1. NAME OF THE MEDICINAL PRODUCT

Xospata 40 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 40 mg gilteritinib (as fumarate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Round, light yellow film-coated tablet, debossed with the company logo and '235' on the same side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Xospata is indicated for the treatment of patients who have relapsed or refractory acute myeloid leukaemia (AML) with FMS-like tyrosine kinase 3 (FLT3) mutations.

Select patients based on a positive FLT3 mutation test.

4.2 Posology and method of administration

Posology
Xospata is to be prescribed only by physicians who specialize in hematology and/or hemato-oncology.

The recommended starting dose of Xospata is 120 mg (three 40 mg tablets) once-daily.

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 after 4 weeks of treatment, the dose can be increased to 200 mg (five 40 mg tablets) once-daily.

Xospata may be re-initiated in patients following hematopoietic stem cell transplantation (HSCT).

Assess blood chemistries, including creatine phosphokinase, prior to the initiation of treatment with Xospata, on day 15 of cycle 1 and monthly for the duration of therapy.

Perform electrocardiogram (ECG) prior to initiation of treatment with Xospata, on day 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles. Interrupt and/or reduce the dose of Xospata in patients who have a QTcF >500 msec.

If differentiation syndrome is suspected, administer systemic corticosteroids and initiate hemodynamic monitoring until symptom resolution. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt Xospata until signs and symptoms are no longer severe. Treatment with Xospata can be resumed at the same dose when signs and symptoms improve to Grade 2 (moderate) or lower.

Interrupt Xospata for other Grade 3 (severe) or greater toxicity considered related to the drug. Resume at a reduced dose when the toxicity resolves or improves to Grade 1 (mild).

Interrupt treatment with Xospata one week prior to administration of the conditioning regimen for HSCT. Treatment can be resumed 30 days after HSCT if engraftment was successful, the patient did not have grade ≥2 acute graft versus host disease and was in composite complete remission (CRc) (see section 5.1).

The daily dose can be reduced from 120 mg to 80 mg or 200 mg to 120 mg.

Xospata should be administered at about the same time each day. If a dose is missed or not taken at the usual time, the dose should be administered as soon as possible on the same day, and patients should return to the normal schedule the following day. If vomiting occurs after dosing, patients should not take another dose but should return to the normal schedule the following day.

Elderly
No dose adjustment is required in patients ≥65 years of age (see section 5.2).

Hepatic Impairment
No dose adjustment is required for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Xospata has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) (see section 5.2).

Renal impairment
No dose adjustment is required in patients with mild, moderate or severe renal impairment (see section 5.2).

Paediatric population
There are no data to support the safety and efficacy of Xospata use in children. Therefore, Xospata is not recommended for use in children.

Method of administration
Xospata is for oral use.
The tablets can be taken with or without food. They should be swallowed whole with water and should not be broken or crushed.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. Anaphylactic reactions have been reported (see section 4.8).

4.4 Special warnings and precautions for use

Differentiation Syndrome
Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms and other clinical findings of differentiation syndrome in patients treated with gilteritinib included fever, dyspnea, pleural effusion, pericardial effusion, pulmonary edema, hypotension, rapid weight gain, peripheral edema, rash, and renal dysfunction. Some cases had concomitant acute febrile neutrophilic dermatosis. Differentiation syndrome occurred as early as 1day and up to 82 days after Xospata initiation and has been observed with or without concomitant leukocytosis.

If differentiation syndrome is suspected, initiate corticosteroids and hemodynamic monitoring until improvement. Taper corticosteroids after resolution of symptoms. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment.
If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt Xospata until signs and symptoms are no longer severe (see section 4.2).

Posterior Reversible Encephalopathy Syndrome
There have been reports of posterior reversible encephalopathy syndrome (PRES) with symptoms including seizure and altered mental status. Symptoms have resolved after discontinuation of Xospata. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinue Xospata in patients who develop PRES.

Prolonged QT interval
Xospata has been associated with prolonged cardiac ventricular repolarization (QT Interval) (see section 5.2). Interrupt and/or reduce the dose of Xospata in patients who have a QTcF >500 msec (see sections 4.2 and 5.1).
Hypokalemia or hypomagnesemia may increase the QT prolongation risk. Correct hypokalemia or hypomagnesemia prior to and during Xospata administration.

Pancreatitis
There have been reports of pancreatitis; however, an association with Xospata has not been confirmed. Evaluate and monitor patients who develop signs and symptoms suggestive of pancreatitis.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of Other Drugs on Xospata
Concomitant use of Xospata with drugs that are strong inducers of CYP3A/P-gp (e.g., rifampin, phenytoin, St. John's wort) should be avoided as they can decrease the plasma exposure of Xospata (see section 5.2).

Concomitant use of Xospata with drugs that are strong inhibitors of CYP3A and/or P-gp (e.g., voriconazole, itraconazole, posaconazole, clarithromycin, erythromycin, captopril, carvedilol, ritonavir, azithromycin) should be used with caution as they can increase the plasma exposure of Xospata (see section 5.2).

Effects of Xospata on Other Drugs
Based on *in vitro* data, Xospata may reduce the effects of drugs that target 5HT2B receptor or sigma nonspecific receptor (e.g., escitalopram, fluoxetine, sertraline). Avoid concomitant use of these drugs with Xospata unless use is considered essential for the care of the patient (see section 5.2).
Xospata is an inhibitor of P-gp, breast cancer resistant protein (BCRP) and OCT1 *in vitro*. As Xospata may inhibit transporters at a therapeutic dose, caution is advised during coadministration of Xospata with substrates of P-gp (e.g., digoxin, dabigatran etexilate), BCRP (e.g., mitoxantrone, rosuvastatin) and OCT1 (e.g., metformin) (see section 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy
Gilteritinib can cause fetal harm based upon findings from animal studies. Xospata showed suppressed fetal growth, embryo-fetal deaths and teratogenicity in the embryo-fetal development studies in rats. Advise pregnant women of the potential risk to a fetus (see section 5.3).

Breast-feeding
There is no information regarding the presence of Xospata in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies, gilteritinib and/or its metabolite(s) were distributed to the tissues in infant rats via the milk. Breastfeeding is not recommended during Xospata treatment and for at least 2 months after the last dose (see section 5.3).

Fertility
Pregnancy testing

Pregnancy testing is recommended for females of reproductive potential within seven days prior to initiating Xospata treatment (see section 5.3).

Contraception

Advise females of reproductive potential to use effective contraception during treatment and for at least 6 months after the last dose of Xospata (see section 5.3).
Advise males of reproductive potential to use effective contraception during treatment and for at least 4 months after the last dose of Xospata.

4.7 Effects on ability to drive and use machines

Xospata has the potential to influence 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.

4.8 Undesirable effects

The safety evaluation of gilteritinib is based on 319 patients (including 246 patients in the ADMIRAL trial) with relapsed or refractory AML who received at least one dose of 120 mg gilteritinib daily (see section 5.1). At the time of final analysis cutoff, the median duration of exposure to gilteritinib was 111 days (range 4 to 1320 days).

The most common adverse reactions (≥10%) were alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, diarrhea, fatigue, nausea, constipation, cough, peripheral edema, dyspnea, blood alkaline phosphatase increased, dizziness, hypotension, pain in extremity, asthenia, blood creatine phosphokinase increased, arthralgia and myalgia.

The most frequent serious adverse reactions (≥2%) reported in patients were acute kidney injury, diarrhea, ALT increased, dyspnea, AST increased, hypotension and differentiation syndrome.

Tabulated summary of adverse reactions

Adverse reactions observed during clinical studies are listed below by frequency category. 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 grouping, adverse reactions are presented in order of decreasing frequency.

Table 1: Adverse Reactions Reported in Patients with Relapsed or Refractory AML for Gilteritinib 120 mg daily versus Salvage Chemotherapy (Any Grade)

SOC	Preferred Term	Any Grade					
		Integrated Safety Set		ADMIRAL Trial (2215-CL-0301)			
		Gilteritinib 120 mg daily (N=319)		Gilteritinib 120 mg daily (N=246)		Salvage Chemotherapy (N=109)	
		%	Frequency	%	Frequency	%	Frequency
Cardiac disorders	Electrocardiogram QT prolonged	8.8	Common	6.9	Common	0	-
	Pericardial effusion	4.1	Common	4.5	Common	0	-
	Pericarditis	1.6	Common	2	Common	0	-
	Cardiac failure	1.3	Common	1.6	Common	0	-

SOC	Preferred Term	Any Grade					
		Integrated Safety Set		ADMIRAL Trial (2215-CL-0301)			
		Gilteritinib 120 mg daily (N=319)		Gilteritinib 120 mg daily (N=246)		Salvage Chemotherapy (N=109)	
		%	Frequency	%	Frequency	%	Frequency
Gastrointestinal disorders	Diarrhea	35.1	Very common	32.9	Very common	29.4	Very common
	Nausea	29.8	Very common	32.1	Very common	33	Very common
	Constipation	28.2	Very common	30.9	Very common	14.7	Very common
General disorders and administration site conditions	Fatigue	30.4	Very common	28.5	Very common	12.8	Very common
	Peripheral edema	24.1	Very common	24	Very common	11.9	Very common
	Asthenia	13.8	Very common	15.4	Very common	9.2	Common
	Malaise	4.4	Common	4.9	Common	1.8	Common
Immune system disorders	Anaphylactic reaction	1.3	Common	1.2	Common	0	-
Investigations	Alanine aminotransferase increased	37.6	Very common	41.9	Very common	9.2	Common
	Aspartate aminotransferase increased	37.6	Very common	40.2	Very common	11.9	Very common
	Blood alkaline phosphatase increased	20.7	Very common	22.8	Very common	1.8	Common
	Blood creatine phosphokinase increased	12.5	Very common	13.4	Very common	0	-
Musculoskeletal and connective tissue disorders	Pain in extremity	14.7	Very common	14.6	Very common	7.3	Common
	Arthralgia	12.5	Very common	11.4	Very common	5.5	Common
	Myalgia	12.5	Very common	14.2	Very common	3.7	Common
	Musculoskeletal pain	4.1	Common	4.5	Common	1.8	Common
Nervous system disorders	Dizziness	20.4	Very common	19.5	Very common	1.8	Common
	Posterior reversible encephalopathy syndrome	0.6	Uncommon	0.4	Uncommon	0	-
Renal and urinary disorders	Acute kidney injury	6.6	Common	6.5	Common	3.7	Common
Respiratory, thoracic and mediastinal disorders	Cough	28.2	Very common	29.3	Very common	10.1	Very common
	Dyspnea	24.1	Very common	23.6	Very common	6.4	Common
	Differentiation syndrome	3.4	Common	3.7	Common	-	-
Vascular disorders	Hypotension	17.2	Very common	17.5	Very common	7.3	Common

Table 2: Adverse Reactions Reported in Patients with Relapsed or Refractory AML for Gilteritinib 120 mg daily versus Salvage Chemotherapy (≥Grade 3)

SOC	Preferred Term	≥Grade 3					
		Integrated Safety Set		ADMIRAL Trial (2215-CL-0301)			
		Gilteritinib 120 mg daily (N=319)		Gilteritinib 120 mg daily (N=246)		Salvage Chemotherapy (N=109)	
		%	Frequency	%	Frequency	%	Frequency
Cardiac disorders	Electrocardiogram QT prolonged	2.5	Common	1.6	Common	0	-
	Pericardial effusion	0.9	Uncommon	1.2	Common	0	-
	Pericarditis	0	-	0	-	0	-
	Cardiac failure	1.3	Common	1.6	Common	0	-
Gastrointestinal disorders	Diarrhea	4.1	Common	3.7	Common	2.8	Common
	Nausea	1.9	Common	2	Common	0	-

SOC	Preferred Term	≥Grade 3					
		Integrated Safety Set		ADMIRAL Trial (2215-CL-0301)			
		Gilteritinib 120 mg daily (N=319)		Gilteritinib 120 mg daily (N=246)		Salvage Chemotherapy (N=109)	
		%	Frequency	%	Frequency	%	Frequency
	Constipation	0.6	Uncommon	0.8	Uncommon	0	-
General disorders and administration site conditions	Fatigue	3.1	Common	2.4	Common	1.8	Common
	Peripheral edema	0.3	Uncommon	0.4	Uncommon	0	-
	Asthenia	2.5	Common	2.4	Common	1.8	Common
	Malaise	0	-	0	-	0	-
Immune system disorders	Anaphylactic reaction	1.3	Common	1.2	Common	0	-
Investigations	Alanine aminotransferase increased	11.6	Very common	13.8	Very common	4.6	Common
	Aspartate aminotransferase increased	12.5	Very common	14.6	Very common	1.8	Common
	Blood alkaline phosphatase increased	2.2	Common	2.8	Common	0	-
	Blood creatine phosphokinase increased	4.7	Common	5.3	Common	0	-
Musculoskeletal and connective tissue disorders	Pain in extremity	0.6	Uncommon	0.8	Uncommon	0.9	Uncommon
	Arthralgia	1.3	Common	1.6	Common	0.9	Uncommon
	Myalgia	0.3	Uncommon	0.4	Uncommon	0	-
	Musculoskeletal pain	0.3	Uncommon	0	-	0.9	Uncommon
Nervous system disorders	Dizziness	0.3	Uncommon	0.4	Uncommon	0	-
	Posterior reversible encephalopathy syndrome	0.6	Uncommon	0.4	Uncommon	0	-
Renal and urinary disorders	Acute kidney injury	2.2	Common	1.2	Common	1.8	Common
Respiratory, thoracic and mediastinal disorders	Cough	0.3	Uncommon	0.4	Uncommon	0	-
	Dyspnea	4.4	Common	4.1	Common	2.8	Common
	Differentiation syndrome	2.2	Common	2	Common	-	-
Vascular disorders	Hypotension	7.2	Common	7.7	Common	2.8	Common

Table 3: New or Worsening Laboratory Abnormalities (>20%) Detected in Patients with Relapsed or Refractory AML

		Integrated Safety Set		ADMIRAL Trial (2215-CL-0301)			
		Gilteritinib 120 mg daily (N=319)		Gilteritinib 120 mg daily (N=246)		Salvage Chemotherapy (N=109)	
	Grade	%	Frequency	%	Frequency	%	Frequency
Alanine aminotransferase increased	Any	82.1	Very common	83.3	Very common	47.7	Very common
	≥3	12.9	Very common	12.6	Very common	2.8	Common
Aspartate aminotransferase increased	Any	80.6	Very common	81.3	Very common	38.5	Very common
	≥3	10.3	Very common	10.2	Very common	1.8	Common
Blood creatine phosphokinase increased	Any	53.9	Very common	51.2	Very common	0.9	Uncommon
	≥3	6.3	Common	6.5	Common	0	-
Blood alkaline phosphatase increased	Any	68.7	Very common	68.3	Very common	42.2	Very common
	≥3	1.6	Common	1.6	Common	0	-

4.9 Overdose

In the event of an overdose, stop treatment with Xospata and initiate general supportive measures taking into consideration the long half-life estimated at 113 hours.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action
Xospata is a small molecule FMS-like tyrosine kinase 3 (FLT3) and AXL tyrosine kinase inhibitor. Xospata demonstrated the ability to inhibit FLT3 receptor signaling 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.

Pharmacodynamic effects
In patients with relapsed or refractory AML receiving Xospata 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.

Prolonged QT interval
A concentration-related increase in change from baseline of QTcF (ΔQTcF) was observed across Xospata doses ranging from 20 to 450 mg. The predicted mean change from baseline of QTcF at the mean steady-state C_{max} (282.0 ng/mL) at the 120 mg daily dose was 4.96 msec with an upper 1-sided 95% CI = 6.20 msec. Of 317 patients treated with Xospata at 120 mg with a post-baseline QTc value in clinical trials, 4 patients (<1.3%) experienced a QTcF >500 msec.
Additionally, across all doses, 2.3% of patients with relapse/refractory AML had a maximum post-baseline QTcF interval >500 msec.

Clinical efficacy and safety

ADMIRAL study (2215-CL-0301)

The ADMIRAL trial is a Phase 3, open-label, multicenter, randomized clinical trial of adult patients with relapsed or refractory AML and a FLT3 mutation. FLT3 mutations were identified by a diagnostic test. The trial compares the safety and efficacy of gilteritinib therapy (120 daily dose) to one of the following salvage chemotherapies:

- cytarabine 20 mg twice daily by subcutaneous (SC) or intravenous (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)
- mitoxantrone 8 mg/m^2, etoposide 100 mg/m^2 and cytarabine 1000 mg/m^2 once daily by IV for 5 days (days 1 through 5)
- granulocyte colony-stimulating factor 300 mcg/m^2 once daily by SC for 5 days (days 1 to 5), fludarabine 30 mg/m^2 once daily by IV for 5 days (days 2 through 6), cytarabine 2000 mg/m^2 once daily by IV for 5 days (days 2 through 6), idarubicin 10 mg/m^2 once daily by IV for 3 days (days 2 through 4).

Patients included were relapsed or refractory after first line AML therapy and were stratified by response to prior AML treatment and preselected chemotherapy, i.e. high or low intensity. While the study included patients with various AML-related cytogenetic abnormalities, patients with acute promyelocytic leukaemia (APL) or therapy-related AML were excluded.

Sixteen patients were randomised but not treated in the study (1 patient in the gilteritinib arm and 15 patients in the chemotherapy arm). Gilteritinib was given orally at a starting dose of 120 mg daily until unacceptable toxicity or lack of clinical benefit. Dose reductions were allowed, to manage adverse reactions, and dose increases were allowed, for those patients who did not respond at the starting dose of 120 mg.

Of the patients who were pre-selected to receive salvage chemotherapy, 60.5% were randomised to high intensity and 39.5% to low intensity. MEC and FLAG-Ida were given for up to two cycles depending on response to first cycle. LoDAC and azacitidine were given in continuous 4-week cycles until unacceptable toxicity or lack of clinical benefit.

The efficacy of gilteritinib was evaluated in a pre-planned interim analysis of 142 patients that were randomized to the gilteritinib arm. At the final analysis, overall survival (OS) was evaluated in 371 patients randomized in a 2:1 ratio (247 in the gilteritinib arm and 124 in the salvage chemotherapy arm).

The baseline demographic and disease characteristics are shown in the table below.

Table 4: ADMIRAL Trial: Baseline Demographic and Disease Characteristics in Patients with Relapsed or Refractory AML

Demographic and Disease Characteristics	**Gilteritinib (120 mg daily) + Salvage Chemotherapy N=371**
Demographics	
Age (Years) Median (Min, Max)	62 (19, 85)
Age Categories, n (%)	
<65 years	216 (58.2)
≥65 years	155 (41.8)

Demographic and Disease Characteristics	Gilteritinib (120 mg daily) + Salvage Chemotherapy N=371
Sex, n (%)	
Male	170 (45.8)
Female	201 (54.2)
Race, n (%)	
White	220 (59.3)
Asian	102 (27.5)
Black or African American	21 (5.7)
Native Hawaiian or Other Pacific Islander	1 (0.3)
Other	6 (1.6)
Unknown/Missing	21 (5.7)
Disease Characteristics n (%)	
Baseline ECOG, n (%)	
0-1	311 (83.8)
≥2	60 (16.2)
Relapsed AML, n (%)	225 (60.6)
Refractory AML, n (%)	146 (39.4)
FLT3 Mutation Status, n (%)[a]	
ITD alone	328 (88.4)
TKD alone	31 (8.4)
ITD and TKD	7 (1.9)
Cytogenetic Risk Status, n (%)	
Favorable	5 (1.3)
Intermediate	271 (73)
Unfavorable	37 (10)
Other	58 (15.6)
Response to Prior Therapy, n (%)	
Relapse within 6 months after allogeneic HSCT	48 (12.9)
Relapse after 6 months after allogeneic HSCT	25 (6.7)
Primary refractory without HSCT	146 (39.4)
Relapse within 6 months after CRc and no HSCT	101 (27.2)
Relapse after 6 months after CRc and no HSCT	51 (13.7)
Transfusion Dependent at Baseline, n (%)	197 (80.1)

AML: acute myeloid leukemia; FLT3: FMS-related tyrosine kinase 3; ITD: internal tandem duplication; TKD: D835/1836 tyrosine kinase domain point mutation; ECOG PS: Eastern Cooperative Oncology Group performance status; CRc: Composite complete remission (complete remission [CR] + complete remission with incomplete hematologic recovery [CRi] + complete remission with incomplete platelet recovery [CRp]); HSCT: Hematopoietic stem cell transplantation.

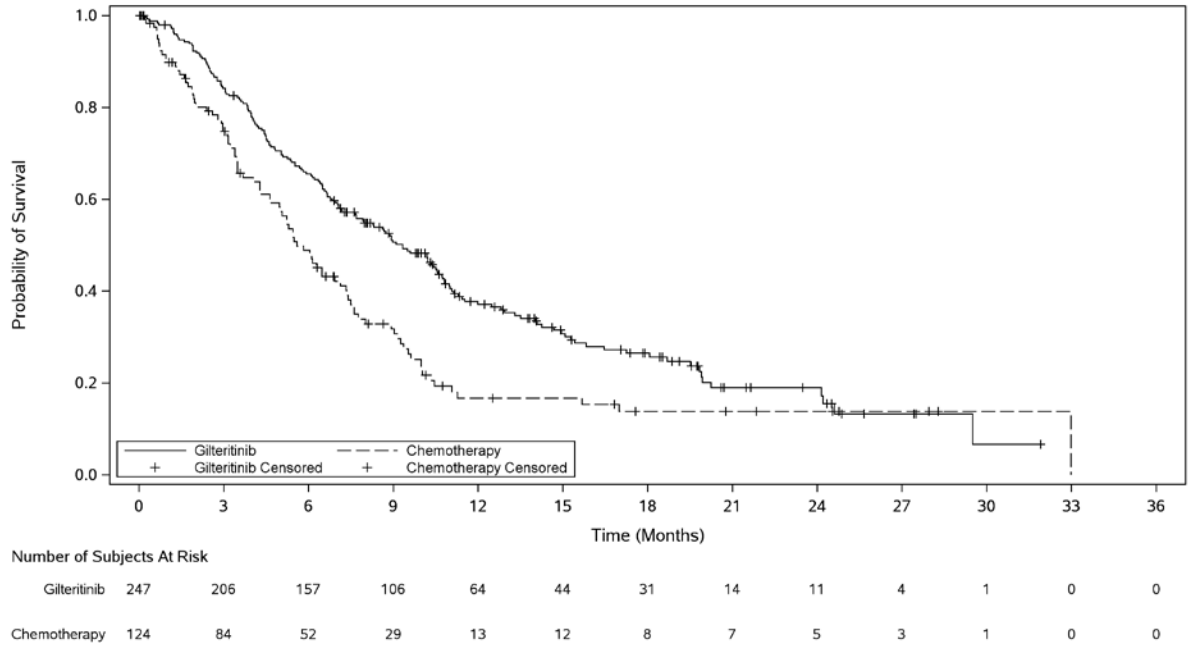
[a]The remaining 5 patients were negative by the diagnostic test.

The primary efficacy endpoint for the final analysis was OS, measured from the date of randomization until death by any cause (number of events analyzed was 261). Patients randomized to the gilteritinib arm had significantly longer survival compared to the chemotherapy arm (HR 0.637; 95% CI 0.490 – 0.830; 1 sided p-value: 0.0004). The median OS was 9.3 months for patients receiving gilteritinib and 5.6 months for those receiving chemotherapy (Table 5, Figure 1).

Table 5: ADMIRAL Trial Overall Survival in Patients with Relapsed or Refractory AML

	Gilteritinib (N=247)	**Chemotherapy (N=124)**
Deaths, n (%)	171 (69.2%)	90 (72.6%)
Median in months (95% CI)	9.3 (7.7, 10.7)	5.6 (4.7, 7.3)
Hazard Ratio (95% CI)	0.637 (0.490, 0.830)	
p-value (1-sided)	0.0004	
1-year survival rate, % (95% CI)	37.1 (30.7, 43.6)	16.7 (9.9, 25)

Figure 1: Kaplan-Meier plot of overall survival in ADMIRAL study



A modified analysis of event free survival (EFS), defined as a failure to obtain a composite complete remission (CRc) with failures assigned as an event on date of randomization, relapse, or death from any cause, including events and initiation of new anti-leukemia treatments reported in long-term follow up, showed an improvement with a median EFS of 2.3 months for gilteritinib versus 0.7 months for salvage chemotherapy HR 0.499 (95% CI 0.387, 0.643) and 1-sided p<0.0001.
Efficacy was supported by the rate of complete remission (CR)/complete remission with partial hematologic recovery (CRh), the duration of CR/CRh (DOR), and the rate of conversion from transfusion dependence to transfusion independence. The efficacy results are shown in the table below.

Table 6: ADMIRAL Trial Efficacy Results in Patients with Relapsed or Refractory AML

Remission Rate	**Gilteritinib (120 mg daily) N=247**	**Chemotherapy (N=124)**
CR[a] n/N (%)	52/247 (21.1)	13/124 (10.5)

Remission Rate	Gilteritinib (120 mg daily) N=247	Chemotherapy (N=124)
95% CI[b]	16.1, 26.7	5.7, 17.3
Median DOR[c] (months)	NR	1.8
95% CI	11, NR	NE, NE
CRh[d] n/N (%)	32/247 (13)	6/124 (4.8)
95% CI[b]	9, 17.8	1.8, 10.2
Median DOR[c] (months)	4	NE
95% CI	2.1, 5.3	NE, NE
CR/CRh n/N (%)	84/247 (34)	19/124 (15.3)
95% CI[b]	28.1, 40.3	9.5, 22.9
Median DOR[c] (months)	11	1.8
95% CI	4.6, NR	NE, NE

CI: confidence interval; NR: not reached; NE: not estimable.

a. CR was defined as an absolute neutrophil count $\geq$1.0 x 10^9/L, platelets $\geq$100 x 10^9/L, normal marrow differential with <5% blasts, must have been red blood cells, platelet transfusion independent and no evidence of extramedullary leukemia.
b. The 95% CI rate was calculated using the exact method based on binomial distribution.
c. DOR was defined as the time from the date of either first CR or CRh until the date of a documented relapse of any type.
d. CRh was defined as marrow blasts <5%, partial hematologic recovery absolute neutrophil count $\geq$0.5 x 10^9/L and platelets $\geq$50 x 10^9/L, no evidence of extramedullary leukemia and could not have been classified as CR.

For patients who achieved a CR/CRh, the median time to first response was 3.7 months (range: 0.9 to 10.6 months) in the gilteritinib arm and 1.2 months (range: 1 to 2.6 months) in the salvage chemotherapy arm. The median time to best response of CR/CRh was 3.8 months (range: 0.9 to 16 months) in the gilteritinib arm and 1.2 months (range: 1 to 2.6 months) in the salvage chemotherapy arm.

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

CHRYSALIS Trial (2215-CL-0101)

The efficacy of gilteritinib was evaluated in an open-label, multicenter, dose escalation, clinical trial (CHRYSALIS trial) investigating the safety, tolerability, pharmacokinetics and pharmacodynamics of gilteritinib therapy in patients with relapsed or refractory AML and a FLT3 mutation. FLT3 mutations were identified by local results.

The baseline demographic and disease characteristics are shown in the table below.

Table 7: CHRYSALIS Trial Baseline Demographic and Disease Characteristics in Patients with Relapsed or Refractory AML

Demographic and Disease Characteristics	Gilteritinib (120 mg daily) N=56
Demographics	
Age (Years) Median (Min, Max)	59 (23, 87)
Age Categories, n (%)	
<65 years	38 (67.9)
$\geq$65 years	18 (32.1)

Demographic and Disease Characteristics	Gilteritinib (120 mg daily) N=56
Sex, n (%)	
Male	26 (46.4)
Female	30 (53.6)
Race, n (%)	
White	49 (87.5)
Black or African American	3 (5.4)
Asian	1 (1.8)
Other	3 (5.4)
Disease Characteristics n (%)	
ECOG PS, n (%)	
0-1	41 (73.2)
≥2	15 (26.8)
FLT3 Mutation Status, n (%)	
ITD alone	47 (83.9)
TKD alone	6 (10.7)
ITD and TKD	3 (5.4)
Cytogenetic Risk Status, n (%)	
Favorable	1 (1.8)
Intermediate	38 (67.9)
Unfavorable	7 (12.5)
Other	10 (17.9)
Prior Stem Cell Transplant for AML, n (%)	19 (33.9)
Transfusion Dependent at Baseline, n (%)	52 (92.9)
Number of Prior Anticancer Regimens, n (%)	
1	14 (25)
2	18 (32.1)
≥3	24 (42.9)

AML: acute myeloid leukemia; FLT3: FMS-related tyrosine kinase 3; ITD: internal tandem duplication; TKD: tyrosine kinase domain; ECOG PS: Eastern Cooperative Oncology Group performance status.

Efficacy was established on the basis of the rate of CR/CRh, the duration of CR/CRh (DOR), and the rate of conversion from transfusion dependence to transfusion independence. Efficacy for patients who received gilteritinib at the 120 mg daily dose level are represented in the table below.

Table 8: CHRYSALIS Trial Efficacy Results in Patients with Relapsed or Refractory AML

Remission Rate	Gilteritinib (120 mg daily) N=56
CR[a] n/N (%)	7/56 (12.5)
95% CI[b]	5.2, 24.1
Median DOR[c] (months)	NR
95% CI[e]	2.8, NE

CRh[d] n/N (%)	6/56 (10.7)
95% CI[b]	4, 21.9
Median DOR[c] (months)	2.1
95% CI[e]	0.6, 2.8
CR/CRh n/N (%)	13/56 (23.2)
95% CI[b]	13, 36.4
Median DOR[c] (months)	10.1
95% CI[e]	1.8, NE

CI: confidence interval; NE: not estimable; NR: not reached.

a. CR was defined as an absolute neutrophil count >1.0 x 10^9/L, platelets ≥100 x 10^9/L, normal marrow differential with <5% blasts, must have been red blood cells, platelet transfusion independent and no evidence of extramedullary leukemia.
b. The 95% CI rate was calculated using the exact method based on binomial distribution.
c. DOR was defined as the time from the date of either first CR or CRh until the date of a documented relapse of any type.
d. CRh was defined as marrow blasts <5%, partial hematologic recovery absolute neutrophil count ≥0.5 x 10^9/L and platelets ≥50 x 10^9/L, no evidence of extramedullary leukemia and could not have been classified as CR.
e. Calculated using Kaplan-Meier estimate.

For patients who achieved a CR/CRh, the median time to first response of CR/CRh was 1.9 months (range: 1 to 9.2 months), and the median time to best response of CR/CRh was 2.1 months (range: 1 to 12 months).
Among the 52 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 11 (21.2%) became independent of RBC and platelet transfusions during any 56-day post-baseline period. Of the 4 patients who were independent of both RBC and platelet transfusions at baseline, 3 (75.0%) remained transfusion independent during any 56-day post-baseline period.

5.2 Pharmacokinetic properties

Absorption
Following oral administration of tablet formulations, peak Xospata concentrations are observed at a median t_{max} approximately between 4 and 6 hours in healthy volunteers and patients with relapsed or refractory AML. Xospata undergoes first-order absorption with an estimated absorption rate (k_a) of 0.43 hr^{-1} with a lag time of 0.34 hours based on population pharmacokinetic (PK) modeling. Median steady-state maximum concentration (C_{max}) is 282.0 ng/mL (CV% = 50.8), and area under the plasma concentration curve during 24-hour dosing interval (AUC_{0-24}) is 6180 ng·hr/mL (CV% = 46.4) after once-daily dosing of 120 mg Xospata. Steady-state plasma levels are reached by 15 days of once-daily dosing with an approximate 10-fold accumulation.

Effect of food
In healthy adults, Xospata C_{max} and AUC decreased by approximately 26% and less than 10%, respectively, when a single 40 mg dose of Xospata was coadministered with a high fat meal compared to Xospata exposure in fasted state. Median t_{max} was delayed 2 hours when Xospata was administered with a high-fat meal. Xospata can be administered with or without food.

Distribution
The population estimates of central and peripheral volume of distribution were 1092 L and 1100 L, respectively. These data indicate Xospata distributes extensively outside of plasma, which may indicate extensive tissue distribution. *In vivo* plasma protein binding in humans is approximately 90% and Xospata is primarily bound to albumin.

Biotransformation
Based on *in vitro* data, Xospata 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.

Elimination

After a single dose of [^{14}C]-Xospata, Xospata is primarily excreted in feces with 64.5% of the total administered dose recovered in feces. Renal excretion is a minor elimination pathway with 16.4% of the total dose recovered in urine as unchanged drug and metabolites. Xospata plasma concentrations declined in a bi-exponential manner with a population mean estimated half-life of 113 hours. The estimated apparent clearance (CL/F) based on the population PK model is 14.85 L/h.

Linearity

Xospata exhibits linear, dose-proportional pharmacokinetics in patients with relapsed or refractory AML at doses ranging from 20 mg to 450 mg administered once-daily.

Special populations

No clinically meaningful effect on the pharmacokinetics of Xospata was observed for the following covariates: age (20 years to 90 years), race (Caucasian, Black, Asian or Other), mild hepatic impairment [defined as total bilirubin ≤ upper limit of normal (ULN) and aspartate transaminase (AST) >ULN or total bilirubin 1 to 1.5 times ULN and any AST], sex, body weight (36 kg to 157 kg), and body surface area (1.29 to 2.96 m^2).

Hepatic impairment

The effect of hepatic impairment on Xospata pharmacokinetics has been studied in subjects with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment. Results indicate unbound Xospata exposure in subjects with mild or moderate hepatic impairment is comparable to that observed in subjects with normal hepatic function. Xospata has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

In non-AML patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, unbound Xospata exposure is comparable to that observed in subjects with normal liver function. The effect of mild hepatic impairment on Xospata exposure was also assessed using the population PK model and the results demonstrate little difference in predicted steady-state Xospata exposure relative to a typical patient with relapsed or refractory AML normal liver function. These data suggest Xospata dose adjustment is not warranted in patients with mild or moderate hepatic impairment. Xospata has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

Renal impairment

A clinical assessment of the effect of renal function on Xospata exposure was not conducted based on nonclinical and clinical data that indicate renal excretion is a minor elimination route. Although the population PK model included serum creatinine, a marker of renal function, as a statistically significant covariate, the impact on Xospata exposure was less than 2-fold and not considered clinically meaningful. Therefore, impaired renal function is not expected to significantly affect Xospata exposure indicating dose adjustment is not warranted in patients with renal impairment.

Drug Interaction Studies

Effects of Other Drugs on gilteritinib

CYP3A/P-gp Inducers

Gilteritinib exposure decreased approximately 70% when gilteritinib was coadministered with a strong CYP3A/P-gp inducer (rifampicin). Concomitant medications that are strong CYP3A/P-gp inducers should be avoided during gilteritinib therapy.

CYP3A and/or P-gp Inhibitors

Gilteritinib exposure increased approximately 2.2-fold when gilteritinib was coadministered with a strong CYP3A and P-gp inhibitor (itraconazole) in healthy adult subjects and approximately 1.5-fold

in patients with relapsed or refractory AML. It is recommended that concomitant medications that are strong CYP3A and/or P-gp inhibitors be used with caution during gilteritinib therapy as they can increase the plasma exposure of gilteritinib.

In vitro experiments demonstrated that gilteritinib is a substrate of BCRP.

Effects of gilteritinib on Other Drugs
Based on *in vitro* data, gilteritinib may reduce the effects of drugs that target $5HT_{2B}$ receptor or sigma nonspecific receptor. Avoid concomitant use of these drugs with gilteritinib unless use is considered essential for the care of the patient.

Gilteritinib may potentially inhibit BCRP, P-gp and OCT1 at clinically relevant concentrations.

5.3 Preclinical safety data

Gilteritinib showed a concentration-dependent suppression effect on the human ether-a-go-go related gene (hERG) current in hERG-transfected HEK293 cells. The IC50 was 1.6 × 10−5 mol/L (8.84 mcg/mL).

Gilteritinib increased the currents via CaV1.2 calcium channel in Chinese hamster ovary cells and KV7.1/minK potassium channel in HEK293 cells at 1 × 10−6 mol/L (553 ng/mL) and higher concentrations.

In rats treated with gilteritinib, decreased urination at 30 mg/kg and higher and decreased defecation at 100 mg/kg were observed. In dogs treated with gilteritinib, retching at 3 mg/kg, vomiting and positive fecal 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.

No repeat-dose studies with dosing duration longer than 13 weeks and no carcinogenicity studies have been conducted.

Gilteritinib did not induce gene mutation in the *in vitro* reversion test in bacteria. Similarly, gilteritinib did not induce chromosomal aberrations in the *in vitro* chromosomal aberration test in mammalian cells. The *in vivo* micronucleus test showed that gilteritinib has a potential to induce micronuclei in mice.

Gilteritinib showed no potential to induce phototoxicity to cultured mammalian cells.

Gilteritinib showed suppressed fetal growth, embryo-fetal deaths and teratogenicity in the embryo-fetal development studies in rats. The no-observed adverse effect level (NOAEL) for dams and embryo-fetal development was 10 mg/kg per day. No embryo-fetal development study in rabbits was conducted.

The effects on pre- and post-natal development and maternal function are unknown.

In the pivotal juvenile animal toxicity study in rats, dosing from postnatal day 4 to 42, the minimum lethal dose level was 2.5 mg/kg per day which was lower than the 20 mg/kg per day dose, the minimal lethal dose in adult rats. In the preliminary (non-GLP) dose range finding study (dosing from postnatal day 4 to up to day 21), gastrointestinal bleeding suggested by abnormal stool color (dark red) was noted at 10 mg/kg per day and higher, indicating that the gastrointestinal tract is one of the target organs as in adult rats.

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

After single oral administration to lactating rats, milk concentrations of radioactivity were higher than radioactivity in maternal plasma at 4- and 24-hours post-dose and no radioactivity was detected in all tested maternal samples at 48 hours or later post-dose. The radioactivity was detected in the infant tissues examined, except for the brain, at 4, 24, 48, and 72 h post-dose, indicating that gilteritinib-derived components are distributed to the infant tissues through breast milk.

In the 1-week oral repeated dose toxicity study in rats, interstitial pneumonia in the lung and vacuolar change in the rod-cone layer of the retina were observed at 30 mg/kg per day. In the 13-week oral repeated dose toxicity study in rats, deaths occurred at 20 mg/kg per day. Target organ toxicity was identified in the gastrointestinal tract, lymphohematopoietic system, eye, lung, kidney and liver. The no-observed adverse effect level (NOAEL) was lower than 2.5 mg/kg per day.

In the 4-week oral repeated dose study in dogs, mortality/moribundity occurred at 10 mg/kg per day or more. Target organ toxicity was identified in the gastrointestinal tract, lymphohematopoietic system, eye, kidney and liver. The NOAEL was 1 mg/kg per day.

In the 13-week oral repeated dose study in dogs, mortality occurred at 5 mg/kg per day. Target organ toxicity was identified in the lung, urinary bladder, epithelial tissue, gastrointestinal tract, lymphohematopoietic system, eye, kidney and liver. The NOAEL was 1 mg/kg per day.

Reversibility of most of the test article-related changes was indicated by the end of the 4-week recovery period.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate, hypromellose, talc, macrogol, titanium dioxide and iron oxide yellow.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiration date is indicated on the packaging.

6.4 Special precautions for storage

Store below 30 ºC. Store in the original package in order to protect from light.

6.5 Nature and contents of container

OPA/aluminium/PVC/aluminium blisters containing 21 film-coated tablets.

Each pack contains 84 film-coated tablets.

7. MARKETING AUTHORIZATION HOLDER

Manufactured by
Astellas Pharma Inc. Yaizu Technology Center
Shizuoka, Japan

Imported by
Astellas Pharma (Thailand) Co., Ltd.
Bangkok, Thailand

8. MARKETING AUTHORIZATION NUMBERS

1C 15/65 (NC)

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

26 August 2022

10. DATE OF REVISION OF THE TEXT

June 2024