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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

XOSPATA

Gilteritinib

Procedure no: EMA/PAM/0000301487

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Steps taken for the assessment		
Description	**Planned date**	**Actual Date**
CHMP Rapporteur AR	17 Nov 2025	14 Nov 2025
CHMP comments	1 Dec 2025	n/a
Updated CHMP Rapporteur AR	4 Dec 2025	n/a
CHMP outcome	11 Dec 2025	11 Dec 2025

Administrative information

Procedure resources	
Rapporteur:	**Name: Ingrid Wang**

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1. Introduction

On 10 September 2025, the MAH submitted results from a prematurely terminated paediatric study 2215-CL-0603 for XOSPATA, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The paediatric study 2215-CL-0603, a Phase 1/2, multicenter, open-label, single arm, dose escalation and expansion study of gilteritinib combined with chemotherapy in children, adolescents and young adults with FMS-like tyrosine kinase 3 (FLT3)/Internal Tandem Duplication (ITD) positive relapsed or refractory (R/R) acute myeloid leukemia (AML) was part of a clinical development program. A line listing of all the concerned studies is annexed.

A Paediatric Investigation Plan (PIP; EMEA-002064-PIP01-16-M06) was agreed with EMA for the development of gilteritinib for the treatment of R/R and newly diagnosed FLT3/ITD positive AML in the paediatric population from 6 months to less than 18 years of age. The current study 2215-CL-0603, is part of this PIP program. The study design included 2 phases (Phase 1: dose escalation phase and Phase 2: dose expansion phase). The sponsor decided not to open the Phase 2 expansion part of the study and terminated the study after completion of the Phase 1 dose finding part for Group 1 (i.e., patients in the age 2 to < 21 years). This was agreed with EMA (PIP modification M06; EMA decision P/0289/2024 of 16 August 2024). According to the MAH, the decision to terminate the study was based upon enrolment challenges due to the rarity of R/R AML in children and not related to any safety or efficacy issues.

Gilteritinib is a FLT3 and AXL inhibitor which is approved in several countries globally.

In the EU, gilteritinib was initially approved 24 October 2019 for 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)."*

Xospata has orphan designation.

Extract from current posology: for adults the recommended starting dose is 120 mg gilteritinib (three 40 mg tablets) once daily. In the absence of a response [patient did not achieve a composite complete remission (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.

Before taking gilteritinib, relapsed or refractory AML patients must have confirmation of FMS-like tyrosine kinase 3 (FLT3) mutation (internal tandem duplication [ITD] or tyrosine kinase domain [TKD]) using a validated test. Xospata may be re-initiated in patients following haematopoietic stem cell transplantation (HSCT).

Currently the safety and efficacy of Xospata in children aged below 18 years has not yet been established. No data is available. Due to *in vitro* binding to 5HT2B, there is a potential impact on cardiac development in patients less than 6 months of age.

The MAH does not apply for a paediatric indication nor proposes to modify any sections of the SmPC within this procedure.

2.2. Information on the pharmaceutical formulation used in the study

Tablet formulations of Xospata (gilteritinib 40 mg film-coated tablets and 10 mg film-coated mini-tablets) were used in Study 2215-CL-0603.

As part of the paediatric program, a 10 mg mini-tablet formulation was developed. This formulation was downsized to improve the ease of swallowing for paediatric patients. The mini-tablet can be swallowed intact or compounded into a suspension.

Participants in Study 2215-CL-0603 could be given the original formulation, mini-tablets, a combination of mini-tablets and the original formulation or an oral suspension that could be created from the mini-tablets with water or grape juice. Participants unable to swallow a tablet could be given the drinkable suspension. Five participants took the 10 mg mini-tablet only, 2 participants took the 40 mg tablet only, and 2 participants took both the 40 mg tablet and the 10 mg mini-tablet. Seven participants in this study took tablets only, 1 participant took both tablets and suspension and 1 took suspension only.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for the paediatric study 2215-CL-0603.

In March 2024, the MAH submitted a request to EMA for a modification of the agreed PIP. The modification concerned a proposal for stopping the paediatric development of gilteritinib in patients with R/R FLT3/ITD positive AML and terminating the above-mentioned study because of enrolment challenges which made it very difficult to conduct the study. The MAH pointed to estimations stating that the total number of children relapsing each year with FLT3 mutations in North America, Europe, Australia, New Zealand and Japan taken together is approximately 30 (Pearson et al, 2020). In addition, there is other FLT3 inhibitors also competing for the small number of patients.

The PDCO agreed to the modification of the PIP and adopted a positive opinion in June 2024 followed by an EMA decision in August 2024. This implies that the MAH now has refined the intended target population of the PIP to patients with newly diagnosed FLT3/ITP positive AML. Consequently, Study 2215-CL-0604 in this population will be critical to ensure that optimum data generation is achieved.

Below, the results generated from the prematurely terminated study 2215-CL-0603 is briefly presented. No extension of the indication nor modifications of the SmPC are applied for by the MAH, based on data from this study.

2.3.2. Clinical study

Study 2215-CL-0603

Phase 1/2, multicenter, open-label, single arm, dose escalation and expansion study of gilteritinib combined with chemotherapy in children, adolescents and young adults with FMS-like tyrosine kinase 3 (FLT3)/Internal Tandem Duplication (ITD) positive relapsed or refractory (R/R) acute myeloid leukemia (AML)

Description

Methods

This was an open-label, single-arm, phase 1/2 study to evaluate the safety, PK and antileukemic activity of gilteritinib in children, adolescents and young adults with FLT3/ITD positive R/R AML.

The study design consisted of 2 phases:

• Phase 1 (Dose Escalation Phase)

• Phase 2 (Dose Expansion Phase)

Dose escalation in Phase 1 was to be performed in 3 groups based on the age of the participant:

- Group 1: Dose Escalation in participants from 2 years to less than 21 years of age
- Group 2: Dose Escalation in participants from 1 year to less than 2 years of age
- Group 3: Dose Escalation in participants from 6 months to less than 1 year of age

The study was conducted at 6 centres that enrolled patients in the US, Spain, Italy, UK and Germany. It was planned to enrol 9 participants per dose level in Phase 1 and 52 response evaluable subjects in Phase 2.

Induction therapy in Phase 1 consisted of up to 2 cycles of gilteritinib plus fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG). One cycle was defined as 28 days of treatment. During each cycle, FLAG (cycle 1 and 2) chemotherapy was administered on days -1 to 5 and gilteritinib was administered once per day on days 8 to 21 at the assigned dose levels below:

Level	Dose
-1	1 mg/kg/day (maximum 60 mg/day) #
1	2 mg/kg/day (maximum 120 mg/day) *
2	3 mg/kg/day (maximum 180 mg/day) **
* Starting dose of gilteritinib for Group 1; # Starting dose of gilteritinib for Groups 2 and 3 ** To be evaluated only if there is lack of toxicity or acceptable DLT profile combined with the lack of sufficient gilteritinib activity observed at the Dose Level 1 (2 mg/kg/day). Not applicable for sites in the USA.	

Dose-limiting toxicity (DLT) assessment occurred during the first cycle only. PK parameters, response assessment and biological activity were evaluated during cycle 1 and/or cycle 2.

Dose escalation, stay or de-escalation between the dose levels in Groups 1, 2 and 3 was to be guided by a standard 3 + 3 design. The recommended phase 2 dose (RP2D) and/or maximum tolerated dose (MTD) was to be selected based on a Dose Escalation Committee's (DEC) review of all available data at each dose level, including safety data, PK data (if available), response data and gilteritinib biologic activity data.

As already mentioned above, Phase 2 was not conducted as the MAH decided to terminate the study after completion of Phase 1 for Group 1.

Only the study schema for Phase 1 is therefore shown below.

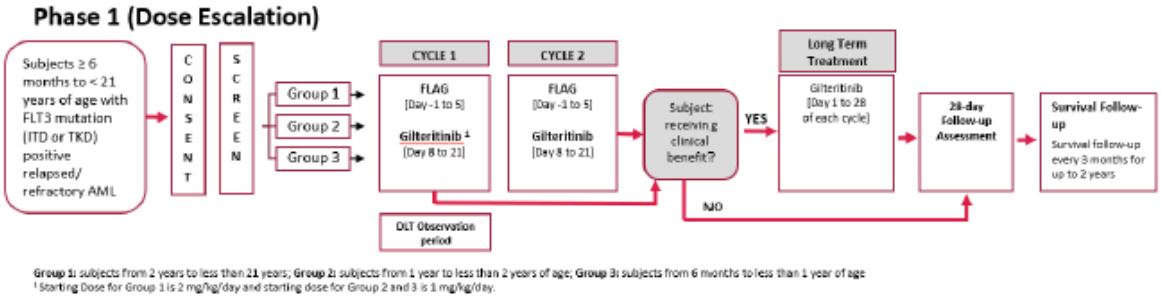

Figure 1. Study schema - Phase 1

A subject completing 1 or 2 treatment cycles had the option to participate in long-term treatment (LTT) with gilteritinib (for up to 2 years).

Study participants

Key inclusion criteria (Phase 1)

Participants were to be ≥ 6 months and < 21 years of age and positive for FLT3 (ITD and/or TKD mutation) in bone marrow or blood as determined by the local institution. Participants had to have a diagnosis of AML according to the French-American-British classification with ≥ 5% blasts in the bone marrow, with or without extramedullary disease (except subjects with active CNS leukemia). The subjects had to be in first or greater relapse or refractory to induction therapy with no more than 1 attempt at remission induction (up to 2 induction cycles). Participants had to be fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy or radiotherapy prior to entering the study. For participants who underwent hematopoietic stem cell transplant (HSCT), at least 90 days had to elapse since HSCT, and participants were not to have active graft-versus-host disease (GVHD).

Key exclusion criteria (Phase 1)

Participants were to be excluded if they had active CNS leukemia; uncontrolled or significant cardiovascular disease; were receiving or planned to receive concomitant chemotherapy, radiation therapy or immunotherapy other than as specified in the protocol; had an active malignant tumor other than AML or required treatment with concomitant drugs that were strong inducers of cytochrome P450 (CYP)3A/P-gp.

Treatments

The study drug was gilteritinib available as a tablet containing 40 mg of active ingredient and a mini tablet containing 10 mg of active ingredient.

The co-administered drugs consisted of induction therapy with fludarabine, cytarabine and granulocyte colony-stimulating factor (FLAG) regimen from day -1 to day 5 for cycle 1 and cycle 2.

Proposed initial dose of gilteritinib is selected based on recommended phase 3 dose in adults (120 mg once daily) and pediatric simulation based on the human popPK model (based on data from studies conducted in healthy volunteers and AML patients). This simulation indicated that comparable exposure as observed in adults would be achieved with a daily dose of 3 mg/kg. Due to the lack of clinical data in adults for the combination of gilteritinib and FLAG, the starting dose in children aged 2 years to less than 21 years of age was set to 2 mg/kg to provide a safety margin.

Objective(s)

Phase 1 (Dose escalation phase)

Primary objective

Determine the maximum tolerated dose (MTD) and/or optimally safe and biologically active recommended phase 2 dose (RP2D) of gilteritinib given in sequential combination with FLAG in children, adolescents and young adults with R/R FLT3 (ITD and/or TKD) AML.

Secondary objectives

- Assess the safety, tolerability and toxicities of gilteritinib when given in sequential combination with FLAG in children, adolescents, and young adults with R/R FLT3/ITD AML
- Evaluate FLT3 inhibition due to gilteritinib treatment
- Characterize gilteritinib pharmacokinetics
- Perform serial measurements of minimal residual disease (MRD) and examine the relationship with study endpoints
- Obtain preliminary estimates of 1-year event-free survival (EFS) and overall survival (OS) rate
- Assess the acceptability and palatability of the formulation.

Outcomes/endpoints

Phase 1 (Dose escalation phase)

Primary endpoint

Determination of MTD and/or RP2D.

The RP2D was stated to be a dose, which was safe (i.e., had an acceptable DLT profile) and demonstrated complete remission (CR), a high degree of gilteritinib biologic activity (as measured by plasma inhibitory activity [PIA]), or a combination of both.

For the dose to be considered biologically active, at least 7 of 9 subjects at the RP2D dose in each group had to demonstrate CR, a high degree of gilteritinib biologic activity (as measured by PIA), or a combination of both with the following conditions for PIA:

- Subjects that completed 2 induction cycles had to achieve PIA of > 90% for at least 3 of 4 trough time points;
  or
- Subjects that completed only 1 induction cycle had to achieve PIA of > 90% at 2 of 2 trough time points.

Definition of CR: patient must have bone marrow regenerating normal hematopoietic cells and achieve a morphologic leukemia-free state and must have an absolute neutrophil count (ANC) ≥ 1 x 10^9/L and platelet count ≥ 100 x 10^9/L and normal marrow differential with < 5% blasts, and they will be red blood cell (RBC) and platelet transfusion independent (defined as 1 week without RBC transfusion and 1 week without platelet transfusion). There should be no evidence of extramedullary leukemia.

Secondary endpoints

- Inhibition of phosphorylated FLT3 (pFLT3) measured by PIA assay
- Gilteritinib plasma concentration
- Pharmacokinetic parameters (e.g., oral clearance [CL/F], apparent volume of distribution [Vd/F], Cmax, tmax, AUC) of gilteritinib
- Safety, tolerability and toxicity assessments of gilteritinib when given in combination with FLAG
- EFS rate
- OS rate
- MRD assessment
- Acceptability and palatability assessment of the formulation

Blood samples for PK (1.0 ml/sample) were collected at the following time points:

• Cycle 1 day 8 – Predose

- Cycle 1 day 15 (±2 days) – Predose
- Cycle 1 day 21 (±2 day) – Predose and 4 to 6 hours
- Cycle 2 day 15 (±2 days) – Predose

It is not reported how gilteritinib concentrations were determined. Reference is made to a Laboratory manual not included in the submitted files.

Sample size

Group 1: Three subjects were to be enrolled in a cohort at 1 of a series of doses of gilteritinib with a starting dose of 2 mg/kg/day according to a standard 3 + 3 design. Additional subjects were to be accrued as needed to ensure that gilteritinib activity was assessable in at least 9 subjects.

Group 2 and 3: the study was terminated after completion of the Phase 1 part for Group 1, and no patients were therefore enrolled into these groups.

Randomisation and blinding (masking)

Not applicable as Phase 1 of the study was open label and single arm.

Statistical methods

The rates of CRc, CR, OS and EFS were summarised using descriptive statistics.

For efficacy the Full Analysis Set (FAS) was used and consisted of all subjects who were enrolled and received at least 1 dose of the treatment regimen.

For safety the Safety Analysis Set (SAF) was used and consisted of all subjects who took at least 1 dose of the treatment regimen.

The Minimal Residual Disease Analysis Set (MAS) consisted of a subset of the FAS for which subjects were enrolled, received at least 1 dose of the treatment regimen, and had at least 1 post-baseline sample with MRD data.

Pharmacokinetic analysis: The pharmacokinetic analysis set (PKAS) consisted of the administered population for which sufficient plasma concentration data was available to facilitate derivation of at least one pharmacokinetic parameter and for whom the time of dosing on the day of sampling is known.

A listing of the individual plasma concentration-time data for gilteritinib was presented (CSR, Table 9.4.1.1). Gilteritinib plasma concentrations were summarized by study day and sample collection window using descriptive statistics, including number of participants, mean, SD, minimum, median, maximum, geometric mean and CV of the mean and geometric mean. Due to the limited data, the planned pediatric popPK could not be conducted and only C_{trough} and apparent C_{max} parameters were reported.

Pharmacodynamic analysis: The Pharmacodynamic Analysis Set (PDAS) consisted of the administered population for which sufficient pharmacodynamic measurements were collected. An ex-vivo plasma inhibitory activity (PIA) assay was employed to determine FLT3 inhibition relative to baseline FLT3 levels. Data were summarized using descriptive statistics, including number of participants, mean, SD, minimum, median, maximum, geometric mean and CV of the mean and geometric mean. PIA was assessed pre-dose during Cycle 1 and Cycle 2. For the dose to be considered biologically active, at least 7 of 9 subjects must achieve PIA of > 90% for at least 3 of 4 trough time points. Alternatively, if

participants completed only 1 induction cycle, PIA of > 90% must have been achieved at 2 of 2 trough time points.

Results

Participant flow

Of 10 patients, 9 patients were enrolled into Group 1 while one patient was considered a screen failure. No patients were withdrawn. Five patients completed the treatment while 4 patients discontinued due to progressive disease.

Recruitment

Study initiation date (date of first informed consent) was 04 Sep 2020. Primary completion date (date of last evaluation) was 11 Mar 2025.

Baseline data

Table 1. Demographic characteristics (Full Analysis Set)

Parameter	Gilteritinib 2 mg/kg/day Escalation Phase (N = 9)
Sex, n (%)	
Male	6 (66.7)
Female	3 (33.3)
Race, n (%)	
White	9 (100)
Ethnicity, n (%)	
Not Hispanic or Latino	8 (88.9)
Hispanic or Latino	1 (11.1)
Age, years	
Mean (SD)	11.9 (2.4)
Median (min, max)	13.0 (8, 15)
Age group, n (%)	
6 to < 12 years	3 (33.3)
12 to < 18 years	6 (66.7)
BMI, kg/m^2 [a]	
Mean (SD)	17.3 (4.0)
Median (min, max)	16.0 (13, 27)

BMI: body mass index; max: maximum; min: minimum.

Three participants had relapsed before entering the study and 6 participants were refractory. One patient was found to have a diagnosis of acute lymphocytic leukemia (ALL).

Number analysed

The full analysis set (FAS), and the safety analysis set both consisted of 9 participants while the minimal residual disease (MRD) analysis set consisted of 5 participants.

Pharmacokinetic results

All 9 enrolled participants were included in the PKAS. A total of 29 quantifiable gilteritinib concentrations were available for analysis. Pediatric participants in this study had mean (range) steady-state apparent C_{max} and C_{trough} values of 439 (260 to 783) and 225.3 (113 to 524) ng/mL.

Pharmacodynamic results

All 9 enrolled participants were part of the PDAS. Combined data is presented in Figure 2. In 4 participants, biological activity was confirmed by achieving > 90% PIA inhibition at the required number of time points. Two participants achieved > 90% PIA inhibition at all 4 time points and 2 participants who only received 1 cycle of induction therapy achieved > 90% PIA inhibition at 2 time points. The protocol defined criterion for determining biological activity of gilteritinib in at least 7 of 9 participants was not met.

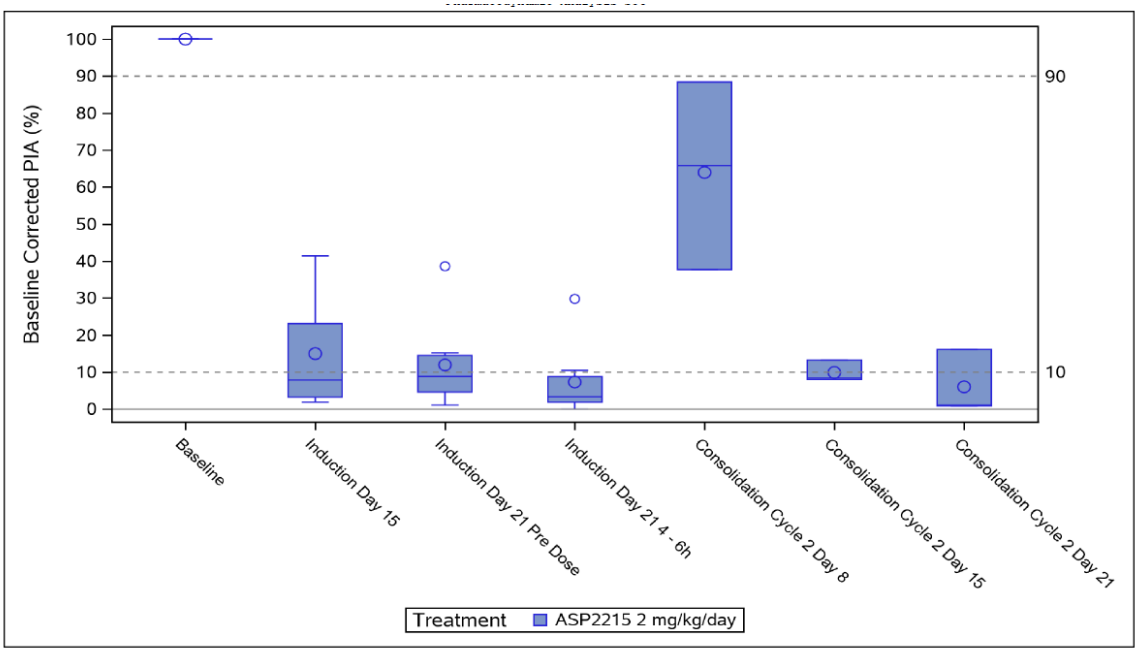

Figure 2. Baseline-corrected PIA during induction and consolidation (2215-CL-0603 CSR Figure 4)

Efficacy results

CRc and CR rates

Of the 9 participants, 6 participants obtained a response. Three (33.3%) participants had a best overall response (BOR) of CR, and 3 (33.3%) participants had a BOR of CRi (i.e., CR with incomplete hematologic recovery). Among the 3 patients with CRi, one patient turned out to have ALL and not AML. The composite complete remission (CRc) rate was estimated to be 66.7% (95% CI: 29.9%, 92.5%) and the CR rate 33.3% (95% CI: 7.5%, 70.1%). The median duration of CR was non-estimable (range 55 to 849 days).

Of note, for the dose to be considered biologically active, at least 7 of 9 subjects at the RP2D dose in each group had to demonstrate CR, a high degree of gilteritinib biologic activity (as measured by PIA) or a combination of both. This was not fulfilled.

Event-free Survival (EFS)

Table 2. Event-free survival, derived response assessment (FAS)

Measure	Gilteritinib 2mg/kg/day Escalation Phase (N=9)
EFS Events, n (%)	5 (55.6%)
Relapse	2 (22.2%)
Treatment Failure	3 (33.3%)
Death	0
Censored, n (%)	4 (44.4%)
Duration of EFS, Days[a]	
Median (95% CI)	123.00 (1.00, NE)
Range	<1.00, 908.00+>
EFS Rate, % (95% CI)[b]	
At 6 months	41.67% (10.90%, 70.77%)
At 1 year	41.67% (10.90%, 70.77%)
At 2 years	41.67% (10.90%, 70.77%)

"+" indicates censoring

EFS: event-free survival; FAS: full analysis set; NE: non-estimable.

a Based on Kaplan-Meier estimate

b EFS rate and 95% CI are estimated using Kaplan-Meier method and Greenwood formula.

Overall Survival (OS)

Table 3. Overall survival (FAS)

Measure	Gilteritinib 2mg/kg/day Escalation Phase (N=9)
Deaths, n (%)	4 (44.4%)
Censored, n (%)	5 (55.6%)
Duration of OS, Months[a]	
Median (95% CI)	NE (4.80, NE)
Range	<4.80, 45.01+>
OS Rate, % (95% CI)[b]	
At 6 months	77.78% (36.48%, 93.93%)
At 1 year	55.56% (20.42%, 80.45%)
At 2 years	55.56% (20.42%, 80.45%)

"+" indicates censoring

CI: confidence interval; FAS: full analysis set; NE: non-estimable; OS: overall survival.

a Based on Kaplan-Meier estimate

b Survival rate and 95% CI were estimated using Kaplan-Meier method and Greenwood formula.

Minimal Residual Disease (MRD)

Five participants achieving CRc were assessed for MRD. Of these, 4 achieved MRD negativity (defined as FLT3-ITD to total FLT3 sequencing reads of $< 10^{-4}$) in at least 1 post-baseline time point. One participant achieved MRD negativity as early as C2D28. Three participants who entered the long-term treatment (LTT) phase and were MRD negative maintained MRD negativity until the end of LTT or pre-HSCT visit. The 1 participant who did not achieve MRD negativity was found to have a diagnosis of ALL after enrolment and had only 1 post-baseline MRD time point assessed (C2D28).

Transplantation

Four of 9 patients underwent HSCT during the study period (i.e., a rate of 44.4%). Of these, 3 patients had responded to study treatment and were in remission at the time of transplant. They remained in

remission after transplant through study close out. The fourth participant who received on-study transplant had not responded to study treatment. This participant experienced progressive disease shortly after transplant and passed away.

Safety results

The safety analysis set consisted of nine paediatric participants enrolled in age Group 1 (2 to < 21 years of age) in the dose escalation phase at the starting dose level of 2 mg/kg/day gilteritinib. No participants were enrolled in age Groups 2 (1 to < 2 years of age) or 3 (6 months to < 1 year of age).

The median number of dosing days was 28.0 days (range 14 to 757 days). Overall, 3 (33.3%) participants had a dose interruption.

Of the nine participants, 8 were DLT evaluable. No participants experienced a DLT.

Three participants received 2 cycles of FLAG in combination with gilteritinib 2 mg/kg/day, while 6 participants received 1 cycle of FLAG in combination with gilteritinib 2 mg/kg/day.

Three participants received maintenance treatment with gilteritinib 2 mg/kg/day. Two participants completed maintenance treatment, and 1 participant discontinued due to ALT increased.

Overviews of treatment-emergent adverse events (TEAEs) and common TEAEs by SOC/PT are displayed in Table 4 and Table 5.

Table 4. Overview of Treatment-emergent Adverse Events (Safety Analysis Set)

	Gilteritinib 2 mg/kg/day Escalation Phase (N = 9) n (%)
All TEAEs	9 (100)
Study intervention-related[a] TEAEs	9 (100)
Serious TEAEs[b]	7 (77.8)
Study intervention-related[a] Serious TEAEs[b]	4 (44.4)
TEAEs leading to death	0
TEAEs leading to withdrawal of treatment	1 (11.1)
Study intervention-related[a] TEAE leading to withdrawal of treatment	1 (11.1)
Grade 3 or Higher TEAEs	9 (100)
Death[c]	4 (44.4)

SAE: serious adverse event; TEAE: treatment-emergent adverse event. a. A reasonable possibility that the event may have been caused by the study intervention as assessed by the investigator. If relationship is missing then it is considered as study intervention related. b. Includes SAEs upgraded according to the sponsor's medical review process, if any upgrade was done. c. All reported deaths after the first study intervention administration

Table 5. Common (≥ 2 Participants in Any Treatment Group) Treatment-emergent Adverse Events (Safety Analysis Set)

SOC Preferred Term	Gilteritinib 2 mg/kg/day Escalation Phase (N=9)
All TEAEs	9 (100.0%)
Blood and lymphatic system disorders	8 (88.9%)
Anaemia	5 (55.6%)
Febrile neutropenia	5 (55.6%)
Thrombocytopenia	2 (22.2%)
Gastrointestinal disorders	7 (77.8%)
Nausea	5 (55.6%)
Diarrhoea	4 (44.4%)
Vomiting	4 (44.4%)
Abdominal pain	3 (33.3%)
Abdominal pain upper	2 (22.2%)
General disorders and administration site conditions	7 (77.8%)
Pyrexia	6 (66.7%)
Immune system disorders	3 (33.3%)
Graft versus host disease in liver	2 (22.2%)
Infections and infestations	7 (77.8%)
Device related infection	2 (22.2%)
Sepsis	2 (22.2%)
Injury, poisoning and procedural complications	3 (33.3%)
Allergic transfusion reaction	2 (22.2%)
Investigations	9 (100.0%)
Alanine aminotransferase increased	7 (77.8%)
Aspartate aminotransferase increased	7 (77.8%)
Blood bilirubin increased	3 (33.3%)
Blood creatine phosphokinase increased	3 (33.3%)
Blood lactate dehydrogenase increased	3 (33.3%)
Platelet count decreased	3 (33.3%)
White blood cell count decreased	3 (33.3%)
Blood creatinine increased	2 (22.2%)
Lymphocyte count decreased	2 (22.2%)
Metabolism and nutrition disorders	5 (55.6%)
Hypomagnesaemia	3 (33.3%)
Hypophosphataemia	3 (33.3%)
Hyperglycaemia	2 (22.2%)
Hyperkalaemia	2 (22.2%)
Hypermagnesaemia	2 (22.2%)
Hyperphosphataemia	2 (22.2%)
Hypoalbuminaemia	2 (22.2%)
Hypokalaemia	2 (22.2%)
Nervous system disorders	3 (33.3%)
Headache	3 (33.3%)
Respiratory, thoracic and mediastinal disorders	5 (55.6%)
Cough	4 (44.4%)
Epistaxis	2 (22.2%)
Hypoxia	2 (22.2%)
Tachypnoea	2 (22.2%)
Skin and subcutaneous tissue disorders	6 (66.7%)
Rash	4 (44.4%)
Pain of skin	2 (22.2%)
Pruritus	2 (22.2%)
Vascular disorders	2 (22.2%)
Hypertension	2 (22.2%)

All participants experienced TEAEs, 1 or more study-intervention-related TEAE and NCI-CTCAE Grade 3 or higher TEAEs.

The most common TEAEs were ALT increased, and AST increased (77.8% each). The most common study-intervention-related TEAE was ALT increased (66.7%). The most common TEAEs with NCI-CTCAE Grade 3 or higher were anemia and ALT increased (55.6% each).

Treatment-emergent SAEs were reported in 7 (77.8%) participants and 44.4% of participants reported serious study-intervention-related TEAEs.

There were no TEAEs leading to death and 1 TEAE of ALT increased led to withdrawal of treatment. AESIs were reported in all participants. The most commonly reported AESI was ALT increase (88.9%).

Overall, 4 deaths occurred during the post-treatment follow-up period. None of the deaths were attributed to study treatment.

Study-intervention related TEAEs are presented in the table below.

Table 6. Study Intervention-related Treatment-emergent Adverse Events in ≥ 2 Participants (Safety Analysis Set)

SOC Preferred Term	Gilteritinib 2 mg/kg/day Escalation Phase (N=9)
All study intervention-related TEAEs	9 (100.0%)
Blood and lymphatic system disorders	5 (55.6%)
Anaemia	3 (33.3%)
Febrile neutropenia	2 (22.2%)
Thrombocytopenia	2 (22.2%)
Gastrointestinal disorders	6 (66.7%)
Nausea	4 (44.4%)
Vomiting	4 (44.4%)
General disorders and administration site conditions	4 (44.4%)
Pyrexia	3 (33.3%)
Investigations	8 (88.9%)
Alanine aminotransferase increased	6 (66.7%)
Aspartate aminotransferase increased	5 (55.6%)
Lymphocyte count decreased	2 (22.2%)
Platelet count decreased	2 (22.2%)

2.3.3. Discussion on clinical aspects

This report concerns the clinical results of Study 2215-CL-0603 which is part of the PIP (EMEA-002064-PIP01-16-M06) for Xospata (gilteritinib). The study was an open-label, single-arm, phase 1/2 study intended to evaluate the safety, PK and antileukemic activity of gilteritinib used in sequential combination with chemotherapy in children, adolescents and young adults with FLT3/ITD positive R/R AML. The study design originally included 2 phases: Phase 1 - Dose Escalation Phase (in 3 age groups) and Phase 2 – Dose Expansion Phase. However, in March 2024, the MAH proposed to stop the paediatric development of gilteritinib in patients with R/R FLT3/ITD positive AML. This decision was justified by enrolment challenges, making it very difficult to conduct the study, and the MAH underlined that the termination was not related to safety or efficacy issues. The intention of the MAH is now to

focus on paediatric patients with newly diagnosed FLT3/ITP positive AML which is the target population of the on-going study 2215-CL-0604.

The PDCO agreed to the modification of the PIP and adopted a positive opinion in June 2024 followed by an EMA decision in August 2024.

As a consequence of the decision to prematurely terminate Study 2215-CL-0603, only the Phase 1 dose finding part for Group 1 (2 to <21 years of age) was completed. No participants were enrolled in age Groups 2 (1 to < 2 years of age) or 3 (6 months to < 1 year of age) Furthermore, the Phase 2 extension part of Study 2215-CL-0603 was not conducted.

The primary endpoint for Phase 1 was to determine MTD and/or RP2D. In total, 9 paediatric participants were included in Group 1. Six of the patients had refractory and 3 patients relapsed FLT3/ITD positive AML. However, it was later discovered that 1 patient had ALL and not AML. The median age was 13 years with a range from 8 to 15 years. All of the 9 patients received a dose of 2 mg/kg/day. The protocol-defined criteria for determining biological activity by PIA or CR (please refer to "Primary endpoint" above for the specific criteria) at this dose was not reached. However, based on the available data, the Dose Escalation Committee (DEC) still endorsed 2 mg/kg/day up as the RP2D for participants 2 years to less than 18 years of age.

Due to the limited amount of data available, the PK of gilteritinib could not be fully characterised and only an approximate C_{max} and C_{trough} values are reported.

In regards to efficacy 6 of 9 patients achieved a clinical response in Phase 1. The best overall response was CR for 3 patients and CRi for 3 patients (of note, one of the 3 patients with CRi turned out to have ALL). The duration of CR was not possible to estimate. Overall, the majority of the patients achieved a clinical response, however, the efficacy results were descriptive and can merely be viewed as preliminary. Additionally, the study design (single arm trial) prevents any meaningful interpretations of the time-dependent parameters EFS and OS. Hence, no definitive conclusions can be drawn based on these limited data.

The safety data from a very limited number of paediatric subjects did not reveal any new or significant safety concerns. The most commonly reported drug-related events of increased ALT and AST are well known and very commonly reported ADR for gilteritinib in the adult population. The observed safety profile seems overall consistent with delivery of myelosuppressive chemotherapy in an R/R pediatric AML population.

Conclusion

The clinical results from the prematurely terminated study 2215-CL-0603 in children with FLT3/ITD positive R/R AML are noted. With the closure of further paediatric development in the R/R clinical setting, the on-going study 2215-CL-0604 performed in children with newly diagnosed FLT3/ITD positive AML becomes a stand-alone paediatric development considering that Xospata is not approved for adults in this clinical setting. Consequently, Study 2215-CL-0604 will be crucial to ensure that optimum data generation in children is achieved in support of a potential front-line indication.

Even though the data from Study 2215-CL-0603 were limited and it is not possible to draw any definitive conclusions, the results might potentially support the further exploration of gilteritinib and its use in paediatric patients in the forthcoming Study 2215-CL-0604.

This P46 PAM is considered fulfilled, solely based on the fact that study data have been provided. No changes in the indication nor any other sections of the SmPC are proposed by the MAH. The Rapporteur agrees that the clinical data from study 2215-CL-0603 do not merit inclusion in the SmPC.

3. Overall conclusion and recommendation

☒ **Fulfilled:**

No regulatory action required. Based on the data submitted, it is agreed that no amendments of the SmPC are warranted.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non-clinical studies

Product Name: Xospata Active substance: gilteritinib

Study title	Study number	Date of completion	Date of submission of final study report
A preliminary 18-day oral repeated-dose dose range finding study of ASP2215 hemifumarate in juvenile rats	2215-TX-0015	23-Feb-2018	07-Feb-2019
A 39-day repeated-dose oral toxicity study of ASP2215 hemifumarate in juvenile rats with a 28-day recovery period	2215-TX-0016	27-Aug-2018	07-Feb-2019

Clinical studies

Product Name: Xospata Active substance: gilteritinib

Study title	Study number	Date of completion	Date of submission of final study report
Open-label, single arm study to evaluate the pharmacokinetic, safety and anti-tumour activity of gilteritinib used in sequential combination with chemotherapy in paediatric patients from 6 months to less than 18 years of age (and young) adults with FLT3/ITD positive relapse/refractory acute myeloid leukaemia with a dose-finding phase (phase 1)	2215-CL-0603	17-Mar-2025	10-Sep-2025
Open-label, single arm study to evaluate the pharmacokinetic, safety and efficacy of gilteritinib used in sequential combination with chemotherapy in paediatric patients from 6 months to less than 18 years of age (and young adults) with FLT3/ITD positive newly diagnosed acute myeloid leukaemia	2215-CL-0604	N/A	N/A
Extrapolation, modelling and simulation study:	Not available yet	N/A	N/A

Modelling and simulation study to simulate and predict gilteritinib exposure in children from 6 months to less than 18 years of age with acute myeloid leukaemia			
Extrapolation, modelling and simulation study: Physiologically-based modelling study to simulate gilteritinib exposure in populations of children from 6 months to less than 18 years of age with AML (introduced during EMEA-002064-PIP01-16-M03)	Not available yet	N/A	N/A