Name of Sponsor/Company: Astellas Pharma Global Development Inc.		
Name of Finished Product: Not available		
Name of Active Ingredient: Gilteritinib		

SYNOPSIS

Title of Study:

A Phase 1, Open-label Study to Investigate the Absorption, Metabolism and Excretion of [^{14}C]-ASP2215 in Patients with Advanced Solid Tumors

Investigators/Coordinating Investigator:

[redacted]

Study Center:

Cleveland Clinic (Cleveland, Ohio, US)

Publication Based on the Study:

Not applicable

Study Period:

1Q2016 to 2Q2017

Study Initiation Date (Date of First Evaluation):

04 Mar 2016

Study Completion Date (Date of Last Evaluation):

19 Jun 2017

Phase of Development: Phase 1

Objectives:

Primary Objective

- To evaluate the pharmacokinetics of [^{14}C]-gilteritinib, in particular, the routes of excretion and extent of metabolism of gilteritinib following administration of a single dose of [^{14}C]-gilteritinib after repeated doses of gilteritinib tablets.

Secondary Objectives

- To evaluate the safety of repeated oral administration of gilteritinib in patients with advanced solid tumors.
- To identify the metabolic profile of gilteritinib in plasma, urine and feces after a single oral dose of [^{14}C]-gilteritinib.

Methodology:

This was a phase 1, open-label study to investigate the absorption, metabolism and excretion of [^{14}C]-gilteritinib in patients with advanced solid tumors. On study days 1 through 7, patients received a single dose of study drug (tablets) once daily. On day 8, patients returned to the clinical unit to receive a single dose of study drug (tablets) and had a 12-lead electrocardiogram (ECG) performed. On days 9 through 14, patients received a single dose of study drug (tablets) once daily. On day 14, patients were admitted to the clinical research unit, and on day 15 patients received a single dose of study drug (solution). Patients were discharged before day 29 if they met the discharge criteria.

In the event [^{14}C]-radioactivity counts indicated that radioactivity in urine or feces did not meet the discharge criteria or recovery of radioactivity was insufficient, the patient was required to stay in the clinical unit until day 29 if the criteria had not been met sooner.

Blood, plasma, urine and feces samples for absorption, metabolism and excretion assessments were collected at scheduled intervals.

On days 16 through 47, patients received gilteritinib 120 mg once daily. At approximately study days 36 and 45, patients returned to the clinic for additional sample collection to extrapolate elimination of [^{14}C]-radioactivity in plasma, whole blood, urine and feces.

Following completion of the radiolabeled portion of the study, patients were assessed by the investigator for consideration to enroll in the rollover study (Study 2215-CL-0109) if based on the investigator's opinion continued participation was medically appropriate.

Number of Patients (Planned, Enrolled and Analyzed):

A sample size of up to 8 patients was planned for this study to ensure there were at least 4 evaluable patients. Eight patients signed informed consent of which 2 patients were screen failures (discontinued before allocation to treatment). Subsequently 6 patients were allocated to treatment. Of these, 3 (50.0%) patients discontinued from treatment; the primary reasons for discontinuation were adverse event (AE) (1 [16.7%] patient) and progressive disease (2 [33.3%] patients). Two (33.3%) patients discontinued from the study; the primary reasons for discontinuation were withdrawal by the patient (1 [16.7%] patient) and withdrawal of the patient as determined by the sponsor (1 [16.7%] patient). All (6 [100%]) patients allocated to treatment were included in the safety analysis set and 5 (83.3%) patients were included in the pharmacokinetic analysis set.
Two (33.3%) patients entered the rollover study.

Diagnosis and Main Criteria for Inclusion:

Male or female patients with advanced solid tumors who were ≥ 18 years of age who provided written informed consent and to whom all of the inclusion and none of the exclusion criteria applied were eligible for inclusion in this study.

Treatment with concomitant drugs that were moderate or strong cytochrome P 450 (CYP)3A4 inhibitors, strong inhibitors or inducers of P-glycoprotein (P-gp), or substrates of multidrug and toxin extrusion was to be avoided with the exception of drugs that were considered absolutely essential for the care of the patient. Precaution was to be used in treatment of gilteritinib with concomitant drugs that were substrates of CYP3A4, P-gp, and breast cancer resistance protein, since the enzyme or transporters were shown to be inhibited by gilteritinib in in vitro studies.

The need for palliative radiotherapy was considered indicative of disease progression, and thus patients requiring palliative radiotherapy were to be discontinued from study drug. Patients were not to receive any other investigational drugs while on study drug.

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

Gilteritinib tablets were supplied as 40 mg of active ingredient.

Gilteritinib was taken orally once daily at a dose of 120 mg without food for at least 2 hours before and 1 hour after dosing. Gilteritinib was self administered at home when patients were not scheduled for clinic visits. Patients were instructed to take the daily dose with water as close to the same time each morning as possible. If a patient forgot to take a dose in the morning and it was before 13:00, the patient was to be instructed to take their dose. If the patient forgot to take the daily dose and it was after 13:00, the patient was to be instructed to wait for the next morning to dose. If vomiting occurred after dosing, the patient was not to take another dose on that day, and was to wait until the next morning to dose again.

Gilteritinib 120 mg was taken once daily on study days 1 through 14 and days 16 through 47.

On day 15, each patient was given orally a single dose solution containing a total of 120 mg gilteritinib including 100 μCi [^{14}C]-gilteritinib (1.84 or 1.68 mg/100 μCi).

- Gilteritinib 40 mg tablets
  - Lot number: 14071G; [redacted]
  - Lot number: 14071G; [redacted]
- 120 mg gilteritinib including 100 μCi [^{14}C]-gilteritinib solution
  - Batch number: RLM098; [redacted]
  - Batch number: RLM118; [redacted]

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

After a screening period of 13 days, eligible patients, who had signed an informed consent form to participate in the study, received study drug. On study days 1 through 7 and days 16 through 47 patients received gilteritinib tablets once daily at a dose of 120 mg and on day 15, each patient was given orally a single dose solution containing a total of 120 mg gilteritinib including 100 μCi [^{14}C]-gilteritinib (1.84 or 1.68 mg/100 μCi).

Criteria for Evaluation:

Pharmacokinetic Assessments:

The pharmacokinetic endpoints in this study were focused on the absorption, metabolism and excretion of [^{14}C]-gilteritinib following the administration of a single dose of 120 mg gilteritinib including 100 μCi [^{14}C]-gilteritinib (1.84 or 1.68 mg/100 μCi) after repeated doses of gilteritinib tablets in patients with advanced solid tumors. The pharmacokinetic endpoints were as follows:

- Radioactivity in whole blood (AUC_{tau}, C_{max}, t_{max}, $t_{½}$ and CL/F)
- Radioactivity in plasma (AUC_{tau}, C_{max}, t_{max}, $t_{½}$, and CL/F)
- Radioactivity ratio of whole blood/plasma concentrations per time point and AUC
- Excretion rate and cumulative excretion of radioactivity in urine
- Cumulative excretion of radioactivity in feces
- Gilteritinib in plasma: AUC_{tau}, C_{max}, t_{max}, and CL/F

- Gilteritinib in urine: amount excreted in urine Ae_{tau}, CL_R and Ae_{tau}%
- Metabolite profiling of gilteritinib in plasma, urine and feces

Safety Assessments:

Safety was assessed through:

- AEs
- Clinical laboratory tests (hematology, biochemistry, coagulation and urinalysis)
- Vital signs (supine blood pressure, pulse rate and body temperature)
- Physical examinations
- 12-lead ECGs
- Ophthalmologic examination

Statistical Methods:

Pharmacokinetics:

Descriptive statistics (number of patients, mean, SD, coefficient of variation, geometric mean, median, minimum, and maximum) were used to summarize plasma and urine data for gilteritinib and concentrations of total radioactivity in plasma and whole blood were summarized.

Standard graphics, including both normal and semi-logarithmic mean concentration-time profiles, spaghetti plots and individual patient plasma concentration-time profiles for gilteritinib in plasma and urine and total radioactivity concentrations in plasma and whole blood were produced. Mean profiles of cumulative total radioactivity excreted and percent of dose excreted in urine were also produced.

Mass balance was determined from radioactivity recovery and concentration of gilteritinib in urine and feces. The amount excreted and percentage of dose excreted were tabulated by collection interval as well as the cumulative amount excreted and the cumulative percentage of dose excreted at each collection interval.

The cumulative percent of administered radioactivity recovered and concentration of gilteritinib in urine and feces (if applicable) up to 768 hours (day 47) or until the time point of the last sample collection were tabulated and summarized.

The following graphic displays for radioactivity in whole blood, plasma, whole blood to plasma ratio, total radioactivity, total % radioactivity, urine, feces, and emesis (if applicable) were produced:

- Mean radioactivity-time profile (both normal and semi-logarithmic scale).
- Overlay plot of individual patient radioactivity-time profiles (spaghetti plot).
- Individual patient radioactivity-time profiles

Individual plasma and urinary gilteritinib concentrations (and possible metabolites) were summarized at each time point.

Safety:

AEs were coded using MedDRA (version 17.1). The number and percentage of each event were computed and summarized by body system. The AE was graded by National Cancer Institute – Common Terminology Criteria for Adverse Event (NCI-CTCAE) grade (version 4.03).

The number and percentage of patients with treatment-emergent adverse events (TEAEs), serious TEAEs, TEAEs leading to discontinuation and TEAEs related to the study drug were summarized by SOC and preferred term. Additional AE tabulations were described in the SAP.

An AE with onset at any time from first dosing until last scheduled procedure was classified as treatment-emergent for inclusion in the summary tabulations.

Descriptive statistics were provided for clinical laboratory tests, vital signs and 12-lead ECGs.

A shift analysis table summarizing shifts from baseline in overall ophthalmologic examinations (normal, abnormal not clinically significant and abnormal clinically significant) is provided.

Summary tables for Eastern Cooperative Oncology Group (ECOG) performance status by visit were produced.

Summary of Results/Conclusions:

Patient disposition and analysis sets can be found in [Table 1].

Demographic and baseline characteristics of patients with advanced solid tumor can be found in [Table 2].

Pharmacokinetic Results:

Steady-state gilteritinib plasma concentrations after multiple doses of 120 mg gilteritinib were markedly greater than [^{14}C]-radioactivity observed after a single dose of 120 or 240 mg [^{14}C]-gilteritinib. Mean steady-state gilteritinib concentration was approximately 224 ng/mL at 744 hours postdose.

After administration of [^{14}C]-gilteritinib, [^{14}C]-radioactivity was less than the lower limit of quantification (LLOQ) in blood by 216 hours postdose in all patients (LLOQ range: 55.2 to 64.6 ng-eq/mL). Similarly, [^{14}C]-radioactivity in plasma was less than the LLOQ (range: 48.6 to 60.2 ng-eq/mL) by 216 hours postdose in 4 of the 5 patients.

After a single dose of [^{14}C]-gilteritinib, mean maximum [^{14}C]-radioactivity concentrations (t_{max}) were observed between 3 to 4 hours postdose in whole blood and/or plasma. Similarly, gilteritinib plasma concentrations peaked between 3 and 4 hours during the 24-hour dosing interval. In individual patients, maximum [^{14}C]-radioactivity concentrations ranged from 2 to 8 hours in blood and 2 to 4 hours in plasma.

Mean blood-to-plasma concentration ratios ranged from 0.791 to 1.38 for all patients through 192 hours postdose. Mean blood-to-plasma ratios of AUC_{tau} were not greatly different than 1.00, indicating radioactivity had a low tendency to partition into blood cells relative to plasma [Table 3].

Urine [^{14}C]-radioactivity concentrations were quantifiable through a minimum of 264 hours postdose. Levels of [^{14}C]-radioactivity in feces and gilteritinib urine concentrations were quantifiable for all patients through the last collection interval.

The overall mean total recovery of radioactivity in urine, feces and toilet tissue samples was 81.0% (interpolated to 91.3%) over the 768-hour collection period. Approximately 77% of the administered radioactivity was

recovered in the first 288 hours postdose. Recovery of radioactivity from toilet tissue accounted for < 0.1% of the dose. A mean of 64.5% of the dose was recovered in feces (interpolated to 73.4%) and 16.4% was recovered in urine (interpolated to 17.9%). Similarly, approximately 10% or less of the administered dose was excreted in urine as unchanged gilteritinib during the 24-hour postdose collection period, indicating renal excretion is a minor elimination route of gilteritinib [Table 4].

Metabolite profiling and steady-state metabolite pharmacokinetics were also evaluated. Metabolite profiling results are reported in a separate report (Study 2215-ME-0028). There were 3 predominant circulating metabolites identified in plasma: AS3397391 (M17) (formed via oxidation), AS3322943 (M16) and AS2651096 (M10) (both formed via N-dealkylation). Steady-state pharmacokinetic parameters for the 3 predominant metabolites are summarized in [Table 5]. The mean overall exposure, (i.e., AUC_{24}) of these metabolites relative to ASP2215 (MPR) is less than 10%.

Safety Results:

Overall, all (6 [100%]) patients who received the study drug experienced at least 1 TEAE, drug-related TEAE and serious adverse event (SAE). The majority of TEAEs reported were maximum NCI-CTCAE grades 1 and 2.

The most commonly reported TEAEs were fatigue in the SOC general disorders and administration site conditions, and aspartate aminotransferase (AST) increased in the SOC investigations, each reported for 4 (66.7%) patients. The following TEAEs were reported for 3 (50.0%) patients: anemia in the SOC blood and lymphatic system disorders, alanine aminotransferase (ALT) increased in the SOC investigations, hyperglycemia in the SOC metabolism and nutrition disorders, and proteinuria in the SOC renal and urinary disorders [Table 6].

The most commonly reported drug-related TEAEs were AST increased in the SOC investigations reported for 4 (66.7%) patients, followed by fatigue in the SOC general disorders and administration site conditions, and ALT increased in the SOC investigations, each reported for 3 (50.0%) patients.

NCI-CTCAE grade 3 or higher TEAEs, drug-related TEAEs and SAEs were experienced by 5, 3 and 4 patients, respectively. The majority of TEAEs reported were maximum NCI-CTCAE grades 1 and 2. The most commonly reported maximum NCI-CTCAE grade 3 TEAE was ALT increased in the SOC investigations. Maximum NCI-CTCAE grade 4 TEAEs reported were lymphocyte count decreased in the SOC investigations and dyspnea in the SOC respiratory, thoracic and mediastinal disorders, and the maximum NCI-CTCAE grade 5 TEAE reported was chondrosarcoma in the SOC neoplasms benign, malignant and unspecified.

Overall, SAEs were reported for 6 (100%) patients. The most commonly reported SAE was overdose in the SOC injury, poisoning and procedural complications, which was reported for 2 (33.3%) patients. Drug-related SAEs were reported for 4 (66.7%) patients. These SAEs were overdose, ALT increased, anemia and confusion [Table 7].

A TEAE leading to death was reported for 1 (16.7%) patient. On day 40, the patient experienced NCI-CTCAE grade 4 dyspnea which was considered by the investigator to be life-threatening (urgent intervention indicated) and not related to study drug. The patient was intubated for respiratory support after admission to the intensive care unit due to acute hypoxic respiratory failure. Treatment with empiric vancomycin and zosyn was started. An initial attempt to wean the patient off the ventilator was unsuccessful. On day 45, a pleurx catheter was inserted in the left side which drained 1.1 L fluid and allowed the patient to be extubated on day 46. The patient

was transferred to a hospice on day 46 and died on day 47 due to NCI-CTCAE grade 5 progression of chondrosarcoma.

TEAEs which led to discontinuation of study drug were reported for 2 (33.3%) patients. One of these TEAEs (anemia in the SOC blood and lymphatic system disorders) was considered by the investigator as possibly related to the study drug. The other TEAE (dyspnea in the SOC respiratory, thoracic and mediastinal disorders) was considered by the investigator as not related to the study drug and disease progression was rather considered to be the primary reason for discontinuation.

TEAEs which led to reduction of study drug administration were reported for 1 (16.7%) patient. These TEAEs were ALT and AST increased (in the SOC investigations) and were considered by the investigator as probably related to study drug.

TEAEs which led to interruption of study drug administration were reported for 5 (83.3%) patients. Of these TEAEs, overdose in the SOC injury, poisoning and procedural complications, ALT and AST increased in the SOC investigations, and confusion in the SOC psychiatric disorders were considered by the investigator as possibly or probably related to the study drug, while generalized muscle weakness and right lower rib cage pain (in the SOC musculoskeletal and connective tissue disorders), cough (in the SOC respiratory, thoracic and mediastinal disorders), and other chest tightness (in the SOC general disorders and administrative site conditions) were considered by the investigator as not related to the study drug. The most common SOC that included TEAEs which led to dose interruption was investigations reported for 2 (33.3%) patients.

TEAEs of special interest observed in this study included muscular weakness (1 [16.7] patient) in the SOC musculoskeletal and connective tissue disorders and AST increased (4 [66.7%] patients), ALT increased (3 [50.0%] patients) and gamma-glutamyltransferase (GGT) increased (2 [33.3%] patients) in the SOC investigations. All TEAEs of special interest were considered by the investigator to be possibly or probably related to study drug with the exception of the event of muscular weakness. Most events were mild in severity (≤ NCI-CTCAE grade 2) with the exception of 2 (33.3%) patients who experienced NCI-CTCAE grade 3 events of ALT increased.

For the following hematology test parameters, patients had baseline values < NCI-CTCAE grade 3 that shifted to worst postbaseline values ≥ NCI-CTCAE grade 3: hemoglobin (1 [20.0%] patient), lymphocytes (1 [20.0%] patient) and platelets (1 [16.7%] patient). For the following biochemistry test parameters, patients had baseline values < NCI-CTCAE grade 3 that shifted to worst postbaseline values ≥ NCI-CTCAE grade 3: ALT (2 [33.3%] patients) and sodium (1 [16.7%] patient).

For ALT, 3 (50.0%) and 2 (33.3%) patients experienced an increase to > 3 x upper limit of normal (ULN) and > 5 x ULN, respectively. For AST, 2 (33.3%) patients experienced an increase to > 3 x ULN. For ALT and/or AST > 3 x ULN, 2 (33.3%) patients experienced an increase to 3 x ULN.

There were no patients with total bilirubin (TBL) > 2 x ULN, or ALT and/or AST > 3 x ULN and TBL > 2 x ULN.

Clinically significant liver abnormalities requiring further liver function investigation were reported for 2 patients. Both these patients experienced TEAEs of ALT and AST increased which was considered by the investigator as possibly or probably related to study drug. There were no reports of study drug interruptions due to liver abnormalities.

Mean changes from baseline to postbaseline assessment time points for vital signs, including systolic and diastolic blood pressure, pulse rate, body temperature, height, weight and body mass index were summarized. Mean changes in vital signs fluctuated but no potentially clinically significant vital sign values were reported.

Patients had both normal and abnormal ECG findings throughout the study, except on day 36 when all ECG findings were normal. None of the abnormal ECG findings were considered to by clinically significant.

Overall, no corrected QT interval using Fridericia's formula (QTcF) values were observed to be > 480 msec and no mean QTcF changes from baseline were observed to be > 30 msec. At baseline, all (6 [100%]) patients had a baseline QTcF of ≤ 450 msec. A maximum postbaseline QTcF of > 450 msec was observed in 1 (16.7%) patient. The mean maximum value of QTcF change from baseline was 17.89 msec.

There were no reports of pregnancies during the study.

None of the abnormal chest X-ray findings were considered by the investigator to be clinically significant.

Mean changes from baseline to day 47 assessment time points for visual acuity measurement were summarized. Baseline ophthalmoscopy abnormalities were observed for 1 (16.7%) patient; the abnormalities were for retina, macula, choroid and optic nerve assessments. These abnormalities were considered by the investigator to be not clinically significant. No postbaseline abnormalities were observed.

No patients had an ECOG performance score of ≥ 3 by the end of treatment, assessed from baseline. One patient died due to disease progression. Study drug administration was discontinued prematurely for this patient and no ECOG assessment was performed around the time of death.

CONCLUSIONS:

Mean maximum concentrations (t_{max}) of gilteritinib and [^{14}C]-radioactivity were observed between 3 to 4 hours postdose in whole blood and/or plasma. [^{14}C]-radioactivity has low partitioning into blood cells as evidenced by mean blood-to-plasma concentration ratios ranging from 0.791 to 1.38. Mean total recovery of the administered dose of [^{14}C]-radioactivity over the 768-hour collection period was 81.0%. Mean [^{14}C]-radioactivity recovered in feces as percent of dose administered was 64.5% (interpolated to 73.4%) and 16.4% in urine (interpolated to 17.9%). The majority (approximately 77%) of [^{14}C]-radioactivity was recovered in feces and urine within 288 hours postdose.

The primary route of [^{14}C]-radioactivity elimination is into feces with renal excretion being a minor route. Gilteritinib is the primary circulating species in plasma and is metabolized to 3 predominant metabolites, AS3397391 (M17) (formed via oxidation), AS3322943 (M16) and AS2651096 (M10) (both formed via N-dealkylation). The exposure of metabolite relative to parent was less than 10% for each metabolite.

Overall, all patients who received the study drug experienced at least 1 TEAE, drug-related TEAE and SAE. The most commonly reported TEAEs were fatigue and AST increased, and the most commonly reported drug-related TEAE was AST increased. The most commonly reported SAE and drug-related SAE was overdose.

The majority of TEAEs reported were maximum NCI-CTCAE grades 1 and 2. The most commonly reported maximum NCI-CTCAE grade 3 TEAE was ALT increased. Maximum NCI-CTCAE grade 4 TEAEs reported were lymphocyte count decreased and dyspnea, and the maximum NCI-CTCAE grade 5 TEAE reported was chondrosarcoma.

A TEAE leading to death was reported. This TEAE of progression of chondrosarcoma was considered by the investigator as not related to the study drug.

One of the TEAEs (anemia) which led to discontinuation of study drug was considered by the investigator as possibly related to the study drug. The other TEAE (dyspnea) was considered by the investigator as not related to the study drug and disease progression was rather considered to be the primary reason for discontinuation.

TEAEs which led to reduction of study drug administration were overdose, ALT increased and AST increased, and were considered by the investigator as probably related to study drug.

TEAEs which led to interruption of study drug administration were ALT and AST increased, and confusion. These TEAEs were considered by the investigator as possibly or probably related to the study drug, while generalized muscle weakness and right lower rib cage pain, cough, and other chest tightness were considered by the investigator as not related to the study drug. The most common SOC that included TEAEs which led to dose interruption was investigations.

TEAEs of special interest observed in this study included muscular weakness, AST increased, ALT increased and GGT increased; all events were considered possibly or probably related to study drug with the exception of muscular weakness.

For hematology test parameters, patients had baseline values < NCI-CTCAE grade 3 that shifted to worst postbaseline values ≥ NCI-CTCAE grade 3 for hemoglobin, lymphocytes and platelets. For the biochemistry test parameters, patients had baseline values < NCI-CTCAE grade 3 that shifted to worst postbaseline values ≥ NCI-CTCAE grade 3 for ALT and sodium.

Clinically significant liver abnormalities requiring further liver function investigation were reported for 2 patients but there were no reports of study drug interruptions due to liver abnormalities.

Mean changes in vital signs fluctuated but no potentially clinically significant vital sign values were reported.

ECG abnormalities were observed across time points; however, none of these abnormalities were considered to be clinically significant.

None of the abnormal chest X-ray findings were considered by the investigator to be clinically significant.

No postbaseline abnormalities were observed ophthalmic examination.

No patients had an ECOG performance score of ≥ 3 by the end of treatment, assessed from baseline. One patient died due to disease progression. Study drug administration was discontinued prematurely for this patient and no ECOG assessment was performed around the time of death.

Overall, repeated oral doses of 120 mg gilteritinib were safe and well tolerated in patients with advanced solid tumors.

Date of Report: 14 Feb 2018

Table 1 Patient Disposition and Analysis Sets (All Patients Allocated to Treatment)

Analysis Set	Gilteritinib 120 mg (n = 6) n (%)
Allocated to Treatment	6 (100)
Treatment Discontinuation	3 (50.0)
Study Discontinuation	2 (33.3)
Study Rollover	2 (33.3)
Safety Analysis Set†	6 (100)
Pharmacokinetic Analysis Set‡	5 (83.3)

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

‡ A subset of the safety analysis set for which concentration data were available to facilitate derivation of at least 1 primary pharmacokinetic parameter and for whom the time of dosing on the day of sampling was known.

Source: End-of-Text Tables 12.1.1.2, 12.1.1.3 and 12.1.1.4

Table 2 Summary of Demographics and Baseline Characteristics (Safety Analysis Set)

Parameter Category/Statistics	Gilteritinib 120 mg (n = 6)†
Sex, n (%)	
Male	3 (50.0)
Female	3 (50.0)
Ethnicity, n (%)	
Not Hispanic or Latino	6 (100)
Race, n (%)	
White	6 (100)
Black or African American	0
Asian	0
Other	0
Age, years	
Mean (SD)	61.7 (9.6)
Median	59.0
Min - Max	49 - 75
Age Group, years	
< 65	4 (66.7)
≥ 65	2 (33.3)
Weight (kg)	
Mean (SD)	88.2 (34.0)
Median	83.9
Min - Max	37 - 134
Height (cm)	
Mean (SD)	174.2 (10.9)
Median	177.5
Min - Max	161 - 187

Table continued on next page

Parameter Category/Statistics	Gilteritinib 120 mg (n = 6)†
BMI (kg/m^2)	
Mean (SD)	32.8 (9.7)
Median	26.9
Min - Max	24 - 45
ECOG Performance Status, n (%)	
Grade 0	1 (16.7)
Grade 1	5 (83.3)
Grade 2	0
Grade 3	0
Grade 4	0
Grade 5	0

BMI: body mass index (weight [kg]/height^2 [m^2]); ECOG: Eastern Cooperative Oncology Group; Max: maximum; Min: minimum.

† n = 6 except for height and BMI where n = 5.

Source: End-of-Text Tables 12.1.2.1 and 12.6.5.1

Table 3 Summary Statistics of Blood-to-plasma Ratios of AUC_{tau} for [^{14}C]-radioactivity (Pharmacokinetic Analysis Set)

Parameter Statistic	[^{14}C]-Radioactivity	
	120 mg (n = 2)	240 mg (n = 2)
$(AUC_{tau})_{blood}/(AUC_{tau})_{plasma}$		
Mean (SD)	0.8514 (0.002383)	1.361 (0.3793)
GM	0.8513	1.334
%CV	0.3	27.9
Median	0.8514	1.361
Min - Max	0.850 – 0.853	1.09 – 1.63

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

CV: coefficient of variation; GM: geometric mean; Max: maximum; Min: minimum.

Source: End-of-Text Table 12.4.2.5

Table 4 Summary of Cumulative Recovery of [^{14}C]-radioactivity in Urine and Feces (Pharmacokinetic Analysis Set)

	[^{14}C]-radioactivity									
	Mean (SD) Ae (µg-eq)		Mean (SD) Af (µg-eq)		Mean Total Recovery (SD)		Mean %Dose		Overall Mean Recovery (%Dose)	
	ASP2215									
Matrix	120 mg (n = 2)	240 mg (n = 2)	120 mg (n = 2)	240 mg (n = 2)	120 mg (n = 2)	240 mg (n = 2)	Noninterpolated	Interpolated	Noninterpolated	Interpolated
Urine	24200 (NA)	30200 (NA)	NA	NA	98500	192000	16.4	17.9	81.0	91.3
Feces	NA	NA	74000 (NA)	161000 (NA)			64.5	73.4		

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

Ae: cumulative amount excreted in urine; Af: cumulative amount excreted in feces; NA: not applicable.

Source: Radioanalysis in Support of Clinical Protocol No. 2215-CL-0105 [Appendix 13.3], Tables 9 and 10

Table 5 Metabolite Steady-state Plasma Pharmacokinetic Parameters of Gilteritinib (Pharmacokinetic Analysis Set)

Parameter Statistic	Metabolite					
	AS3322943 (M16)		AS3397391 (M17)		AS2651096 (M10)	
	120 mg (n = 2)	240 mg (n = 2)	120 mg (n = 2)	240 mg (n = 2)	120 mg (n = 2)	240 mg (n = 2)
C_{max} (ng/mL)						
Mean (SD)	47.45 (35.99)	34.15 (0.07071)	44.50 (28.85)	35.10 (7.778)	62.35 (47.59)	33.05 (2.899)
GM	40.05	34.15	39.55	34.67	52.49	32.99
%CV	75.9	0.2	64.8	22.2	76.3	8.8
Median	47.45	34.15	44.50	35.10	62.35	33.05
Min - Max	22.0 – 72.9	34.1 – 34.2	24.1 – 64.9	29.6 – 40.6	28.7 – 96.0	31.0 – 35.1
t_{max} (h)						
Median	1.500	3.045	1.500	18.14	2.490	2.275
Min - Max	0 – 3.00	2.07 – 4.02	0 – 3.00	12.3 – 24.0	1.98 – 3.00	0.530 – 4.02
AUC_{24} (h•ng/mL)†						
Mean (SD)	1049 (816.4)	770‡	976.5 (674.6)	682‡	1086 (806.9)	414‡
GM	875.8	NA	852.1	NA	924.5	NA
%CV	77.8	NA	69.1	NA	74.3	NA
Median	1049	NA	976.5	NA	1086	NA
Min - Max	472 – 1626	NA	499 – 1454	NA	516 – 1657	NA
MPR						
n	3		3		3	
Mean (SD)	0.08807 (0.01064)		0.08338 (0.003626)		0.06734 (0.02243)	
GM	0.08762		0.08333		0.06454	
%CV	12.1		4.3		33.3	
Median	0.09074		0.08154		0.07294	
Min - Max	0.0763 – 0.0971		0.0810 – 0.0876		0.0426 – 0.0864	

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

CV: coefficient of variation; GM: geometric mean; Max: maximum; Min: minimum; NA: not applicable.

† $AUC_{24} = AUC_{tau}$

‡ n = 1

Source: End-of-Text Tables 12.4.2.1.2, 12.4.2.1.3 and 12.4.2.1.4

Table 6 Treatment-emergent Adverse Events by SOC, Preferred Term and NCI-CTCAE Grade (v4.03) (Safety Analysis Set)

MedDRA v17.1 SOC Preferred Term‡	Maximum NCI-CTCAE Grade† Total n = 6 n (%)
Overall	**6 (100)**
Blood and Lymphatic System Disorders	**3 (50.0)**
Anaemia	3 (50.0)
Endocrine Disorders	**1 (16.7)**
Hyperthyroidism	1 (16.7)
Eye Disorders	**1 (16.7)**
Ulcerative keratitis	1 (16.7)

Table continued on next page

MedDRA v17.1 SOC Preferred Term‡	Maximum NCI-CTCAE Grade† Total n = 6 n (%)
Gastrointestinal Disorders	**3 (50.0)**
Abdominal pain upper	1 (16.7)
Constipation	2 (33.3)
General Disorders and Administrative Site Conditions	**4 (66.7)**
Chest discomfort	1 (16.7)
Fatigue	4 (66.7)
Pain	1 (16.7)
Pyrexia	1 (16.7)
Infections and Infestations	**1 (16.7)**
Urinary tract infection	1 (16.7)
Injury, Poisoning and Procedural Complications	**3 (50.0)**
Overdose	2 (33.3)
Procedural pain	1 (16.7)
Investigations	**5 (83.3)**
Activated partial thromboplastin time prolonged	1 (16.7)
Alanine aminotransferase increased	3 (50.0)
Aspartate aminotransferase increased	4 (66.7)
Blood cholesterol increased	1 (16.7)
Blood creatinine increased	1 (16.7)
Gamma-glutamyltransferase increased	2 (33.3)
International normalized ratio increased	1 (16.7)
Lymphocyte count decreased	1 (16.7)
Metabolism and Nutrition Disorders	**5 (83.3)**
Decreased appetite	1 (16.7)
Hyperglycaemia	3 (50.0)
Hypermagnesaemia	1 (16.7)
Hypertriglyceridaemia	1 (16.7)
Hyperuricaemia	1 (16.7)
Hypoalbuminaemia	1 (16.7)
Hypokalaemia	1 (16.7)
Hyponatraemia	1 (16.7)
Hypophosphataemia	1 (16.7)
Musculoskeletal and Connective Tissue Disorders	**3 (50.0)**
Back pain	2 (33.3)
Muscular weakness	1 (16.7)
Musculoskeletal chest pain	1 (16.7)

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MedDRA v17.1 SOC Preferred Term‡	Maximum NCI-CTCAE Grade† Total n = 6 n (%)
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	**2 (33.3)**
Chondrosarcoma	1 (16.7)
Prostate cancer	1 (16.7)
Nervous System Disorders	**3 (50.0)**
Dizziness	2 (33.3)
Headache	2 (33.3)
Paraesthesia	1 (16.7)
Psychiatric Disorders	**1 (16.7)**
Confusional state	1 (16.7)
Renal and Urinary Disorders	**3 (50.0)**
Proteinuria	3 (50.0)
Reproductive System and Breast Disorders	**1 (16.7)**
Vaginal perforation	1 (16.7)
Respiratory, Thoracic and Mediastinal Disorders	**2 (33.3)**
Cough	1 (16.7)
Dyspnoea	1 (16.7)
Epitaxis	1 (16.7)
Haemoptysis	1 (16.7)

The safety analysis set consisted of all enrolled patients who received at least 1 dose of study drug.

† Within an SOC patients may have reported more than 1 type of adverse event. At each level of summarization, a patient was counted only once if reported 1 or more events.

‡ For each preferred term, each patient was only counted once at the maximum intensity.

NCI-CTCAE: National Cancer Institute - Common Terminology Criteria for Adverse Event

Source: End-of-Text Table 12.6.1.2.1

Table 7 Serious Treatment-emergent Adverse Events by SOC, Preferred Term and NCI-CTCAE Grade (v4.03) (Safety Analysis Set)

MedDRA v17.1 SOC Preferred Term‡	Maximum NCI-CTCAE Grade† Total n = 6 n (%)
Overall	**6 (100)**
Blood and Lymphatic System Disorders	**1 (16.7)**
Anaemia	1 (16.7)
General Disorders and Administrative Site Conditions	**1 (16.7)**
Chest discomfort	1 (16.7)
Injury, Poisoning and Procedural Complications	**2 (33.3)**
Overdose	2 (33.3)
Investigations	**1 (16.7)**
Alanine aminotransferase increased	1 (16.7)
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	**2 (33.3)**
Chondrosarcoma	1 (16.7)
Prostate cancer	1 (16.7)
Psychiatric Disorders	**1 (16.7)**
Confusional state	1 (16.7)
Respiratory, Thoracic and Mediastinal Disorders	**1 (16.7)**
Dyspnoea	1 (16.7)

The safety analysis set consisted of all enrolled patients who received at least 1 dose of study drug.

† Within an SOC patients may have reported more than 1 type of adverse event. At each level of summarization, a patient was counted only once if reported 1 or more events.

‡ For each preferred term, each patient was only counted once at the maximum intensity.

NCI-CTCAE: National Cancer Institute - Common Terminology Criteria for Adverse Event

Source: End-of-Text Table 12.6.1.5.1