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Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Vanflyta (quizartinib)
Treatment of acute myeloid leukaemia
EU/3/09/622

Sponsor: Daiichi Sankyo Europe GmbH

Note

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

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1. Product and administrative information

Product	
Designated active substance	N-(5-tert-Butylisoxazol-3-yl)-N'-{4-[7-(2-(morpholin-4-yl)ethoxy) imidazo[2,1-b][1,3]benzothiazol-2-yl]phenyl}urea di-hydrochloride salt
Other name(s)	--
International Non-Proprietary Name	Quizartinib
Tradename	Vanflyta
Orphan condition	Treatment of acute myeloid leukaemia
Sponsor's details:	Daiichi Sankyo Europe GmbH Zielstattstrasse 48 Thalkirchen-Obersendling 81379 Munich Bavaria Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	Ambit Europe Limited
COMP opinion	9 February 2009
EC decision	23 March 2009
EC registration number	EU/3/09/622
Post-designation procedural history	
Transfer of sponsorship	Transfer from Ambit Europe Limited to Daiichi Sankyo Europe GmbH– EC decision of 26 June 2015 Transfer from Daiichi Sankyo Europe GmbH to Daiichi Sankyo Development Ltd – EC decision of 8 August 2016
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Johann Lodewijk Hillege / Janet Koenig
Applicant	Daiichi Sankyo Europe GmbH
Application submission	23 June 2022
Procedure start	18 August 2022
Procedure number	EMA/H/C/005910
Invented name	Vanflyta
Proposed therapeutic indication	Vanflyta is indicated in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by VANFLYTA single-agent maintenance therapy for adult patients with newly diagnosed acute myeloid leukaemia (AML) that is FLT3-ITD positive. Further information on Vanflyta can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/vanflyta

CHMP opinion	14 September 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Frauke Naumann-Winter / Maria Elisabeth Kalland
Sponsor's report submissions	22 March 2023 and 22 June 2023
COMP discussion and adoption of list of questions	11-13 July 2023
Oral explanation	5 September 2023
Sponsor's removal request received	8 September 2023
Removal confirmed	19 September 2023

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2009 was based on the following grounds:

- acute myeloid leukaemia (hereinafter referred to as "the condition") was estimated to be affecting less than 2 in 10,000 persons in the Community, at the time the application was made;
- the condition is chronically debilitating and life-threatening, in particular due to high mortality rate of refractory or relapsed disease;
- although satisfactory methods of treatment of the condition have been authorised in the Community, sufficient justification has been provided that N-(5-tert-Butylisoxazol-3-yl)-N'-{4-[7-(2-(morpholin-4-yl)ethoxy) imidazo[2,1-b][1,3]benzothiazol-2-yl]phenyl}urea di-hydrochloride salt may be of significant benefit to those affected by the condition.

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) includes a heterogeneous group of neoplastic disorders characterized by the proliferation and accumulation of immature haematopoietic cells of the myeloid line. The disease is associated with termination in cellular differentiation and uncontrolled proliferation of clonal immature malignant myeloblasts in the bone marrow and blood (Scheinberg et al, 2001), which results in a deficiency of red blood cells, normal white blood cells, and platelets. AML remains primarily a disease of older adults, with a median age at diagnosis of around 70 years (Heuser et al., 2020). The incidence of AML across all age groups is higher in males than in females and increases with age (Löwenberg et al, 2016; Shallis et al, 2019).

AML can be divided into de novo and secondary disease (Scheinberg et al, 2001; Appelbaum et al, 2001). Patients presenting with de novo AML often do not have any identifiable risk factor. Secondary causes for AML include previous myelodysplastic syndromes (MDS), Down's syndrome, Fanconi's anaemia, ataxia-telangiectasia, long-term treatment consequences of certain chemotherapeutic

agents, and exposure to environmental hazards (e.g., benzene). The common feature of all AML is genetic mutation, which results in visible cytogenetic abnormalities in 70% of the patients when the leukaemia cells are karyotyped. As a result, various genes are increased or decreased in expression, resulting in the neoplastic state of the disease.

The proposed product quizartinib (Vanflyta) is an inhibitor of the receptor tyrosine kinase FLT3 (FMS-like tyrosine kinase 3). Wild-type (WT) FLT3 is overexpressed in nearly all cases of AML, and FLT3 mutations represent one of the most common genetic alterations, occurring in approximately 30% of adult patients with newly diagnosed AML (Kennedy and Smith, 2020; Papaemmanuil et al., 2016). Quizartinib and its major metabolite AC886 competitively bind to the adenosine triphosphate (ATP) binding pocket of FLT3 with high affinity. Quizartinib and AC886 inhibit FLT3 kinase activity, preventing autophosphorylation of the receptor, thereby inhibiting further downstream FLT3 receptor signalling and blocking FLT3-ITD-dependent cell proliferation.

The proposed therapeutic indication "Vanflyta is indicated in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, followed by Vanflyta single-agent maintenance therapy for adult patients with newly diagnosed acute myeloid leukaemia (AML) that is FLT3-ITD positive" falls within the scope of the designated orphan condition "Treatment of acute myeloid leukaemia".

There are two types of FLT3 mutations: 1) FLT3-internal tandem duplication (ITD) and 2) point mutations or deletion in the tyrosine kinase domain (TKD). The FLT3-ITD mutation is more common than the FLT3-TKD mutation, being found in 20-25% versus 7-10% of all AML cases. Females present with FLT3-ITD mutant AML more frequently than males, and there is evidence that the incidence of FLT3-ITD mutations decreases with age, with an incidence of up to 35% in patients between 20 and 59 years old compared with 16-20% in patients >60 years old (Konig and Levis, 2015). The presence of an FLT3-ITD mutation confers an unfavourable prognosis, while FLT3-TKD mutations have not been associated with a consistent prognostic impact (Mead et al., 2007).

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The clinical presentation of AML is directly related to ineffective haematopoiesis; patients typically present with signs and symptoms of fatigue, haemorrhage, as well as infections and fever. Furthermore, the uncontrolled proliferation of malignant blasts results in the accumulation of a large number of abnormal, immature myeloblasts in the bone marrow (BM), peripheral blood, and in various organs such as the central nervous system, lymph nodes, skin, liver and spleen. If untreated, AML progresses rapidly and is fatal in weeks to months. Patients die due to infection, bleeding, or complications related to a large volume of abnormal cells in the vasculature.

The sponsor claimed that no significant changes have been identified in the seriousness of AML since the orphan designation was granted in 2009.

When treated with intensive chemotherapy alone, patients with FLT3-ITD positive AML have higher relapse rates (Levis, 2004) and inferior overall survival (OS) than patients with an FLT3 WT disease (Yanada, 2005). Significant improvements in survival outcomes of patients with FLT3-ITD (+) AML have been reported with allogeneic haematopoietic stem cell transplantation (allo-HSCT) compared with chemotherapy or autologous-HSCT. However, relapse following allo-HSCT remains high in these

patients compared with those without FLT3-ITD mutations, with a higher 2-year relapse incidence (30% vs. 16%; p = 0.006) and lower leukaemia-free survival (58% vs. 71%; p = 0.04), respectively (Döhner, 2017, Schlenk, 2014). AML had the shortest survival of all adult leukaemia; 5-year survival was only 24% (Shallis et al., 2019). Relapsed disease and the leukaemia-associated complications are the most common causes of death in all age groups (Short 2018). Most patients with AML continue to die of their disease or its disease-related complications, usually within 6-18 months of diagnosis.

The COMP considers the condition to be both 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 severe nature of AML earlier acknowledged by the COMP remains acceptable for this procedure

Number of people affected or at risk

At the time of the orphan designation in 2009, the COMP concluded that the condition was estimated to be affecting less than 2 in 10,000 persons in the European Community.

The sponsor chosen the interactive web-based European Cancer Information System (ECIS; 2020) database and the International Agency for Research on Cancer's (IARC's) Global Cancer Observatory (GCO, formerly GLOBOCAN; 2020) platform as the primary epidemiological data sources to determine the current prevalence of AML in the 27 European Union member states (EU27).

Based on the review of the updated epidemiological data sources found and the assumptions made, the sponsor proposed a prevalence for AML of 1.2 in 10,000 persons in the EU27.

Three different prevalence estimates of AML were calculated based on the following approaches:

The prevalence of AML was calculated based on age-standardised incidence rates of leukaemia reported by ECIS of 14.1 per 100,000 people for the EU27 in 2020. The prevalence was calculated using the standard formula P (point prevalence) = I (incidence) × D (mean duration) under the assumptions of stable incidence and duration of the condition. A factor of 0.27 was employed in the estimation of the age-standardised incidence of AML, which was then multiplied with the expected mean disease duration of 3 years according to survival data from ECIS. The AML prevalence for the EU27 was estimated to be 1.14 per 10,000 persons (14.1/100,000 × 27% × 3 years).

In addition, 5-year partial prevalence of AML was calculated using data from GCO. The estimated 5-year prevalence of leukaemia (acute and chronic) in the EU27 is 4.4 per 10,000 persons (ranging from 2.3 per 10,000 persons in Bulgaria to 6.5 per 10,000 persons in Belgium). Approximately 18% to 27% of all leukaemia cases in the EU27 corresponds to AML (Dong et al., 2020). Based on the upper bound of 27%, the 5-year AML prevalence was estimated to be 1.2 per 10,000 persons in the EU27 (ranging from 0.6 per 10,000 population in Bulgaria and 1.8 per 10,000 persons in Belgium; Table 1). The 5-year estimates were used to account for 17.15% of patients who live longer than 5 years (ECIS, 2020).

Furthermore, the sponsor calculated the 3-year partial prevalence of AML. The mean disease duration was estimated to be 3 years based on the AML survival data derived from ECIS. The 3-year partial prevalence of leukaemia in the EU27 was estimated to be 2.9 per 10,000 persons. The 3-year partial prevalence of AML was accordingly calculated to be 0.8 per 10,000 persons (2.9 per 10,000 × 0.27).

Table 1. Estimated number of 5-year prevalent cases of leukaemia and estimated prevalence of AML in the European Union in 2020

Country	5-year Prevalence	Proportions per 10,000	Estimated Prevalence of AML
Austria	3769	4.2	1.1
Belgium	7484	6.5	1.8
Bulgaria	1590	2.3	0.6
Croatia	1395	3.4	0.9
Cyprus	422	3.5	0.9
Czech Republic	4382	4.1	1.1
Denmark	2752	4.8	1.3
Estonia	576	4.3	1.2
Finland	2108	3.8	1.0
France	33,511	5.1	1.4
Germany	41,688	5.0	1.4
Greece	5125	4.9	1.3
Hungary	3780	3.9	1.1
Ireland	2016	4.1	1.1
Italy	26,829	4.4	1.2
Latvia	798	4.2	1.1
Lithuania	1482	5.4	1.5
Luxembourg	215	3.4	0.9
Malta	128	2.9	0.8
The Netherlands	7434	4.3	1.2
Poland	13,170	3.5	0.9
Portugal	4228	4.1	1.1
Romania	5266	2.7	0.7
Slovakia	2247	4.1	1.1
Slovenia	921	4.4	1.2
Spain	17,230	3.7	1.0
Sweden	4173	4.1	1.1
United Kingdom	32,969	4.8	1.3
EU-27	194,719	4.4	1.2

AML = acute myeloid leukaemia; EU-27 = 27 European Union member states
Source: GLOBOCAN 202026

The sponsor concluded that the estimated prevalence of AML in the EU27 is below the threshold of 5.0 per 10,000 persons, corresponding to approximately 1.2 per 10,000 persons (range depending on source and method used: 0.8 to 1.2 per 10,000 persons), with a country-specific range of 0.6 to 1.8 per 10,000 persons.

Although crude estimates rather than age-standardised estimates should have been considered, the COMP agreed with the overall approach of prevalence estimation in view of known natural course of the disease and the large difference of the estimate to the orphan designation threshold. The COMP

considered that a prevalence of approximately 1.1 in 10,000 persons based on regional registries for the European community and a systematic literature search is acceptable.

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 sponsor provided tabled overviews of centrally and nationally approved medicinal products in the EU/EEA for the treatment of patients with AML who are fit or unfit for intensive chemotherapy together with their approved indications. Therapies authorised for AML patients include cytarabine (Aracytine, Aracytin, Cytosar, generics), daunorubicin (Cerubidine, Dauoblastin), daunorubicin in combination with cytarabine (Vyxeos liposomal), doxorubicin (Caelyx, generics), idarubicine (Zavedos, Zacorist, generics), mitoxantrone, 6-mercaptopurine, L-asparaginase, melphalan (Phelinun), hydrocarbamide/ hydroxyurea, vincristine sulphate, cyclophosphamide, tioguanine (Lanvis, Thiosix, generics), etoposide (Vepesid, generics), decitabine (Dacogen, Dakogen), parenteral forms of azacitidine (Vidaza, generics), low-dose oral azacitidine (Onureg), venetoclax (Venclyxto), histamine dihydrochloride (Ceplene), midostaurin (Rydapt), gemtuzumab ozogamicin (Mylotarg), gilteritinib (Xospata), glasdegib (Daurismo), and ivosidenib (Tibsovo). Most of the approved medicinal products, apart from azacitidine, cytarabine, idarubicin, and gilteritinib, are limited to treatment of patients with newly diagnosed AML in the first-line setting.

The sponsor also referred to the European LeukemiaNet (ELN) recommendations and the European Society for Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment, and follow-up of adult patients with AML, which describe the current treatment algorithms recommended for these patients (Döhner et al. 2022, Heuser et al. 2020). The standard treatment strategy for patients with newly diagnosed AML includes either intensive induction and consolidation chemotherapy or non-intensive treatment. The choice between intensive and non-intensive approaches is largely determined by considerations of a patient's fitness to tolerate the intensive approach. Therapy for patients in complete remission (CR) consists of either consolidation chemotherapy, or autologous- or allo-HSCT. In both the ESMO and ELN guidelines, patients are still encouraged to participate in clinical trials whenever possible.

The proposed indication of Vanflyta (quizartinib) is in combination with standard cytarabine and anthracycline induction and standard cytarabine consolidation chemotherapy, and as continuation monotherapy following consolidation, for the treatment of adult patients with newly diagnosed AML that is FLT3-ITD mutation-positive.

Table 2 below includes the medicinal products authorized in EU for the treatment of newly diagnosed AML patients.

The medicinal products Daurismo (glasdegib), Dacogen (decitabine), Tibsovo (ivosidenib), Venclyxto (venetoclax), parenteral forms of azacitidine (Vidaza and generics), and Onureg (low-dose oral azacitidine), are authorised for the treatment of patients with previously untreated AML who are not eligible for standard induction chemotherapy, and they are therefore not considered as satisfactory methods for the target patient population of quizartinib.

First-line treatment options for newly diagnosed AML patients eligible for intensive salvage therapy include the standard 7+3 regimen (7 days of cytarabine combined with 3 days of an anthracycline backbone such as daunorubicin, idarubicin, or mitoxantrone) and IDAC (intermediate dose cytarabine), with or without Mylotarg (gemtuzumab ozogamicin) for CD33-positive AML patients, or Rydapt (midostaurin) for patients being FLT3-ITD or FLT3-TKD positive. Vyxeos liposomal (fixed-ratio combination of daunorubicin and cytarabine) is another treatment option for patients being 60 years or older who are diagnosed with therapy-related AML or AML with myelodysplasia-related cytogenetic changes.

Whereas Vyxeos liposomal is not considered as a satisfactory method for the entire target population of quizartinib, Rydapt (midostaurin) and Mylotarg (gemtuzumab ozogamicin) are both considered as satisfactory methods relevant for a discussion on the significant benefit of quizartinib in AML since their approved therapeutic indications cover previously untreated AML patients who are FLT3-ITD positive and eligible for standard induction chemotherapy.

Table 2. EU approved products for treatment of newly diagnosed AML patients

Name of the authorised orphan product (INN/ common name)	**Approved therapeutic indication**	**Significant benefit discussion needed**
Rydapt (midostaurin)	Rydapt is indicated: • 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; • as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM AHN), or mast cell leukaemia (MCL).	Yes
Mylotarg (gemtuzumab Ozogamicin)	MYLOTARG 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).	Yes
Vyxeos Liposomal (daunorubicin/ Cytarabine)	Vyxeos is indicated for the treatment of adults with newly diagnosed, therapy-related acute myeloid leukaemia (t-AML) or AML with myelodysplasia-related changes (AML-MRC).	No
Daurismo (glasdegib)	Daurismo is indicated, in combination with low-dose cytarabine, for the treatment of newly diagnosed de novo or secondary acute myeloid leukaemia (AML) in adult patients who are not candidates for standard induction chemotherapy.	No

Dacogen (decitabine)	Treatment of adult patients with newly diagnosed de novo or secondary acute myeloid leukaemia (AML), according to the World Health Organisation (WHO) classification, who are not candidates for standard induction chemotherapy.	No
Vidaza (azacitidine)	Vidaza is indicated for the treatment of adult patients who are not eligible for HSCT with: AML with 20-30% blasts and multi-lineage dysplasia, according to WHO classification AML with >30% marrow blasts according to the WHO classification	No
Venclyxto (venetoclax)	Venclyxto in combination with a hypomethylating agent is indicated for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy.	No
Tibsovo (ivodidenib)	Tibsovo in combination with azacitidine is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy.	No

Significant benefit

The sponsor received protocol assistance from EMA regarding the evidence needed to demonstrate significant benefit of quizartinib over existing methods of treatment for patients with newly diagnosed FLT3-ITD positive AML on 24 September 2015, which was before the approval of Rydapt. At the time of the initiation of study AC220-A-U302, chemotherapy was the standard treatment for AML and placebo along with standard chemotherapy was therefore chosen as the comparator (hereafter referred to as placebo). The screening and enrolment into study AC220-A-U302 was consequently well underway when Rydapt was approved on 18 September 2017 (Procedure No. EMEA/H/C/004095).

The sponsor claimed significant benefit of quizartinib (Vanflyta) based on improved efficacy versus the medicinal products considered as satisfactory methods for the treatment of adult patients with newly diagnosed AML who are eligible for standard induction chemotherapy and have FLT3-ITD mutation-positive disease. While the European guidelines recommend add-on treatment with midostaurin (Rydapt) for patients with FLT3 positive AML, Mylotarg are also indicated for patients with newly diagnosed AML fit for standard induction chemotherapy who do not have FLT3 positive disease.

The primary data supporting the efficacy and safety of Vanflyta in newly diagnosed FLT3-ITD mutation-positive AML in the marketing authorization application were obtained from a randomised, double-blind, placebo-controlled, phase 3 study, study AC220-A-U302 (also known as QuANTUM-First). The study enrolled 539 adult patients between 18 and 75 years of age (25% were 65 years or older), who were newly diagnosed with FLT3-ITD positive AML, as determined prospectively by a clinical study assay. Patients were randomised (1:1) to receive quizartinib 35.4 mg once daily (n = 268) or placebo (n = 271) for two weeks in each cycle in combination with standard chemotherapy (induction followed by consolidation for responding patients) followed by single-agent maintenance therapy with quizartinib (26.5 mg once daily for two weeks and 53 mg once daily thereafter) or placebo for up to 36 cycles (28 days/cycle). The majority of the patients (72.4%) had intermediate cytogenetics risk status

at baseline. FLT3-ITD variant allele frequency (VAF) was 3-25% in 35.6% of patients, between 25-50% in 52.1% of patients and greater than 50% in 12.1% of patients.

The primary efficacy measure was OS defined as the time from randomisation until death from any cause. The pivotal study AC220-A-U302 met its primary endpoint of OS with a HR of 0.776 (95% CI: 0.615- 0.979) and a 2-sided p value of 0.03.

Significant benefit of Vanflyta (quizartinib) over Mylotarg (gemtuzumab ozogamicin)

Mylotarg (gemtuzumab ozogamicin) is a humanised anti-CD33 immunoglobulin G4 antibody chemically linked to a calicheamicin-based cytotoxic warhead. According to the ESMO guidelines, gemtuzumab ozogamicin is recommended for CD33 (+) AML patients (defined as patients with ≥30% blasts expressing CD33 in the pivotal phase 3 study ALFA-0701 that led to gemtuzumab ozogamicin approval) in combination with standard chemotherapy ("7 + 3" regimen) in the first induction cycle but not in the second induction cycle. This ESMO recommendation is based primarily on the results of the meta-analysis of 5 studies of gemtuzumab ozogamicin, which showed that subjects with favourable cytogenetic risk benefited most from the addition of gemtuzumab ozogamicin. Indeed, in this subgroup of subjects, 6-year OS was improved by 20.7% (with 75.5% of subjects estimated to be still alive). Study ALFA 0701 contributed to the meta-analysis only with 3.6% (9/251) of the subjects with favourable cytogenetic risk. Of note, study ALFA-0701 demonstrated a trend toward longer OS with gemtuzumab ozogamicin combined with standard chemotherapy versus standard chemotherapy alone, without reaching statistical significance.

The sponsor also discussed the results and the outcomes of study AC220-A-U302 and argued that Mylotarg has been approved by the EMA for combination therapy with daunorubicin and cytarabine for the treatment of patients ≥15 years old with previously untreated, de novo CD33 (+) AML, except acute promyelocytic leukaemia. Gemtuzumab ozogamicin did not show a benefit for patients with adverse cytogenetic characteristics. In the warning and precautions section of the Mylotarg SmPC, it is specified that "The efficacy of Mylotarg has been shown in AML patients with favourable- and intermediate-risk cytogenetics, with uncertainty regarding the size of the effect in patients with adverse cytogenetics." In study AC220-A-U302, treatment with quizartinib resulted in an OS improvement for the overall population with FLT3-ITD positive AML, in which the majority of subjects exhibited intermediate or unfavourable cytogenetic risk.

COMP conclusion

The sponsor discussed the results and the outcomes of study AC220 A U302 which according to the sponsor demonstrated that quizartinib combined with chemotherapy followed by continuation monotherapy improves the OS of newly diagnosed subjects with FLT3-ITD positive AML, thereby showing significant benefit of quizartinib over chemotherapy alone. However, the sponsor should provide additional data to support their claim of significant benefit for quizartinib over Mylotarg in newly diagnosed AML patients with FLT3-ITD positive disease who are fit for standard induction chemotherapy. Methodologically sound indirect comparisons to the authorised satisfactory methods could be useful to establish a significant benefit.

Significant benefit of Vanflyta (quizartinib) over Rydapt (midostaurin)

Rydapt (midostaurin) is a first-generation, type I multikinase inhibitor. Midostaurin inhibits FLT3 signalling by binding to the ATP binding site of the receptor when FLT3 is in the active conformation.

Rydapt is indicated for adult patients with newly diagnosed FLT3 positive AML, in combination with standard chemotherapy (daunorubicin and cytarabine) as induction therapy, in combination with high-dose cytarabine as consolidation therapy, and as single-agent maintenance therapy for patients in CR.

There is no age restriction for the use of midostaurin; however, in the elderly population (≥60 years), midostaurin should be used only if patients are eligible to receive intensive induction chemotherapy, have adequate performance status, and do not present with significant comorbidities.

The approval of midostaurin was based on a pivotal, randomised, double-blind, phase 3 study (RATIFY), which included 717 subjects aged up to 59 years with newly diagnosed FLT3 positive AML. While the results of the RATIFY study were positive, there are some important caveats to consider. The median age of the study population was 47.9 years (range: 18 to 60.9 years). Most subjects presented with de novo AML (95%), ECOG performance status (PS) of 0 or 1 (88.3%), and normal karyotype (68.6%) according to the modified ELN classification. Overall, 77.4% of subjects had FLT3-ITD mutations (of whom 47.6% had a low allelic ratio [<0.7]) and 22.6% had FLT3-TKD mutations. Notably, the proportion of subjects with FLT3-TKD mutations was significantly larger than that seen in the general AML population (ranging from 7% to 10%), perhaps biasing the results toward this less aggressive disease subtype.

The study population of the pivotal study AC220-A-U302 differs from that of the RATIFY study as it included subjects with a less favourable prognosis given the strict inclusion of subjects with FLT3-ITD positive AML and of elderly subjects fit to receive standard chemotherapy. A total of 539 adult subjects aged between 18 and 75 years were enrolled in the study. The median age of the study population was 56.0 years (range: 20 to 75 years); although the majority of subjects were younger than 65 years, there was a substantial proportion of subjects aged ≥65 years (70 [26.1%] and 65 [24.0%] subjects in the quizartinib and placebo groups, respectively). Most subjects had de novo AML, and all were FLT3-ITD positive (with VAF of ≥3% to ≤25% in 35.6% of subjects, >25% to ≤50% in 52.1% of subjects, and >50% in 12.1% of subjects). At screening, most subject (455 [84.4%]) had an ECOG PS of 0 or 1 and an intermediate or unfavourable cytogenetic risk (436 [80.9%]).

Subjects with ECOG PS >2 and/or age-related comorbidities, such as severe cardiac disorder (e.g., congestive heart failure requiring treatment, ejection fraction ≤50%, or chronic stable angina), severe pulmonary disorder (e.g., diffusing capacity of the lungs for carbon monoxide ≤65% or forced expiratory volume in the first second ≤65%), creatinine clearance <45 mL/min, hepatic disorder with total bilirubin >1.5 × upper limit of normal, or any other comorbidity that the physician assesses to be incompatible with intensive chemotherapy are considered ineligible for intensive chemotherapy and excluded from clinical studies. Despite this, the population in study AC220-A-U302 included a sizeable proportion of subjects with baseline comorbidities. Indeed, a total of 233 subjects (87.9%) in the quizartinib group and 241 subjects (89.9%) in the placebo group had ongoing medical conditions at baseline, specifically:

- Infections in 58 subjects (21.9%) and 69 subjects (25.75%), respectively.
- Respiratory disorders (including asthma, chronic obstructive pulmonary disease, and dyspnoea) in 47 subjects (17.7%) and 55 subjects (20.5%), respectively.
- Blood disorders in 42 subjects (15.8%) and 42 subjects (15.7%), respectively.
- Cardiac disorders (including cardiac arrythmias such as atrial fibrillation and ischaemic heart disease) in 30 subjects (11.3%) and 28 subjects (10.4%), respectively.
- Diabetes mellitus in 19 subjects (7.2%) and 27 subjects (10.1%), respectively.

Based on the above data, the population of study AC220-A-U302 can be considered comparable to the target patient population with newly diagnosed AML eligible for intensive induction and consolidation chemotherapy.

According to the Rydapt summary of product characteristics (SmPC), prophylactic antiemetics should be administered with midostaurin in accordance with local medical practice as per patient tolerance. An increased frequency of corrected QT interval (QTc) prolongation was noted in midostaurin treated patients; however, a mechanistic explanation for this observation was not found. Similar to quizartinib, caution is warranted in patients at risk of QTc prolongation (e.g., due to concomitant medicinal products and/or electrolyte disturbances). Interval assessments of QT by electrocardiogram should be considered if midostaurin is taken concurrently with medicinal products that can prolong QT interval. In addition, interstitial lung disease (ILD) and pneumonitis, in some cases fatal, have occurred in subjects treated with midostaurin monotherapy or in combination with chemotherapy. Patients should be monitored for pulmonary symptoms indicative of ILD or pneumonitis, and treatment with midostaurin should be discontinued in patients who experience pulmonary symptoms indicative of ILD or pneumonitis without an infectious aetiology that are ≥Grade 3.

Midostaurin safety profile in elderly subjects (aged 61 to 70 years) was further investigated in a single arm phase 2 study (Study AMLSG 16-10). Results of this study from 2 different reports showed that there was a high number of dose reductions and administration interruptions in both the elderly and young subjects, mostly due to infections and gastrointestinal toxicity (Schlenk et al., 2019; Döhner et al., 2022), which remains an issue for oral drugs.

In study AC220-A-U302, the nature of treatment emergent adverse events (TEAEs) in the quizartinib group was generally similar across the age subgroups. The main safety risks for quizartinib were QT prolongation/ventricular arrhythmia, myelosuppression, and infection. There were no significant differences in the safety profile in subject subpopulations including the elderly. Elderly subjects experienced a higher incidence of fatal infection and may be less able to tolerate toxicities due to their generally lower health status with concurrent medical conditions and polypharmacy. Given that infections were the most common fatal TEAE in elderly subjects in both groups, with numerically higher incidence in the quizartinib group, the proposed SmPC specifies that patients aged >65 years should be closely monitored for occurrence of infections during induction.

In the RATIFY study, OS was significantly longer in the midostaurin group than in the placebo group (HR = 0.78 [95% CI: 0.63,0.96]; 1-sided p = 0.009) (Stone et al., 2017). In study AC220-A-U302, the HR for OS in the subgroup of subjects aged <60 years (n = 323/539; 59.9%) was 0.684 (95% CI: 0.493, 0.949), demonstrating quizartinib benefit in this younger population. Compared with the 22% reduction in the risk of death observed with midostaurin, the reduction of 31.6% observed with quizartinib represents a treatment advancement for this subgroup of patients with newly diagnosed FLT3-ITD positive AML. In the RATIFY study, a differential effect of midostaurin was observed based on the type of FLT3 mutation, with HRs of 0.65 (95% CI: 0.39, 1.08) in subjects with FLT3-TKD positive AML versus 0.81 (95% CI: 0.6, 1.11) in subjects with FLT3-ITD low AML and 0.80 (95% CI: 0.57, 1.12) in subjects with FLT3-ITD high AML. As noted by Stone and colleagues the observed benefit of midostaurin in FLT3-ITD low subjects, where mutations other than FLT3 may function as drivers, may be due to the multitarget effects of midostaurin via inhibition of alternate or additional pathways (Stone et al., 2017). In addition, in the RATIFY study, cumulative incidence of relapse (CIR) at 2 years of follow up was approximately 40%, while in the overall population of study AC220-A-U302, it was 31.2% in the quizartinib group versus 43.3% in the placebo group.

The usual daily dose of midostaurin is 50 mg (2 capsules) twice daily at approximately 12-hour intervals, while quizartinib is to be taken once daily. This different posology may represent an advantage for patients, improving compliance and quality of life (QoL). Notably, study AC220-A-U302 explored the impact of quizartinib on QoL for adult patients with FLT3-ITD positive AML. Patient-reported outcome data showed clinically meaningful improvement in QoL over time in both subjects

treated with quizartinib and placebo. When comparing QoL measures between treatment groups, the differences between them did not exceed the minimal clinically important difference of 10 points, suggesting no detrimental impact on QoL results from the addition of quizartinib to standard chemotherapy for newly diagnosed FLT3-ITD positive AML.

In conclusion, the sponsor argued that although the RATIFY study demonstrated an improvement in OS for subjects aged <60 years, the greatest benefit was seen in subjects with an FLT3-TKD AML. Quizartinib demonstrated an OS benefit in a population with a less favourable prognosis, as it strictly included subjects with FLT3-ITD positive disease and a sizeable proportion of elderly subjects (aged up to 75 years) with manageable safety profile.

COMP conclusion

The COMP concluded that the sponsor should provide additional data to support their claim of significant benefit for quizartinib over Rydapt in newly diagnosed AML patients with FLT3-ITD positive disease who are fit for standard induction chemotherapy. Conductance of methodologically sound indirect comparisons to the authorised satisfactory methods could be useful to establish a significant benefit.

4. COMP list of issues

- Significant benefit

The significant benefit of quizartinib in terms of improved efficacy over the authorised medicinal products Rydapt and Mylotarg is not considered to be established based on the data presented. The sponsor should therefore provide additional data to support their claim of significant benefit for quizartinib over these two products in newly diagnosed AML patients with FLT3-ITD positive disease who are fit for standard induction chemotherapy. Conductance of methodologically sound indirect comparisons, including thorough comparison of the baseline characteristics of the studied patient populations, to the authorised satisfactory methods could be useful to establish a significant benefit.