333).

The FDA's Assessment:
The reviewer's analysis on the transplantation results agree with the results presented in this section by applicant.

Transfusion Conversion Rate; Transfusion Maintenance Rate

The Applicant's Position:
Transfusion conversion rate and transfusion maintenance rate were only defined for the patients in the gilteritinib arm.

Patients were classified as transfusion independent at baseline if there were no red blood cell (RBC) or platelet transfusions within the baseline period (defined as 28 days prior to the first dose to 28 days after the first dose); otherwise, patients were classified as transfusion dependent at baseline. Patients were classified as transfusion independent postbaseline if the patient had 1 consecutive 8-week period without any RBC or platelet transfusion from 29 days after the first dose until the last dose date. For patients who were on treatment ≤ 4 weeks or patients who were on treatment > 4 weeks but < 12 weeks and there was no RBC or platelet transfusion within the postbaseline period, the postbaseline transfusion status was considered not evaluable; otherwise, patients were considered postbaseline transfusion dependent. Both transfusion conversion rate and maintenance rate were defined for patients who had evaluable postbaseline transfusion status.

Among the 197 patients who were dependent on RBC and/or platelet transfusions at baseline, 68 (34.5%) became independent of RBC and platelet transfusions during any 56-day post-baseline period. For the 49 patients who were independent of both RBC and platelet transfusions at baseline, 29 (59.2%) remained transfusion-independent during any 56-day post-baseline period.

The FDA's Assessment:

The reviewer's analysis of transfusion conversion rate and transfusion maintenance rate is provided in the table below. Only patients treated with gilteritinib were included in the analysis (n=246). The results agree with the results presented in the section by sponsor.

Table 17 Reviewer's Summary of Transfusion Conversion Rate and Transfusion Maintenance Rate

Post-Baseline	Baseline		
	Independent	Dependent	Total
Independent	29 (59.2%)	68 (34.5%)	97
Dependent	12 (24.5%)	110 (55.8%)	122
Not evauable	8 (16.3%)	19 (9.6%)	27
Total	49	197	246

Source: FDA analysis

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Multigene Mutational Analysis

The Applicant's Position:
A multigene mutational analysis was conducted to assess the relationship of efficacy of gilteritinib and mutational status of AML-related genes. Four mutational subgroups were identified in at least (b) (4) The response rate and median OS were similar in patients receiving gilteritinib regardless of mutational subgroup and between mutation positive and negative patients within each mutational subgroup. Patients receiving gilteritinib maintained a higher CR/CRh rate and median OS than patients receiving chemotherapy in all mutational subgroups.

Dose/Dose Response

The Applicant's Position:
In Study 2215-CL-0301, gilteritinib demonstrated efficacy at the 120 mg dose in patients who have R/R AML with an FLT3 mutation. OS was significantly longer in the gilteritinib arm (median, 9.3 months) compared with the salvage chemotherapy arm (median, 5.6 months) using a Kaplan-Meier estimate (HR: 0.637; 95% CI: 0.490, 0.830; 1-sided P-value: 0.0004). The survival probability was higher in the gilteritinib arm compared with the salvage chemotherapy arm at 6 months (65.5% versus 48.9%) and 12 months (37.1% versus 16.7%). With patients censored at the time of HSCT, OS was significantly longer in the gilteritinib arm compared with the salvage chemotherapy arm (median OS: 8.3 months versus 5.3 months) using a Kaplan-Meier estimate (HR: 0.575; 95% CI: 0.434, 0.762; 1-sided P value: < 0.0001). The survival probability was higher in the gilteritinib arm compared with the salvage chemotherapy arm at 12 months (30.5% versus 8.7%). The OS treatment effect was consistent across most analyzed subgroups.

In the gilteritinib arm, 78 patients had a dose increase to 200 mg from 120 mg, and 58 patients had a dose decrease to 80 mg from 120 mg. Overall, median OS was similar in the gilteritinib arm for patients whose dose was increased (200-mg dose; 8.9 months), decreased (80-mg dose; 10.8 months) or remained at 120 mg (8.9 months). The survival probability was also similar in the gilteritinib arm for patients whose dose was increased, decreased or remained at 120 mg at 6 months (69.9%, 69.0 % and 61.3%, respectively) and 12 months (33.3 %, 44.4% and 36.2%, respectively).

Additional analyses were conducted to assess the impact of dose modifications (dose reductions and dose escalations) on CR/CRh in the pooled Response Analysis Set (RAS). These assessments suggest that patients can reduce to 80 mg once daily to manage AEs without diminishing CR/CRh response. Furthermore, in the gilteritinib arm, 78 patients (31.6%) increased gilteritinib dose to 200 mg after not achieving CR/CRh at completion of

1 cycle of gilteritinib therapy. Five of the 78 patients (6.4%) achieved CR or CRh after dose increase without undergoing HSCT. (b) (4)

The FDA's Assessment:

(b) (4)

Durability of Response

The Applicant's Position:

Overall, Study 2215-CL-0301 showed significantly longer OS and durable responses in patients who received gilteritinib 120 mg compared with patients receiving salvage chemotherapy, as well as transfusion independence. Furthermore, the OS and response rates observed in the phase 3 study compares favorably to OS and response rates from the literature for R/R AML patients treated with salvage chemotherapy [Roboz et al, 2014]. The achievement of CR is a central treatment goal for patients with AML, and the achievement of CRh (in the absence of CR) is expected to reduce the risk of infection and/or bleeding in AML patients by reducing the risk of severe cytopenias. Achievement of CR or CRh criteria and/or a reduced requirement for transfusion are expected to result in decreased risk of infection and bleeding for AML patients, thereby providing substantive clinical benefits.

Relative to the survival prognosis observed with salvage chemotherapy in FLT3 mutation positive R/R AML, these data suggest gilteritinib will have clinically meaningful therapeutic benefit in the treatment of patients with FLT3 mutation positive R/R AML.

The FDA's Assessment:

FDA notes that the median duration of CR+CRh of 7.4 months and the median duration of CR of 14.8 months is clinically meaningful for a drug with a survival benefit compared to standard of care therapies.

Persistence of Effect

The Applicant's Position:
No additional information beyond that provided in the results section of Study 2215-CL-0301 is provided in the current submission.

The FDA's Assessment:
See section on duration of response above.

Efficacy Results – Secondary or Exploratory Clinical Outcome Assessment (PRO) Endpoints

The Applicant's Position:
The change from baseline in BFI fatigue score, FACIT-Dys-SF and functional limitations subscales scores, FACT-Leu total score and dizziness and mouth sore subscales scores for cycle 2, day 1 were similar in the gilteritinib arm compared with the salvage chemotherapy arm. However, the majority of salvage chemotherapy patients finished the study by cycle 2 of treatment; due to the small sample size of the salvage chemotherapy arm, comparisons between the treatment arms should be interpreted with caution. The incidence of hospitalization was similar between the gilteritinib arm and the salvage chemotherapy arm (85.4% versus 79.8%). In both arms, the type of hospitalization was nonintensive care unit for most patients (96.2% in the gilteritinib arm and 92.9% in the salvage chemotherapy arm).

The FDA's Assessment:
FDA noted that the proportion of patients with follow-up PRO assessments even as early as Cycle 2 Day 1 was so disproportionate (231 (94%) on the gilteritinib arm vs 18 (15%) on the chemotherapy arm) as to obviate any meaningful comparison between arms, so these data were not evaluated further.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:
Not applicable.

The FDA's Assessment:

Impact of Poststudy Therapy on OS: As shown in Table 7, there was an imbalance between study arms in poststudy therapies, including HSCT for patients not in CR. Several additional analyses were performed to ensure that the difference in OS was not driven solely by the poststudy therapy. These additional analyses showed that the difference in OS between study arms was still significant when a) OS was censored at HSCT (Table 8); b) HSCT was used as a time-dependent covariate; c) patients who underwent HSCT were removed from the analysis;

and d) HSCT, intensive chemotherapy and alternative FLT3 inhibitor were used as binary (yes/no) independent covariates.

Subgroup Analysis of CR/CRh: In the subgroup analysis of CR/CRh in the original submission, it was noted that the response rate was low in the subgroups with a TKD mutation and in black patients. Table 18 shows the CR/CRh using the updated data in this final analysis.

Table 18 Study 0301 - CR/CRh by Subgroup

	N[a]	CR/CRh n, %	
AGE			
< 65 years	138	26	19%
>=65 years	105	29	28%
>= 75 years	28	7	25%
SEX			
Female	129	36	28%
Male	114	19	17%
RACE			
White	142	36	25%
Asian	69	18	26%
Black	13	0	0%
Other/Missing	19	1	5%
Ethnicity			
Not Hispanic Or Latino	217	54	25%
Hispanic Or Latino	12	0	0%
Unknown	14	1	7%
ECOG PS			
0-1	202	44	22%
>=2	41	11	27%
Region			
North America	110	23	21%
Europe	68	16	24%
Asia	65	16	25%
FLT3 Mutation Type			
FLT3-ITD Alone	215	49	23%
FLT3-TKD Alone	21	3	14%
FLT3-ITD and FLT3-TKD	7	3	43%
Relapse Type			
Primary Refractory	97	19	20%
Refractory Relapse	146	36	25%
Prior HSCT			
No	196	39	20%
Yes	47	16	34%

Source: FDA analysis
[a]Using CDx-positive patients from Study 0301

Clinical TL Review Comment: The results of the subgroup analysis again show no responses in black patients and in patients of Hispanic ethnicity; this may be explained by the low response rate and the small numbers of patients. A larger integrated analysis would be helpful. This updated analysis does show responses in patients with a TKD mutation. The uncertainty remaining from the subgroup analysis will be addressed by the pending PMR.

Resource Utilization: The Applicant reported no difference between study arms in the incidence of hospitalization or the duration of hospitalization (Study 0301 Clinical Study Report Table 38). FDA also evaluated the days of hospitalization per days of treatment exposure (H/EX) and found no significant difference between study arms; median H/EX 0.15 (range 0 - 1.50) for the gilteritinib arm and 0.21 (range 0 - 0.80) for the chemotherapy arm.

8.2. Integrated Review of Effectiveness

8.2.1. Assessment of Efficacy Across Trials

The Applicant's Position:
Not applicable. The assessment of efficacy for this application is based on 1 trial.

The FDA's Assessment:
Not applicable to this labeling revision.

8.2.2. Integrated Assessment of Effectiveness

The Applicant's Position:
Not applicable. The assessment of efficacy for this application is based on 1 trial.

The FDA's Assessment:
Not applicable to this labeling revision.

8.3. Review of Safety

The Applicant's Position [Module 2.7.4]:
The clinical development program for gilteritinib consists of studies in healthy volunteers, hepatic-impaired volunteers and patients with NSCLC, solid tumors, or AML. As of the final analysis data cutoff date of 17 Sep 2018, a total of 179 healthy subjects and 764 patients have received at least 1 dose of gilteritinib.

Overall, gilteritinib has a nonclinical safety pharmacology and toxicology profile that is acceptable for the treatment of patients with relapsed or refractory FLT3 mutation positive AML at the proposed therapeutic dose.

The integrated R/R AML safety population consisted of FLT3 mutation positive and negative patients from phase 1/2 studies 2215-CL-0101 and 2215-CL-0102 and the phase 3 study 2215-CL-0301.

In the integrated R/R AML safety population, in the integrated gilteritinib 120 mg group:

- 99.4% of patients had at least 1 TEAE, 93.4% of patients had at least 1 Grade 3 or higher TEAE and 80.9% of patients had at least 1 SAE. The most frequently occurring TEAEs, Grade 3 or higher TEAEs and SAEs were generally associated with the known pathophysiology of AML [O'Donnell et al, 2017].
- Based on investigator assessment, 83.1% of patients had at least 1 drug-related TEAE, 60.2% of patients had at least 1 Grade 3 or higher drug-related TEAE and 33.9% of patients had at least 1 drug-related SAE. The most frequently reported drug-related TEAEs included alanine aminotransferase (ALT) increased (25.4%), aspartate aminotransferase (AST) increased (24.5%) and anemia (20.1%). The most frequently reported Grade 3 or higher drug-related TEAEs included anemia (16.9%), febrile neutropenia (12.2%), thrombocytopenia (11.6%) and platelet count decreased (11.3%).
- 70.8% of patients died due to any cause and 29.8% of patients experienced TEAEs leading to death. AML was the most common TEAE leading to death (11.9%). TEAEs leading to death were considered drug-related by the investigator for 3.8% (12/319) of patients. In each of the cases where a patient experienced a drug-related TEAE leading to death, an alternative etiology other than gilteritinib treatment could plausibly explain the event that led to death.
- 21.9% of patients had TEAEs leading to withdrawal of treatment and 10.0% of patients had drug-related TEAEs leading to withdrawal of treatment based on investigator assessment. AML was the most frequently reported TEAE leading to withdrawal of treatment (2.8% of patients) and AST increased (1.3% of patients) and ALT increased and pneumonia (0.9% of patients, each) were the most common drug-related TEAE leading to withdrawal of treatment.

In general, increases in liver function tests, most notably ALT and AST, and elevations in creatine kinase were mostly Grade 1 or 2 in severity, were reversible upon drug interruption and seldom resulted in patient discontinuation from treatment. In the integrated gilteritinib 120 mg group, 6 patients (1.9% of patients) withdrew from treatment due to increases in AST, 5 patients (1.6% of patients) withdrew from treatment due to increases in ALT, and 1 patient (0.3% of patients) withdrew from treatment due to increases in creatine kinase. Elevations in creatine kinase were not consistently associated with attendant increases in serum aldolase. In the integrated gilteritinib 120 mg group, the percentage of patients experiencing a maximum postbaseline QTcF value > 450 to ≤ 480 msec was 30.6%, with 4.4% and 1.3% of patients experiencing a maximum postbaseline QTcF value of > 480 to ≤ 500 msec or > 500 msec, respectively. In the 2215-CL-0301 study, only 1 patient (0.4%) had a postbaseline QTcF value of > 500 msec, and no patients discontinued the study due to QT prolongation.

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

The safety profile of gilteritinib was similar for the integrated gilteritinib 120 mg group in both the R/R AML safety population and the subset of the integrated R/R AML safety population that was positive for FLT3 mutation. Based on an assessment of TEAE by subpopulations of demographic variables, no specific safety precautions are warranted by sex, age, or other demographic factors. The tolerability profile of gilteritinib in these ongoing studies appears to be similar to the integrated R/R AML safety population.

Important identified risks associated with gilteritinib treatment, based on the clinical data, include posterior reversible encephalopathy syndrome (PRES) and QT prolongation. Pancreatitis is an important potential risk associated with treatment with gilteritinib.

8.3.1. Safety Review Approach

The Applicant's Position:
The safety evaluations performed in the clinical studies conducted as part of the gilteritinib clinical development program were consistent with ICH guidelines. TEAEs and SAEs were defined according to ICH E2A guidelines. AEs were reported using the investigator's verbatim term and coded by the sponsor using Medical Dictionary for Regulatory Activities (MedDRA) terms. The events were graded using the National Cancer Institute-Common Terminology Criteria for Adverse Event [NCI-CTCAE] version 4.03.

The Applicant determined AEs of interest for gilteritinib to evaluate and monitor safety. AEs of interest were tabulated by system organ class (SOC) and PT.

The identified prespecified risks of interest for gilteritinib are: PRES, Cardiac Failure, Pericarditis and Pericardial Effusion, Arrhythmia Due to QT Prolongation, Creatine Phosphokinase Increased (NCI-CTCAE ≥ Grade 3) and Myopathy, Teratogenicity and Embryo-fetal Deaths, Liver Transaminase Increased, Differentiation Syndrome, Squamous Cell Carcinoma of the Skin, Gastrointestinal Obstruction, Gastrointestinal Perforation and Gastrointestinal Hemorrhage. Although not prespecified in the integrated summary of safety (ISS) SAP, pancreatitis and anaphylaxis were also included as AEs of interest based on the results of ongoing safety assessments. The summarization of AEs of interest was based on standardized MedDRA queries (SMQs), where available. If an SMQ was not available, then search strategies using a comprehensive list of PTs and/or Lower Level Terms (MedDRA, Version 19.1) or individual case reviews were used for detecting AEs of interest.

Concentration – Safety Modeling Analyses

An exploratory exposure-response model analysis evaluating gilteritinib was performed using pooled data sets from Studies 2215-CL-0101, 2215-CL-0102 and 2215-CL-0301 (final analysis

data cutoff of 17 Sep 2018). The relationships between gilteritinib plasma concentration and change from baseline in QTcF (ΔQTcF), creatine kinase (ΔCK), aspartate aminotransferase (ΔAST) and alanine aminotransferase (ΔALT) were assessed using linear/nonlinear mixed effects models within the SAS® NLMIXED procedure, with concentrations as a fixed effect and patients as a random effect. The population-predicted mean of safety variables were calculated using the final model without random effects.

A full description of the methods used for these modeling analyses is provided in the gilteritinib concentration-safety analysis report (Study 2215-PK-0006).

The FDA's Assessment:
FDA cannot substantiate the applicant's statement that "The most frequently occurring TEAEs, Grade 3 or higher TEAEs and SAEs were generally associated with the known pathophysiology of AML."

Given that FDA reviewed the integrated safety data including Studies 2215-CL-0101 and 2215-CL-0102 during the initial NDA review, and given that the patient population across studies is the same, FDA focused its safety analyses for this sNDA on the updated data from the randomized Study 2215-CL-0301. However, FDA agrees with the applicant's assessment of the integrated safety set (ISS) including patients with R/R AML treated with a starting dose of 120 mg gilteritinib across studies. Top-line safety results reported by the applicant for the ISS are similar to those seen on Study 0301 alone (see Table below).

Major safety events on Study 2215-CL-0301

Safety parameter	Gilteritinib (N=246)	Chemotherapy (N=109)
Total deaths	170 (69%)	81 (74%)
On-treatment deaths[1]	74 (30%)	17 (16%)
On-treatment fatal TEAEs[1]	71 (29%)	16 (15%)
All grade TEAEs	246 (100%)	107 (98%)
Gr ≥ 3 TEAEs	236 (96%)	94 (86%)
TESAEs	204 (83%)	33 (30%)

All-cause discontinuation	208 (85%)	90 (83%)
TEAE with discontinuation	58 (24%)	13 (12%)

Source: FDA analysis
[1]On or within 30 days after the last dose of gilteritinib
[2]Within 30 days following the first dose of gilteritinib

Given that patients on Study 2215-CL-0301 were predetermined to receive either low- or high-intensity chemotherapy prior to randomization, FDA examined top-line safety results in both patient populations, as shown in the Table below. The analysis focused on the first 30 days of therapy when most patients were still receiving treatment on both arms.

Major safety events on Study 2215-CL-0301 by predetermined treatment intensity, first 30 days

	Preselected Low Intensity Therapy		**Preselected High Intensity Therapy**	
	Gilteritinib (N=97)	**Chemotherapy (N=41)**	**Gilteritinib (N=149)**	**Chemotherapy (N=68)**
Total deaths	4 (4%)	7 (17%)	1 (1%)	5 (7%)
On-treatment deaths[1]	4 (4%)	7 (17%)	1 (1%)	5 (7%)
On-treatment fatal TEAEs[1]	4 (4%)	7 (17%)	1 (1%)	4 (6%)
All grade TEAEs	94 (97%)	37 (90%)	143 (96%)	68 (100%)
Gr ≥ 3 TEAEs	75 (77%)	31 (76%)	111 (74%)	59 (87%)
TESAEs	45 (46%)	18 (44%)	54 (36%)	10 (15%)
All-cause discontinuation	9 (9%)	28 (68%)	7 (5%)	47 (69%)
TEAE with discontinuation	2 (2%)	5 (12%)	5 (3%)	4 (6%)

Source: FDA analysis
[1]On or within 30 days after the last dose of gilteritinib
[2]Within 30 days following the first dose of gilteritinib

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

The higher incidence of total deaths and SAEs in patients preselected to receive low- vs high-intensity chemotherapy suggests that the two groups of patients represent distinct patient populations with unique safety profiles. Furthermore, the relative toxicity of gilteritinib compared to chemotherapy varies greatly between the intensity groups. For example, all-grade and grade ≥ 3 TEAEs are higher in the patients treated with high-intensity chemotherapy on the control arm when compared to patients preselected for high-intensity chemotherapy on the gilteritinib arm. However, in patients preselected for low-intensity therapy, gilteritinib appears to be more toxic than the low-intensity chemotherapy on the control arm. In summary, given different top-line comparative safety profiles in patients designated for high- versus low-intensity chemotherapy, FDA focused its analyses on these 2 populations separately and proposes to include 2 adverse event and laboratory tables in the PI based on predetermined treatment intensity.

Reviewer comments: Of note, the SAEs on the high-intensity chemotherapy arm are lower than the gilteritinib arm, but this is likely due to those patients being hospitalized for the duration of their salvage chemotherapy.

8.3.2. Review of the Safety Database

The Applicant's Position:
The safety profile for gilteritinib is derived from studies in healthy volunteers, hepatic-impaired volunteers and patients with either NSCLC, solid tumors or AML. As of the final analysis data cutoff date of 17 Sep 2018, a total of 179 healthy subjects and 764 patients have received at least 1 dose of gilteritinib.

The following safety populations were included in the overall safety evaluation presented in this document. Safety assessments and/or listings for ongoing studies and studies with healthy subjects or non-AML cancer patients will be provided in the supplemental NDA.

- **Integrated R/R AML Safety Population**: This population includes all patients who received at least 1 dose of study drug in Studies 2215-CL-0101, 2215-CL-0102 or 2215-CL-0301 with R/R AML. The study populations, dosing regimens and safety assessment plans for each of these 3 studies were similar (gilteritinib dosed on 28 day cycles, similar inclusion and exclusion criteria, similar definitions for AEs and other safety assessments), making these studies suitable for pooled analyses.
- **Study 2215-CL-0301 Safety Population**: This population includes all patients with R/R AML who received at least 1 dose of study drug in Study 2215-CL-0301. This population was used for subgroup analyses based on the stratification factors unique to this study and for a safety analysis of patients who had a dose escalation to gilteritinib 200 mg.

Since the 2215-CL-0301 gilteritinib arm comprised the majority of the integrated gilteritinib 120 mg group, no meaningful comparisons can be made between these 2 populations.

Overall Exposure

The integrated R/R AML safety population included a total of 522 patients who received at least 1 dose of gilteritinib and included 252 patients from Study 2215-CL-0101 (completed study), 24 patients from Study 2215-CL-0102 (completed study) and 246 patients from Study 2215-CL-0301 (final analysis data cutoff date: 17 Sep 2018) [Table 19]. Of those, 319 patients received a starting dose of gilteritinib 120 mg (including all 246 patients from Study 2215-CL-0301). In Study 2215-CL-0301, 109 patients received at least 1 dose of salvage chemotherapy.

Table 19 Number of Patients by Study Protocol and Treatment Group – Integrated R/R AML Safety Population

Study	Integrated Data†		Study 2215-CL-0301	
	Gilteritinib 120 mg	Gilteritinib Total	Gilteritinib 120 mg	Chemo
Controlled trials conducted for this indication				
2215-CL-0301	246	246	246	109
All other than controlled trials for this indication				
2215-CL-0101‡	69	252	0	0
2215-CL-0102‡	4	24	0	0
Total	319	522	246	109

AML: acute myeloid leukemia; Chemo: chemotherapy; ISS: integrated summary of safety; R/R: relapsed or refractory.
†Integrated data includes patients in Studies 2215-CL-0101, 2215-CL-0102 and 2215-CL-0301 who received at least 1 dose of gilteritinib 120 mg (gilteritinib 120 mg group) or any dose of gilteritinib (gilteritinib total group; doses ranging from gilteritinib 20 to 450 mg). ‡For patients with dose adjustments, dose groups were based on the initial dose.
Source: ISS.ADSL Table 13.1.1.3

In the integrated gilteritinib 120 mg group, the median average daily dose was 120 mg/day (ranging from 46 to 273 mg/day) and the median duration of exposure was 111 days (ranging from 4 to 1320 days) [Table 20]. The duration of exposure was ≥ 28 to < 84 days for 31.0% (99/319) of patients, ≥ 84 to <168 days for 27.3% (87/319) of patients and ≥ 168 days for 35.4% (113/319) of patients. The median number of dosing days for patients was 106 days, ranging from 4 to 1313 days. The median relative dose intensity was 100%, ranging from 39% to 227%. Dose increases were experienced by 35.4% (113/319) of patients and dose decreases were experienced by 25.7% (82/319) of patients. Overall, 47.3% (151/319) of patients experienced at least one day of gilteritinib dose interruption.

In Study 2215-CL-0301, because the majority of salvage chemotherapy patients finished the study after either completion of 1 cycle of treatment with a CRc or completion of 2 cycles of treatment, the duration of exposure (median [min, max]) was longer in the 2215-CL-0301 gilteritinib arm compared with the salvage chemotherapy arm (126 [4, 885] days versus 28 [5, 217] days) [Table 20]. Longer exposure durations were experienced by more patients in the

2215-CL-0301 gilteritinib arm compared with the salvage chemotherapy arm in the range of ≥ 84 to < 168 days (27.6% versus 5.5%) and ≥ 168 days (37.4% versus 3.7%).

Table 20 Study Drug Exposure – Integrated R/R AML Safety Population

	Integrated Data†		Study 2215-CL-0301		
	Gilteritinib 120 mg	Gilteritinib Total	Gilteritinib 120 mg		Chemo
	(N = 319)	(N = 522)	Overall (N = 246)	No Dose Escalation (N = 168)	(N = 109)
Duration of Exposure Days‡					
n	319	522	246	168	109
Mean (SD)	181.2 (199.8)	156.1 (190.5)	180.7 (168.5)	186.2 (183.1)	39.9 (37.0)
Median (min, max)	111.0 (4, 1320)	88.0 (3, 1320)	126.0 (4, 885)	116.0 (4, 885)	28.0 (5, 217)
Duration of Exposure Days‡, n (%)					
≤ 5	1 (0.3)	6 (1.1)	1 (0.4)	1 (0.6)	1 (0.9)
≥ 6 to < 28	19 (6.0)	60 (11.5)	10 (4.1)	10 (6.0)	10 (9.2)
≥ 28 to < 84	99 (31.0)	179 (34.3)	75 (30.5)	55 (32.7)	88 (80.7)
≥ 84 to < 168	87 (27.3)	131 (25.1)	68 (27.6)	38 (22.6)	6 (5.5)
≥ 168	113 (35.4)	146 (28.0)	92 (37.4)	64 (38.1)	4 (3.7)
Number of Dosing Days§					
n	319	521	246	168	109
Mean (SD)	173.6 (192.2)	146.9 (180.0)	172.7 (162.7)	177.1 (176.2)	9.5 (10.3)
Median (min, max)	106.0 (4, 1313)	85.0 (3, 1313)	114.0 (4, 885)	107.5 (4, 885)	6.0 (1, 70)
Dosing, n (%)					
Increases	113 (35.4)	171 (32.8)	78 (31.7)	0	8 (7.3)
Decreases	82 (25.7)	103 (19.7)	75 (30.5)	58 (34.5)	9 (8.3)
Interruptions	151 (47.3)	224 (42.9)	122 (49.6)	84 (50.0)	5 (4.6)
Cumulative Dose (mg)					
n	319	521	246	168	NA
Mean (SD)	21911.3 (25954.3)	20116.4 (25506.1)	20985.2 (19682.6)	19138.8 (19572.1)	--
Median (min, max)	13640.0 (480, 259800)	11880.0 (60, 259800)	13980.0 (480, 106200)	11140.0 (480, 106200)	--
Average Daily Dose (mg/day)¶					
n	319	521	246	168	NA
Table continued on next page					
Mean (SD)	127.2 (28.1)	143.6 (61.4)	123.9 (25.8)	110.6 (15.2)	--
Median (min, max)	120.0 (50, 290)	120.0 (20, 402)	120.0 (50, 192)	120.0 (50, 120)	--
Dose Intensity (mg/day)††					
n	319	521	246	168	NA
Mean (SD)	122.7 (30.1)	137.1 (60.4)	119.1 (28.2)	105.8 (19.3)	--
Median (min, max)	120.0 (46, 273)	120.0 (13, 400)	120.0 (46, 192)	120.0 (46, 120)	--

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

	Integrated Data†		Study 2215-CL-0301		
	Gilteritinib 120 mg	Gilteritinib Total	Gilteritinib 120 mg		Chemo
	(N = 319)	(N = 522)	Overall (N = 246)	No Dose Escalation (N = 168)	(N = 109)
Relative Dose Intensity (%)‡‡					
n	319	521	246	168	109
Mean (SD)	102.2 (25.1)	102.1 (26.4)	99.2 (23.5)	88.2 (16.1)	98.2 (35.1)
Median (min, max)	100.0 (39, 227)	100.0 (23, 292)	100.0 (39, 160)	100.0 (39, 100)	99.6 (10, 322)

AML: acute myeloid leukemia; Chemo: chemotherapy; HSCT: hematopoietic stem cell transplant; ISS: integrated summary of safety; Max: maximum; Min: minimum; R/R: relapsed or refractory.
Note: The calculation of duration of exposure for 13 patients with on-study HSCT did not exclude the on-study HSCT period for Study CL-0101. The HSCT information in Study CL-0102 was not collected.
†Integrated data includes patients in Studies 2215-CL-0101, 2215-CL-0102 and 2215-CL-0301 who received at least 1 dose of gilteritinib 120 mg (gilteritinib 120 mg group) or any dose of gilteritinib (gilteritinib total group; doses ranging from gilteritinib 20 to 450 mg). ‡Defined as (last date of exposure) – (first dose date) + 1 – (on-study HSCT period for patients who underwent on-study HSCT. §Defined as the number of days with nonzero dosing. ¶Defined as (cumulative dose) / (number of dosing days. ††Defined as (cumulative dose/ duration of exposure) for gilteritinib. ‡‡Defined as (dose intensity/planned dose intensity) *100%.
Source: ISS.ADSL Tables 13.2.1.2 and 13.2.1.2.1

Dose Escalation to Gilteritinib 200 mg in Study 2215-CL-0301

In Study 2215-CL-0301, all patients randomized to the gilteritinib arm began at a starting dose of 120 mg but had the option of receiving an escalated dose of 200 mg based on lack of efficacy, as assessed by the investigator. However, the majority of patients in the 2215-CL-0301 gilteritinib arm (168/246) did not experience a dose escalation and generally had similar exposure to study drug as the overall 2215-CL-0301 gilteritinib arm.

For patients in Study 2215-CL-0301 who were administered an escalated dose of gilteritinib 200 mg based on lack of efficacy at the starting dose of gilteritinib 120 mg, the median number of dosing days for patients before dose escalation was 42.0 days, ranging from 26 to 531 days. The median number of dosing days for patients after dose escalation was 48.0 days, ranging from 1 to 756 days.

The FDA's Assessment:

FDA agrees with the applicant's assessment of median duration of exposure in the ISS across Studies 2215-CL-0101, 2215-CL-0102, and 2215-CL-0301. FDA performed an independent analysis of exposure based on the data submitted for Study 2215-CL-0301 and the results are listed in the Table below.

Exposure on Study 2215-CL-0301

Duration of Therapy	Gilteritinib (N=246)	Chemotherapy (N=109)
Median (range), mos	4.1 (0.1-29.1)	0.9 (0.2-7.1)
0-<3	95 (39%)	101 (93%)
3-<6	67 (27%)	6 (6%)
6-<9	34 (14%)	2 (2%)
9-<12	15 (6%)	0
≥12	35 (15%)	0
Median (range), cy	5 (1-33)	1 (1-7)

Source: FDA analysis

FDA agrees with the applicant's assessment that exposure was longer on the gilteritinib arm. FDA also performed an analysis of exposure on both arms by predetermined treatment intensity.

Exposure by preselected treatment intensity

Duration of Therapy	Preselected Low Intensity Therapy		Preselected High Intensity Therapy	
	Gilteritinib (N=97)	Chemotherapy (N=41)	Gilteritinib (N=149)	Chemotherapy (N=68)
Median (range), mos	4.2 (0.1-25.7)	0.9 (0.2-7.1)	4.0 (0.3-29.1)	0.9 (0.2-3.4)
0-<3	37 (38%)	34 (83%)	58 (39%)	67 (99%)
3-<6	23 (24%)	5 (12%)	44 (30%)	1 (2%)
6-<9	18 (19%)	2 (5%)	16 (11%)	0
9-<12	7 (7%)	0	8 (5%)	0
≥12	12 (12%)	0	23 (15%)	0
Median (range), cy	5 (1-27)	1 (1-7)	5 (1-33)	1 (1-2)

Source: FDA analysis

Even though the low-intensity therapies used on the control arm were given in continuous cycles until disease progression or excess toxicity, it is notable that the duration of exposure was still only a median of 1 cycle (range 1-7). Therefore, FDA focused all comparative safety analyses on the first 30 days of therapy. Beyond 30 days, FDA considered only toxicities on the gilteritinib arm that were more common or worsened in severity over time.

FDA requested that the applicant perform an analysis of dose intensity by treatment cycle for the gilteritinib arm on Study 2215-CL-0301 to assess tolerability over time. The results are displayed in the Table below.

Summary of relative dose intensity of gilteritinib by cycle

Cycle	Subjects (n)	ASP2215 (N=246) Relative Dose Intensity		
		<80%	80%-120%	>120%
1	(b) (6)	5/246 (2.0%)	241/246 (98.0%)	0
2		28/230 (12.2%)	160/230 (69.6%)	42/230 (18.3%)
3		34/192 (17.7%)	108/192 (56.3%)	50/192 (26.0%)
4		32/149 (21.5%)	81/149 (54.4%)	36/149 (24.2%)
5		31/120 (25.8%)	61/120 (50.8%)	28/120 (23.3%)
6		28/106 (26.4%)	54/106 (50.9%)	24/106 (22.6%)
7		24/95 (25.3%)	52/95 (54.7%)	19/95 (20.0%)
8		22/81 (27.2%)	46/81 (56.8%)	13/81 (16.0%)
9		21/70 (30.0%)	39/70 (55.7%)	10/70 (14.3%)
10		18/54 (33.3%)	31/54 (57.4%)	5/54 (9.3%)
11		15/52 (28.8%)	32/52 (61.5%)	5/52 (9.6%)
12		16/45 (35.6%)	25/45 (55.6%)	4/45 (8.9%)
>12		14/41 (34.1%)	23/41 (56.1%)	4/41 (9.8%)

Source: Module 1.11.3, Response to January 7, 2019 Request

Reviewer comments: The treatment intensity results indicate that tolerability of gilteritinib declined over time. In the first 3 treatment cycles, < 20% of patients received < 80% relative dose intensity per cycle. However, in cycles 4 and beyond, an increasing number of patients received < 80% dose relative dose intensity. Beyond cycle 12, 34% of patients received < 80% relative dose intensity. Well-tolerated therapies generally have > 80% relative dose intensity per cycle.

Relevant characteristics of the safety population:

The Applicant's Position:

The demographic and baseline characteristics for the SAF population were similar to those for the ITT. In the integrated gilteritinib 120 mg group, the median age was 61.0 years, with 42.6% (136/319) of patients aged ≥ 65 years. In this population, 53.3% (170/319) of patients were female, 65.5% (203/319) were White, 23.9% (74/319) were Asian, 5.5% (17/319) were Black or African American and 3.5% (11/319) were Other. A baseline ECOG status of 0 or 1 was reported for the majority of patients with a status of 1 reported for 50.2% (160/319) of patients and a status of 0 reported for 31.3% (100/319) of patients. Median weight and height were 71.0 kg and 167.0 cm, respectively.

There were no meaningful differences in demographic and baseline characteristics between the 2215-CL-0301 gilteritinib and salvage chemotherapy treatment arms.

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

The FDA's Assessment:

Given the differences in safety profile by predetermined treatment intensity, FDA analyzed baseline demographics in the SAF population by predetermined treatment intensity. Results are displayed in the Table below.

Key demographics safety population Study 2215-CL-0301 by predetermined treatment intensity

Variable		Preselected Low Intensity Therapy		Preselected High Intensity Therapy	
		Gilteritinib (N=97)	Chemotherapy (N=41)	Gilteritinib (N=149)	Chemotherapy (N=68)
Age (years)	Median (range) ≥ 65 ≥ 75	70 (26-84) 65 (67%) 24 (25%)	68 (28-85) 27 (66%) 9 (22%)	57 (20-76) 41 (28%) 4 (3%)	54 (19-78) 17 (25%) 2 (3%)
Gender	Male Female	43 (44%) 54 (56%)	15 (37%) 26 (63%)	73 (49%) 76 (51%)	33 (49%) 35 (52%)
Race	White Asian Black or AA Other/unk	59 (61%) 26 (27%) 3 (3%) 9 (9%)	21 (51%) 17 (42%) 0 3 (7%)	85 (57%) 43 (29%) 11 (7%) 10 (7%)	43 (63%) 12 (18%) 7 (10%) 6 (9%)
ECOG PS	Median (range)	1 (0-2)	1 (0-2)	1 (0-3)	1 (0-3)
Pre-selected chemo	Aza/FLAG-IDA LDAC/MEC	N/A N/A	25 (61%) 16 (39%)	N/A N/A	40 (59%) 28 (41%)
FLT3 mutation	ITD alone TKD alone ITD+TKD Other	83 (86%) 14 (14%) 0 0	38 (93%) 3 (7%) 0 0	132 (89%) 7 (5%) 7 (5%) 3 (2%)	61 (90%) 6 (9%) 0 1 (1%)
Cytogenetic risk	Intermediate Poor Favorable Missing	69 (71%) 12 (12%) 4 (4%) 12 (12%)	27 (66%) 4 (10%) 0 10 (24%)	112 (75%) 14 (9%) 0 23 (15%)	51 (75%) 6 (9%) 1 (2%) 10 (15%)
Secondary AML	Yes	20 (21%)	4 (10%)	19 (13%)	4 (6%)
Primary refractory	Yes	41 (42%)	18 (44%)	57 (38%)	24 (35%)
Prior HSCT	Yes	18 (19%)	8 (20%)	29 (19%)	13 (19%)
Prior FLT3i	Yes	13 (13%)	5 (12%)	19 (13%)	6 (9%)

Source: FDA analysis

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Reviewer comments: FDA notes that the median age is substantially higher in patients preselected for low-intensity chemotherapy. Most patients treated with low-intensity chemotherapy received azacitidine and most patients treated with high-intensity chemotherapy received FLAG-IDA. The number of patients with secondary AML remains higher on the gilteritinib arm in both patient subsets. Interestingly, both patient subsets were equally likely to have underwent prior HSCT.

Adequacy of the safety database:

The Applicant's Position:
The gilteritinib safety database reflects extensive safety-related data captured throughout the course of development and provides sufficient information to characterize the safety profile of gilteritinib. As of the data cutoff date of 17 Sep 2018, a total of 179 healthy subjects and 764 patients have received at least 1 dose of gilteritinib. (b) (4) Overall, the Applicant believes that the safety database is adequate to characterize the safety profile of gilteritinib.

The FDA's Assessment:
FDA agrees with the applicant's assessment.

8.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:
No issues regarding data integrity and submission quality.

The FDA's Assessment:
The data integrity and submission quality are sufficient for FDA review.

Categorization of Adverse Event

The Applicant's Position:
The categorization of AEs is presented in Section 8.3.1.

The FDA's Assessment:
FDA agrees with the applicant's AEs of special interest listed in Section 8.3.1. In addition, FDA found that various eye disorders, neuropathy, and acute neutrophilic dermatosis occurred

more frequently on the gilteritinib arm of Study 0301; thus, these were added as AEs of special interest.

Routine Clinical Tests

The Applicant's Position:
As part of the overall safety evaluation of gilteritinib, routine clinical laboratory parameters were collected for patients. These included:

- Hematology laboratory parameters (absolute neutrophil count [ANC], hemoglobin and platelets)
- Hematology laboratory parameter shifts from baseline to worst postbaseline based on NCI-CTCAE (v4.03) for events that were ≥ Grade 3
- Chemistry laboratory parameters with NCI-CTCAE (v4.03) Grades 3/4 including routine measures of liver function (ALT, AST, alkaline phosphatase and bilirubin), with additional information on liver function tests
- Chemistry laboratory parameter shifts from baseline to worst postbaseline based on NCI-CTCAE (v4.03) for events that were ≥ Grade 3
- Coagulation parameters
- Urinalysis parameters
- Listings for clinical laboratory parameters for ongoing AML studies.

The FDA's Assessment:
FDA agrees with the applicant's assessment.

8.3.4. Safety Results

Deaths

The Applicant's Position:
In the integrated gilteritinib 120 mg group, 70.8% (226/319) of patients died due to any cause. In the integrated gilteritinib 120 mg group, 29.8% (95/319) of patients experienced TEAEs leading to death. AML was the most common TEAE leading to death (11.9% [38/319]), followed by septic shock (2.2% [7/319]), sepsis (1.9% [6/319]), pneumonia (1.6% [5/319]) and cardiac arrest (1.3% [4/319]); all other TEAEs leading to death were reported in < 1.0% of patients in the integrated gilteritinib 120 mg group.

TEAEs leading to death were considered drug related by the investigator for 3.8% (12/319) of patients in the integrated gilteritinib 120 mg group. These included 3 events of pneumonia (0.9%), 2 events each of large intestine perforation and septic shock (0.6%) and 1 event each of cardiac failure congestive, cellulitis, cerebral hemorrhage, depressed level of consciousness,

intestinal ischemia, neutropenia, respiratory failure and ventricular fibrillation (0.3% each). These 12 patients were considered by the sponsor to have alternative etiologies for these TEAEs leading to death other than gilteritinib use.

The FDA's Assessment:
FDA performed an assessment of deaths in patients in the SAF population of Study 0301. The Table below indicates major death events on Study 0301 by preselected treatment intensity.

Deaths on Study 2215-CL-0301 by predetermined treatment intensity

	Preselected Low Intensity Therapy		Preselected High Intensity Therapy		All patients	
	Gilteritinib (N=97)	Chemotherapy (N=41)	Gilteritinib (N=149)	Chemotherapy (N=68)	Gilteritinib (N=246)	Chemotherapy (N=109)
Total deaths	74 (76%)	32 (78%)	96 (64%)	49 (72%)	170 (69%)	81 (74%)
30-day mortality[1]	4 (4%)	7 (17%)	1 (1%)	5 (7%)	5 (2%)	12 (11%)
60-day mortality[2]	12 (12%)	10 (24%)	7 (5%)	9 (13%)	19 (8%)	19 (17%)
On-treatment deaths[3]	44 (45%)	11 (27%)	30 (20%)	6 (9%)	74 (30%)	17 (16%)
On-treatment fatal ARs[3]	2 (2%)	1 (2%)	3 (2%)	3 (4%)	12 (5%)	4 (4%)

Source: FDA analysis
[1]Within 30 days following the first dose of treatment
[2]Within 60 days following the first dose of treatment
[3]On or within 30 days after the last dose of treatment

Reviewer comments: It is notable that the 30- and 60-day mortality rates are remarkably lower on the gilteritinib arm compared to the chemotherapy arm, regardless of predetermined treatment intensity. The decrease in early deaths may contribute to much of the OS benefit seen with gilteritinib, despite CR rates that were not substantially different overall between the arms.

FDA reviewed individual patient narratives from the 91 patients with on-treatment deaths on both arms to confirm the causes of death. In general, the narratives were well-written.

Of the 74 on-treatment deaths on the gilteritinib arm, causes of death were primary disease (n=57), intercurrent condition (n=12), and adverse drug reactions (n=5) including cardiac arrest

(n=3), differentiation syndrome (n=1), and pancreatitis (n=1). Of the 17 on-treatment deaths on the control arm, causes of death were primary disease (n=13) and adverse drug reactions (n=4) including one each of hemorrhagic stroke, multiple organ failure, respiratory failure, and septic shock. FDA agreed with the applicant's assessment of causality for most deaths, except for the 24 listed in the Table below.

Study 2215-CL-0301 – FDA-adjudicated deaths within 30 days that were discrepant with applicant adjudication

Arm	Subject (b) (6)	Death Day	Days since last dose	FDA Root COD	Applicant Root COD
Gilteritinib		162	4	Adverse reaction (cardiac arrest)	Primary disease
Gilteritinib		287	1	Adverse reaction (cardiac arrest)	Intercurrent condition
Gilteritinib		198	4	Primary disease	Adverse reaction (infection)
Gilteritinib		119	17	Primary disease	Adverse reaction (infection)
Gilteritinib		70	13	Primary disease	Adverse reaction (lung infection)
Gilteritinib		72	12	Primary disease	Adverse reaction (respiratory infection)
Gilteritinib		121	9	Primary disease	Adverse reaction (infectious colitis)
Gilteritinib		69	7	Primary disease	Adverse reaction (septic shock)
Gilteritinib		35	7	Primary disease	Adverse reaction (ARDS)
Gilteritinib		80	2	Primary disease	Adverse reaction (septic shock)
Gilteritinib		407	1	Primary disease	Adverse reaction (infective endocarditis)
Gilteritinib		42	1	Primary disease	Adverse reaction (cellulitis)
Gilteritinib		6	0	Primary disease	Adverse reaction (PNA)
Gilteritinib		75	0	Primary disease	Adverse reaction (septic shock)
Gilteritinib		9	0	Primary disease	Adverse reaction (sepsis)
Gilteritinib		186	0	Primary disease	Adverse reaction (chest infection)

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Arm	Subject	Death Day	Days since last dose	FDA Root COD	Applicant Root COD
Gilteritinib	(b) (6)	127	0	Primary disease	Adverse reaction (ICH)
Gilteritinib		74	1	Intercurrent condition	Adverse reaction (aspiration PNA)
Chemotherapy		176	23	Primary disease	Adverse reaction (digestive bleeding)
Chemotherapy		22	21	Primary disease	Adverse reaction (sepsis)
Chemotherapy		42	20	Primary disease	Adverse reaction (sepsis)
Chemotherapy		20	14	Primary disease	Adverse reaction (sepsis)

Source: FDA analysis
Abbreviations: ARDS, acute respiratory distress syndrome; CHF, congestive heart failure; COD, cause of death; DS, differentiation syndrome; ICH, intracranial hemorrhage; PNA, pneumonia

As per the Table above, 2 cases that the applicant designated as due to primary disease (n=1) or intercurrent condition (n=1) were deemed at least possibly related to an adverse drug reaction of gilteritinib. These case narratives are described in detail below. FDA assessed primary disease as the root cause of death for cases of infection or hemorrhage when active AML was verified using the narratives and/or laboratory data (n=15 cases discrepant with the applicant on the gilteritinib arm and 4 cases on the chemotherapy arm; see Table above). Furthermore, FDA deemed one case related to an intercurrent condition when a patient died of aspiration pneumonia, while the Sponsor considered this an adverse reaction.

Narratives for patients listed in the Table above with deaths at least possibly related to gilteritinib, when discrepant with the applicant's assessment, are listed below.

Subject (b) (6): This was a 74-year-old man with a history of hyperlipidemia, atherosclerosis, chronic obstructive pulmonary disease, type 2 diabetes mellitus, hypertension, congestive heart failure, and atrial fibrillation who was treated with gilteritinib after being preselected for low-intensity chemotherapy. On day 158 of therapy, the patient had cardiac arrest at home and was brought to the hospital by emergency medical services. He apparently had 30 minutes without cardiopulmonary resuscitation. It was noted that at home, the patient was chronically hypoxic and on oxygen. The patient was intubated and unresponsive. He developed acute kidney injury post cardiac arrest, hyperkalemia, AML progression, and anoxic brain injury. He was transferred to an intensive care unit and placed on a hypothermia protocol but developed persistent coma. Support was discontinued, and the patient expired. ANC on last check normal, but he did have blasts in peripheral blood and in the marrow on last check.

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Reviewer comments: Although this patient clearly had comorbidities and active AML, he died of cardiac arrest at home while still on active therapy with gilteritinib, a medication with known QT prolonging potential. Therefore, FDA considers this death to be at least possibly related to gilteritinib.

Subject (b) (6): This was a 67-year-old man who received gilteritinib after being preselected for high-intensity chemotherapy. On day 287, the patient experienced cardiac arrest that was deemed not related. The patient died on the same day due to cardiac arrest that was suspected by the investigator to be related to an arrhythmia due to electrolyte disturbances. FDA could not rule out the possibility that gilteritinib may have contributed to this cardiac arrest.

Serious Adverse Events

The Applicant's Position:
In the integrated gilteritinib 120 mg group, 80.9% (258/319) of patients experienced at least 1 SAE. The most frequently reported SAEs by MedDRA PT were febrile neutropenia (29.8% [95/319]), AML (13.5% [43/319]), pyrexia (13.2% [42/319]) and pneumonia (12.2% [39/319]). When adjusted by patient-year, the following SAEs were numerically higher in the 2215-CL-0301 gilteritinib arm (patient-year, 121.7) compared with the salvage chemotherapy arm (patient-year, 11.9): ALT increased (0.14 events per patient-year vs no events) and pyrexia (0.35 events per patient-year vs 0.17 events per patient-year).

Drug-related Serious Adverse Events as Assessed by the Investigator

In the integrated gilteritinib 120 mg group, 33.9% (108/319) of patients experienced at least 1 SAE considered drug related by the investigator. The most frequently reported drug-related SAEs by MedDRA PT were febrile neutropenia (7.5% [24/319]), ALT increased (3.4% [11/319]) and AST increased (3.1% [10/319]).

When adjusted by patient-year, the following drug-related SAEs were numerically higher in the 2215-CL-0301 gilteritinib arm (patient-year, 121.7) compared with the salvage chemotherapy arm (patient-year, 11.9): ALT increased (0.12 events per patient-year vs no events) and pyrexia (0.02 events per patient-year vs no events).

Drug-related Serious Adverse Events as Assessed by the Sponsor

As assessed by the sponsor, the most frequent nonhematological drug-related SAEs (≥5%) reported in patients were dyspnea (9%), transaminase increased (5%), syncope (5%) and noninfectious diarrhea (5%).

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The FDA's Assessment:

FDA disagrees with the applicant's assessment of SAEs by patient-years. FDA performed an analysis of all treatment-emergent SAEs (TESAEs) and TESAEs by treatment intensity within the first 30 days of starting therapy on both arms, as well as TESAEs beyond 30 days of therapy on the gilteritinib arm of Study 0301.

Note that AEs followed by a "" in this section denote grouped terms defined in Appendix 14.4.

A TESAE occurring within 30 days after the last dose of gilteriitnib was reported for 204 (83%) of patients on the gilteritinib arm and 33 (30%) on the chemotherapy arm. The most frequently occurring (≥ 5%) TESAEs on the gilteritinib arm included febrile neutropenia (31%), pneumonia* (22%), sepsis* (17%), fever (13%), dyspnea* (9%), transaminase increased* (7%), renal impairment* (7%), and infectious diarrhea* (5%).

Considering only the first 30 days on therapy, TESAEs occurred in 99 (40%) of patients on the gilteritinb arm and 28 (26%) on the chemotherapy arm. The most frequently occurring (≥ 5%) TESAEs during the first 30 days of therapy are included in the Table below, listed by preselected treatment intensity and overall.

TESAEs (≥ 5%) in first 30 days of therapy on Study 2215-CL-0301 by preselected treatment intensity and overall

PT/Grouped term	Preselected Low Intensity Therapy		Preselected High Intensity Therapy		All patients	
	Gilteritinib (N=97)	Chemotherapy (N=41)	Gilteritinib (N=149)	Chemotherapy (N=68)	Gilteritinib (N=246)	Chemotherapy (N=109)
Total TESAEs	42 (43%)	18 (44%)	53 (36%)	12 (18%)	99 (40%)	28 (26%)
Febrile neutropenia	16 (17%)	3 (7%)	18 (12%)	4 (6%)	34 (14%)	7 (6%)
Pneumonia*	7 (7%)	2 (5%)	7 (5%)	3 (4%)	14 (6%)	5 (5%)
Sepsis*	5 (5%)	0	4 (3%)	7 (10%)	9 (4%)	7 (6%)
Fever	2 (2%)	1 (2%)	9 (6%)	0	11 (4%)	1 (1%)

Source: FDA analysis
*Grouped terms (see Appendix 14.4)

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In patients preselected for low-intensity chemotherapy, the only SAEs occurring ≥ 2% more frequently on the gilteritinib arm in the first 30 days were febrile neutropenia (17% vs 7%), pneumonia* (7% vs 5%), sepsis* (5% vs 0%), transaminase increased* (3% vs 0%), myalgia/arthralgia* (2% vs 0%), mucositis* (2% vs 0%), and DIC (2% vs 0%). In patients preselected for high-intensity chemotherapy, the only SAEs occurring ≥ 2% more frequently on the gilteritinib arm in the first 30 days were febrile neutropenia (12% vs 6%), pyrexia (6% vs 0%), transaminase increased* (3% vs 0%), thrombocytopenia* (3% vs 0%), neutrophil count decreased (3% vs 0%), and hypotension (2% vs 0%).

Reviewer comments: As expected, SAEs were higher for patients preselected for low-intensity therapy. While pneumonia and sepsis were more common on the gilteritinib arm in patients preselected for low-intensity therapy, the incidences were the roughly the same or lower on the gilteritinib arm in patients preselected for high-intensity therapy.

Beyond 30 days, TESAEs occurred in 181 (74%) of patients on the gilteritinib arm, including 79 (81%) of those preselected for low-intensity chemotherapy and 102 (69%) preselected for high-intensity chemotherapy. SAEs beyond 30 days on the gilteritinib arm that were ≥ 5% (total patients; preselected for low- vs high-intensity chemotherapy) were febrile neutropenia (22%; 21% vs 23%), pneumonia* (18%; 23% vs 15%), sepsis* (15%; 18% vs 13%), fever (10%; 10% vs 9%), dyspnea* (8%; 4% vs 11%), and renal impairment* (6%; 6% vs 6%). TESAEs that only made the ≥ 5% cutoff in the low-intensity patients were transaminase increased* (9%) and noninfectious diarrhea* (6%). A TESAE that only made the ≥ 5% cutoff in the high-intensity patients was infectious diarrhea* (6%).

Reviewer comments: Overall, the incidence of TESAEs increased over time on the gilteritinib arm, as may be expected for a continuously administered therapy for R/R AML. Pneumonia, sepsis, and transaminase increased were more common in the patients preselected for low-intensity chemotherapy, as one might expect for this older patient population.

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

Treatment-emergent Adverse Events Leading to Withdrawal of Treatment

In the integrated gilteritinib 120 mg group, 21.9% (70/319) of patients reported TEAEs leading to withdrawal of treatment and 10.0% (32/319) of patients reported drug-related TEAEs leading to withdrawal of treatment. The most frequently reported TEAEs leading to withdrawal of treatment were AML (2.8% [9/319]), AST increased (1.9% [6/319]), ALT increased and lung infection (1.6% [5/319], each) and sepsis, AML recurrent and septic shock (1.3% [4/319], each); all other TEAEs leading to withdrawal of treatment were reported in ≤ 3/319 (0.9%) patients each.

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When adjusted by patient-year, the following TEAEs leading to withdrawal of treatment were numerically higher in the 2215-CL-0301 gilteritinib arm (patient-year, 121.7) compared with the salvage chemotherapy arm (patient-year, 11.9): AST increased (0.04 events per patient-year vs no events), ALT increased (0.03 events per patient-year vs no events) and sepsis and pneumonia (0.02 events per patient-year vs no events, each).

Drug-related Treatment-emergent Adverse Events Leading to Withdrawal of Treatment as Assessed by the Investigator
In the integrated gilteritinib 120 mg group, 10.0% (32/319) of patients reported drug-related TEAEs leading to withdrawal of treatment as assessed by the investigator. The most frequently reported drug-related TEAEs leading to withdrawal of treatment as assessed by the investigator were AST increased (1.3% [4/319]) and ALT increased and pneumonia (0.9% [3/319], each); all other TEAEs leading to withdrawal of treatment were reported in ≤ 2/319 (0.6%) of patients each.

When adjusted by patient-year, the following drug-related TEAEs leading to withdrawal of treatment were numerically higher in the 2215-CL-0301 gilteritinib arm (patient-year, 121.7) compared with the salvage chemotherapy arm (patient-year, 11.9): AST increased (0.03 events per patient-year vs no events), and ALT increased, pneumonia and septic shock (0.02 events per patient-year vs no events, each).

Drug-related Treatment-emergent Adverse Events Leading to Withdrawal of Treatment as Assessed by the Sponsor
In the integrated gilteritinib 120 mg group, 5.0% (16/319) of patients reported drug-related TEAEs leading to withdrawal of treatment as assessed by the sponsor. The most frequently reported drug-related TEAEs leading to withdrawal of treatment were AST increased (1.9% [6/319]) and ALT increased (1.6% [5/319]); all other drug-related TEAEs leading to withdrawal of treatment were reported in ≤ 2/319 (0.6%) of patients each.

Drug-related TEAEs leading to withdrawal of treatment were numerically higher in the 2215-CL-0301 gilteritinib arm (5.3% [13/246]) compared with the salvage chemotherapy arm (no patients); however, the number of events was too small to make any meaningful comparisons between groups.

The FDA's Assessment:
FDA disagrees with the applicant's assessment of TEAEs leading to withdrawal of treatment between the arms by patient-years. FDA performed an analysis of all TEAEs leading to withdrawal and TEAEs leading with withdrawal by treatment intensity within the first 30 days of starting therapy on both arms, as well as TEAEs leading to withdrawal beyond 30 days of therapy on the gilteritinib arm of Study 0301.

Note that AEs followed by a "" in this section denote grouped terms defined in Appendix 14.4.

TEAEs leading to withdrawal occurred in 58 (24%) of patients on the gilteritinib arm and 13 (12%) of patients on the chemotherapy arm. The most common TEAEs leading to withdrawal of gilteritinib are shown in the Table below in decreasing order. The table includes only those events that occurred in ≥ 1% of subjects.

Study 2215-CL-0301 – AEs Leading to Discontinuation in ≥ 1% Patients

Preferred Term	Gilteritinib (N=246)	Chemotherapy (N=109)
Pneumonia*	9 (4%)	1 (1%)
Sepsis*	7 (3%)	1 (1%)
Transaminase increased*	6 (2%)	0
Dyspnea*	4 (2%)	3 (3%)

Source: FDA analysis
* Includes grouped terms (see Appendix 14.4)

Considering only the first 30 days on therapy, TEAEs leading to discontinuation occurred in 7 (3%) of patients on the gilteritinb arm and 9 (8%) on the chemotherapy arm. No TEAE (or grouped term) led to withdrawal in > 1 patient on the gilteritinib arm during the first 30 days of therapy.

Beyond 30 days, TEAEs leading to dose discontinuation occurred in 51/246 (21%) of patients on the gilteritinib arm, including 19/97 (20%) of those preselected for low-intensity chemotherapy and 32/149 (21%) preselected for high-intensity chemotherapy. TEAEs leading to discontinuation beyond 30 days on the gilteritinib arm in ≥ 1% of patients (total patients; preselected for low- vs high-intensity chemotherapy) were pneumonia* (3%; 2% vs 4%), sepsis* (3%; 5% vs 1%), transaminase increased* (2%; 1% vs 3%), and dyspnea* (1%; 2% vs 1%).

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:
In the integrated gilteritinib 120 mg group, dose increases were experienced by 35.4% (113/319) of patients and dose decreases were experienced by 25.7% (82/319) of patients. Overall, 47.3% (151/319) of patients experienced at least one day of gilteritinib dose interruption.

In the integrated gilteritinib 120 mg group, 12.9% (41/319) of patients experienced TEAEs leading to dose reduction. Of those patients, 11.0% (35/319) experienced TEAEs leading to dose reduction that were attributed by the investigator as drug-related. Treatment-emergent

AEs leading to drug interruption were experienced by 45.1% (144/319) of patients and drug-related TEAEs leading to dose interruption were experienced by 30.4% (97/319) of patients.

The FDA's Assessment:
FDA disagrees with the applicant's assessment of TEAEs leading to dose interruption and reduction. FDA performed an analysis of TEAEs leading to dose interruption and reduction on Study 0301. Note that AEs followed by a "*" in this section denote grouped terms defined in Appendix 14.4.

Dose interruption

TEAEs leading to dose interruption occurred in 112 (46%) of patients on the gilteritinib arm and 5 (5%) of patients on the chemotherapy arm of Study 0301. The most common TEAEs leading to interruption of gilteritinib are shown in the Table below in decreasing order. The table includes only those events that occurred in > 2% of subjects on the gilteritinib arm of Study 2215-CL-0301.

TEAEs leading to dose interruption (> 2%) on Study 2215-CL-0301

PT/Grouped term	Gilteritinib (N=246)	Chemotherapy (N=109)
Transaminase increased*	27 (11%)	0
Febrile neutropenia	19 (8%)	1 (1%)
Pneumonia*	12 (5%)	1 (1%)
Fever	9(4%)	1(1%)
Sepsis*	8 (3%)	1 (1%)
Thrombocytopenia	6 (2%)	1 (1%)
Myositis*	6 (2%)	0

Source: FDA analysis
*Includes grouped terms (see Appendix 14.4)

Reviewer comments: It is not surprising that treatment interruptions were much more common for the continuously-administered gilteritinib, when compared to the short-course therapies on the control arm, particularly given the imbalance in exposure duration between the arms.

Dose reduction
Dose reductions due to TEAEs occurred in 35 (14%) of patients on the gilteritinib arm and 1 (1%) of patients on the chemotherapy arm. The most common TEAEs leading to dose reductions of gilteritinib are shown in the Table below in decreasing order. The table includes only those events that occurred in > 1% of subjects on Study 2215-CL-0301.

TEAEs (>1%) leading to dose reductions on Study 2215-CL-0301

Preferred Term	Gilteritinib (N=246)	Chemotherapy (N=109)
Neutropenia*	7 (3%)	0
Transaminase increased*	6 (2%)	1 (1%)
ECG QT prolonged	3 (1%)	0
Thrombocytopenia	3 (1%)	0
Rash*	3 (1%)	0

Source: FDA analysis
*Includes grouped terms (see Appendix 14.4)

Reviewer comments: Although cytopenias are not thought to be ADRs of gilteritinib, thrombocytopenia has led to dose interruptions and reductions of gilteritinib and neutropenia led to dose reductions in a small percentage of patients.

Significant Adverse Events

The Applicant's Position:
TEAEs leading to intervention, including withdrawal of treatment and dose reduction, are discussed above. Select adverse events of special interest are discussed in [Section 8.3.5].

The FDA's Assessment:
FDA agrees with the applicant's assessment.

Treatment-emergent Adverse Events and Adverse Drug Reactions

The Applicant's Position:

Treatment-emergent Adverse Events

In the integrated gilteritinib 120 mg group, 99.4% of patients had at least 1 TEAE, 93.4% of patients had at least 1 Grade 3 or higher TEAE and 80.9% of patients had at least 1 serious TEAE. The 2215-CL-0301 gilteritinib arm had similar incidences of TEAEs. In each population (gilteritinib 120 mg group and 2215-CL-0301 gilteritinib arm), the most frequently occurring TEAEs, Grade 3 or higher TEAEs and serious TEAEs were generally associated with the known pathophysiology of AML [O'Donnell et al, 2017].

The most frequently reported TEAEs by MedDRA PT occurring in the integrated gilteritinib 120 mg group included anemia (44.8% [143/319]), febrile neutropenia (43.9% [140/319]), diarrhea (35.1% [112/319]), pyrexia (41.1% [131/319]), ALT increased (37.6% [120/319]), AST increased (37.6% [120/319]), fatigue (30.4% [97/319]), nausea (29.8% [95/319]), cough and

constipation (28.2% [90/319], each), hypokalemia (25.7% [82/319]), dyspnea and edema peripheral (24.1% [77/319], each), thrombocytopenia (23.8% [76/319]), headache (23.5% [75/319]), platelet count decreased (21.3% [68/319]), blood alkaline phosphatase increased (20.7% [22/319]), vomiting (21.0% [67/319]) and dizziness (20.4% [65/319]) [Table 21].

Grade 3 or Higher Treatment-emergent Adverse Events

In the integrated gilteritinib 120 mg group, 93.4% (298/319) of patients reported at least 1 Grade 3 or higher TEAE. The most frequently reported Grade 3 or higher TEAEs in the integrated gilteritinib 120 mg group included febrile neutropenia (42.9% [137/319]), anemia (36.1% [115/319]), thrombocytopenia (20.7% [66/319]) and platelet count decreased (20.1% [64/319]). Each of these events is commonly associated with the pathophysiology of AML [O'Donnell et al, 2017].

Drug-related Treatment-emergent Adverse Events as Assessed by the Investigator

In the integrated gilteritinib 120 mg group, 83.1% of patients reported at least 1 drug-related TEAE and 60.2% of patients reported at least 1 Grade 3 or higher drug-related TEAE. The most frequently reported drug-related TEAEs included ALT increased (25.4%), AST increased (24.5%) and anemia (20.1%). The most frequently reported Grade 3 or higher drug-related TEAEs included anemia (16.9%) and platelet count decreased (11.3%). The 2215-CL-0301 gilteritinib arm had similar incidences of drug-related TEAEs (overall: 83.7% vs 83.1%, respectively).
In the integrated gilteritinib 120 mg group, 60.2% (192/319) of patients reported Grade 3 or higher drug-related TEAEs. The most frequently reported Grade 3 or higher drug-related TEAEs in the integrated gilteritinib 120 mg group included anemia (16.9% [54/319]), febrile neutropenia (12.2% [39/319]), thrombocytopenia (11.6% [37/319]) and platelet count decreased (11.3% [36/319]).

When adjusted by patient-year, the following Grade 3 or higher drug-related TEAEs were numerically higher in the 2215-CL-0301 gilteritinib arm (patient-year, 121.7) compared with the salvage chemotherapy arm (patient-year, 11.9): ALT increased (0.19 events per patient-year vs 0.17 events per patient-year), AST increased (0.20 events per patient-year vs 0.08 events per patient-year), blood alkaline phosphatase increased (0.01 events per patient-year vs no events) and blood creatine phosphokinase increased (0.05 events per patient-year vs no events).

Drug-related Treatment-emergent Adverse Events as Assessed by the Sponsor

For gilteritinib, TEAEs that were determined to be drug-related by the Sponsor are discussed in the [Adverse Drug Reactions] section below.

Table 21 Treatment-emergent Adverse Events (≥ 10% of Integrated Gilteritinib 120 mg Patients) by System Organ Class, Preferred Term and Severity – Integrated R/R AML Safety Population

MedDRA (v19.1) System Organ Class Preferred Term	Integrated Data†				Study 2215-CL-0301							
	Gilteritinib 120 mg		Gilteritinib Total		Gilteritinib 120 mg				Chemotherapy			
	All	≥ Grade 3	All	≥ Grade 3	All		≥ Grade 3		All		≥ Grade 3	
	N = 319		N = 522		N = 246	PY = 121.7 E (E/PY)	N = 246	PY = 121.7 E (E/PY)	N = 109	PY = 11.9 E (E/PY)	N = 109	PY = 11.9 E (E/PY)
Overall, n (%)	**317 (99.4)**	**298 (93.4)**	**519 (99.4)**	**482 (92.3)**	**246 (100)**	**8464 (69.55)**	**236 (95.9)**	**2354 (19.34)**	**107 (98.2)**	**1596 (134.12)**	**94 (86.2)**	**505 (42.44)**
General Disorders and Administration Site Conditions	**254 (79.6)**	**48 (15.0)**	**398 (76.2)**	**88 (16.9)**	**198 (80.5)**	**616 (5.06)**	**33 (13.4)**	**36 (0.30)**	**61 (56.0)**	**165 (13.87)**	**10 (9.2)**	**15 (1.26)**
Pyrexia	131 (41.1)	13 (4.1)	182 (34.9)	21 (4.0)	105 (42.7)	179 (1.47)	8 (3.3)	9 (0.07)	32 (29.4)	59 (4.96)	4 (3.7)	6 (0.50)
Fatigue	97 (30.4)	10 (3.1)	158 (30.3)	21 (4.0)	70 (28.5)	102 (0.84)	6 (2.4)	6 (0.05)	14 (12.8)	18 (1.51)	2 (1.8)	2 (0.17)
Oedema peripheral	77 (24.1)	1 (0.3)	125 (23.9)	5 (1.0)	59 (24.0)	77 (0.63)	1 (0.4)	1 (0.01)	13 (11.9)	19 (1.60)	0	0
Asthenia	44 (13.8)	8 (2.5)	71 (13.6)	12 (2.3)	38 (15.4)	53 (0.44)	6 (2.4)	6 (0.05)	10 (9.2)	11 (0.92)	2 (1.8)	2 (0.17)
Investigations	**249 (78.1)**	**153 (48.0)**	**383 (73.4)**	**235 (45.0)**	**191 (77.6)**	**1702 (13.99)**	**129 (52.4)**	**614 (5.05)**	**59 (54.1)**	**252 (21.18)**	**47 (43.1)**	**133 (11.18)**
Alanine aminotransferase increased	120 (37.6)	37 (11.6)	160 (30.7)	49 (9.4)	103 (41.9)	247 (2.03)	34 (13.8)	42 (0.35)	10 (9.2)	20 (1.68)	5 (4.6)	5 (0.42)
Aspartate aminotransferase increased	120 (37.6)	40 (12.5)	172 (33.0)	55 (10.5)	99 (40.2)	251 (2.06)	36 (14.6)	45 (0.37)	13 (11.9)	21 (1.76)	2 (1.8)	2 (0.17)
Platelet count decreased	68 (21.3)	64 (20.1)	102 (19.5)	96 (18.4)	56 (22.8)	256 (2.10)	54 (22.0)	207 (1.70)	28 (25.7)	76 (6.39)	27 (24.8)	59 (4.96)
Blood alkaline phosphatase increased	22 (20.7)	7 (2.2)	91 (17.4)	8 (1.5)	56 (22.8)	113 (0.93)	7 (2.8)	9 (0.07)	2 (1.8)	2 (0.17)	0	0
Neutrophil count decreased	50 (15.7)	48 (15.0)	70 (13.4)	65 (12.5)	42 (17.1)	167 (1.37)	42 (17.1)	124 (1.02)	12 (11.0)	28 (2.35)	12 (11.0)	19 (1.60)

MedDRA (v19.1) System Organ Class Preferred Term	Integrated Data†				Study 2215-CL-0301							
	Gilteritinib 120 mg		Gilteritinib Total		Gilteritinib 120 mg				Chemotherapy			
	All	≥ Grade 3	All	≥ Grade 3	All		≥ Grade 3		All		≥ Grade 3	
	N = 319		N = 522		N = 246	PY = 121.7 E (E/PY)	N = 246	PY = 121.7 E (E/PY)	N = 109	PY = 11.9 E (E/PY)	N = 109	PY = 11.9 E (E/PY)
Blood creatinine increased	42 (13.2)	4 (1.3)	75 (14.4)	8 (1.5)	29 (11.8)	65 (0.53)	3 (1.2)	4 (0.03)	4 (3.7)	4 (0.34)	0	0
Blood creatine phosphokinase increased	40 (12.5)	15 (4.7)	70 (13.4)	28 (5.4)	33 (13.4)	96 (0.79)	13 (5.3)	20 (0.16)	0	0	0	0
Table continued on next page												
White blood cell count decreased	38 (11.9)	35 (11.0)	51 (9.8)	47 (9.0)	34 (13.8)	128 (1.05)	32 (13.0)	84 (0.69)	19 (17.4)	27 (2.27)	19 (17.4)	26 (2.18)
Gastrointestinal Disorders	**246 (77.1)**	**63 (19.7)**	**397 (76.1)**	**106 (20.3)**	**192 (78.0)**	**818 (6.72)**	**48 (19.5)**	**71 (0.58)**	**80 (73.4)**	**228 (19.16)**	**9 (8.3)**	**11 (0.92)**
Diarrhoea	112 (35.1)	13 (14.1)	188 (36.0)	25 (4.8)	81 (32.9)	136 (1.12)	9 (3.7)	10 (0.08)	32 (29.4)	37 (3.11)	3 (2.8)	3 (0.25)
Nausea	95 (29.8)	6 (1.9)	143 (27.4)	10 (1.9)	79 (32.1)	122 (1.00)	5 (2.0)	5 (0.04)	36 (33.0)	41 (3.45)	0	0
Constipation	90 (28.2)	2 (0.6)	141 (27.0)	2 (0.4)	76 (30.9)	94 (0.77)	2 (0.8)	3 (0.02)	16 (14.7)	18 (1.51)	0	0
Vomiting	67 (21.0)	3 (0.9)	106 (20.3)	6 (1.1)	53 (21.5)	80 (0.66)	1 (0.4)	1 (0.01)	15 (13.8)	16 (1.34)	0	0
Stomatitis	43 (13.5)	7 (2.2)	68 (13.0)	10 (1.9)	34 (13.8)	45 (0.37)	6 (2.4)	6 (0.05)	16 (14.7)	20 (1.68)	4 (3.7)	4 (0.34)
Abdominal pain	42 (13.0)	6 (1.9)	63 (12.1)	8 (1.5)	37 (15.0)	44 (0.36)	5 (2.0)	5 (0.04)	16 (14.7)	17 (1.43)	0	0
Infections and Infestations	**243 (76.2)**	**165 (51.7)**	**381 (73.0)**	**267 (51.1)**	**199 (80.9)**	**659 (5.41)**	**133 (54.1)**	**296 (2.43)**	**56 (51.4)**	**107 (8.99)**	**25 (22.9)**	**52 (4.37)**
Pneumonia	59 (18.5)	43 (13.5)	91 (17.4)	68 (13.0)	43 (17.5)	66 (0.54)	29 (11.8)	39 (0.32)	8 (7.3)	11 (0.92)	5 (4.6)	7 (0.59)
Blood and Lymphatic System Disorders	**241 (75.5)**	**220 (69.0)**	**373 (71.5)**	**338 (64.8)**	**189 (76.8)**	**1147 (9.42)**	**176 (71.5)**	**768 (6.31)**	**78 (71.6)**	**237 (19.92)**	**75 (68.8)**	**171 (14.37)**

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MedDRA (v19.1) System Organ Class Preferred Term	Integrated Data†				Study 2215-CL-0301							
	Gilteritinib 120 mg		Gilteritinib Total		Gilteritinib 120 mg				Chemotherapy			
	All	≥ Grade 3	All	≥ Grade 3	All		≥ Grade 3		All		≥ Grade 3	
	N = 319		N = 522		N = 246	PY = 121.7 E (E/PY)	N = 246	PY = 121.7 E (E/PY)	N = 109	PY = 11.9 E (E/PY)	N = 109	PY = 11.9 E (E/PY)
Anaemia	143 (44.8)	115 (36.1)	207 (39.7)	166 (31.8)	116 (47.2)	481 (3.95)	100 (40.7)	247 (2.03)	38 (34.9)	80 (6.72)	33 (10.3)	45 (3.78)
Febrile neutropenia	140 (43.9)	137 (42.9)	220 (42.1)	216 (41.4)	115 (46.7)	184 (1.51)	113 (45.9)	181 (1.49)	40 (36.7)	52 (4.37)	40 (36.7)	52 (4.37)
Thrombocytopenia	76 (23.8)	66 (20.7)	102 19.5)	89 (17.0)	63 (25.6)	298 (2.45)	56 (22.8)	229 (1.88)	18 (16.5)	42 (3.53)	18 (16.5)	35 (2.94)
Neutropenia	39 (12.2)	39 (12.2)	55 (10.5)	54 (10.3)	33 (13.4)	109 (0.90)	33 (13.4)	80 (0.66)	16 (14.7)	19 (1.60)	15 (13.8)	17 (1.43)
Table continued on next page												
Respiratory, Thoracic and Mediastinal disorders	**208 (65.2)**	**61 (19.1)**	**336 (64.4)**	**110 (21.1)**	**163 (66.3)**	**491 (4.03)**	**46 (18.7)**	**68 (0.56)**	**38 (34.9)**	**70 (5.88)**	**12 (11.0)**	**16 (1.34)**
Cough	90 (28.2)	1 (0.3)	135 (25.9)	1 (0.2)	72 (29.3)	98 (0.81)	1 (0.4)	1 (0.01)	11 (10.1)	13 (1.09)	0	0
Dyspnoea	77 (24.1)	14 (4.4)	123 (23.6)	25 (4.8)	58 (23.6)	77 (0.63)	10 (4.1)	10 (0.08)	7 (6.4)	10 (0.84)	3 (2.8)	3 (0.25)
Epistaxis	58 (18.2)	3 (0.9)	98 (18.8)	5 (1.0)	42 (17.1)	51 (0.42)	2 (0.8)	2 (0.02)	8 (7.3)	8 (0.67)	1 (0.9)	1 (0.08)
Metabolism and Nutrition Disorders	**203 (63.6)**	**101 (31.7)**	**320 (61.3)**	**158 (30.3)**	**165 (67.1)**	**900 (7.40)**	**85 (34.6)**	**192 (1.58)**	**58 (53.2)**	**164 (13.78)**	**35 (32.1)**	**50 (4.20)**
Hypokalaemia	82 (25.7)	33 (10.3)	122 (23.4)	43 (8.2)	71 (28.9)	183 (1.50)	32 (13.0)	42 (0.35)	34 (31.2)	49 (4.12)	12 (11.0)	14 (1.18)
Hypocalcaemia	58 (18.2)	15 (4.7)	92 (17.6)	27 (5.2)	47 (19.1)	110 (0.90)	12 (4.9)	13 (0.11)	6 (5.5)	14 (1.18)	1 (0.9)	1 (0.08)
Decreased appetite	55 (17.2)	5 (1.6)	86 (16.5)	9 (1.7)	44 (17.9)	54 (0.44)	5 (2.0)	5 (0.04)	20 (18.3)	22 (1.85)	5 (4.6)	5 (0.42)
Hypomagnesaemia	52 (16.3)	1 (0.3)	79 (15.1)	1 (0.2)	39 (15.9)	67 (0.55)	0	0	12 (11.0)	15 (1.26)	0	0

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MedDRA (v19.1) System Organ Class Preferred Term	Integrated Data†				Study 2215-CL-0301							
	Gilteritinib 120 mg		Gilteritinib Total		Gilteritinib 120 mg				Chemotherapy			
	All	≥ Grade 3	All	≥ Grade 3	All		≥ Grade 3		All		≥ Grade 3	
	N = 319		N = 522		N = 246	PY = 121.7 E (E/PY)	N = 246	PY = 121.7 E (E/PY)	N = 109	PY = 11.9 E (E/PY)	N = 109	PY = 11.9 E (E/PY)
Hypophosphataemia	47 (14.7)	25 (7.8)	64 (12.3)	39 (7.5)	41 (16.7)	70 (0.58)	20 (8.1)	30 (0.25)	5 (4.6)	5 (0.42)	4 (3.7)	4 (0.34)
Hyperglycaemia	42 (13.2)	19 (6.0)	60 (11.5)	28 (5.4)	36 (14.6)	62 (0.51)	18 (17.3)	24 (0.20)	14 (12.8)	20 (1.68)	9 (8.3)	12 (1.01)
Hyponatraemia	42 (13.2)	19 (6.0)	69 (13.2)	30 (5.7)	33 (13.4)	81 (0.67)	16 (16.5)	36 (0.30)	6 (5.5)	7 (0.59)	3 (2.8)	3 (0.25)
Hypoalbuminaemia	39 (12.2)	5 (1.6)	67 (12.8)	10 (1.9)	32 (13.0)	64 (0.53)	3 (1.2)	5 (0.04)	7 (6.4)	11 (0.92)	2 (1.8)	2 (0.17)
Nervous System Disorders	**175 (54.9)**	**37 (11.6)**	**284 (54.4)**	**67 (12.8)**	**135 (54.9)**	**352 (2.89)**	**30 (12.2)**	**39 (0.32)**	**30 (27.5)**	**53 (4.45)**	**5 (4.6)**	**5 (0.42)**
Headache	75 (23.5)	4 (1.3)	101 (19.3)	5 (1.0)	64 (26.0)	92 (0.76)	3 (1.2)	3 (0.02)	16 (14.7)	18 (1.51)	0	0
Table continued on next page												
Dizziness	65 (20.4)	1 (0.3)	101 (19.3)	3 (0.6)	48 (19.5)	65 (0.53)	1 (0.4)	2 (0.02)	2 (1.8)	2 (0.17)	0	0
Dysgeusia	35 (11.0)	0	56 (10.7)	0	25 (10.2)	28 (0.23)	0	0	5 (4.6)	5 (0.42)	0	0
Musculoskeletal and Connective Tissue Disorders	**172 (53.9)**	**23 (7.2)**	**252 (48.3)**	**36 (6.9)**	**136 (55.3)**	**313 (2.57)**	**17 (6.9)**	**22 (0.18)**	**35 (32.1)**	**62 (5.21)**	**5 (4.6)**	**6 (0.50)**
Pain in extremity	47 (14.7)	2 (0.6)	66 (12.6)	4 (0.8)	36 (14.6)	44 (0.36)	2 (0.8)	2 (0.02)	8 (7.3)	12 (1.01)	1 (0.9)	1 (0.08)
Arthralgia	40 (12.5)	4 (1.3)	65 (12.5)	6 (1.1)	28 (11.4)	45 (0.37)	4 (1.6)	5 (0.04)	6 (5.5)	8 (0.67)	1 (0.9)	1 (0.08)
Myalgia	40 (12.5)	1 (0.3)	56 (10.7)	3 (0.6)	35 (14.2)	45 (0.37)	1 (0.4)	1 (0.01)	4 (3.7)	4 (0.34)	0	0
Back pain	38 (11.9)	3 (0.9)	52 (10.0)	6 (1.1)	29 (11.8)	33 (0.27)	2 (0.8)	2 (0.02)	13 (11.9)	13 (1.09)	1 (0.9)	1 (0.08)

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MedDRA (v19.1) System Organ Class Preferred Term	Integrated Data†				Study 2215-CL-0301							
	Gilteritinib 120 mg		Gilteritinib Total		Gilteritinib 120 mg				Chemotherapy			
	All	≥ Grade 3	All	≥ Grade 3	All		≥ Grade 3		All		≥ Grade 3	
	N = 319		N = 522		N = 246	PY = 121.7 E (E/PY)	N = 246	PY = 121.7 E (E/PY)	N = 109	PY = 11.9 E (E/PY)	N = 109	PY = 11.9 E (E/PY)
Skin and Subcutaneous Tissue Disorders	**169 (53.0)**	**23 (7.2)**	**276 (52.9)**	**33 (6.3)**	**133 (54.1)**	**334 (2.74)**	**18 (7.3)**	**20 (0.16)**	**43 (39.4)**	**63 (5.29)**	**7 (6.4)**	**7 (0.59)**
Rash	48 (15.0)	2 (0.6)	65 (12.5)	2 (0.4)	36 (14.6)	48 (0.39)	1 (0.4)	1 (0.01)	10 (9.2)	10 (0.84)	1 (0.9)	1 (0.08)
Vascular Disorders	**132 (41.4)**	**54 (16.9)**	**206 (39.5)**	**79 (15.1)**	**106 (43.1)**	**174 (1.43)**	**46 (18.7)**	**55 (0.45)**	**25 (22.9)**	**35 (2.94)**	**7 (6.4)**	**8 (0.67)**
Hypotension	55 (17.2)	23 (7.2)	92 (17.6)	37 (7.1)	43 (17.5)	50 (0.41)	19 (7.7)	21 (0.17)	8 (7.5)	9 (0.76)	3 (2.8)	3 (0.25)
Hypertension	41 (12.9)	22 (6.9)	67 (12.8)	29 (5.6)	34 (13.8)	57 (0.47)	20 (8.1)	24 (0.20)	10 (9.2)	11 (0.92)	4 (3.7)	5 (0.42)
Eye Disorders	**125 (39.2)**	**8 (2.5)**	**170 (32.6)**	**11 (2.1)**	**97 (39.4)**	**180 (1.48)**	**5 (2.0)**	**5 (0.04)**	**12 (11.0)**	**19 (1.60)**	**0**	**0**
Dry eye	33 (10.3)	1 (0.3)	41 (7.9)	1 (0.2)	24 (9.8)	25 (0.21)	1 (0.4)	1 (0.01)	3 (2.8)	3 (0.25)	0	0
Injury, Poisoning and Procedural Complications	**112 (35.1)**	**18 (5.6)**	**177 (33.9)**	**34 (6.5)**	**85 (34.6)**	**161 (1.32)**	**13 (5.3)**	**16 (0.13)**	**23 (21.1)**	**35 (2.94)**	**3 (2.8)**	**3 (0.25)**
Table continued on next page												
Fall	34 (10.7)	9 (2.8)	59 (11.3)	14 (2.7)	21 (8.5)	35 (0.29)	5 (2.0)	5 (0.04)	2 (1.8)	2 (0.17)	1 (0.9)	1 (0.08)
Psychiatric Disorders	**92 (28.8)**	**9 (2.8)**	**152 (29.1)**	**17 (3.3)**	**76 (30.9)**	**121 (0.99)**	**8 (3.3)**	**9 (0.07)**	**18 (16.5)**	**23 (1.93)**	**2 (1.8)**	**3 (0.25)**
Insomnia	48 (15.0)	1 (0.3)	71 (13.6)	1 (0.2)	40 (16.3)	44 (0.36)	0	0	6 (5.5)	6 (0.50)	0	0
Renal and Urinary Disorders	**88 (27.6)**	**15 (4.7)**	**150 (28.7)**	**30 (5.7)**	**70 (28.5)**	**118 (0.97)**	**12 (4.9)**	**13 (0.11)**	**14 (12.8)**	**19 (1.60)**	**3 (2.8)**	**4 (0.34)**
Cardiac Disorders	**83 (26.0)**	**31 (9.7)**	**146 (28.0)**	**54 (10.3)**	**67 (27.2)**	**115 (0.94)**	**25 (10.2)**	**39 (0.32)**	**17 (15.6)**	**21 (1.76)**	**4 (3.7)**	**6 (0.50)**

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MedDRA (v19.1) System Organ Class Preferred Term	Integrated Data†				Study 2215-CL-0301							
	Gilteritinib 120 mg		Gilteritinib Total		Gilteritinib 120 mg				Chemotherapy			
	All	≥ Grade 3	All	≥ Grade 3	All		≥ Grade 3		All		≥ Grade 3	
	N = 319		N = 522		N = 246	PY = 121.7 E (E/PY)	N = 246	PY = 121.7 E (E/PY)	N = 109	PY = 11.9 E (E/PY)	N = 109	PY = 11.9 E (E/PY)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**73 (22.9)**	**56 (17.6)**	**120 (23.0)**	**99 (19.0)**	**57 (23.2)**	**72 (0.59)**	**44 (17.9)**	**54 (0.44)**	**11 (10.1)**	**17 (1.43)**	**5 (4.6)**	**10 (0.84)**
Acute myeloid leukaemia	43 (13.5)	43 (13.5)	82 (15.7)	82 (15.7)	33 (13.4)	38 (0.31)	33 (13.4)	38 (0.31)	4 (3.7)	6 (0.50)	4 (3.7)	6 (0.50)
Immune System Disorders	**44 (13.8)**	**16 (5.0)**	**63 (12.1)**	**21 (4.0)**	**35 (14.2)**	**73 (0.60)**	**13 (5.3)**	**17 (0.14)**	**3 (2.8)**	**5 (0.42)**	**1 (0.9)**	**2 (0.17)**
Hepatobiliary Disorders	**37 (11.6)**	**16 (5.0)**	**62 (11.9)**	**20 (3.8)**	**31 (12.6)**	**55 (0.45)**	**13 (5.3)**	**16 (0.13)**	**4 (3.7)**	**5 (0.42)**	**1 (0.9)**	**2 (0.17)**
Reproductive System and Breast Disorders	**32 (10.0)**	**2 (0.6)**	**46 (8.8)**	**5 (1.0)**	**24 (9.8)**	**28 (0.23)**	**2 (0.8)**	**2 (0.02)**	**8 (7.3)**	**8 (0.67)**	**0**	**0**

AML: acute myeloid leukemia; E: number of events; Incl: including; ISS: integrated summary of safety; NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Events; PY: patient-year; R/R: relapsed or refractory.
Sorting order: Descending order in the integrated gilteritinib 120-mg group by system organ class and preferred term within system organ class. In the case of ties, alphabetical order was applied.
Patients were counted once under maximum NCI-CTCAE grade.
†Integrated data includes patients in Studies 2215-CL-0101, 2215-CL-0102 and 2215-CL-0301 who received at least 1 dose of gilteritinib 120 mg (gilteritinib 120 mg group) or any dose of gilteritinib (gilteritinib total group; doses ranging from gilteritinib 20 to 450 mg).
Sources: ISS.ADAE Table 13.4.3.2 and Table 13.4.17.2, Study 2215-CL-0301 ADAE, ADSL Table 12.6.1.2.1.2 and Table 12.6.1.17.1.2

Treatment-emergent Adverse Events – 60-day Analysis

The evaluation of safety in the first 60 days in the gilteritinib and salvage chemotherapy arms is presented herein for Study 2215-CL-0301 [Astellas Response Sequence 0034, 07 Jan 19]. It should be noted that the median duration of treatment is 1 cycle in the majority of patients in the salvage chemotherapy arm and, as such, the 60-day analysis still includes longer exposure in the gilteritinib arm.

In the gilteritinib arm, 97.2% (239/246) of patients experienced at least 1 TEAE in the first 60 days and 94.6% (210/222) experienced at least 1 TEAE after 60 days. In the salvage chemotherapy arm, 97.2% (106/109) of patients experienced at least 1 TEAE in the first

60 days. The tolerability profile of gilteritinib in the first 60 days appears to be similar to the profile after 60 days.

In the first 60 days, the following nonhematological TEAEs (≥ 10% of patients in either treatment group) occurred at a higher incidence in the gilteritinib arm versus the salvage chemotherapy arm (difference of ≥ 2 %): constipation (22.0% versus 14.7%), fatigue (19.5% versus 11.9%), edema peripheral (14.2% versus 11.9%), asthenia (11.0% versus 7.3%), AST increased (31.3% versus 11.0%), ALT increased (30.9% versus 8.3%), blood alkaline phosphatase increased (17.1% versus 1.8%), blood creatine phosphokinase increased (10.2% versus 0%), hypocalcemia (12.2% versus 5.5%), myalgia (11.4% versus 2.8%), dizziness (13.0% versus 1.8%), insomnia (10.2% versus 4.6%), cough (15.9% versus 9.2%), dyspnea (12.6% versus 4.6%), epistaxis (11.0% versus 6.4%) and hypotension (12.6% versus 7.3%).

In the first 60 days, the following nonhematological serious TEAEs (≥ 3.0% of patients in either treatment group) occurred at a higher incidence in the gilteritinib arm versus the salvage chemotherapy arm: pyrexia (6.1% versus 0.9%), pneumonia (4.5% versus 2.8%), AST increased (4.1% versus 0%) and ALT increased (3.3% versus 0%).

In the first 60 days, the following nonhematological Grade 3 or higher TEAEs (≥ 5.0% of patients in either treatment group) occurred at a higher incidence in the gilteritinib arm versus the salvage chemotherapy arm: AST increased (10.6% versus 1.8%), ALT increased (8.9% versus 4.6%) and hyponatremia (5.3% versus 2.8%).

In the gilteritinib arm, the following nonhematological Grade 3 or higher TEAEs (≥ 5.0% of patients) occurred at a higher incidence after 60 days compared to the first 60 days: acute myeloid leukemia (13.1% versus 1.6%), pneumonia (9.0% versus 4.1%), lung infection (6.8% versus 2.8%), hypokalemia (10.8% versus 4.1%), hyperglycemia (5.4% versus 2.4%), hypophosphatemia (6.8% versus 2.8%) and hypertension (6.3% versus 2.8%).

Adverse Drug Reactions (ADRs)

For gilteritinib, the following events were determined to be drug related by the sponsor via thorough causality assessment, taking the following into consideration: event frequency, seriousness of event, potential mechanism of action, the target patient population and the control arm of the randomized trial. The frequency presented for ADRs in this section reflect the frequency of grouped terms.

The most frequent nonhematological serious ADRs (≥5%) reported in patients were dyspnea (9%), transaminase increased (5%), syncope (5%) and noninfectious diarrhea (5%).

Overall, 16 of 319 patients (5.0%) discontinued gilteritinib treatment permanently due to an adverse reaction. The most common ADRs (>1%) leading to discontinuation were AST increased (1.9%) and ALT increased (1.6%). The most common adverse reactions (≥20%) were transaminase increased (47%), myalgia/arthralgia (45%), fatigue/malaise (44%), edema (38%), noninfectious diarrhea (35%), dyspnea (35%), rash (32%), syncope (32%), cough (28%), constipation (28%), hypotension (22%) and blood alkaline phosphatase increased (21%).

Other clinically significant ADRs occurring in ≤ 10% of patients included: electrocardiogram QT prolonged (9%), cardiac failure (7%), pericardial effusion (4%), pericarditis (2%), differentiation syndrome (1%), anaphylactic reaction (1%) and PRES (1%). PRES, QT prolongation, anaphylactic reaction and differentiation syndrome are discussed further in [Section 8.3.5].

Sponsor Rationale for Preferred or Grouped Terms That Have Not Been Included in the List of ADRs

The following table lists preferred or grouped terms that have not been included in the ADR section of the proposed label and the sponsor rationale.

Table 22 Preferred or Grouped Terms Not Included in the List of ADRs and Sponsor Rationale

Preferred or Grouped Term	Sponsor Rationale
Pneumonia	TEAE: 7.3% gilteritinib vs. 6.4% chemotherapy in first 60 days Serious TEAE: 4.5% gilteritinib vs. 2.8% chemotherapy in first 60 days Grade 3 or higher: 4.1% gilteritinib vs. 3.7% chemotherapy in first 60 days Grouped term-pneumonia new: 34.1% gilteritinib vs. 14.7% chemotherapy Overall TEAE E/PY: 0.54 gilteritinib vs. 0.92 chemotherapy Pneumonia is considered a common event for the underlying disease under study (AML) and the TEAE rate for this term is similar between the gilteritinib and chemotherapy arm.
Sepsis	TEAE: 4.1% gilteritinib vs. 4.6% chemotherapy in first 60 days Serious TEAE: 4.1% gilteritinib vs. 4.6% chemotherapy in first 60 days Grade 3 or higher: : 4.1% gilteritinib vs. 4.6% chemotherapy in first 60 days Grouped term-sepsis new: 15.4% gilteritinib vs. 11.0% chemotherapy Serious TEAE E/PY: 0.19 gilteritinib vs. 0.92 chemotherapy Sepsis is considered a common event for the underlying disease under study, and the TEAE rate for this term is similar between the gilteritinib and chemotherapy arm.
Fever	(Pyrexia) TEAE: 19.5% gilteritinib vs. 28.4% chemotherapy in first 60 days Serious TEAE: 6.1% gilteritinib vs. 0.9% chemotherapy in first 60 days Grade 3 or higher: 2.4% gilteritinib vs. 3.7% chemotherapy in first 60 days Grouped term-fever 42.7% gilteritinib vs. 29.4% chemotherapy Overall TEAE E/PY: 1.47 gilteritinib vs. 4.96 chemotherapy Pyrexia is considered a common event for the underlying disease under study, and the TEAE rate for this term is similar between the gilteritinib and chemotherapy arms.
Lung infection	TEAE: 3.3% gilteritinib vs. 2.8% chemotherapy in first 60 days Serious TEAE: 1.6% gilteritinib vs. 2.8% chemotherapy in first 60 days Grade 3 or higher: : 2.8% gilteritinib vs. 2.8% chemotherapy in first 60 days

Preferred or Grouped Term	Sponsor Rationale
	Serious TEAE E/PY: 0.14 gilteritinib vs. 0.50 chemotherapy Lung infection is considered a common event for the underlying disease under study, and the TEAE rate for this term is similar between the gilteritinib and chemotherapy arm.
Blood creatinine increased	TEAE: 6.1% gilteritinib vs. 3.7% chemotherapy in first 60 days Serious TEAE: 0.4% gilteritinib vs. 0% chemotherapy in first 60 days Grade 3 or higher: : 1.2% gilteritinib vs. 0% chemotherapy in first 60 days Overall TEAE E/PY: 0.53 gilteritinib vs. 0.34 chemotherapy Review of the data reveal that majority of elevated creatinine cases are laboratory findings of increase from baseline that are within normal range. Such changes are commonly seen in patients with AML receiving multiple medications. Additionally, the rate of blood creatinine increased is similar between the gilteritinib and chemotherapy arms..
Hyperbilirubinemia	(Blood bilirubin increased) TEAE: 5.7% gilteritinib vs. 5.5% chemotherapy in first 60 days Serious TEAE: 0.8% gilteritinib vs. 0% chemotherapy in first 60 days Grade 3 or higher: : 2.4% gilteritinib vs. 0.9% chemotherapy in first 60 days (Hepatobiliary Disorders) Overall TEAE E/PY: 0.45 gilteritinib vs. 0.42 chemotherapy Grouped term – bilirubin increase: 12.2% gilteritinib vs. 10.1% chemotherapy This laboratory abnormality has multiple etiologies and the rate of hyperbilirubinemia is similar between the gilteritinib and chemotherapy arms.
Myositis	The grouped term for myositis consists primarily of PTs of blood creatine phosphokinase increased and myalgia. Blood creatine phosphokinase increased is considered an adverse drug reaction, and myalgia is included as an adverse drug reaction in the myalgia/arthralgia grouped term.
Nausea	TEAE: 19.9% gilteritinib vs. 32.1% chemotherapy in first 60 days Serious TEAE: 0% gilteritinib vs. 0% chemotherapy in first 60 days Grade 3 or higher: : 0.4% gilteritinib vs. 0% chemotherapy in first 60 days Overall TEAE E/PY: 1.00 gilteritinib vs. 3.45 chemotherapy Grouped term – nausea: 32.1% gilteritinib vs. 33.0% chemotherapy Nausea is considered a common event for the disease under study, and the TEAE rate for this term is lower in the gilteritinib than the chemotherapy arm in the first 60 days.
Stomatitis	TEAE: 6.1% gilteritinib vs. 14.7% chemotherapy in first 60 days Serious TEAE: 0% gilteritinib vs. 0.9% chemotherapy in first 60 days Grade 3 or higher: : 0.8% gilteritinib vs. 3.7% chemotherapy in first 60 days Overall TEAE E/PY: 0.37 gilteritinib vs. 1.68 chemotherapy Grouped term – stomatitis: 28.9% gilteritinib vs. 28.4% chemotherapy Stomatitis is considered a common event for the disease under study, and the TEAE rate for this term is lower in the gilteritinib arm than the chemotherapy arm in the first 60 days..
Vomiting	TEAE: 10.2% gilteritinib vs. 11.9% chemotherapy in first 60 days Serious TEAE: 0% gilteritinib vs. 0% chemotherapy in first 60 days Grade 3 or higher: : 0.4% gilteritinib vs. 0% chemotherapy in first 60 days Overall TEAE E/PY: 0.66 gilteritinib vs. 1.34 chemotherapy Grouped term – vomiting: 22.8% gilteritinib vs. 13.8% chemotherapy Vomiting is considered a common event for the disease under study, and the TEAE rate for this term is similar between the gilteritinib and chemotherapy arm Additionally, patients are on multiple concomitant medications that contribute to this event.
Abdominal pain	TEAE: 9.8% gilteritinib vs. 14.7% chemotherapy in first 60 days Serious TEAE: 0.4% gilteritinib vs. 0% chemotherapy in first 60 days Grade 3 or higher: : 1.2% gilteritinib vs. 0% chemotherapy in first 60 days

Preferred or Grouped Term	Sponsor Rationale
	Overall TEAE E/PY: 0.36 gilteritinib vs. 1.43 chemotherapy Grouped term – abdominal pain: 19.1% gilteritinib vs. 19.3% chemotherapy Abdominal pain is considered a common event for the disease under study, and the TEAE rate for this term is lower in the gilteritinib arm than the chemotherapy arm Patients are also on multiple concomitant medications that contribute to this event.
Headache	TEAE: 14.6% gilteritinib vs. 14.7% chemotherapy in first 60 days Serious TEAE: 0.8% gilteritinib vs. 0% chemotherapy in first 60 days Grade 3 or higher: : 0.4% gilteritinib vs. 0% chemotherapy in first 60 days Overall TEAE E/PY: 0.76 gilteritinib vs. 1.51 chemotherapy Grouped term – headache new: 26.0% gilteritinib vs. 14.7% chemotherapy Headache is considered a common event for the disease under study, and the TEAE rate for this term is similar between the gilteritinib and chemotherapy arm.
Hypokalemia	TEAE: 15.9% gilteritinib vs. 28.4% chemotherapy in first 60 days Serious TEAE: 0% gilteritinib vs. 0.9% chemotherapy in first 60 days Grade 3 or higher: : 4.1% gilteritinib vs. 10.1% chemotherapy in first 60 days Overall TEAE E/PY: 1.50 gilteritinib vs. 4.12 chemotherapy Hypokalemia has multiple etiologies in this patient population, and the rate of this event is lower in the gilteritinib arm compared to the chemotherapy arm.
Decreased appetite	TEAE: 7.7% gilteritinib vs. 17.4% chemotherapy in first 60 days Serious TEAE: 0% gilteritinib vs. 0% chemotherapy in first 60 days Grade 3 or higher: : 1.2% gilteritinib vs. 4.6% chemotherapy in first 60 days Overall TEAE E/PY: 0.44 gilteritinib vs. 1.85 chemotherapy Decreased appetite is considered a common event for the disease under study, and the TEAE rate for this term is lower in the gilteritinib arm than the chemotherapy arm.
Hypomagnesemia	TEAE: 6.1% gilteritinib vs. 10.1% chemotherapy in first 60 days Serious TEAE: 0% gilteritinib vs. 0% chemotherapy in first 60 days Grade 3 or higher: : 0.4% gilteritinib vs. 0% chemotherapy in first 60 days Overall TEAE E/PY: 0.55 gilteritinib vs. 1.26 chemotherapy Hypomagnesemia has multiple etiologies in this patient population including calcineurin inhibitors, and the rate of this event is lower in the gilteritinib arm compared to the chemotherapy arm.
Hyperglycemia	TEAE: 6.1% gilteritinib vs. 12.8% chemotherapy in first 60 days Serious TEAE: 0% gilteritinib vs. 0.9% chemotherapy in first 60 days Grade 3 or higher: : 2.4% gilteritinib vs. 8.3% chemotherapy in first 60 days Overall TEAE E/PY: 0.51 gilteritinib vs. 1.68 chemotherapy Grouped term – hyperglycemia: 17.1% gilteritinib vs. 13.8% chemotherapy Hyperglycemia has multiple etiologies in this patient population, and the rate of this event is lower in the gilteritinib arm compared to the chemotherapy arm.
Hypoalbuminemia	TEAE: 6.9% gilteritinib vs. 6.4% chemotherapy in first 60 days Serious TEAE: 0% gilteritinib vs. 0% chemotherapy in first 60 days Grade 3 or higher: : 0.4% gilteritinib vs. 1.8% chemotherapy in first 60 days Overall TEAE E/PY: 0.53 gilteritinib vs. 0.92 chemotherapy Hypoalbuminemia has multiple etiologies in this patient population and the rate of this event is similar between the gilteritinib arm and chemotherapy arm.
Hypophosphatemia	TEAE: 6.5% gilteritinib vs. 4.6% chemotherapy in first 60 days Serious TEAE: 0% gilteritinib vs. 0% chemotherapy in first 60 days Grade 3 or higher: : 2.8% gilteritinib vs. 3.7% chemotherapy in first 60 days Overall TEAE E/PY: 0.58 gilteritinib vs. 0.42 chemotherapy Hypophosphatemia has multiple etiologies in this patient population and the rate of this event is similar between the gilteritinib arm and chemotherapy arm.
Hypertension	TEAE: 4.5% gilteritinib vs. 8.3% chemotherapy in first 60 days

Preferred or Grouped Term	Sponsor Rationale
	Serious TEAE: 0% gilteritinib vs. 0.9% chemotherapy in first 60 days Grade 3 or higher: : 2.8% gilteritinib vs. 3.7% chemotherapy in first 60 days Overall TEAE E/PY: 0.47 gilteritinib vs. 0.92 chemotherapy Grouped term – hypertension: 15.0% gilteritinib vs. 9.2% chemotherapy Hypertension is considered a common event for this patient population, and the TEAE rate for this term is lower in the gilteritinib arm compared to the chemotherapy arm.
Renal impairment	(acute kidney injury) TEAE: 3.3% gilteritinib vs. 3.7% chemotherapy in first 60 days Serious TEAE: 3.3% gilteritinib vs. 3.7% chemotherapy in first 60 days Grade 3 or higher: : 2.0% gilteritinib vs. 0.9% chemotherapy in first 60 days (Renal and Urinary Disorders) Overall TEAE E/PY: 0.97 gilteritinib vs. 1.60 chemotherapy (acute kidney injury) Serious TEAE E/PY: 0.16 gilteritinib vs. 0.42 chemotherapy Grouped term – renal impairment: 17.5% gilteritinib vs. 7.3% chemotherapy Renal impairment has multiple etiologies in this patient population and the rate of this event is similar between the gilteritinib arm and chemotherapy arm.
Dry eye	TEAE: 3.7% gilteritinib vs. 2.8% chemotherapy in first 60 days Serious TEAE: 0% gilteritinib vs. 0% chemotherapy in first 60 days Grade 3 or higher: : 0.4% gilteritinib vs. 0% chemotherapy in first 60 days Overall TEAE E/PY: 0.21 gilteritinib vs. 0.25 chemotherapy Dry eye is a common event, and the TEAE rate for this term is similar between the gilteritinib and chemotherapy arm

E: number of events; ISS: Integrated Summary of Safety; PY: patient-year; TEAE: treatment-emergent adverse event.
Source: Astellas Response Sequence 0034, 07 Jan 19; ADAE, ADSL Tables 12.6.1.2.1.1.1.99, 12.6.1.6.1.1.1.99 and 12.6.1.17.1.1.1.99; ISS Adhoc ADAEAD2 Table 13.4.18.2.3.99; Study 2215-CL-0301 ADAE, ADSL Tables 12.6.1.2.1.2 and 12.6.1.6.2

The FDA's Assessment:

FDA disagrees with the applicant's assessment of TEAEs and ADRs. FDA's analysis focused on the first 30 days of therapy when most patients were still receiving treatment on both arms. Furthermore, FDA performed an analysis of TEAEs beyond 30 days on the gilteritinib arm.

A total of 237 (96%) of patients on gilteritinib arm versus 105 (96%) of patients on the chemotherapy arm experienced a TEAE in the first 30 days, which is expected for the patient population. Most experienced a grade 3 or higher TEAE in first 30 days as well (186 [76%] on the gilteritinib arm and 90 [83%] on the chemotherapy arm).

Patients pre-selected for low-intensity therapy had 94 (97%) all-grade TEAEs in the first 30 days on the gilteritinib arm versus 37 (90%) on the chemotherapy arm and 75 (77%) grade ≥ 3 TEAEs on the gilteritinib arm versus 31 (76%) on the chemotherapy arm. Patients pre-selected for high-intensity therapy had 143 (96%) all-grade TEAEs in the first 30 days on the gilteritinib arm versus 68 (100%) on the chemotherapy arm and 111 (74%) grade ≥ 3 TEAEs on the gilteritinib arm versus 59 (87%) on the chemotherapy arm. Given the different comparative safety profiles, FDA analyzed safety by arm in the first 30 days by preselected treatment intensity.

Non-laboratory TEAEs occurring either on study treatment or within 30 days after

discontinuation of study treatment on Study 0301 within the first 30 days of therapy in patients preselected for low-intensity therapy are summarized by PT/grouped term in the Table below. TEAEs occurring in at least 10% of patients are included in the Table.

Study 2215-CL-0301 – Non-laboratory TEAEs in ≥ 10% of patients on the gilteritinib arm in the first 30 days of therapy in patients preselected for low-intensity chemotherapy by PT/grouped term

PT/Grouped term	Gilteritinib (N=97)		Chemotherapy (N=41)	
	All grades	Grades 3-5	All grades	Grades 3-5
Transaminase increased*	35 (36%)	9 (9%)	6 (15%)	1 (2%)
Febrile neutropenia	26 (27%)	25 (26%)	5 (12%)	5 (12%)
Myalgia/arthralgia*	21 (22%)	2 (2%)	7 (17%)	0
Fatigue/malaise*	20 (21%)	4 (4%)	9 (22%)	1 (2%)
Haemorrhage*	20 (21%)	1 (1%)	10 (24%)	0
Edema*	19 (20%)	1 (1%)	5 (12%)	0
Mucositis*	19 (20%)	1 (1%)	7 (17%)	1 (2%)
Constipation	13 (13%)	1 (1%)	5 (12%)	0
Diarrhea	12 (12%)	0	2 (5%)	0
Pyrexia	11 (11%)	0	7 (17%)	0
Dyspnea*	11 (11%)	3 (3%)	2 (5%)	2 (5%)
Nausea	10 (10%)	0	7 (17%)	0
Rash*	10 (10%)	2 (2%)	2 (5%)	0
Pneumonia*	10 (10%)	7 (7%)	5 (12%)	2 (5%)

Source: FDA analysis
*Includes grouped terms (see Appendix 14.4)

FDA disagrees with the applicant's assessment that mucositis, fever, and nausea are not ADRs of gilteritinib. A decreased incidence compared to the control arm does not rule out an ADR and biological plausibility and tyrosine kinase inhibitor (TKI) class effects are considered in our evaluation of ADRs. First, mucositis was more common on the gilteritinib arm in patients preselected for low-intensity chemotherapy and mucositis is a class effect of TKIs. Second, fever was a common SAE on the gilteritinib arm of Study 0301, led to dose interruption, and increased in incidence after 30 days (33%). Fever is also a component of the differentiation syndrome and acute febrile neutrophilic dermatosis that has been observed with gilteritinib. Third, nausea is a common AE of gilteritinib and increased in incidence after 30 days on the gilteritinib arm on Study 0301.

FDA proposes to add febrile neutropenia to labeling given that incidence was higher on the gilteritinib arm in patients preselected for low-intensity chemotherapy.

Although hemorrhage and pneumonia were common TEAEs, incidences were lower on the

gilteritinib arm in patients preselected for both low- and high-intensity chemotherapy. FDA considers pneumonia and hemorrhage to be consequences of the underlying disease, as opposed to ADRs, of gilteritinib.

Non-laboratory TEAEs occurring either on study treatment or within 30 days after discontinuation of study treatment on Study 0301 within the first 30 days of therapy in patients preselected for high-intensity therapy are summarized by PT/grouped term in the Table below. TEAEs occurring in at least 10% of patients are included in the Table.

Study 2215-CL-0301 – Non-laboratory TEAEs in ≥ 10% of patients on the gilteritinib arm in the first 30 days of therapy in patients preselected for high-intensity chemotherapy by PT/grouped term

PT/grouped term	Gilteritinib (N=149)		Chemotherapy (N=68)	
	All grades	Grades 3-5	All grades	Grades 3-5
Myalgia/arthralgia*	56 (38%)	1 (1%)	20 (29%)	3 (4%)
Transaminase increased*	46 (31%)	15 (10%)	11 (16%)	5 (7%)
Fatigue/malaise*	36 (24%)	1 (1%)	9 (13%)	2 (3%)
Constipation	29 (20%)	0	10 (15%)	0
Febrile neutropenia	26 (17%)	26 (17%)	30 (44%)	30 (44%)
Haemorrhage*	25 (17%)	1 (1%)	16 (24%)	4 (6%)
Pyrexia	25 (17%)	2 (1%)	21 (31%)	4 (6%)
Rash	23 (15%)	1 (1%)	21 (31%)	2 (3%)
Nausea	23 (15%)	0	26 (38%)	0
Dyspnea*	20 (13%)	1 (1%)	9 (13%)	6 (9%)
Neuropathy*	19 (13%)	0	0	0
Cough	18 (12%)	1 (1%)	5 (7%)	0
Edema*	20 (13%)	0	13 (19%)	0
Mucositis*	18 (12%)	0	30 (44%)	5 (7%)
Headache	17 (11%)	0	12 (18%)	0
Dizziness*	17 (11%)	0	2 (3%)	0
Abdominal pain*	16 (11%)	0	16 (24%)	0

Source: FDA analysis
*Includes grouped terms (see Appendix 14.4)

FDA disagrees with the applicant's assessment that headache and abdominal pain are not ADRs of gilteritinib. Headache is a common AE of gilteritinib and increased in incidence after 30 days on Study 0301. Abdominal pain is a common AE of gilteritinib, despite the decreased incidence on the gilteritinib arm of Study 0301 compared to the control arm. Thus, FDA proposes to include these ADRs in labeling.

Furthermore, FDA proposes to add neuropathy* to labeling given a significantly higher incidence on the gilteritinib arm compared to the control arm. Although neuropathy peripheral did not meet the threshold of ≥ 10% in patients preselected for low-intensity chemotherapy, it occurred in 6 (6%) of those patients on the gilteritinib arm compared to 0% on the control arm.

Events on the gilteritinib arm beyond 30 days of therapy were analyzed separately (Table below). A total of 234/246 (95%) of patients on the gilteritinib arm experienced any grade TEAE and 208/246 (85%) experienced a grade 3 or higher TEAE after 30 days of therapy. TEAEs occurring in at least 10% of patients are included in the table below.

Study 2215-CL-0301 – Nonlaboratory TEAEs in ≥ 10% of patients on the gilteritinib arm by PT beyond 30 days

	Gilteritinib (n=246)	
PT/Grouped term	**All grades**	**Grade 3+**
Transaminase increased*	101 (41%)	38 (15%)
Myalgia/arthralgia*	86 (35%)	13 (5%)
Febrile neutropenia	84 (34%)	83 (34%)
Fever	82 (33%)	6 (2%)
Hemorrhage*	78 (32%)	11 (5%)
Pneumonia*	77 (31%)	57 (23%)
Rash*	75 (31%)	9 (4%)
Mucositis*	73 (30%)	19 (8%)
Diarrhea	71 (29%)	8 (3%)
Fatigue/malaise*	71 (29%)	7 (3%)
Dyspnea*	67 (27%)	25 (10%)
Edema*	67 (27%)	5 (2%)
Nausea	58 (24%)	5 (2%)
Cough	52 (21%)	0
Eye disorders*	48 (20%)	2 (1%)
Headache	47 (19%)	3 (1%)
Sepsis*	47 (19%)	42 (17%)
Vomiting	45 (18%)	1 (<1%)
Constipation	41 (17%)	2 (1%)
Renal impairment*	41 (17%)	7 (3%)
Hypotension*	36 (15%)	13 (5%)
Abdominal pain*	35 (14%)	5 (2%)
Decreased appetite*	35 (14%)	4 (2%)
Dizziness*	30 (12%)	1 (<1%)
Hypertension*	30 (12%)	17 (7%)
Fungal infection*	28 (11%)	7 (3%)
Arrhythmia*	27 (11%)	7 (3%)
Blood CPK increased	27 (11%)	11 (5%)

	Gilteritinib (n=246)	
PT/Grouped term	**All grades**	**Grade 3+**
Bilirubin increase*	25 (10%)	12 (5%)

Source: FDA analysis
*Includes grouped terms (see Appendix 14.4)

The incidence of transaminase increased*, febrile neutropenia, fever, hemorrhage*, pneumonia*, rash*, mucositis*, diarrhea, fatigue/malaise*, dyspnea*, edema*, nausea, cough, eye disorders*, headache, hypotension*, renal impairment*, sepsis*, vomiting, arrhythmia*, blood CPK increased, bilirubin increase*, decreased appetite*, hypertension*, and fungal infection*, increased after 30 days on the gilteritinib arm. Incidence of abdominal pain*, constipation, dizziness*, and myalgia/arthralgia* were similar before and after 30 days.

Reviewer comments: All-grade TEAEs were similar in incidence, overall, over time on the gilteritinib arm. However, grade 3 or higher TEAEs increased over time, which may be expected for a patient population with R/R AML on continuous therapy. Many common toxicities of gilteritinib increased over time, including transaminase increases and myalgias, among others. The applicant submitted a list of excluded ADRs. However, many were difficult to exclude conclusively, for the reasons outlined above. Laboratory abnormalities will be considered separately and presented in the common laboratory abnormalities Table in the label.

Laboratory Findings

The Applicant's Position:
In the integrated R/R AML safety population, at the 120 mg dose level, mean and median values for ANC, hemoglobin and platelets remained generally stable throughout the time course of gilteritinib treatment. Most patients experienced at least 1 postbaseline shift to low values for ANC, hemoglobin or platelets, consistent with the known pathophysiology of AML [O'Donnell et al, 2017].

Overall, data suggest that gilteritinib administration does not have clinically meaningful effects on coagulation. In addition, gilteritinib was not associated with clinically meaningful effects on urinalysis laboratory parameters.

Exposure-related increases were observed for AST, ALT and creatine kinase (Report 2215-PK-0006) based on exposure-safety analyses of gilteritinib. However, these increases did not translate to a high incidence of Grade 3 AEs or study discontinuation. Among patients receiving 120 mg gilteritinib, 8/317 (2.5%) patients experienced ALT and/or AST values that were > 3 x upper limit of normal (ULN) combined with total bilirubin values > 2 x ULN in the

sample. In each case, the sponsor has assessed that the patient did not experience gilteritinib-related drug-induced liver injury, and that there are more plausible etiologies for the observed laboratory abnormalities than gilteritinib use. These data suggest a low risk for hepatotoxicity at the recommended starting dose.

In the integrated R/R AML safety population, gilteritinib was associated with dose- and concentration-dependent increases in liver function tests, most notably ALT and AST, and elevations in creatine kinase. In general, these increases were mostly Grade 1 or 2 in severity, were reversible upon drug interruption and seldom resulted in patient discontinuation from treatment: in the total integrated 120 mg gilteritinib population, 5/319 (1.6%) patients withdrew from treatment due to increases in ALT, 6/319 (1.9%) patients withdrew from treatment due to increases in AST, and 1/319 (0.3%) patient withdrew from treatment due to increases in creatine kinase. Elevations in creatine kinase were not consistently associated with increases in aldolase.

The FDA's Assessment:

FDA disagrees with the applicant's assessment of laboratory abnormalities. FDA conducted an independent assessment of post-baseline laboratory abnormalities in patients on Study 2215-CL-0301. First, FDA analyzed laboratory abnormalities in the first 30 days on both treatment arms according to whether patients were predetermined to receive low- versus high-intensity chemotherapy.

New or worsening laboratory abnormalities (≥ 20%) in patients preselected for low-intensity chemotherapy on Study 2215-CL-0301 in the first 30 days

PT/Grouped term	Gilteritinib			Chemotherapy		
	N	All grades	Grades 3-4	N	All grades	Grades 3-4
Leukocytes decreased	92	72 (78%)	53 (58%)	39	21 (54%)	14 (36%)
Platelets decreased	92	60 (65%)	53 (58%)	39	27 (69%)	24 (62%)
Hemoglobin decreased	92	52 (57%)	35 (38%)	39	18 (46%)	10 (26%)
ALT increased	95	43 (45%)	7 (7%)	41	8 (20%)	1 (2%)
ANC decreased	92	40 (43%)	38 (41%)	39	20 (51%)	18 (46%)
Hypocalcemia	95	38 (40%)	3 (3%)	41	2 (5%)	0
AST increased	95	32 (34%)	5 (5%)	41	5 (12%)	0
Hypoalbuminemia	95	24 (25%)	0	41	9 (22%)	0
Hyperglycemia	95	23 (24%)	2 (2%)	41	17 (41%)	2 (5%)
ALP increased	95	22 (23%)	0	41	7 (17%)	0
Hyponatremia	95	20 (21%)	6 (6%)	41	8 (20%)	2 (5%)

Source: FDA analysis
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase

As per FDA's assessment in the original NDA review, cytopenias on therapy with gilteritinib were deemed unrelated to the study drug, but rather, the underlying disease.

FDA proposes to include only grade 3 or higher laboratory abnormalities in the updated label given the high incidence of low-grade laboratory abnormalities in patients with AML. Hypoalbuminemia and hyperglycemia were deemed unrelated to gilteritinib. No patients preselected for low-intensity therapy had grade 3-4 hypoalbuminemia and less patients on the gilteritinib arm had grade 3-4 hyperglycemia.

New or worsening laboratory abnormalities (≥ 20%) in patients preselected for high-intensity chemotherapy on Study 2215-CL-0301 in the first 30 days

PT/Grouped term	Gilteritinib			Chemotherapy		
	N	All grades	Grades 3-4	N	All grades	Grades 3-4
Leukocytes decreased	138	114 (83%)	95 (69%)	59	55 (93%)	55 (93%)
Platelets decreased	138	78 (57%)	64 (46%)	59	43 (73%)	43 (73%)
AST increased	149	74 (50%)	8 (5%)	65	14 (22%)	2 (3%)
ALT increased	149	73 (49%)	7 (5%)	66	13 (20%)	1 (2%)
Hemoglobin decreased	138	68 (49%)	30 (22%)	59	35 (59%)	24 (41%)
ANC decreased	139	72 (52%)	67 (48%)	52	27 (52%)	25 (48%)
ALP increased	149	51 (34%)	1 (1%)	66	10 (15%)	0
Hyperglycemia	149	41 (28%)	3 (2%)	66	30 (45%)	6 (9%)
Creatine kinase increased	149	39 (26%)	1 (1%)	66	1 (2%)	0
Hypocalcemia	149	36 (24%)	2 (1%)	66	41 (62%)	3 (5%)

Source: FDA analysis
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase

The laboratory comparisons are different in patients preselected for high-intensity chemotherapy. Hypoalbuminemia and hyponatremia did not meet the cutoffs for ≥20% on the gilteritinib arm. Cytopenias were generally more common with the high-intensity chemotherapy on the control arm, as expected. However, neutropenia was just as common on the gilteritinib arm.

Of note, both hypophosphatemia and triglycerides increased are considered to be associated with gilteritinib, even though their overall incidences were < 20% on the gilteritinib arm. The incidences of grade 3-4 hypophosphatemia for patients preselected for low-intensity chemotherapy were 3% gilteritinib vs 9% chemotherapy and for high-intensity were 4% gilteritinib vs 8% chemotherapy. Hypophosphatemia increased in incidence on the gilteritinib arm of Study 0301 following 30 days, including grade 3-4 hypophosphatemia in 12% of patients beyond 30 days. Furthermore, hypophosphatemia is a class effect of TKIs. As for triglycerides, incidences of grade 3-4 increases for patients preselected for low-intensity chemotherapy were

2% gilteritinib vs 0% chemotherapy and for high-intensity were 1% gilteritinib vs 0% chemotherapy.

New or worsening laboratory abnormalities (≥ 20%) in patients on the gilteritinib arm of Study 2215-CL-0301 after 30 days

PT/Grouped term	Gilteritinib		
	N	All grades	Grades 3-4
Leukocytes decreased	214	169 (79%)	127 (59%)
AST increased	226	156 (69%)	15 (7%)
ALT increased	226	151 (67%)	21 (9%)
Hemoglobin decreased	214	133 (62%)	98 (46%)
Platelets decreased	214	128 (60%)	120 (56%)
Creatine kinase increased	226	119 (53%)	14 (6%)
ALP increased	226	112 (50%)	3 (1%)
Hyperglycemia	226	110 (49%)	22 (10%)
Hypocalcemia	226	106 (47%)	11 (5%)
ANC decreased	215	95 (44%)	89 (41%)
Hypoalbuminemia	226	89 (39%)	8 (4%)
Hyponatremia	226	60 (27%)	20 (9%)
Hypophosphatemia	226	59 (26%)	27 (12%)
Triglycerides increased	226	55 (24%)	12 (5%)

Source: FDA analysis
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase

A total of 8 patients (3%) on the gilteritinib arm of Study 2215-CL-0301 experienced ALT and/or AST values > 3 x ULN combined with a total bilirubin value > 2 x ULN in the same sample. Only 1 patient (1%) met these criteria on the control arm. FDA reviewed narratives for all of the potential Hy's law cases. Two patients had alkaline phosphatase elevation ≥ 2 x ULN and 3 patients met Hy's law criteria several days after discontinuing gilteritinib. FDA ruled out drug-induced liver injury in the remaining cases based on plausible alternative causes, including sepsis (n=2) and concomitant medication (n=1).

Vital Signs

The Applicant's Position:
In the integrated gilteritinib 120 mg group, modest postbaseline increases in systolic blood pressure (SBP) and diastolic blood pressure (DBP) and body weight were observed. No obvious postbaseline changes were observed in pulse rate or body temperature.

In the integrated gilteritinib 120 mg group, 12.2% (39/319) of patients experienced a potentially

clinically significant (PCS) increase in pulse rate, 3.8% (12/319) of patients experienced a PCS increase in SBP and 2.2% (7/319) of patients experienced a PCS increase in DBP.

Although not adjusted by patient-year, in the 2215-CL-0301 gilteritinib arm, 10.6% (26/246) of patients experienced a PCS increase in pulse rate, 3.7% (9/246) of patients experienced a PCS increase in SBP and 2.0% (5/246) of patients experienced a PCS increase in DBP. In the salvage chemotherapy arm, 4.6% (5/109) of patients experienced a PCS increase in pulse rate, 0.9% (1/109) of patients experienced a PCS increase in SBP and no patients experienced a PCS increase in DBP.

The FDA's Assessment:
FDA agrees with the Sponsor's assessment.

Electrocardiograms (ECGs)

The Applicant's Position:
In the integrated gilteritinib 120 mg group, 56.1% (179/319) of patients had an abnormal baseline ECG and 78.2% (248/317) of patients had an abnormal postbaseline ECG. The following ECG abnormalities had higher postbaseline incidences compared with baseline: sinus tachycardia (34.7% [110/317] vs 16.9% [54/319]), T-wave flat (28.1% [89/317] vs 11.9% [38/319]), atrial premature complexes (24.9% [79/317] vs 8.5% [27/319]), ventricular premature complexes (21.8% [69/317] vs 8.2% [26/319]), other (12.0% [38/317] vs 0.9% [3/319]) and prolonged QTc interval (10.1% [32/317] vs 0.6% [2/319]).

Although there were similar overall baseline incidences of ECG abnormalities between the 2215-CL-0301 gilteritinib and salvage chemotherapy treatment arms (56.9% [140/246] vs 56.0% [61/109]), the incidence of overall postbaseline ECG abnormalities was higher in the 2215-CL-0301 gilteritinib arm compared with the salvage chemotherapy arm (75.8% [185/244] vs 48.5% [49/101]). The following ECG abnormalities had higher postbaseline incidences in the 2215-CL-0301 gilteritinib arm compared with the salvage chemotherapy arm: sinus tachycardia (30.7% [75/244] vs 19.8% [20/101]), atrial premature complexes (23.4% [57/244] vs 10.9% [11/101]), ventricular premature complexes (18.0% [44/244] vs 6.9% [7/101]) and first degree atrioventricular block (13.9% [34/244] vs 4.0% [4/101]).

The FDA's Assessment:
FDA agrees with the applicant's assessment. In addition, FDA performed an analysis of post-baseline QTcF in patients treated on Study 2215-CL-0301. Of note, there were 2 patients who did not have post-baseline QTcF on the gilteritinib arm and 8 patients without a post-baseline QTcF on the chemotherapy arm.

Analysis of Maximum Post-Baseline Absolute QTcF, Study 22215-CL-0301

Parameter	Gilteritinib (N=244)	Chemotherapy (N=101)
Maximum post-baseline absolute QTcF, n (%)		
≤450 msec	166 (68%)	93 (92%)
>450 to ≤480 msec	69 (28%)	8 (8%)
>480 to ≤500 msec	8 (3%)	0
>500 msec	1 (<1%)	0
Maximum post-baseline increase in QTcF, n (%)		
≤30 msec	172 (70%)	85 (84%)
>30 to ≤60 msec	62 (25%)	14 (14%)
>60 msec	12 (5%)	2 (2%)

Source: FDA analysis

Immunogenicity

The Applicant's Position:

No specific clinical studies on immunogenicity were performed.

The FDA's Assessment:

FDA agrees with the applicant's assessment.

8.3.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position:

A more detailed analysis is provided for the following safety issues: QT prolongation, PRES, pancreatitis, hypersensitivity/anaphylaxis and differentiation syndrome. In addition, data regarding teratogenicity and embryo-fetal deaths is provided in this section.
Of note, in Study 2215-CL-0301, total patient-year was 121.7 and 11.9 for the gilteritinib 120 mg arm and salvage chemotherapy arm, respectively.

The FDA's Assessment:

In addition to the AESIs listed above by the applicant, FDA performed an analysis of the AESIs in the Table below that occurred on the gilteritinib arm at any time on Study 2215-CL-0301.

Other adverse events of special interest on Study 2215-CL-0301

Preferred Term	Gilteritinib (n=246)		Chemotherapy (n=109)	
	All grades	Grade 3-5	All grades	Grade 3-5
Transaminase increased*	131 (53%)	57 (23%)	18 (17%)	6 (6%)
Bilirubin increased*	30 (12%)	15 (6%)	11 (10%)	2 (2%)
Myalgia/arthralgia*	125 (51%)	16 (7%)	33 (30%)	5 (5%)

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Blood CPK increased	33 (13%)	13 (5%)	0	0
Eye disorders*	60 (24%)	2 (1%)	5 (5%)	0
Neuropathy*	43 (18%)	2 (1%)	0	0
Pericardial effusion	11 (5%)	3 (1%)	0	0
Pericarditis/myocarditis*	7 (3%)	2 (1%)	0	0
Cardiac failure*	9 (4%)	8 (3%)	1 (1%)	1 (1%)
Acute neutrophilic dermatosis	5 (2%)	1 (<1%)	0	0
Large intestine perforation	2 (1%)	2 (1%)	0	0

Source: FDA analysis
*Grouped term defined in Appendix 14.4

Most of the ADRs listed in the Table above were recognized on review of the original NDA and included in current labeling.

Transaminase increased, bilirubin increased

All-grade and grade 3-4 incidence of transaminase increase is higher on the gilteritinib arm of Study 0301 than the integrated dataset included in current labeling (53% vs 41% and 23% vs 16%, respectively). However, bilirubin increased is about the same (all-grade 12% vs 11% and grade ≥ 3 6% vs 5%, respectively).

Reviewer comments: Although the incidence of transaminase increased is higher on Study 0301 than that included in current labeling, bilirubin increased is about the same and there were no cases of confirmed drug-induced liver injury with gilteritinib. Therefore, FDA does not recommend elevation of this ADR to Warnings and Precautions at this time.

Myalgia/arthralgia, blood CPK increased

Myalgia/arthralgia was slightly higher in incidence in Study 0301 compared to current labeling, but grade 3-5 cases were similar in incidence. While the PT blood CPK increased was reported in 13% of patients, laboratory analyses over the entire treatment period showed that 126/244 (52%) of patients experienced post-baseline increases in CPK. A total of 16/244 (7%) experienced grade 3-4 post-baseline increases in CPK. These incidence rates are very similar to what is reported in current labeling. FDA recommends inclusion of myalgias/arthralgias and creatine kinase increased in Section 6 of labeling with the updated incidence rates.

Eye disorders

On review of the safety data from Study 0301, FDA noted several eye disorders, which were more common on the gilteritinib arm compared to the chemotherapy arm. When the analysis is limited to the first 30 days of therapy in the low-intensity group, the incidence was 7% vs 2%,

respectively. In the high-intensity group, the incidence of eye disorders was 7% vs 4%, respectively. Beyond 30 days, the incidence of eye disorders was 20%. Of the 60 (24%) patients that experienced eye disorders at any time, the most common PTs (≥ 2 patients each) were vision blurred (8%), cataract (3%), retinopathy (2%), photophobia (2%), vitreous floaters (2%), eye pain (1%), punctate keratitis (1%), vitreous detachment (1%), diplopia (1%), eye naevus (1%), foreign body sensation in eyes (1%), ocular hyperaemia (1%), visual acuity reduced (1%), and visual field defect (1%). Grade 3-4 events were rare and included only 1 case each of cataract and diabetic retinopathy. FDA recommends including eye disorders in Section 6 of labeling.

Neuropathy

Neuropathy was a newly-recognized ADR during review of this sNDA. Incidence of all-grade neuropathy events were common on the gilteritinib arm and were not seen on the chemotherapy arm. PTs in the grouped term included paresthesia (9%), neuropath peripheral (3%), hypoesthesia (3%), peripheral sensory neuropathy (2%), neuralgia (2%), hyperaesthesia (1%), and carpal tunnel syndrome, neuromyopathy, and sensory loss in 1 patient (<1%) each. Grade 3-4 events were rare and included only one case each of carpal tunnel syndrome and neuromyopathy. FDA recommends including neuropathy in Section 6 of labeling.

Pericardial effusion

Pericardial effusion was seen in 11 (5%) of patients on the gilteritinib arm of Study 0301 compared to no patients on the chemotherapy arm. Thus, the incidence is similar to the 3% currently reported in the PI. There were 3 (1%) grade ≥ 3 events. One (1%) of patients on the gilteritinib arm preselected for low- and high-intensity chemotherapy developed pericardial effusion in the first 30 days. Beyond 30 days on the gilteritinib arm, 10 (4%) of patients experienced pericardial effusion. FDA recommends including the updated incidence of pericardial effusion in Section 6 of the PI.

FDA additionally performed a pooled analysis of pericardial effusion in patients with R/R AML treated with the recommended dose of gilteritinib on Studies 0301 (N=246), 0101 (N=69), and 0102 (N=4). Out of the 319 total patients, 13 (4%) experienced pericardial effusion.

Pericarditis/myocarditis

Pericarditis/myocarditis was reported in 3% of patients on the gilteritinib arm compared to no patients on the chemotherapy arm. PTs included pericarditis (2%), myocarditis (1%), and 1 event of pericardial hemorrhage (<1%). The incidence of this ADR is similar to the 2% incidence included in current labeling. FDA recommends including the updated incidence of pericarditis/myocarditis in Section 6 of the PI.

FDA additionally performed a pooled analysis of pericarditis/myocarditis in patients with R/R AML treated with the recommended dose of gilteritinib on Studies 0301 (N=246), 0101 (N=69), and 0102 (N=4). Out of the 319 total patients, 7 (2%) experienced pericarditis/myocarditis.

Cardiac failure

Cardiac failure was reported in 4% of patients on the gilteritinib arm of Study 0301. PTs included cardiac failure (2%), ejection fraction decreased (1%), cardiac failure congestive (1%), and 1 subject (<1%) each of cardiomyopathy, cardiomegaly, and chronic left ventricular failure. In the first 30 days of therapy in patients preselected for low-intensity therapy, the incidence of cardiac failure on the gilteritinib vs chemotherapy arm was 2% vs 0%. In patients preselected for high-intensity therapy, the incidences were 1% vs 2%, respectively. Beyond 30 days on the gilteritinib arm, the incidence of cardiac failure was 2%. FDA recommends including the updated incidence of cardiac failure in Section 6 of the PI.

FDA additionally performed a pooled analysis of cardiac failure in patients with R/R AML treated with the recommended dose of gilteritinib on Studies 0301 (N=246), 0101 (N=69), and 0102 (N=4). Out of the 319 total patients, 12 (4%) experienced cardiac failure.

Acute neutrophilic dermatosis

Acute neutrophilic dermatosis was noted in 5 (2%) of patients on the gilteritinib arm of Study 0301 compared to no patients on the control arm. One patient had a grade 3 event. FLT3 inhibitor-induced neutrophilic dermatosis has been previously described (Fathi et al, Blood 2013). Given the biological plausibility for this adverse reaction in patients treated with a targeted differentiating therapy, FDA recommends including the incidence of this ADR in Section 6 of labeling.

FDA additionally performed a pooled analysis of acute febrile neutrophilic dermatosis in patients with R/R AML treated with the recommended dose of gilteritinib on Studies 0301 (N=246), 0101 (N=69), and 0102 (N=4). Out of the 319 total patients, 8 (3%) experienced acute febrile neutrophilic dermatosis.

Large intestine perforation

Large intestine perforation occurred in 2 (1%) of patients on the gilteritinib arm of Study 0301 compared to no patients on the chemotherapy arm. Both events were fatal. FDA recommends including the incidence of this ADR in Section 6 of labeling.

FDA additionally performed a pooled analysis of large intestine perforation in patients with R/R

AML treated with the recommended dose of gilteritinib on Studies 0301 (N=246), 0101 (N=69), and 0102 (N=4). Out of the 319 total patients, 2 (1%) experienced large intestine perforation, both from Study 0301.

QT Prolongation

The Applicant's Position:

Treatment-emergent Adverse Events
In the integrated gilteritinib 120 mg group, TEAEs within this category were experienced by 15.7% (50/319) of patients. The most frequent TEAEs by PT within this category were ECG QT prolonged (8.8% [28/319]) and syncope (5.0% [16/319]. Cardiac arrest was experienced by 1.3% (4/319) of patients and medical review of these cases did not reveal QT prolongation. When adjusted by patient-year, the overall incidence of TEAEs within this category was higher in the gilteritinib arm (patient-year, 121.7) compared with the salvage chemotherapy arm (patient-year, 11.9) (0.38 events per patient-year versus 0.17 events per patient year).

In the integrated gilteritinib 120 mg group, 7.2% (23/319) of patients experienced TEAEs within this category that were considered related to drug by the investigator. Serious TEAEs within this category were experienced by 5.3% (17/319) of patients in the integrated gilteritinib 120 mg group. Drug-related SAEs within this category, as assessed by the investigator, were experienced by 6 patients (1.9%) in the integrated gilteritinib 120 mg group (PTs: electrocardiogram QT prolonged [3 patients], syncope [2 patients] and ventricular fibrillation [1 patient]).

Grade 3 or higher TEAEs within this category were experienced by 8.5% (27/319) of patients in the integrated gilteritinib 120 mg group (PTs: syncope [14 patients], electrocardiogram QT prolonged [8 patients], cardiac arrest [4 patients], cardio-respiratory arrest [1 patient], and ventricular fibrillation and ventricular tachycardia [1 patient each]). Drug-related Grade 3 or higher TEAEs, as assessed by the investigator, within this category were experienced by 6 patients (1.9%) in the integrated gilteritinib 120 mg group (PTs: electrocardiogram QT prolonged [3 patients], syncope [2 patients] and ventricular fibrillation [1 patient]).
Although not a commonly reported event, the incidence of ECG QT prolonged occurred at numerically lower incidence in the dose escalated 200 mg group compared with the non-dose escalated 120 mg group (3.8% [3/78] vs 8.3% [14/168]).

Note: The search strategy for arrhythmias due to QT prolongation was SMQ broad term "Torsade de Pointes/QT prolongation."

ECG QTcF Values
In the integrated gilteritinib 120 mg group, the majority of patients (96.6% [308/319]) had a

QTcF value ≤ 450 msec at baseline and no patients had a QTcF value > 500 msec at baseline. The percentage of patients experiencing a maximum postbaseline QTcF value > 450 to ≤ 480 msec was 30.6% (97/317), with 4.4% (14/317) and 1.3% (4/317) of patients experiencing a maximum postbaseline QTcF value of > 480 to ≤ 500 msec or > 500 msec, respectively. The percentage of patients experiencing maximum postbaseline changes of < 0 msec was 6.6% (21/317), ≥ 0 to ≤30 msec was 59.9% (190/317), >30 to ≤ 60 msec was 26.8% (85/317) and > 60 msec was 6.6% (21/317). Additionally, an exposure-response model evaluating gilteritinib and ΔQTcF indicated the predicted increase in ΔQTcF associated with steady-state concentrations of gilteritinib after once daily administration of 120 mg is 4.96 msec, with an upper 1-sided 95% CI (6.20 msec). This upper limit is less than 10 msec, and suggests the predicted ΔQTcF is not clinically significant.

In the 2215-CL-0301 gilteritinib arm, only 1 patient (0.4%) had a maximum postbaseline QTcF value of > 500 msec. No patients in the salvage chemotherapy arm had a maximum postbaseline QTcF value of > 500 msec and no patients in either 2215-CL-0301 treatment arm discontinued the study due to QT prolongation and there were no incidents of Torsade de Pointes. For the 9 patients in the 2215-CL-0301 gilteritinib arm who experienced postbaseline QTcF > 480 msec, the median time to postbaseline QTcF > 480 msec was 43.0 days.

The FDA's Assessment:
On Study 2215-CL-0301, the incidence of all-grade PTs in the broad SMQ for Torsade de pointes/QT prolongation on the gilteritinib arm was 35/246 (14%). This included 17 (7%) patients with electrocardiogram QT prolonged, 12 (5%) patients with syncope, 4 (2%) with cardiac arrest, 3 (1%) with ventricular tachycardia, and one patient with cardio-respiratory arrest. Grade ≥ 3 PTs in this broad SMQ occurred in 20 (8%) of patients. This included 4 (2%) of patients with electrocardiogram QT prolonged, 12 (5%) patients with syncope, 4 (2%) with cardiac arrest, and one each of ventricular tachycardia and cardio-respiratory arrest.
FDA recommends maintaining QT prolongation in Warnings and Precautions.

PRES

The Applicant's Position:
In the integrated gilteritinib 120 mg group, TEAEs within this category were experienced by 3.1% (10/319) of patients. The most frequent TEAE by PT within this category was delirium (2.2% [7/319]).

When adjusted by patient-year, the overall incidence of TEAEs within this category was not numerically higher in the gilteritinib arm (patient-year, 121.7) compared with the salvage chemotherapy arm (patient-year, 11.9) (0.09 events per patient-year vs 0.34 events per patient-year). However, the PT of PRES was only experienced in the 2215-CL-0301 gilteritinib arm (0.01 events per patient-year) and not in the salvage chemotherapy arm (no events per patient-year).

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A drug-related TEAE within this category (PT: PRES) was experienced by 1 patient (0.3%) in the integrated gilteritinib 120 mg group. Serious TEAEs within this category were experienced by 0.6% (2/319) of patients in the integrated gilteritinib 120 mg group. A drug-related SAE within this category (PT: PRES) was experienced by 1 patient (0.3%) in the integrated gilteritinib 120 mg group.

Grade 3 or higher TEAEs within this category were experienced by 1.3% (4/319) of patients in the integrated gilteritinib 120 mg group. A drug-related Grade 3 or higher TEAE within this category (PT: PRES) was experienced by 1 patient (0.3%) in the integrated gilteritinib 120 mg group.

The FDA's Assessment:
FDA agrees with the applicant that PRES occurred in only one patient on Study 0301. One patient on each arm had an event of encephalopathy. FDA additionally performed a pooled analysis of PRES in patients with R/R AML treated with the recommended dose of gilteritinib on Studies 0301 (N=246), 0101 (N=69), and 0102 (N=4). Out of the 319 total patients, 2 (1%) experienced PRES.

Pancreatitis

The Applicant's Position:
Although pancreatitis was not prespecified as an AE of special interest, it was selected by the sponsor as an AE of special interest based on ongoing safety assessments.
In the integrated gilteritinib 120 mg group, TEAEs within this category were experienced by 0.9% (3/319) of patients. The only TEAE by PT within this category was pancreatitis (0.9% [3/319]). None of these events were considered drug related.

When adjusted by patient-year, the overall incidence of TEAEs within this category was higher in the gilteritinib arm (patient-year, 121.7) compared with the salvage chemotherapy arm (patient-year, 11.9); 0.03 events per patient-year versus no events per patient-year). By PT, pancreatitis was experienced only by patients in the 2215-CL-0301 gilteritinib arm compared with no patients in the salvage chemotherapy arm (0.03 events per patient-year versus no events per patient-year).

Drug-related TEAEs within this category were not experienced by any patients in the integrated gilteritinib 120 mg group . Serious TEAEs within this category were experienced by 0.9% (3/319) of patients in the integrated gilteritinib 120 mg group. Grade 3 or higher TEAEs within this category were experienced by 0.3% (1/319) of patients in the integrated gilteritinib 120 mg group.

The FDA's Assessment:
FDA performed an analysis of the grouped term pancreatitis (see Appendix 14.4) on Study 0301. The overall incidence on the gilteritinib arm was 11 (5%) versus 1 (1%) on the chemotherapy arm; grade ≥ 3 events occurred in 1% vs 1% of patients, respectively. Of the 11 patients on the gilteritinib arm, PTs included amylase increased (3%), lipase increased (2%), and pancreatitis (1%). One case of pancreatitis was fatal. In the first 30 days of therapy, the incidence in patients preselected for low-intensity was 1 (1%) on the gilteritinib arm and 1 (2%) on the chemotherapy arm. No patients preselected for high-intensity chemotherapy on either arm experienced pancreatitis in the first 30 days. Beyond 30 days, the incidence of pancreatitis occurred in 10 (4%) of patients on the gilteritinib arm and was more common in patients preselected for low-intensity vs high-intensity therapy (6% vs 3%).

FDA additionally performed a pooled analysis of the grouped term pancreatitis in patients with R/R AML treated with the recommended dose of gilteritinib on Studies 0301 (N=246), 0101 (N=69), and 0102 (N=4). Out of the 319 total patients, 12 (4%) experienced pancreatitis.

FDA recommends updating the label to include the incidence of pancreatitis in Warnings and Precautions (currently states "rare reports"). Pancreatitis should also be listed in Section 6 under "Other clinically significant adverse reactions occurring in ≤ 10% of patients."

Hypersensitivity/Anaphylaxis

The Applicant's Position:
Although hypersensitivity/anaphylaxis was not prespecified as an AE of special interest, it was selected by the sponsor as an AE of special interest based on ongoing safety assessments. In the integrated gilteritinib 120 mg group, TEAEs within this category were experienced by 40.4% (129/319) of patients. The most frequent TEAEs by PT within this category were rash (15.0% [48/319]) and face edema (5.3% [17/319]).

When adjusted by patient-year, the overall incidence of TEAEs within this category was not numerically higher in the gilteritinib arm (patient-year, 121.7) compared with the salvage chemotherapy arm (patient-year, 11.9); (1.68 events per patient-year versus 4.54 events per patient-year).

Drug-related TEAEs, as assessed by the investigator, within this category were experienced by 13.5% (43/319) patients in the integrated gilteritinib 120 mg group. Serious TEAEs within this category were experienced by 4.4% (14/319) of patients in the integrated gilteritinib 120 mg group, including 1.3% (4/319) of patients who experienced an anaphylactic reaction. Per investigator assessment, drug-related SAEs within this category were experienced by 1.6% (5/319) in the integrated gilteritinib 120 mg group, including 0.3% (1/319) of patients who experienced an anaphylactic reaction.

Grade 3 or higher TEAEs within this category were experienced by 7.8% (25/319) of patients in the integrated gilteritinib 120 mg group, including 1.3% (4/319) of patients who experienced an anaphylactic reaction. Per investigator assessment, drug-related Grade 3 or higher TEAEs within this category were experienced by 2.5% (8/319) in the integrated gilteritinib 120 mg group, including 0.3% (1/319) of patients who experienced an anaphylactic reaction.

The FDA's Assessment:
FDA performed an assessment of hypersensitivity based on the grouped term defined in Appendix 14.4. The incidence on the gilteritinib arm was 22 (9%) versus 9 (8%) on the chemotherapy arm. Grade ≥ 3 events occurred in 3% vs 3% of patients, respectively. All-grade PTs on the gilteritinib arm included urticaria (4%), drug hypersensitivity (2%), anaphylactic reaction (1%), dermatitis allergic (1%), and 1 each (<1%) of angioedema, erythema multiforme, and hypersensitivity. Grade ≥ 3 PTs included anaphylactic reaction (1%), urticaria (1%), and drug hypersensitivity (1%). Although the incidence across the arms was equivalent (even considering a much longer duration of therapy on the gilteritinib arm), the incidence of hypersensitivity reactions with gilteritinib should be noted in Section 6 of labeling.

FDA additionally performed a pooled analysis of hypersensitivity in patients with R/R AML treated with the recommended dose of gilteritinib on Studies 0301 (N=246), 0101 (N=69), and 0102 (N=4). Out of the 319 total patients, 26 (8%) experienced hypersensitivity.

Differentiation Syndrome

In the integrated gilteritinib 120 mg group, only 1 TEAE within this category (PT: acute promyelocytic leukemia differentiation syndrome) was experienced by 0.9% (3/319) of patients. Of these, 2 patients (0.6% [2/319]) experienced a drug-related event of acute promyelocytic leukemia differentiation syndrome.

In Study 2215-CL-0301, only 1 patient (0.4% [1/246]) in the gilteritinib arm experienced a nondrug-related event of acute promyelocytic leukemia differentiation syndrome and no events were experienced by patients in the salvage chemotherapy arm.
In the integrated gilteritinib 120 mg group, no patients experienced a serious event of acute promyelocytic leukemia differentiation syndrome, but 1 patient (0.3% [1/319]) experienced a drug-related Grade 3 or higher event.

An assessment for all cases of differentiation syndrome and suspected differentiation syndrome using the algorithmic approach based on the Montesinos et al scoring system in addition to using "acute promyelocytic leukemia differentiation syndrome" alone was completed for patients treated with gilteritinib in Study 2215-CL-0301 (Astellas Response Sequence 0035, dated 14 Jan 19). Each case was assessed, and it was determined that there were 5 additional possible cases of differentiation syndrome. There is no strong evidence of association of

gilteritinib with differentiation syndrome and even if all possible cases are accepted as differentiation syndrome, all cases were mild and self-limiting. Differentiation syndrome is currently included in Section 6.1 of the approved label and the 5 additional possible cases of differentiation syndrome do not warrant labeling revisions for differentiation syndrome.

The FDA's Assessment:

FDA performed an independent analysis of differentiation syndrome (DS) using an algorithmic approach. Per Montesinos et al (Montesinos et al. 2009), the diagnosis of DS is made according to the presence of the following signs and symptoms: (1) dyspnea, (2) unexplained fever, (3) weight gain greater than 5 kg, (4) unexplained hypotension, (5) acute renal failure, and (6) a chest radiograph demonstrating pulmonary infiltrates or pleuropericardial effusion. Patients with 4 or more of these features are classified as having severe DS and those with 2 or 3 features are considered to have moderate DS. No single feature is diagnostic. Patients with alternative explanations, such as pulmonary hemorrhage, septic shock, pneumonia, or cardiac failure are considered to not have DS. Deaths were attributed to DS when they occurred in patients with severe DS and were not explained by infection, hemorrhage, or other causes.

- Identified all unique subject IDs meeting ≥ 2 of the criteria in the table below (exception: at least one of "acute promyelocytic leukemia differentiation syndrome")
- Stated relationship to study drug irrelevant
- Only considered post-baseline data points occurring within the first 90 days of therapy
- At least 2 criteria had a start date within 7 days of one another
- Searched for concomitant, defined using PTs Leukocytosis, Hyperleukocytosis, or White blood cell count increased, or laboratory results showing Leukocytes (10^9/L) > 10 within 7 days before or after clinical signs/symptoms

FDA criteria for identifying cases of possible DS

Part A: Report[1] of ≥ 1 of the following is considered a case of possible DS:	
Category	**Adverse event[2]**
Investigator-reported DS	acute promyelocytic leukemia differentiation syndrome
Part B: Report[1, 3] of ≥ 2 of the following categories of events is considered a case of possible DS:	
Category	**Adverse event[2] or vital sign abnormality**
Dyspnea	Acute respiratory failure, cardiopulmonary failure, cardio-respiratory arrest, cardio-respiratory distress, cough, dyspnoea, dyspnoea exertional, respiratory arrest, respiratory distress, respiratory failure
Fever	Pyrexia, febrile neutropenia, or temperature ≥ 38.3°C
Weight gain	Capillary leak syndrome, fluid overload, fluid retention, generalized oedema, hydraemia, hypervolemia, oedema, oedema peripheral, peripheral swelling, weight increased, or weight > 5 kg from baseline
Hypotension	Hypotension or systolic blood pressure < 90 mmHg

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Acute renal failure	Acute kidney injury, acute prerenal failure, anuria, blood creatinine increased, cardiorenal syndrome, hepatorenal failure, prerenal failure, renal failure, renal failure acute, renal impairment, renal injury, or creatinine (µmol/L) > 26.52 µmol/L above baseline or 1.5 x above baseline
Pulmonary infiltrates or pleuropericardial effusion	Acute interstitial pneumonitis, acute lung injury, acute pulmonary oedema, acute respiratory distress syndrome, atypical pneumonia, lower respiratory tract infection, lower respiratory tract inflammation, lung infection, lung infiltration, non-cardiogenic pulmonary edema, pericardial effusion, pleural effusion, pneumonia, pneumonitis, pulmonary congestion, pulmonary oedema, pulmonary toxicity
Multiple organ dysfunction	Multiple organ dysfunction syndrome, cytokine release syndrome

Source: FDA analysis
[1] Only data points occurring in the first 90 days of therapy were included
[2] All adverse event terms are listed as preferred terms
[3] A criterion from Part B must have a start date within 7 days of another criterion from Part B to be included as a case of possible DS

Using the requested approach, the applicant identified 100/246 (41%) patients with the Montesinos algorithm, of which they determined 5 (2%) to be at least possibly related to DS. FDA's analysis using the Montesinos approach (results provided by Flora Mulkey, MS) identified 111/246 (45%) total patients on the gilteritinib arm of Study 0301. FDA reviewed narratives from all new cases of potential DS since the initial submission. Two subjects ((b) (6) [fatal]) were previously determined to have possible DS during the initial NDA review. Seven newly determined cases of DS are listed in the Table below. Thus, the true incidence of DS on the gilteritinib arm of Study 0301 appears to be 9/246 (4%).

Newly determined cases of DS on the gilteritinib arm of Study 2215-CL-0301

Subject	Day(s)	Severity[1]	Fatal	Leukocytosis[2]	Applicant Assessment	Alternative explanation
(b) (6)	28	Moderate	No	No	Possible	None
	2	Moderate	No	No	Unlikely	None
	38	Moderate	No	No	Possible	None
	21	Moderate	No	No	Unlikely	None
	44	Moderate	No	Yes	Possible	None
	35	Moderate	No	No	Unlikely	None
	43	Moderate	No	No	Unlikely	Pneumonia

Source: FDA analysis
[1]Per scoring system reported by Montesinos et al (Montesinos et al. 2009). Unknown cases were investigator-reported cases where individual symptoms of the syndrome were not captured in the AE data or case narratives.
[2]WBC > 10 x 10^9/L or an AE of leukocytosis, hyperleukocytosis, or white blood cell count increased within 7 days of the first DS event

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

As seen in the Table above, there were 5 cases where FDA disagreed with the applicant's assessment that DS was unlikely. These cases are described below:

Subject (b) (6): This was a 62-year-old man who was randomized to the gilteritinib arm after being preselected for high-intensity chemotherapy. He developed a fever and chills on day 2 of therapy. Chest x-ray was normal. Grade 2 pulmonary edema developed on day 5 and he was treated with furosemide. He also had a grade 2 cough. Cultures were negative. On day 7, biopsy of the skin showed neutrophilic dermatosis. He was treated with Augmentin and prednisone for Sweet's syndrome. The pulmonary edema recovered on day 15. The patient did not have concomitant leukocytosis. ANC was 110 on day 1, decreased, and recovered to 136 on day 15. Blasts in the blood started to decrease on day 15. The patient eventually had marrow response. In light of the unexplained fever, pulmonary edema, and cough in the setting of neutrophilic dermatosis requiring steroids, FDA considers this case to represent at least possible DS.

Subject (b) (6): This was a 61-year-old woman randomized to the gilteritinib arm who developed grade 1 pyrexia on day 21 of therapy. On day 22, she had grade 1 rash and was treated with antibiotics. On day 27, gilteritinib was increased to 200 mg based on lack of response, and on the same day, she developed round, infiltrated, and purpuric lesions on the lower limbs and face and extensor surfaces of her elbows. She was hospitalized due to acute febrile neutrophilic dermatosis (grade 3), possibly related to gilteritinib. She was treated with antibiotics and steroids. On day 28, she experienced an increase in creatinine. Of note, ANC rose from 170 on day 14 to 510 on day 28. Marrow blasts went from 78% at baseline to 65% on day 28. Peripheral blasts dropped significantly from baseline to day 28. The patient eventually achieved a marrow response to therapy. Given the fever and AKI in the setting of acute febrile neutrophilic dermatosis requiring steroids, FDA considers this case to be at least possible DS.

Subject (b) (6): This was a 72-year-old man randomized to the gilteritinib arm who developed a grade 2 pleural effusion and grade 2 peripheral edema on day 35 of therapy. WBC was not elevated, but ANC increased from up from 405 at baseline to 832 on day 29. Myeloblasts decreased from baseline in the bone marrow and peripheral blood. In the absence of a clear alternative explanation, FDA considers this case at least possibly related to DS.

Subject (b) (6): This was a 60-year-old woman randomized to the gilteritinib arm who developed a grade 3 pneumonia on day 19 and was treated with antibiotics and steroids. AST and ALT increased on day 21 and gilteritinib was interrupted. On day 31, gilteritinib was resumed at a dose of 80 mg. On day 43, the patient developed grade 3 febrile neutropenia and grade 2 drug eruption possibly related to gilteritinib. The drug eruption increased to grade 3 in severity on day 44 and she was treated with hydroxyzine. On day 48, she developed grade 2 edema. Prednisolone was started for her drug eruption on that same day. Gilteritinib was

interrupted on day 49 and then resumed on day 56. ANC was 20 on day 42, but increased to 1817 on day 59. No blasts in the peripheral blood since day 8 and stable blasts in the marrow at 11% on day 59. Given the unexplained fever and edema in the setting of a drug eruption requiring treatment with steroids around the same time as rise in ANC, FDA suspects possible DS. An alternative etiology of the fever could have been her ongoing pneumonia.

There was one case recovered by the algorithm that the applicant adjudicated as possibly related to DS, which FDA deemed unlikely DS. This was in Subject (b) (6). On day 15, the patient had mildly elevated creatinine (still within normal range) and grade 1 cough. There was no information in the narrative describing these events. There were no blasts in the peripheral blood since day 1 and ANC was roughly stable from baseline. The symptoms were sufficiently mild and nonspecific that FDA adjudicated this case as unlikely DS.

Of the 10 total cases of DS, all were moderate per the Montesinos scoring system, but 2/10 (20%) were fatal. A total of 4/10 (40%) were associated with grade 3 or higher adverse reactions. A unique aspect of DS cases in patients treated with gilteritinib was the appearance of a rash in 3/10 (30%) of cases, 2 of which were noted to be an acute febrile neutrophilic dermatosis. This has been reported to be a potential manifestation of differentiation syndrome in patients treated with FLT3 inhibitors (Fathi et al, Blood 2013)

Based on the occurrence of this severe and potentially fatal syndrome in patients treated with gilteritinib, FDA recommends upgrading DS to a boxed warning to increase awareness of this adverse reaction, as well as to provide guidance for diagnosis and treatment.

FDA additionally performed a pooled analysis of DS in patients with R/R AML treated with the recommended dose of gilteritinib on Studies 0301 (N=246), 0101 (N=69), and 0102 (N=4). Out of the 319 total patients, 11 (3%) experienced DS. In addition to the 9 patients with DS on Study 0301 noted above, 2 patients from Study 0101 were determined to have DS during the initial NDA review (one of which, Subject (b) (6), was noted to be fatal).

Teratogenicity and Embryo-fetal Deaths

No AEs of interest related to teratogenicity and embryo-fetal deaths were reported, and no patients were pregnant or have become pregnant during any of the gilteritinib clinical studies to date. Nonclinical data suggest gilteritinib may be genotoxic and may cause embryo-fetal toxicity. However, there are no adequate, well-controlled studies evaluating the effect of gilteritinib in pregnant women.

The FDA's Assessment:

FDA agrees with the applicant's assessment.

8.3.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:
No new information is provided in the current submission.

The FDA's Assessment:
FDA confirms the applicant's assessment. The PRO tool used in this study were not sufficient to assess the patient's experience with toxicities, and the data were too incomplete for even exploratory evaluations.

8.3.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:
No new information is provided in the current submission.

The FDA's Assessment:
FDA confirms the applicant's assessment.

8.3.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:
No new information is provided in the current submission.

The FDA's Assessment:
FDA confirms the applicant's assessment.

8.3.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development
The Applicant's Position:
No assessment of human carcinogenicity or tumor development was performed.

The FDA's Assessment:
FDA confirms the applicant's assessment.

Human Reproduction and Pregnancy
The Applicant's Position:
No new information is provided in the current submission.

The FDA's Assessment:
FDA confirms the applicant's assessment.

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

No new information is provided in the current submission.

The FDA's Assessment:

FDA confirms the applicant's assessment.

8.3.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

A summary of safety from postmarketing data is not available. The first PADER will be submitted by 30 days after the data lock point of 28 Feb 2019.

The FDA's Assessment:

FDA confirms the applicant's assessment.

8.3.11. Integrated Assessment of Safety

The Applicant's Position:

The review of safety in this submission was based on the integrated gilteritinib 120 mg group at the recommended starting dose of gilteritinib 120 mg once daily with median exposure of 111 days (range: 4 to 1320 days). Event rates for individual AEs were of low incidence and generally not treatment limiting.

The 2 important identified risks include PRES and QT prolongation; pancreatitis is an important potential risk. There were 3 confirmed cases of PRES in the clinical development program and 1 in compassionate use. Two were considered related; when drug was withdrawn, all events resolved.

In the exposure-safety model evaluating gilteritinib and ΔQTcF, the predicted increase in ΔQTcF associated with steady state concentrations of gilteritinib after once daily administration of 120 mg is 4.96 msec, with an upper 1-sided 95% CI (6.20 msec). This upper limit is less than 10 msec, and suggests the predicted ΔQTcF is not clinically significant. In clinical studies in the integrated gilteritinib 120 mg group, drug-related Grade 3 QT prolongation (PT: ECG QT prolonged) was observed in 3 patients. No patients in any clinical study discontinued gilteritinib treatment due to QT prolongation. In the case of Grade 3 QT prolongation, the recommended action is interruption of gilteritinib, with resumption at a reduced dose when QTcF is ≤ Grade 1. Pancreatitis was observed in 3 patients in the integrated gilteritinib 120 mg group; none of

these events were considered drug related. Grade 3 or higher pancreatitis was observed in 1 patient. When pancreatitis is diagnosed, the recommended action is interruption of gilteritinib, with resumption at a reduced dose of 80 mg when pancreatitis is resolved. There is no strong evidence of association of gilteritinib with differentiation syndrome. Other risks that have been identified in the clinical program at the 120 mg dose include cardiac failure, pericarditis and pericardial effusion. The Grade 3 event rate for cardiac failure was 3.8% (including terms of cardiac failure, cardiac failure congestive and ejection fraction decreased); there was 1 Grade 3 event reported for pericardial effusion. Patients with R/R AML have often been treated with 1 or more lines of chemotherapy, some of which are known to be cardiotoxic.

There have been no reported cases of pregnancy or lactation in the clinical development program. There are no adequate and well-controlled studies using gilteritinib in pregnant women. In nonclinical studies, gilteritinib is considered genotoxic (micronucleus positive), and demonstrated embryo-fetal development toxicity in rats. The use of gilteritinib in pregnancy should be avoided.

Gilteritinib is associated with dose- and concentration-dependent increases in liver function tests, most notably ALT and AST, and elevations in creatine kinase. In general, these increases were mostly Grade 1 or 2 in severity, were reversible upon drug interruption and seldom resulted in patient discontinuation from treatment. Creatine kinase elevations were not accompanied by clinical events such as myositis or rhabdomyolysis, and as such did not require dose modification. Based on the exposure-response analyses for selected safety and efficacy endpoints on data from 2215-CL-0101, 2215-CL-0102 and 2215-CL-0301, exposure-related increases were observed for creatine kinase, AST, ALT and QTcF. However, these increases did not translate to a high incidence of Grade 3 AEs or study discontinuation.

This risk evaluation for gilteritinib in the treatment of pediatric patients with R/R AML has not been conducted; therefore, gilteritinib is not recommended for use in the pediatric population. Gilteritinib was well tolerated in adults with R/R AML. These patients usually have multiple comorbidities and are taking multiple concomitant medications. In the gilteritinib 120 mg group, only 5.0% of patients discontinued treatment due to an adverse drug reaction. The AEs of interest have been thoroughly evaluated, are well described, generally do not represent major safety concerns and, where appropriate, have been addressed in product labeling. There is no additional risk monitoring recommended.

In summary, gilteritinib was well tolerated, associated risks are manageable and only a small fraction of patients discontinued treatment due to adverse drug reactions.

The FDA's Assessment:
FDA disagrees with the applicant's assessment of safety. FDA performed analyses on the SAF

population of Study 2215-CL-0301. Median duration of exposure on the gilteritinib arm was 4.2 months (range 0.1-29.1) and on the chemotherapy arm was 0.9 months (range 0.2-7.1). Therefore, comparative safety analyses between the arms were performed on the first 30 days of therapy.

An overview of the safety profile for gilteritinib in patients with R/R AML on Study 0301 is listed in the Tables below; first, comparing safety between the arms in the first 30 days, and next, including safety over the entire treatment period. ADRs listed are non-laboratory ADRs.

Major safety events on Study 2215-CL-0301 in the first 30 days on both arms by preselected treatment intensity

	Preselected Low Intensity Therapy		Preselected High Intensity Therapy	
	Gilteritinib (N=97)	Chemotherapy (N=41)	Gilteritinib (N=149)	Chemotherapy (N=68)
Total deaths	4 (4%)	7 (17%)	1 (1%)	5 (7%)
On-treatment deaths[1]	4 (4%)	7 (17%)	1 (1%)	5 (7%)
On-treatment fatal ARs[1]	0	1 (2%)	1 (1%)	3 (4%)
All grade TEARs	84 (87%)	29 (71%)	133 (89%)	67 (99%)
Gr ≥ 3 TEARs	38 (39%)	12 (29%)	50 (34%)	46 (68%)
TESARs	29 (30%)	6 (15%)	33 (22%)	6 (9%)
All-cause discontinuation	9 (9%)	28 (68%)	7 (5%)	47 (69%)
TEAR with discontinuation	1 (1%)	1 (2%)	3 (2%)	1 (1%)

Source: FDA analysis
[1]On or within 30 days after the last dose of gilteritinib

Major safety events over the entire treatment period

Safety parameter	Gilteritinib (N=246)	Chemotherapy (N=109)
Total deaths	170 (69%)	81 (74%)
30-day mortality[1]	5 (2%)	12 (11%)
60-day mortality[2]	19 (8%)	19 (17%)
On-treatment deaths[3]	74 (30%)	17 (16%)

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Fatal TEARs	5 (2%)	4 (4%)
All-grade TEARs	241 (98%)	99 (91%)
Gr ≥ 3 TEARs	183 (74%)	66 (61%)
TESARs	141 (57%)	16 (15%)
All-cause discontinuation	208 (85%)	90 (83%)
TEAR with discontinuation	22 (9%)	5 (5%)

Source: FDA analysis
[1]Within 30 days following the first dose of treatment
[2]Within 60 days following the first dose of treatment
[3]On or within 30 days after the last dose of gilteritinib

Overall, the randomized Study 2215-CL-0301 confirmed the already known safety profile of gilteritinib. The study population was monitored for deaths, SAEs, common AEs, and common laboratory tests.

A total of 74 (30%) on the gilteritinib arm died during or within 30 days after study treatment, compared to 17 (16%) on the chemotherapy arm. Considering only the first 30 days, when most patients were still being treated on the control arm, on-treatment deaths on the gilteritinib vs chemotherapy arms were 4% vs 17% in patients preselected for low-intensity chemotherapy and 1% vs 7% in patients preselected for high-intensity therapy. The most frequent cause of death on both treatment arms was the primary disease. Treatment-related fatal ARs on the gilteritinib arm included cardiac arrest, differentiation syndrome, and pancreatitis. Causes of treatment-related death on the chemotherapy arm were hemorrhagic stroke, multiple organ failure, respiratory failure, and septic shock.

Gilteritinib was generally well-tolerated. The most common (incidence ≥ 15% and ≥ 2% more frequent on the gilteritinib arm) non-laboratory treatment-emergent ARs in the first 30 days of treatment in patients preselected for low-intensity chemotherapy were transaminase increased, febrile neutropenia, myalgia/arthralgia, edema, and mucositis, and in patients preselected for high-intensity chemotherapy were myalgia/arthralgia, transaminase increased, fatigue/malaise, and constipation. The most frequent grade ≥ 3 ARs (incidence ≥ 5% and ≥ 2% more frequent on the gilteritinib arm) in patients preselected for low-intensity chemotherapy were febrile neutropenia and transaminase increased, and in patients preselected for high-intensity chemotherapy was just transaminase increased. The most frequent serious AR in the first 30 days of therapy was febrile neutropenia, which occurred at a higher rate on the gilteritinib (14%) versus the chemotherapy arm (6%).

Reviewer comments: A new common ADR compared to current labeling is febrile neutropenia, given an incidence higher on the gilteritinib arm than the chemotherapy arm in patients treated with low-intensity chemotherapy.

Transaminase increased was the most common toxicity beyond 30 days of therapy, with 41% incidence of all-grade and 15% incidence of grade 3 or higher transaminase increased. Other non-laboratory ARs occurring in ≥ 20% of patients in the gilteritinib arm beyond 30 days of therapy were myalgia/arthralgia, febrile neutropenia, fever, rash, mucositis, diarrhea, fatigue/malaise, dyspnea, edema, nausea, cough, and eye disorders. Most of these events were mild-moderate in severity, except for febrile neutropenia (34% grade ≥ 3) and dyspnea (10% grade ≥ 3).

Reviewer comments: Eye disorders is a new ADR, identified based on increasing incidence over time on the gilteritinib arm.

Discontinuation due to AR occurred in 9% of patients on the gilteritinib arm versus 5% on the chemotherapy arm. The most frequent AR leading to discontinuation of gilteritinib were transaminase increased (2%) and dyspnea (2%).

The important risks of PRES, prolonged QT interval, pancreatitis, and embryo-fetal toxicity remain unchanged based on the updated safety data. However, an increased incidence of DS was noted (4%, compared to 1% in current labeling) and led to 1 death. Therefore, the addition of a boxed warning and Medication Guide for DS is indicated to notify providers and patients of the risk and provide information about appropriate mitigation strategies.

FDA additionally performed a pooled analysis of safety in patients with R/R AML treated with the recommended dose of gilteritinib on Studies 0301 (N=246), 0101 (N=69), and 0102 (N=4). Out of the 319 total patients, median duration of exposure to gilteritinib was 3.6 months (range 0.1 to 43.4 months). Fatal adverse reactions occurred in 5 (2%) of patients. These included cardiac arrest (1%) and one case each of differentiation syndrome and pancreatitis. The most frequent (≥ 5%) nonhematological serious adverse reactions reported in patients were fever (13%), dyspnea (9%), renal impairment (8%), transaminase increased (6%) and noninfectious diarrhea (5%).

In the pooled R/R AML population (N=319), 91 (29%) required a dose interruption due to an adverse reaction; the most common adverse reactions leading to dose interruption were aspartate aminotransferase increased (6%), alanine aminotransferase increased (6%) and fever (4%). Twenty patients (6%) required a dose reduction due to an adverse reaction. Twenty-two (7%) discontinued XOSPATA treatment permanently due to an adverse reaction. The most common (>1%) adverse reactions leading to discontinuation were aspartate aminotransferase

increased (2%) and alanine aminotransferase increased (2%).

Of the 319 patients, all-grade nonhematological ADRs in ≥ 10% of patients included transaminase increased (51%), myalgia/arthralgia (50%), fatigue/malaise (44%), fever (41%), mucositis (41%), edema (40%), rash (36%), noninfectious diarrhea (35%), dyspnea (35%), nausea (30%), cough (28%), constipation (28%), eye disorders (25%), headache (24%), dizziness (22%), hypotension (22%), vomiting (21%), renal impairment (21%), abdominal pain (18%), neuropathy (18%), insomnia (15%) and dysgeusia (11%). The most frequent (≥5%) grade ≥3 nonhematological adverse reactions reported in patients were transaminase increased (21%), dyspnea (12%), hypotension (7%), mucositis (7%), myalgia/arthralgia (7%), and fatigue/malaise (6%). Shifts to grades 3-4 nonhematologic laboratory abnormalities included phosphate decreased 42/309 (14%), alanine aminotransferase increased 41/317 (13%), sodium decreased 37/314 (12%), aspartate aminotransferase increased 33/317 (10%), calcium decreased 19/312 (6%), creatine kinase increased 20/317 (6%), triglycerides increased 18/310 (6%), creatinine increased 10/316 (3%), and alkaline phosphatase increased 5/317 (2%).

In general, ADRs observed on Study 0301 were comparable to those seen in the R/R AML pooled safety population.

Overall, given the historically poor survival of patients with R/R FLT3-mutated AML, the level of toxicity observed with gilteritinib is acceptable for the clinical benefit observed.

SUMMARY AND CONCLUSIONS

8.4. Statistical Issues

In the Phase 3 Study 2215-CL-030, gilteritinib demonstrated a statistically significant improvement in the OS primary efficacy endpoint compared to the salvage chemotherapy. The FDA reviewers verified the analyses results in the OS endpoint and conduct sensitivity analyses to assess whether the results were robust, all of which were consistent with the prespecified analyses. However, the interpretation of the overall OS result may need consider the following statistical issues:

- The reviewer's sensitivity analysis using the PPS demonstrated that the HR was 0.84 with 95% CI of (0.60,1.18) using stratified Cox PH model. P-value was 0.31 using stratified log-rank test. The median OS was numerically higher in the gilteritinib arm compared with salvage chemotherapy arm. The nonsignificant result may be due to the small sample size in PPS.
- OS improvement was consistent across all pre-specified stratification subgroups, with exception of patients who had an unfavorable cytogenetic risk status at baseline (HR:1.63; 95% CI :0.69, 3.848).

- Log rank test is most powerful under the assumption of proportional hazard. However, the OS results show that the hazards in the two treatment arms were not proportional. Violation of proportional hazard does not necessarily make the log rank test invalid but may make the estimated treatment effect difficult to interpret. Log rank test and median of survival may not be the optimal statistics to estimate the treatment effect when the assumption of proportional hazards was not met.
- The post baseline transplant distributions are different between two arms. Such difference does not appear to have impact on the OS results.
- The study failed to demonstrate a statistically significant improvement in EFS based on sponsor derived EFS endpoint. In addition, FDA does not agree with sponsor's definition of EFS.
- There exists imbalance follow up time between the two arms for evaluation of the EFS efficacy endpoint with patients in the gilteritinib arm appear to have longer follow-up time. Such imbalance may bias treatment effect estimate.

The statistical issues outlined above do not preclude the finding that the data support efficacy.

8.5. Conclusions and Recommendations

The FDA's Assessment:
The review team was able to verify or clarify the efficacy and safety endpoints as provided by the Applicant. The review team recommends approval of the labeling revision to update the safety results, add the survival results, and provide additional update results for CR/CRh and for achievement of transfusion independence.

Primary Statistical Reviewer	Statistical Team Leader
	Donna Przepiorka, MD, PhD
Primary Clinical Reviewer	Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:
This Application was not discussed by the Oncologic Drug Advisory Committee or any other external consultants.

10 Pediatrics

The Applicant's Position:
No new information is provided in the current submission.

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

The FDA's Assessment:
Confirmed.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The FDA's Assessment:

Summary of Significant Labeling Changes

Section	Applicant's Proposed Labeling	FDA Approved Labeling
Section 2.2 (Recommended Dosage)	Revised to provide guidance regarding (b) (4)	The data available do not support this instruction. Therefore, FDA rejects this revision.
Section 6 (Adverse Reactions)	Revised to include data from the final analysis of Study 2215-CL-0301 (ADMIRAL).	FDA agrees with including new safety data from the final analysis of ADMIRAL, but recommends changes to the format and content, including comparison of safety data between the arms in the first 30 days of therapy by preselected treatment intensity.
Section 14 (Clinical Studies)	Revised to include data from the final analysis of Study 2215-CL-0301 (ADMIRAL).	FDA agrees with including the data from the final analysis of ADMIRAL. (b) (4)

12 Appendices

12.1. References

The Applicant's References (a*vailable upon request)*

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12.2. Financial Disclosure

The Applicant's Position:
As specified in Module 1.3.4, Financial Certification and Disclosure (Sequence 0000), and in Module 1.11.3, Response to 03 October 2018 Request (Sequence 0021) of the original NDA approved on 28 November 2018, there were no financial disclosures for any investigator or subinvestigator with the exception of 1 subinvestigator (b) (4) There are no additional financial disclosures for any investigator or subinvestigator.

The FDA's Assessment:
Agree with the applicant's assessment.

Covered Clinical Study (Name and/or Number):* 2215-CL-0101 (CHRYSALIS)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
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		

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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 ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number):* 2215-CL-0301 (ADMIRAL)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1,134 investigators at 107 sites		
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 Sponsor of covered study: 0		
Is an attachment provided with details	Yes ☒	No ☐ (Request details from

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of the disclosable financial interests/arrangements:		Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	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 ☒	No ☐ (Request explanation from Applicant)

12.3. OCP Appendices

None

12.4. Additional Safety Analyses Conducted by FDA

Grouped preferred terms are displayed in the Table below.

Grouped Term	Preferred Terms
abdominal pain	abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness, epigastric discomfort, gastrointestinal pain
arrhythmia	arrhythmia, atrial fibrillation, atrial flutter, atrial tachycardia, atrioventricular block first degree, bradycardia, extrasystoles, heart rate irregular, sinus bradycardia, sinus node dysfunction, sinus tachycardia, supraventricular tachycardia, tachycardia, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation, ventricular tachycardia
bilirubin increased	bilirubin conjugated increased, blood bilirubin increased, hyperbilirubinaemia, jaundice, ocular icterus
cardiac failure	cardiac failure, cardiac failure congestive, cardiomyopathy, cardiomegaly, chronic left ventricular failure, diastolic dysfunction, ejection fraction decreased, restrictive cardiomyopathy
cytopenia	bone marrow failure, cytopenia, pancytopenia
decreased appetite	decreased appetite; hypophagia
DIC	activated partial thromboplastin time prolonged, antithrombin III decreased, disseminated intravascular coagulation, fibrin D dimer increased, fibrin degradation products increased, hyperfibrinolysis, international normalised ratio increased, prothrombin time prolonged
dizziness	balance disorder, coordination abnormal, dizziness, dizziness postural, vertigo
dyspnea	acute respiratory failure, acute respiratory distress syndrome, dyspnea, dyspnoea exertional, hypoxia, orthopnoea, oxygen saturation decreased, pulmonary oedema, respiratory distress, respiratory failure, tachypnoea, wheezing

Grouped Term	Preferred Terms
edema	eye oedema, oedema, face oedema, fluid overload, fluid retention, generalized oedema, hypervolaemia, lip oedema, localized oedema, lymphoedema, oedema peripheral, peripheral swelling, periorbital oedema, scrotal oedema, swelling face
eye disorders	amblyopia, asthenopia, borderline glaucoma, cataract, cataract nuclear, chorioretinal atrophy, cornea verticillate, corneal erosion, detachment of retinal pigment epithelium, diabetic retinopathy, diplopia, eye naevus, eye oedema, eye pain, eye swelling, glaucoma, hemianopia homonymous, keratitis, foreign body sensation in eyes, lenticular opacities, macular degeneration, macular fibrosis, maculopathy, ocular discomfort, ocular hyperaemia, ocular hypertension, optical coherence tomography abnormal, photophobia, photopsia, pinguecula, posterior capsule opacification, punctate keratitis, retinal depigmentation, retinal detachment, retinal exudates, retinal oedema, retinopathy, retinopathy hypertensive, subretinal fluid, vision blurred, visual acuity reduced, visual field defect, visual impairment, vitreous degeneration, vitreous detachment, vitreous floaters
fatigue/malaise	asthenia, fatigue, lethargy, malaise
fungal infection	anal candidiasis, bronchitis fungal, bronchopulmonary aspergillosis, candida infection, coccidioidomycosis, eye infection fungal, fungaemia, fungal infection, fungal rhinitis, fungal skin infection, fungal test positive, laryngitis fungal, lower respiratory tract infection fungal, mucormycosis, oral candidiasis, oral fungal infection, oropharyngeal candidiasis, oropharyngitis fungal, pulmonary mycosis, respiratory moniliasis, respiratory tract infection fungal, sinusitis fungal, skin candida, systemic candida, systemic mycosis, tongue fungal infection, vulvovaginal candidiasis, vulvovaginal mycotic infection
gastrointestinal hemorrhage	gastric haemorrhage, gastrointestinal haemorrhage, haematemesis, haematochezia, haemorrhoidal haemorrhage, lower gastrointestinal haemorrhage, melaena, occult blood positive, rectal haemorrhage, small intestinal haemorrhage, upper gastrointestinal haemorrhage
GVHD	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
headache	Headache, head discomfort, sinus headache, tension headache
hemorrhage	catheter site haematoma, catheter site haemorrhage, conjunctival haemorrhage, epistaxis, eye haemorrhage, genital haemorrhage, gingival bleeding, haemorrhage, haemorrhage subcutaneous, haematoma, haematuria, haemoptysis, mouth haemorrhage, mucosal haemorrhage, muscle haemorrhage, optic disc haemorrhage, oral mucosa haematoma, pericardial haemorrhage, post procedural haematoma, post procedural haemorrhage, pulmonary alveolar haemorrhage, pulmonary haemorrhage,

Grouped Term	Preferred Terms
	renal haematoma, renal haemorrhage, retinal haemorrhage, retroperitoneal haemorrhage, skin haemorrhage, subcutaneous haematoma, tongue haematoma, tooth socket haemorrhage, uterine haemorrhage, vaginal haemorrhage, vitreous haemorrhage
hyperglycemia	blood glucose increased, diabetes mellitus, diabetes mellitus inadequate control, glucose tolerance impaired, hyperglycaemia, type 2 diabetes mellitus
hypersensitivity	anaphylactic reaction, angioedema, dermatitis allergic, drug hypersensitivity, erythema multiforme, hypersensitivity, urticaria
hypertension	blood pressure increased, hypertension, orthostatic hypertension, secondary hypertension
hyponatremia	hyponatraemia, hyponatraemic syndrome
hypotension	blood pressure decreased, blood pressure orthostatic, circulatory collapse, hypotension, orthostatic hypotension, shock
infectious diarrhea	bacterial colitis, clostridium difficile colitis, clostridium difficile infection, clostridium test positive, diarrhoea infectious, enterocolitis bacterial, enterocolitis infectious, gastroenteritis clostridial, gastroenteritis Escherichia coli, gastroenteritis viral, infectious colitis, norovirus test positive, pseudomembranous colitis
intestinal perforation	duodenal perforation, intestinal perforation, large intestine perforation
leukopenia	leukopenia, white blood cell count decreased
mucositis	angina bullosa haemorrhagica, aphthous ulcer, colitis, duodenitis, enteritis, enterocolitis, gastric ulcer, gastritis, gastroenteritis, gingival pain, gingival ulceration, gingivitis, large intestinal ulcer, laryngeal inflammation, lip blister, lip ulceration, mucosal inflammation, mouth hemorrhage, mouth ulceration, neutropenic colitis, oesophageal pain, oral discomfort, oral mucosal blistering, oral mucosal erythema, oral pain, oropharyngeal discomfort, oropharyngeal pain, pharyngeal inflammation, proctalgia, proctitis, stomatitis, stomatitis necrotizing, swollen tongue, tongue discomfort, tongue ulceration
myalgia/arthralgia	arthralgia, arthritis, back pain, bone pain, coccydynia, flank pain, limb discomfort, medial tibial stress syndrome, myalgia, muscle contracture, musculoskeletal discomfort, musculoskeletal pain, muscle rupture, muscle spasms, musculoskeletal stiffness, muscle twitching, neck pain, non-cardiac chest pain, osteoarthritis, pain, pain in extremity, pain in jaw, polyarthritis, sacroiliitis
neuropathy	axonal neuropathy, carpal tunnel syndrome, hyperaesthesia, hypoaesthesia, neuralgia, neuromyopathy, neuropathy peripheral, peripheral sensory neuropathy, demyelinating polyneuropathy, paraesthesia, polyneuropathy, radicular pain, sensory loss
noninfectious diarrhea	diarrhea, diarrhoea haemorrhagic
pancreatitis	amylase increased, lipase increased, pancreatitis, pancreatitis acute

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Grouped Term	Preferred Terms
pericarditis/ myocarditis	myocarditis, pericardial fibrosis, pericardial haemorrhage, pericardial rub, pericarditis
pneumonia	atypical pneumonia, pneumonia, lung infection, pneumonia fungal, respiratory syncytial virus infection, respiratory tract infection, respiratory tract infection bacterial, respiratory tract infection fungal, respiratory tract infection viral, lung infiltration, organizing pneumonia, lower respiratory tract infection bacterial, lower respiratory tract infection fungal, lower respiratory tract infection viral, lower respiratory tract inflammation, lung infection pseudomonal, pneumonia aspiration, pneumonia respiratory syncytial viral, pneumonitis, pulmonary mycosis, interstitial lung disease, lower respiratory tract infection, pneumonia viral, pneumonia bacterial, respiratory moniliasis
pruritus	Pruritus, pruritus allergic, pruritus generalized, pruritus genital
rash	acne, acute febrile neutrophilic dermatosis, dermatitis, dermatitis acneiform, dermatitis bullous, dermatitis contact, dermatosis, drug eruption, dermatitis exfoliative, eczema, eczema asteatotic, epidermolysis, erythema nodosum, hyperkeratosis, lichen planus, lichenification, lichenoid keratosis, macule, erythema, palmar-plantar erythrodysaesthesia syndrome, neurodermatitis, neutrophilic dermatosis, papule, perivascular dermatitis, photosensitivity reaction, psoriasis, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash popular, rash pruritic, rash pustular, rash vesicular, rosacea, seborrheic dermatitis, skin candida, skin disorder, skin exfoliation, skin hyperpigmentation, skin hypopigmentation, skin lesion, skin necrosis, skin papilloma, skin plaque, skin ulcer, toxic skin eruption
renal impairment	acute kidney injury, acute prerenal failure, azotaemia, blood creatinine increased, blood urea increased, chronic kidney disease, glomerular filtration rate decreased, oliguria, renal disorder, renal failure, renal impairment, renal injury, renal tubular necrosis, tubulointerstitial nephritis
seizure	epilepsy, seizure, seizure like phenomena
sepsis	sepsis, bacteremia, Enterobacter bacteraemia, Enterococcal bacteraemia, Enterococcal sepsis, Enterobacter sepsis, Escherichia bacteraemia, Escherichia sepsis, urosepsis, septic shock, bacterial sepsis, Klebsiella bacteraemia, meningitis bacterial, neutropenic sepsis, Pseudomonal bacteraemia, Pseudomonal sepsis, Staphylococcal bacteraemia, Streptococcal bacteraemia, Streptococcal sepsis, systemic bacterial infection, systemic infection
syncope	loss of consciousness, syncope
transaminase increased	ascites, aspartate aminotransferase increased, alanine aminotransferase increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased, hepatic congestion, hepatic function abnormal, ischaemic hepatitis, transaminases increased, liver function test increased, hepatic enzyme increased, hepatic failure, hepatocellular injury, hepatotoxicity, drug-induced liver injury

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Grouped Term	Preferred Terms
visual impairment	vision blurred, visual acuity reduced, visual impairment
vomiting	hematemesis, vomiting

(b) (4)

[redacted]

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13 Division Director (OB)

Thomas E. Gwise, PhD
Deputy Division Director (OB)

14 Division Director (DHP)

I agree with the recommendation of the review divisions to approve this supplement.

Albert Deisseroth, MD, PhD
Supervisory Associate Division Director (DHP)

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/s/

ROSA J LEE-ALONZO
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KELLY J NORSWORTHY
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05/29/2019 11:57:22 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211349Orig1s001

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 29, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 211349/S-001
Product Name and Strength:	Xospata (gliteritinib) tablets, 40 mg
Applicant/Sponsor Name:	Astellas Pharma US, Inc. (Astellas)
FDA Received Date:	May 1, 2019 and May 16, 2019
OSE RCM #:	2019-418-1
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Division of Hematology Products (DHP) requested that we review the revised container label and carton labeling for Xospata (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to a proposed Medication Guide submitted by the Applicant on May 1, 2019 and May 16, 2019 with subsequent changes to the container label and carton labeling. (b) (4)

2 CONCLUSION

The Applicant submitted a revised container label and carton labeling received on May 1, 2019 for Xospata. In addition, the Applicant submitted a proposed Medication Guide on May 1, 2019 and May 16, 2019. The proposed Medication Guide is acceptable from a medication error perspective. The revised container label and carton labeling are unacceptable from a medication error perspective. The Medication Guide Statement on the revised container label and carton labeling do not indicate that the Medication Guide shall be provided to each patient to whom the drug product is dispensed.

3 RECOMMENDATIONS FOR ASTELLAS

We recommend the following be implemented prior to approval of this SUPPLEMENT:

A. General Comments (Container labels & Carton labeling)

1. The Medication Guide statement shall instruct the authorized dispenser to provide a Medication Guide to each patient to whom the drug product is dispensed and shall state how the Medication Guide is provided. Your proposed statement does not appear to state to whom the Medication Guide is dispensed. Consider if the statement "Dispense enclosed Medication Guide to each patient." is appropriate and satisfies the regulation 21 CFR 208.24(d).

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/s/

NICOLE B GARRISON
05/29/2019 07:25:44 AM

HINA S MEHTA
05/29/2019 08:09:23 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: 5/9/19

To: Rosa Lee-Alonzo, Regulatory Project Manager, DHP

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Rachael Conklin, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kevin Wright, Team Leader, OPDP

Subject: OPDP Labeling Comments for XOSPATA® (gilteritinib) tablets, for oral use

NDA: 211349, S-001

In response to DHP's consult request dated February 5, 2019, OPDP has reviewed the proposed product labeling (PI) and Medication Guide (MG) for for XOSPATA® (gilteritinib) tablets, for oral use (Xospata) S-001. This supplement adds OS data from the final analysis in the ADMIRAL Trial. This supplement also updates the Warnings and Precautions section for Differentiation Syndrome and adds a Boxed Warning for Differentiation Syndrome. Section 6.1 was also updated.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI emailed to OPDP on April 26, 2019, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the MG were sent under separate cover.

Thank you for your consult. If you have any questions, please contact Rachael Conklin at 240-402-8189 or rachael.conklin@fda.hhs.gov.

PI

OPDP does not have any comments on the PI at this time.

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RACHAEL E CONKLIN
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 3, 2019
To:	Ann Farrell, MD Director **Division of Hematology Products (DHP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rachael Conklin, MSN, RN Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	XOSPATA (gilteritinib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 211349
Supplement Number:	S-001
Applicant:	Astellas Pharm US, Inc.

1 INTRODUCTION

On February 22, 2019, Astellas Pharma US, Inc., submitted for the Agency's review a Prior Approval Supplement (PAS)-Efficacy to their New Drug Application (NDA) 211349/S-001 for XOSPATA (gilteritinib) tablets, for oral use. With this supplement, the Applicant provides revised labeling based on the final analysis of study 2215-CL-0301 (ADMIRAL). On April 26, 2019 the Applicant submitted updated Prescribing Information, proposed boxed warning text for Differentiation Syndrome and a Medication Guide (MG) to replace the Patient Package Insert (PPI) as requested by the Agency in an email correspondence dated March 15, 2019.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on February 24, 2019 and February 5, 2019, respectively, for DMPP and OPDP to review the Applicant's proposed MG for XOSPATA (gilteritinib) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft XOSPATA (gilteritinib) tablets Medication Guide received on April 26, 2019, and received by DMPP and OPDP on April 26, 2019.
- Draft XOSPATA (gilteritinib) tablets Prescribing Information (PI) received on April 24, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 26, 2019.
- Approved XOSPATA (gilteritinib) tablets labeling dated November 28, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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SUSAN W REDWOOD
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RACHAEL E CONKLIN
05/06/2019 10:03:21 AM

BARBARA A FULLER
05/06/2019 10:24:51 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 15, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	NDA 211349
Product Name and Strength:	Xospata (gilteritinib) tablets, 40 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Astellas Pharma US, Inc. (Astellas)
FDA Received Date:	December 17, 2019, January 18, 2019, January 22, 2019, January 24, 2019 and February 22, 2019
OSE RCM #:	2019-418
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

Astellas submitted a supplement for Xospata (gilteritinib) tablets to update the Prescribing Information (PI) for Xospata based on the final analysis of study 2215-CL-0301 (ADMIRAL). Based on the final analysis of study 2215-CL-030 (b) (4) Subsequently, the Division of Hematology Products (DHP) requested that we review the proposed Xospata prescribing information (PI) and patient information for areas of vulnerability that may lead to medication errors.

2 BACKGROUND

NDA 211349 was approved on November 28, 2018 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. It is available in a 40 mg tablet.

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C
FDA Adverse Event Reporting System (FAERS)*	D- N/A
Other	E- N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 FINDINGS AND RECOMMENDATIONS

We performed a risk assessment of the PI and Patient Information for Xospata (gilteritinib) tablets to determine whether there are significant concerns in terms of safety, related to preventable medication errors. We find the Patient Information acceptable from a medication error perspective. We note inconsistent use of the "- "symbol in the Highlights of the PI and in Section 2.2 *Recommended Dosage* of the PI. We recommend revising the dosage statement by removing the symbol "- ". We also note the storage statement advises to "keep in original container"; (b) (4) We discussed this with CMC and they stated the product may be light sensitive if exposed to direct outdoor light only. Thus, the "keep in original container" can

be changed to include only a precautionary statement in the PI to protect the product from light.

Additionally, (b) (4) Tables 2 below includes the identified medication error issues with the submitted prescribing information (PI), our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Hematology Products (DHP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	There is inconsistent use of the symbol "- "in the dosage statement for the 120 mg dose. For example, the Highlights of the Prescribing Information the dosage statement appears as "120 mg orally once-daily". However, the Full Prescribing Information, the dosage statement appears as "120 mg orally once daily with or without food".	The dosage statement should appear consistent throughout the Highlights of the Prescribing Information and the Prescribing Information.	Consider revising the dosage statement to remove the symbol. Revise "120 mg orally once-daily" to "120 mg orally once daily."
Full Prescribing Information – Section 2 Dosage and Administration			
(b) (4)			

Table 2. Identified Issues and Recommendations for Division of Hematology Products (DHP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	(b) (4)		Consider revising Table 1 to include all dose modifications for Xospata. Table 1: Dosage Modifications for Xospata-Related Toxicities

Adverse Reaction	Recommended Action
Posterior Reversible Encephalopathy Syndrome	Discontinue XOSPATA.
QTc interval greater than 500 msec	Interrupt XOSPATA. • Resume XOSPATA at 80 mg when QTc interval returns to within 30 msec of baseline or less than or equal to 480 msec.
QTc interval increased by >30 msec on ECG on day 8 of cycle 1	•Confirm with ECG on day 9. • If confirmed, consider dose reduction to 80 mg.
Pancreatitis	(b) (4)

(b) (4)

(b) (4)

(b) (4)

Table 2. Identified Issues and Recommendations for Division of Hematology Products (DHP)				
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION	
			Other Grade 3* or higher toxicity considered related to treatment.	• Interrupt XOSPATA until toxicity resolves or improves to Grade 1*. • Resume XOSPATA at 80 mg. (b) (4) [redacted]
Full Prescribing Information – Section 16 How Supplied/Storage and Handling				
1.	The storage statement advises to "keep in original container" (b) (4) [redacted]	Improper storage may lead to product stability issues.	We recommend revising the storage statement to include the statement, "Protect from light" and deleting the statement, "Keep in original container".	

Table 3. Identified Issues and Recommendations for Astellas Pharma US, Inc. (Astellas) (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	The storage statement advises to "keep in original container" (b) (4) [redacted]	Improper storage may lead to product stability issues.	We recommend revising the storage statement to include the statement, "Protect from light" and deleting the statement, "Keep in original container".

5 CONCLUSION

Our evaluation of the proposed Xospata Patient Information did not identify areas of vulnerability that may lead to medication errors. However, we recommend removing the "-

"symbol in the dosage statement, revising the storage statement and including all dose modifications in the dose modification table. With the revision to the storage statement in the Prescribing Information, we recommend revising the container label and carton labeling to be consistent with the Prescribing Information. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Astellas Pharma US, Inc. (Astellas) so that recommendations are implemented prior to approval of this NDA Supplement.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Xospata that Astellas Pharma US, Inc. (Astellas) submitted on March 7, 2019.

Table 4. Relevant Product Information for Xospata	
Initial Approval Date	November 28, 2018
Active Ingredient	gliterinib
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.
Route of Administration	Oral
Dosage Form	Tablets
Strength	40 mg
Dose and Frequency	The recommended starting dose of Xospata is 120 mg orally once daily. (b) (4)
How Supplied	Xospata (gilteritinib) 40 mg tablets are supplied as light yellow, round-shaped, film-coated tablets debossed with the Astellas logo and '235' on the same side. Xospata tablets are available in the following package size: • Bottles of 90 tablets with Child Resistant Closure
Storage	Store Xospata tablets at 20ºC to 25ºC (68°F to 77°F); excursions permitted between 15ºC to 30ºC (59°F to 86°F) [See USP Controlled Room Temperature]. Keep in original container.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 7, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, Xospata. Our search identified three previous label and labeling reviews[a,bc], and we considered our previous recommendations to see if they are applicable for this current review.

[a] Ogbonna, C. Label and Labeling Review for Xospata (NDA 211349). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUL 24. RCM No.: 2018-641.

[b] Ogbonna, C. Label and Labeling Review for Xospata (NDA 211349). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 AUG 10. RCM No.: 2018-641-1.

[c] Ogbonna, C. Label and Labeling Review for Xospata (NDA 211349). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 09. RCM No.: 2018-641-2.

APPENDIX C. ISMP NEWSLETTERS

C.1 Methods

On March 7, 2019, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

Table 5. ISMP Newsletters Search Strategy

ISMP Newsletter(s)	Acute Care ISMP Medication Safety Alert Community/Ambulatory Care ISMP Medication Safety Alert Nurse Advise-ERR Long-Term Care Advise-ERR ISMP Canada Safety Bulletin Pennsylvania Patient Safety Advisory
Search Strategy and Terms	Match Exact Word or Phrase: Xospata

C.2 Results

The search retrieved no relevant articles associated with label and labeling for Xospata.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Xospata labels and labeling submitted by Astellas Pharma US, Inc. (Astellas).

- Prescribing Information (Image not shown) received on January 22, 2019
- Patient Information (Image not shown) received on January 22, 2019

F.2 Label and Labeling Images

Prescribing Information and Patient Information

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[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/

NICOLE B GARRISON
03/15/2019 02:32:31 PM

HINA S MEHTA
03/15/2019 06:16:05 PM