Patient guide
The marketing of Xospata is subject to a risk management plan (RMP) including a Patient guide. The Patient guide, emphasizes important safety information that the patient should be aware of before and during treatment.
Please explain to the patient the need to review the card before starting treatment.

Prescriber guide
This product is marketed with prescriber providing important safety information. Please ensure you are familiar with this material as it contains important safety information.

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 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).

4.2 Posology and method of administration

Treatment with Xospata should be initiated and supervised by a physician experienced in the use of anti-cancer therapies.

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) (see Table 1).

Posology

The recommended starting dose is 120 mg gilteritinib (three 40 mg tablets) once daily.

Blood chemistries, including creatine phosphokinase, should be assessed prior to initiation of treatment, on day 15 and monthly for the duration of treatment.

An electrocardiogram (ECG) should be performed before initiation of gilteritinib treatment, on day 8 and 15 of cycle 1 and prior to the start of the next three subsequent months of treatment (see sections 4.4 and 4.8).

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 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.

Dose modifications

Table 1. Xospata dose interruption, reduction and discontinuation recommendations in patients with relapsed or refractory AML

Criteria	**Xospata dosing**
Differentiation syndrome	• If differentiation syndrome is suspected, administer corticosteroids and initiate hemodynamic monitoring (see section 4.4). • Interrupt gilteritinib if severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids. • Resume gilteritinib at the same dose when signs and symptoms improve to Grade 2[a] or lower.
Posterior reversible encephalopathy syndrome	• Discontinue gilteritinib.
QTcF interval >500 msec	• Interrupt gilteritinib. • Resume gilteritinib at a reduced dose (80 mg or 120 mg[b]) when QTcF interval returns to within 30 msec of baseline or ≤ 480 msec.
QTcF interval increased by >30 msec on ECG on day 8 of cycle 1	• Confirm with ECG on day 9. • If confirmed, consider dose reduction to 80mg.
Pancreatitis	• Interrupt gilteritinib until pancreatitis is resolved. • Resume treatment with gilteritinib at a reduced dose (80 mg or 120 mg[b]).
Other Grade 3[a] or higher toxicity considered related to treatment.	• Interrupt gilteritinib until toxicity resolves or improves to Grade 1[a]. • Resume treatment with gilteritinib at a reduced dose (80 mg or 120 mg[b]).
Planned HSCT	• Interrupt treatment with gilteritinib 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 CRc.[c]

a. Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe,, Grade 4 is life-threatening.
b. The daily dose can be reduced from 120 mg to 80 mg or from 200 mg to 120 mg.

c. CRc is defined as the remission rate of all CR (see section 5.1 for definition of CR), CRp [achieved CR except for incomplete platelet recovery (<100 x 10^9/L)] and CRi (achieved all criteria for CR except for incomplete haematological recovery with residual neutropenia <1 x 10^9/L with or without complete platelet recovery).

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 is not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment, as safety and efficacy have not been evaluated in this population (see section 5.2).

Renal impairment
No dose adjustment is necessary in patients with mild or moderate renal impairment. There is no clinical experience in patients with severe renal impairment (see section 5.2).

Paediatric population
Xospata is not indicated for children and adolescents under 18 years old.
The safety and efficacy of Xospata in children aged below 18 years has not yet been established.

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.

4.4 Special warnings and precautions for use

Differentiation syndrome
Gilteritinib has been associated with differentiation syndrome (see section 4.8).
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 (see sections 4.2 and 4.8).

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.

Posterior reversible encephalopathy syndrome
There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving Xospata (see section 4.8). 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). Discontinuation of Xospata in patients who develop PRES is recommended (see sections 4.2 and 4.8).

Prolonged QT interval
Gilteritinib has been associated with prolonged cardiac ventricular repolarisation (QT Interval) (see sections 4.8 and 5.1). QT prolongation can be observed in the first three months of treatment with gilteritinib. Therefore, electrocardiogram (ECG) should be performed prior to initiation of treatment, on day 8 and 15 of cycle 1, and prior to the start of the next three 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.

Xospata should be interrupted in patients who have a QTcF >500 msec (see section 4.2).

The decision to re-introduce gilteritinib treatment after an event of QT prolongation should be based on a careful consideration of benefits and risks. If Xospata is re-introduced at a reduced dose, ECG should be performed after 15 days of dosing, and prior to the start of the next three subsequent months of treatment. In clinical studies, 12 patients had QTcF >500 msec. Three patients interrupted and re-initiated treatment without recurrence of QT prolongation.

Pancreatitis
There have been reports of pancreatitis. 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 (see section 4.2).

Interactions
Co-administration of CYP3A/P-gp inducers may lead to decreased gilteritinib exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of gilteritinib with strong CYP3A4/P-gp inducers should be avoided (see section 4.5).

Caution is required when concomitantly prescribing gilteritinib with medicinal products that are strong inhibitors of CYP3A, P-gp and/or breast cancer resistant protein (BCRP) (such as, but not limited to, voriconazole, itraconazole, posaconazole and clarithromycin) because they can increase gilteritinib exposure. Alternative medicinal products that do not strongly inhibit CYP3A, P-gp and/or BCRP activity should be considered. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for toxicities during administration of gilteritinib (see section 4.5).

Gilteritinib may reduce the effects of medicinal products that target $5HT_{2B}$ receptor or sigma nonspecific receptors. Therefore, concomitant use of gilteritinib with these products should be avoided unless use is considered essential for the care of the patient (see section 4.5).

Embryofoetal toxicity and contraception

Pregnant women should be informed of the potential risk to a foetus (see sections 4.6 and 5.3). Females of reproductive potential should be advised to have a pregnancy test within seven days prior to starting treatment with Xospata and to use effective contraception during treatment with Xospata and for at least 6 months after stopping treatment. Women using hormonal contraceptives should add a barrier method of contraception. Males with female partners of reproductive potential should be advised to use effective contraception during treatment and for at least 4 months after the last dose of Xospata.

4.5 Interaction with other medicinal products and other forms of interaction

Gilteritinib is primarily metabolised by CYP3A enzymes, which can be induced or inhibited by a number of concomitant medicinal products.

Effects of other medicinal products on Xospata

CYP3A/P-gp Inducers

Concomitant use of Xospata with strong CYP3A/P-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 rifampicin (600 mg), a strong CYP3A/P-gp inducer, to steady state with a single 20 mg dose of gilteritinib decreased gilteritinib mean C_{max} by 27% and mean AUC_{inf} by 70%, respectively, compared to subjects administered a single dose of gilteritinib alone (see section 4.4).

CYP3A, P-gp and/or BCRP inhibitors

Strong inhibitors of CYP3A, P-gp and/or BCRP (e.g., voriconazole, itraconazole, posaconazole, clarithromycin, erythromycin, captopril, carvedilol, ritonavir, azithromycin) can increase gilteritinib plasma concentrations. A single, 10 mg dose of gilteritinib co-administered with itraconazole (200 mg once daily for 28 days), a strong CYP3A, P-gp and BCRPinhibitor, 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 relapsed or refractory AML when co-administered with a strong CYP3A, P-gp and/or BCRPinhibitor (see section 4.4).

Effects of Xospata on other medicinal products

Gilteritinib as an inhibitor or inducer

Gilteritinib is not an inhibitor or inducer of CYP3A4 or an inhibitor of MATE1 *in vivo*. The pharmacokinetics 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 relapsed or refractory AML. Additionally, the pharmacokinetics 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 relapsed or refractory AML.

Gilteritinib is an inhibitor of P-gp, BCRP and OCT1 *in vitro*. As no clinical data is available, it cannot be excluded that gilteritinib could inhibit these transporters at a therapeutic dose. Caution is advised during co-administration of gilteritinib with substrates of P-gp (e.g., digoxin, dabigatran etexilate), BCRP (e.g., mitoxantrone, methotrexate, rosuvastatin) and OCT1 (e.g., metformin).

$5HT_{2B}$ receptor or sigma nonspecific receptor

Based on *in vitro* data, gilteritinib may reduce the effects of medicinal products that target $5HT_{2B}$ receptor or sigma nonspecific receptor (e.g., escitalopram, fluoxetine, sertraline).

Avoid concomitant use of these medicinal products with Xospata unless use is considered essential for the care of the patient.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females
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 (see section 4.4).

Pregnancy
Gilteritinib can cause foetal harm when administered to pregnant women. There are no or limited amount of data from the use of gilteritinib in pregnant women. Reproductive studies in rats have shown that gilteritinib caused suppressed foetal growth, embryo-foetal deaths and teratogenicity (see section 5.3). Xospata is not recommended during pregnancy and in women of childbearing potential not using effective contraception.

Breast-feeding
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 (see section 5.3).

A risk to 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.

Fertility
There are no data on the effect of gilterinitib on human fertility.

4.7 Effects on ability to drive and use machines

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 (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety of Xospata was evaluated in 319 patients with relapsed or refractory AML who have received at least one dose of 120 mg gilteritinib.

The most frequent adverse reactions with gilteritinib were alanine aminotransferase (ALT) increased (82.1%), aspartate aminotransferase (AST) increased (80.6%), blood alkaline phosphatase increased (68.7%), blood creatine phosphokinase increased (53.9%), diarrhoea (35.1%), fatigue (30.4%), nausea (29.8%), constipation (28.2%), cough (28.2%), peripheral oedema (24.1%), dyspnea (24.1%), dizziness (20.4%), hypotension (17.2%), pain in extremity (14.7%), asthenia (13.8%), arthralgia (12.5%) and myalgia (12.5%).

The most frequent serious adverse reactions were acute kidney injury (6.6%), diarrhoea (4.7%), ALT increased (4.1%), dyspnea (3.4%), AST increased (3.1%) and hypotension (2.8%). Other clinically significant serious adverse reactions included differentiation syndrome (2.2%), electrocardiogram QT prolonged (0.9%) and posterior reversible encephalopathy syndrome (0.6%).

Tabulated list 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 frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse reactions

Adverse drug reaction	**All Grades %**	**Grades ≥3 %**	**Frequency category**
Immune system disorders			
Anaphylactic reaction	1.3	1.3	Common
Nervous system disorders			
Dizziness	20.4	0.3	Very common
Posterior reversible encephalopathy syndrome	0.6	0.6	Uncommon
Cardiac disorders			
Electrocardiogram QT prolonged	8.8	2.5	Common
Pericardial effusion	4.1	0.9	Common
Pericarditis	1.6	0	Common
Cardiac failure	1.3	1.3	Common
Vascular disorders			
Hypotension	17.2	7.2	Very common
Respiratory, thoracic and mediastinal disorders			
Cough	28.2	0.3	Very common
Dyspnoea	24.1	4.4	Very common
Differentiation syndrome	3.4	2.2	Common
Gastrointestinal disorders			
Diarrhoea	35.1	4.1	Very common
Nausea	29.8	1.9	Very common
Constipation	28.2	0.6	Very common
Hepatobiliary disorders			
Alanine aminotransferase increased*	82.1	12.9	Very common
Aspartate aminotransferase increased*	80.6	10.3	Very common
Musculoskeletal and connective tissue disorders			
Blood creatine phosphokinase increased*	53.9	6.3	Very common
Blood alkaline phosphatase increased*	68.7	1.6	Very common
Pain in extremity	14.7	0.6	Very common
Arthralgia	12.5	1.3	Very common
Myalgia	12.5	0.3	Very common
Musculoskeletal pain	4.1	0.3	Common
Renal and urinary disorders			
Acute kidney injury	6.6	2.2	Common
General disorders and administration site conditions			
Fatigue	30.4	3.1	Very common
Peripheral oedema	24.1	0.3	Very common
Asthenia	13.8	2.5	Very common
Malaise	4.4	0	Common

* Frequency is based on central laboratory values.

Description of selected adverse reactions

Differentiation syndrome

Of 319 patients treated with Xospata in the clinical studies, 11 (3%) experienced 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 clinical findings of differentiation syndrome in patients treated with Xospata included fever, dyspnoea, pleural effusion, pericardial effusion, pulmonary oedema, hypotension, rapid weight gain, peripheral oedema, rash, and renal dysfunction. Some cases had concomitant acute febrile neutrophilic dermatosis. Differentiation syndrome occurred as early as one day and up to 82 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. For recommendations in case of suspected differentiation syndrome see sections 4.2 and 4.4.

PRES

Of the 319 patients treated with Xospata in the clinical studies, 0.6% experienced posterior reversible encephalopathy syndrome (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. Symptoms have resolved after discontinuation of treatment (see sections 4.2 and 4.4).

QT prolongation

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 (see sections 4.2, 4.4 and 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
http://sideeffects.health.gov.il

4.9 Overdose

There is no known specific antidote for Xospata. In the event of an overdose, treatment with Xospata should be stopped. Patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic and supportive treatment initiated, taking into consideration the long half-life estimated at 113 hours.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors, ATC code: L01EX13

Mechanism of action

Gilteritinib fumarate is a FLT3 and AXL inhibitor.
Gilteritinib inhibits FLT3 receptor signalling and proliferation in cells exogenously expressing FLT3 including FLT3-ITD, FLT3-D835Y, and FLT3-ITD-D835Y, and it induces apoptosis in leukemic cells expressing FLT3-ITD.

Pharmacodynamic effects
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.

Prolonged QT interval
A concentration-related increase in change from baseline of QTcF was observed across gilteritinib 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.

Clinical efficacy and safety
Relapsed or refractory AML
Efficacy and safety were evaluated in the active-controlled, phase 3 study (2215-CL-0301).

ADMIRAL study (2215-CL-0301)
The ADMIRAL study is a Phase 3, open-label, multicentre, randomised clinical study of adult patients with relapsed or refractory AML with a FLT3 mutation as determined by the LeukoStrat® CDx FLT3 Mutation Assay. In this study, 371 patients were randomised in a 2:1 ratio to receive gilteritinib or one of the following salvage chemotherapies (247 in the gilteritinib arm and 124 in the salvage chemotherapy arm):

- cytarabine 20 mg twice daily by subcutaneous injection (SC) or intravenous infusion (IV) for 10 days (days 1 through 10) (LoDAC)
- 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) (MEC)
- 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) (FLAG-Ida).

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 demographic and baseline characteristics were well-balanced between the two treatment arms. The median age at randomisation was 62 years (range 20 to 84 years) in the gilteritinib arm and 62 years (range 19 to 85 years) in the salvage chemotherapy arm. In the study 42% of patients were 65 years or older and 12% were 75 years or older. Fifty-four percent of the patients were female. Most patients in the study were Caucasian (59.3%); 27.5% Asian, 5.7%

Black, 4% other races and 3.5% unknown. The majority of patients (83.8%) had an ECOG performance status score of 0 or 1. Patients had the following confirmed mutations: FLT3-ITD alone (88.4%), FLT3-TKD alone (8.4%) or both FLT3-ITD and FLT3-TKD (1.9%). Twelve percent of patients received previous treatment with another FLT3 inhibitor. A majority of patients had AML with intermediate risk cytogenetics (73%), 10% had unfavourable, 1.3% had favourable and 15.6% had unclassified cytogenetics.

Prior to treatment with gilteritinib, 39.4% of patients had primary refractory AML and the majority of these patients were classified as refractory after 1 cycle of chemotherapy induction treatment, 19.7% had relapsed AML after an allogeneic haematopoietic stem cell transplant (HSCT) and 41% had relapsed AML with no allogeneic HSCT.

The primary efficacy endpoint for the final analysis was OS in the intent-to-treat (ITT) population, measured from the date of randomisation until death by any cause (number of events analysed was 261). Patients randomised 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. Efficacy was further supported by the rate of complete remission (CR)/complete remission with partial haematologic recovery (CRh) (Table 3, Figure 1).

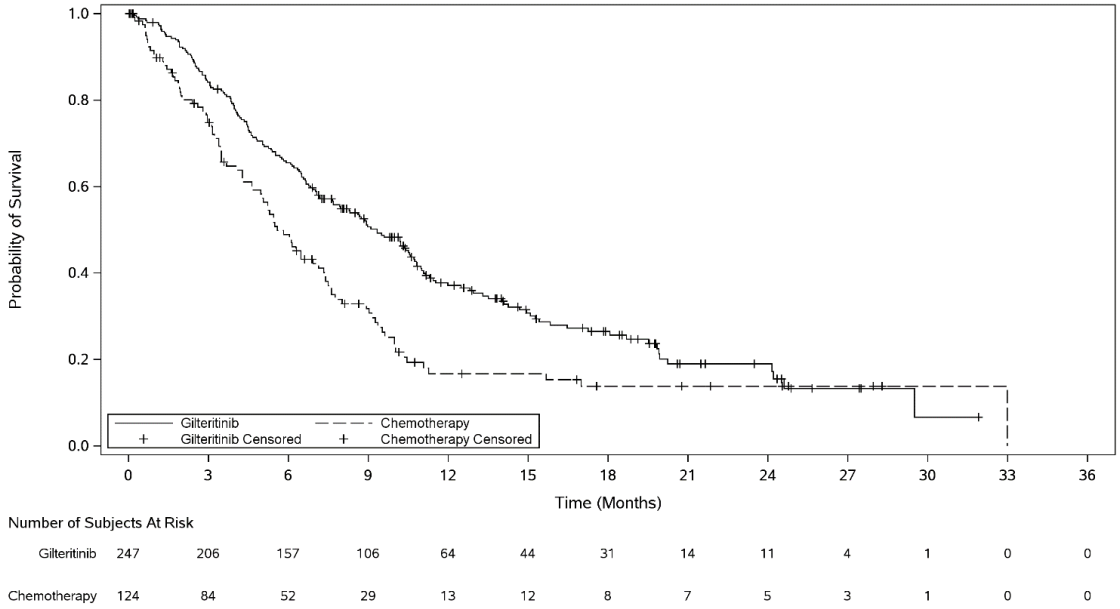
Table 3: ADMIRAL study overall survival and complete remission in patients with relapsed or refractory AML

	Gilteritinib (N=247)	**Chemotherapy (N=124)**
Overall survival		
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)
Complete remission		
CR[a] (95% CI[b])	21.1% (16.1, 26.7)	10.5% (5.7, 17.3)
CRh[c] (95% CI[b])	13% (9, 17.8)	4.8% (1.8, 10.2)
CR/CRh (95% CI[b])	34% (28.1, 40.3)	15.3% (9.5, 22.9)

CI: confidence interval

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. CRh was defined as marrow blasts <5%, partial haematologic 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.

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



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.

CHRYSALIS study (2215-CL-0101)
The supportive Phase 1/2 dose-escalation study 2215-CL-0101 included 157 patients with FLT3 mutated AML treated with either 1 or >1 prior lines of treatment 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.

The response rate (CR/CRh) observed in Study 2215-CL-0101 in the patients who received more than 1 line of prior therapy was 21.4% and 15.7% for the 120 mg dose and the combined dose levels, respectively. The median OS was 7.2 months and 7.1 months for the 120 mg dose and the combined dose levels, respectively.

5.2 Pharmacokinetic properties

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 relapsed or refractory AML. Gilteritinib undergoes first-order absorption with an estimated absorption rate (k_a) of 0.43 h^{-1} with a lag time of 0.34 hours based on population PK modelling. 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·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.

Effect of food
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.

Distribution

The population estimate of central and peripheral volume of distribution were 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 albumin.

Biotransformation

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.

Transporter drug-drug interactions

In vitro experiments demonstrated that gilteritinib is a substrate of P-gp and BCRP. Gilteritinib may potentially inhibit BCRP, P-gp and OCT1 at clinically relevant concentrations (see section 4.5).

Elimination

After a single dose of [^{14}C] -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 apparent clearance (CL/F) based on the population PK model is 14.85 L/h.

Linearity/non-linearity

In general, gilteritinib exhibited linear, dose-proportional pharmacokinetics after single and multiple dose administration at doses ranging from 20 to 450 mg in patients with relapsed or refractory AML.

Special populations

A population pharmacokinetic analysis was performed to evaluate the impact of intrinsic and extrinsic covariates on the predicted exposure of gilteritinib in patients with relapsed or refractory AML. Covariate analysis indicated that age (20 years to 90 years), and body weight (36 kg to 157 kg) were statistically significant; however predicted change in gilteritinib exposure was less than 2-fold.

Hepatic impairment

The effect of hepatic impairment on gilteritinib pharmacokinetics was studied in subjects with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment. 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 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 relapsed or refractory AML and normal liver function.

Gilteritinib has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

Renal impairment
A dedicated renal impairment study has not been conducted to assess of the effect of renal impairment on gilteritinib pharmacokinetics. The effect of mild or moderate renal impairment was evaluated using a population pharmacokinetic 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. The effect of severe renal impairment on gilteritinib exposure has not been investigated (see section 4.2).

5.3 Preclinical safety data

Adverse reactions not observed in clinical studies, but seen in animals (safety pharmacology/repeat dose toxicity) at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Safety pharmacology
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.

Repeat dose toxicity
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.

Genotoxicity
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.

Reproductive toxicity
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.

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.

Juvenile animal toxicity study
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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Mannitol
Hydroxypropylcellulose, low-substitutedHydroxypropylcellulose
HydroxypropylcelluloseMagnesium stearate

Film-coating
Hypromellose
Macrogol
Talc
Titanium dioxide
Iron oxide yellow

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.
It is recommended to store in room temperature.
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.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Name of manufacturer

Astellas Pharma Europe B.V., Meppel, the Netherlands

8. Name of registration holder

Astellas Pharma International B.V. Israel.

9. MARKETING AUTHORISATION NUMBER(S)

165-30-36203-00

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