26 June 2020
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Daurismo (glasdegib maleate)
Treatment of acute myeloid leukaemia
EU/3/17/1923
Sponsor: Pfizer Europe MA EEIG

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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1. Product and administrative information

Product	
Active substances(s) at the time of orphan designation	Glasdegib maleate
Other name(s)	-
International Non-Proprietary Name	Glasdegib
Tradename	Daurismo
Orphan condition	Treatment of acute myeloid leukaemia
Sponsor's details	Pfizer Europe MA EEIG Boulevard De La Plaine 17 1050 Brussels Brussels-Capital Region Belgium
Orphan medicinal product designation procedural history	
Sponsor/applicant	Pfizer Limited
COMP opinion date	7 September 2017
EC decision date	16 October 2017
EC registration number	EU/3/17/1923
Post-designation procedural history	
Transfer of sponsorship	Transfer from Pfizer Limited to Pfizer Europe MA EEIG - EC decision of 3 October 2018
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	A. Moreau / S. B. Sarac
Applicant	Pfizer Europe MA EEIG
Application submission date	29 April 2019
Procedure start date	23 May 2019
Procedure number	EMA/H/C/004878
Invented name	Daurismo
Proposed therapeutic indication	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. Further information on Daurismo can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Daurismo
CHMP opinion date	30 April 2020
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	K. Penttila / F. Naumann-Winter
Sponsor's report submission date	14 October 2019
COMP discussion, adoption of list of questions (via written procedure)	21-23 April, 4 May 2020
COMP cancelation of oral hearing date	18 May 2020
COMP opinion date	20 May 2020

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2017 designation was based on the following grounds:

The sponsor Pfizer Limited submitted on 15 June 2017 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing glasdegib maleate 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 glasdegib maleate was considered justified based on preliminary clinical data showing complete response when the product is used in combination with decitabine and cytarabine;
- the condition is life-threatening and chronically debilitating due to the consequences of the 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 condition was estimated to be affecting approximately 1.1 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 glasdegib maleate will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a complete response in patients when the product was used in combination with decitabine and cytarabine. 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 glasdegib maleate, 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 an orphan condition for the purpose of orphan designation and maintenance.

The approved therapeutic indication "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" 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 a positive benefit/risk assessment from CHMP, please see EPAR.

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. 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

The Sponsor has re-estimated the prevalence for overall acute myeloid leukaemia (AML) in the European Union (EU) for 2019 by accounting for the proportion of survival among patients diagnosed with AML. The prevalence of AML was estimated to be 1.3 cases per 10,000 population in 2019 based on regional registries and a systematic literature search.

Table 1.

Table 1. Selected Observational Studies Reporting Overall Incidence or Prevalence of AML in Europe

Country	Study Population	Rates per 10,000 population [¥]
Netherlands (Dinmohamed et al 2016)	The study population consisted of adult patients diagnosed with AML (n = 12,032) recorded in the Netherlands Cancer Registry from 1989 to 2012. Median age of diagnosis was 66 years.	Incidence Rate: 0.3 Prevalence: NR
Denmark (Ostgard et al 2013)	The study population consisted of 2,665 AML patients (15 years of age and above) recorded in the Danish National Acute Leukemia Registry from 2000-2011; The median age of diagnosis was not reported.	Incidence Rate: 0.5 Prevalence: NR
France (Le Guyader-Peyrou et al 2016)	The study population consisted of 2,791 AML patients collected from 14 French registries in 2012. Median age of diagnosis was 71 years.	Incidence Rate: 0.3 (men); 0.2 (women) Prevalence: NR
Germany (Nennecke et al 2014)	The study population consisted of 5,277 AML cases (15 years of age and above) diagnosed during 2001–2010 and extracted from the data submitted by German population-based cancer registries to the Robert Koch Institute in early 2013. The median age of diagnosis was not reported.	Incidence Rate: 0.3 Prevalence: NR
UK (Roman et al 2016)	The study population consisted AML patients (1,190 new; 1,411 prevalent) reported from the Haematological Malignancy Research Network from 2004 to 2013 and followed through to 2015. The median age of diagnosis was 71 years. Reported prevalence year 2015.	Incidence Rate: 0.5 Prevalence: 0.44 - 0.90[*]
Italy (Trama et al 2012)	The Surveillance of Rare Cancers in Italy collaborated with the RARECARE project by pooling data from 20 Italian population-based cancer registries 1995-2002. The median age of diagnosis for AML was not reported. Reported prevalence year 2003.	Incidence Rate: 0.5 Prevalence: 1.5

Prevalence of AML in Europe

Country	Study Population	Rates per 10,000 population [¥]
Nordic Countries[§] (Engholm et al 2016; Engholm et al 2010)	The NORDCAN database and program provides data from the national cancer registries in the Nordic countries. Prevalence data for AML age-standardized to European population for ages 20 to 85+ were reported for the year 2016. Median age of diagnosis was not reported. Reported prevalence year 2016.	Incidence Rate: NR Prevalence: Denmark: 1.24 Finland: 1.25 Iceland: 1.17 Norway: 1.06 Sweden: 1.18 Overall: 1.19
Sweden (Juliusson et al 2017)	The Swedish AML registry was utilized to identify and characterize Swedish citizens surviving on 01 January 2014 after an AML diagnosis made during 1997-2013 (n = 1,337). Median age of diagnosis was 51 years. Reported prevalence year 2014.	Incidence Rate: NR Prevalence: 1.4
European Union (Visser et al 2012, Gatta et al 2011)	Surveillance of Rare Cancers in Europe (RARECARE) collected data on cancers from 89 population-based cancer registries in 21 European countries diagnosed from 1978 to 2002 for all ages. The population covered 32% of the EU-27 population. Prevalence estimates in the EU for 2 years after diagnosis, 5 years after diagnosis and 15 years after diagnosis were 0.28, 0.47 and 0.77 per 10,000 population. Reported prevalence was estimated for year 2008.	Incidence Rate: 0.37 Prevalence: 1.1

*Annual incidence rates per 10,000 population; Prevalence were period estimates per 10,000 population.
[§]NORDCAN (http://www.ancr.nu) accessed 20 November 2019. European Age Standardised Proportions presented from site.
*10-year prevalence estimate shown as largest amount reported in the UK study. Roman et al. also reported 3-year prevalence estimate of 0.44 per 10,000 population and 5-year prevalence estimate of 0.6 per 10,000 population.
AML: acute myeloid leukemia; UK: United Kingdom; RARECARE: Surveillance of Rare Cancers in Europe; NR: not reported

Overall 1- and 5-year survival proportions across the EU were obtained from literature: 37% and 19%, respectively (Visser et al 2012). Because overall estimates for 2-, 3-, 4-, 6-, 7-, 8-, 9-, and 10-year survival proportions in Europe were not available in the literature, to be conservative the 1-year survival proportion was applied for 2- to 4- year survival and the 5- year survival proportion for 6- to 10-year survival.

The number of cases alive in 2019 according to the year of diagnosis (except 2019) was estimated by applying the number of incident AML cases in each year to corresponding survival proportions. For example, the number of incident AML cases in 2009 was multiplied by the 10-year survival proportion to obtain the number of AML cases diagnosed in 2009 who were alive in 2019. All incident cases diagnosed in 2019 were considered alive in 2019.Total number of AML cases in 2019 was the sum of cases alive from each year of diagnosis over a 10-year period. The total prevalent AML cases (i.e. 68,965) were divided by the 2019 EU population. Therefore, the AML prevalence for 2019 is projected to be 1.3 per 10,000 population in the EU.

The COMP accepted this final estimation.

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).

Xospata (gilteritinib) has been recently authorised and is indicated as monotherapy for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation.

The COMP also considered the latest European Society for Medical Oncology (ESMO) treatment guideline from M. Heuser, Y. Ofran, N. Boissel, S. Brunet Mauri, C. Craddock, J. Janssen, A. Wierzbowska & C. Buske, on behalf of the ESMO Guidelines Committee Ann Oncol (2020); 31(0): 0-0.

Significant benefit

The sponsor is proposing that their product glasdegib when used in combination will offer a significant benefit in adult patients who are not candidates for standard induction chemotherapy. The therapeutic indication is:

"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".

The table below summarises, within the current treatment algorithm, which patient population the sponsor is targeting.

Table 2.

	Newly diagnosed	**R/R**	**Maintenance**
Fit	**Induction** • "7+3" AraC + daunorubicin • [idarubicin • Rydapt in combination with 7+3 **(FLT3** mutated) • Mylotarg in combination with 7+3 (**CD33**+)		Rydapt

	Newly diagnosed	R/R	Maintenance
	Consolidation • intermediate-dose cytarabine or autoSCT • **alloSCT**		
Non-fit	Azacitidine Decitabine Low dose cytarabine ***GLASDEGIB+LDAC***	Azacitidine	Ceplene in combination with interleukin 2 (not shown for patients >60)
Fitness not mentioned	Vyxeos (secondary AML; compared to 7+3)	Xospata mono (FLT3)	
"Old" broad labels (neither line nor fitness mentioned	Cytarabine; Etoposide; L-Asparaginase, cyclophosphamide, doxorubicin, daunorubucin, idarubicin mercaptopurine, mitoxantrone, vincristine sulfate,		

The claim for significant benefit uses both clinically relevant advantage and major contribution to patient care claims although the greatest effort by the sponsor is made to prove a clinically relevant advantage. Daurismo is administered as an oral formulation. The other products used in the target patient population are given iv or sc.

To support the significant benefit, data from the pivotal study B1371003 has been submitted. B1371003 was a multi-centre, open-label Phase 1b/2 study to evaluate the safety and efficacy of glasdegib when administered in combination with first-line treatment regimens for AML and high-risk MDS. Efficacy of glasdegib + LDAC was mainly supported by the Phase 2 and especially the portion of the trial, in which patients unfit for intensive induction were recruited. Patients who were not candidates for intensive chemotherapy were randomised (2:1) to receive either glasdegib + LDAC or LDAC alone and were stratified by prognostic risk factor (good/intermediate or poor) based on cytogenetics.

Although the sponsor came twice for Protocol Assistance, they did not raise a question on significant benefit.

Claim for Significant benefit based on a clinically relevant advantage

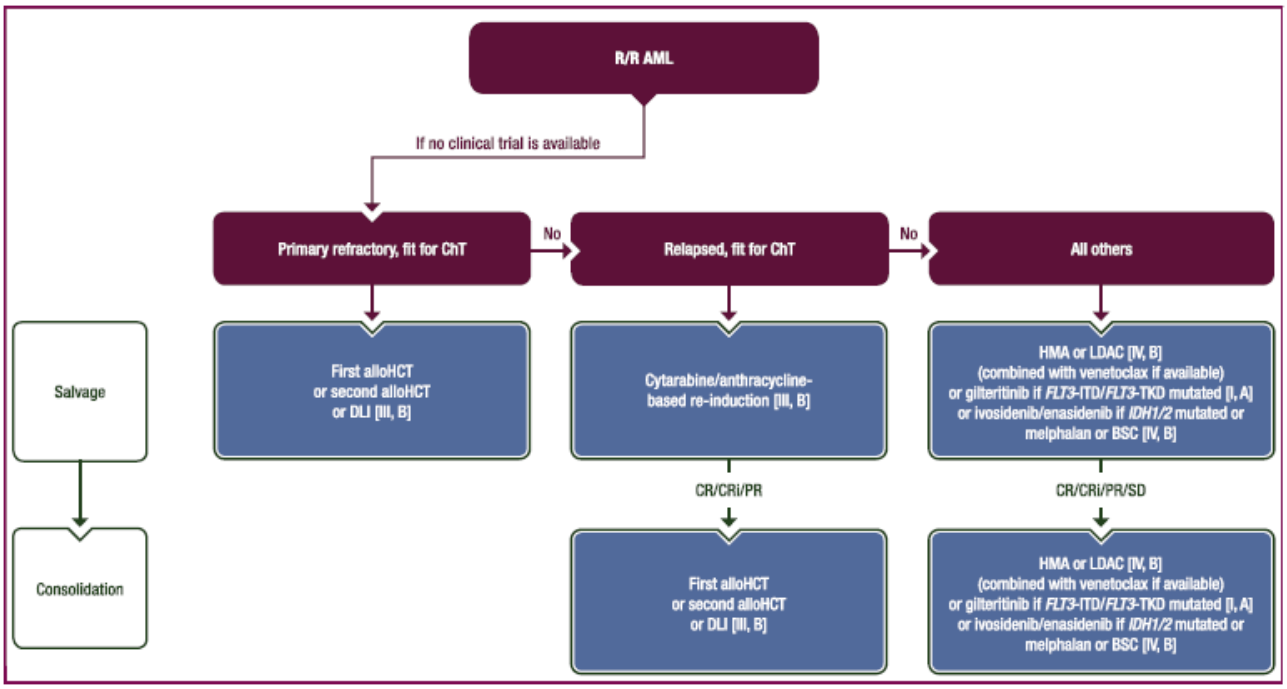
The proposed therapeutic indication the sponsor has submitted targets elderly adult patients who are unfit for standard chemotherapy. The 2020 ESMO Guidelines for diagnosis, treatment and follow-up of adult patients with AML, which have just appeared online (M. Heuser, Y. Ofran, N. Boissel, S. Brunet Mauri, C. Craddock, J. Janssen, A. Wierzbowska & C. Buske, on behalf of the ESMO Guidelines Committee Ann Oncol (2020); 31(0): 0-0), state the following with respect to the standard of care:

Primary refractory and relapsed AML patients not eligible for standard chemotherapy (ChT)

The therapeutic options in unfit AML patients aim at controlling disease progression and minimising treatment-related mortality (TRM). In FLT3-mutated patients, we recommend treatment with

gilteritinib, which showed a favourable response rate and improved OS compared with ChT (mOS 9.3 versus 5.6 months) [I, A] [89]. Quizartinib also showed a survival benefit in relapsed/refractory FLT3-ITD-mutated patients but was not approved in Europe (mOS 6.2 versus 4.7 months) [100]. If the patient is considered ineligible, azacitidine or decitabine (HMA) should be applied if LDAC was given in first line, and LDAC may be applied in favourable- and intermediate-risk patients if an HMA was given initially [IV, C] (Figure below). In a cohort of 655 relapsed/refractory AML patients treated with azacitidine or decitabine, the CR/CRi rate was found to be 16.3% with mOS of 6.7 months, with no differences observed between agents [101]. If available, venetoclax in combination with HMA or LDAC is a promising second-line treatment with overall response rates of 21%–43% [87,88]. In IDH1/IDH2mut patients, inhibitors ivosidenib [102] and enasidenib [103], respectively, show considerable activity as single agents in relapsed/refractory patients, and will expand the treatment options once they become available.

Figure 1.



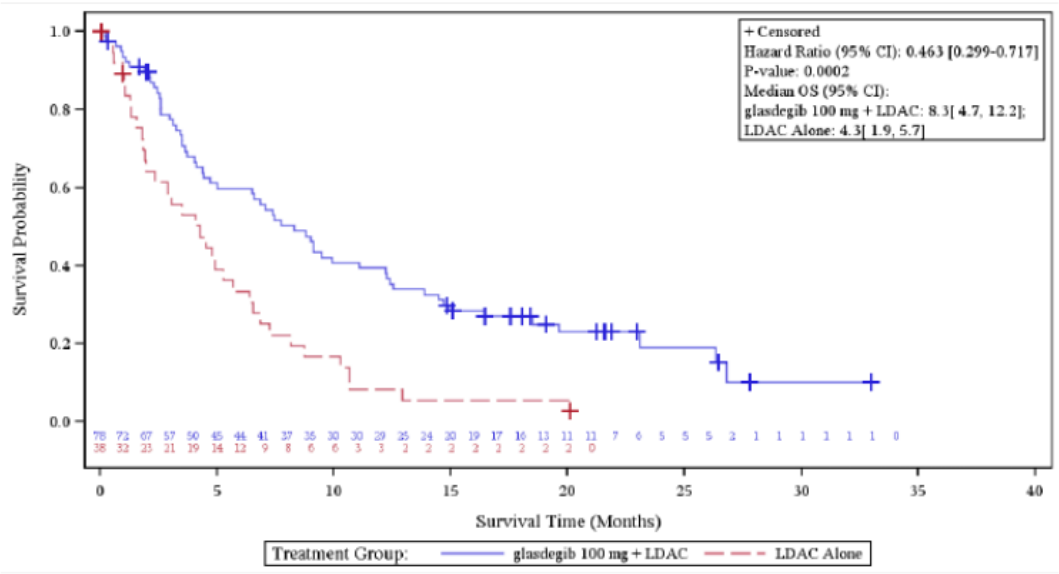
Treatment algorithm for second-line treatment in relapsed/refractory AML patients. alloHCT, allogeneic hematopoietic cell transplantation; AML, acute myeloid leukaemia; BSC, best supportive care; ChT, chemotherapy; CR, complete remission; CRi, complete remission with incomplete haematological recovery; DLI, donor lymphocyte infusion; HMA, hypomethylating agent; LDAC, low-dose cytarabine; PR, partial remission; R/R, relapsed/refractory; SD, stable disease.

The combination of venetoclax, and ivosidenib or enasidenib in patients with IDH1/IDH2mut have not received a marketing authorisation in Europe for treatment in this target patient population. These products therefore are used off-label and are not considered in the assessment of significant benefit. Thus, the target patient population identified by the sponsor has three authorised options: LDAC, azacitadine and decitabine which are considered standard of care (SOC).

Data submitted from the pivotal study B1371003 show a median overall survival in 78 AML patients treated with the combination was 8.3 months (95% CI 4.7, 12.2) compared to SOC in 38 patients with LDAC alone of 4.3 months (95 CI 1.9, 5.7); HR=0.463 with p=0.0002. In the 49 AML patients with good/intermediate cytogenetic prognostic risk group, the median overall survival was 11.1 months (95% CI 7.1, 14.9) in the active treatment arm compared to 4.4 (95% CI 1.8, 8.7) in 21 patients with

good/ intermediate prognoses in the standard arm; HR=0.417 with p=0.0011. The median overall survival in 29 patients with poor prognostics and newly diagnosed AML, treated by glasdegib + LDAC was 4.4 months (95% CI 3.4, 9.1) compared to a median overall survival of 3.1 months (95% CI 1.1. 6.4) in 17 patients with poor prognostic features and treated by LDAC alone; HR=0.528 with p=0.0269.

Figure 2. Kaplan-Meier Plot of Overall Survival in AML Patients in the Study B1371003 Phase 2 Non-Intensive Population



Stratified per IVRS. Upper (blue) curve=glasdegib + LDAC; lower (red) curve=LDAC alone CI=confidence interval, LDAC=low-dose cytarabine; OS=overall survival; SCE=summary of clinical efficacy; IVRS=Interactive Voice Response System

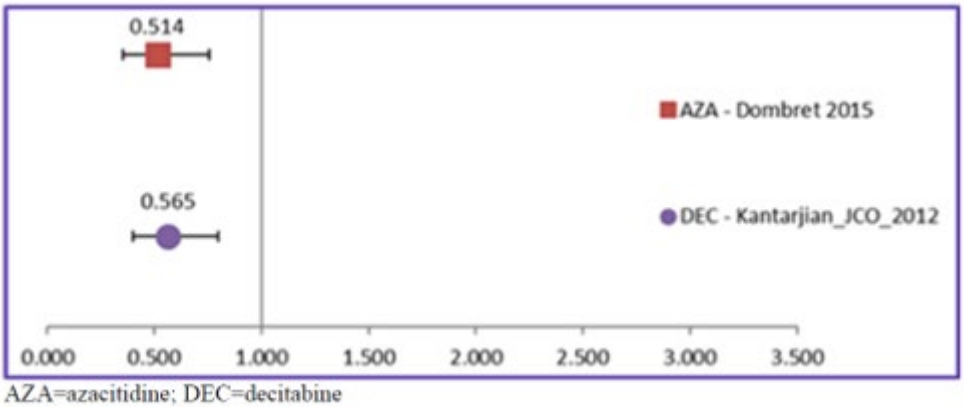
The clinical data provides the basis of a better overall survival when unfit patients receive combination treatment with glasdegib and LDAC than LDAC used alone. It can be accepted that a glasdegib + LDAC combination will offer a clinically relevant advantage in unfit elderly adult AML patients over LDAC alone.

The **clinically relevant advantage** over LDAC was adequately supported by a head-to-head comparison in a randomised trial. For the demonstration of significant benefit over azacitidine and decitabine, the sponsor used two indirect methods.

First, aggregate data were compared in an Indirect Trial Comparison (ITC) based on the clinical trials which compared one of the substances to LDAC. OS data from subgroups for each of the three selected studies were extracted. For glasdegib + LDAC, only patients with AML and not MDS were included (n=116). In the azacitidine trial, investigators decided for each patient what was the most appropriate azacitidine comparator: best supportive care (BSC), LDAC, or intensive chemotherapy (IC) prior to randomization. Patients were then randomly assigned to receive azacitidine or the investigator's predetermined choice of treatment. To align patient populations most closely, the subgroup of azacitidine patients who were pre-selected for suitability to receive LDAC, and who were randomized to receive azacitidine (n=154), against the LDAC arm (n=158) were included in the ITC analysis. The decitabine trial only reported OS results for a pooled LDAC/BSC population, so results were included for patients receiving decitabine (n=242) and LDAC/BSC (n=243). This methodology is likely an overestimation of decitabine's effect compared to LDAC and ultimately results in a conservative indirect comparison vis-à-vis glasdegib.

With the selected studies, a network of RCTs was established that applied the LDAC treatment arm as the common point of reference. Results from the classical ITC showed a significant OS advantage of halving the risk (hazard) for glasdegib + LDAC compared with either azacitidine [HR 0.51, 95% CI, 0.31, 0.85] or decitabine (HR 0.56, 95% CI, 0.35, 0.91). All 95% CIs are <1.0, indicating statistical significance in favour of glasdegib +LDAC for the OS endpoint (Figure 3).

Figure 3. ITC results for OS: Glasdegib+LDAC Versus Azacitidine or Decitabine



AZA=azacitidine; DEC=decitabine

This conclusion using aggregate data was further supported by using individual patient data (IPD) from the glasdegib trial and by comparing the reported aggregate outcomes from the AZA or DEC trials in the setting of a Simulated Trial Comparison (STC). Here, the populations were statistically adjusted (and hence matched) for differences in baseline covariates between the study populations. It does retain the full patient dataset which is important for small trials (as here). Different assumptions and statistical models were tested, and all conclude on a HR (95%CI) (OS) of well below 1.

When conducting STC, the researcher is constrained by the ability only to use data that are actually reported for the published comparator trials. While it is not possible to mitigate every limitation that exists, each ITC and STC model that the sponsor applied resulted in a consistent, significant OS benefit for glasdegib +LDAC over both azacitidine and decitabine.

Major Contribution to Patient Care

While the sponsor makes a thorough overview of publications on the benefits for home care in general, as well as refers to interviews with AML patients, no data on PROs or QoL were actually reported from the pivotal study by the sponsor. As the study was open-label such data would anyway have been of limited value. The sponsor also highlighted the advantage of having home-based care especially during the COVID pandemic.

The COMP considered that the justification on significant benefit was adequate, particularly with regards to a clinically relevant advantage.

In conclusion the COMP considered they could recommend maintaining the orphan designation.

4. COMP position adopted on 20 May 2020

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 1.3 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 the 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;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Daurismo may be of significant benefit still holds. The sponsor has established with direct comparison data that the combination of low dose cytarabine with Daurismo will offer an improved overall survival when compared to low dose cytarabine used as monotherapy. In addition, the sponsor has provided an indirect comparison to azacitadine and decitabine to the combination of low dose cytarabine with Daurismo showing the combination to offer a better overall survival to monotherapy with either azacitadine or decitabine. The COMP considered that this constituted a clinically relevant advantage.

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 Daurismo, glasdegib maleate, for treatment of acute myeloid leukaemia (EU/3/17/1923) is not removed from the Community Register of Orphan Medicinal Products.