24 October 2019
EMADOC-2005359794-175863
EMA/OD/0000006592
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Note

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

Xospata (gilteritinib)
Treatment of acute myeloid leukaemia
EU/3/17/1961
Sponsor: Astellas Pharma Europe B.V.

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

Table of contents

1. Product and administrative information

Product	
Active substance	Gilteritinib
International Non-Proprietary Name	Gilteritinib
Initial orphan condition	Treatment of acute myeloid leukaemia
Pharmaceutical form	Tablet
Route of administration	Oral use
Pharmaco-therapeutic group (ATC Code)	L01XE
Sponsor's details:	Astellas Pharma Europe B.V. Sylviusweg 62 2333 BE Leiden Zuid-Holland The Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Astellas Pharma Europe B.V.
COMP opinion date	7 December 2017
EC decision date	17 January 2018
EC registration number	EU/3/17/1961
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	B. Bolstad, N. Karpova
Applicant	Astellas Pharma Europe B.V.
Application submission date	7 February 2019
Procedure start date	27 February 2019
Procedure number	EMA/H/C/004752
Invented name	Xospata
Therapeutic 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). Further information on Xospata can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/xospata
CHMP opinion date	19 September 2019
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	K. Penttilä, M. Kalland
Sponsor's report submission date	26 March 2019
COMP discussion and adoption of list of questions	16-18 July 2019
Oral explanation	11 September 2019
COMP opinion date (adopted via written procedure)	23 September 2019

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2018 designation was based on the following grounds:

The sponsor Astellas Pharma Europe B.V. submitted on 22 September 2017 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing gilteritinib for treatment of acute myeloid leukaemia (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing gilteritinib was considered justified based on preliminary clinical data demonstrating that patients responded to treatment;
- the condition is life threatening and chronically debilitating due to the consequences of bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections. The condition progresses rapidly and is fatal within days to weeks or a few months if left untreated. The overall 5-year relative survival with the currently available treatments is approximately 22%;
- the condition was estimated to be affecting approximately 1 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing gilteritinib will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that relapsed or refractory patients responded to treatment. There are currently no authorised treatments for this patient population. The Committee considered that this constitutes a clinically relevant advantage.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing gilteritinib as an orphan medicinal product for the orphan indication: treatment of acute myeloid leukaemia.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Acute myeloid leukaemia (AML) is a disease characterised by rapid, uncontrolled proliferation of malignant clonal haematopoietic stem cells that accumulate as immature, undifferentiated cells (blasts) and lead to impaired production of normal haematopoietic elements, which in turn leads to anaemia, neutropenia, and thrombocytopenia. The COMP continues to accept AML as orphan condition for the purpose of orphan designation and maintenance.

Xospata (gilteritinib) is a small molecule FMS-like tyrosine kinase 3 (FLT3) and AXL tyrosine kinase inhibitor for oral administration.

The currently proposed therapeutic 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)" falls within the scope of the designated orphan condition "Treatment of acute myeloid leukaemia".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP. Please refer to the European public assessment report (EPAR) of Xospata.

Chronically debilitating and/or life-threatening nature

At the time of initial designation, the COMP agreed that the condition was chronically debilitating and life-threatening. At the time of this review, AML is presented to the COMP to remain chronically debilitating and life threatening. The most recent reported data from the US SEER database reports an annual age-adjusted mortality rate of AML of 2.8 per 100,000. Outcomes are worse for patients aged ≥ 60 years, with CR rates in the range of 40% to 55% and poor long-term survival rates.

The COMP concluded that the condition remains life threatening and chronically debilitating due to the consequences of bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections. The condition progresses rapidly and is fatal within a few months if left untreated.

Number of people affected or at risk

At the time of designation the prevalence was agreed to be approximately 1 per 10,000.

For this review the prevalence was presented to the COMP to remain less than 5 per 10,000 and was estimated to be 1.36 per 10,000. The sponsor provided an overview of various population based registries reporting on the prevalence of AML in Europe (table 1). The RARECAREnet data were relatively outdated with data collection up to 2008. The Swedish and NORDCAN datasets provide the more recent prevalence figures. The NORDCAN project, a database of epidemiological cancer data for Denmark, Finland, the Faroe Islands, Greenland, Iceland, Norway and Sweden, reported an overall AML prevalence of 1.35 per 10,000 at the end of 2016 for the 5 Nordic countries collectively (Denmark, Finland, Iceland, Norway and Sweden). On the basis of the provided data, the COMP accepted a prevalence estimate of approximately 1.4 per 10,000.

Table 1. Prevalence data overview as provided by the sponsor

Source (Country or Region)	Estimated prevalence (year corresponding to data collection)	Notes
RARECAREnet† (EU-28)	1.36 per 10000 (2008)	Based on data from 26 European cancer registries
Swedish cancer registries‡ (Sweden)	1.37 per 10000 (2014)	Based on data from a nationally-representative population-based registry
NORDCAN§ (Nordic countries combined: Denmark, Finland, Iceland, Norway, Sweden)	1.35 per 10000 (2016)	Based on data from nationally-representative, population-based cancer registries

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The following products were identified to be authorised for the treatment of the orphan condition: histamine dihydrochloride, decitabine, azacitidine, daunorubicin, idarubicin, mitoxantrone, etoposide, cytarabine (Ara-C), thioguanine, L-asparaginase, doxorubicin, vincristine sulphate, cyclophosphamide.

Rydapt (midostaurin) has been authorised in combination with standard daunorubicin and cytarabine induction and high dose cytarabine consolidation chemotherapy, and for patients in complete response followed by Rydapt single agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation positive.

Vyxeos (daunorubicin and cytarabine) has been authorised for the treatment of adults with newly diagnosed, therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).

Mylotarg (gemtuzumab ozogamicin) has recently been authorised and is indicated for combination therapy with daunorubicin (DNR) and cytarabine (AraC) for the treatment of patients age 15 years and above with previously untreated, de novo CD33-positive acute myeloid leukaemia (AML), except acute promyelocytic leukaemia (APL).

The COMP also took into consideration the latest European Society for Medical Oncology (ESMO) treatment guideline from Fey and Buske 2013 discussing the current treatment options for AML in adult patients (Ann Oncol 2013; 24 (Suppl 6): vi138-vi143).

Significant benefit

The COMP noted that Xospata is a small molecule FMS-like tyrosine kinase 3 (FLT3) and AXL tyrosine kinase inhibitor for oral administration for authorisation in the R/R AML setting. EMA protocol assistance prior to marketing authorisation was requested, however the demonstration of significant benefit was not prospectively discussed with the COMP.

Significant benefit had to be demonstrated in adult patients who have relapsed or refractory acute myeloid leukaemia (R/R AML) with a FLT3 mutation. For this patient population, the latest ESMO guideline outlines that carefully selected patients with an HLA-matched donor may be offered allogeneic stem cell transplantation, albeit with limited chances of success and at the cost of considerable morbidity from this procedure. For patients unsuited to this approach, best standard of care (BSC) or palliative systemic treatment is often a reasonable option with, at least, limited toxic effect. Taking into consideration the ESMO guideline and the authorisation status of medicinal products in AML, it was considered that significant benefit would need to be established over medicinal products that are authorised in leukaemia and/or AML and are used in the salvage therapy of R/R AML.

The results of study 2215-CL-0301 (ADMIRAL) have been presented to demonstrate significant benefit over the currently authorised salvage therapies. ADMIRAL was a phase 3, open-label, multicenter, randomised study of Xospata versus salvage chemotherapy in patients with FLT3 positive AML refractory to or relapsed after first-line treatment with or without HSCT consolidation. The results of this clinical trial were assessed as pivotal evidence by the CHMP (please also refer to the EPAR of Xospata).

A total of 371 patients were enrolled and randomised to gilteritinib (247 subjects) or salvage chemotherapy (124 subjects). Patients were randomised in a 2:1 ratio to receive gilteritinib 120 mg once daily (the dose could be titrated according to protocol or to one the 4 salvage chemotherapy regimens (high-intensity chemotherapy [MEC or FLAG-IDA] or low-intensity chemotherapy [LoDAC or azacitidine]). All patients in the ITT previously received induction chemotherapy for AML, which included known and investigational anticancer agents.

In detail, the comparator chemotherapy regimens were:

1. LoDAC: low intensity chemotherapy, 20 mg cytarabine was administered twice daily by subcutaneous (sc) or intravenous (iv) injection for 10 days.
2. Azacitidine: low intensity chemotherapy, 75 mg/m^2 azacitidine was administered daily by sc or iv injection for 7 days.
3. MEC: high intensity chemotherapy
    - Mitoxantrone 8 mg/m^2 per day was administered by iv for 5 days (days 1 through 5).
    - Etoposide 100 mg/m^2 per day was administered by iv for 5 days (days 1 through 5).
    - Cytarabine 1000 mg/m^2 per day was administered by iv for 5 days (days 1 through 5).
4. FLAG-IDA: high intensity chemotherapy
    - G-CSF 300 µg/m2 per day was administered by sc/iv for 5 days (days 1 through 5). Additional G-CSF by sc/iv was recommended 7 days after completing chemotherapy until absolute neutrophil count (ANC) > 0.5 X 10^9/L.
    - Fludarabine 30 mg/m^2 per day was administered by iv for 5 days (days 2 through 6).
    - Cytarabine 2000 mg/m^2 per day was administered by iv for 5 days (days 2 through 6).
    - Idarubicin 10 mg/m^2 per day was administered by iv for 3 days (days 2 through 4).

The co-primary endpoints were (a) overall survival (OS) defined as the time from the date of randomisation until the date of death from any cause, and (b) complete remission/complete remission with partial hematological recovery (CR/CRh), defined as the number of patients who achieved either CR or CRh at any of the postbaseline visits divided by the number of patients in the analysis

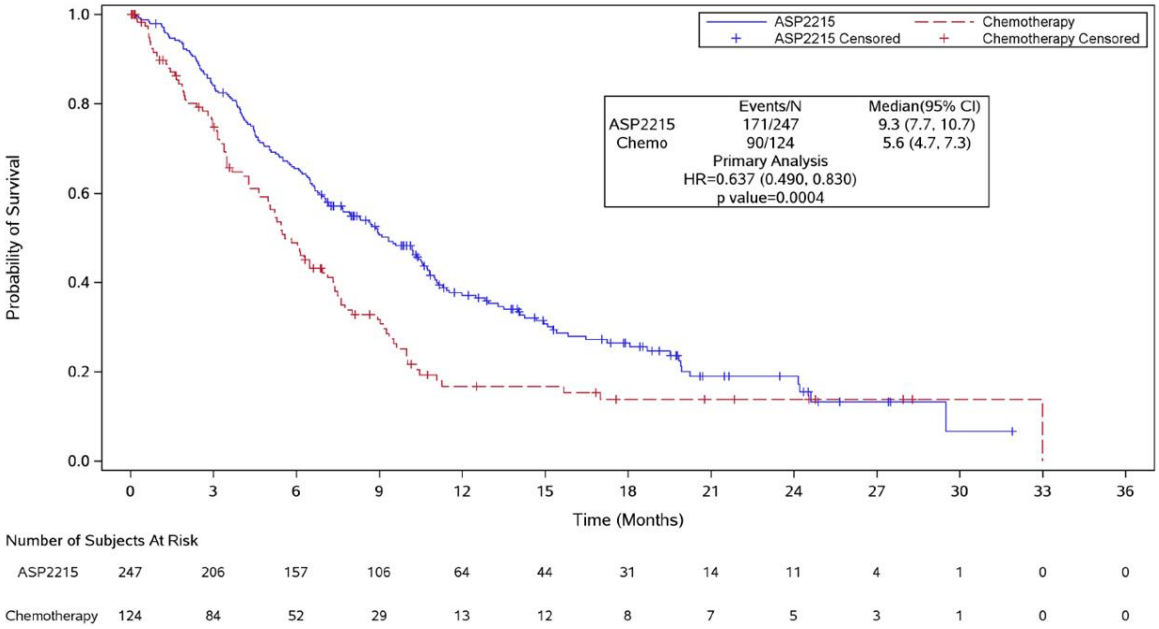
population. Key and other secondary endpoint included event-free survival (EFS) and CR rate. For the CHMP assessment, the final OS analysis was considered the primary efficacy outcome measure.

The primary endpoint (OS) in the ITT population showed a statistically significant increase in OS, with a HR of 0.637 (95% CI: 0.490- to 0.830, p=0.0004 one-sided log rank test) and a median OS of 9.3 months and 5.6 months in the gilteritinib and salvage chemotherapy arms, respectively (table 1 and figure 1).

Table 2. Study 2215-CL-0301 (ADMIRAL): Overall Survival ITT

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

Figure 1. Study 2215-CL-0301 (ADMIRAL): Kaplan-Meier Plot of Overall Survival by Treatment Arm (ITT)



Subgroup analyses were provided comparing overall survival, complete remission rate and composite complete remission rate between the gilteritinib arm and the four different treatment selections on the control arm in study 2215-CL-0301 (ADMIRAL): low-dose cytarabine (LoDAC), azacitidine, MEC (mitoxantrone, etoposide, cytarabine) and FLAG-IDA (G-CSF, fludarabine, cytarabine, idarubicin). The subgroup comparisons included patients randomised to the gilteritinib arm that were pre-selected for low intensity chemotherapy (LIC) versus LoDAC and azacitidine respectively, and patients randomised to the gilteritinib arm that were pre-selected for high intensity chemotherapy (HIC) versus MEC and FLAG-IDA respectively. It should be noted that these are post-hoc subgroup analyses and the trial was not formally powered to show improved effects in the subgroups. Nevertheless, the results suggest a consistent treatment effect on OS across the analysed subgroups. For gilteritinib (preselected LIC) vs LoDAC, the median OS was 6.4 months vs 2.8 months (HR 0.567 [95% CI: 0.306, 1.050]), with a composite complete remission (CRc) rate of 49% vs 0. For gilteritinib (preselected LIC) vs azacitidine, the median OS was 6.4 months vs 5.1 months (HR 0.557 [95% CI: 0.353, 0.879]), with a CRc rate of 49% vs 6.3%. For the gilteritinib (preselected HIC) vs MEC, the median OS was 10.5 months vs 5.0 months (HR 0.408 [95% CI: 0.260, 0.641), with a CRc rate of 57.7% vs 39.4%. For the gilteritinib (preselected HIC) vs FLAG-IDA the median OS was 10.5 months vs 7.5 months, (HR 0.891 [95% CI: 0.577, 1.377]), with a CRc rate of 57.7% vs 28.6%.

The COMP considered that most of the authorised salvage therapies in R/R leukaemia and AML were used in the comparator arm of the ADMIRAL study. Anthracyclines like doxorubicin and daunorubicin have been authorised as salvage therapies in the R/R AML setting and were not studied in the ADMIRAL trial. However, the anthracycline idarubicin was used as part of the comparator regimen FLAG-IDA. Therefore, the COMP considered that significant benefit over this class of medicines in R/R AML salvage therapy was sufficiently justified on the basis of the presented comparative clinical data of Xospata over the FLAG-IDA regimen.

In conclusion, the pivotal study 2215-CL-0301 (ADMIRAL) provided evidence that Xospata extended overall survival when directly compared against commonly used salvage regimens in the intensive and non-intensive setting. The COMP considered that the observed improvement in overall survival

constitutes a clinically relevant advantage over current satisfactory methods in adult R/R AML patients with FLT3 mutation.

4. COMP position adopted on 23 September 2019

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of acute myeloid leukaemia (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 1.4 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to the consequences of bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections. The condition progresses rapidly and is fatal within a few months if left untreated;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, Xospata is of significant benefit to adult patients who have relapsed or refractory (R/R) acute myeloid leukemia (AML) with a FLT3 mutation. Significant benefit over currently authorised intensive and non-intensive salvage regimens was demonstrated in an open-label, multicenter, randomised phase 3 study in patients with FLT3 positive R/R AML comparing Xospata with salvage chemotherapy, with the option of two different non-intensive salvage chemotherapies (low dose cytarabine and azacitidine) or two different commonly used intensive chemotherapies MEC (mitoxantrone, etoposide, cytarabine) and FLAG-IDA (G-CSF, fludarabine, cytarabine, idarubicin). The data demonstrated that Xospata treatment resulted in a statistically significant improvement in overall survival compared to salvage chemotherapy. The COMP concluded that this constitutes a clinically relative advantage in patients affected by the condition due to an improvement in clinical efficacy.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Xospata, gilteritinib, EU/3/17/1961 for treatment of acute myeloid leukaemia is not removed from the Community Register of Orphan Medicinal Products.