Name of Sponsor/Company: Astellas Pharma Development US		
Name of Finished Product: Not available		
Name of Active Ingredient: Gilteritinib (ASP2215)		

SYNOPSIS

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

Investigators/Coordinating Investigator:

[redacted] MD, PhD

Study Center(s):

Study 2215-CL-0101 was conducted at 27 sites in the US, Germany and Italy.

Publication Based on the Study:

Perl AE, Altman JK, Cortes J, Smith C, Litzow M, Baer MR, et al. Selective inhibition of FLT3 by gilteritinib in relapsed or refractory acute myeloid leukemia: a multicentre, first-in-human, open-label, phase 1-2 study. Lancet Oncol. 2017;18(8):1061-75.

Levis MJ, Perl AE, Altman JK, Gocke CD, Bahceci E, Hill J, et al. A next-generation sequencing-based assay for minimal residual disease assessment in AML patients with FLT3-ITD mutations. Blood Advances. 2018;2(8):825-31.

Study Period:

09 Oct 2013 to 07 Mar 2018 (version 3.0)

Study Initiation Date (Date of First Enrollment):

09 Oct 2013

Study Completion Date (Date of Last Evaluation):

07 Mar 2018

Phase of Development:

Phase 1/2

Objectives:

The primary objectives of the study were to assess the safety and tolerability, including determination of the maximum tolerated dose (MTD) of oral gilteritinib in patients with relapsed or treatment-refractory acute myeloid leukemia (AML) and to determine the pharmacokinetic parameters of gilteritinib.

The secondary objectives of the study were to investigate the anti-leukemic activity of various doses of gilteritinib in patients with AML, evaluate the effect of strong or moderate cytochrome P450-isozyme 3A4 (CYP3A4) inhibitors on the pharmacokinetics of gilteritinib, evaluate the potential induction of CYP3A4 by gilteritinib by assessment of midazolam pharmacokinetics, and evaluate the effect of gilteritinib on multidrug and toxin extrusion 1 (MATE1) substrates by assessment of cephalexin pharmacokinetics.

Methodology:

This study was an open-label, dose escalation, first-in-human study in patients with relapsed or refractory AML, with concomitant expansion cohort for multiple doses. Patients with AML who relapsed after or were refractory to induction or salvage treatment were selected for this study. Patients were assigned in Cohort 1 or randomized in Cohort 2 to one of the open dose levels as defined in the statistical methodology section of the protocol. At least 10 patients with FLT3 mutations (ITD or activating point mutations) were to be enrolled to each expanded dose level (including the patients in Cohort 2). Dose levels at and above 120 mg would be further expanded (when found to be tolerable in Cohort 1) based on the efficacy results observed in escalation and expansion cohorts as described in the statistical section of the protocol.

Re-screening was allowed, with a limit of 2 re-screenings for any potential patient. Re-enrollment into the trial was permissible for patients who discontinued treatment for reasons other than toxicity or disease progression as long as they fulfilled all Inclusion and Exclusion Criteria. All patients that re-enrolled were enrolled into Cohort 2 and followed the assigned Schedule of Assessments as if they were a new patient.

At least 42 evaluable patients with FLT3 mutations were to be enrolled in dose levels selected for further expansion. One cycle was defined as 28 days and the patient received oral gilteritinib daily. The study treatment continued until one of the discontinuation criteria was met or until rollover into Study 2215-CL-0109.

The starting dose level of gilteritinib was 20 mg daily and the decision to dose escalate to the next dose level was made based on the assessment of safety variables including occurrence of grade 2 adverse events (AE) or dose limiting toxicities (DLTs).

Number of Patients (Planned, Enrolled and Analyzed):

The dose expansion phase planned to enroll up to 250 patients in the expansion cohort, depending on the number of dose levels expanded. The total number of patients estimated for enrollment was between 2 and 270 patients.

Three hundred and forty-seven patients were consented for the study. Of these, 25 were allocated to treatment for the dose escalation phase and an additional 240 randomized to the dose expansion phase, which includes 5 patients who were re-enrolled into the study. Two hundred and fifty-two unique patients received at least 1 dose of study drug and were included in the Safety Analysis Set (SAF).

Diagnosis and Main Criteria for Inclusion:

Male or female patients ≥ 18 years of age, inclusive, at the time of obtaining informed consent, who provided written informed consent and to whom all the inclusive and none of the exclusion criteria applied, were eligible for inclusion in this study. Female patients must have been of nonchildbearing potential or child-bearing potential with testing and birth control requirements and male patients and their female spouse/partners who were of childbearing potential must have been using 2 forms of highly effective birth control. Patients had to be defined as morphologically documented primary or secondary AML by the World Health Organization criteria

(Swerdlow et al, 2008) and fulfilled one of the following: refractory to at least 1 cycle of induction chemotherapy or relapsed after achieving remission with a prior therapy.

Patients had to have an Eastern Cooperative Oncology Group performance status ≤ 2. Patients' interval from prior treatment to time of study drug administration was at least 2 weeks for cytotoxic agents (except hydroxyurea given for controlling blast cells), or at least 5 half-lives for prior experimental agents or noncytotoxic agents. Patients must have been suitable for oral administration of study drug.

Test Product, Dose and Mode of Administration, Batch Numbers:

Gilteritinib was available either as 10 or 100 mg tablets contained within blister cards, supplied as 140 tablets per carton (10 cards per carton and 14 tablets per card), or as 40 or 100 mg tablets, contained within 30 count bottles.

- Gilteritinib 10 mg tablets, lot numbers: CLR-9006456-001, CLR-9006456-002, CLR-9006456-008, CLR-9006456-014, CLR-9006456-008 (initial packaging)/CLR-9006456-015 (over label)
- Gilteritinib 40 mg tablets (F), lot numbers: CLR-9006456-019, CLR-9006456-020, CLR-9006456-019 (initial packaging)/CLR-90006456-021 (over label), CLR-9006456-020 (initial packaging)/CLR-90006456-022 (over label), CLR-9006456-020 (initial packaging)/CLR-90006456-022 (over label)/CLR-90006456-027 (over label), CLR-9006456-020 (initial packaging)/CLR-90006456-022 (over label)/CLR-90006456-029 (over label), CLR-9006456-030
- Gilteritinib 100 mg tablets, lot numbers: CLR-9006456-003, CLR-9006456-004, CLR-9006456-009, CLR-9006456-010, CLR-9006456-009 (initial packaging)/CLR-9006456-016 (over label), CLR-9006456-010 (initial packaging)/CLR-9006456-017 (over label), CLR-9006456-005 (initial packaging)/CLR-9006456-028 (over label)

Duration of Treatment (or Duration of Study, if applicable):

Screening occurred from days -14 to -3 before study drug administration at the clinic on day -2 for the escalation cohort and day 1 for expansion cohort. One dose daily in 28-day cycles until a discontinuation criterion was met.

Reference Product, Dose and Mode of Administration, Batch Numbers:

Gilteritinib was administered orally without food for at least 2 hours before and 1 hour after dosing. Patients were instructed to take the daily dose with water as close to the same time each morning as possible.

Criteria for Evaluation:

Safety Analyses:

Safety analyses consisted of data summaries of AEs, DLTs and other safety parameters. The number and percent of patients experiencing 1 or more AE(s) was summarized by cohort and dose level. The relationship to study drug, time of onset and severity of AE was also summarized. Adverse events were coded to system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Efficacy Analyses:

Complete remission (CR) rate, composite complete remission rate, overall response rate, duration of confirmed response, overall survival (OS), event-free survival (EFS), leukemia-free survival, and duration of remission

were summarized using descriptive statistics. The survival curve and median for time-to-event variables were estimated using the Kaplan-Meier method and were reported along with the corresponding 95% confidence interval (CI). To explore the relationship between dose level and CR response, a dose-response model (logistic regression) was fitted to the binary CR response with FLT3 mutation status, the first and second order of logarithm transformed dose as independent covariates for all patients from the dose escalation and dose expansion cohorts. The CR response rate for each dose level was estimated with 2-sided 95% CI from this model.

Pharmacokinetics Analyses:

Plasma concentrations and pharmacokinetic parameters were summarized by cohort using descriptive statistics, including number of patients, mean, standard deviation (SD), minimum, median, maximum, geometric mean, and coefficient of variation (CV) of the mean and geometric mean. Time-course of drug concentrations was plotted as appropriate.

Patients with sufficient pharmacokinetic samples had pharmacokinetic parameter estimates for gilteritinib, including calculation of AUC_{24}, C_{max}, C_{trough} and t_{max} using standard non-compartmental analyses.

Statistical Methods:

The Full Analysis Set (FAS) consisted of all patients who were enrolled and received at least 1 dose of study drug and who had at least 1 posttreatment data point. Re-enrolled patients were excluded from FAS. All 3 patients enrolled at site [redacted] were excluded from the FAS due to concerns with this site's compliance to GCP, but remained within the SAF. The FAS was used for summaries of efficacy data, as well as selected demographic and baseline characteristics.

All patients who received at least 1 dose of study drug (SAF) had at least 1 posttreatment data point. Thus, the FAS included all patients who received at least 1 dose of study drug (SAF) with the exception of the 3 patients enrolled at site [redacted] who were excluded from the FAS due to concerns with this site's GCP compliance.

The Per Protocol Set (PPS) included all patients of the FAS who did not meet criteria for exclusion from PPS. The PPS was used for sensitivity analyses of efficacy data.

The SAF consisted of all patients who received at least 1 dose of study drug. Re-enrolled patients were excluded from the SAF. The SAF was used for summaries of demographic and baseline characteristics and all safety and tolerability related variables. The SAF was also used for sensitivity analyses of efficacy data.

The Pharmacokinetics Analysis Set (PKAS) consisted of the subset of the SAF for which sufficient plasma concentration data were available to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling was known.

The Pharmacodynamic Analysis Set (PDAS) included the patients from the SAF for whom sufficient pharmacodynamic measurements were collected.

The Re-Enrolled Analysis Set included patients who discontinued treatment for reasons other than toxicity or disease progression and were re-enrolled into the expansion phase and received at least 1 dose of study drug after re-enrollment.

The Post-HSCT Analysis Set included patients who received at least 1 dose of study drug and 1) underwent on-study HSCT and resumed gilteritinib after HSCT and/or 2) discontinued the treatment for HSCT and were re-enrolled into the study and received at least 1 dose of study drug after re-enrollment.

The minimal residual disease (MRD) Analysis Set (MAS) included all patients who were enrolled and received at least 1 dose of study drug, were centrally confirmed as FLT3-ITD positive and had a baseline and at least 1 post-baseline sample with MRD data.

A modified 3 + 3 design with an accelerated titration was applied in the dose escalation cohort as described in the Study Design Overview section of the protocol. A 2-parameter Bayesian logistic regression was used to model the dose-toxicity relationship on DLT. Patients in either dose escalation cohort or dose expansion cohorts who completed at least 1 treatment cycle or experience DLTs were included in the model-fitting process to provide the complete safety information. The estimated DLT rates based on the Bayesian logistic regression model for each dose level were provided as references for dose escalation procedures in dose escalation cohort and safety monitoring in dose expansion cohort. If the DLT rate for an expanded dose level was equal or higher than 20% with a posterior probability of 80%, then the enrollment to the dose level was paused and the safety was reassessed.

As a dose level was decided to be expanded, up to 17 patients were enrolled for the dose level in the dose expansion phase (to have a total of 20 patients enrolled at a dose level including the patients from dose escalation cohort). When > 1 dose levels were expanded in the dose expansion cohort (Cohort 2), the newly enrolled patients were randomized to one of the open expanded dose levels, based on the relative chance of (20 – n) in each dose level, where n was the number of patients already enrolled in the dose level, including both the dose escalation and expansion phases.

If 10 patients without FLT3 mutations (ITD or activating point mutations) were enrolled into an expanded dose level (including the patients in the dose escalation cohort and dose expansion cohort), only patients with FLT3 mutations could have been enrolled to the dose level.

Any dose level in the dose expansion cohort would be stopped if no composite complete remission (CRc) was achieved in > 6 patients who completed 2 treatment cycles or < 2 CRcs in more than 12 patients were achieved.

To improve guidance for Recommended Phase 2 Dose, dose levels at and above 120 mg were further expanded (when found to be tolerable in Cohort 1) based on the efficacy results observed in escalation and expansion cohorts. Approximately 40 additional Cohort 2 patients were to be enrolled at these dose levels to bring the total enrolled to approximately 60 patients at the dose level inclusive of Cohort 1 patients. A minimum of 42 evaluable (received 2 cycles of treatment or discontinued for progressive disease) FLT3 mutated patients were to be enrolled.

The increased patient numbers would enable us to more accurately estimate the actual response rate (CRc) for a dose level based on the observed response rate. With approximately 42 evaluable FLT3 mutated patients, the 90% 1-sided CI was about 10% below the observed response rate for each dose level. If the estimated response rate was 50%, we would have been 90% sure that the real response rate was higher than 40%. Response rate was continuously monitored for each dose level and the enrollment would have been stopped if the response rate for that dose level was at a 90% significance level, < 45% based on Wald's Sequential Probability Ratio Test with 25% as the unacceptable low response rate and 80% power.

Summary of Results/Conclusions:

Patient disposition for various populations is presented in Table 1 and a summary of demographics and baseline characteristics of all randomized patients by local FLT3 mutation status can be found in Table 2

Efficacy Results:

Response Assessment:

Response was assessed based on central assessment supplemented by local assessment (i.e., derived response) and investigator reported response. For tables based on the FAS and PPS, patients are included in the planned dose level. For tables based on the SAF, patients are included in the dose group of the initial dose received prior to any dose increase or decrease, unless otherwise noted. Based on the derived response at end of treatment in the FLT3 mutation positive patients (local FLT3 testing, FAS), 71 patients achieved CRc for a CRc rate of 37.2%, and the best overall response rate (i.e., CRc + partial remission [PR]) was 48.7% Table 3. In the FLT3 mutation negative patients (local FLT3 testing, FAS), the CRc rate and best overall response rate were 8.6% (5/58) and 12.1% (7/58), respectively.

The dose expansions for the 20 and 40 mg dose levels were closed early due to insufficient efficacy; as a result, efficacy evaluations were focused on the 80, 120, 200 and 300 mg dose groups. When analyzed by original planned doses, the derived CRc rate for FLT3 mutation positive patients (local testing) in the 80, 120, 200 and 300 mg dose groups was 41.7%, 46.4%, 40.4% and 30%, respectively. The CR/complete remission with partial hematological recovery (CRh) rate for the total FLT3 mutation positive patients (local testing) was 19.4%; for the 80, 120, 200 and 300 mg dose groups, the CR/CRh rate was 25.0%, 23.2%, 19.1% and 30%, respectively.

Duration of Response:

For the population of FLT3 mutation positive patients, the median duration of CRc was 148.0 days (95% CI: 86.0, 420.0). The median duration of response (DOR) was 147.0 days (95% CI: 97.0, 307.0). A slight trend toward increasing DOR with increasing dose was observed. Similar results were observed when FLT3 status was determined by central testing. There was no clear dose-dependent trend in time to remission across dose groups. Patients with a response of CR/CRh had a median DOR of 383.0 days (95% CI: 136.0, NE). Overall median time to first CR/CRh in FLT3 mutation positive patients was 57.0 days, ranging from 27 to 280 days; and median time to best CR/CRh for locally evaluated FLT3 mutation positive patients was 59.0 days, ranging from 27 to 364 days.

Overall Survival:

For the population of FLT3 mutation positive patients, the median overall survival (OS) from Kaplan-Meier estimates for dose groups ≥ 80 mg gilteritinib was 218.0 days Table 4. The survival probability was 85.7% at 8 weeks, 56.2% at 26 weeks, and 24.9% at 1 year. A total of 136 (80.5%) of the 169 FLT3 mutation positive patients in the ≥ 80 mg dose group had OS events and 33 (19.5%) patients were censored. Median OS was 119.0 days (95% CI: 74.0, 144.0) for the total population of FLT3 mutation negative patients (n = 58 total, 56 OS events, 2 patients censored); with a survival probability of 67.2% at 8 weeks, 30.3% at 26 weeks, and 3.6% at 1 year.

Kaplan-Meier plots for OS for FLT3 mutation positive and FLT3 mutation negative patients assessed by local testing are displayed for all gilteritinib dose groups in Figure 1. Kaplan-Meier plots for OS for FLT3 mutation positive patients locally evaluated in ≥ 80 mg dose groups are displayed in Figure 2. Consistent with best

overall response data, FLT3 mutation negative patients showed no dose-dependent trend toward improved OS with increasing gilteritinib dose. In FLT3 mutation positive patients, 20 mg trended towards poorer OS compared to dose groups 40 mg and above. The 450 mg dose group had a low number of patients evaluable for OS (n = 2). The dose group with the most favorable overall trend for OS was the 120 mg dose group, followed by the 200 mg and 80 mg dose groups, followed by the 300 mg dose group Figure 2. In FLT3 mutation positive patients in gilteritinib dose groups 80 mg and above, longer survival time was observed in patients who achieved CRc or PR compared to patients who did not achieve a response Figure 3. Similarly, in this same population, patients in first relapse demonstrated more favorable OS compared to patients with > 1 line of AML therapy [Figure 4].

Event-free and Leukemia-free Survival:

For the population of FLT3 mutation positive patients by local testing, the median EFS by derived response from Kaplan-Meier estimates ranged between 93.5 and 121.0 days for the 80, 120 and 200 mg gilteritinib dose groups Table 5. For these same dose groups, the event-free probability at 8 weeks ranged from 78.5% to 91.7%, and at 26 weeks ranged from 10.0% to 33.8%.

For the population of FLT3 mutation positive patients by local testing, the median leukemia-free survival (LFS) by derived response from Kaplan-Meier estimates ranged between 98.0 and 146.0 days for the 80, 120, and 200 mg gilteritinib dose groups. For these same dose groups, the leukemia-free probability at 8 weeks ranged from 65.9% to 80.2%, and at 26 weeks ranged from 26.7% to 42.5%.

Pharmacokinetic Results:

Gilteritinib exhibits linear, dose-proportional pharmacokinetics in patients with relapsed or refractory AML at doses ranging from 20 to 450 mg administered once daily. Mean plasma concentration-time profiles of gilteritinib by dose cohort are presented in Figure 5 and Figure 6 after single (day -2) and multiple (cycle 1 day 15) dose administration of gilteritinib, respectively, in patients with relapsed or refractory AML. Median t_{max} was observed between 2 and 6 hours following single and multiple dosing. At 120 mg, the recommended Phase 2 dose, the median C_{max} and AUC_{24} were 282 ng/mL and 6180 ng·h/mL, respectively, after multiple dose administration. The estimated $t_{1/2}$ ranged from 45 to 159 hours. Given the long half-life, extensive accumulation was observed with gilteritinib concentrations increasing by up to 10-fold after multiple dose administration. Steady-state gilteritinib concentrations were achieved by day 15 after once daily dosing.

Although a trend to increased gilteritinib exposure with coadministration of a moderate or strong CYP3A4 inhibitor was observed, the increase was less than 2-fold suggesting a low potential for a clinically significant drug-drug interaction (DDI).

The CYP3A4 induction activity of gilteritinib on midazolam, a CYP3A4 substrate, was assessed in a subset of patients with relapsed or refractory AML. Coadministration of midazolam and cephalexin did not appear to result in a significant DDI given the approximate 10% increase in midazolam exposure compared to administration of midazolam alone. These results suggest CYP3A4 induction via gilteritinib is minor and coadministration of gilteritinib and CYP3A4 substrates is not expected to result in clinically significant differences in systemic exposure of CYP3A4 substrates.

Coadministration of gilteritinib with cephalexin, a MATE1 substrate, did not result in markedly different cephalexin exposure (less than 10% decrease) or urinary excretion (less than 20% decrease) compared to that

observed after administration of cephalexin alone. These results suggest coadministration of gilteritinib and a MATE1 substrate is not expected to result in a clinically-relevant DDI.

Pharmacodynamic Results:

Twenty-one patients had a molecular response, all at doses of ≥ 80 mg. In patients who received doses of ≥ 80 mg, the CR/CRh rate was 66.7% in patients with a molecular response compared to 13.5% in patients without a molecular response. Median OS was 428 days in patients with a molecular response and 199 days in patients without a molecular response.

In patients who received doses of ≥ 80 mg, the CR/CRh rate was 76.9% in MRD negative patients compared to 17.1% in MRD positive patients. Median OS was 658 days in MRD negative patients and 213 days in MRD positive patients.

Gilteritinib exhibits rapid and sustained inhibition of FLT3 phosphorylation as characterized by an ex vivo plasma inhibitory assay (PIA) method. In samples collected from patients with relapsed or refractory AML, greater than 90% inhibition of FLT3 phosphorylation was observed by cycle 1 day 8 at gilteritinib doses of ≥ 80 mg.

Mutational analysis of tyrosine kinase receptor AXL (AXL) and E3 ubiquitin-protein ligase c-CBL (c-CBL) was conducted in addition to FLT3, and variants were detected in both genes. Several variants detected in both genes had variant allelic frequencies (VAFs) < 1%, making the clinical significance of these variants unclear. In addition, several variants in both genes had VAFs in the range of 40% to 50%, suggesting these may be single nucleotide polymorphisms (SNPs). Regardless of the VAF of AXL and c-CBL variants, 4 of 5 patients receiving ≥ 80 mg doses with both a co-occurring FLT3 mutation and AXL variant responded to treatment, demonstrating that alterations in AXL do not negatively impact response to gilteritinib. Similarly, 5 of 8 patients receiving ≥ 80 mg doses with a co-occurring FLT3 mutation and c-CBL variant responded to treatment, demonstrating that the majority of alterations in c-CBL do not negatively impact response to gilteritinib. There were too few patients with FLT3 mutations other than ITD or TKD-D835 to assess any relationship with response to gilteritinib in this study.

Safety Results:

A total of 31 DLT evaluable patients experienced a DLT during the study. Overall, 98.8% (249/252) of the patients reported at least 1 treatment-emergent adverse event (TEAE). The most frequent TEAEs occurring in ≥ 10% of patients in any dose group were febrile neutropenia (39.7% [100/252]), diarrhea (38.1% [96/252]) and anemia (35.3% [89/252]) [Table 6].

Overall, study drug-related TEAEs were experienced by 75.0% (189/252) of patients (58.8% [10/17] of patients in the 20 mg dose group, 50.0% [8/16] of patients in the 40 mg dose group, 75.0% [18/24] of patients in the 80 mg dose group, 79.7% [55/69] of patients in the 120 mg dose group, 77.7% [80/103] of patients in the 200 mg dose group, 75.0% [15/20] of patients in the 300 mg dose group and 100% [3/3] patients in the 450 mg dose group).

There were 105 patients with TEAEs leading to on-study patient deaths within the SAF. The majority of the deaths were attributed to disease progression. Six of the deaths were possibly attributed to gilteritinib administration and 1 death was probably attributed to gilteritinib administration. A total of 7 deaths occurred more than 28 days after the last dose of gilteritinib.

Overall, there were a total of 210 (83.3%) patients who reported serious adverse events (SAEs) during the study Table 7; 76 (30.2%) patients reported SAEs that were considered to be drug-related. Serious adverse events were reported in 58.8% (10/17) of patients in the 20 mg dose group, 87.5% (14/16) of patients in the 40 mg dose group, 87.5% (21/24) of patients in the 80 mg dose group, 76.8% (53/69) of patients in the 120 mg dose group, 91.3% (94/103) of patients in the 200 mg dose group, 80.0% (16/20) of patients in the 300 mg dose group and 66.7% (2/3) of patients in the 450 mg dose group.

Overall, 34.5% (87/252) of patients experienced TEAEs resulting in permanent discontinuation. Treatment-emergent AEs resulting in permanent discontinuation of study drug were reported in 23.5% (4/17) of patients in the 20 mg dose group, 31.3% (5/16) of patients in the 40 mg dose group, 50.0% (12/24) of patients in the 80 mg dose group, 17.4% (12/69) of patients in the 120 mg dose group, 45.6% (47/103) of patients in the 200 mg dose group, 30.0% (6/20) of patients in the 300 mg dose group and 33.3% (1/3) of patients in the 450 mg dose group. Of these patients, 1 patient in the 20 mg dose group, 1 patient in the 40 mg dose group, 4 patients of the 80 mg dose group, 5 patients of the 120 mg dose group, 10 patients of the 200 mg dose group and 3 patients of the 300 mg dose group experienced drug-related TEAEs leading to discontinuation. There were no patients in the 450 mg dose group with drug-related TEAEs that led to discontinuation.

Overall, the percentage of patients with maximum NCI-CTCAE grade 3 or higher TEAEs was 90.9% (229/252). The percentage of patients with maximum NCI-CTCAE grade 3 or higher TEAEs was 70.6% (12/17) of patients in the 20 mg dose group, 93.8% (15/16) of patients in the 40 mg dose group, 91.7% (22/24) of patients in the 80 mg dose group, 87.0% (60/70) of patients in the 120 mg dose group, 98.1% (101/103) of patients in the 200 mg dose group, 80.0% (16/20) of patients in the 300 mg dose group and 100% (3/3) of patients in the 450 mg dose group.

CONCLUSIONS:

Gilteritinib exhibits linear, dose-proportional pharmacokinetics in patients with relapsed or refractory AML at doses ranging from 20 to 450 mg administered once daily. Median t_{max} was observed between 2 and 6 hours following single and multiple dosing. After multiple doses of 120 mg, the median C_{max} and AUC_{24} were 282 ng/mL and 6180 ng·h/mL, respectively. The estimated $t_{1/2}$ ranged from 45 to 159 hours. Steady-state gilteritinib concentrations were achieved by day 15 after once daily dosing. Overall, the pharmacokinetics of gilteritinib appear suitable for once daily dosing.

The observed CRc rate at end of treatment for FLT3 mutation positive in initial dose groups of ≥ 80 mg was 41.4%, with an additional 10.6% of patients achieving PR. Median DOR for these patients was 147 days, median OS was 218.0 days, with survival probabilities of 56.2% at 26 weeks and 24.9% at 1 year. Response rates in FLT3-mutation negative patients were low.

Gilteritinib was generally well-tolerated at doses up to 300 mg in this study. The MTD for the study was determined to be 300 mg. Based on exposure, response and safety data, a starting dose of 120 mg gilteritinib is expected to result in adequate drug exposure for clinical efficacy for phase 3 studies in patients with FLT3 mutation positive relapsed/refractory AML, while providing an acceptable safety profile without the need for dose adjustment in patients receiving concomitant treatment with strong or moderate CYP3A4 inhibitors.

Date of Report: Reissued, 15 Nov 2018

Table 1 Patient Disposition by Escalation/Expansion Phase and Dose

	Gilteritinib											
	20 mg§§§			40 mg			80 mg			120 mg		
n (%)	Escl (N = 5)	Exp (N = 11)	Comb (N = 16)	Escl (N = 3)	Exp (N = 15)	Comb (N = 18)	Escl (N = 3)	Exp (N = 21)	Comb (N = 24)	Escl (N = 3)	Exp (N = 70)	Comb (N = 73)
Allocated to treatment†	5 (100)	0	5 (31.3)	3 (100)	0	3 (16.7)	3 (100)	0	3 (12.5)	3 (100)	0	3 (4.1)
Randomized‡	0	11 (100)	11 (68.8)	0	15 (100)	15 (83.3)	0	21 (100)	21 (87.5)	0	70 (100)	70 (95.9)
SAF§, ††	5 (100)	12 (109.1)	17 (106.3)	3 (100)	13 (86.7)	16 (88.9)	3 (100)	21 (100)	24 (100)	3 (100)	66 (94.3)	69 (94.5)
FAS¶, ††	5 (100)	11 (100)	16 (100)	3 (100)	13 (86.7)	16 (88.9)	3 (100)	21 (100)	24 (100)	3 (100)	67 (95.7)	70 (95.9)
PPS‡‡	4 (80.0)	9 (81.8)	13 (81.3)	3 (100)	11 (73.3)	14 (77.8)	3 (100)	18 (85.7)	21 (87.5)	3 (100)	64 (91.4)	67 (91.8)
PKAS§§	5 (100)	12 (109.1)	17 (106.3)	3 (100)	12 (80.0)	15 (83.3)	3 (100)	21 (100)	24 (100)	3 (100)	66 (94.3)	69 (94.5)
PDAS¶¶	5 (100)	12 (109.1)	17 (106.3)	3 (100)	13 (86.7)	16 (88.9)	3 (100)	21 (100)	24 (100)	3 (100)	66 (94.3)	69 (94.5)
Re-enrolled analysis set†††	0	0	0	0	0	0	0	0	0	0	1 (1.4)	1 (1.4)
Post-HSCT analysis set‡‡‡	0	0	0	0	0	0	0	0	0	0	3 (4.3)	3 (4.1)
	200 mg			300 mg			450 mg			Total		
n (%)	Escl (N = 4)	Exp (N = 106)	Comb (N = 110)	Escl (N = 3)	Exp (N = 17)	Comb (N = 20)	Escl (N = 4)	Exp (N = 0)	Comb (N = 4)	Escl (N = 25)	Exp (N = 240)	Comb (N = 265)
Allocated to treatment†	4 (100)	0	4 (3.6)	3 (100)	0	3 (15.0)	4 (100)	0	4 (100)	25 (100)	0	25 (9.4)
Randomized‡	0	106 (100)	106 (96.4)	0	17 (100)	17 (85.0)	0	0	0	0	240 (100)	240 (90.6)
SAF§, ††	3 (75.0)	100 (94.3)	103 (93.6)	3 (100)	17 (100)	20 (100)	3 (75.0)	0	3 (75.0)	23 (92.0)	229 (95.4)	252 (95.1)
FAS¶, ††	3 (75.0)	97 (91.5)	100 (90.9)	3 (100)	17 (100)	20 (100)	3 (75.0)	0	3 (75.0)	23 (92.0)	226 (94.2)	249 (94.0)
PPS‡‡	3 (75.0)	85 (80.2)	88 (80.0)	2 (66.7)	13 (76.5)	15 (75.0)	3 (75.0)	0	3 (75.0)	21 (84.0)	200 (83.3)	221 (83.4)
PKAS§§	3 (75.0)	100 (94.3)	103 (93.6)	3 (100)	17 (100)	20 (100)	3 (75.0)	0	3 (75.0)	23 (92.0)	228 (95.0)	251 (94.7)
PDAS¶¶	3 (75.0)	81 (76.4)	84 (76.4)	3 (100)	17 (100)	20 (100)	3 (75.0)	0	3 (75.0)	23 (92.0)	210 (87.5)	233 (87.9)
Re-enrolled analysis set†††	0	4 (3.8)	4 (3.6)	0	0	0	0	0	0	0	5 (2.1)	5 (1.9)
Post-HSCT analysis set‡‡‡	0	13 (12.3)	13 (11.8)	0	0	0	0	0	0	0	16 (6.7)	16 (6.0)

All allocated and randomized patients.

Comb: combined escalation and expansion phase; Escl: escalation phase; Exp: expansion phase; FAS: Full Analysis Set; HSCT: hematopoietic stem cell transplant; PDAS: Pharmacodynamic Analysis Set; PKAS: Pharmacokinetic Analysis Set; PPS: Per Protocol Set; SAF: Safety Analysis Set.

† For patients in dose escalation phase.

‡ For patients in dose expansion phase.

§ All patients who received at least 1 dose of study drug.

¶ All patients who received at least 1 dose of study drug and who had at least 1 posttreatment data point.

†† All patients who received at least 1 dose of study drug (SAF) had at least 1 posttreatment data point. Thus, the FAS included all patients who received at least 1 dose of study drug (SAF) with the exception of the 3 patients enrolled at site [redacted] who were excluded from the FAS due to concerns with this site's GCP compliance.

‡‡ All patients of the FAS who did not meet criteria for exclusion from PPS.

Footnotes continued on next page

§§ All patients from the SAF for which sufficient plasma concentration data were available to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling was known.

¶¶ All patients from the SAF for whom sufficient pharmacodynamic measurements were collected.

††† All patients who discontinued treatment for reasons other than toxicity or disease progression and were re-enrolled into the expansion phase and received at least 1 dose of study drug after re-enrollment.

‡‡‡ The Post-HSCT Analysis Set included patients who received at least 1 dose of study drug and met either of the following criteria: underwent on-study HSCT and resumed gilteritinib after HSCT or discontinued the treatment for HSCT and were re-enrolled into the study and received at least 1 dose of study drug after re-enrollment.

§§§ The SAF, PKAS and PDAS had percentages >100% in 20 mg dose level, because Patient [redacted] was randomized to 120 mg but received initial dose of 20 mg by mistake. The patient is summarized under the actual initial dose for SAF, PKAS, and PDAS. Thus, there were 16 patients randomized to 20 mg but 17 patients had an actual initial dose of 20 mg.

Source: Table 12.1.1.2

Table 2 Demographic Characteristics by Local FLT3 Mutation Status – Safety Analysis Set

Characteristic	FLT3+ (N = 194)	FLT3- (N = 58)	Total (N = 252)
Sex, n (%)			
Male	92 (47.4)	37 (63.8)	129 (51.2)
Female	102 (52.6)	21 (36.2)	123 (48.8)
Ethnicity, n (%)			
Hispanic or Latino	9 (4.6)	2 (3.4)	11 (4.4)
Not Hispanic or Latino	185 (95.4)	56 (96.6)	241 (95.6)
Race, n (%)			
White	171 (88.1)	42 (72.4)	213 (84.5)
Black or African American	9 (4.6)	7 (12.1)	16 (6.3)
Asian	7 (3.6)	0	7 (2.8)
Other	7 (3.6)	9 (15.5)	16 (6.3)
Age (years)			
n	194	58	252
Mean (SD)	57.7 (15.2)	63.4 (14.0)	59.0 (15.1)
Min - max	21 - 87	29 - 90	21 - 90
Median	60.0	66.5	62.0
Age Group, n (%)			
< 65	121 (62.4)	20 (34.5)	141 (56.0)
≥ 65	73 (37.6)	38 (65.5)	111 (44.0)
Weight (kg)			
n	191	58	249
Mean (SD)	73.77 (18.29)	80.26 (16.56)	75.29 (18.08)
Min - max	40.8 – 127.6	44.5 – 118.6	40.8 – 127.6
Median	70.30	78.95	73.00
Height (cm)			
n	182	54	236
Mean (SD)	169.18 (9.77)	170.61 (10.65)	169.51 (9.97)
Min - max	149.90 – 190.50	148.00 – 192.00	148.00 – 192.00
Median	169.20	172.35	170.00
BMI (kg/m^2)			
n	182	54	236
Mean (SD)	25.64 (5.64)	27.58 (5.05)	26.08 (5.56)
Min - max	14.81 – 43.93	16.35 – 40.94	14.81 – 43.93
Median	24.70	27.39	25.23

All patients who received at least 1 dose of study drug.

BMI: body mass index; FLT3: FMS-like tyrosine kinase 3; Max: maximum; Min: minimum.

Source: Table 12.1.2.1.1.1

Table 3 Response Assessment Stratified by Local FLT3 Mutation Status (Derived Response) – Full Analysis Set

	Number of Mutation Patients n (%) [95% CI]†								
	FLT3 mutation positive‡								FLT3 mutation negative‡
Best Overall Response	**20 mg (N = 14)**	**40 mg (N = 8)**	**80 mg (N = 12)**	**120 mg (N = 56)**	**200 mg (N = 89)**	**300 mg (N = 10)**	**450 mg (N = 2)**	**Total (N = 191)**	**Total (N = 58)**
End of Cycle 2									
CR	0	0	1 (8.3) [0.2, 38.5]	2 (3.6) [0.4, 12.3]	3 (3.4) [0.7, 9.5]	1 (10.0) [0.3, 44.5]	0	7 (3.7) [1.5, 7.4]	1 (1.7) [0.0, 9.2]
CRp	0	0	0	2 (3.6) [0.4, 12.3]	6 (6.7) [2.5, 14.1]	1 (10.0) [0.3, 44.5]	0	9 (4.7) [2.2, 8.8]	0
CRi	1 (7.1) [0.2, 33.9]	0	4 (33.3) [9.9, 65.1]	19 (33.9) [21.8, 47.8]	21 (23.6) [15.2, 33.8]	1 (10.0) [0.3, 44.5]	0	46 (24.1) [18.2, 30.8]	4 (6.9) [1.9, 16.7]
PR	0	3 (37.5) [8.5, 75.5]	3 (25.0) [5.5, 57.2]	5 (8.9) [3.0, 19.6]	7 (7.9) [3.2, 15.5]	3 (30.0) [6.7, 65.2]	1 (50.0) [1.3, 98.7]	22 (11.5) [7.4, 16.9]	2 (3.4) [0.4, 11.9]
NR	10 (71.4) [41.9, 91.6]	5 (62.5) [24.5, 91.5]	3 (25.0) [5.5, 57.2]	24 (42.9) [29.7, 56.8]	41 (46.1) [35.4, 57.0]	3 (30.0) [6.7, 65.2]	1 (50.0) [1.3, 98.7]	87 (45.5) [38.3, 52.9]	43 (74.1) [61.0, 84.7]
NE	3 (21.4) [4.7, 50.8]	0	1 (8.3) [0.2, 38.5]	4 (7.1) [2.0, 17.3]	11 (12.4) [6.3, 21.0]	1 (10.0) [0.3, 44.5]	0	20 (10.5) [6.5, 15.7]	8 (13.8) [6.1, 25.4]
End of Treatment									
CR	0	0	2 (16.7) [2.1, 48.4]	7 (12.5) [5.2, 24.1]	10 (11.2) [5.5, 19.7]	1 (10.0) [0.3, 44.5]	0	20 (10.5) [6.5, 15.7]	1 (1.7) [0.0, 9.2]
CRp	0	0	0	2 (3.6) [0.4, 12.3]	8 (9.0) [4.0, 16.9]	1 (10.0) [0.3, 44.5]	0	11 (5.8) [2.9, 10.1]	0
CRi	1 (7.1) [0.2, 33.9]	0	3 (25.0) [5.5, 57.2]	17 (30.4) [18.8, 44.1]	18 (20.2) [12.4, 30.1]	1 (10.0) [0.3, 44.5]]	0	40 (20.9) [15.4, 27.4]	4 (6.9) [1.9, 16.7]
PR	1 (7.1) [0.2, 33.9]	3 (37.5) [8.5, 75.5]	3 (25.0) [5.5, 57.2]	4 (7.1) [2.0, 17.3]	7 (7.9) [3.2, 15.5]	3 (30.0) [6.7, 65.2]	1 (50.0) [1.3, 98.7]	22 (11.5) [7.4, 16.9]	2 (3.4) [0.4, 11.9]
NR	9 (64.3) [35.1, 87.2]	5 (62.5) [24.5, 91.5]	3 (25.0) [5.5, 57.2]	23 (41.1) [28.1, 55.0]	35 (39.3) [29.1, 50.3]	3 (30.0) [6.7, 65.2]	1 (50.0) [1.3, 98.7]	79 (41.4) [34.3, 48.7]	43 (74.1) [61.0, 84.7]
NE	3 (21.4) [4.7, 50.8]	0	1 (8.3) [0.2, 38.5]	3 (5.4) [1.1, 14.9]	11 (12.4) [6.3, 21.0]	1 (10.0) [0.3, 44.5]	0	19 (9.9) [6.1, 15.1]	8 (13.8) [6.1, 25.4]
CRc rate	1 (7.1) [0.2, 33.9]	0	5 (41.7) [15.2, 72.3]	26 (46.4) [33.0, 60.3]	36 (40.4) [30.2, 51.4]	3 (30.0) [6.7, 65.2]	0	71 (37.2) [30.3, 44.4]	5 (8.6) [2.9, 19.0]
Response rate	2 (14.3) [1.8, 42.8]	3 (37.5) [8.5, 75.5]	8 (66.7) [34.9, 90.1]	30 (53.6) [39.7, 67.0]	43 (48.3) [37.6, 59.2]	6 (60.0) [26.2, 87.8]	1 (50.0) [1.3, 98.7]	93 (48.7) [41.4, 56.0]	7 (12.1) [5.0, 23.3]
CR/CRh rate	1 (7.1) [0.2, 33.9]	0	3 (25.0) [5.5, 57.2]	13 (23.2) [13.0, 36.4]	17 (19.1) [11.5, 28.8]	3 (30.0) [6.7, 65.2]	0	37 (19.4) [14.0, 25.7]	NA
CRh rate	1 (7.1) [0.2, 33.9]	0	1 (8.3) [0.2, 38.5]	6 (10.7) [4.0, 21.9]	7 (7.9) [3.2, 15.5]	2 (20.0) [2.5, 55.6]	0	17 (8.9) [5.3, 13.9]	NA

Footnotes on next page

All patients who were enrolled and received at least 1 dose of study drug and who had at least 1 posttreatment data point.

Patients are included in the dose group of the initial dose received prior to any dose increase or decrease.

CRc rate = CR + CRp + CRi. Response rate = CRc + PR.

CI: confidence interval; CR: complete remission; CRc: composite CR; CRh: CR with partial hematological recovery; CRi: CR with incomplete hematological recovery; CRp: CR with incomplete platelet recovery; FLT3: FMS-like tyrosine kinase; NA: not applicable; NE: not evaluable; NR: no response; PR: partial remission.

† Exact 95% CI was estimated using the binomial distribution.

‡ Based on local FLT3 mutation testing.

Source: Table 12.3.1.1.1.1, Table 12.3.2.3

Table 4 Overall Survival for Locally Evaluated FLT3 Mutated Patients in the ≥ 80 mg Dose Groups – Full Analysis Set

Parameter Category/ Statistics	80 mg (N = 12)	120 mg (N = 56)	200 mg (N = 89)	300 mg (N = 10)	450 mg (N = 2)	Total (N = 169)
Patient status, n (%)						
n	12	56	89	10	2	169
Events	12 (100)	43 (76.8)	70 (78.7)	9 (90.0)	2 (100)	136 (80.5)
Censored	0	13 (23.2)	19 (21.3)	1 (10.0)	0	33 (19.5)
Kaplan-Meier quartiles (days)						
Minimum	18.0	12.0	12.0	20.0	51.0	12.0
Q1 (95% CI)	112.5 [18.0, 194.0]	99.0 [57.0, 190.0]	91.0 [57.0, 121.0]	65.0 [20.0, 157.0]	51.0 [51.0, 357.0]	99.0 [73.0, 118.0]
Median (95% CI)	197.5 [61.0, 329.0]	246.0 [190.0, 309.0]	214.0 [126.0, 264.0]	157.0 [20.0, 218.0]	204.0 [51.0, 357.0]	218.0 [161.0, 253.0]
Q3 (95% CI)	317.0 [194.0, 1181.0]	559.0 [309.0, NE]	354.0 [291.0, 510.0]	185.0 [157.0, 491.0]	357.0 [51.0, 357.0]	362.0 [323.0, 510.0]
Maximum	1181.0	694.0	658.0	419.0	357.0	1181.0
Survival probability % [95% CI]						
8 weeks	91.7 [53.9, 98.8]	87.5 [75.6, 93.8]	85.2 [75.9, 91.1]	80.0 [40.9, 94.6]	50.0 [0.6, 91.0]	85.7 [79.4, 90.2]
12 weeks	83.3 [48.2, 95.6]	82.1 [69.4, 90.0]	77.1 [66.7, 84.6]	70.0 [32.9, 89.2]	50.0 [0.6, 91.0]	78.5 [71.4, 84.0]
26 weeks	58.3 [27.0, 80.1]	65.7 [51.6, 76.6]	51.8 40.6, 61.8]	36.0 [9.0, 64.8]	50.0 [0.6, 91.0]	56.2 [48.2, 63.4]
52 weeks	16.7 [2.7, 41.3]	31.0 [19.1, 43.6]	24.2 [15.4, 34.1]	12.0 [0.7, 40.8]	0 NE	24.9 [18.4, 32.0]

All patients who were enrolled and received at least 1 dose of study drug and who had at least 1 posttreatment data point.

Percentages were calculated based on the total number of patients with non-missing event/censored value.

OS was defined as the time from the date of first dose of study drug until the date of death from any cause. For a patient who was not known to have died by the end of study follow-up, OS was censored at the date of last contact.

CI: confidence interval; FLT3: FMS-like tyrosine kinase; NE: not estimated; OS: overall survival; Q1: first quartile; Q3: third quartile.

Source: Table 12.3.3.6.1

Table 5 Event-free Survival for Locally Evaluated FLT3 Mutated Patients (Derived Response) – Full Analysis Set

Parameter Category / Statistics	80 mg (N = 12)	120 mg (N = 56)	200 mg (N = 89)	300 mg (N = 10)
Patient status, n (%)				
n	12	56	89	10
Events	11 (91.7)	48 (85.7)	76 (86.5)	9 (90.0)
Censored	1 (8.3)	8 (14.3)	13 (14.6)	1 (10.0)
Kaplan-Meier quartiles (days)				
Minimum	18.0	12.0	12.0	11.0
Q1 [95% CI]	64.5 [18.0, 78.0]	76.0 [38.0, 92.0]	58.0 [44.0, 84.0]	65.0 [11.0, 85.0]
Median [95% CI]	93.5 [61.0, 127.0]	112.0 [92.0, 143.0]	121.0 [92.0, 155.0]	85.0 [11.0, 157.0]
Q3 [95% CI]	127.0 [78.0, 1181.0]	177.0 [140.0, 297.0]	239.0 [176.0, 346.0]	111.0 [75.0, 491.0]
Maximum	389.0	411.0	532.0	491.0
Survival probability % [95% CI]				
8 weeks	91.7 [53.9, 98.8]	78.5 [65.3, 87.2]	80.2 [70.1, 87.2]	78.8 [38.1, 94.3]
12 weeks	50.0 [20.8, 73.6]	72.9 [59.1, 82.7]	65.8 [54.6, 74.8]	56.3 [20.9, 80.9]
26 weeks	10.0 [0.6, 35.5]	23.9 [13.3, 36.2]	33.8 [23.7, 44.3]	11.3 [0.6, 39.1]
52 weeks	10.0 [0.6, 35.5]	10.0 [3.7, 20.0]	14.9 [8.0, 23.8]	11.3 [0.6, 39.1]

All patients who were enrolled and received at least 1 dose of study drug and who had at least 1 posttreatment data point.

Percentages were calculated based on the total number of patients with non-missing event/censored value.

EFS was defined as the time from the date of first dose of study drug until the date of documented relapse, treatment failure or death. For a patient with none of these events, EFS was censored at the date of last disease assessment.

CI: confidence interval; EFS: event-free survival; FLT3: FMS-like tyrosine kinase; NE: not estimated; Q1: first quartile; Q3: third quartile.

Source: Table 12.3.4.1.1.1

Table 6 Most Frequent (≥ 10% in Any Combined Dose Level) Combined TEAEs by Dose Level and Total – Safety Analysis Set

MedDRA V20.0 System Organ Class Preferred Term	Gilteritinib							
	20 mg (N = 17) n (%)	40 mg (N = 16) n (%)	80 mg (N = 24) n (%)	120 mg (N = 69) n (%)	200 mg (N = 103) n (%)	300 mg (N = 20) n (%)	450 mg (N = 3) n (%)	Total (N = 252) n (%)
Overall	**17 (100.0)**	**16 (100.0)**	**23 (95.8)**	**67 (97.1)**	**103 (100.0)**	**20 (100.0)**	**3 (100.0)**	**249 (98.8)**
Blood and Lymphatic System Disorders								
Febrile neutropenia	6 (35.3)	8 (50.0)	6 (25.0)	24 (34.3)	47 (45.6)	9 (45.0)	0	100 (39.7)
Anaemia	4 (23.5)	4 (25.0)	9 (37.5)	27 (39.1)	37 (35.9)	7 (35.0)	1 (33.3)	89 (35.3)
Thrombocytopenia	0	1 (6.3)	3 (12.5)	13 (18.8)	20 (19.4)	2 (10.0)	0	39 (15.5)
Neutropenia	0	0	0	6 (8.7)	14 (13.6)	2 (10.0)	0	22 (8.7)
Leukocytosis	1 (5.9)	1 (6.3)	1 (4.2)	6 (8.7)	7 (6.8)	3 (15.0)	0	19 (7.5)
Cardiac Disorders								
Tachycardia	1 (5.9)	0	2 (8.3)	2 (2.9)	12 (11.7)	0	0	17 (6.7)
Sinus tachycardia	1 (5.9)	3 (18.8)	1 (4.2)	2 (2.9)	6 (5.8)	0	0	13 (5.2)
Angina pectoris	2 (11.8)	0	0	0	2 (1.9)	0	0	4 (1.6)
Sinus bradycardia	0	0	1 (4.2)	0	2 (1.9)	0	1 (33.3)	4 (1.6)
Cardiac arrest	0	0	1 (4.2)	0	0	0	1 (33.3)	2 (0.8)
Ear and Labyrinth Disorders								
Ear pain	3 (17.6)	0	0	0	3 (2.9)	0	0	6 (2.4)
Eye Disorders								
Dry eye	0	0	1 (4.2)	9 (13.0)	6 (5.8)	0	0	16 (6.3)
Conjunctival haemorrhage	1 (5.9)	0	4 (16.7)	0	3 (2.9)	0	0	8 (3.2)
Eye oedema	0	0	0	0	1 (1.0)	0	1 (33.3)	2 (0.8)
Gastrointestinal Disorders								
Diarrhoea	1 (5.9)	2 (12.5)	7 (29.2)	31 (44.9)	47 (45.6)	6 (30.0)	2 (66.7)	96 (38.1)
Constipation	2 (11.8)	2 (12.5)	6 (25.0)	14 (20.3)	33 (32.0)	2 (10.0)	0	59 (23.4)
Nausea	3 (17.6)	3 (18.8)	6 (25.0)	16 (23.2)	30 (29.1)	1 (5.0)	0	59 (23.4)
Vomiting	3 (17.6)	1 (6.3)	7 (29.2)	14 (20.3)	23 (22.3)	1 (5.0)	0	49 (19.4)
Stomatitis	1 (5.9)	1 (6.3)	0	8 (11.6)	15 (14.6)	2 (10.0)	1 (33.3)	28 (11.1)
Abdominal pain	2 (11.8)	1 (6.3)	1 (4.2)	5 (7.2)	16 (15.5)	0	1 (33.3)	26 (10.3)
Mouth haemorrhage	0	0	1 (4.2)	2 (2.9)	8 (7.8)	1 (5.0)	1 (33.3)	13 (5.2)
Dysphagia	1 (5.9)	0	0	2 (2.9)	7 (6.8)	3 (15.0)	0	13 (5.2)
Gastrointestinal haemorrhage	0	0	2 (8.3)	2 (2.9)	4 (3.9)	2 (10.0)	0	10 (4.0)
Colitis	0	0	0	3 (4.3)	3 (2.9)	0	1 (33.3)	7 (2.8)
General Disorders and Administration Site Conditions								
Fatigue	5 (29.4)	5 (31.3)	9 (37.5)	27 (39.1)	35 (34.0)	5 (25.0)	1 (33.3)	87 (34.5)
Oedema peripheral	4 (23.5)	3 (18.8)	5 (20.8)	18 (26.1)	31 (30.1)	2 (10.0)	1 (33.3)	64 (25.4)
Pyrexia	1 (5.9)	3 (18.8)	3 (12.5)	24 (34.8)	32 (31.1)	5 (25.0)	0	68 (27.0)
Asthenia	3 (17.6)	0	4 (16.7)	6 (8.7)	19 (18.4)	1 (5.0)	0	33 (13.1)
Chills	1 (5.9)	0	3 (12.5)	5 (7.2)	12 (11.7)	0	0	21 (8.3)
Mucosal inflammation	0	1 (6.3)	1 (4.2)	7 (10.1)	12 (11.7)	2 (10.0)	0	23 (9.1)
Oedema	1 (5.9)	0	4 (16.7)	3 (4.3)	6 (5.8)	0	0	14 (5.6)
Gait disturbance	0	0	0	0	1 (1.0)	0	1 (33.3)	2 (0.8)
Infections and Infestations								
Sepsis	0	2 (12.5)	8 (33.3)	10 (14.5)	19 (18.4)	0	0	39 (15.5)
Pneumonia	1 (5.9)	2 (12.5)	2 (8.3)	16 (23.2)	19 (18.4)	2 (10.0)	0	42 (16.7)
Urinary tract infection	0	0	4 (16.7)	11 (15.9)	7 (6.8)	1 (5.0)	0	23 (9.1)
Bacteraemia	1 (5.9)	0	8 (33.3)	5 (7.2)	7 (6.8)	0	0	21 (8.3)
Upper respiratory tract infection	0	2 (12.5)	3 (12.5)	8 (11.6)	5 (4.9)	0	0	18 (7.1)
Lung infection	0	1 (6.3)	0	4 (5.8)	11 (10.7)	0	0	16 (6.3)
Cellulitis	0	0	2 (8.3)	8 (11.6)	4 (3.9)	0	0	14 (5.6)
Skin infection	0	1 (6.3)	3 (12.5)	4 (5.8)	4 (3.9)	0	0	12 (4.8)
Sinusitis	1 (5.9)	0	1 (4.2)	3 (4.3)	1 (1.0)	1 (5.0)	1 (33.3)	8 (3.2)

Table continued on next page

MedDRA V20.0 System Organ Class Preferred Term	Gilteritinib							
	20 mg (N = 17) n (%)	40 mg (N = 16) n (%)	80 mg (N = 24) n (%)	120 mg (N = 69) n (%)	200 mg (N = 103) n (%)	300 mg (N = 20) n (%)	450 mg (N = 3) n (%)	Total (N = 252) n (%)
Septic shock	0	0	3 (12.5)	0	4 (3.9)	0	0	7 (2.8)
Urinary tract infection enterococcal	2 (11.8)	0	0	1 (1.4)	1 (1.0)	0	0	4 (1.6)
Clostridial infection	0	0	0	0	0	1 (5.0)	0	1 (0.4)
Injury, Poisoning and Procedural Complications								
Fall	1 (5.9)	0	2 (8.3)	13 (18.8)	20 (19.4)	0	1 (33.3)	37 (14.7)
Contusion	1 (5.9)	1 (6.3)	3 (12.5)	3 (4.3)	10 (9.7)	0	1 (33.3)	19 (7.5)
Transfusion reaction	0	0	1 (4.2)	3 (4.3)	1 (1.0)	2 (10.0)	0	7 (2.8)
Investigations								
Aspartate aminotransferase increased	1 (5.9)	1 (6.3)	4 (16.7)	20 (29.0)	36 (35.0)	3 (15.0)	3 (100.0)	68 (27.0)
Alanine aminotransferase increased	1 (5.9)	1 (6.3)	4 (16.7)	16 (23.2)	26 (25.2)	3 (15.0)	1 (33.3)	52 (20.6)
Platelet count decreased	3 (17.6)	3 (18.8)	2 (8.3)	12 (17.4)	19 (18.4)	2 (10.0)	1 (33.3)	42 (16.7)
Blood creatinine increased	1 (5.9)	2 (12.5)	5 (20.8)	13 (18.8)	21 (20.4)	1 (5.0)	0	43 (17.1)
Blood alkaline phosphatase increased	2 (11.8)	0	4 (16.7)	10 (14.5)	15 (14.6)	1 (5.0)	1 (33.3)	33 (13.1)
Neutrophil count decreased	3 (17.6)	0	1 (4.2)	8 (11.6)	14 (13.6)	1 (5.0)	0	27 (10.7)
Blood creatine phosphokinase increased	0	0	0	7 (10.1)	18 (17.5)	1 (5.0)	1 (33.3)	27 (10.7)
Blood bilirubin increased	1 (5.9)	2 (12.5)	4 (16.7)	3 (4.3)	14 (13.6)	0	0	24 (9.5)
Electrocardiogram QT prolonged	0	0	1 (4.2)	11 (15.9)	9 (8.7)	0	0	21 (8.3)
White blood cell count decreased	0	0	0	4 (5.8)	13 (12.6)	0	0	17 (6.7)
Transaminases increased	0	0	2 (8.3)	6 (8.7)	6 (5.8)	2 (10.0)	0	16 (6.3)
Weight increased	0	0	0	2 (2.9)	12 (11.7)	0	0	14 (5.6)
Activated partial thromboplastin time prolonged	1 (5.9)	0	0	1 (1.4)	4 (3.9)	0	1 (33.3)	7 (2.8)
Metabolism and Nutrition Disorders								
Hypokalaemia	6 (35.3)	2 (12.5)	3 (12.5)	10 (14.5)	25 (24.3)	1 (5.0)	0	47 (18.7)
Hypocalcaemia	1 (5.9)	2 (12.5)	3 (12.5)	11 (15.9)	24 (23.3)	1 (5.0)	1 (33.3)	43 (17.1)
Hyponatraemia	0	1 (6.3)	4 (16.7)	9 (13.0)	20 (19.4)	1 (5.0)	0	35 (13.9)
Decreased appetite	1 (5.9)	1 (6.3)	5 (20.8)	11 (15.9)	19 (18.4)	1 (5.0)	0	38 (15.1)
Hypoalbuminaemia	1 (5.9)	1 (6.3)	4 (16.7)	7 (10.1)	18 (17.5)	1 (5.0)	1 (33.3)	33 (13.1)
Hypomagnesaemia	2 (11.8)	1 (6.3)	3 (12.5)	13 (18.8)	17 (16.5)	0	0	36 (14.3)
Hyperglycaemia	1 (5.9)	0	0	6 (8.7)	14 (13.6)	0	2 (66.7)	23 (9.1)
Hypophosphataemia	2 (11.8)	0	1 (4.2)	6 (8.7)	11 (10.7)	2 (10.0)	0	22 (8.7)
Hyperkalaemia	0	1 (6.3)	1 (4.2)	5 (7.2)	9 (8.7)	0	1 (33.3)	17 (6.7)
Hyperuricaemia	0	2 (12.5)	0	4 (5.8)	11 (10.7)	0	0	17 (6.7)
Dehydration	0	1 (6.3)	0	1 (1.4)	11 (10.7)	1 (5.0)	0	14 (5.6)
Musculoskeletal and Connective Tissue Disorders								
Arthralgia	0	0	5 (20.8)	12 (17.4)	17 (16.5)	1 (5.0)	0	35 (13.9)
Pain in extremity	1 (5.9)	1 (6.3)	2 (8.3)	11 (15.9)	12 (11.7)	1 (5.0)	1 (33.3)	29 (11.5)
Back pain	1 (5.9)	0	2 (8.3)	9 (13.0)	10 (9.7)	0	0	22 (8.7)
Myalgia	1 (5.9)	1 (6.3)	0	5 (7.2)	14 (13.6)	0	0	21 (8.3)
Muscular weakness	0	1 (6.3)	0	8 (11.6)	4 (3.9)	0	1 (33.3)	14 (5.6)
Bone pain	2 (11.8)	0	2 (8.3)	1 (1.4)	7 (6.8)	0	0	12 (4.8)

Table continued on next page

MedDRA V20.0 System Organ Class Preferred Term	Gilteritinib							
	20 mg (N = 17) n (%)	40 mg (N = 16) n (%)	80 mg (N = 24) n (%)	120 mg (N = 69) n (%)	200 mg (N = 103) n (%)	300 mg (N = 20) n (%)	450 mg (N = 3) n (%)	Total (N = 252) n (%)
Pain in jaw	2 (11.8)	0	1 (4.2)	1 (1.4)	0	0	0	4 (1.6)
Flank pain	0	0	0	0	1 (1.0)	0	1 (33.3)	2 (0.8)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)								
Acute myeloid leukaemia	3 (17.6)	5 (31.3)	5 (20.8)	10 (14.5)	20 (19.4)	5 (25.0)	0	48 (19.0)
Nervous System Disorders								
Dizziness	1 (5.9)	2 (12.5)	6 (25.0)	17 (24.6)	26 (25.2)	0	0	52 (20.6)
Headache	2 (11.8)	1 (6.3)	3 (12.5)	11 (15.9)	14 (13.6)	2 (10.0)	0	33 (13.1)
Dysgeusia	2 (11.8)	2 (12.5)	2 (8.3)	9 (13.0)	11 (10.7)	2 (10.0)	0	28 (11.1)
Neuropathy peripheral	0	0	1 (4.2)	7 (10.1)	5 (4.9)	2 (10.0)	1 (33.3)	16 (6.3)
Syncope	0	0	0	3 (4.3)	11 (10.7)	1 (5.0)	0	15 (6.0)
Lethargy	1 (5.9)	0	4 (16.7)	1 (1.4)	3 (2.9)	1 (5.0)	0	10 (4.0)
Haemorrhage intracranial	2 (11.8)	0	0	1 (1.4)	1 (1.0)	0	0	4 (1.6)
Psychiatric Disorders								
Insomnia	2 (11.8)	1 (6.3)	3 (12.5)	8 (11.6)	13 (12.6)	2 (10.0)	0	29 (11.5)
Confusional state	0	2 (12.5)	3 (12.5)	4 (5.8)	10 (9.7)	1 (5.0)	0	20 (7.9)
Mental status changes	0	1 (6.3)	3 (12.5)	0	3 (2.9)	2 (10.0)	0	9 (3.6)
Renal and Urinary Disorders								
Acute kidney injury	1 (5.9)	3 (18.8)	3 (12.5)	5 (7.2)	14 (13.6)	1 (5.0)	0	27 (10.7)
Pollakiuria	0	1 (6.3)	0	0	7 (6.8)	2 (10.0)	0	10 (4.0)
Respiratory, Thoracic and Mediastinal Disorders								
Dyspnoea	3 (17.6)	6 (37.5)	5 (20.8)	19 (27.5)	30 (29.1)	2 (10.0)	0	65 (25.8)
Cough	3 (17.6)	1 (6.3)	7 (29.2)	18 (26.1)	27 (26.2)	3 (15.0)	0	59 (23.4)
Epistaxis	3 (17.6)	4 (25.0)	4 (16.7)	16 (23.2)	20 (19.4)	5 (25.0)	1 (33.3)	53 (21.0)
Hypoxia	1 (5.9)	2 (12.5)	3 (12.5)	7 (10.1)	14 (13.6)	1 (5.0)	0	28 (11.1)
Pleural effusion	1 (5.9)	0	1 (4.2)	4 (5.8)	12 (11.7)	1 (5.0)	0	19 (7.5)
Oropharyngeal pain	2 (11.8)	2 (12.5)	0	5 (7.2)	8 (7.8)	0	0	17 (6.7)
Nasal congestion	0	0	3 (12.5)	3 (4.3)	9 (8.7)	0	1 (33.3)	16 (6.3)
Respiratory failure	0	0	1 (4.2)	1 (1.4)	11 (10.7)	2 (10.0)	0	15 (6.0)
Dysphonia	0	0	0	1 (1.4)	2 (1.9)	2 (10.0)	0	5 (2.0)
Skin and Subcutaneous Tissue Disorders								
Rash	0	2 (12.5)	0	11 (15.9)	11 (10.7)	0	1 (33.3)	25 (9.9)
Ecchymosis	1 (5.9)	0	2 (8.3)	3 (4.3)	8 (7.8)	2 (10.0)	0	16 (6.3)
Petechiae	2 (11.8)	0	1 (4.2)	0	15 (14.6)	1 (5.0)	0	19 (7.5)
Rash maculopapular	2 (11.8)	1 (6.3)	1 (4.2)	3 (4.3)	7 (6.8)	0	0	14 (5.6)
Hyperhidrosis	0	0	3 (12.5)	1 (1.4)	4 (3.9)	0	0	8 (3.2)
Pain of skin	0	0	0	1 (1.4)	5 (4.9)	2 (10.0)	0	8 (3.2)
Skin lesion	0	0	1 (4.2)	1 (1.4)	6 (5.8)	2 (10.0)	0	10 (4.0)
Vascular Disorders								
Hypotension	1 (5.9)	0	4 (16.7)	12 (17.4)	29 (28.2)	1 (5.0)	0	47 (18.7)
Hypertension	1 (5.9)	1 (6.3)	1 (4.2)	7 (10.1)	16 (15.5)	1 (5.0)	0	27 (10.7)
Embolism	0	0	0	0	0	0	1 (33.3)	1 (0.4)

All patients who received at least 1 dose of study drug. TEAEs occurring in ≥10% of patients in any combined (escalation and expansion phase) dose level.

Number of patients (n) and percentage of patients (%) are shown.

Sorting order: alphabetical by SOC and by frequency for PT.

PT: preferred term; SOC: system organ class; TEAE: treatment-emergent adverse event.

Source: Table 12.6.1.3.1

Table 7 Serious Treatment-emergent Adverse Events – Safety Analysis Set

MedDRA V20.0 System Organ Class Preferred Term	Gilteritinib							
	20 mg (N = 17) n (%)	40 mg (N = 16) n (%)	80 mg (N = 24) n (%)	120 mg (N = 69) n (%)	200 mg (N = 103) n (%)	300 mg (N = 20) n (%)	450 mg (N = 3) n (%)	Total (N = 252) n (%)
Overall	**10 (58.8)**	**14 (87.5)**	**21 (87.5)**	**53 (76.8)**	**94 (91.3)**	**16 (80.0)**	**2 (66.7)**	**210 (83.3)**
Blood and Lymphatic System Disorders	**5 (29.4)**	**8 (50.0)**	**8 (33.3)**	**22 (31.9)**	**45 (43.7)**	**8 (40.0)**	**1 (33.3)**	**97 (38.5)**
Febrile neutropenia	4 (23.5)	8 (50.0)	6 (25.0)	19 (27.5)	37 (35.9)	6 (30.0)	0	80 (31.7)
Leukocytosis	1 (5.9)	0	0	2 (2.9)	3 (2.9)	1 (5.0)	0	7 (2.8)
Anaemia	0	0	1 (4.2)	0	4 (3.9)	0	1 (33.3)	6 (2.4)
Neutropenia	0	0	0	1 (1.4)	2 (1.9)	0	0	3 (1.2)
Pancytopenia	0	0	0	0	2 (1.9)	0	0	2 (0.8)
Thrombocytopenia	0	0	0	0	2 (1.9)	0	0	2 (0.8)
Disseminated intravascular coagulation	0	0	0	0	1 (1.0)	1 (5.0)	0	2 (0.8)
Haemolytic anaemia	0	0	1 (4.2)	0	0	0	0	1 (0.4)
Cardiac Disorders	**0**	**0**	**3 (12.5)**	**7 (10.1)**	**12 (11.7)**	**0**	**1 (33.3)**	**23 (9.1)**
Atrial fibrillation	0	0	0	3 (4.3)	3 (2.9)	0	0	6 (2.4)
Cardiac failure congestive	0	0	1 (4.2)	0	2 (1.9)	0	0	3 (1.2)
Supraventricular tachycardia	0	0	0	1 (1.4)	2 (1.9)	0	0	3 (1.2)
Acute myocardial infarction	0	0	1 (4.2)	0	1 (1.0)	0	0	2 (0.8)
Cardiac arrest	0	0	1 (4.2)	0	0	0	1 (33.3)	2 (0.8)
Myocarditis	0	0	0	0	2 (1.9)	0	0	2 (0.8)
Pericardial effusion	0	0	0	1 (1.4)	1 (1.0)	0	0	2 (0.8)
Atrial thrombosis	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Atrioventricular block second degree	0	0	1 (4.2)	0	0	0	0	1 (0.4)
Cardiac failure	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Myocardial infarction	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Pericarditis	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Tachycardia	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Ventricular fibrillation	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Ventricular tachycardia	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Endocrine Disorders	**0**	**0**	**0**	**1 (1.4)**	**0**	**0**	**0**	**1 (0.4)**
Diabetes insipidus	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Eye Disorders	**0**	**0**	**1 (4.2)**	**1 (1.4)**	**0**	**0**	**0**	**2 (0.8)**
Conjunctival oedema	0	0	1 (4.2)	0	0	0	0	1 (0.4)
Papilloedema	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Gastrointestinal Disorders	**0**	**2 (12.5)**	**4 (16.7)**	**12 (17.4)**	**19 (18.4)**	**3 (15.0)**	**1 (33.3)**	**41 (16.3)**
Diarrhoea	0	0	1 (4.2)	5 (7.2)	5 (4.9)	0	1 (33.3)	12 (4.8)
Gastrointestinal haemorrhage	0	0	1 (4.2)	2 (2.9)	2 (1.9)	1 (5.0)	0	6 (2.4)
Vomiting	0	0	1 (4.2)	2 (2.9)	2 (1.9)	0	0	5 (2.0)
Nausea	0	0	0	1 (1.4)	3 (2.9)	0	0	4 (1.6)
Small intestinal obstruction	0	0	1 (4.2)	0	1 (1.0)	1 (5.0)	0	3 (1.2)
Lower gastrointestinal haemorrhage	0	0	0	2 (2.9)	0	0	0	2 (0.8)
Neutropenic colitis	0	0	0	2 (2.9)	0	0	0	2 (0.8)
Colitis	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Dysphagia	0	0	0	0	0	1 (5.0)	0	1 (0.4)
Enteritis	0	1 (6.3)	0	0	0	0	0	1 (0.4)
Enterocolitis	0	1 (6.3)	0	0	0	0	0	1 (0.4)
Gastric haemorrhage	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Haematemesis	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Haematochezia	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Intestinal obstruction	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Intestinal perforation	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Large intestinal ulcer	0	0	0	0	1 (1.0)	0	0	1 (0.4)

Table continued on next page

MedDRA V20.0 System Organ Class Preferred Term	Gilteritinib							
	20 mg (N = 17) n (%)	40 mg (N = 16) n (%)	80 mg (N = 24) n (%)	120 mg (N = 69) n (%)	200 mg (N = 103) n (%)	300 mg (N = 20) n (%)	450 mg (N = 3) n (%)	Total (N = 252) n (%)
Malabsorption	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Pancreatitis	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Pancreatitis acute	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Rectal haemorrhage	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Rectal tenesmus	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Stomatitis	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Swollen tongue	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Upper gastrointestinal haemorrhage	0	0	0	0	0	1 (5.0)	0	1 (0.4)
General Disorders and Administration Site Conditions	**0**	**1 (6.3)**	**2 (8.3)**	**14 (20.3)**	**20 (19.4)**	**3 (15.0)**	**0**	**40 (15.9)**
Pyrexia	0	0	0	10 (14.5)	10 (9.7)	2 (10.0)	0	22 (8.7)
Multi-organ dysfunction syndrome	0	1 (6.3)	0	1 (1.4)	4 (3.9)	0	0	6 (2.4)
Death	0	0	0	2 (2.9)	1 (1.0)	0	0	3 (1.2)
Fatigue	0	0	0	2 (2.9)	1 (1.0)	0	0	3 (1.2)
Mucosal inflammation	0	0	0	0	1 (1.0)	2 (10.0)	0	3 (1.2)
Asthenia	0	0	1 (4.2)	0	0	0	0	1 (0.4)
Chills	0	0	1 (4.2)	0	0	0	0	1 (0.4)
Oedema peripheral	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Sudden death	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Systemic inflammatory response syndrome	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Hepatobiliary Disorders	**0**	**0**	**0**	**2 (2.9)**	**3 (2.9)**	**0**	**0**	**5 (2.0)**
Hyperbilirubinaemia	0	0	0	1 (1.4)	2 (1.9)	0	0	3 (1.2)
Hepatic failure	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Cholecystitis	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Immune System Disorders	**0**	**0**	**1 (4.2)**	**2 (2.9)**	**4 (3.9)**	**0**	**0**	**7 (2.8)**
Acute graft versus host disease in skin	0	0	0	1 (1.4)	3 (2.9)	0	0	4 (1.6)
Anaphylactic reaction	0	0	0	1 (1.4)	1 (1.0)	0	0	2 (0.8)
Acute graft versus host disease	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Acute graft versus host disease in intestine	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Chronic graft versus host disease in skin	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Graft versus host disease in skin	0	0	1 (4.2)	0	0	0	0	1 (0.4)
Infections and Infestations	**3 (17.6)**	**7 (43.8)**	**16 (66.7)**	**27 (39.1)**	**58 (56.3)**	**9 (45.0)**	**0**	**120 (47.6)**
Sepsis	0	2 (12.5)	8 (33.3)	10 (14.5)	19 (18.4)	0	0	39 (15.5)
Pneumonia	1 (5.9)	2 (12.5)	2 (8.3)	13 (18.8)	14 (13.6)	1 (5.0)	0	33 (13.1)
Bacteraemia	1 (5.9)	0	6 (25.0)	2 (2.9)	5 (4.9)	0	0	14 (5.6)
Pneumonia fungal	0	0	0	5 (7.2)	5 (4.9)	1 (5.0)	0	11 (4.4)
Lung infection	0	0	0	2 (2.9)	7 (6.8)	0	0	9 (3.6)
Cellulitis	0	0	0	4 (5.8)	4 (3.9)	0	0	8 (3.2)
Urinary tract infection	0	0	2 (8.3)	3 (4.3)	2 (1.9)	1 (5.0)	0	8 (3.2)
Septic shock	0	0	3 (12.5)	0	4 (3.9)	0	0	7 (2.8)
Clostridium difficile colitis	0	0	0	1 (1.4)	6 (5.8)	0	0	7 (2.8)
Bronchopulmonary aspergillosis	0	0	0	1 (1.4)	3 (2.9)	0	0	4 (1.6)
Clostridium difficile infection	0	0	0	1 (1.4)	2 (1.9)	1 (5.0)	0	4 (1.6)
Skin infection	0	0	1 (4.2)	1 (1.4)	2 (1.9)	0	0	4 (1.6)

Table continued on next page

MedDRA V20.0 System Organ Class Preferred Term	Gilteritinib							
	20 mg (N = 17) n (%)	40 mg (N = 16) n (%)	80 mg (N = 24) n (%)	120 mg (N = 69) n (%)	200 mg (N = 103) n (%)	300 mg (N = 20) n (%)	450 mg (N = 3) n (%)	Total (N = 252) n (%)
Streptococcal bacteraemia	0	0	0	2 (2.9)	1 (1.0)	1 (5.0)	0	4 (1.6)
Upper respiratory tract infection	0	0	1 (4.2)	3 (4.3)	0	0	0	4 (1.6)
Klebsiella bacteraemia	0	0	1 (4.2)	0	2 (1.9)	0	0	3 (1.2)
Enterococcal bacteraemia	0	1 (6.3)	0	0	2 (1.9)	0	0	3 (1.2)
Sinusitis	0	0	1 (4.2)	1 (1.4)	0	1 (5.0)	0	3 (1.2)
Arthritis bacterial	0	0	1 (4.2)	1 (1.4)	0	0	0	2 (0.8)
Clostridium bacteraemia	0	0	0	0	2 (1.9)	0	0	2 (0.8)
Escherichia bacteraemia	0	0	0	1 (1.4)	1 (1.0)	0	0	2 (0.8)
Infection	0	0	0	0	2 (1.9)	0	0	2 (0.8)
Influenza	0	0	0	1 (1.4)	0	1 (5.0)	0	2 (0.8)
Parainfluenzae virus infection	0	0	0	1 (1.4)	1 (1.0)	0	0	2 (0.8)
Respiratory syncytial virus infection	0	0	0	2 (2.9)	0	0	0	2 (0.8)
Soft tissue infection	0	0	0	2 (2.9)	0	0	0	2 (0.8)
Staphylococcal bacteraemia	0	0	1 (4.2)	0	1 (1.0)	0	0	2 (0.8)
Staphylococcal sepsis	0	0	0	0	2 (1.9)	0	0	2 (0.8)
Streptococcal sepsis	0	0	1 (4.2)	0	1 (1.0)	0	0	2 (0.8)
Urosepsis	0	0	1 (4.2)	0	1 (1.0)	0	0	2 (0.8)
Abscess limb	1 (5.9)	0	0	0	0	0	0	1 (0.4)
Bacterial infection	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Clostridial infection	0	0	0	0	0	1 (5.0)	0	1 (0.4)
Corona virus infection	0	0	0	0	0	1 (5.0)	0	1 (0.4)
Device related infection	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Diverticulitis	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Encephalitis viral	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Enterococcal infection	0	0	0	0	0	1 (5.0)	0	1 (0.4)
Enterocolitis infectious	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Epiglottitis	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Escherichia sepsis	0	0	1 (4.2)	0	0	0	0	1 (0.4)
Escherichia urinary tract infection	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Fungaemia	0	1 (6.3)	0	0	0	0	0	1 (0.4)
Gastroenteritis viral	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Hepatic infection	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Herpes zoster	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Oral infection	0	1 (6.3)	0	0	0	0	0	1 (0.4)
Osteomyelitis	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Otitis externa	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Periodontitis	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Periorbital infection	0	0	1 (4.2)	0	0	0	0	1 (0.4)
Pneumonia haemophilus	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Pneumonia parainfluenzae viral	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Pneumonia viral	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Post procedural cellulitis	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Pseudomonas infection	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Pyelonephritis	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Sinusitis fungal	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Skin bacterial infection	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Systemic candida	0	0	0	0	0	1 (5.0)	0	1 (0.4)
Systemic mycosis	0	1 (6.3)	0	0	0	0	0	1 (0.4)
Tooth abscess	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Tooth infection	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Toxic shock syndrome	0	1 (6.3)	0	0	0	0	0	1 (0.4)

Table continued on next page

MedDRA V20.0 System Organ Class Preferred Term	Gilteritinib							
	20 mg (N = 17) n (%)	40 mg (N = 16) n (%)	80 mg (N = 24) n (%)	120 mg (N = 69) n (%)	200 mg (N = 103) n (%)	300 mg (N = 20) n (%)	450 mg (N = 3) n (%)	Total (N = 252) n (%)
Urinary tract infection bacterial	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Urinary tract infection enterococcal	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Injury, Poisoning and Procedural Complications	**0**	**1 (6.3)**	**3 (12.5)**	**4 (5.8)**	**6 (5.8)**	**2 (10.0)**	**0**	**16 (6.3)**
Subdural haematoma	0	1 (6.3)	1 (4.2)	1 (1.4)	2 (1.9)	1 (5.0)	0	6 (2.4)
Fall	0	0	0	2 (2.9)	2 (1.9)	0	0	4 (1.6)
Facial bones fracture	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Hip fracture	0	0	0	0	0	1 (5.0)	0	1 (0.4)
Pelvic fracture	0	0	1 (4.2)	0	0	0	0	1 (0.4)
Post procedural haemorrhage	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Road traffic accident	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Tendon rupture	0	0	1 (4.2)	0	0	0	0	1 (0.4)
Wound complication	0	0	1 (4.2)	0	0	0	0	1 (0.4)
Investigations	**1 (5.9)**	**1 (6.3)**	**1 (4.2)**	**7 (10.1)**	**13 (12.6)**	**1 (5.0)**	**1 (33.3)**	**25 (9.9)**
Blood creatine phosphokinase increased	0	0	0	2 (2.9)	3 (2.9)	0	0	5 (2.0)
Aspartate aminotransferase increased	0	0	0	0	2 (1.9)	1 (5.0)	1 (33.3)	4 (1.6)
Blood bilirubin increased	0	0	0	2 (2.9)	2 (1.9)	0	0	4 (1.6)
Blood creatinine increased	0	0	0	1 (1.4)	2 (1.9)	0	0	3 (1.2)
Ejection fraction decreased	1 (5.9)	1 (6.3)	0	1 (1.4)	0	0	0	3 (1.2)
Alanine aminotransferase increased	0	0	0	0	2 (1.9)	0	0	2 (0.8)
Liver function test increased	0	0	0	2 (2.9)	0	0	0	2 (0.8)
Platelet count decreased	0	0	0	0	2 (1.9)	0	0	2 (0.8)
Transaminases increased	0	0	1 (4.2)	0	1 (1.0)	0	0	2 (0.8)
Blood lactate dehydrogenase increased	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Blood uric acid increased	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Electrocardiogram QT prolonged	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Troponin I increased	0	0	0	0	1 (1.0)	0	0	1 (0.4)
White blood cell count increased	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Metabolism and Nutrition Disorders	**0**	**0**	**2 (8.3)**	**4 (5.8)**	**6 (5.8)**	**1 (5.0)**	**0**	**13 (5.2)**
Hyponatraemia	0	0	1 (4.2)	2 (2.9)	1 (1.0)	0	0	4 (1.6)
Dehydration	0	0	0	1 (1.4)	1 (1.0)	1 (5.0)	0	3 (1.2)
Failure to thrive	0	0	0	1 (1.4)	1 (1.0)	0	0	2 (0.8)
Diabetic ketoacidosis	0	0	1 (4.2)	0	0	0	0	1 (0.4)
Hyperkalaemia	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Hyperuricaemia	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Hypocalcaemia	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Tumour lysis syndrome	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Musculoskeletal and Connective Tissue Disorders	**0**	**0**	**1 (4.2)**	**6 (8.7)**	**6 (5.8)**	**2 (10.0)**	**0**	**15 (6.0)**
Back pain	0	0	0	1 (1.4)	1 (1.0)	0	0	2 (0.8)
Muscular weakness	0	0	0	2 (2.9)	0	0	0	2 (0.8)
Pain in extremity	0	0	0	1 (1.4)	1 (1.0)	0	0	2 (0.8)
Arthralgia	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Joint effusion	0	0	0	0	0	1 (5.0)	0	1 (0.4)
Musculoskeletal chest pain	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Myalgia	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Myositis	0	0	0	1 (1.4)	0	0	0	1 (0.4)

Table continued on next page

MedDRA V20.0 System Organ Class Preferred Term	Gilteritinib							
	20 mg (N = 17) n (%)	40 mg (N = 16) n (%)	80 mg (N = 24) n (%)	120 mg (N = 69) n (%)	200 mg (N = 103) n (%)	300 mg (N = 20) n (%)	450 mg (N = 3) n (%)	Total (N = 252) n (%)
Neck pain	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Necrotising myositis	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Osteonecrosis	0	0	1 (4.2)	0	0	0	0	1 (0.4)
Rhabdomyolysis	0	0	0	0	0	1 (5.0)	0	1 (0.4)
Neoplasms Benign, Malignant and Unspecified (Incl Cysts And Polyps)	**3 (17.6)**	**5 (31.3)**	**6 (25.0)**	**12 (17.4)**	**23 (22.3)**	**5 (25.0)**	**0**	**54 (21.4)**
Acute myeloid leukaemia	3 (17.6)	5 (31.3)	5 (20.8)	10 (14.5)	20 (19.4)	5 (25.0)	0	48 (19.0)
Squamous cell carcinoma	0	0	0	2 (2.9)	1 (1.0)	0	0	3 (1.2)
Squamous cell carcinoma of skin	0	0	0	0	2 (1.9)	0	0	2 (0.8)
Acute myeloid leukaemia recurrent	0	0	1 (4.2)	0	0	0	0	1 (0.4)
Basal cell carcinoma	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Central nervous system leukaemia	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Leukaemia	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Nervous System Disorders	**2 (11.8)**	**1 (6.3)**	**2 (8.3)**	**4 (5.8)**	**14 (13.6)**	**1 (5.0)**	**0**	**24 (9.5)**
Syncope	0	0	0	1 (1.4)	5 (4.9)	0	0	6 (2.4)
Haemorrhage intracranial	2 (11.8)	0	0	1 (1.4)	1 (1.0)	0	0	4 (1.6)
Seizure	0	0	0	1 (1.4)	2 (1.9)	0	0	3 (1.2)
Posterior reversible encephalopathy syndrome	0	0	0	1 (1.4)	1 (1.0)	0	0	2 (0.8)
Aphasia	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Cerebral ischaemia	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Cerebrovascular accident	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Coordination abnormal	0	1 (6.3)	0	0	0	0	0	1 (0.4)
Encephalopathy	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Headache	0	0	0	0	0	1 (5.0)	0	1 (0.4)
Intracranial pressure increased	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Lethargy	0	0	1 (4.2)	0	0	0	0	1 (0.4)
Loss of consciousness	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Neuralgia	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Presyncope	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Radicular pain	0	0	1 (4.2)	0	0	0	0	1 (0.4)
Psychiatric Disorders	**0**	**1 (6.3)**	**1 (4.2)**	**0**	**2 (1.9)**	**0**	**0**	**4 (1.6)**
Confusional state	0	1 (6.3)	0	0	1 (1.0)	0	0	2 (0.8)
Mental status changes	0	0	1 (4.2)	0	1 (1.0)	0	0	2 (0.8)
Renal and Urinary Disorders	**1 (5.9)**	**4 (25.0)**	**4 (16.7)**	**9 (13.0)**	**15 (14.6)**	**2 (10.0)**	**0**	**35 (13.9)**
Acute kidney injury	1 (5.9)	3 (18.8)	3 (12.5)	5 (7.2)	14 (13.6)	1 (5.0)	0	27 (10.7)
Renal failure	0	0	0	1 (1.4)	1 (1.0)	1 (5.0)	0	3 (1.2)
Renal tubular necrosis	0	0	1 (4.2)	1 (1.4)	0	0	0	2 (0.8)
Urinary retention	0	0	0	2 (2.9)	0	0	0	2 (0.8)
Renal injury	0	1 (6.3)	0	0	0	0	0	1 (0.4)
Respiratory, Thoracic and Mediastinal Disorders	**0**	**3 (18.8)**	**5 (20.8)**	**10 (14.5)**	**25 (24.3)**	**3 (15.0)**	**0**	**46 (18.3)**
Respiratory failure	0	0	1 (4.2)	1 (1.4)	11 (10.7)	2 (10.0)	0	15 (6.0)
Hypoxia	0	1 (6.3)	1 (4.2)	2 (2.9)	3 (2.9)	0	0	7 (2.8)
Dyspnoea	0	1 (6.3)	0	1 (1.4)	2 (1.9)	0	0	4 (1.6)
Pleural effusion	0	0	0	2 (2.9)	2 (1.9)	0	0	4 (1.6)
Respiratory distress	0	0	0	2 (2.9)	2 (1.9)	0	0	4 (1.6)
Acute respiratory failure	0	0	0	0	3 (2.9)	0	0	3 (1.2)
Epistaxis	0	0	1 (4.2)	0	1 (1.0)	0	0	2 (0.8)
Pulmonary embolism	0	0	0	1 (1.4)	0	1 (5.0)	0	2 (0.8)

Table continued on next page

MedDRA V20.0 System Organ Class Preferred Term	Gilteritinib							
	20 mg (N = 17) n (%)	40 mg (N = 16) n (%)	80 mg (N = 24) n (%)	120 mg (N = 69) n (%)	200 mg (N = 103) n (%)	300 mg (N = 20) n (%)	450 mg (N = 3) n (%)	Total (N = 252) n (%)
Acute promyelocytic leukaemia differentiation syndrome	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Acute respiratory distress syndrome	0	0	1 (4.2)	0	0	0	0	1 (0.4)
Aspiration	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Haemoptysis	0	0	1 (4.2)	0	0	0	0	1 (0.4)
Laryngeal mass	0	1 (6.3)	0	0	0	0	0	1 (0.4)
Lung infiltration	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Pneumonitis	0	0	0	1 (1.4)	0	0	0	1 (0.4)
Pulmonary haemorrhage	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Skin and Subcutaneous Tissue Disorders	**0**	**0**	**1 (4.2)**	**3 (4.3)**	**4 (3.9)**	**0**	**0**	**8 (3.2)**
Acute febrile neutrophilic dermatosis	0	0	0	2 (2.9)	2 (1.9)	0	0	4 (1.6)
Angioedema	0	0	0	1 (1.4)	1 (1.0)	0	0	2 (0.8)
Rash papular	0	0	1 (4.2)	0	0	0	0	1 (0.4)
Skin lesion	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Vascular Disorders	**1 (5.9)**	**0**	**1 (4.2)**	**5 (7.2)**	**8 (7.8)**	**1 (5.0)**	**1 (33.3)**	**17 (6.7)**
Hypotension	1 (6.3)	0	1 (4.2)	3 (4.3)	5 (4.9)	0	0	10 (4.0)
Haematoma	0	0	0	2 (2.9)	1 (1.0)	0	0	3 (1.2)
Deep vein thrombosis	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Embolism	0	0	0	0	0	0	1 (33.3)	1 (0.4)
Haemorrhage	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Hypertension	0	0	0	0	0	1 (5.0)	0	1 (0.4)
Orthostatic hypotension	0	0	0	0	1 (1.0)	0	0	1 (0.4)
Phlebitis deep	0	0	0	1 (1.4)	0	0	0	1 (0.4)

All patients who received at least 1 dose of study drug.

Number of patients (n) and percentage of patients (%) are shown.

Sorting order: alphabetical by SOC and by frequency for PT.

PT: preferred term; SOC: system organ class; TEAE: treatment-emergent adverse event.

Source: Table 12.6.1.5.1

Figure 1 Kaplan-Meier Plot of Overall Survival Stratified by Local FLT3 Mutation Status – Full Analysis Set

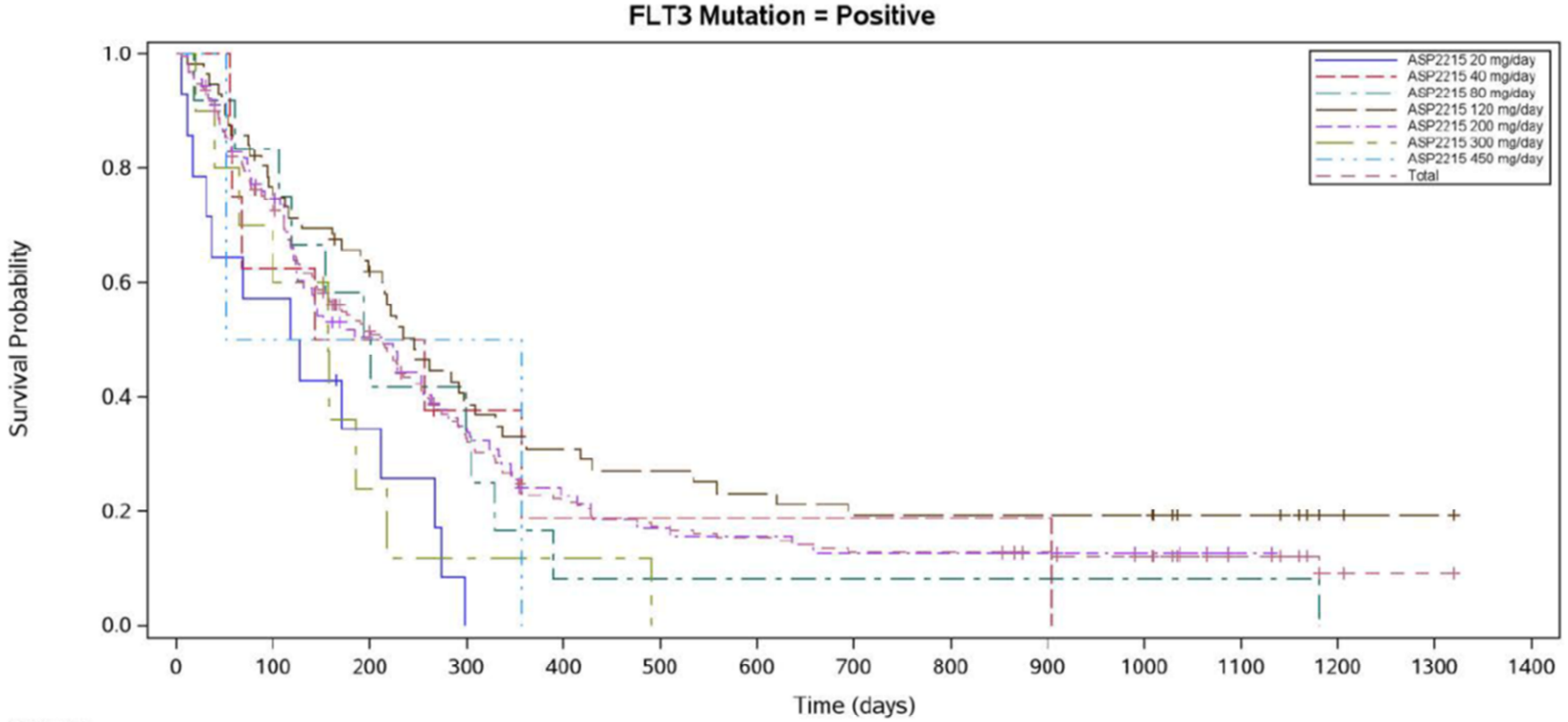
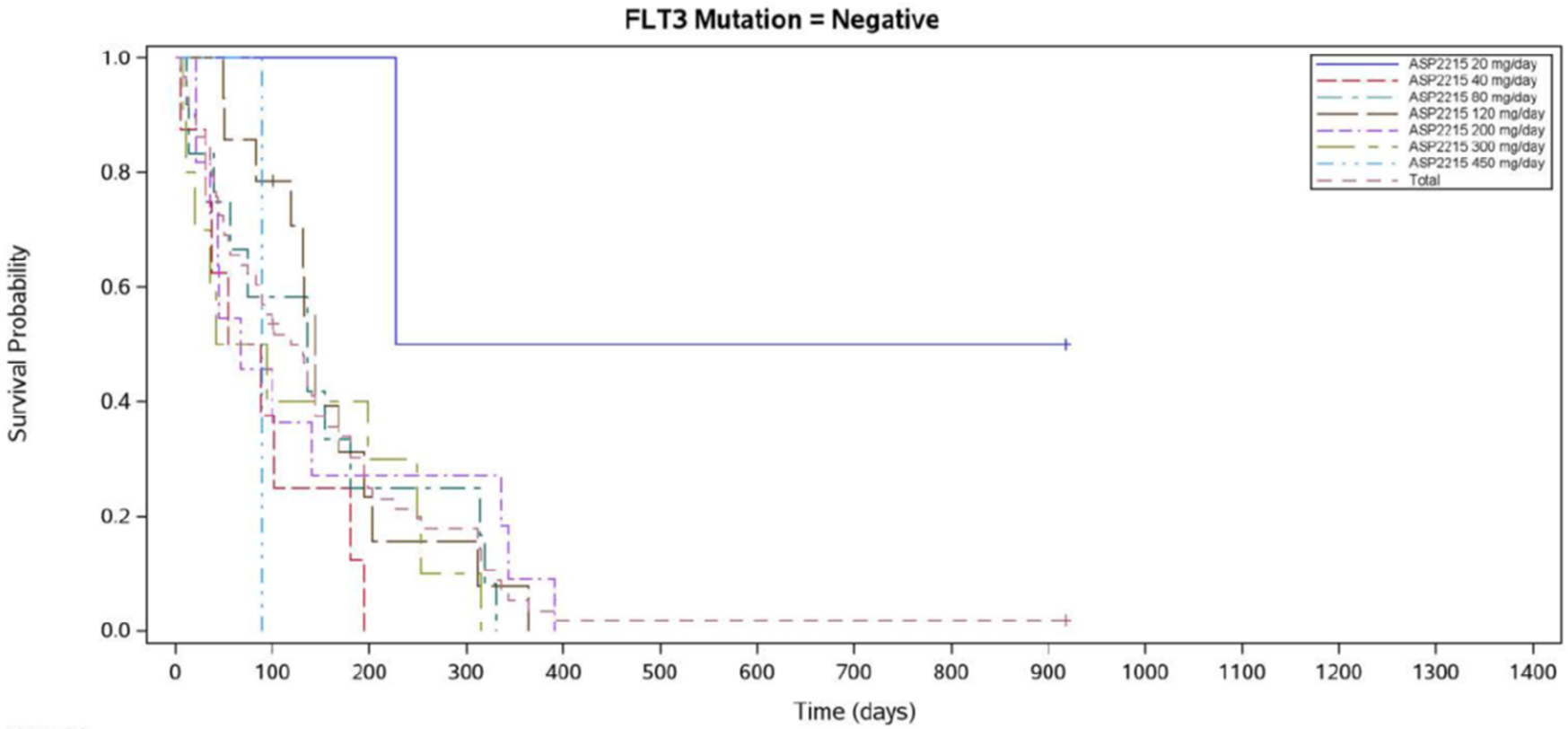


Figure continued on next page



At Risk

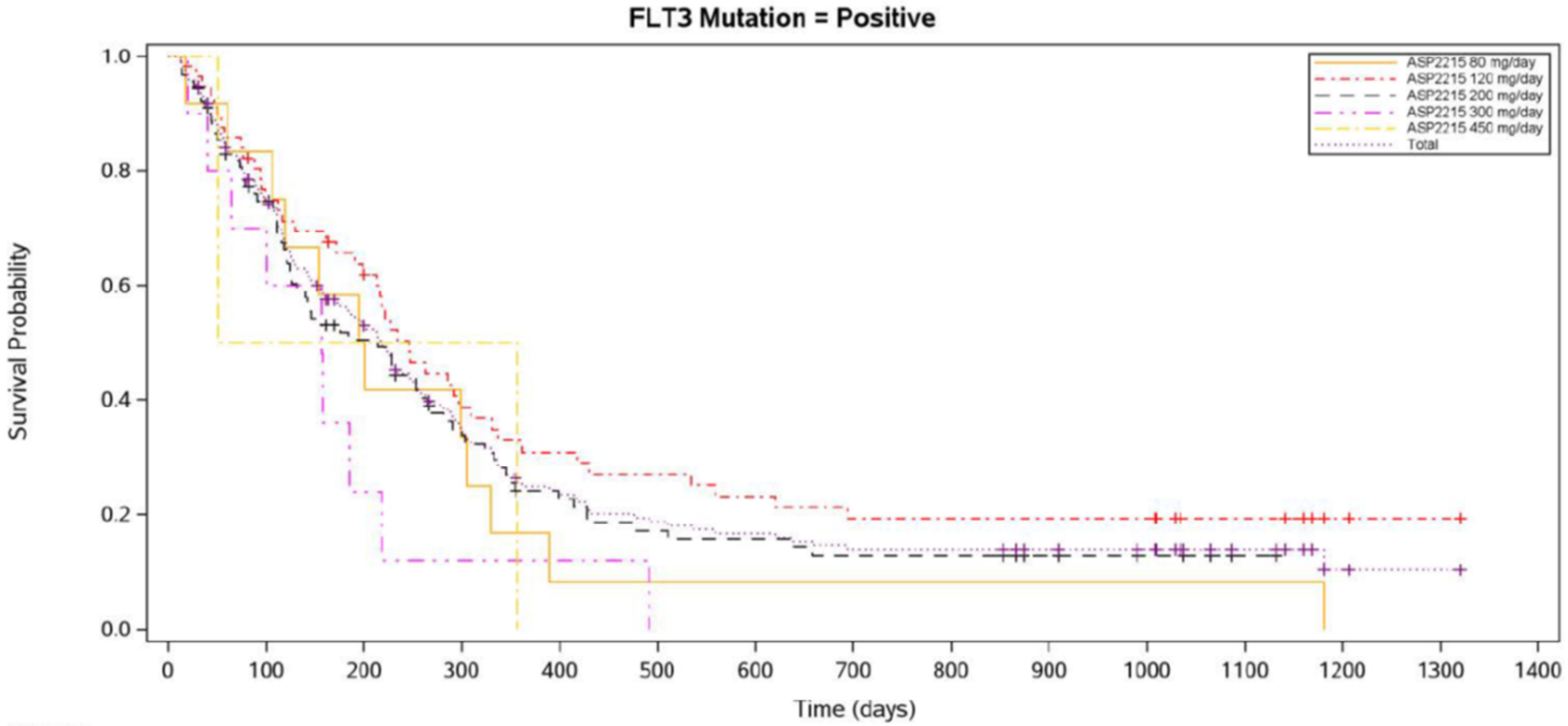
ASP2215 20 mg/day	2	2	2	1	1	1	1	1	1	1
ASP2215 40 mg/day	8	3								
ASP2215 80 mg/day	12	7	3	3						
ASP2215 120 mg/day	14	11	3	2						
ASP2215 200 mg/day	11	5	3	3						
ASP2215 300 mg/day	10	4	3	1						
ASP2215 450 mg/day	1									
Total	58	32	14	10	1	1	1	1	1	1

All patients who were enrolled and received at least 1 dose of study drug and who had at least 1 posttreatment data point.

+ : censored; ASP2215: gilteritinib; FLT3: FMS-like tyrosine kinase.

Source: Figure 12.3.1.1.1

Figure 2 Kaplan-Meier Plot of Overall Survival for Locally Evaluated FLT3 Mutated Patients in ≥ 80 mg Dose Groups – Full Analysis Set

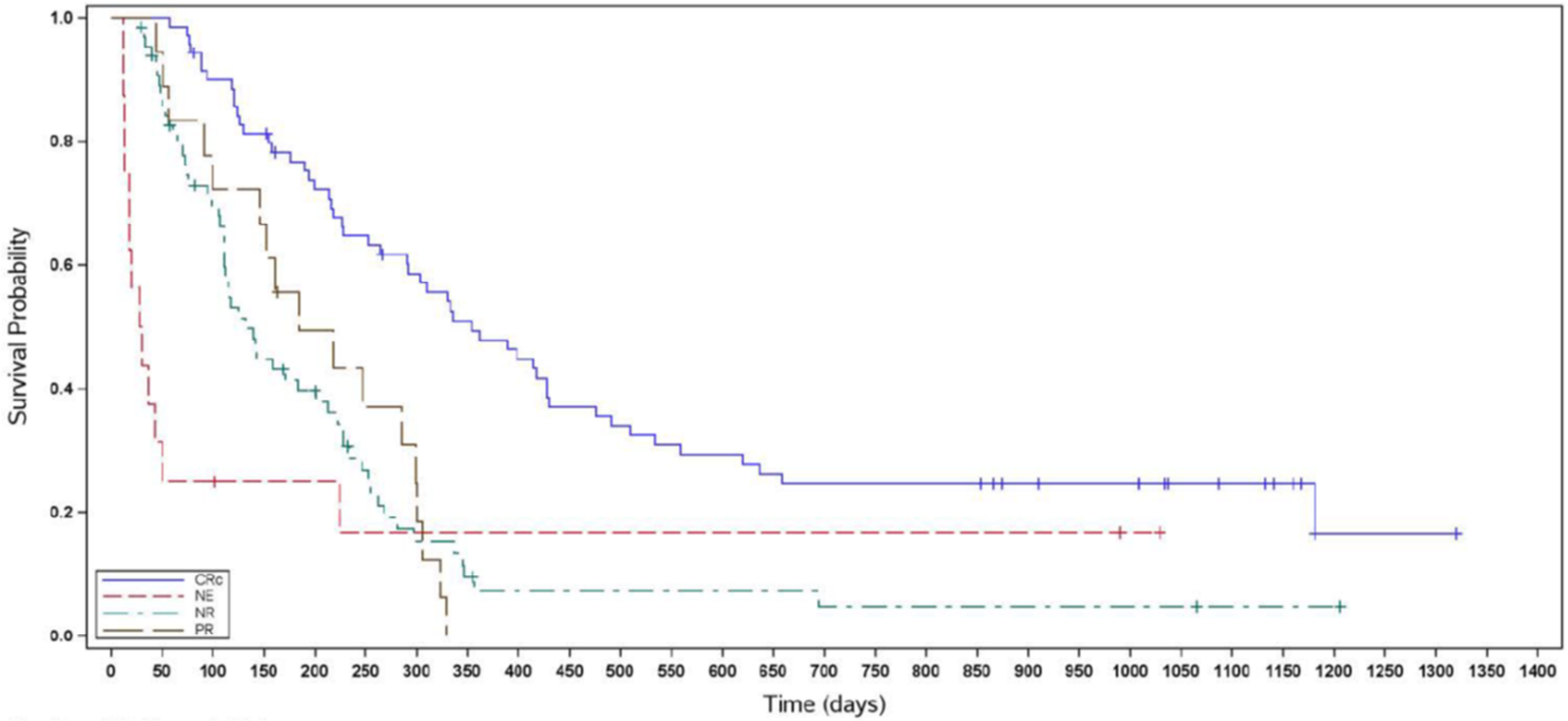


At Risk

ASP2215 80 mg/day	12	10	6	4	1	1	1	1	1	1	1	1		
ASP2215 120 mg/day	56	41	33	20	16	14	12	10	10	10	10	6	2	1
ASP2215 200 mg/day	89	63	40	26	16	12	11	9	9	6	4	1		
ASP2215 300 mg/day	10	7	2	1	1									
ASP2215 450 mg/day	2	1	1	1										
Total	169	122	82	52	34	27	24	20	20	17	15	8	2	1

All patients who were enrolled and received at least 1 dose of study drug and who had at least 1 posttreatment data point.
+ : censored; ASP2215: gilteritinib; FLT3: FMS-like tyrosine kinase.
Source: Figure 12.3.1.5.1

Figure 3 Kaplan-Meier Plot of Overall Survival by Best Overall Response for Locally Evaluated FLT3 Mutated Patients in ≥ 80 mg Dose Groups (Derived Response) – Full Analysis Set

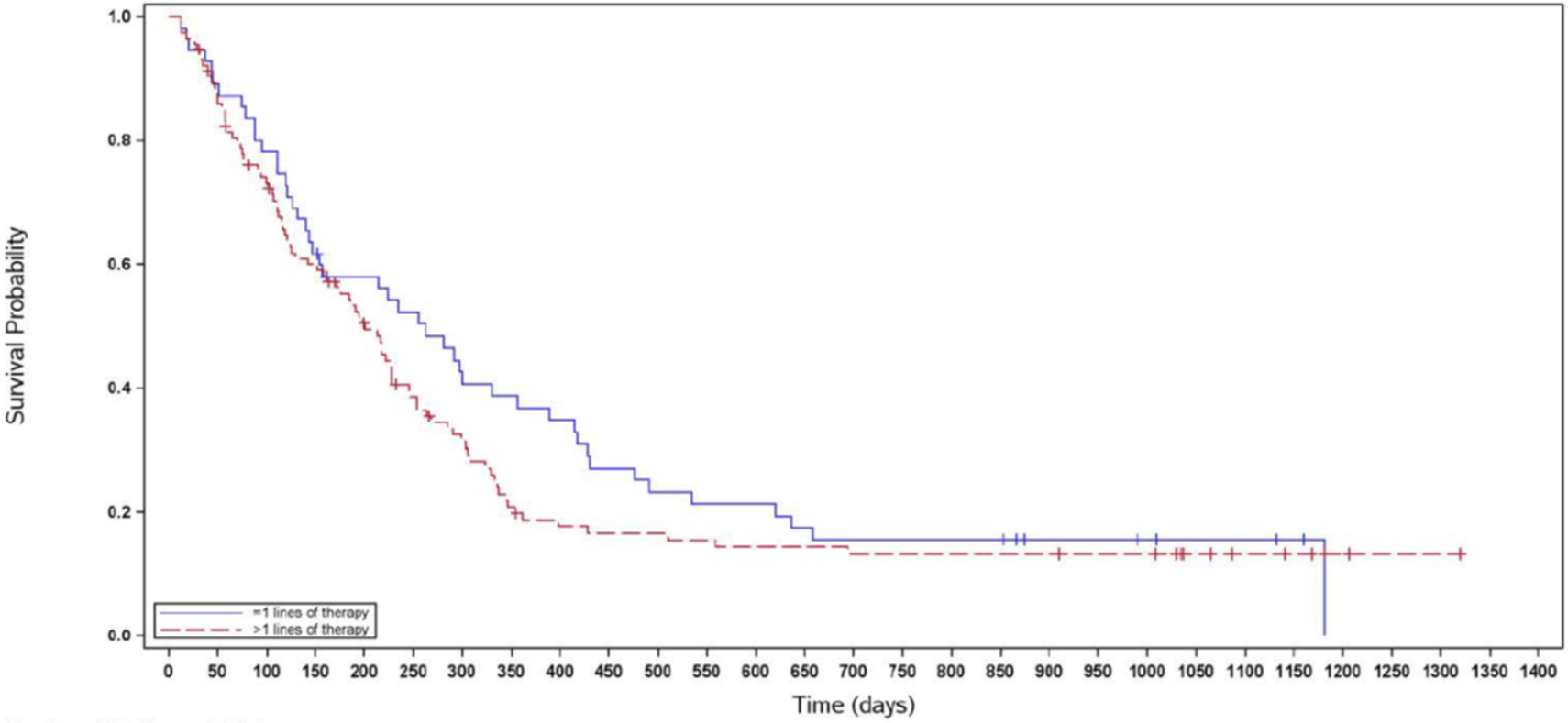


All patients who were enrolled and received at least 1 dose of study drug and who had at least 1 posttreatment data point.

+ : censored; CRc: composite complete response; FLT3: FMS-like tyrosine kinase, NE: not evaluable; NR: no response; PR: partial remission.

Source: Figure 12.3.1.6.1

Figure 4 Kaplan-Meier Plot of Overall Survival by Prior Lines of Therapy for Locally Evaluated FLT3 Mutated Patients in ≥ 80 mg Dose Groups – Full Analysis Set



Number of Subjects At Risk

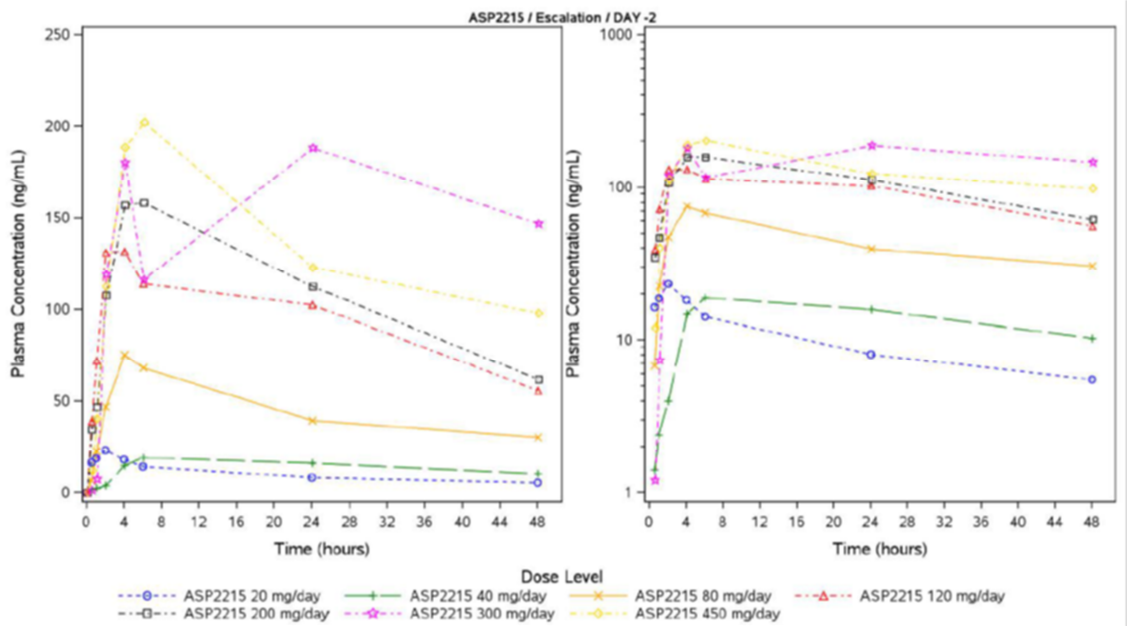
=1 lines of therapy	55	49	43	34	30	27	22	20	18	14	12	11	11	9	8	8	8	8	5	5	4	3	3	2		
>1 lines of therapy	114	98	79	64	52	38	30	20	16	15	15	14	13	13	12	12	12	12	12	11	11	7	5	4	2	1	1

All patients who were enrolled and received at least 1 dose of study drug and who had at least 1 posttreatment data point.

+ : censored; CRc: composite complete response; FLT3: FMS-like tyrosine kinase; NE: not evaluable; NR: no response; PR: partial remission.

Source: Figure 12.3.1.8.1

Figure 5 Mean Gilteritinib Plasma Concentration-Time Profiles after Single Dose (Day -2) Administration in Patients with Relapsed or Refractory AML (Linear and Semi-log Scale) – Pharmacokinetic Analysis Set

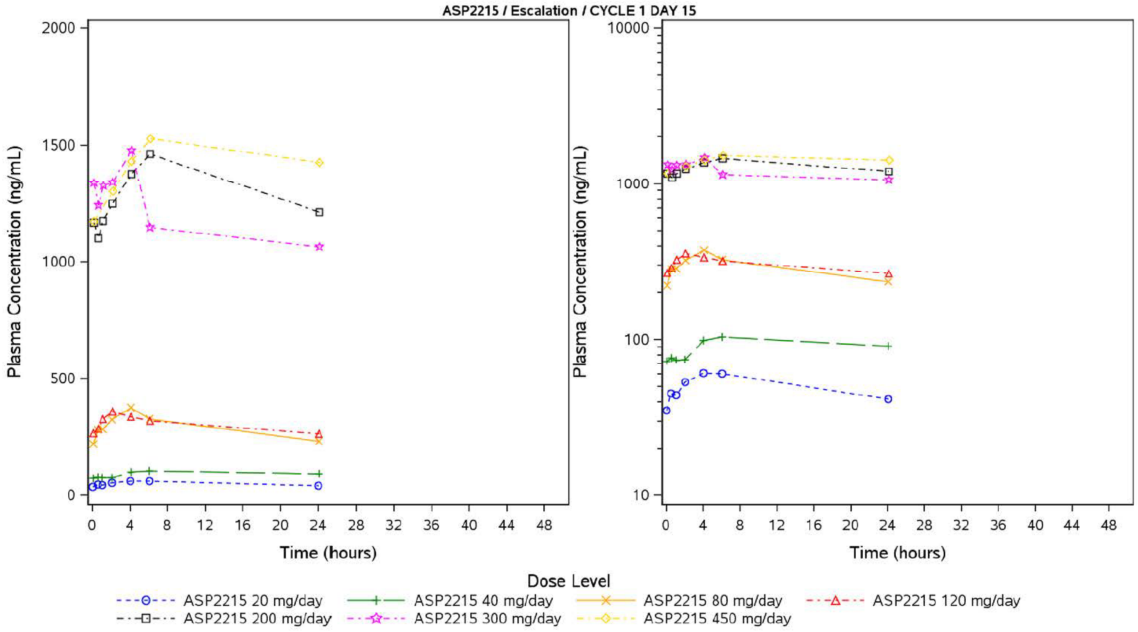


ASP2215: gilteritinib.

All patients who received at least 1 dose of study drug for whom sufficient plasma concentration data were available to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling is known.

Source: Figure 12.4.1.2.1 and Table 12.4.1.1.1

Figure 6 Mean Gilteritinib Plasma Concentration-Time Profiles after Multiple Dose (Cycle 1 Day 15) Administration in Patients with Relapsed or Refractory AML (Linear and Semi-log Scale) – Pharmacokinetic Analysis Set



All patients who received at least 1 dose of study drug for whom sufficient plasma concentration data were available to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling was known.

For Expansion 2B cohort, only subjects with plasma concentration for both cycle 1 day 15 and cycle 2 day 1 were included.

AML: acute myeloid leukemia.

Source: Figure 12.4.1.2.1 and Table 12.4.1.1.1