EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 September 2019
EMA/545585/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

XOSPATA

International non-proprietary name: gilteritinib

Procedure No. EMEA/H/C/004752/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

CPP	Critical process parameter
CQA	Critical Quality Attribute
DIPEA	diisopropylamine
DMF	Dimethyl formamide
DSC	Differential Scanning Calorimetry
FMEA	Failure mode effects analysis
GC	Gas Chromatography
HDPE	High Density Polyethylene
HPC	Hydroxypropylcellulose
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Infrared
KF	Karl Fischer titration
LDPE	Low density polyethylene
L-HPC	low-substituted hydroxypropylcellulose
LDPE	Low Density Polyethylene
NDEA	N-diethylnitrosamine
NDMA	N-dimethylntrosamine
NIR	Near Infrared Spectroscopy
NLT	Not less than
NMP	N-Methyl-2-pyrrolidone
NMT	Not more than
NOR	Normal Operating Range
OPA	Oriented polyamide
Ph. Eur.	European Pharmacopoeia
PVC	Polyvinyl chloride
QTPP	Quality target product profile
RH	Relative Humidity
RTRT	Real Time Release Testing
SmPC	Summary of Product Characteristics
TAMC	Total Aerobic Microbial Count
tmax	Time to achieve Cmax
TG	Thermo-Gravimetry
TLC	Thin layer chromatography
TYMC	Total Combined Yeasts/Moulds Count
UV	Ultraviolet
XR(P)D	X-Ray (Powder) Diffraction
A/G	Albumin/Globulin
AE	adverse event
AKT	Protein Kinase B
ALK	anaplastic lymphoma kinase
ALB	albumin
allo-HSC	allogenic haematopoitic stem cell transplant
ALP	Alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration-time curve
AUC_{24}	area under the concentration-time curve over the 24-hour dosing interval
$AUC_{24,ss}$	AUC at steady state over the 24-hour dosing interval
AUC_{inf}	AUC from the time of dosing extrapolated to time infinity
$AUC_{inf,u}$	AUC from the time of dosing extrapolated to time infinity for unbound concentration
AUC_{last}	AUC from the time of dosing to the last measurable concentration
AXL	AXL receptor tyrosine kinase
BA	Bioavailability
BCRP	Breast cancer resistance protein
BFI	Brief Fatigue Inventory

B/R	Benefit-risk
BSEP	bile salt export pump
BW	body weight
CaV1.2	CaV1.2 calcium channel
Cb/Cp	blood to plasma radioactivity concentration ratio
CHO	Chinese hamster ovary
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
C_{max}	maximum concentration
CNS	Central nervous system
CR	complete remission
CR/CRh	complete remission and complete remission with partial hematological recovery
CRc	composite complete remission
CRh	complete remission with partial hematological recovery
Cri	complete remission with incomplete hematologic recovery
CRp	complete remission with incomplete platelet recovery
CV	coefficient of variation
CYP	Cytochrome P450
DDI	drug-drug interaction
DFS	disease-free survival
DLT	dose-limiting toxicity
DMSO	Dimethyl sulfoxide
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
E_{max}	maximal effective concentration
EML4	echinoderm microtubule-associated protein-like 4
ER	Exposure response
ERK	extracellular signal-regulated kinase
EQ-5D-5L	EuroQol Group-5 Dimension-5 Level
EURD	European Union reference dates
FACT-Leu	Functional Assessment of Cancer Therapy-Leukemia
FACIT-Dys-SF	Functional Assessment of Chronic Illness Therapy-Dyspnea- Short Forms
FAS	full analysis set
FLAG-IDA	fludarabine; cytarabine; idarubicin; G-CSF
FLT3	FMS-like tyrosine kinase 3
FLZ	Fluconazole
Fpen	market penetration factor
Fu	fraction of parent or metabolite available systemically unbound (= free fraction)
fu,gut	fractions of unbound drug in enterocytes
fu,p	fractions of unbound drug in plasma
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
GMR	Geometric LS mean ratio
Gp	glycoprotein
GVHD	Graft versus host disease
HEK293	Human embryonic kidney 293
hERG	Human ether-a-go-go-related gene
HR	hazard ratio
HSCT	hematopoietic stem cell transplantation
IBD	international birth date
IC50	Half maximal inhibitory concentration
ICH	International Conference on Harmonisation
IDAC	intermediate dose cytarabine
I_{max}	maximum inhibitory effect
IRB	Institutional Review Board
IRT	interactive response technology
ITD	internal tandem duplication
ITT	intention to treat
ITZ	itraconazole
iv	intravenous

IWG	international working group
Ka	absorption rate
Kd	equilibrium dissociation constant
KM	Kaplan-Meier
KV7.1/minK	KV7.1/minK potassium channel
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LFS	leukemia-free survival
LoDAC	low dose cytarabine
LS	least squares
LTK	leukocyte tyrosine kinase
MAA	Marketing authorisation application
MAD	multiple ascending dose
MAH	marketing authorisation holder
MATE	multidrug and toxin extrusion
MCH	Mean corpuscular haemoglobin
MCV	Mean corpuscular volume
MDS	Myelodysplastic Syndromes
MEC	mitoxantrone; etoposide; cytarabine
MRAS	modified response analysis set
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
N/A	not applicable/not available
NCI-CTCAE	National Cancer Institute-Common terminology Criteria for Adverse Events
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NE	Not evaluable
NMT	no more than
NOAEL	No Observed Adverse Effect Level
NPM1	nucleophosmin 1
NR	Not reached
NSCLC	non-small-cell lung cancer
NYHA	New York heart association
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OECD	Organisation for Economic Cooperation and Development
OS	overall survival
PAR	Proven acceptable range
PBT	Persistent Bioaccumulative Toxic
PD	pharmacodynamic
PDGFR	platelet-derived growth factor receptor
PEC	Predicted Environmental Concentration
P-gp (PGP)	P-glycoprotein
PGx	Pharmacogenomics
PhV	pharmacovigilance
PI	Product information
PIA	plasma inhibitory activity
PIF	peak inspiratory flow
PIP	Paediatric Investigation Plan
PK	pharmacokinetics
PKAS	Pharmacokinetic Analysis Set
PND	postnatal day
PopPK	population pharmacokinetic
PPS	per protocol set
PR	partial remission
PRES	Posterior Reversible Encephalopathy Syndrome
PRO	Patient reported outcome
PS	performance status
PSUR	Periodic Safety Update Report
PT	Preferred Term
Q	Interdepartmental clearance
QD	once daily
QTcF	Fridericia-corrected QT interval
Rac	accumulation index

RAS	Response Analysis Set
RET	rearranged
RIF	rifampin
RMP	Risk management plan
RMST	Restricted Mean Survival Time
R/R	relapsed or refractory
sc	subcutaneous
SAE	serious adverse event
SD	Sprague Dawley
SmPC	Summary of Product Characteristics
SOC	System organ class
STAT5	Signal transducer and activator of transcription 5
t1/2	terminal elimination half-life
TEAE	treatment-emergent adverse event
TKD	tyrosine kinase domain
TKI	Tyrosine kinase inhibitor
TRKA	Tropomyosin receptor kinase A
t_{max}	time to observed C_{max}
ULN	upper limit of normal
UV-A	ultraviolet A
Vc	Central volume of distribution
Vp	Peripheral volume of distribution
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Astellas Pharma Europe B.V. submitted on 7 February 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for XOSPATA, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 February 2019.

XOSPATA was designated as an orphan medicinal product EU/3/17/1961 on 17 January 2018 in the following condition: treatment of acute myeloid leukaemia.

The applicant applied for the following indication:

Xospata is indicated for the treatment of adult patients who have relapsed or refractory (R/R) acute myeloid leukemia (AML) with a FMS-like tyrosine kinase 3 (FLT3) mutation.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Xospata as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Xospata.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/006/2018 on the agreement of a paediatric investigation plan (PIP) and on the granting of a (product-specific) waiver.

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance gilteritinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Protocol assistance

The applicant received Scientific Advice/Protocol Assistance on the development relevant for the approved indication from the CHMP on 25 June 2015 (EMEA/H/SAH/043/1/2015/III), 14 September 2017 (EMEA/H/SAH/043/1/FU/3/2017/II CORRIGENDUM), and 31 May 2018 (EMEA/H/SA/3789/1/FU/4/2018/PA/II). The Scientific Advice pertained to the following quality, non-clinical and clinical aspects of the dossier:

- The regulatory approach to the proposed definition of starting materials
- Completeness of the overall non-clinical programme
- Adequacy of the clinical pharmacology programme
- A randomised, open label, multicentre pivotal phase 3 study with salvage chemotherapy therapy as comparator: the dose regimens and approach to concomitant medications; the target population and eligibility criteria; the method for identification and selection of FLT3-mutation positive patients; the overall study design to serve as a single pivotal study for Marketing Authorisation Application (MAA); the statistical approach; the suitability of the Patient Reported Outcome (PRO) instruments and their measurement; the adequacy of proposed interim analyses of composite complete remission rates (complete remission (CR)/complete remission with incomplete platelet recovery (CRp)/complete remission with incomplete hematologic recovery (Cri) and CR/complete remission with partial hematological recovery (CRh)) to support conditional or full MAA

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bjorg Bolstad Co-Rapporteur: Natalja Karpova

The application was received by the EMA on	7 February 2019
Accelerated Assessment procedure was agreed-upon by CHMP on	31 January 2019
The procedure started on	27 February 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	30 April 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	3 May 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	6 May 2019
In accordance with Article 6(3) of Regulation (EC) No 726/2004, the	

Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days	
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 May 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	20 June 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	19 July 2019
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	23 July 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 August 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	4 September 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to XOSPATA on	19 September 2019
The CHMP adopted a report on similarity of XOSPATA with Dacogen, Mylotarg, Rydapt, Vyxeos on (Appendix 1)>	19 September 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Xospata is indicated as monotherapy for the treatment of adult patients who have relapsed or refractory (R/R) acute myeloid leukaemia (AML) with a FLT3 mutation.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Acute myeloid leukaemia (AML) accounts for approximately 80% of acute leukaemias diagnosed in adults. It has been estimated that 19,950 people were diagnosed with AML in the US, with a similar incidence in the EU.

Approximately 30% of adult AML patients are refractory to induction therapy. Furthermore, of those who achieve CR, approximately 75% will relapse. The, 5-year survival after first relapse is approximately 10% (1). Patients who are in second relapse or are refractory to first salvage have an extremely poor prognosis, with survival measured in weeks.

In general, the incidence of AML increases with advancing age, with a median age of 66 years. Environmental factors that have long been established to increase the risks of Myelodysplastic Syndromes (MDS) and AML include prolonged exposure to petrochemicals; solvents such as benzene; pesticides and ionizing radiation.

2.1.3. Biologic features

AML is generally characterized by aberrant differentiation and proliferation of malignantly transformed myeloid progenitor cells but can be considered a heterogeneous disease state with various molecular and genetic aetiologies that result in variable clinical outcomes. When untreated or refractory to available treatments, AML results in the accumulation of these transformed cells within the bone marrow, suppression of the production of normal blood cells (resulting in severe neutropenia and/or thrombocytopenia), as well as infiltration of these cells into other organs and tissues, and can be rapidly fatal.

Sub-classifications of AML are commonly described using the World Health Organization (WHO) system, which establishes prognostic subgroups (good, intermediate, poor) based on cytogenetics and evidence of dysplasia. Among the molecular abnormalities, FLT3 mutations are the most common. Two of these mutations are well described in the literature: an ITD in the juxtamembrane domain of FLT3 that is present in 28% to 34% of AML cases and a tyrosine kinase domain (TKD) mutation at around D835 in the activation loop of FLT3, which is present in 11% to 14% of AML cases. Each of these activated mutations in FLT3 is oncogenic and shows transforming activity in cells.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Epidemiological and genetic data have shown that the majority of AML present more than one recurrent alteration, including point mutations, gene rearrangements and chromosomal translocations. Furthermore, it has been suggested that point mutations in transcription factors are sufficient to confer a proliferative and survival advantage to the leukemic clone.

Certain genetic factors appear to predispose patients to poorer outcomes. Mutational status of FLT3, a member of the class III receptor tyrosine kinase, is now well recognized as delineating a subtype of leukaemia with poor prognosis, with a higher relapse rate, a shorter duration of remission from initial therapy (6 months vs 11.5 months for those without FLT3- internal tandem duplication (ITD) mutations), as well as reduced disease-free survival (DFS) (16% to 27% vs 41% at 5 years) and overall survival (OS) (15% to 31% vs 42% at 5 years).

Mutations within the FLT3 gene represent one of the most frequently identified genetic alterations that disturb intracellular signaling networks with a role in leukaemia pathogenesis. FLT3 is a member of the class III receptor tyrosine kinase family that also includes platelet-derived growth factor receptor (PDGFR), macrophage colony-stimulating factor receptor (FMS) and stem cell factor receptor (c-KIT), with which it shares the same structure. Activating mutations in the FLT3 gene, including ITDs and missense point mutations in the TKD, are the molecular abnormalities most frequently observed in the blood cells of AML patients. These mutations lead to the overexpression or constitutive activation of the tyrosine kinase receptor. Many studies indicate that patients with FLT3 mutations have a worse prognosis than patients without FLT3 alterations. In particular, the presence of an FLT3-ITD correlates with an increased risk of relapse and impaired OS. The effect on AML prognosis of the FLT3-TKD mutation has not yet been clearly defined; in several studies, the FLT3-TKD mutation did not seem to affect outcome while other investigations showed opposite results. In addition to cytogenetic abnormalities detected at diagnosis, which are the most important prognostic factor, FLT3 mutations are a significant independent prognostic factor that can influence outcome in terms of survival and duration of CR.

2.1.5. Management

There is no universally accepted standard of care for patients with R/R AML with FLT3 mutations and enrolment in a clinical trial should be prioritised whenever possible. Possible salvage regimens are IDAC (intermediate dose cytarabine) with or without anthracycline, MEC (mitoxantrone; etoposide;

cytarabine) or FLAG-IDA (fludarabine; cytarabine; idarubicin; G-CSF). For unfit patients or patients not suitable for intensive chemotherapy, hypomethylating agents (azacytidine or decitabine frequently used in combination with sorafenib, in AML with FLT3-ITD mutation although sorafenib has not been approved for this indication) or low dose cytarabine (LoDAC) are possible alternatives.

The choice of specific regimen is based on factors such as prior treatment, eligibility for allogeneic HSCT and institutional preference. The aim of treatment is to achieve remission and proceed to allogenic haematopoietic stem cell transplant (allo-HSCT) which offers the best chance of long-term relapse free survival.

About the product

Gilteritinib inhibits FLT3 receptor signalling and proliferation in cells exogenously expressing FLT3 including FLT3 ITD, FLT3 D835Y, and FLT3 ITD D835Y, and it induced apoptosis in leukaemic cells expressing FLT3 ITD.

In patients with relapsed or refractory AML receiving gilteritinib 120 mg, substantial (> 90%) inhibition of FLT3 phosphorylation was rapid (within 24 hours after first dose) and sustained, as characterised by an ex vivo plasma inhibitory activity (PIA) assay (SmPC, section 5.1).

The applicant requested the approval for the following indication:

Xospata is indicated for the treatment of adult patients who have R/R AML with a FLT3 mutation.

The final indications following CHMP review of this application is:

Xospata is indicated as monotherapy for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation (sections 4.2 and 5.1).

The recommended starting dose of Xospata is 120 mg gilteritinib (three 40 mg tablets) once daily (SmPC, section 4.2).

Treatment should continue until the patient is no longer clinically benefiting from Xospata or until unacceptable toxicity occurs. Response may be delayed; therefore, continuation of treatment at the prescribed dose for up to 6 months should be considered to allow time for a clinical response.

In the absence of a response (patient did not achieve a CRc) after 4 weeks of treatment, the dose can be increased to 200 mg (five 40 mg tablets) once daily, if tolerated or clinically warranted (SmPC, section 4.2).

Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the fact that giltertinib had the potential to be effective in the R/R AML subpopulation with FLT-3 mutations. This subgroup of patients has a very poor prognosis and there are currently no approved standard treatments available in the EU. Gilteritinib is an inhibitor of the FLT-3 tyrosin kinase receptor and based on the biological rationale behind this substance, it can potentially address the unmet medical need. The clinical efficacy data for gilteritinib based on the pivotal phase 3 study (demonstrating statistically and clinically meaningful effects on OS) seemed to support that gilteritinib can be an important new therapeutic treatment option.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablet containing 40 mg of gilteritinib (corresponding to 44.2 mg gilteritinib fumarate) as active substance.

Other ingredients are: mannitol (E421), hydroxypropylcellulose, low-substituted hydroxypropylcellulose, magnesium stearate and film-coating composed of hypromellose, talc, macrogol 8000, titanium dioxide and iron oxide yellow (E172).

The product is available in OPA/aluminium/PVC/aluminium blisters as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of gilteritinib fumarate is (*E*)-but-2-enedioic acid;6-ethyl-3-[3-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]anilino]-5-(oxan-4-ylamino)pyrazine-2-carboxamide corresponding to the molecular formula $(C_{29}H_{44}N_8O_3)_2 \bullet C_4H_4O_4$. It has a relative molecular mass of 1221.50 g/mol and the following structure:

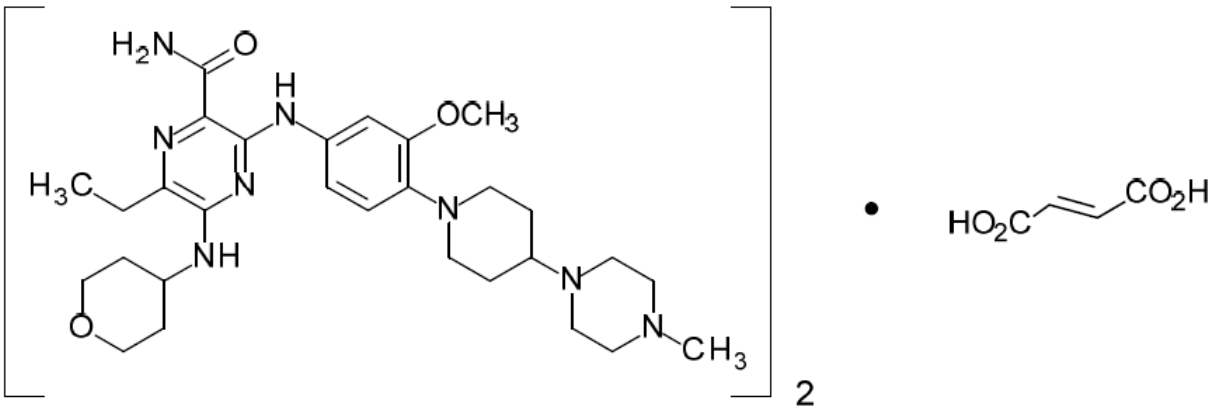


Figure 1: active substance structure

The chemical structure of gilteritinib fumarate was elucidated by a combination of elemental analysis, infrared absorption spectroscopy, ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy, mass spectrometry and ultraviolet-visible absorption spectrophotometry. The solid state properties of the active substance were measured by X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC) and thermogravimetry (TG).

The active substance appears as yellow non-hygroscopic crystals. It is freely soluble in aqueous solution at pH 1-3, soluble at pH 5 and practically insoluble at pH 7 – 11. Gilteritinib fumarate has no optical isomers. Polymorphism has not been observed for the active substance. XPRD studies showed that gilteritinib fumarate is crystalline.

It has been shown that the commercial drug substance synthesis method is designed to consistently deliver only one form of gilteritinib fumarate that showed no change during stability studies.

The Applicant has submitted full details of chemistry, manufacturing process, and quality controls of the active substance.

Manufacture, characterisation and process controls

The active substance is manufactured in several convergent steps from 5 starting materials, followed by salt formation and crystallisation. The manufacturing is carried out by three manufacturers in total. An acceptable QP declaration, based on on-sites audit of all active substance manufacturers has been submitted.

Overall, the manufacturing process contains eight processing steps including the salt formation and the active substance crystallisation step. Seven solid intermediates are isolated, characterized and controlled. Specifications and batch data have been provided for all isolated intermediates. The controls and proposed limits have been adequately discussed by the applicant.

A detailed narrative description of each step, including quantities of starting materials, intermediates, reagents, catalysts and solvents as well as set points and ranges for all process parameters (temperatures, reaction times) and in-process controls have been provided.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The selection of regulatory starting materials was discussed in connection with a CHMP Scientific Advice in 2015. The definition of the starting materials is considered justified and acceptable in line with ICH Q11 principles. For all starting materials their chemical name, structural formula, names and full addresses of manufacturers, their synthetic routes and their specifications have been provided and justified. The carry-over of raw materials, impurities and solvents has been addressed.

A control strategy based on the critical quality attributes (CQAs) of the active substance has been developed. Risk assessment and risk control were performed to identify the CQAs, critical process parameters (CPPs), or critical in-process tests of the active substance. The CQAs are: assay, related substances, mutagenic impurities, residual solvents and elemental impurities. The medicine is intended for oral administration and bioburden is controlled by the active substance manufacturing process. No trends in microbial limit test have been seen in stability data. No crystal polymorphism has been observed. The particle size of the active substance is controlled as part of finished product manufacture.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. These included related substances, residual solvents and elemental impurities. The proposed control strategies for these impurities have been provided.

The applicant was requested to perform a risk assessment for the gilteritinib fumarate manufacturing process in order to evaluate the risk of N-nitrosamines formation and contamination. These results indicate that there is no risk to residue on sodium nitrite/potassium nitrite and N-nitrosamines.

Acceptable information and discussion regarding potential/actual impurities and the proposed control strategies for these impurities have been provided. The active substance gilteritinib fumarate is intended for advanced cancer therapy, and therefore it is outside the scope of ICH M7. Nevertheless, the applicant has described the strategy of the control of mutagenic impurities.

The provided information on the manufacturing process development is considered acceptable. The development of each part of the manufacturing process is discussed in detail. Several manufacturing sites and scales have been employed in the manufacture of intermediates since the start of

development; however, the changes of the sites and scales had no adverse effect on the quality of the drug substance.

Changes made to the route of synthesis during development were described and justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process. Gilteritinib fumarate is packed in double polyethylene bags, closed by cable-ties and then packed in polyethylene tube, which is placed in a steel drum. The information provided regarding the active substance packaging materials is considered acceptable. The material is recognized as safe for use as a food contact material, in compliance with Commission Directive 2002/72/EC and Ph.Eur. 3.1.5 Polyethylene with additives for containers.

Specification

The active substance specification includes tests for description, identification (UV-Vis, IR, fumaric acid by TLC), assay (HPLC), assay (HPLC), related substances (HPLC), residual solvents (GC), water content (KF) and sulphated ash (Ph. Eur.).

The specifications proposed for gilteritinib fumarate are acceptable. They have been established based on the requirements of the ICH guidelines Q3A, Q3C and Q6A and on the results from stability studies. A synthesis related impurity is controlled with a limit above the qualification threshold of ICH Q3A. The limit has been qualified by toxicological studies (see non-clinical section).

Adequate justifications have been provided for the omission of heavy metals, physical form, microbial limit and particle size tests from the specification.

Heavy metals were tested on development batches and the levels observed were always under the limit of detection. The safety assessment for the elemental impurities was also performed based on ICH Q3D (see finished product section). Based on the justification presented, the heavy metals test is not included in the proposed specification.

A test for determination of physical form (polymorphs) is not included. Data from XRPD analyses indicated the presence of only one form of gilteritinib fumarate and showed no change in the polymorphic form during stability studies.

An acceptance criterion for microbial limit test is not proposed for gilteritinib fumarate in line with ICH Q6A decision tree. No trends in microbial limit test have been seen in stability data.

Omission of particle size in the proposed specification has been adequately justified.

Satisfactory description has been provided for the in-house analytical methods and water determination according to Japanese pharmacopoeia. These methods (assay, related substances, determination of residual solvents, water content) in gilteritinib fumarate have been adequately validated in accordance with ICH Q2 (R1) guideline. Stability indicating properties of the HPLC methods used for determination of related substances have been demonstrated by forced degradation studies.

Information from primary and secondary reference standard of gilteritinib fumarate and other reference materials used for the related substances test has been provided.

Batch analysis data of gilteritinib fumarate have been provided. All batches were manufactured by the currently proposed manufacturers using the manufacturing process described in the dossier. All batches were tested according to the proposed specifications and the results demonstrate that the proposed manufacturing process is capable of producing active substance of consistent quality.

Stability

Results from ICH stability studies performed on three pilot scale gilteritinib fumarate batches from the proposed manufacturers stored in the intended commercial package have been provided. Up to 24 months long-term (25°C/60% RH) and 6 months accelerated data (40°C/75% RH) are available. All stability indicating specification parameters were tested. These included: description, Identification (IR), physical form (XRPD), related substances, water and assay. Microbial purity was also evaluated on samples stored under long term conditions (microbial limit test). The analytical methods used in these studies are the same as those for release, except for those for XPRD and microbial limit test, as these are not part of the active substance release specification.

Supportive stability data from three pilot scale batches stored at long term conditions for 36 months and accelerated conditions for 6 months were also provided. Gilteritinib fumarate showed no change in any of the parameters monitored under the long-term condition for 24 months and under the accelerated condition for 6 months for all three batches. No changes were observed in the supportive stability batches either.

Stress testing was performed on one primary pilot scale batch. Samples were stored at 60°C and 40°C/75% RH for 3 months and to light (in accordance with ICH Q1B) for 2 months. Gilteritinib fumarate showed no change under the temperature and humidity conditions. In the photostability condition, slight decomposition was observed in the related substances test, but all results conformed to the specification.

Forced degradation studies were conducted on one of the supportive pilot scale batches. Samples in solid state were exposed to temperature and light . Active substance in liquid form was exposed to acid , oxidation , base , temperature and light.

The presented results from these studies include assay and chromatographic purity results, mass balance calculations and peak purity results. Based on these results, it has been concluded that gilteritinib fumarate is stable, but relatively sensitive to acid condition and oxidation.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period in the proposed container. The proposed storage conditions "This drug substance does not require any special temperature storage conditions. Store in the original package to protect from light" are acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Gilteritinib 40 mg tablets are round light yellow film-coated tablets, debossed with the 'Astellas' logo and '235' on the same side. Gilteritinib tablets 40 mg contain 40 mg of gilteritinib (corresponding to 44.2 mg gilteritinib fumarate).

Other ingredients are: mannitol (E421), hydroxypropylcellulose, low-substituted hydroxypropylcellulose, magnesium stearate and film-coating composed of hypromellose, talc, macrogol 8000, titanium dioxide and iron oxide yellow (E172).

The core tablet is composed of mannitol as a filler, hydroxypropylcellulose as a binder, hydoroxypropylcellulose, low-substituted as a disintegrant, and magnesium stearate as a lubricant. The film-coating is composed of hypromellose, talc, macrogol 8000, titanium dioxide, and iron oxide yellow. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards, where available. Iron oxide yellow (E172) is not described in Ph. Eur. but it complies

with Commission Regulation (EU) No. 231/2012. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The compatibility of gilteritinib fumarate with the excipients included in the tablets was investigated,using binary powder mixtures of the active substance with each excipient . Based on these results, it was concluded that the excipients do not influence the product stability at the proposed formulation ratio, condition of storage and use.

The physicochemical properties of the active substance have been described in the active substance section. Briefly, gilteritinib fumarate is non-hygroscopic, crystalline solid that is produced as only one crystalline form.Gilteritinib fumarate is classified a BCS class IV compound, having both low solubility and low permeability. In addition, the data from a mass balance study (2215-CL-0105) in humans indicated that gilteritinib fumarate can be classified as a compound with incomplete absorption. In order to ensure rapid drug dissolution *in vivo*, it was decided to formulate it into immediate release film-coated tablets.

To proceed with the pharmaceutical development systematically, the quality target product profile (QTPP) for gilteritinib tablets 40 mg was defined as inmmedidate release film-coated tablets for oral administration containing 40 mg of gilteritinib, stable for at least 2 years at room temperature and with sufficient physical strength for handling and transportation. Using this profile, the CQAs necessary to ensure the performance of the finished product were identified: dissolution, assay, uniformity of dosage units, related substances, hardness and friability. These CQAs were then further used to set the acceptance criteria of commercial product applied during both the formulation and the manufacturing process development programs.

The robustness of the formulation (composition) was investigated. Based on the analysis using an Ishikawa diagram (representing the relationship between raw material and commercial finished product quality) and prior knowledge from formulation development trials, a risk assessment on material attributes was performed using Failure Mode Effects Analysis (FMEA) to identify the component attributes of gilteritinib 40 mg tablets. The effects of the inert tablet components and film coating amounts on the CQAs of gilteritinib 40 mg tablets were found to be negligible, indicating that they had no significant impact on the quality of the product.

In addition to the formulation that is intended for marketing, three formulations have been subject to clinical trials.

For phase-1/2 clinical trial [2215-CL-0101] and phase-1 clinical trial [2215-CL-0102], tablets in three strengths, namely 10 mg, 40 mg, and 100 mg, were developed as film coated immediate release tablets For phase 3 clinical trials [2215-CL-0301], and commercialisation, a new 40 mg tablet named as gilteritinib 40 mg tablets was developed as a film coated immediate release tablet.

Comparison of dissolution between the 40 mg tablets used in phase 1/2 and phase 3/commercial gilteritinib 40 mg tablets in 0.1 mol/L hydrochloric acid, acetate buffer (pH 4.5), phosphate buffer (pH 6.8) and water have been submitted. Rapid and comparable dissolution from both tablets in all media was confirmed. In addition, a relative bioavailability study [2215-CL-0110] between those formulations showed a comparable PK profile. The proposed compositions and manufacturing processes for commercial product are the same as used in Phase 3 clinical studies as well used for the primary stability batches.

The dissolution method development has been adequately described. Gilteritinib active substance is adequately soluble for dissolution testing in neutral to acidic pH range as described in the active substance section of this report. The selection of the dissolution media has been justified. To evaluate the discriminatory nature of the method, engineered tablets prepared making slight modifications of the excipient amounts and tablets prepared with a different compression force were prepared. The

dissolution profiles of the engineering tablets which have the changed formulation along with the control tablets obtained by using the proposed quality control (QC) method were presented. The engineering tablets showed slower dissolution than the control tablets in both test conditions. The proposed dissolution method showed discriminability to the formulation change and to the variation of main compression force Thus, the discriminatory power of the dissolution method has been demonstrated.

The manufacturing process is standard. For optimisation of the manufacturing process, risk assessment by FMEA was carried out on manufacturing parameters that might have an impact on the CQAs, based on knowledge obtained during examination of the formulation of the final product and experience from the production of the product used for clinical studies.

The applicant has applied QbD principles in the development of the finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the finished product. Commercial scale manufacturing conditions were selected based on risk assessment of the manufacturing process and the results of the optimisation studies on lab scale. Risk re-assessment of the manufacturing process was carried out after the examination of optimisation of the manufacturing method and scale-up study for commercial scale.

The tablets are packed in aluminium blisters. The blister consists of a unit dose cavity formed from polyamide/aluminum foil/polyvinyl chloride laminated forming foil sealed with an aluminum foil/heat-seal coated lidding foil. The blisters are packed in paperboard cartons.

The PVC film that comes into contact with the drug product complies with EU 10/2011 and its subsequent amendments, including EU 1183/2012, and applicable sections of EC 1935/2004 and EC 2023/2006. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The packaging for commercial bulk holding and transportation has been described. The packaging material complies with the additive requirements listed in European Pharmacopoeia 3.1.5 "Polyethylene with Additives for Containers for Parenteral Preparations and for Ophthalmic Preparations and Commission Regulation 10/2011. To confirm the suitability of this packaging system for gilteritinib 40 mg tablets, bulk stability studies were performed (see stability section).

Manufacture of the product and process controls

The manufacturing process for gilteritinib 40 mg tablets consists of milling of the active substance, wet granulation, blending with disintegrant and lubricant, tablet compression, film-coating with a non-functional coating and packaging. The process is considered to be a standard manufacturing process.

Manufacturing of the bulk product and packaging (primary and secondary) is performed at different sites. The proposed hold time is supported by stability data and justified. Process validation has been performed on three consecutive commercial scale batches at the proposed manufacturing site. All the analytical results are well within acceptance criteria. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), identification (UV, HPLC), related substances (HPLC), uniformity of dosage units (NIR, HPLC) dissolution (Ph. Eur.), microbial limits (Ph. Eur.) and assay (NIR, HPLC).

For uniformity of dosage units and assay, real time release testing by NIR using the core tablets is applied for routine release. Since the film-coating process is not expected to affect assay, this is acceptable.

The applicant has described their procedure for alternative, traditional end-product testing by HPLC (on film-coated tables) in case the NIR result is not available (e.g. equipment failure). The HPLC method using the film-coated tablets is applied for assay in the stability studies. Comparative test results (parallel testing) supporting the relationship between the end-product and the RTRT have been provided.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on batches of gilteritinib tablets were provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

The absence of control for water content has been justified. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analyses have been presented for several batches including the three primary stability batches. All the commercial formulation batches comply with the specification that applied at the time. The results indicate consistency and uniformity of the product, and that the process is under control.

Stability of the product

Stability data from three pilot scale batches of finished product stored for up to 36 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of Xospata are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, assay, related substances, dissolution and water content. Microbial quality (microbial limit test) was also tested on samples stored under long term conditions. The analytical procedures used were the same as those proposed for release, except for water content which is not part of the release specification.

No significant change was observed in any of the parameters tested at the long term or the accelerated storage conditions. The proposed extrapolation of shelf-life period (48 months) beyond the period covered by long-term data (36 months) is therefore accepted.

One of the three primary stability batches was also tested in the stress testing and the photostability testing.

For the stress testing samples were exposed to high temperature and high temperature and humidity in open bottles. Data from 3 and 6 months are available, respectively. No significant changes were observed in the results of description, assay and dissolution at any of the tested conditions. A slight increase in a related substance was observed, but the levels were still within the proposed shelf life specification. There were no other degradation products which increased during the storage. At high temperature a slight decrease in the water content was observed during the storage, whereas a slight increase was observed at high temperature and humidity but all results were within the proposed specification limits.

The photostability testing was conducted according to ICH Q1B guideline. An increase in a related substance was observed above the shelf-life specification (0.2%) when the samples were exposed under D65 lamp.

Since D65 lamp is the one that demonstrates the outdoor daylight, xenon lamp with an optical filter to eliminate radiation below 320 nm was used as the next assessment step to simulate indoor indirect daylight. When the tablets were exposed under this light, no degradation and no changes were observed. Therefore, the tablets do not require protection from indoor light.

When the tablets packed in the commercial packaging configuration, aluminum blisters, were exposed under D65 lamp, all the data met the acceptance criteria and no changes were observed after the light exposure.

Although the tablets were demonstrated to not be affected by indoor light, the storage condition "store in the original package in order to protect from light" applies due to the results observed under standard photostability conditions.

A stability study to support the holding time of the bulk tablets after manufacture and prior to finished product packaging was performed. No significant changes were observed in any of the parameters tested. All the data met the acceptance criteria. Based on the results of this study, and the justification of the relevance of the data from batches packed in the preliminary bulk package, it was concluded that the proposed bulk packaging and holding time under controlled storage conditions not exceeding the conditions evaluated in the bulk stability studies are acceptable.

Nonetheless, the applicant has committed to continue the bulk stability study with the commercial bulk package up to the claimed holding period

Based on available stability data, the proposed shelf-life of 48 months and the storage condition "store in the original package in order to protect from light", as stated in the SmPC (section 6.3), are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The applicant has presented sufficient evidence that the drug substance and the drug product are manufactured under current EU GMP.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3. Non-clinical aspects

2.3.1. Introduction

To clarify characteristics of absorption, distribution, metabolism, and excretion of gilteritinib fumarate, a series of *in vitro* and *in vivo* studies in mice, rats, rabbits, dogs, and cynomolgus monkeys were conducted using 14C-labeled gilteritinib fumarate (14C-gilteritinib fumarate) and non-radiolabeled gilteritinib fumarate. The animal species used in these studies include those used in the pharmacology and toxicity studies. Oral administration was used in most *in vivo* studies as in toxicity studies, which is the same dosing route with that used in clinical studies. In some studies, the different route of administration or dose was used to achieve the aim of the pharmacokinetic investigation. Pharmacokinetics (PK) of gilteritinib-derived components was clarified by investigating tissue distribution of radioactivity after a single and repeated administration of 14C gilteritinib fumarate to rats, plasma protein binding of gilteritinib in animal species, and excretion of radioactivity to urine, bile, and faeces after oral administration to rats and dogs. In addition, *in vitro* metabolism studies using animal and human biomaterials, and *in vivo* metabolic profiling studies in rats, dogs, and humans were conducted. Nonclinical safety of gilteritinib fumarate was evaluated in the following studies: a single-dose toxicity study in rats; repeat-dose toxicity studies in rats and dogs (13-week administration in rats, 4- and 13-week administrations in dogs); genotoxicity studies using bacteria, cultured mammalian cells, and mice; a reproductive and developmental toxicity study in rats; a juvenile animal toxicity study in rats; and other toxicity studies (a repeat-dose toxicity study of an impurity in rats; genotoxicity studies of an impurity using bacteria and cultured mammalian cells; and a phototoxicity study using cultured mammalian cells).

All pivotal toxicology studies and studies on safety pharmacology are Good Laboratory Practice (GLP) compliant.

2.3.2. Pharmacology

Primary pharmacodynamic studies

- ***In vitro***

Inhibitory effect of gilteritinib on FLT3 and other tyrosine kinases

Gilteritinib fumarate inhibited activities of FLT3, nucleophosmin 1 (NPM1)-anaplastic lymphoma kinase (ALK), leukocyte tyrosine kinase (LTK), ALK and AXL kinases by over 50% at 1 nmol/L in a mobility shift assay. At a concentration of 5 nmol/L, more than 50% inhibition of the tyrosine kinase activity of tropomyosin receptor kinase A (TRKA), ROS, RET and MER was also detected (

Table 1).

Table 1: Inhibitory effect of gilteritinib fumarate on tyrosine kinase activity (2215-PH-0006)

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

Gilteritinib fumarate half maximal inhibitory concentration (IC50) for inhibition of FLT3, LTK, AXL, echinoderm microtubule-associated protein-like 4 (EML4)-ALK variant 1 and KIT tyrosine kinase (KIT) kinase activities were determined to 0.291, 0.350, 0.726, 1.2 and 229 nmol/L, respectively (2215-PH-0006, 2215-PH-0017, 2215-PH-0001).

Effects of gilteritinib in cells expressing FLT3 mutants

Gilteritinib fumarate inhibited the proliferation of Ba/F3 cells expressing FLT3-wt, FLT3-ITD, FLT3- D835Y and FLT3-ITD-D835Y with IC50 values of 0.92, 1.8, 1.6 and 2.1 nmol/L, respectively (2215-PH-0009). In Ba/F3 cells expressing FLT3-ITD, the ratios of phosphorylated FLT3 after treatment with gilteritinib fumarate at 0.1, 1 and 10 nmol/L were 78%, 34% and 3%, respectively, compared to the vehicle control. Similarly, the ratios of phosphorylated FLT3 were 74%, 45% and 1% in Ba/F3 cells expressing FLT3-D835Y, and 75%, 42% and 4% in Ba/F3 cells expressing FLT3-ITD-D835Y, respectively. Phosphorylation of STAT5, AKT and extracellular signal-regulated kinase (ERK) was also inhibited by gilteritinib fumarate in these cells (2215-PH-0015).

Effects of gilteritinib in a human AML cell line (MV4-11) expressing FLT3-ITD

Gilteritinib fumarate inhibited the growth of MV4- 11 cells with an IC50 value of 0.92 nmol/L (2215-PH-0008). Treatment of the same cell line with gilteritinib fumarate at 0.1, 1 and 10 nmol/L resulted in FLT3 phosphorylation ratios of 57%, 8% and 1%, respectively, compared to the control (2215-PH- 0010). Downstream molecules of FLT3 such as STAT5, AKT, and ERK phosphorylation were also inhibited by treatment of gilteritinib fumarate. Gilteritinib fumarate at 0.1, 1 and 10 nmol/L showed STAT5 phosphorylation ratios of 114%, 23% and 0%, respectively; AKT phosphorylation of 65%, 48% and 9%, respectively; and ERK phosphorylation of 54%, 22% and 1%, respectively, compared to the vehicle-treated control (2215-PH-0014). The effect of gilteritinib fumarate (1, 3, 10 and 30 nmol/L) on cell cycle distribution was also investigated. Gilteritinib fumarate at 3 and 10 nmol/L increased the population of MV4-11 cells in G1 phase compared to the 0 nmol/L-treated group (2215-PH-9004). Gilteritinib fumarate at 3, 10 and 30 nmol/L increased the annexin-V-positive population in MV4-11 cells, indicating that gilteritinib fumarate induced apoptosis in this cell line (2215-PH-9005).

- ***In vivo***

Effects of gilteritinib in mice subcutaneously xenografted with MV4-11 cells

The antitumour effect of gilteritinib fumarate, given by oral administration at 1, 3, 6 and 10 mg/kg per day, once-daily for 28 days in mice xenografted with MV4-11 cells was examined (2215-PH-0011). Gilteritinib fumarate inhibited the growth or induced the regression of MV4-11 tumours. Gilteritinib fumarate at 6 and 10 mg/kg per day induced complete tumour regression in 4/6 and 6/6 mice, respectively. The body weights (BWs) of the mice treated with gilteritinib fumarate were not affected at any doses tested.

The effect of a single oral administration of gilteritinib fumarate at 1, 3, 6 or 10 mg/kg on the phosphorylation of FLT3 and STAT5 was investigated in tumours from mice xenografted subcutaneously (sc) with MV4-11 cells. Tumours were collected 1, 2, 4, 8, 24 h after the administration. Phosphorylation of FLT3 and STAT5, as detected by immunoprecipitation or electrophoresis + immunodetection of lysates from MV4-11 tumours, was decreased by administration of gilteritinib (2215-PH-9006).

Effects of gilteritinib in mice xenografted with MV4-11 cells into tibia

The effect of once-daily oral administration of gilteritinib fumarate at 30 mg/kg per day on tumour growth (monitored by bioluminescence) and survival were examined in mice inoculated with MV4-11 cells expressing luciferase (MV4-11-luc cells) into the tibia. Either vehicle or gilteritinib fumarate was orally administered once daily for 56 days starting at 15 days after tumour cell inoculation on day 0. Gilteritinib fumarate induced decrease in the tumour growth compared to the control group on day 42. Improvement in survival was observed in the gilteritinib fumarate group compared to the control group. Median survival time of the control group was 61.5 days, whereas no death was observed in the gilteritinib fumarate group until day 168, the final day of observation (2215-PH-0021).

Plasma and intratumoural gilteritinib concentrations in mice subcutaneous (sc) xenografted with MV4-11cells

Plasma and intratumoural concentrations of gilteritinib after a single oral administration of gilteritinib fumarate (1, 6 and 10 mg/kg) in mice sc xenografted with MV4-11 cells were measured (2215-PH-0016). Results for plasma and tumour are shown in Table 2 and Table 3, respectively.

Table 2: Pharmacokinetic parameters of gilteritinib in plasma after a single oral administration of gilteritinib fumarate in mice subcutaneously xenografted with MV4-11 cells (2215-PH-0016)

Gilteritinib fumarate (mg/kg)	C_{max} (ng/mL)	t_{max} (h)	AUC_t (ng·h/mL)	$t_{1/2}$ (h)
1*	6.558	2.0	25.20	2.47
6*	45.90	2.0	269.0	3.56
10	83.01	2.0	492.8	3.14

*Mean of 2 samples were used for 1, 8, and 24 h of 1 mg/kg administered group and for 1 and 4 h of 6 mg/kg administered group.

Table 3: Pharmacokinetic parameters of gilteritinib in tumour after a single oral administration of gilteritinib fumarate in mice subcutaneously xenografted with MV4-11 cells (2215-PH-0016)

Gilteritinib fumarate (mg/kg)	C_{max} (ng/g)	t_{max} (h)	AUC_t (ng·h/g)
1	90.61	4.0	1186
6	772.1	8.0	12880
10	1125	8.0	17330

Secondary pharmacodynamic studies

Effect of gilteritinib fumarate in 3T3 Cells and NCI-H2228 cells expressing EML4-ALK mutants

Gilteritinib fumarate inhibited the proliferation of 3T3 cells expressing EML4-ALK variant 1, 2 and 3 with IC50 values of 0.42, 0.50 and 0.95 nmol/L, respectively (2215-PH-0003). Gilteritinib fumarate inhibited the anchorage-independent growth of NCI-H2228, human non-small-cell lung cancer (NSCLC) cells

endogenously expressing EML4-ALK variant 3, with an IC50 value of 0.74 nmol/L (2215-PH-0002). In NCI-H2228 cells, treatment of gilteritinib fumarate at 0.1, 1 and 10 nmol/L resulted in ALK phosphorylation of 69%, 18% and 2%, respectively, compared to the vehicle-treated control (2215-PH-0004).

Affinity of gilteritinib fumarate to receptors, ion channels, transporters and inhibitory effect of gilteritinib fumarate on enzyme activities

Gilteritinib fumarate at 10 µmol/L showed more than 50% inhibition against specific radio-ligand binding to serotonin 5HT2B (human) receptor, sigma (nonselective, guinea pig) receptor, serotonin 5HT1 (nonselective, rat) receptor and adenosine A1 (rat) receptor, with respective IC50 values of 0.190, 0.615, 4.90 and 4.57 µmol/L. Specific radioligand bindings to all other receptors, ion channels, transporters and tested enzyme activities were not inhibited (less than 50% inhibition) by gilteritinib fumarate at 10 µmol/L (2215-PH-0007). The agonistic and antagonistic effects of gilteritinib fumarate on human serotonin 5HT2B receptor function was examined by measuring intracellular calcium levels in cells expressing human serotonin 5HT2B receptor. Gilteritinib fumarate did not show agonistic activity on human serotonin 5HT2B receptor up to 10 µmol/L. Gilteritinib fumarate inhibited human 5HT2B receptor function with an IC50 value of 5.82 µmol/L (2215-TX-0007).

Safety pharmacology programme

Effects of gilteritinib on the hERG current in HEK293 cells (study 2215-PT-0001, GLP)

Potential effects of gilteritinib (1×10^{-6}, 3×10^{-6}, 1×10^{-5}, and 3×10^{-5} mol/L in 0.1% dimethyl sulfoxide (DMSO)) and positive control E-4031 (1×10^{-7} mol/L) on the human ether-a-go-go-related gene (hERG)-current was tested using the whole-cell patch-clamp technique. The peak amplitude of tail currents was measured in 5 separate cells in each experimental group, and the change rates (suppression rates) of the amplitude 13 minutes after beginning the application were calculated. Subsequently, the hERG-current-suppression rate in each cell was compensated for by the mean suppression rate of the negative control (DMSO group).

The positive control, inhibited hERG tail current, and the compensated suppression rate 13 minutes after beginning the application was 88.4% (statistically significant from the control group).

The compensated suppression rates of gilteritinib at the concentrations of 1×10^{-6}, 3×10^{-6}, 1×10^{-5}, and 3×10^{-5} mol/L were 1.0%, 18.1%, 32.8%, and 70.7%, respectively; statistically significant differences were noted at the three highest doses, when compared to the rate in the negative control group.

The results indicated that gilteritinib suppresses the hERG current in human embryonic kidney 293 (HEK293) cells in a concentration-dependent manner with an IC_{50} of 1.6×10^{-5} mol/L (16 µmol/L, = 8.84 µg/mL).

Effects of gilteritinib on the cardiac ion channels (NaV1.5, CaV1.2 calcium channel (CaV1.2), KV7.1/minK potassium channel (KV7.1/minK), KV4.3, and Kir2.1) in Stably Expressing Cell Lines (study 2215-PT-0006, GLP)

The effects of gilteritinib fumarate (0.09, 1, and 10 µmol/L in 0.1% DMSO) on the cardiac ion channels were investigated using HEK293 cells transfected with NaV1.5 and KV7.1/minK, or chinese hamster ovary (CHO) cells transfected with CaV1.2, KV4.3, and Kir2.1. After 15-min (NaV1.5, KV7.1/minK, KV4.3, and Kir2.1) or 13-min (CaV1.2) exposure, change in each channel current was measured using a patch-clamp technique.

Table 4 Effects of gilteritinib on the cardiac ion channels in Stably Expressing Cell Lines (study 2215-PT-0006, GLP)

Concentration as ASP2215 Hemifumarate (μmol/L)†	0 (Vehicle Control)‡	0.1 (0.0882–0.0887)	1	10
Number of Cells	5	5	5	5
$Na_V1.5$ (%)	0.0 ± 6.1	1.1 ± 6.9	2.2 ± 3.0	1.0 ± 9.4
$Ca_V1.2$ (%)	0.0 ± 7.7	2.0 ± 9.2	−4.3 ± 28.3	−12.3 ± 21.2
$K_V7.1$/minK (%)	0.1 ± 10.5	5.1 ± 5.1	−5.1 ± 20.5	−59.5 ± 10.9**§
$K_V4.3$ (%)	0.0 ± 7.1	−0.2 ± 7.4	−2.4 ± 6.2	3.5 ± 5.3
$K_{ir}2.1$ (%)	0.0 ± 4.7	−2.7 ± 8.3	−3.0 ± 2.8	−0.4 ± 5.5

Numerical data are the values compensated for by the mean suppression rate in the vehicle-control group, and expressed as mean ± SD unless otherwise specified.
Underlined: Test substance-related change. For $Ca_V1.2$, the current increased at 1 and 10 μmol/L in 2 of 5 cells each (compensated individual suppression rate: −33.9% and −34.8% at 1 μmol/L, −24.8% and −43.8% at 10 μmol/L). For $K_V7.1$/minK, the increase was also noted at 1 μmol/L in 1 of 5 cells (compensated individual suppression rate: −38.2%).
**: P<0.01 (statistically significant level)
†: At 0.1 μmol/L, the number in parentheses represents the exposure concentration estimated based on the recovery rates at the time of completing application in the separate stability and adsorption study. At 1 and 10 μmol/L, the concentrations are not compensated because the recovery rates were 93.8%–98.0% in the study.
‡: Vehicle control, dimethylsulfoxide at 0.1 vol%
§: Dunnett's test

Only the compensated suppression rate of KV7.1/minK at 10 μmol/L showed statistically significant difference from the control group. Furthermore, KV7.1/minK current was higher in 1 of 5 cells at 1 μmol/L (the compensated suppression rate: −38.2%), and CaV1.2 current was higher in 2 of 5 cells each at 1 and 10 μmol/L (the compensated suppression rate: −33.9% and −34.8% at 1 μmol/L; −24.8% and −43.8% at 10 μmol/L).

Effects of gilteritinib on hERG trafficking in hERG-transfected HEK293 cells (study 2215-PT-0008, GLP)

The effect of gilteritinib fumarate (0.1, 1, and 10 μmol/L in 0.09% DMSO), negative control (DMSO) and positive control (pentamidine at 30 μmol/L) on hERG trafficking was tested in HEK293 cells. After 24-h exposure, the peak amplitude of tail currents and membrane capacities were measured in 5 separate cells for each group. In the vehicle control group, the current density was 159.7 pA/pF. The hERG-trafficking inhibitor pentamidine reduced the current density to 5.4% ± 1.6% of the negative control. The current densities in the gilteritinib hemifumarate groups at 0.1, 1, and 10 μmol/L, were 74.5%, 75.7%, and 58.6%, respectively, of that in the negative control group, and were not statistically significantly different from controls, although a trend towards lower density compared to controls were indicated in the high dose group. Gilteritinib fumarate did not affect the hERG trafficking at concentrations of up to 10 μmol/L (5.53 μg/mL).

Effects of gilteritinib on action potential duration in ex-vivo human ventricular purkinje fibers from normal male donors (study 2215-PT-0007, non-GLP)

The effects of gilteritinib on action potentials in isolated human cardiac Purkinje fibers from brain-dead male donors were studied at 0.1, 1.0, and 5.0 μM (presumed concentrations: 0.05570 and 0.5219 μM at 0.1 and 1.0 μM nominal concentrations, respectively, and mean actual concentration: 4.245 μM at 5.0 μM nominal concentration (studies 2215-PT-0009, 2215-PT-0010, 2215-PT-0012).The positive control prolonged APD30, APD50, APD90, Triangulation, and STV by 11.78%, 43.20%, 105.76%, 227.01%, and 700.12, respectively, at the 1 Hz pacing frequency. Gilteritinib hemifumarate did not affect any of the evaluated parameters at concentrations up to 4.245 μM (2346 ng/mL).

Effects of gilteritinib hemifumarate on the central nervous system in rats (study 2215-PT-0003, GLP)

Gilteritinib fumarate was suspended in 0.5 w/v % methylcellulose aqueous solution and orally administered once at 10, 30, and 100 mg/kg to 6 male Sprague Dawley (SD) rats per group to investigate the effects on the central nervous system (CNS) for 24 hours following the modified Irwin's method. A satellite group was added to measure plasma concentration of gilteritinib. No gilteritinib-related effects were observed on general activity or behaviour, including spontaneous activity, motor incoordination, central excitation (tremor, twitches or convulsions), reflexes, muscle tonus, or general behaviour. At 30 mg/kg, a decreased number of animals with urination were noted from 4 to 10 h after dosing. At 100 mg/kg, a decreased number of animals with urination was noted from 4 to 24 h after dosing, and

decreased number of animals with defecation was noted from 2 to 24 h after dosing. The time to observed C_{max} (t_{max}) in plasma at 10, 30, and 100 mg/kg was 10, 10, and 8 h, respectively, and the maximum concentration (C_{max}) was 109.71, 318.62, and 805.52 ng/mL respectively.

Effects of gilteritinib hemifumarate on the central nervous system in rats (follow up study, study 2215-PT-0004, GLP).

An additional study with observations until 168 hours was conducted to investigate the reversibility of the effects observed at 100 mg/kg in the study 2215-PT-0003. At 100 mg/kg, a decreased number of animals with urination were observed from 8 through 48 h after dosing, but not from 72 h after dosing onward. Similarly, a decreased number of animals with defecation were observed from 4 through 24 h after dosing, but not from 48 h after dosing onward. The t_{max} value was 10.0 h and the C_{max} value was 729 ng/mL.

Effects of gilteritinib hemifumarate on the cardiovascular and respiratory system in conscious beagle dogs (study 2215-PT-0002, GLP)

Gilteritinib fumarate was suspended in 0.5 w/v% methylcellulose aqueous solution and orally administered once at escalating dose levels of 0 (vehicle, control), 1, 3, 10, 30, and 100 mg/kg to 4 male beagle dogs (fasted overnight). Parameters evaluated included general activity and behaviour, body temperature, blood pressure, heart rate, electrocardiogram (ECG), respiration rate, blood gas, and blood electrolyte concentrations; and plasma drug concentrations. At 3 mg/kg, retching was noted in 1 animal. At 10 mg/kg, vomiting (2 animals) and a positive faecal occult blood reaction (2 animals) were noted. At 30 mg/kg, vomiting and a positive faecal occult blood reaction were noted in 3 and 1 animals, respectively. Blood calcium concentration was also decreased by 7% of pre-dose value 48 h after dosing. At 100 mg/kg, vomiting in all animals, a positive faecal occult blood reaction in 2 animals, and salivation in 1 animal were noted. An increase (11%) and a decrease (3%) in the blood calcium concentration compared to pre-dose value were noted 24 and 48 h post dose, respectively. All of these findings recovered by the end of 1- or 2-week recovery period. Gilteritinib fumarate did not affect body temperature, blood pressure, heart rate, ECG, respiration rate, or blood gas, at any doses tested. The plasma concentration of gilteritinib at 1, 3, 10, 30, and 100 mg/kg had t_{max} values of 8.0, 9.0, 9.5, 13.0, and 9.0 h, respectively, and C_{max} of 13.85, 46.02, 125.64, 265.76, and 257.44 ng/mL, respectively. Vomiting occurred in all animals of the 100 mg/kg group in 9 to 118 min after dosing.

Pharmacodynamic drug interactions

No pharmacodynamic (PD) drug interaction studies have been conducted with gilteritinib (see discussion on non-clinical aspects).

2.3.3. Pharmacokinetics

The radioactivity level in biological samples obtained after administration of 14C-gilteritinib fumarate was measured using a liquid scintillation counter, or by whole body autoradiography. Gilteritinib plasma concentrations in mice, rats, rabbits, and dogs were measured using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS).

After a single intravenous (iv) administration of gilteritinib fumarate to rats and dogs, the plasma concentration of gilteritinib showed two elimination phases and decreased with t1/2 of 6.93 and 25.4 h in rats and dogs, respectively. In patients, the reported half-life following repeated oral dose administration is reported to be even longer (45 to 159 h, ref, study 2215-CL-0101). CLtot and Vss were 3.89 L/h/kg and 25.7 L/kg in rats, and 1.28 L/h/kg and 38.8 L/kg in dogs, respectively. After a single oral administration of gilteritinib fumarate to rats and dogs, t_{max} was 4 to 6.5 h.

C_{max} and area under the concentration-time curve (AUC) from the time of dosing extrapolated to time infinity (AUCinf) increased more than dose-proportionally from 1 to 10 mg/kg in rats, of which tendency was more remarkable from 3 to 10 mg/kg. In dogs, C_{max} and AUCinf increased almost dose-proportionally from 0.3 to 1 mg/kg, and slightly more than dose-proportionally from 1 to 3 mg/kg in dogs. Bioavailability (BA) was 26.8%, 35.8%, and 68.6% at 1, 3, and 10 mg/kg in rats and BA was 88.2%, 88.7%, and 118.4% at 0.3, 1, and 3 mg/kg in dogs, respectively.

A tendency to lower exposure in female dogs compared to male dogs was observed, but there was no consistent gender related differences in rats.

After repeated dose administration retention and slow elimination was observed in the following organs: adrenal gland, thoracic aorta, spleen, thyroid, heart, kidney, testis, femoral muscle, brain, white fat, thymus, submandibular lymph node, bone marrow, and stomach. In these tissues, levels > 10% of the maxima were still detectable 14 days after the last dose. Binding to melanin was evident and C_{max} s of unchanged gilteritinib in the eyeballs of pigmented rats were approximately 30-fold higher than those of non-pigmented rats. The elimination half-life from eyeballs was 409 days. The retention time in pigmented skin was approximately 2-4 weeks, compared to a few days in non-pigmented skin.

After a single oral administration of 14C-gilteritinib fumarate at 1 mg/kg to rats on Day 14 of gestation, radioactivity was detected in the placenta during the whole sample period of 72 hours. In the foetus, the radioactivity concentration was above levels detected in plasma. After a single oral administration of 14C-gilteritinib fumarate at 1 mg/kg to lactating rats on day 14 postpartum, the radioactivity was detected in milk at a concentration > 30 fold the concentration in plasma. Foetal exposure via milk was confirmed by detection of radioactivity in infant tissues.

The *in vitro* plasma protein binding ratios of gilteritinib were 85.1% to 89.6% in normal mice, 75.4% to 84.2% in pharmacological model mice, 77.7% to 79.2% in rats, 75.5% to 78.7% in rabbits, 78.0% to 80.7% in dogs, 81.3% to 82.4% in cynomolgus monkeys, and 90.2% to 90.5% in humans. After a single oral administration of 14C-gilteritinib fumarate at 1 mg/kg to rats and dogs, the blood to plasma radioactivity concentration ratios (Cb/Cp) at 4 and 8 h were 3.42 and 3.09, respectively.

In *in vitro* metabolic profiling studies of gilteritinib in liver microsomes and cryopreserved hepatocytes in mice, rats, rabbits, dogs, cynomolgus monkeys, and humans, the metabolite peaks detected in human liver microsomes and hepatocytes, except for one minor metabolite, were also detected in at least one other species. After a single oral administration of 14C-gilteritinib fumarate at 1 mg/kg to rats and dogs, the major radioactive component of plasma was gilteritinib. Various metabolites were detected in urine, bile, and faeces. Giteritinib was suggested to be metabolized by oxidation, N-dealkylation, and glutathione conjugation. All metabolites detected in humans, except for two minor metabolites (M4 and M6), were detected in at least either rats or dogs.

The major excretion route in rats and dogs was faeces, which is similar to the excretion pattern in patients. After a single oral administration of 14C-gilteritinib fumarate at 1 mg/kg to rats, the cumulative urinary and faecal excretion of radioactivity within 168 h post-dose was 1.4% and 89.9% of the dose, respectively. After a single oral administration of 14C-gilteritinib fumarate at 1 mg/kg to dogs, the cumulative urinary and faecal excretion of radioactivity within 504 h post-dose was 9.5% and 88.1% of the dose, respectively. Enterohepatic circulation of gilteritinib-derived components was also observed in rats.

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity studies were performed in rats and acute toxicity of gilteritinib fumarate was evaluated in a 4-week study in dogs.

Single dose oral toxicity study in Sprague Dawley rats (report nr 2215-TX-0001, GLP)

A single oral gavage dose of gilteritinib fumarate suspended in vehicle (0.5 w/v% methylcellulose aqueous solution) was administered at a dose of 100 or 300 mg/kg to 5 male and 5 female 7 week old Crl:CD SD strain rats per group after overnight fasting. Male and female rats in the 300 mg/kg group died or were sacrificed moribund from 1 to 2 days after dosing; the approximate lethal dose of gilteritinib fumarate in rats was considered to be 300 mg/kg. In animals that died or were moribund, decreased BW, decreased spontaneous activity, hyphema, sparse fur (abdomen), pale skin, decreased stool volume, black stool (a positive fecal occult blood reaction), and hypothermia, were noted. Histopathology of animals that died or were sacrificed moribund showed haemorrhage, epithelial vacuolation, and inflammatory cell infiltration in the duodenum; haemorrhage in the anterior chamber; haemorrhage and erosion in the forestomach, necrosis of the lymphocyte in the ceacal lymphoid follicle; and necrosis of the lymphocyte and haemorrhage in the thymus.

Repeat dose toxicity

An overview of repeat dose toxicity studies conducted with gilteritinib is displayed in Table 5.

Table 5: Pivotal repeat dose toxicity studies (GLP)

Species / strain/ Study ID	**Dose (mg/kg/day) Route**	**n/sex /group Duration**	**Major findings**	**NOAEL mg/kg/ day**
SD rats Study no. 2215-TX-0002	0, 2.5, 5, 10, 20 Oral gavage	Main groups: 15 (0, 10 and 20 mg/kg/day) 10 (2.5 and 5 mg/kg/day) Satellite groups: 9 3 in control group 13 weeks + 4 weeks recovery	**≥ 2.5** mg/kg/day: ↓ BW and BW gain (M) and ↓ lymphocyte/leukocyte count, ↓ γ-globulin fraction and spleen weight (F). **≥ 5** mg/kg/day: dilatation of the sinusoid in the spleen and lymphocyte necrosis in the Peyer's patch (Males+Females). ↓ food consumption, γ-globulin fraction, and spleen weight (M). ↑ erythrocyte count, ↓ mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH), ↑ β-globulin fraction, ↓ albumin (ALB) /globulin (A/G) ratio, ↓ pituitary weight, and microgranuloma in the mesenteric lymph nodes (F). **≥ 10** mg/kg/day: ↓ thymus weight (Males+Females) Male only: ↓ total urinary electrolyte, ↓ MCV and MCH, decreased lymphocyte and leukocyte count, ↑ in aspartate aminotransferase (AST), alanine transaminase (ALT), and relative lung weight, atrophy of the thymus, microgranuloma in the mesenteric lymph node, accumulation of foam cells in the lung (phospholipidosis), microvacuolation in the ileum and cecum. Female only: ↓ BW and BW gain, food consumption, and ALB fraction. **20** mg/kg/day: 2 animals died. Death was likely caused by bacterial infection, with bacterial findings and inflammation in the renal tubule, kidney; cecum and heart (left auricle). Surviving animals: Urinary effects, bone marrow effects (hypocellularity), thymus (necrosis, atrophy), lymp node (atrophy), spleen (atrophy, microgran), kidney (renal lesions, phospholipidosis), lungs (macrophage changes, foam	< 2.5

			cells, increased weight in F), ileum/cecum (microvacuolation in F), eye (inflammatory, histopat), ↓ spontaneous activity (F). gastrointestinal (GI) (↓stool (F), liver . **Recovery:** Full or partial recovery was obtained after the 4 week recovery period.	
Beagle dogs Study no. 2215-TX-0003	0, 1, 10, 100, 1000 2.5, 5 (additional groups, started after discontinuation of administration of 10-1000 mg/kg/day) Oral gavage	4 M (0, 1, 10 mg/kg/day) 4 F (0 and 1 mg/kg/day) 7 M (100 and 1000 mg/kg/day) 6 M + 7 F (2,5 and 5 mg/kg/day groups) 4 weeks + 4 weeks recovery	**≥ 2.5** mg/kg/day: ↓ BW (1M), positive fecal occult blood reaction, ↑ alkaline phosphatase (ALP), ↓ bilirubin, ↑ AST, ↓ ALB + A/G ratio, ↑ globulin, ↓ ALB fraction, ↑ α2-globulin and γ-globulin fractions, and ↓ inorganic phosphorus and calcium (M) and ↑ platelet (1F), atrophy of thymus, necrosis in lymph node **≥ 5** mg/kg/day: diarrhea (3M), reddish stool (pos. occult blood reaction, 1M), vomiting (1M.), ↓ BW (2M). Eye changes in tapetal area and corresponding zones in both eyes, urine effects (M+ 1F) ↑ phospholipidosis and total cholesterol, effects on organ weight and/or histopathology in thymus (M), submandibular and/or mesenteric lymph node, Peyer's patch, ileum, colon, rectum and duodenal mucosal epithelia. **≥ 10** mg/kg/day: 1 animal was sacrificed moribund on day 12 of dosing, and the remaining 3 animals were necropsied after 12 days of dosing due to ↓ food consumption and severe toxicity affecting many organs and tissues. Histopathological findings in testis (degeneration/necrosis, germ cell spermatid giant cell formation), epididymis (necrosis), eyeball. **≥ 100** mg/kg/day: Some animals died or were moribund, resulting in dosing discontinuation after 4 days. Severe toxicity findings in numerous tissues and organs. Histopathological findings (thymus, lymph nodes, oral mucosa), haemorrhage (GI, gallbladder, mucosa, eye) were noted. **1000** mg/kg/day Some animals died or were moribund, resulting in dosing discontinuation after 2 days. 1 animal survived the 4-week recovery period after 2 days of dosing, the remaining 13 animals died or were sacrificed by 6 days after dosing discontinuation. Findings were clinical observations, haematological findings, gross pathology (red discolouration and dark contents in many organs) histopathology (esophageal erosion and increased foam cells in the Peyer's patch). **Recovery:** Full or partial recovery was obtained after the 4 week recovery period. Since necropsy was performed at the end of the dosing period in animals showing changes in phospholipids, total cholesterol, and urine sediment, reversibility of these findings could not be evaluated.	1
Beagle dogs Study no. 2215-TX-0009	0, 1, 2.5, 5 Oral gavage	4 (0 and 1 mg/kg/day) 7 (2.5 and 5 mg/kg/day) 13 weeks + 4 weeks recovery	**≥ 2.5** mg/kg/day: in the foot pad, pos. fecal occult blood reaction, ↑ neutrophile count and platelet, prolonged activated partial thromboplastin time (aPTT), ↑ AST/ALP , ↓ ALB concentration, ↑ in globulin/total protein, ↓ A/G ratio and ALB fraction, and ↑ β-globulin and γ-globulin fractions. Organ changes were noted in lungs (oedema (M), focal interstitial fibrosis (1F), haemorrhage and inflammatory changes in both sexes) and gingiva (inflammation, 1F). **≥ 5** mg/kg/day: 1 male found dead (d42). I male sacrificed moribund day 77 of dosing. In the dead/sacrificed animal: clinical findings. Ophthalmology-findings, urinalysis, haematology, blood chemistry. Gross pathology findings, organ weight changes, histopathology observations (e.g. alveoli, lung, bronchus, thymus, spleen, lymph node, Peyer´s patch, bone marrow, oral mucosa, liver, kidney, pancreas, lacrimal gland, etc). In surviving animals: clinical signs ↓ BW, ↓ food consumption, funduscopy findings, urinalysis changes, haematology findings, gross	1

			pathology findings (lungs, oral mucosa, crust, malar ulcers), organ weight changes. Histopathology changes in many organs electron microscopy findings (liver, kidney, eye/retina). **Recovery:** Full or partial recovery was obtained. The animals showing increased urinary glucose and large unstained cell count and decreased lymphocyte count and serum glucose were necropsied at the end of the dosing period, therefore, reversibility of these findings could not be evaluated.	

Genotoxicity

An overview of the genotoxicity studies conducted with gilteritinib is displayed in

Table 6.

Table 6: Genotoxicity testing of gilteritinib

Type of test (study ID)	Test Substance	Test system (strain)	S9	Concentration/Dose	Results	GLP
	Non-pivotal (screening) studies					
In vitro						
Ames test (2215-TX-3008)	Gilteritinib hemifumarate Test article precipitation:≥2500 µg/plate without S9; 5000 µg/plate with S9	*S. typhimurium (TA1535, TA1537) and E. coli (WP2uvrA)*	±	0, 156-5000 µg/plate Cytotoxicity: TA1535: 5000 µg/plate without S9 TA1537: ≥ 2500 µg g/plate without S9, and 5000 µg /plate with S9	Positive	No
Ames test (2215-TX-3011)	Gilteritinib hemifumarate Test article precipitation:≥2500 µg/plate, with and without S9	*S. typhimurium (TA100, TA98)*	±	0, 156-5000 µg/plate Cytotoxicity: TA100: 5000 µg/plate, with and without S9	Negative	No
Micronucleus (2215-TX-3009)	Gilteritinib hemifumarate	Chinese hamster lung fibroblasts	±	Without S9: 0, 0.0391-0.156 µg/mL With S9:0, 1.25-5 µg/mL	Positive	No
In vivo Micronucleus (2215-TX-3010	Gilteritinib (free)	Mice(male)/ICR		0, 31.3, 62.5, 125, 250 mg/kg (No examination of 31.3 mg/kg group)†	Positive	No
	Pivotal studies					
In vitro						
Ames test (2215-TX-0004)	Gilteritinib hemifumarate No test article precipitation	*S. typhimurium* TA98, TA100, TA1535, TA1537) and E. coli (WP2uvrA)	±	0, 156-5000 µg/plate Cytotoxicity: 2500 µg/plate TA1537, without metabolic activation)	Negative	Yes
Chromosome aberration (2215-TX-0005)	Gilteritinib fumarate	Chinese hamster lung fibroblaster	±	6 h: (±S9) 0.781-50 µg/mL; 24 h (-S9) : 0.0313-2 µg/mL Dose-dependent decrease in the cell proliferation ratio under all treatment conditions	Negative	Yes
In vivo						
Mouse micronucleus (2215-TX-0008)	Gilteritinib hemifumarate	Mouse/Crlj:CD1 (ICR)		Micronucleus test: 0, 20, 65, 200 mg/kg	Positive (males and females in the 65 and 200 mg/kg/day dose groups)	Yes

Carcinogenicity

No carcinogenicity studies have been conducted with gilteritinib (see discussion on non-clinical aspects).

Reproduction Toxicity

- *Dose-range finding study of gilteritinib hemifumarate on embryo-foetal development by oral gavage administration in SD rats (study report no 2215-TX-0010, non-GLP)*

Gilteritinib hemifumarate was administered orally to pregnant rats (12 weeks old when administration started) at dose levels of 0, 5, 20, or 30 mg/kg/day during the period from implantation to closure of the hard palate (from Day 7 to Day 17 of gestation). In the 20 and 30 mg/kg groups, decreases in BW and food consumption were noted from the initiation of dosing in dams. From 20 mg/kg, postimplantation loss rate, low foetal BW, and low numbers of ossified sternebrae and sacral and caudal vertebrae were observed. Visceral and skeletal variations were observed at high frequencies in these groups. In the 30 mg/kg group, anasarca, limb hyperextension, membranous ventricular septum defect, absent kidney, malpositioned kidney, small kidney, malpositioned adrenal, absent uterine horn, fused rib, and hemicentric thoracic centrum were observed as abnormalities. In the 20 mg/kg group, membranous ventricular septum defect was observed as a visceral abnormality in 1 foetus.

- *Embryo-foetal development study of gilteritinib fumarate by oral gavage in SD rats (study report no 2215-TX-0011, GLP)*

Gilteritinib fumarate was administered once daily by oral gavage to 19 to 20 pregnant (SD) rats (12 to 15 weeks of age at the initiation of dosing). The dose levels were 0.3, 3, 10, and 30 mg/kg per day during the period from implantation to closure of the hard palate (from day 7 through 17 of gestation). In dams at the highest dose of 30 mg/kg /day, decrease in BW was noted from the initiation of dosing until necropsy, and a decrease in food consumption was noted from the initiation of dosing until the completion of dosing. In the same dose group of 30 mg/kg/day changes related to gilteritinib was noted. High postimplantation loss rate, low foetal BW, low placental weight, and low numbers of ossified sternebrae and sacral and caudal vertebrae were observed. Anasarca, local oedema, exencephaly, cleft lip, cleft palate, short tail, and umbilical hernia as external abnormalities (frequency of each abnormality were 0.41% to 6.74% and frequency of total abnormalities were 13.53%). Microphthalmia, enlarged atrial chamber, enlarged ventricular chamber, membranous ventricular septum defect, hypoplastic right ventricle, absent kidney, fused kidney, abnormal revolution of kidney, malpositioned kidney, misshapen kidney, small kidney, malpositioned adrenal, and malpositioned ovary as visceral abnormalities (frequency of each finding were 0.75% to 12.21% and frequency of total abnormalities were 32.74%) were observed. Sternoschisis, absent rib, fused rib, fused cervical arch, misaligned cervical vertebra, and absent thoracic vertebra were seen as skeletal abnormalities. The frequency of each abnormality was 0.88% to 1.05%, with a frequency of total abnormalities of 3.69%. Visceral and skeletal variations were also observed at high frequencies.

Based on these results, the maternal and developmental no observed adverse effect level (NOAEL) was considered 10 mg/kg /day. At the NOAEL of 10 mg/kg/day, the gilteritinib exposure (AUC over the 24-hour dosing interval (AUC_{24}) on day 17) was 1930 ng·h/mL which was approximately 0.06 times the exposure at maximum clinical dose (31428 ng·h/mL at 200 mg/kg/day)

Toxicokinetic analysis of plasma exposures to gilteritinib is displayed in Table 7.

Table 7: Mean TK parameters in an embryo-foetal development study of gilteritinib fumarate in pregnant rats, GD 7 and 17

Day of gestation	Dose level (mg/kg)	C_{max} (ng/mL)	t_{max} (h)	AUC24 (ng·h/mL)

7	0.3	0.821	10.0	11.3
	3	25.8	8.0	266
	10	119	6.0	1610
	30	432	10.0	6750
17	0.3	0.847	4.0	11.7
	3	32.1	8.0	307
	10	148	6.0	1930
	30	394	8.0	5880

Dose range finding toxicity study of gilteritinib fumarate in SD rats (study report no 2215-TX-0015, non-GLP)

Gilteritinib was suspended in 0.5 w/v% methylcellulose solution and orally administered once daily for 18 days from postnatal days (PNDs) 4 to 21. The dose levels of 0 (vehicle control), 5, and 10 mg/kg/day gilteritinib were administered to 6 male and 6 female (SD) juvenile rats per group in order to select dose levels of gilteritinib hemifumarate for a definitive GLP study where juvenile animals would be dose from PND 4 to 42.

A satellite group (12 males and 12 females in the control group, and 39 males and 39 females at 5, 10, and 20 mg/kg/day) was added to assess systemic exposure to gilteritinib, and this satellite group included some toxicity evaluation. From 10 mg/kg per day, some animals died or were euthanized due to moribundity, and abnormal stool color (dark red) and/or abdominal distention were observed in moribund or surviving animals.

Juvenile toxicity study of gilteritinib hemifumarate in SD rats (study report no 2215-TX-0016, GLP)

Gilteritinib hemifumarate was suspended in 0.5 w/v% methylcellulose solution and orally administered once daily for 39 days from PND 4 to 42 at dose levels of 0 (vehicle control), 1, 2.5, and 5 mg/kg/day to male and female (SD) juvenile rats (n=12). 6 male and 6 female rats were added to the control and 2.5 and 5 mg/kg/day groups to assess the reversibility of toxicity during a subsequent 28-day recovery period. A satellite group (15 males and 15 females in the control group, and 48 males and 48 females in each test article group) was added to assess systemic exposure.

One male rat in the 2.5 mg/kg per day satellite group showed prone position and hypothermia before dosing on day 9 of dosing, and this animal was then euthanized due to moribundity. Congestion/haemorrhage were observed in the lamina propria of the ileum and in the mucosa of the cecum, and necrosis of the lymphocytes was observed in the thymus cortex. Necrosis of the lymphocytes in the thymus cortex was considered to be a secondary change due to deterioration of the general condition. In the surviving animals, decreased BW and BW gain were noted in males at 5 mg/kg per day and in females at 2.5 mg/kg per day and higher, and decreased food consumption was noted from2.5 mg/kg per day (both sexes).The changes in BW and food consumption noted during the dosing period showed reversibility.

The NOAEL was determined to 1 mg/kg/day, based on the findings in the 2.5 mg/kg/day dose group. Toxicokinetic parameters of gilteritinib are displayed in Table 8.

Table 8: Toxicokinetic parameters of gilteritinib in a juvenile toxicity study in rats, report no 2215-TX-0016

Dose Level (mg/kg/day)	1		2.5		5	
	Males	Female	Males	Female	Males	Female

Mean t_{max} (h)	Day 1 (PND 4)	8	6	24	6	8	8
	Day 17 (PND	4	8	8	4	8	10
	Day 39 (PND	6	6	4	6	6	6
Mean C_{max} (ng/mL)	Day 1 (PND 4)	11.0	9.11	39.5	35.0	84.7	81.2
	Day 17 (PND	9.95	7.68	29.9	30.5	87.6	53.8
	Day 39 (PND	4.24	3.18	12.8	12.4	25.1	29.9
Mean AUC_{24} (ng·h/mL)	Day 1 (PND 4)	187	164	746	641	1540	1490
	Day 17 (PND	77.8	71.8	312	315	1090	854
	Day 39 (PND	39.3	20.8	141	91.3	322	279

Toxicokinetic data

Data presented under ''Reproduction Toxicity'' section.

Local tolerance

Dedicated studies of local tolerance have not been submitted (see discussion on non-clinical aspects).

Other toxicity studies

In 4-Week Repeated Oral Dose Toxicity Study evaluating the synthesis related impurity in Rats (Impurity Toxicity Study, 2215-TX-0012, GLP) the following observations and examinations were performed: clinical signs, BW, food consumption, ophthalmology, hematology, blood chemistry, urinalysis, gross pathology, organ weight, and histopathology. There were no dead or moribund animals. No toxicologically significant changes were noted in any observations, measurements, or examinations in any groups.

Bacterial reverse mutation test was performed with 5 test strains of bacteria (*S. typhimurium* TA100, TA1535, TA98, and TA1537, and *E. coli* WP2*uvrA*) using the preincubation method, in the presence or absence of rat liver S9 (Bacterial Reverse Mutation Test of the related impurity, 2215-TX-0013, GLP). As compared with the negative control, no 2-fold or greater increases or dose-dependent increases in the number of revertant colonies were observed in any test strain, with or without S9, in either the dose range-finding test or the main test. It was concluded that the related impurity did not induce gene mutation in *S. typhimurium* or *E. coli* under the conditions of this study.

A Chromosomal Aberration Test of the synthesis related impurity in Cultured Mammalian Cells (2215-TX-0014, GLP) was performed with CHL cells in short-term treatment for 6 h in the presence of absence of rat liver S9, and in continuous treatment for 24 h without S9. Chromosomal aberrations were analyzed at the following concentrations:2.5, 3, 3.5 and 4 µg/mL in short-term treatment without S9 (the cell proliferation ratio at the highest concentration was 51.4% that of the negative control); 2.5, 3, 3.5, and 4 µg/mL in short-term treatment with S9 (the cell proliferation ratio at the highest concentration was 58.6% that of the negative control); and 2, 2.5, 3, and 3.5 µg/mL in continuous treatment for 24 h without S9 (the cell proliferation ratio at the highest concentration was 52.6% that of the negative control). The number and incidence of cells with structural and numerical chromosomal aberrations were counted and calculated. As compared with the negative control group, no statistically significant increases in the number of cells with structural or numerical chromosomal aberrations were noted in any treatment group. It was concluded that, under the conditions of this study, the related impurity did not induce chromosomal aberrations in CHL cells, regardless of treatment time with or without S9.

As a result, the high dose level in the 4-week toxicity study was the NOAEL for rats, and the synthesis related impurity did not show mutagenicity or clastogenicity. A human equivalent dose calculated based

on the NOAEL in rats multiplied by purity of used test substance, the rat body surface area conversion factor (0.162), and a human BW of 60 kg is higher than the possible maximum intake of this impurity at the maximum clinical dose (200 mg per day), which is calculated based on the acceptance criterion for this impurity in the specification.

A phototoxicity study (report no 2215-TX-0006) was performed with cultured mammalian cells (Balb/c 3T3 cells) at 9.49, 13.3, 18.6, 26.0, 36.4, 51.0, 71.4 and 100 µg/mL, with and without ultraviolet A (UV-A) irradiation. The IC50 was calculated in both the presence and absence of irradiation, and the peak inspiratory flow (PIF) (actual value: 1.018) was less than 2. A PIF value below 2 indicates "no phototoxicity" (according to Organisation for Economic Cooperation and Development (OECD) guideline 432 regarding in vitro 3T3 NRU phototoxicity test).

2.3.5. Ecotoxicity/environmental risk assessment

Table 9.Summary of main study results

Substance (INN/Invented Name): Gilteritinib fumarate; Gilteritinib			
CAS-number (if available): 1254053-84-3 (gilteritinib fumarate) 1254053-43-4 (gilteritinib)			
Persistent Bioaccumulative Toxic (PBT) screening		Result	**Conclusion**
Bioaccumulation potential- log D_{ow} (at pH 7)	OECD107	2.32	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
Predicted environmental concentration of surfacewater (PEC $_{surfacewater}$), based on the refined market penetration factor (F_{pen})	0.0048	µg/L	> 0.01 threshold (N)

2.3.6. Discussion on non-clinical aspects

The non-clinical pharmacology data that have been submitted, they confirmed a role of FLT3 inhibition in the observed anti-proliferative effect induced by gilteritinib fumarate *in vitro* and in animal xenograft models. Kd-values have not been presented, but gilteritinib appears to display comparable inhibitory potency on both wild-type FLT3, FLT3-IDT and FLT3-D835Y. In view of the known role of FLT3, and overexpression of FLT3 and oncogenic FLT3 mutants occurring in AML cells, a therapeutic rationale is justified. The presented *in vitro* and xenograft model results are based on FLT3 forms assumed to be of human origin. Inhibition of EML4-ALK or LTK is not expected to contribute to the effect of gilteritinib in AML, since these kinases have not been reported to play a role in FLT3 mutated AML. In contrast, inhibition of AXL by gilteritinib may translate into antiproliferative effect in AML. In addition, activated AXL is reported to be responsible for resistance to FLT3 inhibitors such as quizartinib and midostaurin in FLT3-ITD positive AML cells.

An IC50 = 5.82 µmol/L for inhibition of 5HT2B function was established (2215-TX-0007). At a daily dose of 120 mg and 200 mg gilteritinib in the phase 1/2 dose escalation/dose expansion study 2215-CL-0101, the median unbound Cmax at day 15 was 22.1-146.2 ng/mL (40.0-264.4 nmol/L). This is approximately 22-145 fold lower than the IC50 for functional inhibition of the serotonin 5HT2B receptor. Taken together, results from non-clinical pharmacology studies suggest low probability of secondary effects of gilteritinib related to targets that are not tyrosine kinases.

Based on *in vitro* data, gilteritinib may reduce the effects of medicinal products that target 5HT2B receptor or sigma nonspecific receptor (e.g., escitalopram, fluoxetine, sertraline). The concomitant use of these medicinal products with Xospata should be avoided unless use is considered essential for the

care of the patient (SmPC section 4.5). Due to *in vitro* binding to 5HT2B (there is a potential impact on cardiac development in patients less than 6 months of age (SmPC section 4.2).

Specific PD interaction studies have not been conducted which is acceptable. The probability of secondary effects of gilteritinib related to targets that are not tyrosine kinases is considered to be low. Concomitant use of other medicinal products targeting FLT3 and/or ALK, is also considered unlikely in view of the approved indications.

In rats, decreased urination at 30 mg/kg and higher and decreased defecation at 100 mg/kg were observed. In dogs, positive faecal occult blood at 10 mg/kg and higher, a decrease in the blood calcium concentration at 30 mg/kg, and salivation and an increase followed by a decrease in the blood calcium concentration at 100 mg/kg were observed. These changes were observed at plasma exposure levels similar to or less than clinical exposure levels. A possible clinical relevance of these findings is unknown. (SmPC, section 5.3).

In patients, QT prolongation was observed, similar to other tyrosine kinase inhibitors (TKIs) (Cortes et al, 2018). The results of *in vitro* and *in vivo* non-clinical studies did however not provide a clear indication of a strong potential to prolong QT in humans. Based on the literature reporting, in some cases, 10% to 20% inhibition of the hERG current can be related to QT prolongation *in vivo* (Jonker et al [2005] and Redfern et al [2003]). Taken together there may be multiple factors contributing to gilteritinib induced QT prolongation seen in patients, such as a weak hERG current suppression and increased CaV1.2 current.

Long half-lifes in dogs and patients support gilteritinib administration once daily. The very wide distribution of gilteritinib in rats suggests a potential for gilteritinib related adverse effects across all tissues and organs, including the CNS. Long retention in pigmented skin and eyes indicates binding to melanin. Concern for phototoxicity in patients was however resolved by the negative outcome of the in vitro NRU phototoxicity test with Balb/c 3T3 cells.

All metabolites detected in humans, except for two minor metabolites (M4 and M6), were detected in rats and/or dogs (species chosen for toxicity testing). The major excretion route in rats and dogs was faeces, which is similar to the excretion pattern in patients.

In the repeated dose toxicity studies in rats and dogs, target organs of toxicity were the gastrointestinal tract (heamorrhage in dogs), lymphohaematopoietic system (lymphocyte necrosis and bone marrow hypocellularity with changes in haematological parameters), eye (inflammation and lens opacity in rats, fundus colour change in dogs, retinal vacuolation), lung (interstitial pneumonia in rats and inflammation in dogs), kidney (renal tubule changes with a positive urine occult blood reaction) and liver (hepatocyte vacuolation), urinary bladder (epithelial vacuolation), epithelial tissue (ulcer and inflammation), and phospholipidosis (lung and kidney in rats). These changes were observed at plasma exposure levels similar to or less than clinical exposure levels. Reversibility of most of the changes was indicated by the end of the 4 week recovery period. A possible clinical relevance of these findings is unknown (SmPC, section 5.3).

GI effects in dogs treated for 4 and 13 weeks showed full or partial recovery except for inflammation in molar and incisor alveoli and gingiva, and were considered by the applicant to be associated with the GI disorder or liver toxicity observed in the 13-week study. The GI tract is a target organ of toxicity and GI-related effects have been observed in patients (some cases of bleeding, perforation and obstruction). Diarrhoea, nausea and constipation are described as very common adverse drug reactions in the SmPC.

The lung effects in animals were noted at low exposure levels when comparing to clinical relevant exposure. Phospholipidosis in rat is however considered to be caused by a common structural feature of gilteritinib as a cationic amphiphilic drug. Oedema, haemorrhage and congestion in the lungs in rats were likely non-specific findings associated with a deteriorated general condition observed following

administration of gilteritinib at a lethal dose. Lung findings in dogs were severe and have also observed in dogs treated with midostaurin. Taken together, the lung findings in dogs are considered clinically relevant as they may predict toxicity mediated by FLT3 inhibition. The concern for lung effects in patients has not been weakened by clinical safety data, because of lung toxicity findings seen in patients. Nevertheless, toxicity is monitorable and the histopathological changes in the lungs of dogs recovered, or tended to recover, during the recovery period.

Recovery (full or partial) were noted regarding changes in the kidney and liver (except for increases in total cholesterol and phospholipids). The liver and kidney/urinary bladder are considered target organs of toxicity and clinical relevance of the findings in these organs cannot be excluded. Effects on the liver and kidneys have been observed in patients (acute kidney injury, increased enzyme levels).

Eye effects were observed in the 13-week dog study and were considered reversible, except for fundus changes that recovered in all except 1 animal. The eye changes observed in rats and dogs were without margin of safety when compared to a therapeutic gilteritinib dose. Distribution of gilteritinib and binding to melanin in eyes of rats was detected in biodistribution studies. The eye is considered a target organ of toxicity in animals. Retina findings have been observed in patients (retinopathy).

Taken together, the adverse findings in the lungs, immune system, bone marrow, hematopoietic system, epithelial tissue, liver, kidney/urinary bladder and GI tract seem to be pharmacologically related and similar to observations from animal studies with the FLT3/KIT inhibitor midostaurin. The mechanism behind the eye toxicity findings in rats and dogs is not fully understood. However, the slight lens opacity noted in rats were without histopathology and the inflammatory changes (conjunctivitis and uveitis) detected in rats could be caused by immunosuppression. The ocular findings in the 4- and 13-week dog studies were reversible and without impairment of visual response test or gait test, indicating no serious impairment in vision. The potential clinical relevance of these findings therefore seems low.

Gilteritinib did not induce gene mutation or chromosomal aberrations in vitro. The *in vivo* micronucleus test showed that gilteritinib has a potential to induce micronuclei in mice (SmPC, section 5.3). This is acceptable under the conditions of an indication covering treatment of adult patients who have R/R AML.

No carcinogenicity studies were performed for gilteritinib. This is in line with recommendations in the International Conference on Harmonisation (ICH) S9, and these studies are not essential to support a marketing application for the proposed patient population.

Since embryo-fetal development toxicities were observed in rat, a confirmatory reproductive toxicity study in a second species is not warranted (Ref. ICH S9).

Gilteritinib showed suppressed foetal growth, and induced embryo foetal deaths and teratogenicity in the embryo foetal development studies in rats at exposure levels similar to clinical exposure levels. Placental transfer of gilteritinib was shown in the rat resulting in transfer of radioactivity to the foetus similar to that observed in maternal plasma (SmPC, section 5.3).

Gilteritinib was excreted into the milk of lactating rats with milk concentrations being higher than in maternal plasma. Gilteritinib was distributed through the breast milk to different tissues, except for the brain, of suckling rats (SmPC, section 5.3).

It is unknown whether gilteritinib or its metabolites are excreted in human milk. Available animal data have shown excretion of gilteritinib and its metabolites in the animal milk of lactating rats and distribution to the tissues in infant rats via the milk. A risk to the breast fed children cannot be excluded. Breast feeding should be discontinued during treatment with Xospata and for at least two months after the last dose (see section 4.6).

In the juvenile toxicity study in rats, the minimum lethal dose level (2.5 mg/kg/day) was much lower than that of adult rats (20 mg/kg/day). The gastrointestinal tract was identified as one of the target organs similar as in adult rats (SmPC, section 5.3).

The embryo-foetal toxicity effects were noted at low exposures compared to the relevant clinical exposure and are considered clinical relevant.

Pregnancy testing is recommended for females of reproductive potential seven days prior to initiating Xospata treatment. Women of childbearing potential are recommended to use effective contraception (methods that result in less than 1% pregnancy rates) during and up to 6 months after treatment. It is unknown whether gilteritinib may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method of contraception. Males of reproductive potential should be advised to use effective contraception during treatment and for at least 4 months after the last dose of Xospata (SmPC, sections 4.4 and 4.6). Embryo-fetal lethality, suppressed fetal growth, and teratogenicity has been categorized as a potential risk in the Risk Management Plan (RMP) (see RMP).

The proposed specification for the related impurity is considered adequately qualified from a non-clinical point of view.

Gilteritinib was not phototoxic in the in vitro NRU phototoxicity test with Balb/c 3T3 cells.

Gilteritinib $PEC_{surfacewater}$ value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. Therefore, gilteritinib is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical documentation submitted was considered adequate. The relevant information has been included in the SmPC (sections 4.4, 4.5, 4.6, 5.1, 5.3).

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with Good Clinical Practice (GCP) as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 10 Summary of main clinical studies in R/R AML

Study Name	Study Objectives	Study Design	Dosage Regimen	Duration of Treatment	Number of Patients Enrolled	Study Status	Efficacy Endpoints
2215-CL-0301	Primary: Determine the clinical benefit of gilteritinib therapy in patients with FLT3-mutated AML who are refractory to or have relapsed after first-line AML therapy as shown with OS compared to salvage chemotherapy. Determine the efficacy of gilteritinib therapy as assessed by the rate of CR/CRh in patients with FLT3-mutated AML who are refractory to or have relapsed after first-line AML therapy. Key Secondary: Determine the overall efficacy in EFS of gilteritinib compared to salvage chemotherapy. Determine the overall efficacy in CR rate of gilteritinib compared to salvage chemotherapy.	Phase 3, open-label, multicenter, randomized study	Gilteritinib starting dose of 120 mg/day, which could have been titrated according to protocol directions, or comparative drugs administered as 28-day cycles and per institutional guidelines (LoDAC, azacitidine, MEC induction chemo-therapy, or FLAG-idarubicin induction chemo-therapy)	For gilteritinib, treatment will continue until the patient meets a treatment discontin-uation criterion	371 patients were randomized	Ongoing (IA1, IA2 and final analysis complete)	Co-Primary Efficacy Endpoints†: OS CR/CRh rate Key Secondary Efficacy Endpoints: EFS CR rate Other Secondary Efficacy Endpoints: leukemia-free survival (LFS) Duration of remission CRh, CRc (CR, CRi, or CRp) rate Transfusion conversion rate and transfusion maintenance rate Transplantation rate

Study Name	Study Objectives	Study Design	Dosage Regimen	Duration of Treatment	Number of Patients Enrolled	Study Status	Efficacy Endpoints
2215-CL-0101	Primary: to assess the safety and tolerability, including determination of the maximum tolerated dose (MTD) of oral gilteritinib in patients with relapsed or treatment-refractory AML and to determine the pharmacokinetic parameters of gilteritinib. Secondary: to investigate the anti-leukemic activity of various doses of gilteritinib in patients with AML, evaluate the effect of strong or moderate CYP3A4 inhibitors on the PK of gilteritinib, evaluate the potential induction of CYP3A4 by gilteritinib by assessment of midazolam PK and evaluate the effect of gilteritinib on MATE1 substrates by assessment of cephalexin PK.	Phase 1/2, open-label, dose escalation, first-in-human study	Gilteritinib 20, 40, 80, 120, 200, 300 or 450 mg/ day	28-day cycles	347 patients consented; 252 unique patients received at least 1 dose of gilteritinib	Completed	Best response including CRc rate and response rate Duration of remission Time to remission OS EFS LFS CR/CRh
2215-CL-0102	Primary: to assess the safety and tolerability of gilteritinib, determine the MTD based on the onset of dose-limiting toxicity (DLT) and/or determine the RD of gilteritinib for the next phase. Secondary: to assess the antileukemic activity of various doses of gilteritinib and determine the pharmacokinetic parameters of gilteritinib.	Phase 1, un-controlled, open-label, dose-escalation study	Gilteritinib 20, 40, 80, 120, 200 or 300 mg/ day	28-day cycles	27 patients enrolled; 24 patients received gilteritinib	Completed	Best response including CRc rate and response rate Duration of remission

2.4.2. Pharmacokinetics

The gilteritinib (ASP2215) hemifumarate clinical pharmacology program consisted of two biopharmaceutic (relative BA and food effect) studies and six clinical pharmacology phase I studies. A population pharmacokinetic (popPK) approach was used to characterise the gilteritinib PK, including the impact of various extrinsic and intrinsic factors. The popPK dataset was comprised of sparse and intensive PK data from healthy volunteers and AML patients in five phase I studies, 1 phase I/II study and 1 phase III study. An overview of clinical studies used to characterize the clinical pharmacology of gilteritinib is

given in Table 11. In addition *in vitro* studies using human biomaterials to investigate plasma protein binding, metabolism and drug-drug interaction (DDI) potential (CYP450, transporters) were conducted.

Table 11. Overview of clinical studies to characterize the clinical pharmacology

Study identifier*	Objectives	Study design	Test product**	Subjects	Number	PK data
0110	Bioavailability	Phase I	Formulation 2 vs. 4	Healthy	42 dosed	Intensive
0113	Food effect	Phase I	Gilteritinib 40 mg Formulation 4	Healthy	32 dosed	Intensive
0106	Hepatic impairment	Phase I	Gilteritinib: 10 mg Formulation 1	Normal hep. function, Child-Pugh A and B	24 dosed	Intensive
0108	DDI	Phase I	Formulation 1	Healthy	81 dosed	Intensive
0101	Primary: safety, tolerability, MTD, and PK of gilteritinib Secondary: antileukemic act., CYP3A4 inhib/ind. impact on PK	Phase I/II, uncontrolled, open-label multicenter, dose escalation	Gilteritinib: 20, 40, 80, 120, 200, 300, 450 mg qd Formulation 1, 2 and 3	R/R AML	265 enrolled (252 dosed): 25 multiple ascending dose (MAD) (23 dosed), 240 expansion (229 dosed, 5 re-enrolled and dosed	Intensive and sparse
0102	Primary: safety, tolerability, MTD Secondary: PK, antileukemic act.	Phase I, uncontrolled, open-label multicenter, dose escalation	Gilteritinib: 20, 40, 80, 120, 200, 300 mg qd Formulation 1 and 3	Japanese R/R AML	27 enrolled (24 dosed)	Intensive Plasma, urine
0301	Efficacy, safety (pivotal study)	Phase III open-label, multicenter, randomised	Gilteritinib 120 mg qd or comparative chemotherapy Formulation 4	FLT3+ R/R AML	Of 371 enrolled, gilteritinib 247 (246 dosed)	Sparse
5101	Safety, RP2D, efficacy, PK of gilteritinib and erlotinib in comb.	Phase Ib/II	Gilteritinib 80 or 120 mg, erlotinib 150 mg Formulation 2	Epidermal growth factor receptor m+ (EGFRm+) NSCLC w/ acquired resistance to EGFR TKI	10 dosed	Intensive
0105	Mass balance	Phase I	Gilteritinib 120 mg qd Formulation 2	Patients with solid tumours	Patients with advanced solid tumors, 6 dosed	Intensive Plasma, urine, faeces

* Study codes are given by the prefix 2215-CL- followed by a four-digit identification number.
** Different gilteritinib formulations were used throughout the clinical pharmacology programme: Formulation 1: 10 mg tablets (A2215-002C); Formulation 2: 40 mg tablets (A2215-004C); Formulation 3: 100 mg tablets (A2215-

003C); Formulation 4: 40 mg tablets identical to the formulation intended for marketing (A2215-005C, gilteritinib tablets 40 mg).

Absorption

Following oral administration of gilteritinib, peak plasma concentrations are observed at a median t_{max} approximately between 4 and 6 hours in healthy volunteers and patients with R/R AML. Gilteritinib undergoes first order absorption with an estimated absorption rate (ka) of 0.43 h 1 with a lag time of 0.34 hours based on population PK modelling. Median steady state C_{max} is 282.0 ng/mL (coefficient of variation (CV)% = 50.8), and area under the plasma concentration curve during 24 hour dosing interval (AUC0-24) is 6180 ng·h/mL (CV% = 46.4) after once daily dosing of 120 mg gilteritinib. Steady state plasma levels are reached within 15 days of once daily dosing with an approximate 10 fold accumulation (SmPC, section 5.2).

In healthy adults, gilteritinib C_{max} and AUC decreased by approximately 26% and less than 10%, respectively, when a single 40 mg dose of gilteritinib was co-administered with a high fat meal compared to gilteritinib exposure in fasted state. Median t_{max} was delayed 2 hours when gilteritinib was administered with a high-fat meal (SmPC, section 5.2).

In healthy adults, gilteritinib Cmax and AUC decreased by approximately 26% and less than 10%, respectively, when a single 40 mg dose of gilteritinib was co administered with a high fat meal compared to gilteritinib exposure in fasted state. Median tmax was delayed 2 hours when gilteritinib was administered with a high fat meal.

Distribution

In the popPK analysis, the apparent central and peripheral volume of distribution were estimated to be 1092 L and 1100 L, respectively. Apparent volume of distribution ranged from 3340 L in healthy subjects with normal hepatic function to 5090 L in subjects with moderate hepatic impairment.

The plasma protein binding of gilteritinib in humans was 90.5% and concentration independent within the concentration range investigated *in vitro* (0.1-10 µg/mL). The major binding protein appears to be human serum ALB. Mean unbound fraction in healthy individuals with normal hepatic function was 0.057, and an increase in the unbound fraction was observed in patients with mild or moderate hepatic impairment.

In the mass balance study (120-240 mg single dose), the blood-to-plasma ratios ranged from 0.85 to 1.36, indicating limited penetration of gilteritinib into red blood cells. A concentration dependency is indicated by the higher ratio observed at the 240 mg dose.

Tissue distribution has not been investigated in humans. Animal data indicate a wide distribution to and retention in different organs, including the brain and bone marrow.

Elimination

In the popPK analysis gilteritinib plasma concentrations declined in a bi-exponential manner with a half-life of 113 hours. The estimated apparent clearance (CL/F) was 14.85 L/h. Gilteritinib clearance is 46% greater in healthy volunteers compared to patients with AML based on the final covariate model. The main elimination route was hepatic metabolism via CYP3A4 enzyme and excretion of metabolites and unchanged substance in both urine and faeces.

In vitro studies investigating metabolite formation in various species (mice, rats, rabbits, dogs, humans) indicated that no major human-specific gilteritinib metabolites were formed by liver microsomes or hepatocytes.

In vitro, gilteritinib is metabolised by CYP3A4 with one metabolite accounting for approximately 1/3 of CYP3A4 metabolism, while other metabolites each accounted for less than 4.8% of metabolism. The identity of the metabolites has not been specified. Metabolism by other CYP enzymes (1A2, 1B1, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A5) was negligible.

In vivo, gilteritinib was extensively metabolised with 14 metabolites (M1, M4, M7-17) detected in plasma in the mass balance study. Several metabolites (M1-17, one unknown) were also detected both in urine and in faeces. No single metabolite in urine or faeces accounted for >2% or >10%, respectively, of administered dose. Up to ~16% (6.3-15.8%) and 24% (11.7-23.8%) of administered dose was found as unchanged substance in urine and faeces, respectively, after 336h.

The postulated metabolic pathways involve at least oxidation, N-dealkylation, glutathione conjugation and glucuronidation. No major inter-individual differences in metabolites were observed in humans. The three metabolites in plasma that were quantified are formed by N-dealkylation (M10 [AS2651096] and M16 [AS3322943]) and N-dealkylation and oxidation (M17 [AS3397391]).

The PK of gilteritinib and the routes of excretion and the extent of metabolism following administration of a single oral dose of [^{14}C]-gilteritinib after repeated doses of gilteritinib tablets was investigated in four evaluable patients with advanced solid tumours.

The overall mean recovery of radioactivity in urine, faeces and toilet tissue samples was 80.9% (interpolated to 91.3%) over the 768-hour collection period. A mean of 64.5% (interpolated to 73.4%) and 16.4% (interpolated to 17.9%) were recovered in faeces and urine, respectively. Up to ~13% of the administered dose was excreted in urine as unchanged gilteritinib. Three (M10, M16, M17) of the fourteen identified metabolites in plasma were quantified. Mean exposure (AUC_{24}) of these metabolites at steady state was less than 10% that of parent substance. Total radioactivity half-life in plasma was comparable to gilteritinib half-life. Clinical data on metabolite PK were obtained only in the mass balance study.

In healthy adults, mean C_{max} (%CV) were 21.6 ng/mL (21.4) and 30.4 ng/mL (38.1) and AUC_{inf} (%CV) were 1800 ng*h/mL (17.3) and 1970 ng*h/mL (30.8) in the fed and fasted group, respectively. Absorption was delayed (2-hour increase in median t_{max}) when gilteritinib was administered with a high-fat meal relative to fasted conditions. Gilteritinib t1/2, CL/F and VZ/F were comparable in the fasted and fed treatment groups.

Dose proportionality and time dependencies

A slightly more-than dose proportional increase in exposure (C_{max} and AUC_{24}) at multiple dosing in R/R AML patients were observed, with a slope estimate of 1.21 (1.02, 1.41) and 1.22 (1.00, 1.43), respectively when all data in the dose range 20-450 mg was considered (study 2215-CL-0101). Similar findings were observed in Japanese R/R AML patients over the 20 to mg 200 mg dose interval.

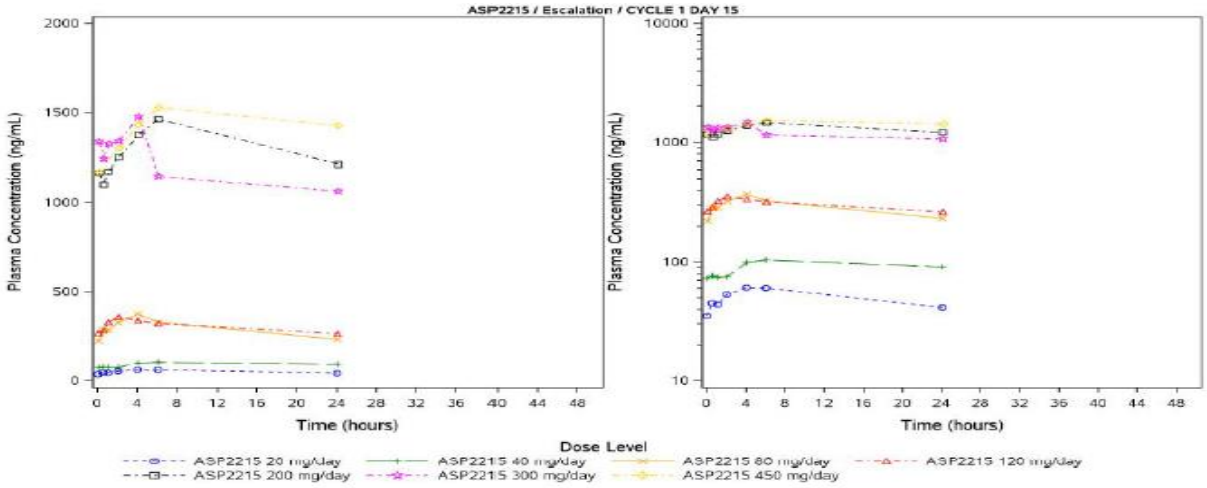


Figure 2. Mean gilteritinib plasma concentration-time profiles after multiple-dose (Cycle 1 Day 15) administration in patients with R/R AML (PK Analysis, study 2215-CL-0101)

Table 12. Statistical assessment of gilteritinib dose proportionality in patients with relapsed or refractory AML – PK Analysis Set, study 2215-CL-0101

Visit	Parameter	Slope Estimate	90% CI
Day -2 (single dose)	AUC_{24} (ng•h/mL)	0.990	(0.788, 1.19)
	C_{max} (ng/mL)	0.808	(0.629, 0.988)
Cycle 1 Day 15 (multiple dose)	AUC_{24} (ng•h/mL)	1.22	(1.00, 1.43)
	C_{max} (ng/mL)	1.21	(1.02, 1.41)

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.

Extensive accumulation of gilteritinib up to ~10-fold (range 3.29-9.64) was observed in R/R AML patients following repeated doses once daily (QD) of gilteritinib compared to single dose administration (C1D1 vs C1D15, study 2215-CL-0101). Up to 8-fold accumulation was observed in Japanese R/R AMPL patients (C1D1 vs. C1D28, study 2215-CL-0102). Steady state was reached after 15 days of once daily dosing.

Special populations

A popPK analysis was performed to evaluate the impact of intrinsic and extrinsic covariates on the predicted exposure of gilteritinib in patients with R/R AML (SmPC, section 5.2).

The effect of hepatic impairment on gilteritinib PK was studied in subjects with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment. Gilteritinib has not been studied in patients with severe hepatic impairment (Child Pugh Class C) (SmPC, section 5.2).

Table 13. Statistical analysis of hepatic impairment on total and unbound gilteritinib PK – PK Analysis Set, study 2215-CL-0106

Parameter	Hepatic Function Group	n	Geometric LS Mean†		Ratio (%) Impaired/Normal‡		90% CI of Ratio‡	
			Total	Unbound	Total	Unbound	Total	Unbound
AUC_{inf} (h•ng/mL)	Mild (Group 1)	8	433.3	27.53	78.88	88.42	(61.10, 101.83)	(65.92, 118.61)
	Moderate (Group 2)	8	337.4	27.54	61.43	88.48	(47.59, 79.30)	(65.97, 118.69)
	Normal (Group 3)	8	549.3	31.13	NA	NA	NA	NA
AUC_{480} (h•ng/mL)	Mild (Group 1)	8	408.4	25.95	78.13	87.59	(60.78, 100.44)	(65.89, 116.43)
	Moderate (Group 2)	8	316.5	25.84	60.55	87.21	(47.10, 77.84)	(65.61, 115.93)
	Normal (Group 3)	8	522.7	29.62	NA	NA	NA	NA
C_{max} (ng/mL)	Mild (Group 1)	8	8.140	0.5171	106.59	119.49	(82.09, 138.39)	(91.25, 156.46)
	Moderate (Group 2)	8	6.242	0.5095	81.73	117.72	(62.95, 106.12)	(89.90, 154.15)
	Normal (Group 3)	8	7.637	0.4328	NA	NA	NA	NA

A dedicated renal impairment study has not been conducted to assess of the effect of renal impairment on gilteritinib PK (SmPC, section 5.2). The popPK model included serum creatinine, a marker of renal function, as a statistically significant covariate, but the impact on gilteritinib exposure was less than 2-fold and less than 1.5-fold different in non-Japanese and Japanese patients with R/R AML, respectively. The effect of severe renal impairment on gilteritinib exposure has not been investigated (SmpC section 4.2).

A population PK analysis was performed to evaluate the impact of intrinsic and extrinsic covariates on the predicted exposure of gilteritinib in patients with R/R AML. In the population PK analysis age and body weight were identified as statistically significant covariates. An overview of studies in the elderly population is displayed in Table 14.

Table 14 Studies in elderly population

	Age 65-74 (Older patients number /total number)		**Age 75-84 (Older patients number /total number)**		**Age 85+ (Older patients number /total number)**	
Controlled Trial	Gilteritinib 78/247 (31.6%)	Chemotherapy 34/124 (27.4%)	Gilteritinib 28/247 (11.3%)	Chemotherapy 14/124 (11.3%)	Gilteritinib 0	Chemotherapy 1/124 (0.3%)
	Gilteritinib		Gilteritinib		Gilteritinib	
Non Controlled Trial	Escalation Phase 0/2	Expansion Phase 10/54 (18.5%)	Escalation Phase 0/2	Expansion Phase 7/54 (13.0%)	Escalation Phase 0/2	Expansion Phase 1/54 (1.9%)

Pharmacokinetic interaction studies

In vitro

A number of *in vitro* studies have been performed. The *in vitro* results are presented below:

Table 15 Overview of the *in vitro* studies results conducted with gilteritinib

Enzyme*	Substrate	Induction	Inhibitor	IC50 (µM)	Clinical relevance
CYP1A2	No	No	No	>100	-
CYP2B6	No	Yes	No	>100	-
CYP2C8	No	Yes	No	>100	-
CYP2C9	No	Yes	No	>100	-
CYP2C19	No	Yes	Yes	61.7	No**
CYP2D6	No	Not invest.	No	>100	-
CYP3A4	Yes	Yes	Yes	62.9 (MDZ) 70.9 (TEST)	Yes: intestine

Transporter	Substrate	Inhibitor	IC50 (µM)	Clinical relevance
Efflux transporters				
P-gp	Yes	Yes	>30	Yes – intestine*
BCRP	No?	Yes	1.41	Yes
MATE1	NA	Yes	0.0543	Yes
MATE2	NA	Yes	47.7	No
Uptake transporters				
OATP1B1	?	Yes	29.4	No
OATP1B3	?	No	>50	-
OAT1	NA	No	>50	-
OAT3	NA	No	>50	-
OCT1	Not invest.	Yes	2.92	Yes
OCT2	NA	Yes	34.9	No

Abbreviations: MDZ=midazolam; TEST=testosterone; not invest.=not investigated; NA=not applicable
* Metabolism by other CYP enzymes (*i.e.* 1B1, 2A6, 2E1, 3A5) was negligible (2215-ME-0001).
** Minor intestinal CYP enzyme.
* Cytotoxicity at concentrations (50 and 100 µM) prevented further determination of IC_{50}.

In vivo

In Study 2215-CL-0101 the effect of strong or moderate CYP3A4 inhibitors on the PK of gilteritinib has been evaluated. This study also evaluated the potential induction of CYP3A4 by gilteritinib through assessment of midazolam PK and the effect of gilteritinib on MATE1 substrates through assessment of cephalexin PK.

An exploratory analysis of the effect of strong and moderate CYP3A4 inhibitors on gilteritinib exposure was performed. Approximately 70% of enrolled patients in the current study required co-administration of strong (voriconazole or posaconazole) or moderate fluconazole FLZ CYP3A4 inhibitors.

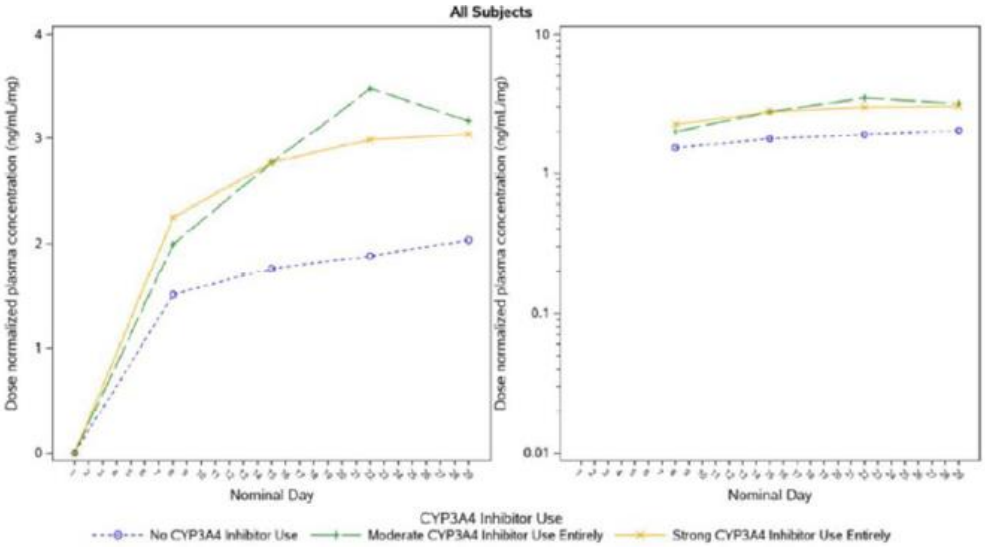


Figure 3.Dose-normalised gilteritinib trough plasma concentration-time profiles (Day -2 through Cycle 2 Day 1) by use of CYP3A inhibitor –PK Analysis Set, study 2215-CL-0101

Patients also received gilteritinib 300 mg QD starting on C1D1 and a single oral dose of 2 mg midazolam on day -1 and C1D15. The geometric LS mean ratios (GMRs) were 111.64% and 123.47% (C_{max}) and 109.46% and 149.90% (AUC_{24}) for midazolam and its metabolite, respectively (Table 16).

Table 16. Statistical comparison of midazolam exposure after administration of midazolam alone or co-administered with gilteritinib – PK Analysis Set, study 2215-CL-0101

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

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.

Reference Treatment = Single dose of 2 mg midazolam syrup.

Test Treatment = Single dose of 2 mg midazolam syrup + 300 mg gilteritinib once daily.

'N' refers to number of DDI evaluable patients which is defined as the patients who have both day -1 and cycle 1 day 15 pharmacokinetic parameter results in expansion 2D cohort.

CI: confidence interval; DDI: drug-drug interaction; LS least squares.

†Corresponds to "Geometric LS Mean for the Numerator" as reflected in the Study 2215-CL-0101 CSR.

‡Corresponds to "Geometric LS Mean for the Denominator" as reflected in the Study 2215-CL-0101 CSR.

§The difference of LS means of log-transformed pharmacokinetic parameters between 1-hydroxymidazolam/midazolam alone and 1-hydroxymidazolam/midazolam + gilteritinib and its 90 % CI are backtransformed to the raw scale and are expressed as percent.

Patients received gilteritinib 200 mg starting on C1D1 and a single dose of 500 mg cephalexin on day -1 and C1D15. Relative to administration of cephalexin alone, cephalexin systemic exposure was comparable when gilteritinib was coadministered with cephalexin as reflected by an approximate minimal decrease (3% to 9%) in C_{max}, AUC from the time of dosing to the last measurable concentration (AUC_{last}) and AUC_{inf} (Table 17).

Table 17. Statistical assessment of the effect of gilteritinib on cephalexin PK after administration of cephalexin alone or co-administered with gilteritinib – PK Analysis Set, study 2215-CL-0101

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

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.

Test Treatment = Single dose of 500 mg cephalexin + 200 mg gilteritinib once daily.

Reference Treatment = Single dose of 500 mg cephalexin.

'N' refers to number of DDI evaluable patients which is defined as the patients who have both day -1 and cycle 1 day 15 pharmacokinetic parameter results in Expansion 2E cohort.
CI: confidence interval; DDI: dose-dose interaction; LS: least squares.

†The difference of LS means of log-transformed pharmacokinetic parameters between cephalexin alone and cephalexin + gilteritinib and its 90% CI are backtransformed to the raw scale and are expressed as percent.

In Study 0108 the effect of the strong CYP3A4 and P-gp inhibitor itraconazole (ITZ), the moderate CYP3A4 inhibitor FLZ and the strong CYP3A4 inducer rifampicin (RIF) on the single-dose PK of gilteritinib, a CYP3A4 and P-gp substrate, was evaluated in 81 healthy adult subjects. The results are summarised in Table 18.

Table 18. Statistical assessment of the interaction effect of itraconazole, fluconazole and rifampin on the PK of gilteritinib – PK Analysis Set, study 2215-CL-0108

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

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.

The analysis was performed on log-transformed pharmacokinetic parameters using a mixed model with treatment as a fixed effect and subject as a random effect. The difference of LS means of log-transformed pharmacokinetic parameters between treatments and its 90% CI are back-transformed to the raw scale and are expressed as a ratio. Dose-normalized gilteritinib pharmacokinetic parameters were used in the RIF + gilteritinib treatment. Reference group is gilteritinib alone treatment.

CI: confidence interval; CSR: clinical study report; FLZ: fluconazole; ITZ: itraconazole; LS: least squares; RIF: rifampin.

†Corresponds to "Geometric LS Mean for the Numerator" as reflected in the Study 2215-CL-0108 CSR.

‡Corresponds to "Geometric LS Mean for the Denominator" as reflected in the Study 2215-CL-0108 CSR.

§200 mg ITZ twice daily on day 1, 200-mg once daily on days 2 to 28 and 10 mg gilteritinib on day 6.

¶400 mg FLZ on day 1, 200 mg once daily on days 2 to 28 and 10-mg gilteritinib on day 6.

††600 mg RIF once daily on days 1 to 21 and 20 mg gilteritinib on day 8.

Pharmacokinetics using human biomaterials

The *in vitro* studies using human biomaterials were conducted to investigate plasma protein binding, metabolism and DDI potential (CYP450, transporters) and are described in respective sections.

2.4.3. Pharmacodynamics

Mechanism of action

Gilteritinib inhibits FLT3 receptor signalling and proliferation in cells exogenously expressing FLT3 including FLT3 ITD, FLT3 D835Y, and FLT3 ITD D835Y, and it induced apoptosis in leukemic cells expressing FLT3 ITD (SmPC, section 5.1).

Primary and Secondary pharmacology

Relationship between gilteritinib exposure and FLT3 phosphorylation in relapsed or refractory (R/R) AML patients

The effect of gilteritinib fumarate on FLT3 phosphorylation was assessed using an ex-vivo PIA assay described by Levis et al. (5). In this PIA assay plasma samples were incubated with Ba/F3 or TF-1 cells transfected with an expression vector containing the ITD-mutated FLT3 coding sequence. Cell lysates were analyzed for FLT3 using immunoprecipitation and antiphophotyrosine immunoblotting was used to detect tyrosine kinase substrates. Densitometry was performed on the immunoblot bands. Inhibition of FLT3 phosphorylation for plasma samples at each time point was calculated by expressing the density of the corresponding band as a percent decrease from the density of the baseline (pretreatment plasma sample) band, which was arbitrarily set at 100%. A total of 233 patients were included in the PD analysis set. Assessment of the relationship between gilteritinib concentration and inhibition of FLT3 phosphorylation showed a good correlation. The time-matched data were characterized using a maximum inhibitory effect (I_{max}) model. Final model parameters are summarized in Table 19.

Table 19. Final model parameter estimates characterizing inhibitory effect of gilteritinib on phosphorylation of FLT3 (2215-CL-0101)

Parameter	Unit	Estimates	RSE (%CV)
Baseline	%	98.9	0.34
I_{max}	%	100	-
IC_{50}	ng/mL	7.55	8.1
IIV on IC_{50}	%	69.2	13.87
Residual variability	%	5.11	12.9

Source: Pharmacokinetic Modeling and Simulation Report, Table 18

A dose-related increase in inhibition of FLT3 phosphorylation was observed across doses ranging from 20 to 450 mg. More than 90% inhibition of FLT3 phosphorylation was observed by cycle 1 day 8 predose at gilteritinib doses of ≥ 80 mg.

Minimal residual disease (MRD) evaluation

The MRD analysis was performed retrospectively on patients at any dose level who were FLT3-ITD positive by central testing at screening/baseline, and had a bone marrow aspirate sample available at baseline/screening and at least one post-baseline time point. Presence or absence of MRD was measured by a FLT3-ITD signal ratio defined as the ratio of FLT3-ITD to total FLT3. A molecular response was defined as an FLT3-ITD signal ratio of ≤ 0.01 at any post baseline time point, and *deep* molecular response was defined as an FLT-ITD signal ratio ≤ 0.0001.

Overall, 108 patients were eligible for MRD analysis; 95 patients at doses of ≥ 80 mg and 13 patients at doses < 80 mg. 21 patients had a molecular response (ratio FLT3-ITD:total FLT3 ≤ 0.1 at any post baseline time point), all at doses of ≥ 80 mg. In patients who received doses of ≥ 80 mg, 58.3% (14/24)

of patients who achieved CR/CRh had a molecular response, while 9.9% (7/71) of patients who did not achieve CR/CRh had a molecular response. The CR/CRh rate was 66.7% in patients with a molecular response compared to 13.5% in patients without a molecular response. In patients who received doses of ≥ 80 mg, 41.7% (10/24) of patients who achieved CR/CRh had a deep molecular response, while 4.2% (3/71) of patients who did not achieve CR/CRh had a *deep* molecular response. The CR/CRh rate was 76.9% in patients with deep molecular response, compared to 17.1% in patients without *deep* molecular response.

AXL, c-CBL and FLT3 Mutational Analysis

All exons of AXL, E3 ubiquitin-protein ligase C-CBL (c-CBL) and FLT3 were sequenced using a capture based NGS assay (data not shown). Due to small number of patients, results from AXL, c-CBL and FLT3 (other than D835) mutational analysis does not allow any conclusion on response to gilteritinib.

Exposure response (ER) analysis – efficacy (2215-PK-0008)

The objective of the study was to explore PK/PD relationships between estimated gilteritinib exposure ($AUC_{24,ss}$, $C_{min,ss}$ and $C_{max,ss}$) and clinical response (CR/CRh) in those patients that were considered clinically evaluable in studies 0301 and 0101, and to explore PK/PD relationships between estimated gilteritinib exposure ($AUC_{24,ss}$ and $C_{min,ss}$, $C_{max,ss}$) and OS in those patients that were considered clinically evaluable in study 0301. No exposure-efficacy relationship could be characterised at the exposure range studied.

In the multiple dose study 0101, mean (SD) AUC24 was 31428 (21412) ng*h/mL and mean Cmax was 1462 (815.1) ng/mL at the maximum clinical dose of 200 mg QD for 15 days (N=2). Mean (SD) AUC24 and mean (SD) Cmax for the 120 mg dose QD for 15 days were 6943 (3221) ng*h/mL and 374.2 (190.1) ng/mL, respectively (N=3).

In the multiple dose study 0102, mean (SD) AUC24 was 21573.86 (6230.86) ng*h/mL and mean Cmax was 1016.28 (295.23) ng/mL at the maximum clinical dose of 200 mg QD for 28 days (N=5). Mean (SD) AUC24 and mean (SD) Cmax for the 120 mg dose QD for 28 days were 13463.35 (NA) ng*h/mL and 680.23 (NA) ng/mL, respectively (N=2).

Concentration-safety analysis based on integrated data

A merged gilteritinib concentration - dCK, dAST, dALT, dALB and dQTcF data set was prepared based on the data from studies 0101 (Data cut off 07.03.2018), 0102 and 0301 (Data cut off 17.09.2018).

The dataset for hematological and QTc analysis consisted of 497 and 487 subjects, respectively. Although large variability was observed, the box plot showed the dependency of safety data on gilteritinib concentration. Statistical significant trends towards increasing levels of ALT, AST, creatinine kinase (CK) and QTc and decreasing levels of ALB with increasing gilteritinib concentrations were shown.

The prediction (upper 1-sided 95%CI) at the 120-mg dose (median C_{max} 282 ng/mL) was 107 U/L (116 U/L) in ΔCK, 15.2 U/L (16.6 U/L) in ΔAST and 18.9 U/L (21.1 U/L) in ΔALT. The prediction of ΔALB was -0.327 g/L (lower 1-sided 95% CI: -0.634 g/L).

The QTc relationship was described by an maximal effective concentration (E_{max})vmodel. The prolongation at the 120 mg dose (median C_{max} 282 ng/mL) was 4.96 msec (upper 1-sided 95%CI: 6.20 msec), which did not reach the 10-msec threshold for regulatory significance. The predicted change in the fridericia-corrected QT interval (QTcF) from baseline at the median $C_{max,ss}$ associated with once-daily doses of 200 mg gilteritinib is 9.93 msec with an upper 95% confidence limit of 12.5 msec. Covariate models on QTc were developed (covariates race, CYP3A4 inhibitors, baseline QTc) revealing only impact of baseline QTc. Patients who had longer baseline QTcF intervals showed smaller ΔQTcF with increasing gilteritinib concentration.

No secondary pharmacology studies have been contucted with gilteritinib.

2.4.4. Discussion on clinical pharmacology

The population estimate of central and peripheral volume of distribution was 1092 L and 1100 L, respectively. These data indicate gilteritinib distributes extensively outside of plasma, which may indicate extensive tissue distribution. *In vivo* plasma protein binding in humans is approximately 90% and gilteritinib is primarily bound to ALB (SmPC, section 5.2).

Based on *in vitro* data, gilteritinib is primarily metabolised via CYP3A4. The primary metabolites in humans include M17 (formed via N -dealkylation and oxidation), M16 and M10 (both formed via N dealkylation) and were observed in animals. None of these three metabolites exceeded 10% of overall parent exposure. The pharmacological activity of the metabolites against FLT3 and AXL receptors is unknown (SmPC, section 5.2).

Absolute bioavailability is not known. After a single dose of [14C] gilteritinib, gilteritinib is primarily excreted in faeces with 64.5% of the total administered dose recovered in faeces. Approximately 16.4% of the total dose was excreted in urine as unchanged drug and metabolites. Gilteritinib plasma concentrations declined in a bi exponential manner with a population mean estimated half-life of 113 hours. The estimated CL/F based on the population PK model is 14.85 L/h (SmPC, section 5.2).

In healthy adults, gilteritinib Cmax and AUC decreased by approximately 26% and less than 10%, respectively, when a single 40 mg dose of gilteritinib was co administered with a high fat meal compared to gilteritinib exposure in fasted state. Median tmax was delayed 2 hours when gilteritinib was administered with a high fat meal (SmPC, section 5.2).The tablets can be taken with or without food (SmPC, section 4.2).

In general, gilteritinib exhibited linear, dose -proportional PK after single and multiple dose administration at doses ranging from 20 to 450 mg in patients with R/R AML (SmPC, section 5.2).

The effect of hepatic impairment on gilteritinib PK was studied in subjects with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment.

Following a 10 mg single oral dose of gilteritinib in the dedicated hepatic impairment study AUC_{inf} decreased by 22% and 35% in the mild and moderate group, respectively, and mean C_{max} decreased by 14% in the moderate group compared to the normal group. Both CL/F and the apparent volume of distribution during the terminal elimination phase (Vz/F) increased with increasing severity of hepatic impairment, while t1/2 was comparable across groups. Unbound gilteritinib exposure in subjects in the mild or moderate hepatic impairment groups was comparable to that observed in subjects in the normal hepatic function group.

Results indicate unbound gilteritinib exposure in subjects with mild or moderate hepatic impairment is comparable to that observed in subjects with normal hepatic function. The effect of mild hepatic impairment [as defined by the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG)] on gilteritinib exposure was also assessed using the population PK model and the results demonstrate little difference in predicted steady-state gilteritinib exposure relative to a typical patient with R/R AML and normal liver function (SmPC, section 5.2).

The effect of mild or moderate renal impairment was evaluated using a popPK model. Serum creatinine, a marker of renal function, was identified as a statistically significant covariate. However, the predicted increase on gilteritinib exposure was less than 2 fold Impaired renal function is thus not expected to significantly affect gilteritinib exposure, indicating dose adjustment is not warranted in patients with mild or moderate renal impairment. The CHMP recommended the applicant to conduct a phase I study to

investigate the effect of renal impairment on the pharmacokinetics, safety and tolerability of gilteritinib compared to subjects with normal renal function (see RMP).

In vitro investigations indicated that gilteritinib was not a substrate of hepatic transporters OATP1B1, OATP1B3 or OCT1, however the data are not conclusive as only one, relatively high concentration of gilteritinib was used. According to the EMA DDI guideline, hepatic uptake transporters OATP1B1 and OATP1B3 should be investigated for substances where hepatic metabolism accounts for ≥25% of total elimination. Additionally, gilteritinib was not found to be a substrate of breast cancer resistance protein (BCRP), however the study should be repeated using four concentrations 0.01-1-fold the therapeutic dose/250 mL in accordance with the EMA DDI guideline. The CHMP recommended the applicant to conduct an *in vitro* study post-approval, designed to investigate gilteritinib as a substrate of BCRP and hepatic uptake transporters OATP1B1, OATP1B3 and OCT1.

Concomitant use of Xospata with strong CYP3A/P glycoprotein (gp) inducers (e.g., phenytoin, rifampin and St. John's Wort) should be avoided because they can decrease gilteritinib plasma concentrations. In healthy subjects, co administration of RIF (600 mg), a strong CYP3A/P gp inducer, to steady state with a single 20 mg dose of gilteritinib decreased gilteritinib mean Cmax by 27% and mean AUC_{inf} by 70%, respectively, compared to subjects administered a single dose of gilteritinib alone (SmPC sections 4.4, 4.5).

Strong inhibitors of CYP3A and/or P gp (e.g., voriconazole, ITZ, posaconazole, clarithromycin, erythromycin, captopril, carvedilol, ritonavir, azithromycin) can increase gilteritinib plasma concentrations. A single, 10 mg dose of gilteritinib co administered with ITZ (200 mg once daily for 28 days), a strong CYP3A and/or P gp inhibitor, to healthy subjects resulted in an approximate 20% increase in mean C_{max} and 2.2 fold increase in mean AUC_{inf} relative to subjects administered a single dose of gilteritinib alone. Gilteritinib exposure increased approximately 1.5 fold in patients with R/R AML when co administered with a strong CYP3A and/or P gp inhibitor (SmpC sections 4.4, 4.5).

Gilteritinib is not an inhibitor or inducer of CYP3A4 or and inhibitor of MATE1 in vivo. The PK of midazolam (a sensitive CYP3A4 substrate) were not significantly (C_{max} and AUC increased approximately 10%) affected after once daily administration of gilteritinib (300 mg) for 15 days in patients with FLT3 mutated R/R AML. Additionally, the PK of cephalexin (a sensitive MATE1 substrate) were not significantly (C_{max} and AUC decreased by less than 10%) affected after once daily administration of gilteritinib (200 mg) for 15 days in patients with FLT3 mutated R/R AML (SmPC section 4.5).

There is no data available on the concomitant use of contraceptive steroids. Gilteritinib is considered a potential human teratogen and the proposed indication could include females of childbearing potential. Appropriate recommendations have been included in the SmPC section 4.6 (See discussion on non-clinical aspects).

Two separate experimental systems should have been used to investigate P-gp inhibition due to the high inter-laboratory variability in the inhibition parameter estimation for P-gp, and an additional study is required. The CHMP recommended the applicant to perform a post-authorization study to investigate the potential of gilteritinib to inhibit P-gp and the bile salt export pump (BSEP).

No exposure-efficacy relationship could be characterised at the exposure range studied. Considering that ER analysis conducted on phase III data mainly can be used to identify major deviations in the adequacy of the selected dosing regimen either in the target or in subpopulations, this is to be expected. No phase II dose-finding study has been conducted, and the ER analysis has not been prospectively planned. Overall, the ER efficacy analysis is exploratory only, and is insufficient to draw any conclusions on the ER relationship or to support the proposed dose regimen.

There was a tendency for increasing QTc prolongation with increasing gilteritinib exposures. At the median $C_{max,ss}$ associated with the proposed dose of 200 mg QD, the upper bound of the predicted change

in QTcF was 12.5 msec. Thus an increased risk of QTc prolongation at the 200 mg dose of gilteritinib cannot be ruled out (see discussion on clinical safety).

2.4.5. Conclusions on clinical pharmacology

The PK and PD of gilteritinib have been reasonably well investigated.

2.5. Clinical efficacy

2.5.1. Dose response study

Study 2215-CL-0101

No formal dose-finding study was conducted.

The dose-escalating study 2215-CL-0101, was a phase 1/2 open-label, first-in-human study in patients with R/R AML, with concomitant expansion cohort for multiple doses.

The primary objectives of this phase 1/2 study were to assess the safety and tolerability, including determination of the MTD of oral gilteritinib in patients with relapsed or treatment-refractory AML, and to determine the pharmacokinetic parameters of gilteritinib.

The secondary objectives of the study were to investigate the antileukemic activity of various doses of gilteritinib in patients with AML and to evaluate the effect of strong or moderate CYP3A4 inhibitors on the PK of gilteritinib (see section ''Pharmacokinetic interaction studies'').

The study consisted of two cohorts:

- Cohort 1 - the initial dose escalation cohort, with up to 10 dose levels. Dose levels were set at around 50% increments. Cohort 1 was designed to determine the MTD based on assessment of DLTs at each dose level;
- Cohort 2 – the dose expansion cohort. Cohort 2 was conducted to further explore expanded dose levels.

Twenty-five patients 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. The doses assessed 20, 40, 80, 120, 200, 300 and 450 mg/day. 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 (AEs) or DLTs. The DLT observation period was 30 days starting with the first dose taken on day -2 and including the first 28-day treatment cycle.

Efficacy endpoints included best response including CR rate, CRc rate and response (CRc + partial remission [PR]) rate, CRh; duration of remission; OS; EFS and LFS.

The study initiation date (Date of First Enrolment) was 9 October 2013 and the study completion date (Date of Last Evaluation) was 7 March 2018.

Median age was 62.0 years. Overall, the duration of AML ranged from less than 1 month to 132.7 months, with a median duration of 9.07 months. Overall, 70.6% (178/252) of patients in the SAF were FTL3-ITD mutation positive and 13.1% (33/252) were FLT3-TKD positive by local testing, with 23.0% of patients (58/252) testing as FLT3 mutation negative. Previous line of AML therapies were 1-3 where 44% (111/252) had received $\geq$3 lines, 26.2% (66/252) 2 lines and 29.8% (75/252) 1 line. The most common recurrent genetic abnormalities (WHO Classification) were AML with mutated NPM1 (27.0%, 68/252), AML with myelodysplasia-related changes (17.1%, 43/252), acute myelomonocytic leukaemia

(11.1%, 28/252), AML without maturation (9.1%, 23/252), AML with maturation (7.5%, 19/252) and AML minimally differentiated (6.3%, 16/252); no other classification occurred in more than 5% of patients. A majority of patients were characterized with intermediate cytogenetic risk (56.7%, 143/252), with intermediate: normal being the single most common characterization (122 patients, 48.4%); 22.2% of patients were characterized with unfavorable cytogenetic risk (56/252) and 2.8% were characterized with favorable cytogenetic risk (7/252).

The MTD established in Study 2215-CL-0101, based on DLTs was 300 mg daily. PD analyses showed that gilteritinib exhibited rapid and sustained inhibition of FLT3 phosphorylation at doses ≥ 80 mg. Similarly, in FLT3 mutation positive patients, the CRc rates at end of treatment were generally low for patients randomized to the 20-mg and 40-mg dose groups (< 10%) and generally similar for patients randomized to the 80 mg (41.7%), 120 mg (46.4%) and 200 mg (40.4%) dose groups.

Response was assessed based on central assessment supplemented by local assessment (i.e., derived response) and investigator-reported response. 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, full analysis set (FAS)) including all doses, 71 patients achieved CRc for a CRc rate of 37.2%, and the best overall response rate (i.e., CRc + PR) was 48.7%.

The CR, CRh, and CR/CRh rates were also assessed per dose group. 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 in the 80-, 120-, 200- and 300-mg dose groups was 41.7%, 46.4%, 40.4% and 30.0%, respectively, and the best overall response rate was 66.7%, 53.6%, 48.3% and 60.0%, respectively.

The CR rate for FLT3 mutation positive patients receiving 120 mg was 12.5%. The derived CRh rate for FLT3 mutation positive patients receiving 120 mg was 10.7% and the CR/CRh rate was 23.2%.The median duration of CRc in FLT3 mutation positive patients in ≥ 80-mg dose groups was 147.0 days (95% CI: 97.0, 307.0). Median time to best response was 56.0 days, ranging from 26 to 364 days.

For the population of FLT3 mutation positive patients, the median OS from Kaplan-Meier (KM) estimates for dose groups ≥ 80 mg gilteritinib was 218.0 days. The survival probability was 85.7% at 8 weeks, 56.2% at 26 weeks, and 24.9% at 1 year.

Table 20 Overall Survival for Locally Evaluated FLT3 Mutated Patients in the ⩾ 80-mg Dose Groups – Full Analysis (Set 2215-CL-0101)

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]

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

The supportive Phase 1/2 dose-escalation study 2215 CL 0101 included 157 patients with FLT3 mutated AML treated with either 1 (N=49) or >1 prior lines of treatment (N=108) in the combined dose group (i.e. 80 mg, 120 mg or 200 mg); 31.2% received 1 prior line of treatment and 68.8% received >1 prior lines of treatment.

Table 21 CR/CRh Rate by Prior Lines of Therapy - Local FLT3 Mutated Subjects Treated with Gilteritinib 80 mg, 120 mg or 200 mg, Full Analysis Set (Study 2215-CL-0101)

Parameter n (%), (95% CI)†	2215-CL-0101			
	1 Line of Therapy		> 1 Line of Therapy	
	Gilteritinib 120 mg/day (N = 14)	Gilteritinib Combined Dose Levels (N = 49)	Gilteritinib 120 mg/day (N = 42)	Gilteritinib Combined Dose Levels (N = 108)
CR/CRh Rate‡	4 (28.6), (8.4, 58.1)	16 (32.7), (19.9, 47.5)	9 (21.4), (10.3, 36.8)	17 (15.7), (9.4, 24.0)
CRh Rate‡	1 (7.1), (0.2, 33.9)	6 (12.2), (4.6, 24.8)	5 (11.9), (4.0, 25.6)	8 (7.4), (3.3, 14.1)
CR Rate‡	3 (21.4), (4.7, 50.8)	10 (20.4), (10.2, 34.3)	4 (9.5), (2.7, 22.6)	9 (8.3), (3.9, 15.2)

Combined dose levels include 80 mg, 120 mg, and 200 mg dose levels.

†Exact 95% confidence interval was estimated using the binomial distribution.

‡CR/CRh rate is defined as the number of subjects who achieve either CR or CRh at any postbaseline visit divided by the number of subjects in the analysis population.CI: confidence interval; CR: complete remission; CRh: complete remission with partial hematological recovery; FLT3: FMS-like tyrosine kinase 3.Sources: Adhoc

Table 22 Overall Survival by Prior Lines of Therapy - Local FLT3 Mutated Patients Treated with Gilteritinib 80 mg, 120 mg or 200 mg, Full Analysis Set

Parameter	2215-CL-0101				2215-CL-0301	
	1 Prior Line of Therapy		> 1 Prior Line of Therapy		1 Prior Line of Therapy	
	Gilteritinib 120 mg/day (N = 14)	Gilteritinib Combined Dose Levels (N = 49)	Gilteritinib 120 mg/day (N = 42)	Gilteritinib Combined Dose Levels (N = 108)	Gilteritinib 120 mg/day (N = 247)	Chemotherapy (N = 124)
Deaths, n (%)	12 (85.7)	41 (83.7)	31 (73.8)	84 (77.8)	171 (69.2)	90 (72.6)
Censored, n (%)	2 (14.3)	8 (16.3)	11 (26.2)	24 (22.2)	76 (30.8)	34 (27.4)
Duration of OS, months†						
1st quartile (95% CI)	7.7 (2.4, 9.8)	3.9 (2.4, 4.8)	3.3 (1.5, 5.6)	3.1 (1.9, 3.8)	4.4 (3.8, 5.1)	3.0 (1.9, 3.5)
Median (95% CI)	10.3 (3.1, 17.5)	8.6 (4.7, 12.8)	7.2 (4.3, 9.4)	7.1 (5.0, 8.3)	9.3 (7.7, 10.7)	5.6 (4.7, 7.3)
3rd quartile (95% CI)	17.5 (9.8, NE)	17.5 (10.8, 38.8)	18.4 (8.1, NE)	11.1 (9.8, 16.8)	18.7 (14.9, 24.1)	10.0 (8.0, 15.7)
Range‡	2.4, 38.1+	0.4, 38.8	0.4, 43.4+	0.4, 43.4+	0.2, 31.9+	< 0.1+, 33.0
OS Rate, % (95% CI)§						
At 6 months	78.6 (47.2, 92.5)	59.2 (44.2, 71.4)	61.3 (44.7, 74.2)	56.6 (46.4, 65.5)	65.5 (59.2, 71.1)	48.9 (39.3, 57.8)
At 12 months	42.9 (17.7, 66.0)	38.0 (24.6, 51.4)	26.8 (14.1, 41.2)	19.9 (12.5, 28.5)	37.1 (30.7, 43.6)	16.7 (9.9, 25.0)
At 24 months	14.3 (2.3, 36.6)	16.9 (7.9, 28.7)	21.4 (10.1, 35.4)	14.0 (7.8, 22.0)	19.0 (12.8, 26.0)	13.8 (7.5, 22.0)
At 36 months	14.3 (2.3, 36.6)	16.9 (7.9, 28.7)	21.4 (10.1, 35.4)	14.0 (7.8, 22.0)	NE (NE, NE)	0.0 (NE, NE)

Combined dose levels include 80 mg, 120 mg, and 200 mg dose levels.
†Based on Kaplan-Meier estimates; ‡+ indicates censoring; §Survival rate and 95% CI were estimated using Kaplan-Meier method and Greenwood formula.

Study 2215 –CL-0102

This was a phase 1 one open-label dose-escalation study in Japanese patients with R/R AML. 27 patients were randomised and 24 received study medication with gilteritinib in doses from 20 to 300 mg. The starting dose level was 20 mg daily. Gilteritinib was to be administered in at least 1 patient at the 20-mg dose level and at least 3 patients at the subsequent dose levels (40, 80, 120, 200 and 300 mg). Patients who had received gilteritinib in a certain dose level were not assigned to another dose level. The DLT observation period was 30 days starting with the first dose in cycle 0 (day -2) and including cycle 1 (the first 28-day treatment cycle).

The best overall response was stratified by central FLT3 mutation status. At end of treatment, in the 5 FLT3 mutation-positive patients, 3 patients achieved CRc with a CRc rate of 60.0% (95% CI: 14.7%, 94.7%) and the response rate was 80.0% (95% CI: 28.4%, 99.5%). In the FLT3 mutation-negative patients, the CRc rate and the response rate were 27.3% (95% CI: 6.0%, 61.0%) and 36.4% (95% CI: 10.9%, 69.2%), respectively (data not shown).

Dose escalation to 200mg

Efficacy

A comparison of response rates during cycle 1 compared to best overall response for patients in Study 2215-CL-0301 who did not escalate to gilteritinib 200 mg per day showed that composite complete remission (CRc) and complete remission (CR) rates were higher in the best overall response compared to the cycle 1 best response (overall CRc rate was 58.9% versus 33.3% for the CRc rate following 1 cycle of treatment; overall CR rate was 24.4% versus 5.4% for the CR rate following 1 cycle of treatment), suggesting that patients benefit from a prolonged exposure to gilteritinib and not all patients who will respond to gilteritinib will reach CR or CRc during the first treatment cycle.

Table 23 Response before Cd2D1 compared to best overall response-study 2215-CL-0301 IIT-Patients who did not increase to 200mg gilteritinib

Parameter, n (%)	Cycle 1 Best Response‡ (n = 168)	Best Overall Response (n = 168)
Best Overall Response§		
CR	9 (5.4)	41 (24.4)
CRp	7 (4.2)	15 (8.9)
CRi	40 (23.8)	43 (25.6)
PR	21 (12.5)	17 (10.1)
NR	71 (42.3)	39 (23.2)
NE	20 (11.9)	13 (7.7)
CRc¶	56 (33.3)	99 (58.9)
Response Rate††	77 (45.8)	116 (69.0)

CR: complete remission; CRc: composite complete remission; CRi: complete remission with incomplete hematologic recovery; CRp: complete remission with incomplete platelet recovery; NE: not evaluable; NR: no response; PR: partial remission

† Includes patients who remained on 120 mg gilteritinib and patients who had a dose reduction to 80 mg gilteritinib.

‡ Defined as the best response up to cycle 2 day 1.

§ Categories were mutually exclusive.

¶ CRc = CR + CRp + CRi

†† Response = CRc + PR

When analysing best overall response in the group of patients who did not respond after cycle 1, the difference in CRc rates between patients who were not escalated to gilteritinib 200 mg per day and those who were escalated to gilteritinib 200 mg per day was small (38.4% vs 40.3%).

Table 24 Best overall response- study 2215-CL-0301 IIT-Patients not responding after cycle 1

Parameter, n (%)	Did Not Escalate to 200 mg Gilteritinib† (n = 112)	Escalated to 200 mg Gilteritinib (n = 72)
Best Overall Response‡		
CR	18 (16.1)	7 (9.7)
CRp	8 (7.1)	4 (5.6)
CRi	17 (15.2)	18 (25.0)
PR	17 (15.2)	16 (22.2)
NR	39 (34.8)	27 (37.5)
NE	13 (11.6)	0
CRc§	43 (38.4)	29 (40.3)
Response Rate¶	60 (53.6)	45 (62.5)

CR: complete remission; CRc: composite complete remission; CRi: complete remission with incomplete hematologic recovery; CRp: complete remission with incomplete platelet recovery; NE: not evaluable; NR: no response; PR: partial remission

† Includes patients who remained on 120 mg gilteritinib and patients who had a dose reduction to 80 mg gilteritinib.

‡ Categories were mutually exclusive.

§ CRc = CR + CRp + Cri

Response = CRc + PR

A summary of OS by dose adjustment in the gilteritinib arm is presented in table below.

Table 25 Summary of OS by Dose Adjustment in the Gilteritinib Arm (ITT) (Study 2215-CL-0301)

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

† Based on Kaplan-Meier estimates; ‡ A "+" indicates censoring; § Survival rate and 95% CI were estimated using the Kaplan-Meier method and the Greenwood formula; ¶ Increased to gilteritinib 200 mg; † † Decreased to gilteritinib 80 mg.

Safety

Comparison of the safety profile (SAEs, ≥ Grade 3 TEAEs and Grade 5 TEAEs) between patients who dose escalated to gilteritinib 200 mg and patients who did not dose escalate is presented in the table below.

Table 26 TEAEs leading to dose interruption of treatment discontinuation in ≥1% of patients who dose escalated to gilteritinib 200mg

SOC Preferred Term MedDRA V19.1 n (%)	Did Not Escalate to 200 mg Gilteritinib† (n = 168)		Escalated to Gilteritinib 200 mg (N = 78)	
	Interruption	Discontinuation	Interruption	Discontinuation
Overall	**78 (46.4)**	**41 (24.4)**	**34 (43.6)**	**17 (21.8)**
Blood and Lymphatic System Disorders	**21 (12.5)**	**3 (1.8)**	**9 (11.5)**	**0**
Anaemia	1 (0.6)	1 (0.6)	1 (1.3)	0
Disseminated intravascular coagulation	0	0	1 (1.3)	0
Febrile neutropenia	13 (7.7)	1 (0.6)	6 (7.7)	0
Pancytopenia	0	1 (0.6)	2 (2.6)	0
Thrombcytopenia	4 (2.4)	0	2 (2.6)	0
Cardiac Disorders	**4 (2.4)**	**4 (2.4)**	**1 (1.3)**	**0**
Cardiac failure	0	0	1 (1.3)	0
Eye Disorders	**3 (1.8)**	**1 (0.6)**	**0**	**1 (1.3)**
Retinopathy	1 (0.6)	1 (0.6)	0	1 (1.3)
Gastrointestinal Disorders	**7 (4.2)**	**2 (1.2)**	**6 (7.7)**	**0**
Abdominal pain	1 (0.6)	0	1 (1.3)	0
Colitis	1 (0.6)	0	1 (1.3)	0
Diarrhoea	2 (1.2)	0	1 (1.3)	0
Enterocolitis	0	0	1 (1.3)	0
Haematemesis	0	0	1 (1.3)	0
Nausea	1 (0.6)	0	1 (1.3)	0
Stomatitis necrotising	0	0	1 (1.3)	0
General Disorders and Administration Site Conditions	**13 (7.7)**	**1 (0.6)**	**5 (6.4)**	**0**
Asthenia	1 (0.6)	0	1 (1.3)	0
Generalised oedema	0	0	1 (1.3)	0
Malaise	1 (0.6)	0	1 (1.3)	0
Pyrexia	7 (4.2)	0	2 (2.6)	0
Hepatobiliary Disorders	**3 (1.8)**	**0**	**1 (1.3)**	**1 (1.3)**
Hepatic function abnormal	1 (0.6)	0	1 (1.3)	0
Cholecystitis	0	0	0	1 (1.3)
Immune System Disorders	**3 (1.8)**	**0**	**2 (2.6)**	**1 (1.3)**
Acute graft versus host disease in intestine	0	0	1 (1.3)	1 (1.3)
Drug hypersensitivity	0	0	1 (1.3)	0
Infections and Infestations	**18 (10.7)**	**13 (7.7)**	**8 (10.3)**	**5 (6.4)**
Endocarditis	0	0	0	1 (1.3)
Device related infection	1 (0.6)	0	1 (1.3)	0
Influenza	0	0	1 (1.3)	0
Lung infection	2 (1.2)	4 (2.4)	0	1 (1.3)
Pneumonia	3 (1.8)	1 (0.6)	1 (1.3)	2 (2.6)
Pneumonia viral	0	0	1 (1.3)	0
Septic shock	2 (1.2)	2 (1.2)	1 (1.3)	2 (2.6)
Sinusitis fungal	0	0	1 (1.3)	0
Skin infection	0	0	3 (3.8)	0
Urinary tract infection	0	0	1 (1.3)	0
Injury, Poisoning and Procedural Complications	**3 (1.8)**	**0**	**1 (1.3)**	**0**
Toxicty to various agents	0	0	1 (1.3)	0

SOC Preferred Term MedDRA V19.1 n (%)	Did Not Escalate to 200 mg Gilteritinib† (n = 168)		Escalated to Gilteritinib 200 mg (N = 78)	
	Interruption	Discontinuation	Interruption	Discontinuation
Investigations	**30 (17.9)**	**7 (4.2)**	**9 (11.5)**	**3 (3.8)**
ALT increased	16 (9.5)	3 (1.8)	3 (3.8)	1 (1.3)
AST increased	14 (8.3)	3 (1.8)	4 (5.1)	2 (2.6)
Blood AP increased	2 (1.2)	1 (0.6)	0	1 (1.3)
Blood bilirubin increased	3 (1.8)	1 (0.6)	1 (1.3)	0
Blood LDH increased	1 (0.6)	0	1 (1.3)	0
ECG QT prolonged	2 (1.2)	0	1 (1.3)	0
Fibrin D dimer increased	0	0	1 (1.3)	0
GGT increased	1 (0.6)	0	1 (1.3)	0
Weight decreased	0	0	1 (1.3)	0
Metabolism and Nutrition Disorders	**3 (1.8)**	**1 (0.6)**	**3 (3.8)**	**0**
Decreased appetite	0	0	1 (1.3)	0
Dehydration	0	0	2 (2.6)	0
Hyperglycemia	0	1 (0.6)	1 (1.3)	0
Hypophosphataemia	2 (1.2)	0	1 (1.3)	0
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**0**	**6 (3.6)**	**1 (1.3)**	**6 (7.7)**
AML	0	2 (1.2)	1 (1.3)	6 (7.7)
Nervous System Disorders	**3 (1.8)**	**2 (1.2)**	**3 (3.8)**	**1 (1.3)**
Carpal tunnel syndrome	0	0	1 (1.3)	0
Cerebral haemorrhage	0	1 (0.6)	0	1 (1.3)
Headache	1 (0.6)	0	1 (1.3)	0
Syncope	1 (0.6)	0	1 (1.3)	0
Renal and Urinary Disorders	**1 (0.6)**	**2 (1.2)**	**1 (1.3)**	**0**
Haematuria	0	0	1 (1.3)	0
Respiratory, Thoracic and Mediastinal Disorders	**6 (3.6)**	**6 (3.6)**	**0**	**1 (1.3)**
Respiratory failure	2 (1.2)	1 (0.6)	0	1 (1.3)
Skin and subcutaneous tissue disorders	5 (3.0)	1 (0.6)	2 (2.6)	0
Drug eruption	1 (0.6)	0	1 (1.3)	0
Rash erythematous	0	0	1 (1.3)	0
Vascular Disorders	**6 (3.6)**	**1 (0.6)**	**2 (2.6)**	**0**
Haematoma	0	0	1 (1.3)	0
Orthostatis hypotension	0	0	1 (1.3)	0

ALT: alanine aminotransferase; AML: acute myeloid leukemia; AP: alkaline phosphatase; AST: aspartate aminotransferase; ECG: electrocardiogram; GGT: gamma-glutamyl transferase; LDH: lactate dehydrogenase; TEAE: treatment-emergent adverse event.

2.5.2. Main study

- **ADMIRAL Study (2215-CL-0301)**

Methods

This was a phase 3 open-label, multicenter, randomized study of ASP2215 versus salvage chemotherapy in patients with R/R AML with FLT3 mutation.

Study Participants

Inclusion Criteria

1. Provision of written informed consent approved by the Institutional Review Board (IRB) or Independent Ethics Committee and privacy language as per national regulations (e.g., HIPAA Authorization for US sites) was obtained from the patient or legally authorized representative prior to any study-related procedures including withdrawal of prohibited medication, if applicable.

2. Patient was considered an adult according to local regulation at the time of signing informed consent.

3. Patient had a diagnosis of primary AML or AML secondary to MDS according to WHO classification (6) as determined by pathology review at the treating institution.

4. Patient was refractory to or relapsed after first-line AML therapy (with or without HSCT)

- Refractory to first-line AML therapy was defined as:

(a) Patient did not achieve CR/CRi/CRp under initial therapy. A patient eligible for standard therapy must have received at least 1 cycle of an anthracycline containing induction block in standard dose for the selected induction regimen. A patient not eligible for standard therapy must have received at least 1 complete block of induction therapy seen as the optimum choice of therapy to induce remission for this patient as per investigator's assessment.

- Untreated first hematologic relapse was defined as:

(b) Patient must have achieved a CR/CRi/CRp as defined by Cheson et al. (7), with first-line treatment and had hematologic relapse.

5. Patient was positive for the FLT3 mutation in bone marrow or whole blood as determined by central testing by FLT3 CDx. In the investigator's opinion, a patient with rapidly proliferative disease and unable to wait for central testing by FLT3 CDx results could have been enrolled based on a local test performed after completion of the last interventional treatment. Patients could have been enrolled from a local test result if they had any of the following FLT3 mutations: FLT3-ITD, FLT3-TKD/D835 or FLT3-TKD/I836.

6. Patient had an ECOG performance status (PS) $\leq$ 2.

7. Patient was eligible for preselected salvage chemotherapy according to investigator assessment.

8. Patient must have met the following criteria as indicated on the clinical laboratory tests:

- Serum AST and alanine aminotransferase (ALT) $\leq$ 2.5 x upper limit of normal (ULN)
- Serum total bilirubin (TBL) $\leq$ 1.5 x ULN
- Serum creatinine $\leq$ 1.5 x ULN or an estimated glomerular filtration rate of > 50 mL/min as calculated by the Modification of Diet in Renal Disease equation.

9. Patient was suitable for oral administration of study drug.

10. Female patient must have been either:

-Of non-childbearing potential: Postmenopausal (defined as at least 1 year without any menses) prior to screening, or documented as surgically sterile (at least 1 month prior to screening)

-Or, if of childbearing potential: Agreed not to try to become pregnant during the study and for 180 days after the final study drug administration.

And had a negative urine pregnancy test at screening, and if heterosexually active, agreed to consistently use highly effective contraception per locally accepted standards in addition to a barrier method starting at screening and throughout the study period and for 180 days after the final study drug administration.

11. Female patient must have agreed not to breastfeed at screening and throughout the study period and for 60 days after the final study drug administration.

12. Female patient must not have donated ova starting at screening and throughout the study period and for 180 days after the final study drug administration.

13. Male patient and their female partners who were of childbearing potential must have been using highly effective contraception per locally accepted standards in addition to a barrier method starting at screening and continue throughout the study period and for 120 days after the final study drug administration.

14. Male patient must not have donated sperm starting at screening and throughout the study period and 120 days after the final study drug administration

15. Patient agreed not to participate in another interventional study while on treatment.

Exclusion Criteria

Patients were excluded from participation if any of the following applied:

1. Patient was diagnosed as having acute promyelocytic leukaemia.

2. Patient had BCR-ABL-positive leukaemia (chronic myelogenous leukaemia in blast crisis).

3. Patient had AML secondary to prior chemotherapy for other neoplasms (except for MDS).

4. Patient was in second or later hematologic relapse or had received salvage therapy for refractory disease.

5. Patient had clinically active CNS leukaemia.

6. Patient had been diagnosed with another malignancy, unless disease-free for at least 5 years. Patients with treated non-melanoma skin cancer, in-situ carcinoma or cervical intraepithelial neoplasia, regardless of the disease-free duration, were eligible for this study if definitive treatment for the condition had been completed. Patients with organ-confined prostate cancer with no evidence of recurrent or progressive disease were eligible if hormonal therapy had been initiated or the malignancy had been surgically removed or treated with definitive radiotherapy.

7. Patient had received prior treatment with gilteritinib or other FLT3 inhibitors (with the exception of sorafenib and midostaurin used in first-line therapy regimen as part of induction, consolidation and/or maintenance).

8. Patient had clinically significant abnormality of coagulation profile, such as disseminated intravascular coagulation.

9. Patient had major surgery within 4 weeks prior to the first study dose.

10. Patient had radiation therapy within 4 weeks prior to the first study dose.

11. Patient had congestive heart failure New York Heart Association (NYHA) class 3 or 4 or patient with a history of congestive heart failure NYHA class 3 or 4 in the past, unless a screening echocardiogram performed within 1 month prior to study entry resulted in a left ventricular ejection fraction that was $\geq$ 45%.

12. Patient had a mean of triplicate QTcF > 450 msec at screening based on central reading.

13. Patient had Long QT Syndrome at screening.

14. Patient had hypokalemia and hypomagnesemia at screening (defined as values below the LLN).

15. Patient required treatment with concomitant drugs that are strong inducers of CYP3A.

16. Patient required treatment with concomitant drugs that are strong inhibitors or inducers of P-gp with the exception of drugs that were considered absolutely essential for the care of the patient.

17. Patient required treatment with concomitant drugs that target serotonin 5-hydroxytryptamine receptor 1 (5HT1R) or 5-hydroxytryptamine receptor 2B (5HT2BR) or sigma nonspecific receptor with the exception of drugs that were considered absolutely essential for the care of the patient.

18. Patient had an active uncontrolled infection.

19. Patient was known to have human immunodeficiency virus infection.

20. Patient had active hepatitis B or C or other active hepatic disorder.

21. Patient had any condition which, in the investigator's opinion, made the patient unsuitable for study participation.

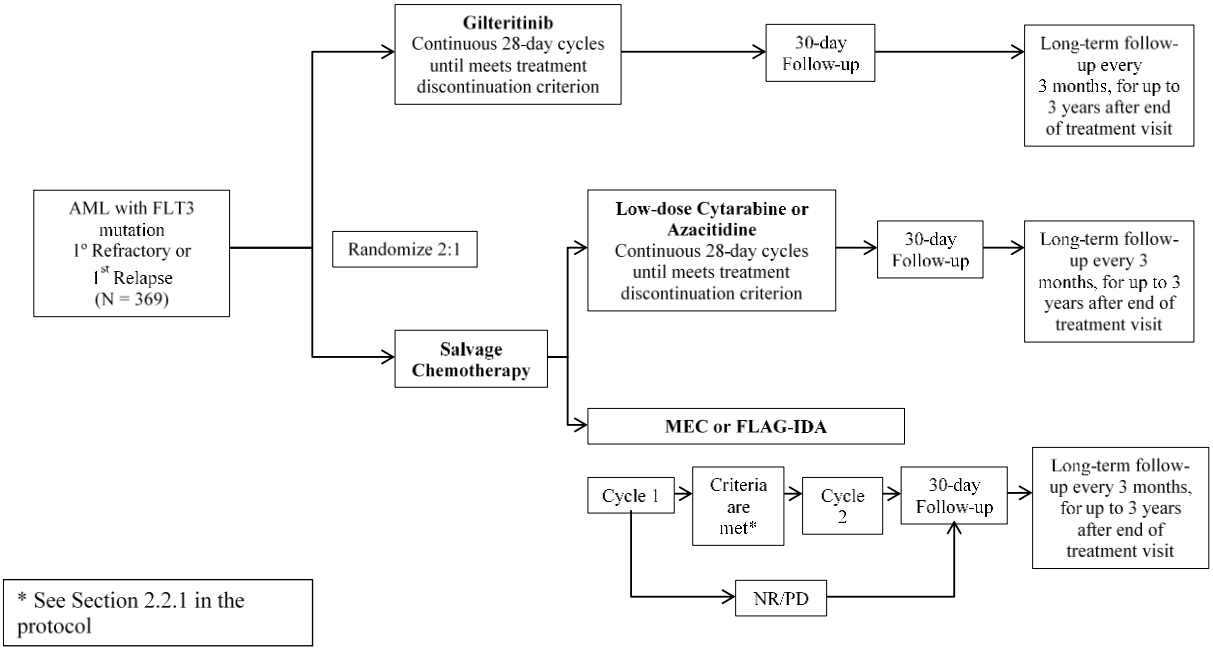
22. Patient had active clinically significant graft versus host disease (GVHD) or was on treatment with systemic corticosteroids for GVHD.

23. Patient had an FLT3 mutation other than the following: FLT3-ITD, FLT3-TKD/D835 or FLT3-TKD/I836.

Treatments

Subjects were randomized to receive either gilteritinib (staring dose 120 mg administered orally once daily) or salvage chemotherapy administered sc [LoDAC] or azacitidine or iv [MEC and FLAG-IDA]). A study flow chart is provided in Figure 4.

Figure 4 Study Design 2215-CL-0301



1º: primary; AML: acute myeloid leukemia; FLT3: FMS-like tyrosine kinase 3; FLAG-IDA: fludarabine, cytarabine and granulocyte colony-stimulating factor with idarubicin; MEC: mitoxantrone, etoposide and intermediate-dose cytarabine; NR: no response; PD: progressive disease.

Gilteritinib tablets were administered orally once daily in continuous 28-day cycles. The starting dose was 120 mg per day (3 tablets of 40 mg), which could be titrated per protocol instructions. Subjects receiving gilteritinib treatment should continue until there was no longer clinical benefit from therapy, until unacceptable toxicity occurred or another discontinuation criterion was met.

Interruption, reduction or escalation in dose of gilteritinib

Dose reductions/interruptions were based on the following criteria: QTcF prolongation, retinopathy, non-hematologic toxicity (Grade 3 or 4), or myelosuppression. Additionally, dosing may have been interrupted or reduced at the investigators discretion if deemed necessary for safety reasons. The gilteritinib dose may be initially reduced to 80 mg per day, and could be further reduced to 40 mg per day if the patient had already experienced clinical benefit. No further dose reductions were allowed (i.e., if a patient was receiving gilteritinib 40 mg and further dose reduction was required, study treatment was discontinued). If the gilteritinib dose was reduced, it was not re-escalated.

Any patients that were off treatment for more than 14 days, other than for HSCT, could only resume treatment after discussion with the medical monitor. Dose escalations to 200 mg per day were allowed in patients on a dose of 120 mg per day who did not achieve a CRc (CR, CRp or CRi) during or after cycle 1, based on bone marrow and hematology results. No further dose escalation was allowed.

Resumption of Treatment After Hematopoietic Stem Cell Transplantation

Gilteritinib could be resumed after HSCT if the following conditions were met:

Subject was between 30 - 90 days post HSCT; Subject had successful engraftment as demonstrated by ANC ≥ 500/mm3 and platelets ≥ 20000/mm3 without transfusions; Subject did not have ≥ grade 2 acute GVHD; Subject was in CRc.

Salvage Chemotherapy:

The investigator pre-selected the specific salvage chemotherapy regimen before randomization of each subject. All regimens were administered as 28-day cycles and per institutional guidelines for chemotherapy product preparation/administration[1]. Options for comparative salvage chemotherapies were limited to the following (all dose levels as defined below must have been followed):

<u>Low intensity chemotherapy</u>

LoDAC (Burnett et al. (8)): 20 mg cytarabine was administered twice daily by sc or intravenous (iv) injection for 10 days.

Azacitidine (Itzykson et al. (9)): 75 mg/m^2 azacitidine was administered daily by sc or iv injection for 7 days.

Institutional guidelines were followed if dose reduction was needed after cycle 1.

Patients who received LoDAC or azacitidine treatment should have continued until meeting a treatment discontinuation criterion.

High intensity chemotherapy

MEC Induction Chemotherapy (Levis et al. (10)):

- Mitoxantrone 8 mg/m^2 per day was administered by iv for 5 days (days 1 through 5).
- Etoposide 100 mg/m^2 per day was administered by iv for 5 days (days 1 through 5).
- Cytarabine 1000 mg/m^2 per day was administered by iv for 5 days (days 1 through 5).

FLAG-IDA Induction Chemotherapy (Parker et al., Pallis et al. (11, 12)) :

- G-CSF 300 µg/m^2 per day was administered by sc/iv for 5 days (days 1 through 5). Additional G-CSF by sc/iv was recommended 7 days after completing chemotherapy until absolute neutrophil count (ANC) > 0.5 X 10^9/L.
- Fludarabine 30 mg/m^2 per day was administered by iv for 5 days (days 2 through 6).
- Cytarabine 2000 mg/m^2 per day was administered by iv for 5 days (days 2 through 6).
- Idarubicin 10 mg/m^2 per day was administered by iv for 3 days (days 2 through 4).

Patients who received MEC or FLAG-IDA received 1 cycle of therapy and were assessed for response on or after day 15, per institutional guidelines. If the bone marrow cellularity was 20% or greater with at least a 50% reduction in blasts, the patient may have received a second cycle of the same chemotherapy. If bone marrow cellularity was between 5% and 20%, the investigator made the decision whether the patient should have received another treatment cycle or should have been observed for recovery. If bone marrow cellularity was 5% or less, the patient was observed for recovery. Patients achieving CR, CRi or CRp may have received a second cycle of chemotherapy at the investigator's discretion.

Objectives

Primary Objectives

- Determine the clinical benefit of gilteritinib in subjects with FLT3-mutated AML who are refractory to or have relapsed after first-line AML therapy as shown with OS compared to salvage chemotherapy.

- Determine the efficacy of gilteritinib as assessed by the rate of CR and CRh in subjects with FLT3-mutated AML who are refractory to or have relapsed after first-line AML therapy (first interim analysis).

Secondary Objectives

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

Other secondary objectives are to evaluate the efficacy of gilteritinib versus salvage chemotherapy in terms of: LFS; Duration of remission; CRh rate; CRc rate; Transfusion conversion rate; transfusion maintenance rate; Transplantation rate; Patient reported fatigue (Brief Fatigue Inventory [BFI]); AEs, safety labs, vital signs, ophthalmologic exams, ECGs; Eastern Cooperative Oncology Group (ECOG) performance scores; Evaluation of gilteritinib (and metabolites as appropriate) plasma concentration and popPK.

Exploratory Objectives

Exploratory objectives included the e valuation of the safety and efficacy of gilteritinib versus salvage chemotherapy in terms of pharmacogenomics (PGx), FLT3 gene mutation status, biomarkers of gilteritinib activity, resource utilization and PROs.

Outcomes/endpoints

Primary endpoint

OS was the primary endpoint for the second interim analysis and in the final analysis. OS was defined as the time from the date of randomization until the date of death from any cause. For a subject who is not known to have died by the end of study follow-up, OS is censored at the date of last contact.

In addition, for the first interim analysis, CR/CRh rate was a co-primary endpoint. CR/CRh was defined as the number of patients who achieved either CR or CRh at any of the post baseline visits divided by the number of patients in the analysis population.

Key secondary endpoints

EFS defined as the time from the date of randomization until the date of documented relapse (excluding relapse after PR), treatment failure or death, within 30 days after the last dose of study drug, whichever occurs first.

Treatment failure includes those patients who discontinued the treatment due to ''progressive disease'' or ''lack of efficacy''.

CR rate defined as the number of subjects who achieve the best response of CR divided by the number of subjects in the analysis population.

Relapse after CR, CRh, CRp or CRi is defined as a reappearance of leukemic blasts in the peripheral blood or $\geq$ 5% blasts in the bone marrow aspirate not attributable to any other cause or reappearance or new appearance of extramedullary leukaemia.

Relapse after PR is similarly defined with reappearance of significant numbers of peripheral blasts and an increase in the percentage of blasts in the bone marrow aspirate to > 25% not attributable to any other cause or reappearance or new appearance of extramedullary leukaemia.

Best response is defined as the best measured response to treatment for all visits (in the order of CR, CRp, CRi, PR, not reached (NR) and not evaluable (NE)) post-baseline.

Other secondary endpoints

- LFS, defined as the time from the date of first CRc until the date of documented relapse (excluding relapse from PR) or death. For a patient who was not known to have relapsed or died, LFS was censored on the date of last relapse-free disease assessment.
- Duration of remission includes duration of CRc, duration of CR/CRh, duration of CRh, duration of CR, duration of CRi, duration of CRp and duration of response (CRc + PR).
  - o Duration of CRc is defined as the time from the date of first CRc until the date of documented relapse for subjects who achieve CRc.
  - o Duration of CR/CRh, CRh, CR, CRp, CRi is defined similarly as duration of CRc.
  - o Duration of response is defined as the time from the date of either first CRc or PR until the date of documented relapse of any type for subjects who achieve CRc or PR.
- CRh rate
- CRc (CR + CRi + CRp) rate
- Transfusion conversion rate; transfusion maintenance rate (gilteritinib arm only):

o Transfusion conversion rate was defined as the number of patients who were transfusion dependent during the baseline period but become transfusion independent during the post baseline period divided by the total number of patients who were transfusion dependent during the baseline period.

o Transfusion maintenance rate was defined as the number of patients who were transfusion independent during the baseline period and still maintained transfusion independence during the post baseline period divided by the total number of patients who were transfusion independent during the baseline period.

- Transplantation rate, defined as the percentage of patients undergoing HSCT post baseline
- BFI developed to assess the severity of fatigue and the impact of fatigue on daily functioning in patients with fatigue due to cancer and cancer treatment.

Exploratory endpoints

- Functional Assessment of Chronic Illness Therapy-Dyspnea- Short Forms [FACIT-Dys-SF] - administered to assess dyspnoea severity and related functional limitations.
- Functional Assessment of Cancer Therapy-Leukemia [FACT-Leu], dizziness and mouth sore.
- EuroQol Group-5 Dimension-5 Level (EQ-5D-5L) Instrument.

Sample size

The study utilized a group sequential design using the O'Brien-Fleming boundaries (non-binding) as implemented by Lan-DeMets alpha/beta spending Method. The overall 0.025 one-sided type I error rate was allocated by 0.0005 and 0.0245 (corresponding to 0.001 and 0.049 for two-sided type I error rates) for the two co-primary efficacy endpoints of CR/CRh and OS, respectively. In subjects randomized into ASP2215 only, an arbitrarily selected nominal alpha of 0.0005 was spent, which was not recycled in the second interim and final analyses.

Two interim analyses and one final analysis were planned. The first interim analysis was planned when approximately 141 subjects are randomized into ASP2215 arm and at least 112 days (4 treatment cycles) post first dose or randomization (for subjects who received no study drug). The second interim analysis was planned when approximately 129 death events had occurred and the final analysis was planned when approximately 258 death events had occurred.

Approximately 369 subjects (the planned sample size with 10% dropout rate) was planned to be randomized in a 2:1 ratio to receive ASP2215 or salvage chemotherapy (246 subjects in the ASP2215 treatment arm and 123 subjects in the salvage chemotherapy arm). The planned 258 death events was calculated to provide about 90% power to detect a difference in OS between the ASP2215 arm with 7.7 months median survival time and salvage chemotherapy arm with 5 months median survival time (hazard ratio (HR) = 0.65) at the overall one-sided 0.0245 significance level.

The co-primary endpoint of CR/CRh rate was to be evaluated only at the first interim analysis. A sample size of 141 subjects was calculated to provides 80% power to exclude a CR/CRh rate of 12% using the two-sided 95% exact CI when the CR/CRh rate of ASP2215 is assumed to be 21% (211 subjects in total: 141 in the ASP2215 arm and 70 in the salvage chemotherapy arm). With a minimum follow-up of 4 treatment cycles are considered to achieve a maximum width of 15.78% for the two-sided 95% exact confidence interval (CI) when the CR/CRh is expected to be in the 5% to 30% range as summarized in below table. A sample size of 141 subjects provides 80% power to exclude a CR/CRh rate of 12% using the two-sided 95% exact CI when the CR/CRh rate of ASP2215 is assumed to be 21%.

The planned sample size with 258 EFS events would provide about 90% power to detect the difference in EFS (6 months median EFS for ASP2215 arm and 3.9 months for salvage chemotherapy arm with HR = 0.65) and > 90% power to detect a difference in CR rate between ASP2215 (with 25% CR rate) and the salvage chemotherapy (with 10% CR rate) at the overall 1-sided 0.0245 significance level.

Randomisation

Subjects were randomized in a 2:1 ratio via an interactive response technology (IRT) to receive ASP2215 or salvage chemotherapy. Randomization was stratified by response to first-line AML therapy and pre-selected salvage chemotherapy.

Prior therapy and response: Primary refractor without HSCT; Relapse within 6 months after CRc and no HSCT ; Relapse within 6 months after allogeneic HSCT; Relapse after 6 months after CRc and no HSCT; Relapse after 6 months after allogeneic HSCT.

Pre-selected chemotherapy (preselected before randomization in both arms): High-intensity chemotherapy (MEC; FLAG-IDA); Low-intensity chemotherapy (LoDAC, Azacitidin).

Blinding (masking)

This was an open-label study.

Statistical methods

Primary Hypothesis

The primary efficacy endpoint of comparing OS in the intention to treat (ITT) population between ASP2215 and the selected salvage chemotherapies had the null and alternative hypotheses:

H_{01}: OS in ASP2215 is worse or equal to the OS in salvage chemotherapy

H_{11}: OS in ASP2215 is better than the OS in salvage chemotherapy

This was tested only at the second interim and final analyses, using the stratified log-rank test (primary test) with strata used in randomization to control for response to first-line AML therapy and preselected salvage chemotherapy. The HR of the treatment effect along with 95% CI was calculated by the stratified Cox proportional hazard model using the same stratification factors.

Sensitivity analyses for OS included the same analysis as primary analysis but on FAS or per protocol set (PPS), or censoring for HSCT or new antileukemia therapy, and stratified Cox proportional hazard models with strata to control for response to first line AML therapy and preselected salvage chemotherapy on ITT, and optionally initiation of new antileukemia therapy as a time-dependent binary covariate on ITT. An additional sensitivity analysis, weighted differences of Kaplan–Meier curves with estimation of difference of Restricted Mean Survival Time (RMST) and its 95% CI by a pre-specified cut-off time at 18 months was carried out.

Further sensitivity analyses were conducted to explore the impact of early censoring, predominantly affecting the chemotherapy arm (see section on ancillary analyses). Analyses covering both the first 8 weeks (EC8) (1 vs 10 censorings in the gilteritinib vs chemotherapy arm) and the first 6 months (EC6M) (6 vs 15 censorings in the gilteritinib vs chemotherapy arms) were performed, using "Bootstrap resampling" and "Tipping point analysis" (Zhao, et al 2014).

The bootstrap resampling analysis was based on a neutral assumption that the survival risk of eraly censored patients was comparable with the survival risk of patients with non- early censoring (by same treatment and stratum).

The tipping point analysis covered the same neutral scenario as the bootstrap resampling, assuming equal hazard for imputed and remaining patients (Θ = 1) (by treatment and strata). In addition, several more conservative assumptions were made, i.e. the analysis imputing censoring up to 6 months included a scenario where a 3- fold decrease in survival risk was assumed for the censored patients in the gilteritinib (Θ = 3) arm combined with an increase of survival risk in the censored patients in the chemotherapy arm (Θ = from 0.1). For this analysis a >85% rejection rate of the null hypothesis with Θ ≥ 0.5 for the chemotherapy arm was reported.

For the first interim analysis, CR/CRh was a co-primary efficacy endpoint. The two-sided 95% exact CI of CR/CRh rate was planned to be calculated for approximately 141 subjects who were randomized into ASP2215 arm and at least 112 days (4 treatment cycles) post first dose, or randomization for subjects who received no study drug, i.e. ASP2215 subjects in the response analysis set (RAS). The lower limit of the 95% CI was compared to the benchmark CR/CRh rate of 12%.

Handling of missing data

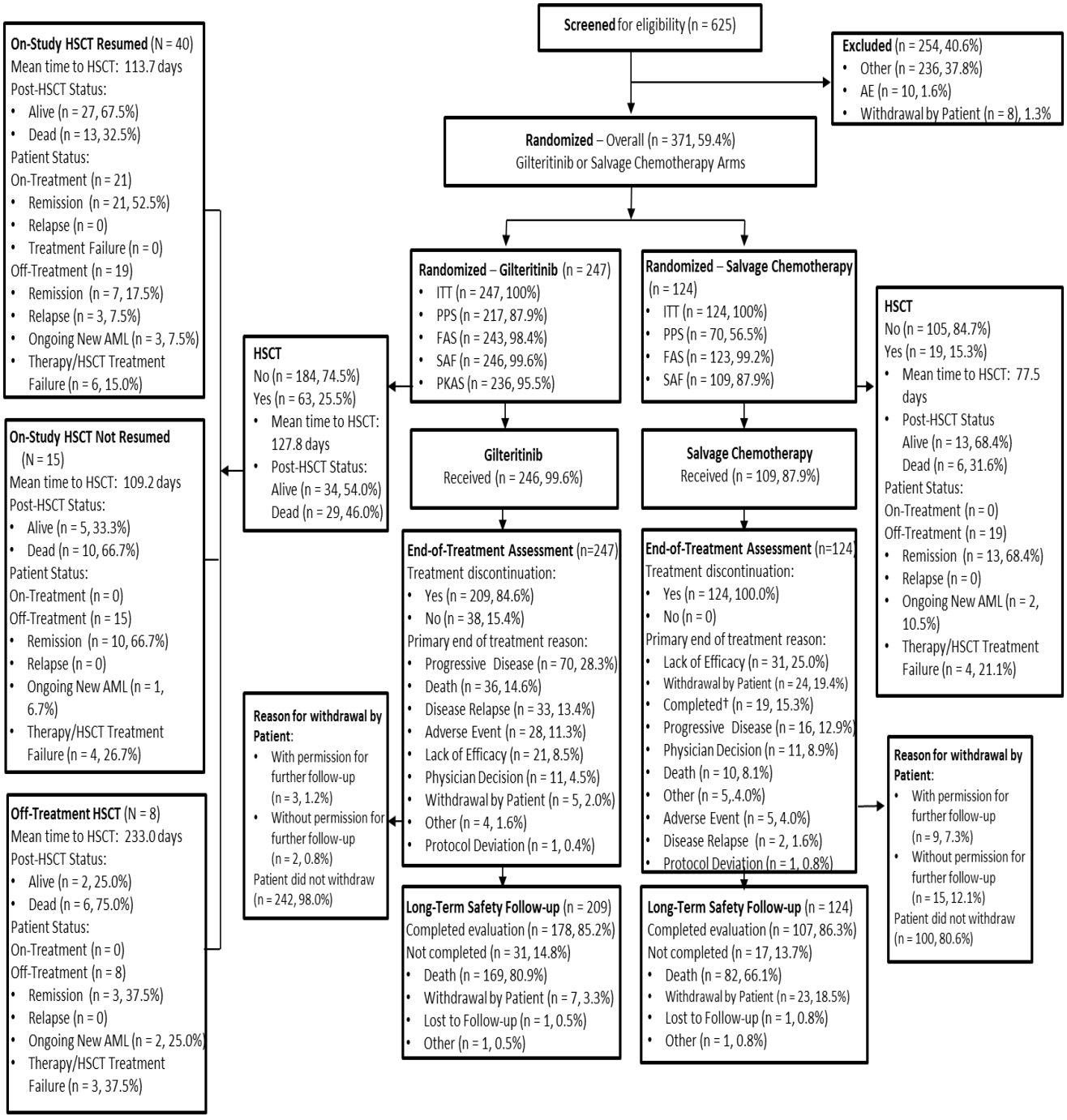
For primary endpoint OS, missing or incomplete death date was imputed as the earliest possible date on or after the date of last contact compatible with the (partial) information available. Partial relapse dates was imputed to the first day of the month of the missing parameter but not earlier than the last disease assessment date. A month and year had to be present or the date was to remain missing.

Missing centrally evaluated bone marrow assessment were imputed with local bone marrow assessment. Non-responder imputation was used for binary response variables.

For OS and EFS analyses, if all events were from one treatment group in at least one stratum combination, or the Cox proportional hazard model did not converge due to small event size in some stratum combinations, the stratum combinations were planned to be pooled as needed, first by successively decreasing the number of levels of response to first-line therapy to three, two and one, and secondly by pooling across preselected chemotherapies.

Results

Participant flow (Study 2215-CL-0301)



Recruitment

The study initiation date (date of first evaluation) was 20 October 2015. The final analysis data cut-off date was 17 September 2018.

Conduct of the study

Protocol Amendments: The protocol (Original Version) was dated 24 March 2015. As of the final analysis data cut-off date of 17 September 2018, there were 8 substantial amendments (listed below) to the protocol in addition to 3 non-substantial amendments.

Substantial Amendment 1 dated 22 June 2015

- The entry criteria were modified:

Inclusion Criterion No. 2 was modified to clarify the eligibility age; Inclusion Criterion No. 4 (second bullet) was modified to define "relapsed after first-line therapy" as untreated relapse patients who had achieved CR/CRi/CRp with first-line treatment and had hematologic relapse; Exclusion Criterion No. 4 was modified to exclude patients who experienced a hematologic relapse after their second or later line of treatment or who received salvage therapy for refractory disease; Exclusion Criterion No. 12 was modified to clarify that patients were excluded if they required treatment with concomitant drugs that are strong inducers of cytochrome P450 (CYP) 3A; A separate exclusion criterion (Criterion No. 13) was added to exclude patients who required treatment with concomitant drugs that are strong inhibitors or inducers of P-glycoprotein (P-gp) or substrates of multidrug and toxin extrusion protein 1 (MATE1) with the exception of drugs that were considered absolutely essential for the care of the patient; An exclusion criterion (Criterion No. 19) was added to exclude patients with active GVHD or who were on treatment with corticosteroids for GVHD.

- The treatment discontinuation criteria were amended:

A discontinuation criterion was added to define lack of efficacy for a patient who was receiving LoDAC, azacitidine or gilteritinib; A discontinuation criterion was modified to clarify that use of hydroxyurea was not a reason for discontinuation; Monitoring for the development of hyperuricemia was added; PRO measurements of BFI, FACT-leu, FACIT-Dys-SF and dizziness/mouth sore were removed from the 30-day follow-up assessment; Clinical efficacy and safety information were updated; The guidelines for gilteritinib dose interruption or reduction were revised by deleting the requirement for 48 hours duration of Grade 3 AEs to interrupt dosing and state that treatment with gilteritinib was interrupted for any related Grade 3 AE; The definition of transfusion independence was changed from 4 weeks to 1 week without red blood cell transfusion and 1 week without platelet transfusion for the CR criterion; No patients were included at time of implementation of Substantial Amendment 1.

Substantial Amendment 2 dated 13 August 2015

The exclusion criteria were modified: Exclusion Criterion No.12 was added to exclude patients with mean QTcF > 450 msec at screening based on central reading; Exclusion Criterion No.13 was added to exclude patients with Long QT Syndrome at screening; Exclusion Criterion No.14 was added to exclude patients with hypokalaemia and hypomagnesemia at screening; HSCT was removed from the discontinuation criteria; 12-lead ECG and pharmacokinetic sampling was added (whole blood samples for plasma pharmacokinetic) to occur on day 8 ± 1 pre-dose; A confirmatory ECG that was to be performed on day 9 and an investigator assessment to consider a dose reduction for a patient if the mean QTcF for a patient from day 1 to day 8 had increased > 30 msec with no other known aetiology was added; The mean QTcF of the triplicate ECG tracings based on central reading was clarified to be used for all treatment decisions; The statement regarding relationship between QTcF interval prolongation and gilteritinib plasma concentrations was updated; A criterion to the dose medication modification category was added to consider reducing the dose of gilteritinib if the mean QTcF from day 1 to day 8 had increased > 30 msec, which was confirmed on day 9 without any other aetiology.

Country-specific Substantial Amendment 3 (Korea) dated 8 October 2015

Inclusion criterion No. 5 was modified to describe the FLT3 mutation types as ITD alone or ITD with concurrent TKD.

Substantial Amendment 4 dated 9 December 2015

Clarification that if bone cellularity was between 5% and 20%, the investigator should have determined whether a patient should have received another treatment cycle was provided; The description of acceptable contraception methods was changed for females in inclusion Criterion No. 10 and for males and their spouse/partners in inclusion Criterion No. 13; The mean of triplicate QTcF > 450 msec was clarified to be cause for exclusion in Criterion No. 12 and the terminology for Long QT Syndrome in exclusion Criterion No. 13 was modified. A precaution regarding the use of gilteritinib with concomitant medications that are known to prolong QT or corrected QT interval (QTc) was added and further instructions were provided to the investigator to check each patient's concomitant drugs for those that might have prolonged QT or QTc interval. A guideline for gilteritinib dose interruption and dose reduction if a patient had a mean of triplicate QTcF > 500 msec was added; The discontinuation criterion that patients receiving MEC or FLAG-IDA who had NR or progressive disease should have been discontinued if it occurred following cycle 1 was clarified.

Country-Specific Substantial Amendment 5 (Korea) dated 31 March 2016

Inclusion Criteria No. 10 and No. 13 were clarified to include all highly effective contraception examples for females and males and their spouse/partners.

Country-specific Substantial Amendment 6 (France) dated 22 June 2016

Language clarifying local requirements for inclusion and exclusion criteria was added: Per local regulations, patients must have consented personally, patients too young or incapable of personal consent were excluded, and patients must have participated in a national social security scheme.

Substantial Amendment 7 dated 8 August 2016

The long-term follow-up was clarified to be every 3 months for up to 3 years from the patient's end of treatment visit; Midostaurin was included as a permitted prior treatment in exclusion Criterion No. 7; Patients with disallowed FLT3 mutation types (exclusion Criterion No. 23) were excluded; patients were included on the basis of local laboratory testing for allowed FLT3 mutation types (inclusion Criterion No. 5). If a subject is enrolled from a local FLT3 test result, the local test must have been performed after the subject's last interventional treatment. A subject's disease's clonal architecture or allelic ratio may have changed because of treatment and may no longer be FLT3 mutation positive. This could result in a negative FLT3 result from the central lab; Exclusion of MATE1 substrates as a concomitant medication restriction was deleted. Donor lymphocyte infusion as an allowed concomitant treatment for AML was included; Discontinuation criteria were clarified to include language stating that patients were eligible to continue treatment until a discontinuation criterion was met or gilteritinib gained a marketing authorization and became commercially available; HR in the interim analysis was included; Disease assessment from bone marrow samples was clarified to only be required for MEC and FLAG-IDA treatment per institutional guidelines on cycle 1 day 15 or later; Gilteritinib clinical and pharmacokinetic data from the 02 Feb 2015 cut-off was updated with data from the 31 Oct 2015 cut-off; Instructions to investigators regarding gilteritinib dose reduction and interruptions were clarified; Methodology for assessment of exposure and compliance were clarified; Laboratory tests administered were updated with the addition of thyroxine, thyroid-stimulating hormone and aPPT. Language to clarify that 2 laboratories were assaying bone marrow samples for different parameters was added; Purposes and conditions of the PGx substudy participation were updated to clarify that genes of relevance to AML patients may be

analyzed in relationship to gilteritinib treatment, and that consenting patients may (instead of will) participate.

Early after implementation of this amendment, a non-substantial amendment was implemented (27 September 2016).

Substantial Amendment 8 dated 20 September 2017

A co-primary objective for Interim Analysis 1 and updated response definitions were added. Co-primary objective of CR/CRh was added including a formal interim analysis for the co-primary endpoint; The secondary objectives and endpoints were updated. Two new secondary objectives/endpoints were added to the study. These secondary objectives are to evaluate the efficacy and safety of ASP2215 therapy versus salvage chemotherapy in terms of: (1) complete remission with partial hematologic recovery (CRh) rate and (2) transfusion conversion rate; transfusion maintenance rate; Additional language was added to describe the collection of concomitant medications; Additional language was added to describe the collection of AEs for patients who underwent HSCT; Statistical analyses for key secondary efficacy endpoints, secondary endpoints and exploratory endpoints were updated.

Protocol Deviations

Overall (for the ITT) as of the final analysis data cut-off date, 11.6 % (43/371) of patients had a protocol deviation.

Table 27 Summary of Protocol Deviations – All Randomized Patients (Study 2215-CL-0301)

Deviation Code, n (%)	Gilteritinib (n = 247)	Chemotherapy (n = 124)	Total (n = 371)
Any deviation†	29 (11.7)	14 (11.3)	43 (11.6)
Entered into the study even though they did not satisfy entry criteria	21 (8.5)	11 (8.9)	32 (8.6)
Received excluded concomitant treatment	6 (2.4)	3 (2.4)	9 (2.4)
Developed withdrawal criteria during the study and were not withdrawn	2 (0.8)	0	2 (0.5)

† No patients met the protocol deviation criteria of received wrong treatment or incorrect dose.

Baseline data

Table 28 Demographic and Baseline Characteristics – ITT (Study 2215-CL-0301)

Parameter Category/Statistic	Gilteritinib 120 mg (n = 247)	Chemotherapy (n = 124)	Total (n = 371)
Sex, n (%)			
Female	131 (53.0)	70 (56.5)	201 (54.2)
Male	116 (47.0)	54 (43.5)	170 (45.8)
Ethnicity, n (%)			
Not Hispanic or Latino	221 (93.6)	116 (96.7)	337 (94.7)
Hispanic or Latino	12 (5.1)	2 (1.7)	14 (3.9)
Unknown	3 (1.3)	2 (1.7)	5 (1.4)
Missing	11	4	15
Race, n (%)			
White (Caucasian)	145 (60.9)	75 (62.5)	220 (59.3)
Asian	69 (29.0)	33 (27.5)	102 (27.5)
Black or African American	14 (5.9)	7 (5.8)	21 (5.7)
Native Hawaiian or Other Pacific Islander	1 (0.4)	0	1 (0.3)
Unknown	4 (1.7)	4 (3.3)	13 (3.5)
Other	5 (2.1)	1 (0.8)	15 (4)
Missing	9	4	13
Age (Years)			
Mean (SD)	59.0 (14.6)	57.6 (14.8)	58.5 (14.7)
Median (min, max)	62.0 (20, 84)	61.5 (19, 85)	62.0 (19, 85)
Age Group (Years), n (%)			
< 65	141 (57.1)	75 (60.5)	216 (58.2)
≥ 65	106 (42.9)	49 (39.5)	155 (41.8)
Region, n (%)			
North America	114 (46.2)	52 (41.9)	166 (44.7)
Europe (Including Turkey, Israel)	68 (27.5)	43 (34.7)	111 (29.9)
Asia	65 (26.3)	29 (23.4)	94 (25.3)
Baseline ECOG, n (%)			
0-1	206 (83.4)	105 (84.7)	311 (83.8)
≥ 2	41 (16.6)	19 (15.3)	60 (16.2)
Weight (kg)			
n	243	124	367
Mean (SD)	72.79 (20.47)	69.91 (19.73)	71.82 (20.25)
Median (min, max)	71.00 (39.0, 157.1)	67.00 (36.5, 157.9)	70.00 (36.5, 157.9)
Height (cm)			
n	234	123	357
Mean (SD)	167.25 (10.31)	166.39 (10.63)	166.95 (10.41)
Median (min, max)	167.00 (140.0, 193.0)	166.00 (137.5, 191.0)	166.50 (137.5, 193.0)
Table continued on next page			
FLT3 Mutation Status by Central Testing by FLT3 CDx, n (%)			
FLT3-ITD alone	215 (87.0)	113 (91.1)	328 (88.4)
FLT3-TKD alone	21 (8.5)	10 (8.1)	31 (8.4)
FLT3-ITD and FLT3-TKD	7 (2.8)	0	7 (1.9)
Others (negative)	4 (1.6)	1 (0.8)	5 (1.3)

Parameter Category/Statistic	Gilteritinib 120 mg (n = 247)	Chemotherapy (n = 124)	Total (n = 371)
Prior Use of FLT3 Inhibitor, n (%)†			
No	215 (87.0)	110 (88.7)	325 (87.6)
Yes	32 (13.0)	14 (11.3)	46 (12.4)
Cytogenetic Risk Status, n (%)			
Intermediate	182 (73.7)	89 (71.8)	271 (73.0)
Unfavorable	26 (10.5)	11 (8.9)	37 (10.0)
Favorable	4 (1.6)	1 (0.8)	5 (1.3)
Other‡	35 (14.2)	23 (18.5)	58 (15.6)

† Prior use of FLT3 inhibitor is defined as 'Yes' if patients received prior AML therapy of midostaurin, sorafenib or quizartinib; otherwise, prior use of FLT3 inhibitor is assigned as 'No'; ‡ The category of “Other” includes those with cytogenetic risk status that cannot be categorized as favorable, intermediate or unfavorable.

Table 29 Targeted disease history – Intention to Treatment Set (Study 2215-CL-0301)

Parameter Category/Statistic	Gilteritinib 120 mg (n = 247)	Chemotherapy (n = 124)	Total (n = 371)
Duration of Disease (months)			
Mean (SD)	7.37 (7.21)	8.07 (9.67)	7.60 (8.11)
Median (min, max)	5.80 (0.6, 65.1)	5.30 (0.5, 52.0)	5.60 (0.5, 65.1)
Antecedent Hematological Disorder, n (%)			
No	206 (83.4)	113 (91.1)	319 (86.0)
Yes	41 (16.6)	11 (8.9)	52 (14.0)
Type of Hematological Disorder, n (%)†			
MDS	34 (13.8)	8 (6.5)	42 (11.3)
Other	7 (2.8)	3 (2.4)	10 (2.7)
Central Nervous System Leukemia, n (%)			
No	244 (98.8)	122 (98.4)	366 (98.7)
Yes	3 (1.2)	2 (1.6)	5 (1.3)
Rapidly Progressing Disease, n (%)			
No	133 (53.8)	69 (55.6)	202 (54.4)
Yes	113 (45.7)	55 (44.4)	168 (45.3)
Other Disease Characteristics, n (%)			
Untreated relapse AML	151 (61.1)	75 (60.5)	226 (60.9)
Primary refractory AML	96 (38.9)	49 (39.5)	145 (39.1)
Median number of relapses (range)	1 (0, 2)	1 (0, 2)	1 (0, 2)
Number of relapses, n (%)			
0	96 (38.9)	49 (39.5)	145 (39.1)
1	147 (59.5)	72 (58.1)	219 (59.0)
2	4 (1.6)	3 (2.4)	7 (1.9)
> 2	0	0	0
WHO Classification, n (%)			
AML with recurrent genetic abnormalities			
AML with mutated NPM1	83 (33.6)	37 (29.8)	120 (32.3)
AML with myelodysplasia-related changes	33 (13.4)	10 (8.1)	43 (11.6)

AML with t(8;21)(q22;q22), RUNX1-RUNX1T1	5 (2.0)	5 (4.0)	10 (2.7)
AML with t(6;9)(q23;q34); DEK-NUP214	5 (2.0)	3 (2.4)	8 (2.2)
AML with mutated CEBPA	4 (1.6)	1 (0.8)	5 (1.3)
AML with t(9;11)(q22;q23); MLLT3-MLL	2 (0.8)	2 (1.6)	4 (1.1)
AML with inv(3)(q21q26.2) or t(3;3)q(21;q26.2); RPN1-EVI1	1 (0.4)	0	1 (0.3)
AML (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1	1 (0.4)	0	1 (0.3)
AML not otherwise categorized			
AML without maturation	34 (13.8)	23 (18.5)	57 (15.4)
AML with maturation	30 (12.1)	9 (7.3)	39 (10.5)
Acute myelomonocytic leukemia	20 (8.1)	10 (8.1)	30 (8.1)
Acute monoblastic/monocytic leukemia	20 (8.1)	14 (11.3)	34 (9.2)
AML minimally differentiated	16 (6.5)	10 (8.1)	26 (7.0)
Acute erythroid leukemia			
Erythroleukemia, erythroid/myeloid	1 (0.4)	2 (1.6)	3 (0.8)
Myeloid Sarcoma	0	1 (0.8)	1 (0.3)
FAB Classification Subtype, n (%)			
Unknown	74 (30.0)	25 (20.2)	99 (26.7)
M1: Acute myeloblastic leukemia, without maturation	45 (18.2)	35 (28.2)	80 (21.6)
M2: AML with differentiation	51 (20.6)	17 (13.7)	68 (18.3)
M4: Acute myelomonocytic leukemia	33 (13.4)	21 (16.9)	54 (14.6)
M5: Acute monoblastic leukemia	27 (10.9)	14 (11.3)	41 (11.1)
M0: Minimally differentiated acute myeloblastic leukemia	15 (6.1)	9 (7.3)	24 (6.5)
M6: Acute erythroid leukemia	2 (0.8)	3 (2.4)	5 (1.3)
Risk Status With Specific Cytogenetic Patterns, n (%)			
Intermediate: Normal	163 (66.0)	78 (62.9)	241 (65.0)
Unknown Risk	32 (13.0)	17 (13.7)	49 (13.2)
Unfavorable: Complex	18 (7.3)	6 (4.8)	24 (6.5)
Intermediate: + 8	11 (4.5)	9 (7.3)	20 (5.4)
Other Risk	8 (3.2)	8 6.5)	16 (4.3)
Favorable: t(8;21)	3 (1.2)	2 (1.6)	5 (1.3)
Unfavorable: del7q	4 (1.6)	0	4 (1.1)
Unfavorable: - 7	3 (1.2)	1 (0.8)	4 (1.1)
Intermediate: - y	3 (1.2)	0	3 (0.8)
Unfavorable: del5q	2 (0.8)	1 (0.8)	3 (0.8)
Intermediate: + 6	1 (0.4)	1 (0.8)	2 (0.5)
Unfavorable: - 5	1 (0.4)	0	1 (0.3)
Favorable: inv(16)	1 (0.4)	0	1 (0.3)
Favorable: t(16;16)	0	1 (0.8)	1 (0.3)

†Only for patients who had antecedent hematological disorder.

Table 30 Baseline Stratification Factors Based on IRT – Intention to Treatment Set, (Study 2215-CL-0301)

Parameter Category	Gilteritinib 120 mg (n = 247) n (%)	Chemotherapy (n = 124) n (%)	Total (n = 371) n (%)
Response to First-line Therapy			
Primary refractory without HSCT	98 (39.7)	48 (38.7)	146 (39.4)
Relapse within 6 months after CRc and no HSCT	67 (27.1)	34 (27.4)	101 (27.2)
Relapse after 6 months after CRc and no HSCT	34 (13.8)	17 (13.7)	51 (13.7)
Relapse within 6 months after allogeneic HSCT	31 (12.6)	17 (13.7)	48 (12.9)
Relapse after 6 months after allogeneic HSCT	17 (6.9)	8 (6.5)	25 (6.7)
Preselected Salvage Chemotherapy			
High-intensity chemotherapy	149 (60.3)	75 (60.5)	224 (60.4)
Low-intensity chemotherapy	98 (39.7)	49 (39.5)	147 (39.6)
Response to First-Line Therapy, Preselected Salvage Chemotherapy			
Primary refractory without HSCT, high-intensity chemotherapy	57 (23.1)	28 (22.6)	85 (22.9)
Primary refractory without HSCT, low-intensity chemotherapy	41 (16.6)	20 (16.1)	61 (16.4)
Relapse within 6 months after CRc and no HSCT, high-intensity chemotherapy	40 (16.2)	21 (16.9)	61 (16.4)
Relapse within 6 months after CRc and no HSCT, low-intensity chemotherapy	27 (10.9)	13 (10.5)	40 (10.8)
Relapse after 6 months after CRc and no HSCT, high intensity chemotherapy	23 (9.3)	11 (8.9)	34 (9.2)
Relapse within 6 months after allogeneic HSCT, low-intensity chemotherapy	16 (6.5)	9 (7.3)	25 (6.7)
Relapse within 6 months after allogeneic HSCT, high-intensity chemotherapy	15 (6.1)	8 (6.5)	23 (6.2)
Relapse after 6 months after allogeneic HSCT, high-intensity chemotherapy	14 (5.7)	7 (5.6)	21 (5.7)
Relapse after 6 months after CRc and no HSCT, low-intensity chemotherapy	11 (4.5)	6 (4.8)	17 (4.6)
Relapse after 6 months after allogeneic HSCT, low-intensity chemotherapy	3 (1.2)	1 (0.8)	4 (1.1)

Numbers analysed

The following study populations were used for analysis of efficacy data:

The ITT population consisted of all patients who were randomized (gilteritinib N = 247; salvage chemotherapy N = 124).

The FAS consisted of all randomized patients with an FLT3 mutation detected by the FLT3 CDx and was used for sensitivity analyses of efficacy data in interim analysis 2 and the final analysis (gilteritinib N = 243; salvage chemotherapy N = 123).

The RAS consisted of patients who were at least 112 days past the first dose of gilteritinib or randomization (for patients who did not receive gilteritinib). It was defined only for interim analysis 1, where it was used for efficacy analyses (gilteritinib N = 142).

The PPS included all patients of the ITT who did not meet any of the protocol defined criteria for exclusion. The PPS was used for sensitivity analyses of efficacy data (gilteritinib arm N = 217; salvage chemotherapy arm N = 124).

The mRAS was defined for Interim Analysis 1 only, where it was used for sensitivity analyses. Included all patients of the RAS who did not meet any 1 of the exclusion criteria listed for PPS, with the criteria on FLT3 mutation modification to "No central FLT3 mutation at baseline" (gilteritinib arm N = 124).

The safety analysis set (SAF) consisted of all subjects who received at least one dose of study treatment (ASP2215 or salvage chemotherapy) and was used for all safety variables (gilteritinib N = 246; salvage chemotherapy N = 109).

The pharmacokinetic analysis set (PKAS) consisted of the subset of the SAF for which at least 1 plasma concentration data is available and for whom the time of dosing on the day of sampling is known.

Outcomes and estimation

- *Primary endpoint - Overall survival (OS)*

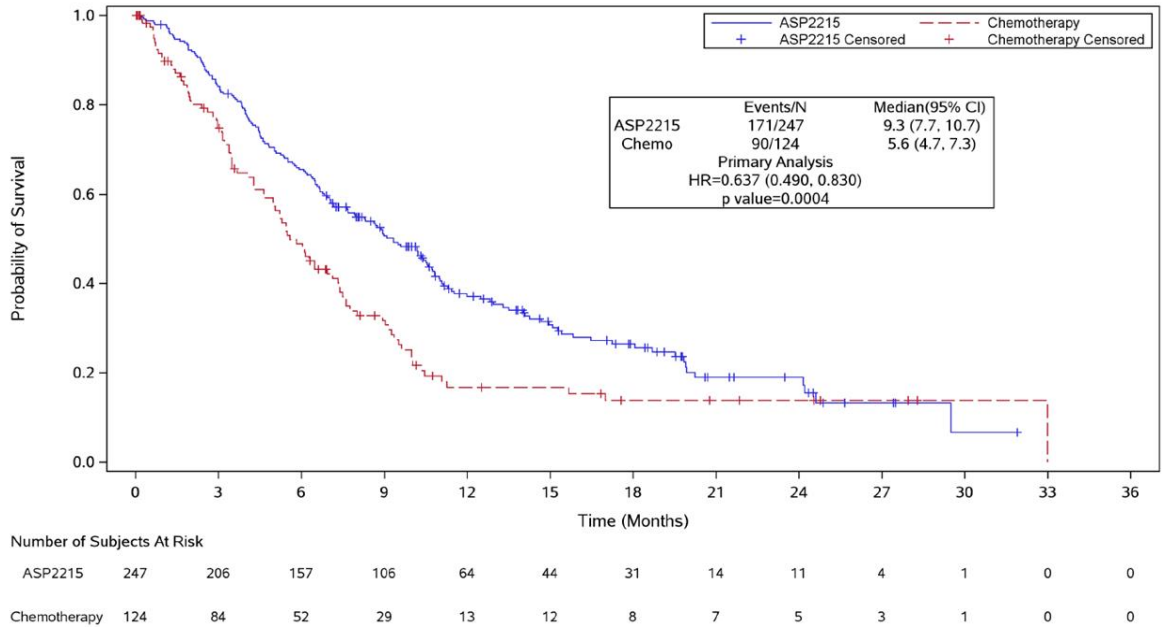
OS analyses for the ITT population are shown in Table 31.

Table 31 Overall Survival ITT (Study 2215-CL-0301) (Data cut 17 September 2018)

Category/ Statistics	Gilteritinib 120 mg (n = 247)	Chemotherapy (n = 124)
Patient Status, n (%)		
Death events	171 (69.2)	90 (72.6)
Censored events	76 (30.8)	34 (27.4)
Duration of Overall Survival, Month†		
Q1 (95% CI)	4.4 (3.8, 5.1)	3.0 (1.9, 3.5)
Median (95% CI)	9.3 (7.7, 10.7)	5.6 (4.7, 7.3)
Q3 (95% CI)	18.7 (14.9, 24.1)	10.0 (8.0, 15.7)
Range‡	0.2, 31.9+	< 0.1+, 33.0
Stratified Analysis (Primary)§		
Log-rank test: P-value [1-sided P-value]	0.0007 [1-sided P-value: 0.0004]	
Wald test: P-value¶	0.0008	
Hazard ratio (95% CI)¶	0.637 (0.490, 0.830)	
Unstratified Analysis		
Log-rank test (P-value)	0.0005	
Wald test: P-value¶	0.0006	
Hazard ratio (95% CI)¶	0.636 (0.491, 0.823)	
Overall Survival Rate % (95% CI)††		
6 months	65.5 (59.2, 71.1)	48.9 (39.3, 57.8)
12 months	37.1 (30.7, 43.6)	16.7 (9.9, 25.0)
24 months	19.0 (12.8, 26.0)	13.8 (7.5, 22.0)
36 months	NE (NE, NE)	0 (NE, NE)
Overall Survival Sensitivity Analysis With Patients Censored at HSCT		
Patient Status, n (%)		
Death events	142 (57.5)	84 (67.7)
Censored events	105 (42.5)	80 (32.3)
Duration of Overall Survival, Months†		
Q1 (95% CI)	4.1 (3.6, 4.6)	3.0 (1.9, 3.5)
Median (95% CI)	8.3 (6.7, 10.2)	5.3 (4.3, 6.1)
Q3 (95% CI)	14.9 (11.1, 18.7)	8.9 (7.3, 9.6)
Range‡	0.2, 27.4+	< 0.1+, 33.0
Stratified Analysis§		
Log-rank test: 1-sided P-value	0.0001 [1-sided P-value: < 0.0001]	
Wald Test: P-Value¶	0.0001	
Hazard ratio (95% CI)¶	0.575 (0.434, 0.762)	
Overall Survival Rate % (95% CI)††		
6 months	62.1 (55.1, 68.4)	43.5 (33.2, 53.4)
12 months	30.5 (23.2, 38.0)	8.7 (3.6, 16.5)
24 months	13.2 (7.3, 20.9)	5.4 (1.6, 12.6)
36 months	NE (NE, NE)	0 (NE, NE)

†Based on Kaplan-Meier estimates; ‡A "+" indicates censoring; §Stratification factors were response to first-line AML therapy and preselected salvage chemotherapy per IRT;m; ¶Based on Cox proportional hazards model. Assuming proportional hazards, an HR of < 1 indicates a reduction in the hazard rate in favor of the gilteritinib arm; ††Survival rate and 95% CI were estimated using the Kaplan-Meier method and the Greenwood formula.

Figure 5 Kaplan-Meier Plot of Overall Survival by Treatment Arm (ITT) (Study 2215-CL-0301)

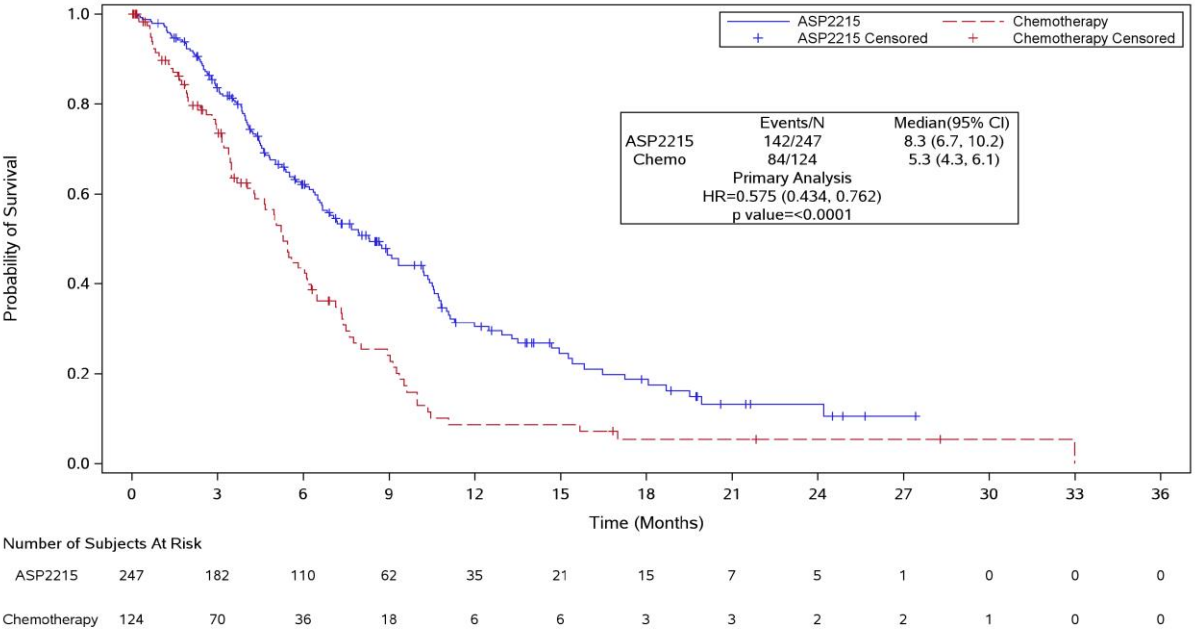


All patients who were randomized (Intention to Treatment Set).

Note: 1-sided P-value is from stratified log-rank test.

ASP2215: gilteritinib; Chemo: chemotherapy; CI: confidence interval; HR: hazard ratio; N: total number of patients.

Figure 6 Kaplan-Meier Plot of OS by Treatment Arm Censoring at HSCT (ITT) (Study 2215-CL-0301)



- *Key secondary endpoint: Complete response rates*

Table 32 Summary of CR Rate (Study 2215-CL-0301)

Parameter Category/Statistics	Gilteritinib (n = 247)	Chemotherapy (n = 124)
Primary Analysis, ITT		
CR Rate, n/N (%) [95% CI]†	52/247 (21.1) [16.1, 26.7]	13/124 (10.5) [5.7, 17.3]
Adjusted treatment difference % [95% CI]‡	10.6 [2.8, 18.4]	
Stratified P-value (primary) [1-sided P-value]‡	0.0106 [1-sided P-value: 0.0053]	
Unstratified P-value [1-sided P-value]§	0.0134 [1-sided P-value: 0.0067]	
Sensitivity Analysis, ITT and Received at Least 1 Dose of Study Drug		
CR Rate, n/N (%) [95% CI]†	52/246 (21.1) [16.2, 26.8]	13/109 (11.9) [6.5, 19.5]
Adjusted treatment difference % [95% CI]‡	9.3 [1.0, 17.6]	
P-value‡	0.0348	
Sensitivity Analysis, ITT With at Least 1 Postbaseline Bone Marrow Assessment		
CR Rate, n/N (%) [95% CI]†	52/232 (22.4) [17.2, 28.3]	13/65 (20.0) [11.1, 31.8]
Adjusted treatment difference % [95% CI]‡	3.3 [-8.1, 14.7]	
P-value‡	0.5693	
Sensitivity Analysis, FAS		
CR Rate, n/N (%) [95% CI]†	50/243 (20.6) [15.7, 26.2]	13/123 (10.6%) [5.7, 17.4]
Adjusted treatment difference % [95% CI]‡	10.0 [2.2, 17.8]	
P-value‡	0.0155	
Sensitivity Analysis, PPS		
CR Rate, n/N (%) [95% CI]†	50/217 (23.0) [17.6, 29.2]	13/70 (18.6) [10.3, 29.7]
Adjusted treatment difference % [95% CI]‡	5.4 [-5.7, 16.6]	
P-value‡	0.3405	
Sensitivity Analysis, ITT, Achieving CR Prior to HSCT¶		
CR Rate, n/N (%) [95% CI]†	34/247 (13.8) [9.7, 18.7]	13/124 (10.5) [5.7, 17.3]
Adjusted treatment difference % [95% CI]‡	3.3 [-4.0, 10.5]	
P-value‡	0.3639	

†Using exact method based on binomial distribution; ‡Based on stratified Cochran-Mantel-Haenszel test. Stratification factors were response to first line AML therapy and preselected salvage chemotherapy per IRT. Treatment differences were adjusted based on pooled strata. Treatment difference = gilteritinib – chemotherapy; §Based on 2-sided Fisher's exact test; ¶The CR rate prior to HSCT was defined as the number of patients who achieved CR at any postbaseline visit prior to HSCT divided by the number of patients in the analysis population.

- *Best response rates*

Table 33 Summary of Best Response Rate – ITT (Study 2215-CL-0301)

Parameter, n (%)	Gilteritinib 120 mg (n = 247)	Chemotherapy (n = 124)
Best overall response†		
Complete remission (CR) 95%CI	52 (21.1) (16.1, 26.7)	13 (10.5) (5.7, 17.3)
Complete remission with incomplete platelet recovery (CRp)	19 (7.7)	0
Complete remission with incomplete hematological recovery (CRi)	63 (25.5)	14 (11.3)
Partial remission (PR)	33 (13.4)	5 (4.0)
No response (NR)	66 (26.7)	43 (34.7)
Not evaluable	14 (5.7)	49 (39.5)
Composite complete remission (CRc)‡	134 (54.3)	27 (21.8)
Complete remission with partial hematologic recovery (CRh) 95%CI	32 (13.0) (9.0, 17.8)	6 (4.8) (1.8, 10.2)
Complete remission and complete remission with partial hematologic recovery (CR/CRh) 95%CI	84 (34.0) (28.1, 40.3)	19 (15.3) (9.5, 22.9)

Parameter, n (%)	Gilteritinib 120 mg (n = 247)	Chemotherapy (n = 124)
Overall response rate§	167 (67.6)	32 (25.8)

†Defined as the best-measured response to treatment across all visits (in the order of CR, CRp, CRi, PR, NR and not evaluable) postbaseline. These categories were mutually exclusive; ‡Patients who achieve the best responses of CR, CRp or Cri; §Response = CRc + PR.

- *Response rates by dose*

In the gilteritinib 120 mg arm, 78 patients had a dose increase to 200 mg from 120 mg. Among those patient with a dose increase, 12 patients (15.4%) experienced CR/CRh after the dose adjustment. Fifty-eight patients had a dose decrease from 120 mg to 80 mg. Among the gilteritinib patients with a dose decrease, 24 patients (41.4%) achieved CR/CRh after the dose adjustment.

- *Event free survival (EFS) (Key secondary)*

Table 34 Event-free Survival – ITT (Study 2215-CL-0301)

Parameter Category/Statistics	Gilteritinib 120 mg (n = 247)	Chemotherapy (n = 124)
EFS Events, n (%)†	189 (76.5)	62 (50.0)
Relapse	75 (30.4)	1 (0.8)
Treatment failure	97 (39.3)	48 (38.7)
Death	17 (6.9)	13 (10.5)
Censored events	58 (23.5)	62 (50.0)
Duration of EFS, Months‡		
Q1 (95% CI)	< 0.1 (NE, NE)	< 0.1 (NE, NE)
Median (95% CI)	2.8 (1.4, 3.7)	0.7 (0.2, NE)
Q3 (95% CI)	8.3 (6.5, 12.1)	NE (3.4, NE)
Range§	< 0.1, 31.2+	< 0.1, 6.6+
Stratified Analysis (Primary)¶		
Log-rank test (primary) (P-value [1-sided P-value])	0.0830 [1-sided P-value: 0.0415]	
Wald test: P-value	0.1521	
HR (95% CI)††	0.793 (0.577, 1.089)	
Table continued on next page		
Unstratified Analysis		
Log-rank test (P-value)	0.1364	
Wald test: P-value	0.2287	
HR (95% CI)††	0.825 (0.604, 1.128)	
EFS Rate % (95% CI) ‡‡		
6 months	33.2 (27.2, 39.3)	27.1 (8.2, 50.6)
12 months	19.8 (14.6, 25.7)	NE (NE, NE)
24 months	12.2 (6.7, 19.6)	NE (NE, NE)
36 months	NE (NE, NE)	NE (NE, NE)
EFS Using the Long-term Follow-up Data of Death and New AML Therapies		
EFS Events, n (%)§§	207 (83.8)	111 (89.5)
Relapse	75 (30.4)	1 (0.8)
Relapse-off treatment	6 (2.4)	8 (6.5)
New AML therapy	3 (1.2)	26 (21.0)
Treatment failure	97 (39.3)	48 (38.7)
Death	26 (10.5)	28 (22.6)
Censored events	40 (16.2)	13 (10.5)
Duration of EFS, Months‡		
Q1 (95% CI)	< 0.1 (NE, NE)	< 0.1 (NE, NE)
Median (95% CI)	2.3 (1.4, 3.6)	0.7 (0.1, 1.3)
Q3 (95% CI)	7.4 (5.7, 10.0)	2.0 (1.7, 2.6)
Range§	< 0.1, 31.2+	< 0.1, 10.0

Parameter Category/Statistics	Gilteritinib 120 mg (n = 247)	Chemotherapy (n = 124)
Stratified Analysis (Primary)¶		
Log-rank test (primary) (P-value [1-sided P-value])	< 0.0001 (1-sided P-value: < 0.0001)	
Wald test: P-value††	< 0.0001	
HR (95% CI)††	0.499 (0.387, 0.643)	
Unstratified Analysis		
Log-rank test (P-value)	< 0.0001	
Wald test: P-value††	< 0.0001	
HR (95% CI)††	0.508 (0.397, 0.651)	
EFS Rate % (95% CI)‡‡		
6 months	30.5 (24.8, 36.3)	5.8 (2.2, 11.8)
12 months	16.3 (11.7, 21.5)	0 (NE, NE)
24 months	9.4 (5.0, 15.5)	0 (NE, NE)
36 months	NE (NE, NE)	0 (NE, NE)

percentages were calculated based on the total number of patients with nonmissing event/censored value.
†Patients were summarized under the categories that occurred first. If treatment failure and death occurred on the same day, patients were summarized under death; ‡Based on Kaplan-Meier estimates; §A "+" indicates censoring; ¶Stratification factors were response to first-line AML therapy and preselected salvage chemotherapy per interactive response technology; ††Based on the Cox proportional hazards model. Assuming proportional hazards, an HR of < 1 indicates a reduction in the hazard rate in favor of the gilteritinib arm;‡‡EFS rate and 95% CI were estimated using the Kaplan-Meier method and the Greenwood formula; §§Patients were summarized under the event categories that occurred first. If treatment failure and death occurred on the same day, patients were summarized under death.

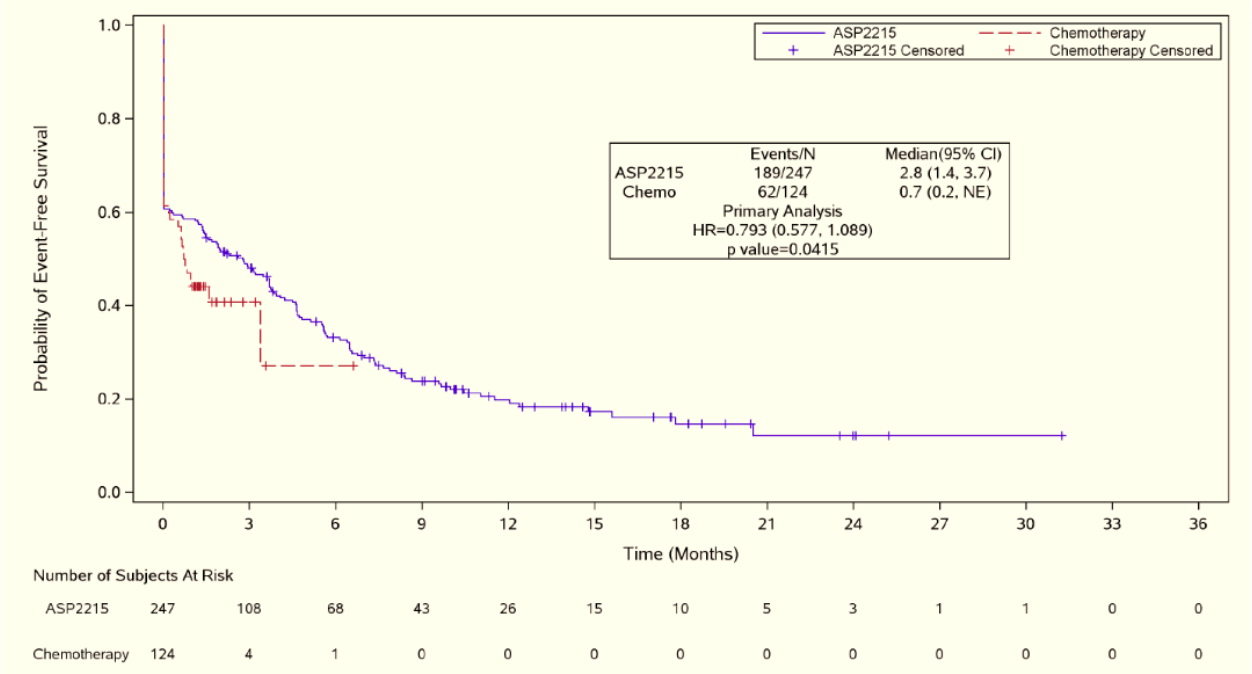


Figure 7 Kaplan-Meier Plot of EFS by Treatment Arm ITT (Study 2215-CL-0301)

- *Other secondary endpoints: Duration of response*

In the ITT population the median (95% CI) duration of CR was 14.8 (11.0, NE) months in the gilteritinib arm and 1.8 (NE, NE) in the salvage chemotherapy arm (Log-Rank test P-value = 0.1189). Results were similar in the analysis of duration of CR/CRh (median of 11 vs 1.8 months, respectively) (data not shown).

- *Transplantation rate*

The transplantation rate was 25.5% (63/247) in the gilteritinib arm and 15.3% (19/124) in the salvage chemotherapy arm. The treatment difference in transplantation rate between the gilteritinib and salvage chemotherapy arms was 10.2% (95% CI: 1.2, 19.1, p=0.0333).

Table 35 Summary of transplantation rate post randomization (ITT) (Study 2215-CL-0301)

Parameter Category/Statistics	Gilteritinib (n = 247)	Chemotherapy (n = 124)
Transplantation Rate, n (%) [95 % CI]†	63 (25.5) [20.2, 31.4]	19 (15.3) [9.5, 22.9]
Treatment difference % [95% Exact CI]‡ Unstratified 2-sided P-value§	10.2 [1.2, 19.1] 0.0333	

† Using exact method based on binomial distribution; ‡ Treatment difference = gilteritinib - chemotherapy. The 95% CIs were asymptotic confidence limits using the normal approximation to the binomial distribution; § Based on 2-sided Fisher's exact test.

Table 36 Best Overall Response Prior to HSCT (Study 2215-CL-0301)

BOR, n (%)	Gilteritinib (N = 63)	Chemotherapy (N = 19)
CRc	40 (63.5)	11 (57.9)
PR	14 (22.2)	1 (5.3)
NR or NE	9 (14.3)	7 (36.8)

BOR: best overall response; CRc: composite complete remission; HSCT: hematopoietic stem cell transplant; NE: not evaluable; NR: no response; PR: partial response. Source: Adhoc Table D60RAPP.OC.36.

- *Leukaemia free survival*

Leukaemia free survival was only applicable to patients with a best response of CRc (gilteritinib 134/247 vs salvage chemotherapy 27/124). The gilteritinib arm had a median LFS (95%CI) of 4.4 months (3.6, 5.2).

- *Transfusion conversion rate; transfusion maintenance rate*

Among the 197 patients who were dependent on RBC and/or platelet transfusions at baseline, 68 became independent of RBC and platelet transfusions during any 56-day postbaseline period; the transfusion conversion rate was 34.5% (95% CI: 27.9, 41.6)]. For the 49 patients who were independent of both RBC and platelet transfusions at baseline, 29 remained transfusion-independent during any 56-day postbaseline period; the transfusion maintenance rate was 59.2% (95% CI: 44.2, 73.0).

Table 37 Shift Table of Transfusion Status (ITT) (Study 2215-CL-0301)

Baseline Transfusion Status	Postbaseline Transfusion Status n = 246 n (%)		
	Independent	Dependent	Not Evaluable
Independent (n = 49)	29 (59.2)	12 (24.5)	8 (16.3)
Dependent (n = 197)	68 (34.5)	110 (55.8)	19 (9.6)

- *Subsequent AML therapies*

Overall in the ITT population, 114 (46.2%) subjects in the gilteritinib arm and 76 (61.3%) subjects in the salvage chemotherapy arm received subsequent AML therapy during the follow-up period, after discontinuation of the study drug. For 143 (75.3%) of the patients subsequent AML therapy regimes were not specified but recorded as «Other».

- *Exploratory endpoints: Patient reported outcomes (PRO)*

The change from baseline in BFI fatigue score, FACIT-Dys-SF and functional limitations subscales scores, FACT-Leu total score and dizziness and mouth sore subscales scores for cycle 2, day 1 were similar in the gilteritinib arm compared with the salvage chemotherapy arm. The median EQ-5D-5L VAS change from baseline score was 0 for the gilteritinib arm and -3.0 for the salvage chemotherapy arm at cycle 2, day 1. The median utility change from baseline score was 0 for the gilteritinib arm and 0.1 for the salvage chemotherapy arm at cycle 2, day 1. For each of the 5 EQ-5D-5L dimension scores, the majority of patients in both treatment arms reported no problem (score of 1) at baseline and at cycle 2, day 1.

Ancillary analyses

Sensitivity analysis of OS

Median OS was also longer in the gilteritinib arm compared with the salvage chemotherapy arm for the sensitivity analyses conducted using the FAS (HR= 0.637; 95% CI:0.488, 0.830, p= 0.0008) and by censoring patients at the time of new antileukemia therapy (HR= 0.447: 95% CI 0.312, 0.639, p< 0.0001). The PPS sensitivity analysis the showed a HR of 0.841 (95% CI: 0.600, 1.180, p=0.1577) with a median OS of 10.3 months for gilteritinib and 7.8 months for salvage chemotherapy.

Resampling and tipping-point analysis for early censored vs non-censored patients

Based on 10,000 resampled datasets, the mean HR estimate was 0.638 (95% CI: 0.605, 0.679) for the analysis covering the first 8 weeks and 0.635 (95% CI: 0.591, 0.687), for the analysis covering the first 6 months. The rejection of the null hypothesis was 100% for both scenarios.

Table 38 Bootstrapping resampling results (based on 10,000 simulation)

Scenario	Estimated HR			Median P-value	Rejection Probability†
	2.5th Percentile	Mean	97.5th Percentile		
EC8	0.605	0.638	0.679	0.0006	100%
EC6M	0.591	0.635	0.687	0.0004	100%

Table 39 Tipping point analysis based on multiple imputation of early censored patients (EC8) - probability of rejecting the null hypothesis

θ for Chemo Arm	θ for Gilteritinib Arm		
	1	2	3
3	1.00	1.00	1.00
2	1.00	1.00	1.00
1	1.00	1.00	1.00
0.9	1.00	1.00	1.00
0.8	1.00	1.00	1.00
0.7	1.00	1.00	1.00
0.6	1.00	1.00	1.00
0.5	1.00	1.00	1.00
0.4	1.00	1.00	1.00
0.3	1.00	1.00	1.00

Note: θ is the hazard ratio of overall survival of EC8 vs non-EC8 (non-early censored) patients, EC8: early censored patients within 8 weeks.

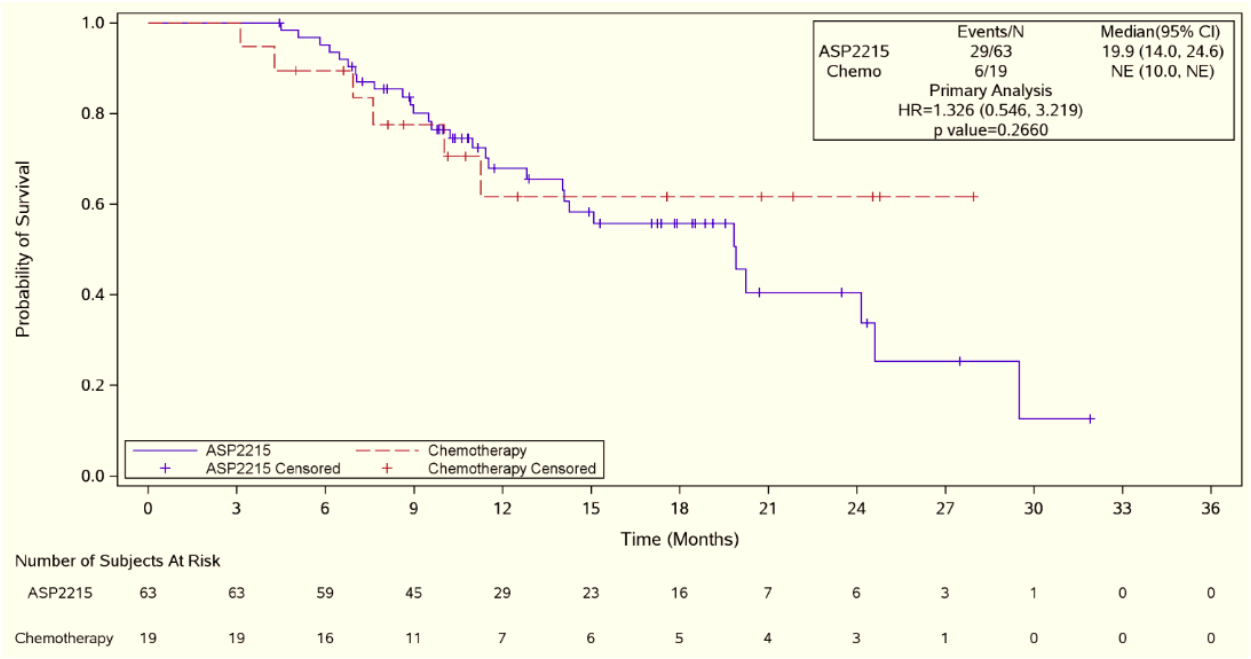
Updated OS analyses including data for previous administrative censoring

An update of the primary OS analysis based on a new data cut off 17 May 2019 was provided. The analysis included no new survival information on the early censored subjects, but several of the

previous administrative censorings had been updated, including 19 and 3 additional deaths in the gilteritinib and chemotherapy arms respectively. Results of the new OS analysis were consistent with the primary analysis (data cut of 17 Sep 2018). Median OS 9.3 and 5.4 months respectively in the gilteritinib and chemotherapy arms, HR: 0.683, 1-sided p= 0.0016 (data not shown).

OS in patients receiving HSCT

Figure 8 KM Plot of OS in Patients Receiving HSCT During Study 2215-CL-0301 in the Gilteritinib and Chemotherapy Arms – Overall – ITT, data cut-off 17-05-2019 (Study 2215-CL-0301)



The majority of patients continued gilteritinib post-HSCT (40/63, 63%). A total of 14 patients did not fulfil the criteria for re-initiation of gilteritinib (including the 8 patients receiving HSCT off-study) and in 9 patients the reason for not reintroducing gilteritinib was not known.

Subgroup analysis OS

Table 40 Subgroup Analysis of Overall Survival – ITT (Study 2215-CL-0301)

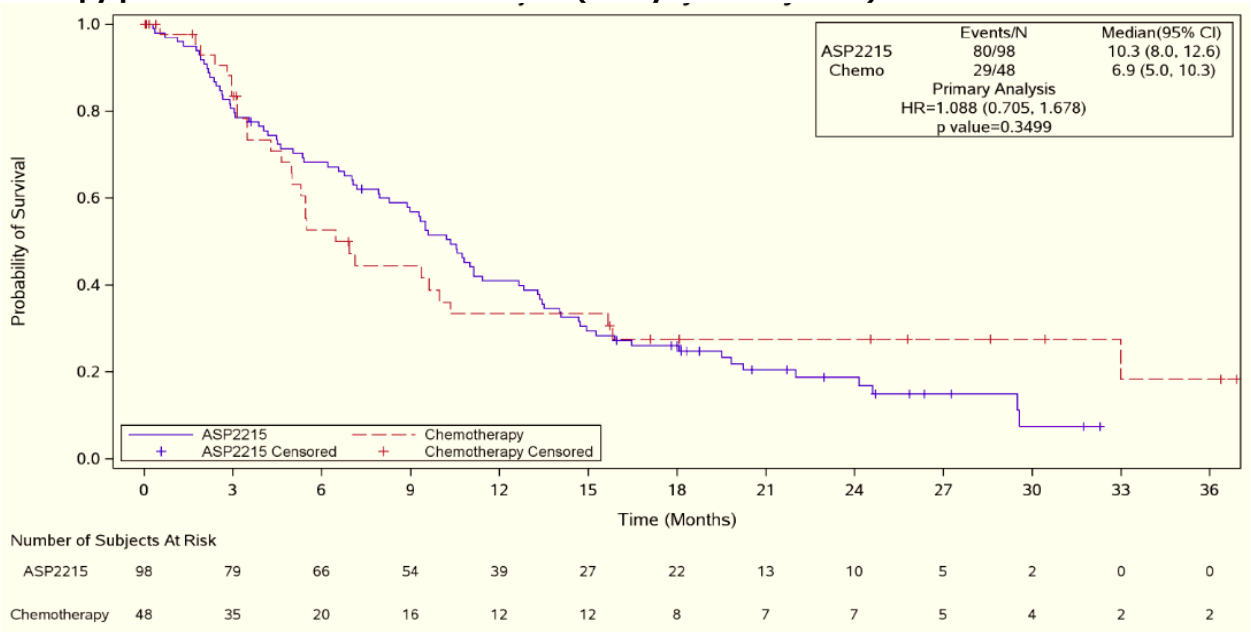
Parameter Category/ Statistics	Gilteritinib 120 mg	Chemotherapy	Hazard Ratio‡	P-value§
Overall Survival, events/N (%), [Median Months]†				
Age				
< 65 years	91/141 (64.5) [10.8]	52/75 (69.3) [6.5]	0.610 (0.432, 0.863)	0.0049
≥ 65 years	80/106 (75.5) [7.2]	38/49 (77.6) [5.1]	0.643 (0.436, 0.948)	0.0249
Sex				
Male	86/116 (74.1) [8.0]	40/54 (74.1) [6.1]	0.717 (0.491, 1.048)	0.0849
Female	85/131 (64.9) [10.8]	50/70 (71.4) [5.5]	0.573 (0.402, 0.816)	0.0018
Race				
White	102/145 (70.3) [7.9]	56/75 (74.7) [5.5]	0.723 (0.520, 1.005)	0.0526
Black or African American	13/14 (92.9) [9.6]	6/7 (85.7) [7.4]	0.538 (0.178, 1.627)	0.2649
Asian	42/69 (60.9) [11.0]	20/33 (60.6) [6.5]	0.342 (0.195, 0.602)	<0.0001
Other/Missing	14/19 (73.7) [8.3]	8/9 (88.9) [5.5]	0.872 (0.359, 2.121)	0.7631
Baseline ECOG				
0-1	138/206 (67.0) [9.6]	78/105 (74.3) [5.6]	0.595 (0.449, 0.788)	0.0003
≥ 2	33/41 (80.5) [6.4]	12/19 (63.2) [6.1]	0.868 (0.446, 1.690)	0.6761
Region				
North America	88/114 (77.2) [8.9]	42/52 (80.8) [6.2]	0.722 (0.497, 1.050)	0.0889
Europe (including Turkey and Israel)	43/68 (63.2) [7.7]	32/43 (74.4) [5.5]	0.674 (0.426, 1.066)	0.0894
Asia	40/65 (61.5) [10.8]	16/29 (55.2) [5.6]	0.378 (0.206, 0.693)	0.0011
FLT3 Mutation Type by Central Testing by FLT3 CDx				
FLT3-ITD alone	145/215 (67.4) [9.3]	81/113 (71.7) [5.6]	0.623 (0.473, 0.820)	0.0007
FLT3-TKD alone	16/21 (76.2) [8.0]	8/10 (80.0) [5.7]	0.693 (0.293, 1.643)	0.4029
FLT3-ITD and FLT3-TKD	6/7 (85.7) [10.2]	0	NE	NE
Others (negative/missing/unknown)	4/4 (100) [10.0]	1/1 (100) [7.6]	0.702 (0.062, 7.918)	0.7741

Prior use of FLT3 inhibitor				
Yes	26/32 (81.3) [6.5]	11/14 (78.6) [4.7]	0.705 (0.346, 1.438)	0.3293
No	145/215 (67.4) [9.6]	79/110 (71.8) [6.0]	0.620 (0.470, 0.818)	0.0007
Cytogenetic Risk Status				
Favorable	3/4 (75.0) [6.9]	1/1 [100) [4.6]	0.702 (0.062, 7.918)	0.7741
Intermediate	119/182 (65.4) [10.2]	63/89 (70.8) [6.1]	0.605 (0.444, 0.824)	0.0013
Unfavorable	22/26 (84.6) [6.7]	7/11 (63.6) [9.4]	1.630 (0.690, 3.848)	0.2585
Other	27/35 (77.1) [8.3]	19/23 (82.6) [3.4]	0.462 (0.254, 0.843)	0.0102
Response to First-line Therapy (per IRT)				
Relapse within 6 months after allogenic HSCT	24/31 (77.4) [6.1]	16/17 (94.1) [3.4]	0.382 (0.195, 0.747)	0.0036
Relapse after 6 months after allogenic HSCT	10/17 (58.8) [10.1]	4/8 (50.0) [11.3]	0.860 (0.264, 2.803)	0.7930
Primary refractory without HSCT	70/98 (71.4) [10.3]	28/48 (58.3) [6.9]	0.990 (0.632, 1.550)	0.9711
Relapse within 6 months after CRc and no HSCT	47/67 (70.1) [8.6]	28/34 (82.4) [5.2]	0.492 (0.304, 0.795)	0.0031
Relapse after 6 months after CRc and no HSCT	20/34 (58.8) [10.5]	14/17 (82.4) [6.1]	0.492 (0.247, 0.978)	0.0402
Preselected Chemotherapy (per IRT)				
High intensity	96/149 (64.4) [10.5]	52/75 (69.3) [6.9]	0.663 (0.471, 0.932)	0.0177
Low intensity	75/98 (76.5) [6.4]	38/49 (77.6) [4.7]	0.563 (0.378, 0.839)	0.0043

†Based on Kaplan-Meier estimates; ‡In each subgroup, the HR was estimated using unstratified Cox proportional hazards model. Assuming proportional hazards, an HR <1 indicates a reduction in hazard rate in favor of gilteritinib arm; §Based on log-rank test.

OS in patients with primary refractory disease

Figure 9 Kaplan-Meier Plot of Overall Survival – in Month Scale by Response to First-Line Therapy per IRT- data cut-off 17-05-2019 (Study 2215-CL-0301)



FLT3 TKD mutations

In the gilteritinib arm, median OS was 8.0 months (95% confidence interval [CI]: 3.5, 11.1) in the FLT3-TKD alone subgroup versus 9.5 months (95% CI: 7.7, 10.7) in the FLT3-ITD subgroup. Survival probability at 6 months was 56.4% (95% CI: 32.8, 74.5) in the FLT3-TKD alone subgroup and 66.2% (95% CI: 59.5, 72.1) in the FLT3-ITD subgroup.

FLT3 ITD allelic ratio

Exploratory analysis based on different FLT-3 ITD allelic ratio cut-off levels have been provided, based on 335 patients that tested positive for FLT3 –ITD before inclusion in the study 2215-CL-0301.

Table 41 Overall Survival by FLT3 Signal Ratio Group–Full Analysis Set (Study 2215-CL-0301)

Parameter Category/ Statistics	N	Gilteritinib 120 mg (N = 222), n (%)	Median Duration of Overall Survival, Months†	N	Chemotherapy (N = 113), n (%)	Median Duration of Overall Survival, Months†	Hazard Ratio (95% CI)‡	Log-Rank Test (P-value)
FLT3 Signal Ratio								
ITD (with or without TKD) < 0.77	113	72 (63.7)	10.6	53	35 (66.0)	6.9	0.795 (0.526, 1.200)	0.2719
ITD (with or without TKD) ≥ 0.77	109	79 (72.5)	7.1	60	46 (76.7)	4.3	0.492 (0.339, 0.714)	0.0001

P-values are based on an unstratified, 2-sided log-rank test.

CI: confidence interval; FLT3: FMS-like tyrosine kinase 3; IDT: internal tandem duplication; TKD: tyrosine kinase domain.

†Based on Kaplan-Meier estimates.

‡Based on an unstratified Cox proportional hazards model. Assuming proportional hazards, a hazard ratio of < 1 indicates a reduction in the hazard rate in favor of the treatment arm.

- *Multigene Analysis*

The screening samples from FLT3 mutation assessment or disease assessment were evaluated by a multigene AML mutation panel to assess the relationship of efficacy of gilteritinib and mutational status of AML-related genes. Four mutational subgroups were identified where a mutation was detected in at least 10% of patients in the multigene analysis set (MAS). These were DNMT3A (31.9%, 115/361), NPM1 (47.9%, 173/361)), WT1 (18%, 65/361)), co-occurring DNMT3A and NPM1 mutations (23.8% 86/361)) and AXL positive blasts (16%). This was as expected based on the reported prevalence of these mutations in patients with FLT3 mutation positive AML (Garg et al. (13)).

The median (95% CI) OS for patients with DNMT3A mutation in the gilteritinib arm was 9.1 (6.3, 11.1) and 5.5 (3.7, 7.4) in the chemotherapy compared to 9.0 (7.1, 10.7) and 5.6 (4.3, 7.5) respectively, in the population without DNMT3A mutation.

The median (95% CI) OS for patients with NPM1 mutation in the gilteritinib arm was 8.3 (6.1, 11.0) and 5.1 (3.4, 6.1) in the chemotherapy arm compared to 9.6 (7.7, 10.8) and 7.1 (4.7, 10.0) respectively, in the population without NPM1 mutation.

For WT1 mutation positive patients the median OS (95% CI) was 9.1 (6.6, 14.7) in the gilteritinib arm and 3.4 (1.9, 5.2) in the chemotherapy compared to 9.0 (7.1, 10.7) and 6.3 (5.2, 7.6) respectively, in the population without WT1 mutation.

The median AXL positive blasts as a percent of the total blast population was 16%. The median OS (95% CI) of gilteritinib-treated patients with greater than or equal to the median AXL positive blast percent

(AXL high) was 10.7 (8.7, 12.5) compared to 8.0 (6.1, 10.4) in the gilteritinib- treated with less than the median AXL positive blast percent (AXL low). Median OS in AXL high and AXL low chemotherapy-treated patients was 6.3 (3.5, 8.0) and 6.1 (4.3, 8.9) respectively.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy (see later sections).

Table 42 Summary of Efficacy for trial 2215-CL-0301

Title: A Phase 3 Open-label, multicenter, randomized study of Gilteritinib fumarate (ASP 2215) versus salvage chemotherapy in patients with R/R AML with FLT3 mutation			
Study identifier	2215-CL-0301, EudraCT 2015-000140-42		
Design	Open-label, multicenter, randomized study, 2-arm		
	Duration of main phase:	Subjects could continue gilteritinib or low intensity chemotherapy until determination by the investigator of no clinical benefit, or unacceptable toxicity. Subjects who received high intensity chemotherapy (MEC or FLAG-IDA) were to receive maximum 2 cycles of therapy	
Hypothesis	Superiority		
Treatments groups	Gilteritinib	120 mg dose oral once daily in continuous 28-day cycles (N=247)	
	Salvage Chemotherapy	*Low intensity* LoDAC: cytarabine 20 mg twice daily by sc or iv for 10 days (days 1 through 10). Azacitidine: 75 mg/m^2 once daily by sc or iv for 7 days (days 1 through 7). Continuous in 28-day cycles *High intensity* MEC Induction Chemotherapy. FLAG-IDA Induction Chemotherapy. Maximum of 2 cycles (N=124)	
Endpoints and definitions	Primary endpoint	OS	Time from the date of randomization until the date of death from any cause.
	Key secondary	CR	Number of patients who achieved CR at any of the post baseline visits divided by the number of patients in the analysis population
	Key secondary	Event free survival (EFS)	The time from the date of randomization until the date of documented relapse (excluding relapse after PR), treatment failure or death from any cause within 30 days after the last dose of study drug, whichever occurred first (earliest of [relapse date, treatment failure date, death date]
	Other secondary	Transplantation rate	Defined as the percentage of patients undergoing HSCT postrandomization
HSCT postDatabase lock	17 September 2018		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (all subjects who are randomized) 17 September 2018 (261 OS events observed)		
Descriptive statistics and estimate variability	Treatment group	Gilteritinib	Chemotherapy
	Number of subject	247	124
	OS (median, in months)	9.3	5.6
	95% CI	7.7, 10.7	4.7, 7.3
	CR n/N (%)	52/247 (21.1)	13/124 (10.5)
	95% CI	16.1, 26.7	5.7, 17.3
	EFS (median, in months) 95% CI	2.8 1.4, 3.7	0.7 0.2, NE

	Transplantation rate n/N(%) 95% CI	63 (25.5) 20.2, 31.4	19 (15.3) 9.5, 22.9
Effect estimate per comparison	Primary OS	Comparison groups	Gilteritinib vs chemotherapy
		HR	0.637
		95% CI	(0.490, 0.830)
		Stratified 1- sided P-value	0.0004
	Key secondary CR	Comparison groups	Gilteritinib vs chemotherapy
		Adjusted Treatment Difference %	10.6
		95% CI	(2.8, 18.4)
	Key secondary EFS	Comparison groups	Gilteritinib vs chemotherapy
		HR	HR 0.793
		95% CI	(0.577, 1.089)
		Stratified 1 sided P-value	0.0415
	Other secondary Transplantation rate	Comparison groups	Gilteritinib vs chemotherapy
		Adjusted treatment difference %	10.2
		95% CI	(1.2, 19.1)
Notes	Stratification factors were response to first-line AML therapy (relapse within 6 months after allogeneic HSCT vs relapse after 6 months after allogeneic HSCT vs primary refractory without HSCT vs relapse within 6 months after CRc and no HSCT vs relapse after 6 months after CRc and no HSCT) and preselected salvage chemotherapy per IRT -high intensity chemotherapy [FLAG-IDA or MEC] vs low intensity chemotherapy [LoDAC or azacitidine])		

Clinical studies in special populations

Table 43. Elderly Patients in Study 2215-CL-0301 and Study 2215-CL-0101 – Full Analysis Set

	Age 65-74 (Older patients number /total number)		**Age 75-84 (Older patients number /total number)**		**Age 85+ (Older patients number /total number)**	
Controlled Trial	Gilteritinib 78/247 (31.6%)	Chemotherapy 34/124 (27.4%)	Gilteritinib 28/247 (11.3%)	Chemotherapy 14/124 (11.3%)	Gilteritinib 0	Chemotherapy 1/124 (0.3%)
	Gilteritinib		Gilteritinib		Gilteritinib	
Non Controlled Trial	Escalation Phase 0/2	Expansion Phase 10/54 (18.5%)	Escalation Phase 0/2	Expansion Phase 7/54 (13.0%)	Escalation Phase 0/2	Expansion Phase 1/54 (1.9%)

Supportive studies

Studies 2215-CL-0101 and 2215-CL-0102 are described under section ''Dose response study''.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The main evidence of efficacy comes from a single pivotal phase III multicenter randomised, open-label study comparing gilteritinib monotherapy (n=247) vs. salvage chemotherapy (n=124) in patients with FLT3 positive AML refractory to or relapsed after first-line treatment with or without HSCT consolidation. The overall design of the study is considered adequate to demonstrate the clinical benefit of gilteritinib 120 mg daily over salvage chemotherapy in R/R AML patients with one prior line of AML therapy.

The open label design is considered acceptable, due to the differences in the mode of administrations of gilteritinib and the different chemotherapy regimens.

As per study design, patients in the high intensity chemotherapy group (60%, treated for 1-2 cycles) reached the long-term follow-up part (with no protocol required bone marrow or clinical and laboratory assessments) several months earlier than patients in the gilteritinib arm, who were treated until lack of clinical benefit. These differences both in frequency and type of follow-up lead to a lack of systematic documentation of response/relapse status beyond 1-2 months post randomisation in the high intensity chemotherapy group.

The sponsor modified response criteria are less stringent than the 2003 International Working Group (IWG) criteria i.e. the IWG criteria lack the CRp definition and are more stringent in the definition of CRi, allowing for either incomplete neutrophil or platelet recovery (not both) with requirement of platelet and red blood cell transfusion independence. A responder analysis using the IWG (2003) criteria showed a reduction of the CRi rate, and thus a substantial decrease in the CRc rate in both treatment arms (54% to 35% for gilteritinib vs 22% to 13% for chemotherapy). Based on these data, it is not clear that the modified criteria are better suited to capture the efficacy of gilteritinib. Nevertheless, the SmPC includes only the CR and CRh rates, and these have been adequately defined in section 5.1, which is considered acceptable.

The inclusion and exclusion criteria are considered adequate to enrol a heterogeneous population with R/R FLT3-ITD (+) AML. The inclusion of patients with ECOG PS $\leq$ 2, patients not eligible for standard first-line therapy, and patients with both short and long duration of CRc following 1st line treatment is supported, as it improves the external validity of the results.

Patients could be defined as refractory after receiving only 1 cycle of induction therapy. This deviates from standard of care (ELN guidelines) which recommends 2 cycles. The majority of patients classified as primary refractory (90/146) had only received 1 cycle of high intensity chemotherapy; this is reflected in section 5.1 of the SmPC.

As would be expected, the number of patients with FLT3-TKD alone mutations was limited. There is no clear indication that the efficacy of gilteritinib in these patients would be substantially reduced since the OS benefit of gilteritinib over chemotherapy is comparable to that observed in patients with FLT ITD mutations, and the non-clinical data indicate that gilteritinib would be effective also in patients with TKD mutations.

There is no standard treatment for R/R AML, and the 4 chemotherapy regimens chosen for the active control arm (two high intensity regimens and tow low intensity regimen) are considered appropriate in the current R/R setting. Allocation of high vs low intensity chemotherapy was at the discretion of the investigator. Despite the lack of pre-specified criteria, it is considered that the pre-randomization assignment of patients and the stratification based on high vs low intensity therapy is sufficient to ensure trial validity and the balanced distribution of patients across treatments.

The starting dose of gilteritinib (120 mg) appears reasonably justified, although data are rather limited. Dose-escalation to 200 mg was allowed at the discretion of the investigator, in patients not achieving a response (CRc) following one treatment cycle. There is an uncertainty with regard to the benefit of the proposed dose escalation strategy in non-responding patients, as it cannot be determined whether the observed increased response rates is due to the increase in gilteritinib dose or the longer treatment duration. Never the less, the dose escalation strategy was a central part of the pivotal study design, (i.e. 31% (78/247) of the patients in the gilteritinib arm actually received the 200 mg dose/day), and the ITT analyses on which the B/R is established includes 78 patients that were dose escalated. Furthermore, there are no data that can reliable establish a lack of benefit for the proposed dose escalation strategy. Therefore, the option to dose escalate non-responding patients should be included in the SmPC.

Supplemental data from the pivotal study confirms that a substantial proportion of patients will only respond after several treatment cycles; therefore, continuation of treatment at the prescribed dose for up to 6 months should be considered to allow time for a clinical response. (SmPC, section 4.2).

The co-primary efficacy endpoint of CR/CRh rate was evaluated at the first interim analysis only. For the second interim analysis and in the final analysis, OS was the primary endpoint and CR and EFS was defined as key secondary endpoints. For the purpose of this assessment, the final OS analysis is considered the primary efficacy outcome measure, in line with the CHMP scientific advice (EMEA/H/SA/3789/1/FU/4/2018/PA/II). The statistical methods are considered acceptable. The group sequential design with hierarchical testing is adequate to control the Type I error for the OS, EFS and CR rate endpoints. Adequate sensitivity and subgroup analyses has been planned and performed.

There were eight protocol amendments defined as substantial. None of these are expected to have substantively affected the overall interpretation of the results. The number of protocol deviations was low, and there were no meaningful differences between treatment arms.

Efficacy data and additional analyses

Patient and disease characteristics, including the stratification factors, were in general well balanced between treatment arms.

The primary endpoint (OS) in the ITT population showed a statistically significant increase in OS, with a HR of 0.637 (95% CI: 0.490- to 0.830, p=0.0004 one-sided log rank test) and a median OS of 9.3 months and 5.6 months in the qilteritinib and salvage chemotherapy arms, respectively. An increase in median OS of 3.7 months is considered clinically relevant in this patient population with a rather poor prognosis. There was a difference in distribution of censored subjects between treatment arms, with more early censored observations occurring in the salvage chemotherapy (15/124) arm compared to the gilteritinib arm (6/247). Most of these censorings were informative. The Bootstrap resampling" and "Tipping point analysis" using multiple imputation (Zhao, et al 2014) analysis confirmed the robustness of the OS results.

The results of the other pre-planned sensitivity analysis (including censoring at HSCT and at time of new antileukemia treatment) are generally consistent with the primary analysis. Patient who had received prior treatment with gilteritinib or other FLT3 inhibitors (with the exception of sorafenib and midostaurin used in first-line therapy regimen as part of induction, consolidation and/or maintenance) were not eligible. The proportion of patients with prior use of FLT3 inhibitors was small (12%). However, also in this subpopulation results were in favour of gilteritinib in terms of CR rate (18% vs 0%) and the HR for OS 0.705 (95%CI: 0.346, 1.438). Thus, exclusion of patients with prior FLT3 inhibitors from the indication was not considered necessary.

Subgroup analyses showed a beneficial effect of gilteritinib over chemotherapy across several prognostic factors such as age, response category to first line therapy, AML risk score, and for patients eligible for low and high intensity treatment. In primary refractory patients the observed median OS benefit was not supported by the HR. However, this discrepancy could be explained by the crossing of survival curves at 15 months, making the HR estimate unreliable. Furthermore, the median OS benefit was supported by a consistent increase in response rates for gilteritinib vs chemotherapy, thus supporting a positive B/R also in this subpopulation.

The EFS endpoint did not meet the pre-specified criteria for statistical significance (HR= 0.93 95% CI 0.577, 1.089, p=0.0830 two-sided log rank test), although a trend towards an increased duration was observed (median 2.8 months vs 0.7 months for gilteritinib vs chemotherapy). The early steep drop in EFS is due to the definition of treatment failures in the analysis (fails to achieve any of the response of CR, CRp or CRi during the treatment) with the event date assigned to randomization date. Treatment

failures assigned to randomisation date constitutes a high proportion (38-39%) of the total EFS events, and by month 3 there were only 108 vs 4 patients included in the number at risk for the chemotherapy and gilteritinib arms, respectively. The lack of long-term (beyond 2 months) systematic documentation of response and relapse status in the high intensity chemotherapy group, and the large proportion of patients with no evaluable post-baseline response assessments in the salvage chemotherapy arm preclude relevant comparisons of response rates and response related time-to event endpoints between the treatment arms, and the benefit evaluation relies heavily on the OS data.

More patients in the gilteritinib arm compared to the salvage chemotherapy arm achieved a response to treatment, including 21.1% vs 10.5% obtaining a CR. A large proportion of patients in the salvage chemotherapy group had "No evaluable post-baseline bone marrow assessment" (39.5% vs 5.7% in the gilteritinib arm) of which the majority were randomized but not treated and patients treated without post baseline assessment. In the ITT population the median (95% CI) duration of CR was 14.8 (11.0, NE) months in the gilteritinib arm and 1.8 (NE, NE) in the salvage chemotherapy arm (Log-Rank test P-value = 0.1189). Results were similar in the analysis of duration of CR/CRh (median of 11 vs 1.8 months, respectively).

Similar to the EFS analysis, the limited follow-up of responses and high censoring rate in the salvage chemotherapy group precludes relevant comparisons of duration of response. In the gilteritinib arm, durable complete responses were achieved.

Transplantation rate was higher in the gilteritinib arm compared to the salvage chemotherapy arm (25.5% vs 15.3%, unstratified p-value 0.033). Post-transplantation outcomes were generally comparable between treatment arms, with the majority of patients being in remission (65% in the gilteritinib arm vs 68% in the chemotherapy arm). OS analyses based on the latest data cut off (17 May 2019) are still immature, but based on the KM curves, OS is comparable up to approximately 20 months after which the number of patients at risk is limited.

Due to the lack of re-randomization following HSCT, the benefit-risk profile of post-HSCT gilteritinib cannot be determined. However, as this was the overall treatment strategy for giteritinib and as there are no comparative data to substantiate long-term benefit in patients not receiving post-transplant treatment, the option to re-initiate gilteritinib following HSCT in is included in section 4.2 of the PI. The pivotal study included R/R AML patients previously treated with only 1 prior line of therapy and could therefore not support the wide claimed indication. Data from the supportive study (2215-CL-0101), including a total of 108 patients treated with >1 previous therapy, indicate that responses, (CR and CRc) are achieved also for patients in later treatment lines, and the reported median OS generally exceeds that observed with chemotherapy both in the clinical pivotal study and in a historical dataset provided (Roboz 2014). Furthermore, there is no clear indication from the PD data on potential resistance mechanisms, to suggest a reduced benefit of gilteritinib vs chemotherapy in later treatment lines. Also the safety data do not indicate any clinically meaningful differences with regards to number of prior treatment lines. Thus, although the magnitude of the clinical benefit of gilteritinib over chemotherapy in later treatment lines cannot be reliably established based on the presented naïve, indirect treatment comparisons, taking into account the totality of the data, the B/R ratio of gilteritinib is considered positive also in patients with > 1 prior treatments.

The OS and CR rates in the gilteritinib arm dose groups $\geqslant$ 80 mg observed in the dose escalation study are considered supportive for the results obtained in the gilteritinib arm in the pivotal efficacy study.

2.5.4. Conclusions on the clinical efficacy

Study 2215-CL-0301 has provided convincing evidence of clinical efficacy of gilteritinib monotherapy in terms of the primary endpoint OS, compared to salvage chemotherapy, in adult patients who have R/R AML with a FLT3 mutation. The statistically significant improvement of 3.7 months in the primary endpoint of OS is considered clinically relevant in the intended target population with a poor prognosis and a high unmet medical need.

2.6. Clinical safety

The safety profile for gilteritinib is derived from studies in healthy volunteers, hepatic-impaired volunteers and patients with either NSCLC, solid tumours or AML. As of the data cut-off date of 17 September 2018, a total of 179 healthy subjects and 764 patients have received at least 1 dose of gilteritinib.

The safety of gilteritinib has been evaluated in 18 clinical studies across different posology and indications. The safety data within the R/R AML patient population have been pooled across 3 studies. The overall safety evaluation included the following safety populations:

- Integrated R/R AML Safety Population: This population is the primary focus of safety assessments and includes all patients who received at least 1 dose of study drug in Studies 2215 CL 0101, 2215 CL-0102 or 2215 CL-0301 with R/R AML. The integrated R/R AML safety population included a total of 522 patients who received at least 1 dose of gilteritinib, comprised of 252 patients from Study 2215-CL-0101 (completed study), 24 patients from Study 2215-CL-0102 (completed study) and 246 patients from Study 2215 CL-0301 (data cut-off date: 17 September 2018). Of these 522 patients, 319 received a starting dose of gilteritinib 120 mg (including all 246 patients from Study 2215-CL-0301).

- Integrated R/R FLT3+ AML Safety Population: This population includes all FLT3 mutation positive (FLT3+) patients who received at least 1 dose of study drug in Studies 2215 CL-0101, 2215 CL 0102 or 2215 CL 0301 with R/R AML. FLT3+ patients are those who were locally assessed as FLT3+ in Studies 2215 CL-0101 and 2215 CL-0102, and those who were centrally assessed as FLT3+ in Study 2215 CL 0301.

- Study 2215-CL-0301 Safety Population: This population includes all patients with R/R AML who received at least 1 dose of study drug in the pivotal Study 2215 CL-0301. This population was used for subgroup analyses based on the stratification factors unique to this study and for a safety analysis of patients who had a dose escalation to gilteritinib 200 mg.

Table 44 Overview of the main studies for evaluation of safety in the R/R AML population

Study ID Location	Study phase	Study population (Study type)	Study design	Treatment regimen	Study status	Subjects in Safety Analysis Set, total and by treatment group (as of 04-Jan-2018)†
2215-CL-0101 US, EU	1/2	R/R AML (safety, MTD, PK, efficacy, DDI)	Open-label dose escalation/expansion	Gilteritinib (20, 40, 80, 120, 200, 300, 450 mg)	Ongoing	252 Gilteritinib: 252
2215-CL-0102 Japan	1	R/R AML (safety, MTD, efficacy, PK, PD)	Open-label dose escalation	Gilteritinib (24, 40, 80, 120, 200, 300 mg	Completed	24 Gilteritinib: 24
2215-CL-0301 Global	3	R/R FLT3+ AML (efficacy, safety, population, PK, PD)	Open-label randomized	Gilteritinib 120 mg vs. chemotherapy‡	Ongoing	355 Gilteritinib: 246 Salvage chemotherapy‡: 109

† The data cutoff date for the ongoing studies was 17-Sep-2018; ‡ Non-gilteritinib salvage chemotherapy randomization options in Study 2215-CL-0301 consisted of LoDAC, azacitidine, MEC or FLAG-IDA.

Patient exposure

Tabular overview of the integrated R/R AML safety population is given in Table 45.

Table 45 Number of Patients by Study Protocol and Treatment Group – Integrated R/R AML Safety Population

Study	Integrated Data†		Study 2215-CL-0301	
	Gilteritinib 120 mg	Gilteritinib Total	Gilteritinib 120 mg	Chemo
2215-CL-0101‡	69	252	0	0
2215-CL-0102‡	4	24	0	0
2215-CL-0301	246	246	246	109
Total	319	522	246	109

†Integrated data includes patients in Studies 2215-CL-0101, 2215-CL-0102 and 2215-CL-0301 who received at least 1 dose of gilteritinib 120 mg (gilteritinib 120 mg group) or any dose of gilteritinib (gilteritinib total group; doses ranging from gilteritinib 20 to 450 mg). ‡For patients with dose adjustments, dose groups were based on the initial dose.

Table 46 Study Drug Exposure – Integrated R/R AML Safety Population

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

Average Daily Dose (mg/day)¶					
n	319	521	246	168	NA
Mean (SD)	127.2 (28.1)	143.6 (61.4)	123.9 (25.8)	110.6 (15.2)	--
Median (Min, Max)	120.0 (50, 290)	120.0 (20, 402)	120.0 (50, 192)	120.0 (50, 120)	--
Dose Intensity (mg/day)††					
n	319	521	246	168	NA
Mean (SD)	122.7 (30.1)	137.1 (60.4)	119.1 (28.2)	105.8 (19.3)	--
Median (Min, Max)	120.0 (46, 273)	120.0 (13, 400)	120.0 (46, 192)	120.0 (46, 120)	--
Relative Dose Intensity (%)‡‡					
n	319	521	246	168	109
Mean (SD)	102.2 (25.1)	102.1 (26.4)	99.2 (23.5)	88.2 (16.1)	98.2 (35.1)
Median (Min, Max)	100.0 (39, 227)	100.0 (23, 292)	100.0 (39, 160)	100.0 (39, 100)	99.6 (10, 322)

†Integrated data includes patients in Studies 2215-CL-0101, 2215-CL-0102 and 2215-CL-0301 who received at least 1 dose of gilteritinib 120 mg (gilteritinib 120 mg group) or any dose of gilteritinib (gilteritinib total group; doses ranging from gilteritinib 20 to 450 mg); ‡Defined as (last date of exposure) – (first dose date) + 1 – (on-study HSCT period for patients who underwent on-study HSCT);§Defined as the number of days with nonzero dosing; ¶Defined as (cumulative dose) / (number of dosing days); ††Defined as (cumulative dose/ duration of exposure) for gilteritinib; ‡‡Defined as (dose intensity/planned dose intensity) *100%

*Dose reduction*s were experienced by 25.7% (82/319) of patients. In the integrated gilteritinib 120 mg group, 12.9% (41/319) of patients experienced TEAEs leading to dose reduction. Of those patients, 11.0% (35/319) experienced TEAEs leading to dose reduction that were attributed by the Investigator as drug-related. At least 1 day of *dose interruption* were experienced by 47.3% (151/319) of patients. TEAEs leading to drug interruption were experienced by 45.1% (144/319) of patients and drug-related TEAEs leading to dose interruption were experienced by 30.4% (97/319) of patients.

All patients randomized to the gilteritinib arm began at a starting dose of 120 mg but had the option of receiving an escalated dose of 200 mg based on lack of efficacy, as assessed by the Investigator. For patients who were administered an escalated dose of gilteritinib 200 mg, the median number of dosing days for patients before dose escalation was 42.0 days, ranging from 26 to 531 days. The median number of dosing days for patients after dose escalation was 48.0 days, ranging from 1 to 756 days. In the integrated gilteritinib 120 mg safety population, dose increase was experienced by 35.4% (113/319) of patients.

Adverse events

An overview of the AEs observed in the integrated R/R AML safety population is given in Table 47.

Table 47 Overview of Treatment-emergent Adverse Events – Integrated R/R AML Safety Population

Parameter	Integrated Data†				Study 2215-CL-0301			
	Gilteritinib 120 mg		Gilteritinib Total		Gilteritinib 120 mg		Chemo	
	N = 319 n (%)	PY = 158 E (E/PY)	N = 522 n (%)	PY = 223 E (E/PY)	N = 246 n (%)	PY = 122 E (E/PY)	N = 109 n (%)	PY = 12 E (E/PY)
TEAE	317 (99.4)	10302 (65.2)	519 (99.4)	15044 (67.5)	246 (100)	8464 (69.4)	107 (98.2)	1596 (133.0)
Drug-related‡ TEAE	265 (83.1)	2426 (15.4)	418 (80.1)	3570 (16.0)	206 (83.7)	2011 (16.5)	71 (65.1)	562 (46.8)
Serious TEAE§	258 (80.9)	1105 (7.0)	425 (81.4)	1796 (8.1)	205 (83.3)	865 (7.1)	34 (31.2)	110 (9.2)
Drug-related‡ serious TEAE§	108 (33.9)	231 (1.5)	170 (32.6)	341 (1.5)	88 (35.8)	193 (1.6)	16 (14.7)	35 (2.9)
TEAE leading to death	95 (29.8)	111 (0.7)	181 (34.7)	205 (0.9)	71 (28.9)	87 (0.7)	16 (14.7)	23 (1.9)
Drug-related‡ TEAE leading to death	12 (3.8)	16 (0.1)	18 (3.4)	22 (0.1)	10 (4.1)	14 (0.1)	5 (4.6)	8 (0.7)
TEAE leading to withdrawal of treatment	70 (21.9)	95 (0.6)	152 (29.1)	210 (0.9)	58 (23.6)	80 (0.7)	13 (11.9)	18 (1.5)
Drug-related‡ TEAE leading to withdrawal of treatment	32 (10.0)	44 (0.3)	58 (11.1)	78 (0.3)	27 (11.0)	37 (0.3)	5 (4.6)	8 (0.7)
Grade 3 or higher TEAE	298 (93.4)	2822 (17.9)	482 (92.3)	4063 (18.2)	236 (95.9)	2354 (19.3)	94 (86.2)	505 (42.1)
Grade 3 or higher drug-related‡ TEAE	192 (60.2)	754 (4.8)	288 (55.2)	1025 (4.6)	153 (62.2)	638 (5.2)	57 (52.3)	227 (18.9)
TEAEs leading to dose reduction	41 (12.9)	55 (0.3)	52 (10.0)	70 (0.3)	35 (14.2)	46 (0.4)	1 (0.9)	7 (0.6)
Drug-related‡ TEAE leading to dose reduction	35 (11.0)	44 (0.3)	44 (8.4)	57 (0.3)	31 (12.6)	40 (0.3)	0	0
TEAE leading to drug interruption	144 (45.1)	338 (2.1)	224 (42.9)	512 (2.3)	112 (45.5)	269 (2.2)	5 (4.6)	9 (0.8)
Drug-related TEAE leading to drug interruption	97 (30.4)	180 (1.1)	138 (26.4)	254 (1.1)	79 (32.1)	153 (1.3)	3 (2.8)	4 (0.3)
TEAE during HSCT Period	34 (10.7)	272 (1.7)	41 (7.9)	351 (1.6)	31 (12.6)	256 (2.1)	0	0
Serious TEAE during HSCT Period	4 (1.3)	7 (0.0)	5 (1.0)	10 (0.0)	4 (1.6)	7 (0.1)	0	0
Death	226 (70.8)	226 (1.4)	386 (73.9)	386 (1.7)	170 (69.1)	170 (1.4)	81 (74.3)	81 (6.8)

†Integrated data includes patients in Studies 2215-CL-0101, 2215-CL-0102 and 2215-CL-0301 who received at least 1 dose of gilteritinib 120 mg (gilteritinib 120 mg group) or any dose of gilteritinib (gilteritinib total group; doses ranging from gilteritinib 20 to 450 mg) ; ‡Possible or probable, as assessed by the Investigator, or records where relationship is missing; §Includes SAEs upgraded by the Sponsor based on review of the Sponsor's list of Always Serious terms, if any update was done.

- *Treatment-emergent adverse events*

An overview of the treatment-emergent adverse events (TEAEs) observed in the integrated R/R AML safety population is given in

Table 48. TEAEs were defined as an AE observed after starting administration of the study drug.

Table 48 Treatment-emergent Adverse Events (≥ 10% of Integrated Gilteritinib 120 mg Patients) by System Organ Class, Preferred Term and Severity – Integrated R/R AML Safety Population

MedDRA (v19.1) System Organ Class Preferred Term	Integrated Data†				Study 2215-CL-0301							
	Gilteritinib 120 mg		Gilteritinib Total		Gilteritinib 120 mg				Chemo			
	All	≥ Grade 3	All	≥ Grade 3	All		≥ Grade 3		All		≥ Grade 3	
	N = 319		N = 522		N = 246	PY = 121.7 E (E/PY)	N = 246	PY = 121.7 E (E/PY)	N = 109	PY = 11.9 E (E/PY)	N = 109	PY =11.9 E (E/PY)
Overall, n (%)	**317 (99.4)**	**298 (93.4)**	**519 (99.4)**	**482 (92.3)**	**246 (100)**	**8464 (69.55)**	**236 (95.9)**	**2354 (19.34)**	**107 (98.2)**	**1596 (134.12)**	**94 (86.2)**	**505 (42.44)**
General Disorders and Administration Site Conditions	**254 (79.6)**	**48 (15.0)**	**398 (76.2)**	**88 (16.9)**	**198 (80.5)**	**616 (5.06)**	**33 (13.4)**	**36 (0.30)**	**61 (56.0)**	**165 (13.87)**	**10 (9.2)**	**15 (1.26)**
Pyrexia	131 (41.1)	13 (4.1)	182 (34.9)	21 (4.0)	105 (42.7)	179 (1.47)	8 (3.3)	9 (0.07)	32 (29.4)	59 (4.96)	4 (3.7)	6 (0.50)
Fatigue	97 (30.4)	10 (3.1)	158 (30.3)	21 (4.0)	70 (28.5)	102 (0.84)	6 (2.4)	6 (0.05)	14 (12.8)	18 (1.51)	2 (1.8)	2 (0.17)
Oedema peripheral	77 (24.1)	1 (0.3)	125 (23.9)	5 (1.0)	59 (24.0)	77 (0.63)	1 (0.4)	1 (0.01)	13 (11.9)	19 (1.60)	0	0
Asthenia	44 (13.8)	8 (2.5)	71 (13.6)	12 (2.3)	38 (15.4)	53 (0.44)	6 (2.4)	6 (0.05)	10 (9.2)	11 (0.92)	2 (1.8)	2 (0.17)
Investigations	**249 (78.1)**	**153 (48.0)**	**383 (73.4)**	**235 (45.0)**	**191 (77.6)**	**1702 (13.99)**	**129 (52.4)**	**614 (5.05)**	**59 (54.1)**	**252 (21.18)**	**47 (43.1)**	**133 (11.18)**
Alanine aminotransferase increased	120 (37.6)	37 (11.6)	160 (30.7)	49 (9.4)	103 (41.9)	247 (2.03)	34 (13.8)	42 (0.35)	10 (9.2)	20 (1.68)	5 (4.6)	5 (0.42)
Aspartate aminotransferase increased	120 (37.6)	40 (12.5)	172 (33.0)	55 (10.5)	99 (40.2)	251 (2.06)	36 (14.6)	45 (0.37)	13 (11.9)	21 (1.76)	2 (1.8)	2 (0.17)
Platelet count decreased	68 (21.3)	64 (20.1)	102 (19.5)	96 (18.4)	56 (22.8)	256 (2.10)	54 (22.0)	207 (1.70)	28 (25.7)	76 (6.39)	27 (24.8)	59 (4.96)
Blood alkaline phosphatase increased	22 (20.7)	7 (2.2)	91 (17.4)	8 (1.5)	56 (22.8)	113 (0.93)	7 (2.8)	9 (0.07)	2 (1.8)	2 (0.17)	0	0
Neutrophil count decreased	50 (15.7)	48 (15.0)	70 (13.4)	65 (12.5)	42 (17.1)	167 (1.37)	42 (17.1)	124 (1.02)	12 (11.0)	28 (2.35)	12 (11.0)	19 (1.60)
Blood creatinine increased	42 (13.2)	4 (1.3)	75 (14.4)	8 (1.5)	29 (11.8)	65 (0.53)	3 (1.2)	4 (0.03)	4 (3.7)	4 (0.34)	0	0
Blood creatine phosphokinase increased	40 (12.5)	15 (4.7)	70 (13.4)	28 (5.4)	33 (13.4)	96 (0.79)	13 (5.3)	20 (0.16)	0	0	0	0
White blood cell count decreased	38 (11.9)	35 (11.0)	51 (9.8)	47 (9.0)	34 (13.8)	128 (1.05)	32 (13.0)	84 (0.69)	19 (17.4)	27 (2.27)	19 (17.4)	26 (2.18)
Gastrointestinal Disorders	**246 (77.1)**	**63 (19.7)**	**397 (76.1)**	**106 (20.3)**	**192 (78.0)**	**818 (6.72)**	**48 (19.5)**	**71 (0.58)**	**80 (73.4)**	**228 (19.16)**	**9 (8.3)**	**11 (0.92)**
Diarrhoea	112 (35.1)	13 (14.1)	188 (36.0)	25 (4.8)	81 (32.9)	136 (1.12)	9 (3.7)	10 (0.08)	32 (29.4)	37 (3.11)	3 (2.8)	3 (0.25)
Nausea	95 (29.8)	6 (1.9)	143 (27.4)	10 (1.9)	79 (32.1)	122 (1.00)	5 (2.0)	5 (0.04)	36 (33.0)	41 (3.45)	0	0
Constipation	90 (28.2)	2 (0.6)	141 (27.0)	2 (0.4)	76 (30.9)	94 (0.77)	2 (0.8)	3 (0.02)	16 (14.7)	18 (1.51)	0	0
Vomiting	67 (21.0)	3 (0.9)	106 (20.3)	6 (1.1)	53 (21.5)	80 (0.66)	1 (0.4)	1 (0.01)	15 (13.8)	16 (1.34)	0	0
Stomatitis	43 (13.5)	7 (2.2)	68 (13.0)	10 (1.9)	34 (13.8)	45 (0.37)	6 (2.4)	6 (0.05)	16 (14.7)	20 (1.68)	4 (3.7)	4 (0.34)
Abdominal pain	42 (13.0)	6 (1.9)	63 (12.1)	8 (1.5)	37 (15.0)	44 (0.36)	5 (2.0)	5 (0.04)	16 (14.7)	17 (1.43)	0	0
Infections and Infestations	**243 (76.2)**	**165 (51.7)**	**381 (73.0)**	**267 (51.1)**	**199 (80.9)**	**659 (5.41)**	**133 (54.1)**	**296 (2.43)**	**56 (51.4)**	**107 (8.99)**	**25 (22.9)**	**52 (4.37)**
Pneumonia	59 (18.5)	43 (13.5)	91 (17.4)	68 (13.0)	43 (17.5)	66 (0.54)	29 (11.8)	39 (0.32)	8 (7.3)	11 (0.92)	5 (4.6)	7 (0.59)

MedDRA (v19.1) System Organ Class Preferred Term	Integrated Data‡				Study 2215-CL-0301							
	Gilteritinib 120 mg		Gilteritinib Total		Gilteritinib 120 mg				Chemo			
	All	≥ Grade 3	All	≥ Grade 3	All		≥ Grade 3		All		≥ Grade 3	
	N = 319		N = 522		N = 246	PY = 121.7 E (E/PY)	N = 246	PY = 121.7 E (E/PY)	N = 109	PY = 11.9 E (E/PY)	N = 109	PY =11.9 E (E/PY)
Blood and Lymphatic System Disorders	**241 (75.5)**	**220 (69.0)**	**373 (71.5)**	**338 (64.8)**	**189 (76.8)**	**1147 (9.42)**	**176 (71.5)**	**768 (6.31)**	**78 (71.6)**	**237 (19.92)**	**75 (68.8)**	**171 (14.37)**
Anaemia	143 (44.8)	115 (36.1)	207 (39.7)	166 (31.8)	116 (47.2)	481 (3.95)	100 (40.7)	247 (2.03)	38 (34.9)	80 (6.72)	33 (10.3)	45 (3.78)
Febrile neutropenia	140 (43.9)	137 (42.9)	220 (42.1)	216 (41.4)	115 (46.7)	184 (1.51)	113 (45.9)	181 (1.49)	40 (36.7)	52 (4.37)	40 (36.7)	52 (4.37)
Thrombocytopenia	76 (23.8)	66 (20.7)	102 19.5)	89 (17.0)	63 (25.6)	298 (2.45)	56 (22.8)	229 (1.88)	18 (16.5)	42 (3.53)	18 (16.5)	35 (2.94)
Neutropenia	39 (12.2)	39 (12.2)	55 (10.5)	54 (10.3)	33 (13.4)	109 (0.90)	33 (13.4)	80 (0.66)	16 (14.7)	19 (1.60)	15 (13.8)	17 (1.43)
Respiratory, thoracic and mediastinal disorders	**208 (65.2)**	**61 (19.1)**	**336 (64.4)**	**110 (21.1)**	**163 (66.3)**	**491 (4.03)**	**46 (18.7)**	**68 (0.56)**	**38 (34.9)**	**70 (5.88)**	**12 (11.0)**	**16 (1.34)**
Cough	90 (28.2)	1 (0.3)	135 (25.9)	1 (0.2)	72 (29.3)	98 (0.81)	1 (0.4)	1 (0.01)	11 (10.1)	13 (1.09)	0	0
Dyspnoea	77 (24.1)	14 (4.4)	123 (23.6)	25 (4.8)	58 (23.6)	77 (0.63)	10 (4.1)	10 (0.08)	7 (6.4)	10 (0.84)	3 (2.8)	3 (0.25)
Epistaxis	58 (18.2)	3 (0.9)	98 (18.8)	5 (1.0)	42 (17.1)	51 (0.42)	2 (0.8)	2 (0.02)	8 (7.3)	8 (0.67)	1 (0.9)	1 (0.08)
Metabolism and Nutrition Disorders	**203 (63.6)**	**101 (31.7)**	**320 (61.3)**	**158 (30.3)**	**165 (67.1)**	**900 (7.40)**	**85 (34.6)**	**192 (1.58)**	**58 (53.2)**	**164 (13.78)**	**35 (32.1)**	**50 (4.20)**
Hypokalaemia	82 (25.7)	33 (10.3)	122 (23.4)	43 (8.2)	71 (28.9)	183 (1.50)	32 (13.0)	42 (0.35)	34 (31.2)	49 (4.12)	12 (11.0)	14 (1.18)
Hypocalcaemia	58 (18.2)	15 (4.7)	92 (17.6)	27 (5.2)	47 (19.1)	110 (0.90)	12 (4.9)	13 (0.11)	6 (5.5)	14 (1.18)	1 (0.9)	1 (0.08)
Decreased appetite	55 (17.2)	5 (1.6)	86 (16.5)	9 (1.7)	44 (17.9)	54 (0.44)	5 (2.0)	5 (0.04)	20 (18.3)	22 (1.85)	5 (4.6)	5 (0.42)
Hypomagnesaemia	52 (16.3)	1 (0.3)	79 (15.1)	1 (0.2)	39 (15.9)	67 (0.55)	0	0	12 (11.0)	15 (1.26)	0	0
Hypophosphataemia	47 (14.7)	25 (7.8)	64 (12.3)	39 (7.5)	41 (16.7)	70 (0.58)	20 (8.1)	30 (0.25)	5 (4.6)	5 (0.42)	4 (3.7)	4 (0.34)
Hyperglycaemia	42 (13.2)	19 (6.0)	60 (11.5)	28 (5.4)	36 (14.6)	62 (0.51)	18 (17.3)	24 (0.20)	14 (12.8)	20 (1.68)	9 (8.3)	12 (1.01)
Hyponatraemia	42 (13.2)	19 (6.0)	69 (13.2)	30 (5.7)	33 (13.4)	81 (0.67)	16 (16.5)	36 (0.30)	6 (5.5)	7 (0.59)	3 (2.8)	3 (0.25)
Hypoalbuminaemia	39 (12.2)	5 (1.6)	67 (12.8)	10 (1.9)	32 (13.0)	64 (0.53)	3 (1.2)	5 (0.04)	7 (6.4)	11 (0.92)	2 (1.8)	2 (0.17)
Nervous System Disorders	**175 (54.9)**	**37 (11.6)**	**284 (54.4)**	**67 (12.8)**	**135 (54.9)**	**352 (2.89)**	**30 (12.2)**	**39 (0.32)**	**30 (27.5)**	**53 (4.45)**	**5 (4.6)**	**5 (0.42)**
Headache	75 (23.5)	4 (1.3)	101 (19.3)	5 (1.0)	64 (26.0)	92 (0.76)	3 (1.2)	3 (0.02)	16 (14.7)	18 (1.51)	0	0
Dizziness	65 (20.4)	1 (0.3)	101 (19.3)	3 (0.6)	48 (19.5)	65 (0.53)	1 (0.4)	2 (0.02)	2 (1.8)	2 (0.17)	0	0
Dysgeusia	35 (11.0)	0	56 (10.7)	0	25 (10.2)	28 (0.23)	0	0	5 (4.6)	5 (0.42)	0	0
Musculoskeletal and Connective Tissue Disorders	**172 (53.9)**	**23 (7.2)**	**252 (48.3)**	**36 (6.9)**	**136 (55.3)**	**313 (2.57)**	**17 (6.9)**	**22 (0.18)**	**35 (32.1)**	**62 (5.21)**	**5 (4.6)**	**6 (0.50)**
Pain in extremity	47 (14.7)	2 (0.6)	66 (12.6)	4 (0.8)	36 (14.6)	44 (0.36)	2 (0.8)	2 (0.02)	8 (7.3)	12 (1.01)	1 (0.9)	1 (0.08)
Arthralgia	40 (12.5)	4 (1.3)	65 (12.5)	6 (1.1)	28 (11.4)	45 (0.37)	4 (1.6)	5 (0.04)	6 (5.5)	8 (0.67)	1 (0.9)	1 (0.08)
Myalgia	40 (12.5)	1 (0.3)	56 (10.7)	3 (0.6)	35 (14.2)	45 (0.37)	1 (0.4)	1 (0.01)	4 (3.7)	4 (0.34)	0	0
Back pain	38 (11.9)	3 (0.9)	52 (10.0)	6 (1.1)	29 (11.8)	33 (0.27)	2 (0.8)	2 (0.02)	13 (11.9)	13 (1.09)	1 (0.9)	1 (0.08)
Skin and Subcutaneous Tissue Disorders	**169 (53.0)**	**23 (7.2)**	**276 (52.9)**	**33 (6.3)**	**133 (54.1)**	**334 (2.74)**	**18 (7.3)**	**20 (0.16)**	**43 (39.4)**	**63 (5.29)**	**7 (6.4)**	**7 (0.59)**
Rash	48 (15.0)	2 (0.6)	65 (12.5)	2 (0.4)	36 (14.6)	48 (0.39)	1 (0.4)	1 (0.01)	10 (9.2)	10 (0.84)	1 (0.9)	1 (0.08)

MedDRA (v19.1) System Organ Class Preferred Term	Integrated Data†				Study 2215-CL-0301							
	Gilteritinib 120 mg		Gilteritinib Total		Gilteritinib 120 mg				Chemo			
	All	≥ Grade 3	All	≥ Grade 3	All		≥ Grade 3		All		≥ Grade 3	
	N = 319		N = 522		N = 246	PY = 121.7 E (E/PY)	N = 246	PY = 121.7 E (E/PY)	N = 109	PY = 11.9 E (E/PY)	N = 109	PY =11.9 E (E/PY)
Vascular Disorders	**132 (41.4)**	**54 (16.9)**	**206 (39.5)**	**79 (15.1)**	**106 (43.1)**	**174 (1.43)**	**46 (18.7)**	**55 (0.45)**	**25 (22.9)**	**35 (2.94)**	**7 (6.4)**	**8 (0.67)**
Hypotension	55 (17.2)	23 (7.2)	92 (17.6)	37 (7.1)	43 (17.5)	50 (0.41)	19 (7.7)	21 (0.17)	8 (7.5)	9 (0.76)	3 (2.8)	3 (0.25)
Hypertension	41 (12.9)	22 (6.9)	67 (12.8)	29 (5.6)	34 (13.8)	57 (0.47)	20 (8.1)	24 (0.20)	10 (9.2)	11 (0.92)	4 (3.7)	5 (0.42)
Eye Disorders	**125 (39.2)**	**8 (2.5)**	**170 (32.6)**	**11 (2.1)**	**97 (39.4)**	**180 (1.48)**	**5 (2.0)**	**5 (0.04)**	**12 (11.0)**	**19 (1.60)**	**0**	**0**
Dry eye	33 (10.3)	1 (0.3)	41 (7.9)	1 (0.2)	24 (9.8)	25 (0.21)	1 (0.4)	1 (0.01)	3 (2.8)	3 (0.25)	0	0
Injury, poisoning and Procedural Complications	**112 (35.1)**	**18 (5.6)**	**177 (33.9)**	**34 (6.5)**	**85 (34.6)**	**161 (1.32)**	**13 (5.3)**	**16 (0.13)**	**23 (21.1)**	**35 (2.94)**	**3 (2.8)**	**3 (0.25)**
Fall	34 (10.7)	9 (2.8)	59 (11.3)	14 (2.7)	21 (8.5)	35 (0.29)	5 (2.0)	5 (0.04)	2 (1.8)	2 (0.17)	1 (0.9)	1 (0.08)
Psychiatric Disorders	**92 (28.8)**	**9 (2.8)**	**152 (29.1)**	**17 (3.3)**	**76 (30.9)**	**121 (0.99)**	**8 (3.3)**	**9 (0.07)**	**18 (16.5)**	**23 (1.93)**	**2 (1.8)**	**3 (0.25)**
Insomnia	48 (15.0)	1 (0.3)	71 (13.6)	1 (0.2)	40 (16.3)	44 (0.36)	0	0	6 (5.5)	6 (0.50)	0	0
Renal and Urinary Disorders	**88 (27.6)**	**15 (4.7)**	**150 (28.7)**	**30 (5.7)**	**70 (28.5)**	**118 (0.97)**	**12 (4.9)**	**13 (0.11)**	**14 (12.8)**	**19 (1.60)**	**3 (2.8)**	**4 (0.34)**
Cardiac Disorders	**83 (26.0)**	**31 (9.7)**	**146 (28.0)**	**54 (10.3)**	**67 (27.2)**	**115 (0.94)**	**25 (10.2)**	**39 (0.32)**	**17 (15.6)**	**21 (1.76)**	**4 (3.7)**	**6 (0.50)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**73 (22.9)**	**56 (17.6)**	**120 (23.0)**	**99 (19.0)**	**57 (23.2)**	**72 (0.59)**	**44 (17.9)**	**54 (0.44)**	**11 (10.1)**	**17 (1.43)**	**5 (4.6)**	**10 (0.84)**
Acute myeloid leukaemia	43 (13.5)	43 (13.5)	82 (15.7)	82 (15.7)	33 (13.4)	38 (0.31)	33 (13.4)	38 (0.31)	4 (3.7)	6 (0.50)	4 (3.7)	6 (0.50)
Immune System Disorders	**44 (13.8)**	**16 (5.0)**	**63 (12.1)**	**21 (4.0)**	**35 (14.2)**	**73 (0.60)**	**13 (5.3)**	**17 (0.14)**	**3 (2.8)**	**5 (0.42)**	**1 (0.9)**	**2 (0.17)**
Hepatobiliary Disorders	**37 (11.6)**	**16 (5.0)**	**62 (11.9)**	**20 (3.8)**	**31 (12.6)**	**55 (0.45)**	**13 (5.3)**	**16 (0.13)**	**4 (3.7)**	**5 (0.42)**	**1 (0.9)**	**2 (0.17)**
Reproductive System and Breast Disorders	**32 (10.0)**	**2 (0.6)**	**46 (8.8)**	**5 (1.0)**	**24 (9.8)**	**28 (0.23)**	**2 (0.8)**	**2 (0.02)**	**8 (7.3)**	**8 (0.67)**	**0**	**0**

AML: acute myeloid leukemia; Chem: chemotherapy; E: number of events; NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Events; PY: patient-year; R/R: relapsed or refractory; TEAE: treatment-emergent adverse event.

Sorting order: Descending order in the integrated gilteritinib 120 mg group by system organ class and preferred term within system organ class. In the case of ties, alphabetical order was applied.

Patients were counted once under maximum NCI-CTCAE grade.

†Integrated data includes patients in Studies 2215-CL-0101, 2215-CL-0102 and 2215-CL-0301 who received at least 1 dose of gilteritinib 120 mg (gilteritinib 120 mg group) or any dose of gilteritinib (gilteritinib total group; doses ranging from gilteritinib 20 to 450 mg).

- *Drug-related Treatment-emergent adverse events*

Drug-related TEAEs refer to events that were assessed by the Investigator as "possibly related" or "probably related" to gilteritinib.

Table 49 Drug-related Treatment-emergent Adverse Events (⩾ 5% of Integrated Gilteritinib 120 mg Patients) by Preferred Term and Severity – Integrated R/R AML Safety Population

MedDRA (v19.1) Preferred Term	Integrated Data†				Study 2215-CL-0301							
	Gilteritinib 120 mg		Gilteritinib Total		Gilteritinib 120 mg				Chemo			
	All	≥ Grade 3	All	≥ Grade 3	All		≥ Grade 3		All		≥ Grade 3	
	N = 319		N = 522		N = 246	PY = 121.7 E (E/PY)	N = 246	PY = 121.7 E (E/PY)	N = 109	PY = 11.9 E (E/PY)	N = 109	PY = 11.9 E (E/PY)
Overall, n (%)	**265 (83.1)**	**192 (60.2)**	**418 (80.1)**	**288 (55.2)**	**206 (83.7)**	**2011 (16.52)**	**153 (62.2)**	**638 (5.24)**	**71 (65.1)**	**562 (47.23)**	**57 (52.3)**	**227 (19.08)**
Alanine aminotransferase increased	81 (25.4)	20 (6.3)	107 (20.5)	27 (5.2)	73 (29.7)	153 (1.26)	19 (7.7)	23 (0.19)	4 (3.7)	9 (0.76)	2 (1.8)	2 (0.17)
Aspartate aminotransferase increased	78 (24.5)	21 (6.6)	108 (20.7)	29 (5.6)	69 (28.0)	149 (1.22)	20 (8.1)	24 (0.20)	7 (6.4)	10 (0.84)	1 (0.9)	1 (0.08)
Anaemia	64 (20.1)	54 (16.9)	82 (15.7)	71 (13.6)	57 (23.2)	152 (1.25)	48 (19.5)	79 (0.65)	25 (22.9)	54 (4.54)	21 (19.3)	28 (2.35)
Thrombocytopenia	43 (13.5)	37 (11.6)	52 (10.0)	44 (8.4)	35 (14.2)	131 (1.08)	30 (12.2)	93 (0.76)	11 (10.1)	27 (2.27)	11 (10.1)	21 (1.76)
Febrile neutropenia	40 (12.5)	39 (12.2)	51 (9.8)	50 (9.6)	39 (15.9)	47 (0.39)	38 (15.4)	46 (0.38)	20 (18.3)	21 (1.76)	20 (18.3)	21 (1.76)
Diarrhoea	39 (12.2)	2 (0.6)	78 (14.9)	8 (1.5)	28 (11.4)	39 (0.32)	1 (0.4)	1 (0.01)	13 (11.9)	13 (1.09)	2 (1.8)	2 (0.17)
Platelet count decreased	39 (12.2)	36 (11.3)	57 (10.9)	52 (10.0)	32 (13.0)	88 (0.72)	30 (12.2)	66 (0.54)	15 (13.8)	42 (3.53)	14 (12.8)	35 (2.94)
Nausea	36 (11.3)	1 (0.3)	56 (10.7)	2 (0.4)	33 (13.4)	40 (0.33)	0	0	25 (22.9)	26 (2.18)	0	0
Blood alkaline phosphatase increased	35 (11.0)	1 (0.3)	43 (8.2)	1 (0.2)	31 (12.6)	44 (0.36)	1 (0.4)	1 (0.01)	2 (1.8)	2 (0.17)	0	0
Fatigue	33 (10.3)	3 (0.9)	60 (11.5)	8 (1.5)	23 (9.3)	34 (0.28)	0	0	7 (6.4)	8 (0.67)	0	0
Blood creatine phosphokinase increased	32 (10.0)	8 (2.5)	58 (11.1)	19 (3.6)	26 (10.6)	54 (0.44)	6 (2.4)	6 (0.05)	0	0	0	0
White blood cell count decreased	32 (10.0)	29 (9.1)	39 (7.5)	36 (6.9)	29 (11.8)	101 (0.83)	26 (10.6)	72 (0.59)	14 (12.8)	20 (1.68)	14 (12.8)	19 (1.60)
Neutrophil count decreased	30 (9.4)	28 (8.8)	39 (7.5)	36 (6.9)	25 (10.2)	66 (0.54)	24 (9.8)	54 (0.44)	9 (8.3)	17 (1.43)	9 (8.3)	12 (1.01)
Constipation	25 (7.8)	0	42 (8.0)	0	19 (7.7)	23 (0.19)	0	0	8 (7.3)	8 (0.67)	0	0
Neutropenia	25 (7.8)	25 (7.8)	34 (6.5)	33 (6.3)	21 (8.5)	38 (0.31)	21 (8.5)	31 (0.25)	9 (8.3)	10 (0.84)	8 (7.3)	9 (0.76)
Dysgeusia	21 (6.6)	0	38 (7.3)	0	16 (6.5)	16 (0.13)	0	0	2 (1.8)	2 (0.17)	0	0
Pyrexia	21 (6.6)	2 (0.6)	29 (5.6)	2 (0.4)	16 (6.5)	21 (0.17)	2 (0.8)	2 (0.02)	9 (8.3)	11 (0.92)	3 (2.8)	3 (0.25)
Electrocardiogram QT prolonged	20 (6.3)	3 (0.9)	29 (5.6)	6 (1.1)	12 (4.9)	15 (0.12)	1 (0.4)	1 (0.01)	0	0	0	0
Headache	20 (6.3)	0	26 (5.0)	0	18 (7.3)	25 (0.21)	0	0	5 (4.6)	7 (0.59)	0	0
Vomiting	20 (6.3)	1 (0.3)	32 (6.1)	3 (0.6)	14 (5.7)	17 (0.14)	0	0	10 (9.2)	10 (0.84)	0	0
Decreased appetite	19 (6.0)	0	30 (5.7)	1 (0.2)	14 (5.7)	16 (0.13)	0	0	11 (10.1)	11 (0.92)	4 (3.7)	4 (0.34)
Myalgia	17 (5.3)	0	26 (5.0)	2 (0.4)	15 (6.1)	18 (0.15)	0	0	0	0	0	0
Oedema peripheral	16 (5.0)	0	31 (5.9)	1 (0.2)	7 (2.8)	8 (0.07)	0	0	5 (4.6)	5 (0.42)	0	0
Rash	16 (5.0)	0	20 (3.8)	0	11 (4.5)	12 (0.10)	0	0	3 (2.8)	3 (0.25)	0	0

- *Adverse Drug Reactions Based on Preferred Term*

Table 50 Adverse Reactions – Integrated R/R AML Safety Population

MedDRA v19.1 System Organ Class Adverse Drug Reaction, n (%)	Integrated Gilteritinib 120 mg (N=319)		
	All Grades %	Grades 3/4 %	Frequency category†
Cardiac disorders			
Pericardial effusion	13 (4.1)	3 (0.9)	Common
Pericarditis	5 (1.6)	0	Uncommon
Cardiac failure	4 (1.3)	4 (1.3)	Uncommon
Gastrointestinal disorders			
Diarrhoea	112 (35.1)	13 (4.1)	Very common
Nausea	95 (29.8)	6 (1.9)	Very common
Constipation	90 (28.2)	2 (0.6)	Very common
General disorders and administration site conditions			
Fatigue	97 (30.4)	10 (3.1)	Very common
Oedema Peripheral	77 (24.1)	1 (0.3)	Very common
Asthenia	44 (13.8)	8 (2.5)	Very common
Malaise	14 (4.4)	0	Common
Immune system disorders			
Anaphylactic reaction	4 (1.3)	4 (1.3)	Common
Investigations			
Blood creatine phosphokinase increased‡	298 (93.4)	10 (3.1)	Very common
Alanine aminotransferase increased‡	262 (82.1)	41 (12.9)	Very common
Aspartate aminotransferase increased‡	257 (80.6)	33 (10.3)	Very common
Blood alkaline phosphatase increased‡	219 (68.7)	5 (1.6)	Very common
Electrocardiogram QT prolonged	28 (8.8)	8 (2.5)	Common
Musculoskeletal and connective tissue disorders			
Pain in extremity	47 (14.7)	2 (0.6)	Very common
Arthralgia	40 (12.5)	4 (1.3)	Very common
Myalgia	40 (12.5)	1 (0.3)	Very common
Musculoskeletal pain	13 (4.1)	1 (0.3)	Common
Nervous system disorders			
Dizziness	65 (20.4)	1 (0.3)	Very common
Posterior reversible encephalopathy syndrome	2 (0.6)	2 (0.6)	Uncommon
Respiratory, thoracic and mediastinal disorders			
Cough	90 (28.2)	1 (0.3)	Very common
Dyspnea	77 (24.1)	14 (4.4)	Very common
Vascular disorders			
Hypotension	55 (17.2)	23 (7.2)	Very common

AML: acute myeloid leukemia; R/R: relapsed or refractory.

†Frequency categories are defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

‡Frequency is based on central laboratory values, further described in [Module 5.3.5.3, ISS, Table 40].

Adverse events of interest

- *Posterior reversible encephalopathy syndrome (PRES)*

Overall, 0.6% (3/522) of patients in the gilteritinib total group experienced the TEAE of PRES PT. In the integrated gilteritinib 120 mg group, 0.6% (2/319) of patients experienced the TEAE of PRES PT. These TEAEs were serious and grade ≥ 3; none resulted in death. In Study 2215-CL-0301, 0.4% (1/246) of gilteritinib 120 mg-treated patients experienced the TEAE of PRES, compared to no patients in the chemotherapy group (0/109).
In addition, 1 patient enrolled in the compassionate use program for gilteritinib (developed PRES 18 days after the last dose of gilteritinib.

- *Differentiation syndrome*

Of 319 patients treated with Xospata in the clinical studies, 11 (3%) experienced differentiation syndrome. Differentiation syndrome occurred as early as two days and up to 75 days after Xospata initiation and has been observed with or without concomitant leukocytosis. Of the 11 patients who experienced differentiation syndrome, 9 (82%) recovered after treatment or after dose interruption of Xospata (SmPC, section 4.8).

- QT prolongation

In the integrated gilteritinib 120 mg group, TEAEs within this category of arrhythmia of QT prolongation were experienced by totally 15.7% (50/319) of patients, and were deemed drug-related in 7.2% (23/319) of patients in this population. The most frequent TEAEs were ECG QT prolonged (8.8% [28/319]; drug-related in 6.3% [20/319]) and syncope (5.0% [16/319]); drug-related in 0.6% [2/319]). One patient (0.3% [1/319]) experienced drug-related ventricular fibrillation.

Serious TEAEs were experienced by 5.3% (17/319) of patients and considered drug-related SAEs in 6 patients (1.9%), these were ECG QT prolonged (3 patients), syncope (2 patients) and ventricular fibrillation (1 patient).

Of the 317 patients treated with gilteritinib at 120 mg with a post baseline QTC value in clinical studies, 4 patients (1%) experienced a QTcF >500 msec. Additionally, across all doses, 12 patients (2.3%) with relapsed/refractory AML had a maximum post baseline QTcF interval >500 msec (SmPC, section 4.8).

- *Serious gastrointestinal disorders*

Overall, 11.3% (59/522) of patients in the gilteritinib total group experienced a TEAE of GI disorder. In the integrated gilteritinib 120 mg group, 10.3% (33/319) of patients experienced an event of GI disorder. These TEAEs were serious; 2 TEAE of GI disorder (in Study 2215-CL-0301) resulted in death. In Study 2215-CL-0301, 0.8% (2/246) of gilteritinib 120 mg-treated patients experienced a TEAE of GI disorder compared to 0.9% patients in the chemotherapy group (1/109).

- *Eye disorders*

Overall, 32.6% (170/522) of patients in the gilteritinib total group experienced a TEAE of eye disorders and 0.6% were serious non-fatal TEAEs (3/522). In the integrated gilteritinib 120 mg group, 39.2% (125/319) of patients experienced an event of eye disorders. These TEAEs were not serious; no TEAE of eye disorders (in Study 2215-CL-0301) resulted in death. In Study 2215-CL-0301, 39.4% (97/246) of gilteritinib 120 mg-treated patients experienced a TEAE of eye disorders compared to 11.0% patients in the chemotherapy group (12/109).

In the integrated gilteritinib 120 mg group, mean (SD) changes in mean visual acuity were 3.402 dB (8.486 dB) and 4.790 dB (10.666 dB) for patients' left and right eyes, respectively, with median (min, max) changes of 1.180 dB (-5.62, 60.00) and 1.980 dB (-5.85, 62.52). Two patients in the integrated

gilteritinib 120 mg group (both in Study 2215-CL-0301) discontinued treatment due to a TEAE of retinopathy; no other TEAEs leading to discontinuation were reported in the system organ class (SOC) of Eye Disorders.

Four treatment-emergent SAEs in the SOC of Eye Disorders were reported for 3 patients in the integrated gilteritinib 120 mg group. Two of these events were experienced by 1 patient in Study 2215-CL-0301 who experienced a Grade 2 event of ocular hyperemia and a Grade 2 event of vision blurred; both events were considered not related to gilteritinib and were reported on the same day. The other 2 events were experienced by 1 patient each, both in Study 2215-CL-0101; 1 patient experienced a Grade 3 event of conjunctival edema, considered possibly related to gilteritinib, and 1 patient experienced a worsening of baseline papilledema considered not related to gilteritinib. No TEAE of eye disorders (in Study 2215-CL-0301) resulted in death.

- *Pulmonary adverse events*

Overall, 64.4% (336/522) of patients in the gilteritinib total group experienced a pulmonary TEAE. In the integrated gilteritinib 120 mg group, 65.2% (208/319) of patients experienced a pulmonary event; 15.4 % (49/319) of patients experienced a serious pulmonary event; and 2.5% (8/319) patients experienced a pulmonary event that resulted in death. In Study 2215-CL-0301, 7 (2.8%) patients experienced a pulmonary event that resulted in death. In Study 2215-CL-0301, 66.3% (163/246) of gilteritinib 120 mg-treated patients experienced a pulmonary TEAE compared to 34.9% of patients in the chemotherapy group (38/109), however when adjusted for exposure of events per patient year, the pulmonary AE rate is 4.03% in the gilteritinib 120 mg treated patients compared to 5.88% of patients in the chemotherapy group.

- *Pancreatitis*

In the integrated gilteritinib 120 mg group, TEAEs within this category were experienced by 0.9% (3/319) of patients. The only TEAE by preferred term (PT) within this category was pancreatitis (0.9% [3/319]). Drug-related TEAEs within this category were not experienced by any patients in the integrated gilteritinib 120 mg group. Grade 3 or higher TEAEs within this category were experienced by 0.3% (1/319) of patients in the integrated gilteritinib 120 mg group and none were considered drug-related. Serious TEAEs within this category were experienced by 0.9% (3/319) of patients in the integrated gilteritinib 120 mg group and none were considered drug-related.

- *Cardiac Failure*

In the integrated gilteritinib 120 mg group, TEAEs within this category were experienced by 6.6% (21/319) of patients. The most frequent TEAEs by PT within this category were pulmonary edema (3.4% [11/319]), ejection fraction decreased (1.6% [5/319]) and cardiac failure (1.3% [4/319]). Drug-related TEAEs within this category were experienced by 1.6% (5/319) of patients in the integrated gilteritinib 120 mg group. Grade 3 or higher TEAEs within this category were experienced by 3.8% (12/319) of patients in the integrated gilteritinib 120 mg group. Drug-related Grade 3 or higher TEAEs within this category were experienced by 4 patients (1.3%) in the integrated gilteritinib 120 mg group (PTs: cardiac failure [2 patients], cardiac failure congestive [1 patient] and ejection fraction decreased [2 patients])

Serious TEAEs within this category were experienced by 1.9% (6/319) of patients in the integrated gilteritinib 120 mg group. Drug-related SAEs within this category were experienced by 3 patients (0.9%) in the integrated gilteritinib 120 mg group (PTs: cardiac failure [2 patients] and cardiac failure congestive [1 patient]).

- *Hypersensitivity/Anaphylaxis*

In the integrated gilteritinib 120 mg group, TEAEs within this category were experienced by 40.4% (129/319) of patients. The most frequent TEAEs by PT within this category were rash (15.0% [48/319])

and face edema (5.3% [17/319]). Drug-related TEAEs within this category were experienced by 13.5% (43/319) of patients in the integrated gilteritinib 120 mg group. Grade 3 or higher TEAEs within this category were experienced by 7.8% (25/319) of patients in the integrated gilteritinib 120 mg group, including 1.3% (4/319) of patients who experienced an anaphylactic reaction. Drug-related grade 3 or higher TEAEs within this category were experienced by 2.5% (8/319) in this population including 0.3% (1/319) of patients who experienced an anaphylactic reaction.

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

Serious adverse event/deaths/other significant events

Serious adverse events

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

Table 51 Serious Treatment-emergent Adverse Events (⩾ 2% of Integrated Gilteritinib 120 mg Patients) by Preferred Term and Relationship to Study Drug – Integrated R/R AML Safety Population

MedDRA (v19.1) Preferred Term	Integrated Data†				Study 2215-CL-0301							
	Gilteritinib 120 mg		Gilteritinib Total		Gilteritinib 120 mg				Chemo			
	N = 319		N = 522		N = 246	PY = 121.7 E (E/PY)	N = 246	PY = 121.7 E (E/PY)	N = 109	PY = 11.9 E (E/PY)	N = 109	PY =11.9 E (E/PY)
	All	Drug-Related‡	All	Drug-Related‡	All		Drug-Related‡		All		Drug-Related‡	
Overall, n (%)	**258 (80.9)**	**108 (33.9)**	**425 (81.4)**	**170 (32.6)**	**205 (83.3)**	**865 (7.11)**	**88 (35.8)**	**193 (1.59)**	**34 (31.2)**	**110 (9.24)**	**16 (14.7)**	**35 (2.94)**
Febrile neutropenia	95 (29.8)	24 (7.5)	157 (30.1)	29 (5.6)	76 (30.9)	112 (0.92)	23 (9.3)	28 (0.23)	9 (8.3)	15 (1.26)	3 (2.8)	3 (0.25)
Acute myeloid leukaemia	43 (13.5)	0	82 (15.7)	0	33 (13.4)	38 (0.31)	0	0	4 (3.7)	6 (0.50)	0	0
Pyrexia	42 (13.2)	3 (0.9)	54 (10.3)	6 (1.1)	32 (13.0)	43 (0.35)	2 (0.8)	2 (0.02)	1 (0.9)	2 (0.17)	0	0
Pneumonia	39 (12.2)	7 (2.2)	61 (11.7)	8 (1.5)	26 (10.6)	40 (0.33)	7 (2.8)	14 (0.12)	4 (3.7)	6 (0.50)	3 (2.8)	3 (0.25)
Sepsis	28 (8.8)	3 (0.9)	61 (11.7)	4 (0.8)	18 (7.3)	23 (0.19)	3 (1.2)	3 (0.02)	7 (6.4)	11 (0.92)	3 (2.8)	5 (0.42)
Acute kidney injury	21 (6.6)	5 (1.6)	44 (8.4)	8 (1.5)	16 (6.5)	20 (0.16)	3 (1.2)	3 (0.02)	4 (3.7)	5 (0.42)	2 (1.8)	2 (0.17)
Lung infection	16 (5.0)	0	24 (4.6)	0	14 (5.7)	17 (0.14)	0	0	5 (4.6)	6 (0.50)	2 (1.8)	3 (0.25)
Diarrhoea	15 (4.7)	2 (0.6)	24 (4.6)	6 (1.1)	10 (4.1)	13 (0.11)	1 (0.4)	3 (0.02)	0	0	0	0
Alanine aminotransferase increased	13 (4.1)	11 (3.4)	15 (2.9)	13 (2.5)	13 (5.3)	17 (0.14)	11 (4.5)	15 (0.12)	0	0	0	0
Bacteraemia	12 (3.8)	1 (0.3)	24 (4.6)	2 (0.4)	10 (4.1)	11 (0.09)	1 (0.4)	1 (0.01)	1 (0.9)	1 (0.08)	1 (0.9)	1 (0.08)
Dyspnoea	11 (3.4)	0	14 (2.7)	0	10 (4.1)	10 (0.08)	0	0	2 (1.8)	2 (0.17)	1 (0.9)	1 (0.8)
Aspartate aminotransferase increased	10 (3.1)	10 (3.1)	14 (2.7)	14 (2.7)	10 (4.1)	14 (0.12)	10 (4.1)	14 (0.12)	0	14 (0.10)	0	0

Cellulitis	10 (3.1)	2 (0.6)	14 (2.7)	2 (0.4)	6 (2.4)	6 (0.05)	2 (0.8)	2 (0.02)	0	0	0	0
Fall	10 (3.1)	1 (0.3)	12 (2.3)	1 (0.2)	8 (3.3)	8 (0.07)	1 (0.4)	1 (0.01)	1 (0.9)	1 (0.08)	0	0
Hypotension	9 (2.8)	2 (0.6)	16 (3.1)	4 (0.8)	6 (2.4)	6 (0.5)	1 (0.4)	1 (0.01)	1 (0.9)	1 (0.8)	0	0
Septic shock	9 (2.8)	2 (0.6)	16 (3.1)	3 (0.6)	9 (3.7)	15 (0.12)	2 (0.8)	3 (0.02)	1 (0.9)	1 (0.08)	0	0
Anaemia	8 (2.5)	5 (1.6)	15 (2.9)	6 (1.1)	8 (3.3)	10 (0.08)	5 (2.0)	5 (0.04)	0	0	0	0
Respiratory failure	8 (2.5)	3 (0.9)	24 (4.6)	4 (0.8)	7 (2.8)	8 (0.07)	3 (1.2)	3 (0.2)	3 (2.8)	5 (0.42)	2 (1.8)	4 (0.34)
Syncope	8 (2.5)	2 (0.6)	13 (2.5)	3 (0.6)	7 (2.8)	8 (0.07)	2 (0.8)	2 (0.02)	0	0	0	0
Acute myeloid leukaemia recurrent	7 (2.2)	0	8 (1.5)	0	7 (2.8)	9 (0.07)	0	0	0	0	0	0
Pneumonia fungal	7 (2.2)	0	13 (2.5)	0	2 (0.8)	2 (0.02)	0	0	0	2 (0.01)	0	0

Deaths

In the integrated gilteritinib 120 mg group, 70.8% (226/319) of patients died due to any cause. In the integrated gilteritinib 120 mg group, 29.8% (95/319) of patients experienced TEAEs leading to death. AML was the most common TEAE leading to death (11.9% [38/319]), followed by septic shock (2.2% [7/319]), sepsis (1.9% [6/319]), pneumonia (1.6% [5/319]) and cardiac arrest and lung infection (1.3% [4/319], each); all other TEAEs leading to death were reported in < 1.0% of patients in the integrated gilteritinib 120 mg group. TEAEs leading to death were considered drug-related by the Investigator for 3.8% (12/319) of patients in the integrated gilteritinib 120 mg group. These included 3 events of pneumonia (0.9%), 2 events each of large intestine perforation and septic shock (0.6%) and 1 event each of cardiac failure congestive, cellulitis, cerebral hemorrhage, depressed level of consciousness, intestinal ischemia, neutropenia, respiratory failure, sepsis and ventricular fibrillation (0.3%, each).

Laboratory findings

Haematology parameters

The table below shows haematology laboratory shifts from baseline to worst post baseline NCI-CTCAE (National Cancer Institute- Common Terminology Criteria for Adverse Events) (v4.03) Grade ≥ 3 for ANC, haemoglobin and platelets. Baseline was defined as the last available measurement prior to the first dose of gilteritinib. Worst post baseline was based on the worst case of all the post baseline visits including unscheduled visits of a patient.

Table 52 Hematology Laboratory Results: Shift Table From Baseline to Worst Postbaseline by NCI-CTCAE (V4.03) Grade ≥ 3 – Integrated R/R AML Safety Population

Treatment Group	Worst Postbaseline Grade	Baseline Grade, n (%)						
		Laboratory Test = Neutrophil Count for Low						
		Grade 0†	Grade 1	Grade 2	Grade 3	Grade 4	Total	No Data
Gilteritinib 120 mg	Grade 3	11 (12.4)	0	5 (16.1)	1 (2.5)	4 (2.8)	21	1
	Grade 4	65 (73.0)	0	25 (80.6)	36 (90.0)	138 (96.5)	264	4
	Total	89	0	31	40	143	303	7
	No Data	1	0	0	0	2	3	6
Gilteritinib Total	Grade 3	16 (12.9)	0	9 (20.9)	4 (6.5)	5 (2.0)	34	1
	Grade 4	84 (67.7)	0	31 (72.1)	54 (87.1)	242 (96.8)	411	6
	Total	124	0	43	62	250	479	9
	No Data	4	0	0	0	3	7	27
CL-0301 Gilteritinib 120 mg	Grade 3	10 (13.2)	0	5 (20.0)	1 (3.3)	2 (1.9)	18	1
	Grade 4	56 (73.7)	0	19 (76.0)	26 (86.7)	102 (97.1)	203	3
	Total	76	0	25	30	105	236	6
	No Data	1	0	0	0	2	3	1
CL-0301 Chemo	Grade 3	4 (9.8)	0	0	1 (9.1)	2 (4.9)	7	0
	Grade 4	29 (70.7)	0	8 (80.0)	8 (72.7)	33 (80.5)	78	0
	Total	41	0	10	11	41	103	0
	No Data	4	0	0	0	2	6	0
		Laboratory Test = Hemoglobin for Low						
		Grade 0†	Grade 1	Grade 2	Grade 3	Grade 4	Total	No Data
Gilteritinib 120 mg	Grade 3	6 (35.3)	44 (46.8)	112 (73.2)	35 (83.3)	0	197	5
	Grade 4	0	0	0	0	0	0	0
	Total	17	94	153	42	0	306	8
	No Data	0	0	2	1	0	3	2
Gilteritinib Total	Grade 3	7 (31.8)	64 (44.8)	168 (66.7)	70 (82.4)	0	309	6
	Grade 4	0	0	0	0	0	0	0
	Total	22	143	252	85	0	502	10
	No Data	0	1	5	1	0	7	3
CL-0301 Gilteritinib 120 mg	Grade 3	5 (33.3)	35 (44.3)	82 (74.5)	24 (77.4)	0	146	4
	Grade 4	0	0	0	0	0	0	0
	Total	15	79	110	31	0	235	7
	No Data	0	0	2	1	0	3	1
CL-0301 Chemo	Grade 3	5 (50.0)	12 (36.4)	22 (42.3)	6 (60.0)	0	45	0
	Grade 4	0	0	0	0	0	0	0
	Total	10	33	52	10	0	105	0
	No Data	0	3	0	1	0	4	0
		Baseline Grade, n (%)						
		Laboratory Test = Platelets for Low						
		Grade 0†	Grade 1	Grade 2	Grade 3	Grade 4	Total	No Data
Gilteritinib 120 mg	Grade 3	5 (15.2)	19 (35.8)	7 (13.7)	7 (8.3)	2 (2.4)	40	2
	Grade 4	12 (36.4)	22 (41.5)	39 (76.5)	76 (90.5)	83 (97.6)	232	5
	Total	33	53	51	84	85	306	8
	No Data	0	1	0	1	1	3	2
Gilteritinib Total	Grade 3	8 (15.7)	24 (30.8)	12 (16.2)	18 (12.2)	5 (3.3)	67	2
	Grade 4	16 (31.4)	39 (50.0)	54 (73.0)	128 (86.5)	146 (96.7)	383	7
	Total	51	78	74	148	151	502	10
	No Data	0	1	0	4	2	7	3
CL-0301 Gilteritinib 120 mg	Grade 3	5 (17.9)	18 (39.1)	4 (10.0)	5 (8.6)	1 (1.6)	33	2
	Grade 4	9 (32.1)	18 (39.1)	32 (80.0)	52 (89.7)	62 (98.4)	173	4
	Total	28	46	40	58	63	235	7
	No Data	0	1	0	1	1	3	1
CL-0301 Chemo	Grade 3	3 (20.0)	3 (11.1)	5 (41.7)	2 (7.7)	0	13	0
	Grade 4	9 (60.0)	20 (74.1)	7 (58.3)	24 (92.3)	24 (96.0)	84	0
	Total	15	27	12	26	25	105	0
	No Data	0	0	2	1	1	4	0

Chemistry

In Table 53, a summary of central chemistry laboratory parameters with Grade 3 or 4 for the integrated R/R AML safety population is provided.

Table 53 Summary of Central Chemistry Laboratory Parameters with Grade 3 or 4 NCI-CTCAE (V4.03) - Integrated R/R AML Safety Population

Parameter Term (n, %)		Integrated Data†		Study 2215-CL-0301	
		Gilteritinib 120 mg	Gilteritinib Total	Gilteritinib 120 mg	Chemo
	Grades	(N = 319)	(N = 522)	(N = 246)	(N = 109)
Creatinine, increased	≥ 1	298 (93.4)	491 (94.1)	228 (92.7)	58 (53.2)
	3/4	10 (3.1)	17 (3.3)	6 (2.4)	0
Aspartate aminotransferase, increased	≥ 1	257 (80.6)	420 (80.5)	200 (81.3)	42 (38.5)
	3/4	33 (10.3)	55 (10.5)	25 (10.2)	2 (1.8)
Hyperglycemia	≥ 1	281 (88.1)	421 (80.7)	232 (94.3)	103 (94.5)
	3/4	32 (10.0)	55 (10.5)	29 (11.8)	13 (11.9)
Alanine aminotransferase, increased	≥ 1	262 (82.1)	412 (78.9)	205 (83.3)	52 (47.4)
	3/4	41 (12.9)	59 (11.3)	31 (12.6)	3 (2.8)
Hypocalcemia	≥ 1	207 (64.9)	354 (67.8)	151 (61.4)	55 (50.5)
	3/4	19 (6.0)	37 (7.1)	16 (6.5)	4 (3.7)
Hypoalbuminemia, albumin	≥ 1	191 (59.9)	345 (66.1)	133 (54.1)	48 (44.0)
	3/4	11 (3.4)	24 (4.6)	8 (3.3)	2 (1.8)
Alkaline phosphatase, increased	≥ 1	219 (68.7)	357 (68.4)	168 (68.3)	46 (42.2)
	3/4	5 (1.6)	5 (1.0)	4 (1.6)	0
Creatine kinase, increased	≥ 1	172 (53.9)	276 (52.9)	126 (51.2)	1 (0.9)
	3/4	20 (6.3)	40 (7.7)	16 (6.5)	0
Hypophosphatemia	≥ 1	163 (51.1)	261 (50.0)	119 (48.4)	45 (41.3)
	3/4	45 (14.1)	74 (14.2)	33 (13.4)	13 (11.9)
Hypokalemia	≥ 1	108 (33.9)	192 (36.8)	79 (32.1)	55 (50.5)
	3/4	28 (8.8)	50 (9.6)	19 (7.7)	17 (15.6)
Hyponatremia	≥ 1	102 (32.0)	158 (30.3)	88 (35.8)	30 (27.5)
	3/4	38 (11.9)	63 (12.1)	30 (12.2)	7 (6.4)
Hypomagnesemia	≥ 1	60 (18.8)	126 (24.1)	46 (18.7)	19 (17.4)
	3/4	0	2 (0.4)	0	1 (0.9)

Safety in special populations

Age group

Table 54 Overview of treatment emergent adverse events by age group after treatment with gilteritinib 120 mg- safety analysis set-Integrated R/R AML safety population

MedDRA Terms	Age < 65 (N = 183) n (%)	Age 65-74 (N = 96) n (%)	Age 75-84 (N = 38) n (%)	Age 85+ (N = 2) n (%)
Total AEs	181 (98.9)	96 (100.0)	38 (100)	2 (100.0)
SAEs – Total†	143 (78.1)	77 (80.2)	37 (97.4)	1 (50.0)
- Fatal	42 (23.0)	33 (34.4)	19 (50.0)	1 (50.0)
- Hospitalization/prolong existing hospitalization	124 (67.8)	73 (76.0)	36 (94.7)	1 (50.0)
- Life-threatening	23 (12.6)	15 (15.6)	5 (13.2)	0
- Disability/incapacity	3 (1.6)	2 (2.1)	1 (2.6)	0
- Other (medically significant)	37 (20.2)	19 (19.8)	9 (23.7)	0
AE leading to drop-out	38 (20.8)	22 (22.9)	10 (26.3)	0
Psychiatric disorders‡	50 (27.3)	26 (27.1)	15 (39.5)	1 (50.0)
Nervous system disorders‡	108 (59.0)	46 (47.9)	20 (52.6)	1 (50.0)
Accidents and injuries§	37 (20.2)	24 (25.0)	12 (31.6)	1 (50.0)
Cardiac disorders‡	46 (25.1)	20 (20.8)	17 (44.7)	0
Vascular disorders‡	77 (42.1)	37 (38.5)	17 (44.7)	1 (50.0)
Cerebrovascular disorders§	9 (4.9)	5 (5.2)	4 (10.5)	0
Infections and infestations‡	132 (72.1)	76 (79.2)	33 (86.8)	2 (100.0)
Anticholinergic syndrome§	113 (61.7)	60 (62.5)	28 (73.7)	2 (100.0)
Quality of life decreased¶	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures¶	56 (30.6)	27 (28.1)	12 (31.6)	1 (50.0)

AE: adverse event; AML: acute myeloid leukemia; R/R: relapsed/refractory; SAE: serious adverse event.
†Includes SAEs upgraded by the sponsor based on review of the Sponsor's list of Always Serious terms, if any update was done.
‡Based on System Organ Class terms.
§Based on Standardized MedDRA Query terms.
¶Based on Preferred Terms.

Gender

A numerical higher incidence of all drug-related TEAEs and Grade 3 or higher TEAEs was reported in females. No meaningful differences were observed in frequencies of drug-related TEAEs or Grade 3 or higher drug-related TEAEs across subgroups of patients with different baseline BW measurements. A numerical higher incidence of drug-related ALT/AST increased, febrile neutropenia, platelet count decreased and blood creatine phosphokinase (CK) increased in Asians compared to the white subgroup. Similar observations were made for Grade 3 or higher TEAEs. All drug-related and Grade 3 or higher drug-related TEAEs were generally similar between subgroups with baseline ECOG status of 0 to 1 vs ≥ 2. A numerical higher incidence of drug related ALT was reported in Asian patients were reported compared to subgroups living in Europe and North America (data not shown).

Safety related to drug-drug interactions and other interactions

No specific safety issues related to possible DDI were identified (see also discussion on clinical pharmacology).

Discontinuation due to adverse events

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

Post marketing experience

Not applicable

2.6.1. Discussion on clinical safety

Overall, the analysed safety population is considered as representative in terms of the targeted population.

In the integrated gilteritinib 120 mg group, the median average daily dose was 120 mg/day (range 50 to 290 mg/day), and the median duration of exposure was 111 days (range 4 - 1320 days). The median number of dosing days was 106 days, ranging from 4 to 1313 days), and the median relative dose intensity was 100%, ranging from 39% to 227%. Increase in number and duration of the most frequent TEAEs by increasing of exposure time on 120 mg gilteritinib seems not to be related to worsening of the grade of TEAEs. The median duration of ≥ Grade 3 diarrhoea, neutropenia, and pyrexia was highest in the integrated total gilteritinib group. Although there was an increase in TEAEs after 60 days compared to the first 60 days, these events were most likely related to AML progression and worsening of the general condition of the patients, rather than gilteritinib treatment. Follow-up period was defined as 30 days or 28 days after the last dose. The 30- or 28-day follow-up was applied as a standard period required for reporting of all AEs that may occur after discontinuation of a study drug. Patients were followed-up after discontinuation until death or withdrawal of consent. The follow up was reported every 3 months. The presented long-term safety data did not reveal any new safety issues.

In the integrated gilteritinib 120 mg group, 99.4% (317/319) of patients experienced at least 1 TEAE, of which drug-related in 83.1% (265/319) of patients. TEAEs with a maximum NCI-CTCAE grade ≥3 were experienced by 93.4% (298/319) of patients, and considered drug-related in 60.2% (192/319) of the patients.

The most frequent adverse reactions with gilteritinib were blood CK increased (93.4%), ALT increased (82.1%), AST increased (80.6%), blood alkaline phosphatase increased (68.7%), diarrhoea (35.1%), fatigue (30.4%), nausea (29.8%), constipation (28.2%), cough (28.2%), peripheral oedema (24.1%), dyspnoea (24.1%), dizziness (20.4%), hypotension (17.2%), pain in extremity (14.7%), asthenia (13.8%), arthralgia (12.5%) and myalgia (12.5%) (SmPC, section 4.8).

The most frequent serious adverse reactions were diarrhoea (4.7%), ALT increased (4.1%), dyspnoea (3.4%), AST increased (3.1%) and hypotension (2.8%). Other clinically significant serious adverse reactions included differentiation syndrome (2.2%), ECG QT prolonged (0.9%) and posterior reversible encephalopathy syndrome (0.6%) (SmPC, section 4.8).

Posterior reversible encephalopathy syndrome (PRES): There have been reports of PRES in patients receiving Xospata (see section 4.8). Of the 319 patients treated with Xospata in the clinical studies, 0.6% experienced PRES. PRES is a rare, reversible, neurological disorder which can present with rapidly evolving symptoms including seizure, headache, confusion, visual and neurological disturbances, with or without associated hypertension and altered mental status. If PRES is suspected, it should be confirmed by brain imaging, preferably magnetic resonance imaging (MRI). Symptoms have resolved after discontinuation of treatment. Discontinuation of Xospata in patients who develop PRES is recommended (SmPC sections 4.2 and 4.8). PRES has been categorized as an identified risk (see RMP).

Differentiation syndrome: Gilteritinib has been associated with differentiation syndrome. Following reassessment as requested, 11 cases was identified (including 1 fatal case). Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life threatening or fatal if not treated. Symptoms and clinical findings of differentiation syndrome include fever, dyspnoea, pleural effusion, pericardial effusion, pulmonary oedema, hypotension, rapid weight gain, peripheral oedema, rash, and renal dysfunction. If differentiation syndrome is suspected, corticosteroid therapy should be initiated along with hemodynamic monitoring until symptom resolution. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, Xospata should be interrupted until signs and symptoms are no longer severe. Corticosteroids can be tapered after resolution of symptoms and should be administered for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment (SmPC sections 4.2, 4.4 and 4.8). Differentiation syndrome has been categorized as an identified risk (see RMP).

QT prolongation: In the integrated gilteritinib 120 mg group, the majority of patients experienced an increase in QTcF value from baseline; although the mean value of QTc shows little change with use of gilteritinib, more patients had abnormally high values while taking gilteritinib than at baseline. No exposure-safety relationship (with respect to increased AST, ALT, CK, and reduced ALB) was characterized. Similar to the exposure-efficacy analysis, there was also an exploratory analysis with limited ability to identify any relationships other than major trends. There is a tendency towards and increased risk of increased absolute OTcF value in patients with a cardiac history. Regarding co-medication with QT prolonging agents; in the total gilteritinib group (across all doses), 11 out of 12 cases with absolute OTcF values >500 msec were observed in patients receiving one or more QT prolonging agents. Three patients interrupted and re-initiated treatment without recurrence of QT prolongation. There were no reported cases of Torsade de Pointes. An increased risk of QTc prolongation at the 200 mg dose compared to 120 mg dose cannot be excluded. However, Torsade de Pointes is included as a safety concern in the RMP to gain more information about this risk. With the proposed ECG monitoring and dose adjustment guidance stated in the SmPC, this risk is considered acceptable. An additional pharmacovigilance (PhV) activity is also included in the PhV plan to characterise this risk further.

Additionally, concomitant use of CYP3A4 inhibitors (that could lead to increased gilteritinib exposure adding to the observed PK variability) as well as drugs with a known potential to prolong QTc is expected to be common in the target population. In study 0301 >80% and >90%, respectively, received such concomitant treatment.

Gilteritinib has been associated with prolonged cardiac ventricular repolarisation (QT Interval) QT prolongation can be observed in the first two months of treatment with gilteritinib. Therefore, ECG should be performed prior to initiation of treatment, on day 15 and prior to the start of the next two subsequent months of treatment. Caution is warranted in patients with relevant cardiac history. Hypokalaemia or hypomagnesaemia may increase the QT prolongation risk. Hypokalaemia or hypomagnesaemia should therefore be corrected prior to and during Xospata treatment (SmPC, sections 4.4, 4.8 and 5.1).

Xospata should be interrupted in patients who have a QTcF >500 msec. If Xospata is re-introduced at a reduced dose, ECG should be performed on day 8 and 15 and prior to the start of the next two subsequent months of treatment (SmPC, sections 4.2, 4.4).

Serious gastrointestinal disorders: Among gilteritinib-treated patients in clinical trials, the events of GI haemorrhage SMQ, GI perforation SMQ and GI obstruction SMQ were generally grade 1 or 2 and non-serious. Estimated 5.7% (30/522) of patients experienced an AE of grade 3 or higher. In two patients, the events of severe GI disorders led to death and in one patient, the event led to treatment discontinuation. Given the severity of the indication being treated, the occurrence of such events in the patient population due to pre-existing conditions and other risk factors, as well as few reports of serious events of GI disorders, the impact on the risk-benefit balance is considered low. An association of the events of GI disorder with gilteritinib therapy has not been confirmed. The overall benefits outweigh the risk in the treatment of AML. Serious GI disorders have been categorized as a potential risk in the RMP and will be followed by routine monitoring (see RMP).

Eye disorders: Ophthalmologic examinations have been performed in the studies to assess visual acuity. Two patients in the integrated gilteritinib 120 mg group (both in Study 2215-CL-0301) discontinued treatment due to a TEAE of retinopathy. Four SAEs in the SOC of Eye Disorders were reported for 3 patients in the integrated gilteritinib 120 mg group. It is unclear whether eye toxicity appears as a single toxicity symptom or always in relation to PRES. From the preclinical documentation, the eye is a target organ of toxicity. Ophthalmologic examinations have been performed in the studies to assess visual acuity, and there are few reports on eye toxicities, including treatment-related AEs. Due to these single reports, it is at present acceptable not to include these events in the product information (PI). However, since eye toxicity is a concern, eye disorders have been categorized a potential risk in the RMP and will be followed by routine monitoring (see RMP).

Pulmonary AEs: In non-clinical studies, lungs were one of the target organs with major findings in rats and dogs. In the integrated population 18.5% (59 patients) experienced pneumonia, of which grade≥3 in 13.5% (43/319), not knowing how many cases are deemed drug-related. In the SOC Respiratory, thoracic and mediastinal disorders a total of 30 patients (9.4%) experienced SAEs, of which 5 patients (1.6%) were drug-related. These five were respiratory failure (3 patients), hypoxia and pleural effusion (1 patient each). In 3 patients (0.9%) experienced TEAE of pneumonia (all considered drug-related) leading to discontinuation of treatment. There were 3 fatal cases due to TEAE of pneumonia. Regarding the serious adverse events (SAEs), there is a clear increase in frequencies in the patients who have escalated to 200 mg dose, including serious events. Differences in SAEs between the patients before dose escalation (still on 120 mg) and after dose escalation to 200 mg is noted, including in the SOCRespiratory, thoracic and mediastinal disorders 3.8% vs. 11.5% [3 vs 9 patients]). Pulmonary toxicity may be symptomatically related to differentiation syndrome. Pulmonary AEs have been have been categorized a potential risk in the RMP (see RMP).

Pancreatitis: Within the category of pancreatitis, TEAEs were reported for 0.9% (3/319) patients, of which none were considered related to gilteritinib. Grade 3 or higher TEAEs and Serious TEAEs were reported for 0.3% (1/319) and 0.9% (3/319) respectively, none were considered related.

Patients who develop signs and symptoms suggestive of pancreatitis should be evaluated and monitored. Xospata should be interrupted and can be resumed at a reduced dose when the signs and symptoms of pancreatitis have resolved (SmpC, sections 4.2 and 4.8). Pancreatitis has been categorized a potential risk in the RMP (see RMP).

Hepatotoxicity: Gilteritinib is associated with dose- and concentration-dependent increases in liver function tests, most notably ALT and AST, and elevations in CK. In general, these increases were mostly Grade 1 or 2 in severity, were reversible upon drug interruption and seldom resulted in patient discontinuation from treatment. CK elevations were not consistently associated with increases in

aldolase. Overall, liver enzyme elevations were frequently observed in patients the integrated gilteritinib 120 mg group, and included elevations of >3, >5, >10 and >20 x ULN of ALT and AST, as well elevated total bilirubin values > 2 x ULN alkaline phosphatase values > 1.5 x ULN.

Renal toxicity: The kidney/urinary bladder are considered target organs of toxicity and clinical relevance of the findings in these organs cannot be excluded as per non-clinical assessment. There have been 44 SAEs of acute kidney injury (8.4%) in the total safety population of gilteritinib. Of these 8 (1.5%) were reported as drug-related serious events of acute kidney injury with gilteritinib. While drug-related acute kidney injury was comparable between gilteritinib and chemo in study 2215-CL-0301, the chemotherapy group included either the nephrotoxic agent cytarabine or azacitidine. The inherent potential of gilteritinib of causing acute kidney injury is still present and relevant for the single patient. That implies that since there seem to be a similar incidence of AKI in both gilteritinib and chemo, gilteritinib seem to have the same degree of nephrotoxicity / nephrotoxic potential as the comparators (cytarabine and azaticidine). The applicant committed to conduct a phase I study to investigate the effect of renal impairment on the pharmacokinetics, safety and tolerability of gilteritinib compared to subjects with normal renal function (see RMP).

Deaths: The percentage of patients in the phase 3 study 2215-CL-0301 with a TEAE leading to death that was considered drug-related was similar in both treatment arms (4.1% in the gilteritinib arm, compared with 4.6% of patients in the salvage chemotherapy arm).

SAEs: In the integrated gilteritinib 120 mg group, 80.9% (258/319) of patients experienced at least 1 serious TEAE of which were drug-related in 33.9% (108/319) of patients. The most frequently reported SAEs by MedDRA PT were febrile neutropenia (29.8% [95/319]), AML (13.5% [43/319]), pyrexia (13.2% [42/319]) and pneumonia (12.2% [39/319]). The most frequently reported drug-related SAEs by MedDRA PT were febrile neutropenia (7.5% [24/319]), ALT increased (3.4% [11/319]) and AST increased (3.1% [10/319]).

Dose modification: In the integrated gilteritinib 120 mg group, dose increases to 200 mg were experienced by 35.4% (113/319) of patients due to lack of efficacy. Dose decreases were experienced by 25.7% (82/319) of patients. In this population 12.9% (41/319) of patients experienced TEAEs leading to dose reduction, the majority [11.0% (35/319)] of which were considered drug-related by the investigator. Overall, 47.3% (151/319) of patients experienced at least 1 day of gilteritinib dose interruption. TEAEs leading to drug interruption were experienced by 45.1% (144/319) of patients and considered drug-related in 30.4% (97/319) of patients.

Due to the limited long-term safety data available, long-term safety data is classified in the RMP as missing information (see RMP).

Although a limited number of patients escalated to 200 mg, these results suggest that the dose is tolerable.
Gilteritinib has minor influence on the ability to drive and use machines. Dizziness has been reported in patients taking Xospata and should be considered when assessing a patient's ability to drive or use machines (SmPC, section 4.7).

From the safety database all the adverse reactions reported in clinical trials have been included in the SmPC.

2.6.2. Conclusions on the clinical safety

The safety profile of gilteritinib at the proposed therapeutic dose of 120 mg was manageable in the R/R AML patients. The most commonly occurring AEs were generally associated with the known pathophysiology of AML, and known toxicity from other TKIs.

2.7. Risk Management Plan

Safety concerns

Table 55 Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Posterior reversible encephalopathy syndrome (PRES) • Differentiation syndrome
Important potential risks	• Torsades de Pointes • Serious GI disorders • Eye disorders • Pulmonary adverse events • Pancreatitis • Embryo-fetal lethality, suppressed fetal growth, and teratogenicity
Missing information	• Safety in patients with renal impairment • Long term safety

Pharmacovigilance plan

Table 56 Ongoing and planned additional pharmacovigilance activities

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
A Phase I Study to Investigate the Effect of Renal Impairment on the Pharmacokinetics, Safety and Tolerability of Gilteritinib Compared to Subjects with Normal Renal Function (planned)	Primary: To evaluate the effect of severe renal impairment on the pharmacokinetics of gilteritinib relative to the pharmacokinetics in healthy subjects with normal renal function Secondary: To evaluate the safety and tolerability of gilteritinib in subjects with severe renal impairment and healthy subjects with normal renal function	Safety in patients with renal impairment	Protocol submission for review: Final study report submission:	Q2 2020 Q2 2022

Table 56 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Evaluation of the effectiveness of the Xospata Routine Risk Minimization Measures (RMMs) and an additional Risk Minimisation Measure (aRMM): A Cross-sectional study among Healthcare Professionals to assess awareness and knowledge (planned)	To evaluate awareness and clinical knowledge of healthcare professionals for selected safety concerns	• Differentiation syndrome • Posterior reversible encephalopathy syndrome (PRES) • Torsades de Pointes	Protocol submission for review: Final study report submission:	Q2 2020 Q2 2022

Risk minimisation measures

Table 57 Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Posterior reversible encephalopathy syndrome (PRES)	Routine risk communication: • SmPC sections 4.2,4.4,4.8 • PL sections 2 and 4. Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation to discontinue gilteritinib in patients who develop PRES is provided in SmPC section 4.2 and 4.4.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • Healthcare professional survey study
Differentiation Syndrome	Routine risk communication: • SmPC sections 4.2; 4.4; 4.8 • PL sections 2 and 4. Routine risk minimization activities recommending specific clinical measures to address the risk: • Recommendation for monitoring is provided in SmPC section 4.4; • Recommendation for treatment interruption of gilteritinib if severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids is provided in SmPC section 4.2 and 4.4. Additional risk minimisation measures: • Healthcare Professional Information • Patient alert card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire for Differentiation Syndrome. Additional pharmacovigilance activities: • Healthcare professional survey study

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.5 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 21 September 2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of gilteritinib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

2.9.1. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Xospata (gilteritinib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Xospata is indicated as monotherapy for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation (see sections 4.2 and 5.1).

3.1.2. Available therapies and unmet medical need

There is no universally accepted standard of care for patients with R/R AML; possible salvage regimens are IDAC with or without anthracycline, MEC or FLAG-IDA. Additionally, there are no definitive studies that showed superiority of any single regimen and patients should be enrolled in a clinical trial whenever possible.

In view of the inherent poor prognosis of R/R FLT3-mutation positive AML and as no therapies are approved in the EU, there is an unmet medical need.

3.1.3. Main clinical studies

The clinical package of gilteritinib was primarily supported by data from a phase 3 open-label, multicentre, randomized study of gilteritinib versus salvage chemotherapy in patients with R/R AML with FLT3 mutation (ADMIRAL Study/2215-CL-0301).

3.2. Favourable effects

ADMIRAL study has provided convincing evidence of clinical efficacy of gilteritinib in terms of the primary endpoint OS, compared to salvage chemotherapy in patients with R/R AML with FLT3 mutation. Results for the primary endpoint (OS) in the ITT population showed a median OS of 9.3 months in the gilteritinib arm and 5.6 months for salvage chemotherapy (HR= 0.637; 95% CI: 0.490 to 0.830; p=0.0004 one-sided log rank test). Sensitivity analysis censoring at HSCT or time of new antileukaemia treatment showed consistent results with the primary analysis for OS.

Subgroup analyses were consistent with the primary efficacy analysis across several prognostic factors such as age, response category to first line therapy, AML risk score, and for patients eligible for low and high intensity treatment.

There was a numerical increase in EFS in the gilteritinib arm, compared to the salvage chemotherapy arm (median 2.8 months (95% CI: 1.4, 3.4) vs 0.7 months (95% CI; 0.2, NE)), but the EFS endpoint did not meet the pre-specified criteria for statistical significance (HR= 0.93 95%: CI 0.577, 1.089, p=0,0415 1-sided log rank test).

Responses were assessed using the sponsor modified 2003 IWG response criteria for AML. The CR rate was higher in the gilteritinib arm, 21.1% (95 % CI: 16.1, 26.7), compared with the salvage chemotherapy arm, 10.5% (95% CI: 5.7, 17.3), with a treatment difference of 10.6% (95% CI: 2,7, 18).

Furthermore, 63 patients (25.5%) in the gilteritinib arm and 19 patients (15.3%) in the salvage chemotherapy arm underwent an allogenic HSCT post protocol treatment.In the supportive study, 2215-CL-0101, the CR rate for FLT3 mutation positive patients receiving 120 mg gilteritinib was 12.5% and the median OS for dose groups ≥ 80 mg gilteritinib was 218.0 days.

3.3. Uncertainties and limitations about favourable effects

The key secondary endpoints (CR and EFS) were of limited value. The lack of long-term (beyond 2 months) systematic documentation of response and relapse status in the high intensity chemotherapy group, and the large proportion of patients with no evaluable post-baseline response assessments in the salvage chemotherapy arm preclude relevant comparisons of response rates and response related time-to event endpoints between the treatment arms. However, despite the lack of support from these endpoints, the robust and clinically relevant benefit on OS is considered sufficient to establish the benefit of gilteritinib.

The benefit-risk of increasing the gilteritinib dose from 120 mg to 200 mg in patients with lack of response following one treatment cycle is unclear. No exposure response relationship has been characterised to justify the dose escalation and it is not possible to differentiate whether the increase in response rates observed following dose-escalation is due to the increased dose or the longer treatment duration. Nevertheless, the dose escalation was part of the treatment strategy in the pivotal trial. Therefore, the option to dose escalate non-responding patients following one treatment cycle is included in the SmPC.

3.4. Unfavourable effects

In the integrated gilteritinib 120 mg group, almost all (99.4%) of patients experienced at least 1 TEAE, of which drug-related in 83.1%. TEAEs with grade ≥3 were experienced by 93.4% of patients, and considered drug-related in 60.2%. The most frequently reported Grade 3 or higher drug related TEAEs in the integrated gilteritinib 120 mg group included anaemia (16.9% [54/319]), febrile neutropenia (12.2% [39/319]), thrombocytopenia (11.6% [37/319]) and platelet count decreased (11.3% [36/319]).

In the integrated gilteritinib 120 mg group, the majority of patients experienced an increase in QTcF value from baseline; although the mean value of QTc shows little change with use of gilteritinib, more patients had abnormally high values while taking gilteritinib than at baseline. The most frequent TEAEs were ECG QT prolonged (8.8% [28/319]; drug-related in 6.3% [20/319]) and syncope (5.0% [16/319]); drug-related in 0.6% [2/319]). One patient (0.3% [1/319]) experienced drug-related ventricular fibrillation. Serious TEAEs were experienced by 5.3% (17/319) of patients and considered drug-related SAEs in 6 patients (1.9%).

Differentiation syndrome was reported for 3% (11/319) of patients. Of the 11 patients who experienced differentiation syndrome, 9 (82%) recovered after treatment or after dose interruption of Xospata. No SAEs were reported, but 1 patient (0.3% [1/319]) experienced a drug-related Grade 3 or higher event.

The percentage of patients in the phase 3 study 2215-CL-0301 with a TEAE leading to death that was considered drug-related was similar in both treatment arms (4.1% in the gilteritinib arm, compared with 4.6% of patients in the salvage chemotherapy arm).

Serious TEAEs were experienced by 80.9% (258/319) of patients, of which were drug-related in 33.9% (108/319) of patients. The most frequently reported drug-related SAEs by MedDRA PT were febrile neutropenia (7.5% [24/319]), ALT increased (3.4% [11/319]) and AST increased (3.1% [10/319]).

TEAEs leading to discontinuation of gilteritinib were experienced by 21.9% (70/319) of patients, of which were considered drug-related in 10.0% (32/319) of patients. The most frequently reported drug-related TEAEs leading to discontinuation of treatment were AST increased (1.3%) and ALT increased and pneumonia (0.9% each).

3.5. Uncertainties and limitations about unfavourable effects

Despite the higher frequencies of Grade ⩾ 3 TEAEs and SAEs in the dose escalated gilteritinib group compared to the non-dose escalated group, the frequency rates of dose interruption and treatment discontinuation were similar across the groups. Although a limited number of patients escalated to 200 mg, these results suggest that the dose escalation is tolerable and no further data is required.

In the integrated gilteritinib 120 mg group, the majority of patients experienced an increase in QTcF value from baseline; although the mean value of QTc shows little change with use of gilteritinib, more patients had abnormally high values while taking gilteritinib than at baseline. There is uncertainty about the precise exposure-safety relationship (with respect to increased AST, ALT, CK, and reduced ALB) although there is a clear increase in frequencies of AEs, including serious events, in the patients who have escalated to the 200 mg dose, despite small number of events due to limited number of patients that was dose escalated. Thus, an increased risk of QTc prolongation at the 200 mg dose compared to 120 mg dose cannot be excluded. Therefore, torsade de pointes is included as a safety concern in the RMP to gain more information about this risk. Also, ECG monitoring and dose adjustment guidance are stated in the SmPC and the risk is considered acceptable.

In non-clinical studies, lungs were one of the target organs with major findings in rats and dogs. In the integrated population 18.5% (59 patients) experienced pneumonia, of which grade≥3 in 13.5% (43/319)

although it is uncertain how many cases are deemed drug-related. Three (3) patients (0.9%) experienced TEAE of pneumonia (all considered drug-related) leading to discontinuation of treatment. There were 3 fatal cases due to TEAE of pneumonia. Pulmonary toxicity may be symptomatically related to differentiation syndrome. Pulmonary AEs have been have been categorized a potential risk in the RMP (see RMP).

3.6. Effects Table

Table 58 Effects Table for gilteritinib in adult patients who have R/R AML with a FLT3 mutation (Study/2215-CL-0301, cut-off date: 17 September 2018)

Effect	Short Description	Unit	Treatment Gilteritinib N=247	Control chemotherapy N=124	Uncertainties/ Strength of evidence	References
Favourable Effects						
OS	Median time from randomisation until death by any cause	Months	9.3 (7.7, 10.7)	5.6 (4.7, 7.3)	- HR= 0.637 95% CI: 0.490 to 0.830, p=0.0004 - Due to the lack of re-randomization following HSCT, the additional benefit conferred by post-HSCT gilteritinib cannot be determined - key secondary endpoints (CR and EFS) were of limited value	Study/2215-CL-0301
Unfavourable Effects (1)						
Drug related TEAE	- All grades - Grade ≥3	%	83.1 60.2	65.1 52.3		Integrated R/R AML safety population
ALT increased	- All grades - Grade ≥3	%	82.1 12.9	47.7 2.8		
Diarrhoea	- All grades - Grade ≥3	%	35.1 4.1	29.4 2.8		
Nausea	- All grades - Grade ≥3	%	29.8 1.9	33 0		
Fatigue	- All grades - Grade ≥3	%	30.4 3.1	12.8 0		
Electrodiagram QT prolonged	- All grades - Grade ≥3	%	8.8 2.5	0 0		
Myalgia	- All grades - Grade ≥3	%	12.5 0.3	0 0		

Abbreviations: AML: acute myeloid leukemia; CI: Confidence interval; HR: Hazard ratio; OS: Overall survival; TEAE: treatment emergent adverse event; ALT: alanine aminotransferase
Notes (1): Integrated 120 mg gilteritinib population: n=319 and Chemotherapy: n=109

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The most important effect observed is the statistically significant and clinically relevant improvement in OS. This OS benefit appears robust across several sensitivity analyses with conservative assumptions.

Gilteritinib at the proposed therapeutic dose of 120 mg was manageable in the population of R/R AML patients studied considering the disease, and the most commonly occurring AEs were generally associated with the known pathophysiology of AML, and known toxicity from other TKIs.

3.7.2. Balance of benefits and risks

Given the poor prognosis of patients with AML, the treatment effect of gilteritinib is considered clinically relevant, and has been robustly demonstrated in the single pivotal study that was submitted. The safety profile of gilteritinib at the proposed therapeutic dose of 120 mg was manageable in the R/R AML patients and is acceptable in view of the therapeutic context.

Therefore, the benefit-risk balance for gilteritinib in the proposed indication is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

The pivotal study included R/R AML patients previously treated with only 1 prior line of therapy. In order to support the broad indication claim, additional analyses of patients receiving >1 prior treatment in the supportive, study (2215-0101) were conducted. These indicated that responses, i.e. CR and CRc are achieved also for patients in later treatment lines, and the reported median OS generally exceeds that observed with chemotherapy both in the clinical pivotal study and when compared to a published historical dataset. Furthermore, there is no clear indication from the PD data on potential resistance mechanisms, to suggest a reduced benefit of gilteritinib vs chemotherapy in later treatment lines. Also the safety data did not indicate any clinically meaningful differences with regards to number of prior treatment lines. Thus, taking into account the totality of the data, the B/R ratio of gilteritinib is considered positive also in patients with > 1 prior treatments.

3.8. Conclusions

The overall Benefit-Risk balance of XOSPATA is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Xospata is not similar to Rydapt, Vyxeos, Mylotarg and Dacogen within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of XOSPATA is favourable in the following indication:

Xospata is indicated as monotherapy for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation (see sections 4.2 and 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the conditions

described below.

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to the launch of Xospata in each Member State the MAH must agree about the content and format of the physician educational material, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority. The patient alert card will be integrated in the packaging and the content will be agreed as part of the labelling (Annex III of the SmPC).

The educational material is aimed at haematologists who treat patients with leukemias including AML, and patients with AML prescribed Xospata to further inform prescribers and patients regarding the important identified risk of differentiation syndrome.

The MAH shall ensure that in each Member State where Xospata is marketed, haematologists who are expected to prescribe Xospata, and patients who are expected to use Xospata are provided with the following educational materials:

- Physician educational material
- Patient Alert Card

<u>Physician educational material:</u>

- The Summary of Product Characteristics
- Educational tool targeting prescribers:
    - Information on Xospata, including the approved indication according to the SmPC.
    - Description of the signs and symptoms of differentiation syndrome.
    - Management of differentiation syndrome.

<u>The patient information pack:</u>

- Patient information leaflet
- Patient alert card
    - Patient alert card:
        - Information for patients that Xospata treatment may cause differentiation syndrome.
        - Description of signs or symptoms of the safety concern and when to seek medical care if differentiation syndrome is suspected
        - A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using Xospata.
        - Contact details of the treating physician who has prescribed Xospata.
        - Needs to be carried all the time and presented to any healthcare professional.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that gilteritinib is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

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