5 July 2023
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Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Inaqovi (cedazuridine, decitabine)
Treatment of acute myeloid leukaemia
EU/3/21/2548

Sponsor: Otsuka Pharmaceutical Netherlands B.V.

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 substances	Cedazuridine, decitabine
Other name	-
International Non-Proprietary Name	Cedazuridine, decitabine
Tradename	Inaqovi
Orphan condition	Treatment of acute myeloid leukaemia
Sponsor's details:	Otsuka Pharmaceutical Netherlands B.V. Herikerbergweg 292 1101 CT Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Otsuka Pharmaceutical Netherlands B.V.
COMP opinion	12 November 2021
EC decision	10 December 2021
EC registration number	EU/3/21/2548
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Filip Josephson / Carolina Prieto Fernandez
Applicant	Otsuka Pharmaceutical Netherlands B.V.
Application submission	26 July 2022
Procedure start	18 August 2022
Procedure number	EMA/H/C/0005823
Invented name	Inaqovi
Proposed therapeutic indication	Inaqovi is indicated as monotherapy for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for standard induction chemotherapy. Further information on Inaqovi can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/inaqovi
CHMP opinion	20 July 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Karri Penttila / Frauke Naumann-Winter
Sponsor's report submission	23 May 2023
COMP discussion and adoption of list of questions	13-15 June 2023
Sponsor's removal request	28 June 2023
Removal from the Union Register	5 July 2023

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2021 designation was based on the following grounds:

"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 cedazuridine, decitabine was considered justified based on preliminary clinical data showing responses in de novo or secondary acute myeloid leukaemia;
- 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 1.7 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 cedazuridine, decitabine will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data which demonstrate similar efficacy with currently approved therapies for AML patients who are ineligible for intensive induction chemotherapy. The oral fixed-dose combination might reduce the burden of parenteral therapies.

The Committee considered that this constitutes a major contribution to patient care.

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 cumulatively fulfilled. The COMP therefore recommends the designation of this medicinal product, containing cedazuridine, decitabine as an orphan medicinal product for the orphan condition: treatment of acute myeloid leukaemia".

3. Review of criteria fo r 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, which results in a deficiency of red blood cells, normal white blood cells, and platelets. AML mainly affects adults, with the median age at diagnosis of 70 years and an increasing incidence with age. 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.

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 target patient population of the proposed medicinal product is adult patients with newly diagnosed AML who are ineligible for standard induction chemotherapy.

The proposed product, Inaqovi is a fixed-dose combination tablet for oral administration, containing 35 mg decitabine and 100 mg cedazuridine. Cedazuridine, is a cytidine deaminase (CDA) inhibitor. It is a new chemical entity without antineoplastic activity but allowing oral administration of decitabine instead of iv. Decitabine is a known substance, previously approved at a dose of 20 mg/m2 by intravenous infusion over 1 hour repeated daily for 5 consecutive days (i.e., a total of 5 doses per treatment cycle).

The currently applied therapeutic indication "Inaqovi is indicated as monotherapy for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible 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 the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

According to the sponsor, no significant changes have been identified in the seriousness of AML since the orphan designation was granted in 2021.

AML remains a life threatening and chronically debilitating condition 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 (Döhner 2022; Khwaja 2016). AML progresses rapidly and is fatal within days to weeks or a few months if left untreated (Short 2018). For most adult patients, AML is incurable (Newell 2021); although, in some paediatric AML subsets cure rates of up to 70% are achievable (Short 2018). AML had the shortest survival of all adult leukaemias; 5-year survival was only 24% (Shallis 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.

Number of people affected or at risk

The sponsor proposed a prevalence of 1.3 in 10,000 persons. This was based on the most recently available cancer registry data from countries across the EU/EAA. The sponsor included the per-country prevalence directly reported by a registry if this was obviously complete prevalence. In some cases, these data are reported as "prevalence" (RARECARENet 13.6 and Czech registry 10.4) or "total prevalence" (NORDCAN 18.8). In these cases, it was assumed to be "complete prevalence" for the respective country/region. For the Netherlands, long-landmark (20-year) prevalence is reported which is assumed to approximate to complete prevalence of patients with uncured AML. Since the median age at diagnosis of AML is approximately 70 years, whilst the median age at death of an average EU/EEA citizen is on the order of 80 years (Eurostat 2022), a 10-year partial prevalence of AML as reported in some registry data (Belgium 14.0; the Netherlands 12.6; NORDCAN 10.1) may be closest to the true prevalence of AML. Whereas total/20-year prevalence as reported by the Netherlands and NORDCAN registries (and potentially RARECARENet and the Czech registry) may reflect to some extent an accumulation over time of surviving cured patients. However, since the proportion of cured patients is unknown in any of the registry data, a conservative approach was adopted, using the longest reported landmark prevalence from the Netherlands as the estimated complete prevalence for that country in the calculation of the complete prevalence of AML in the EU/EEA.

Where only incidence and landmark survival rates (generally 5-year) are reported by a registry, the sponsor used these data to derive an estimated country-specific total prevalence using two different methods. The first one was based on the standard formula $P = I \times D$ from reported incidence and average disease duration derived from Dutch (3.9 years) or NORDCAN (5.7 years). For the second method, the sponsor assumed that the survival curves in each country are essentially of the same shape, and only moved up or down relative to each other based on differences in annual incidence. This scaling approach based on a single data point (5-year relative survival) can only ever be an approximate. Based on the above, the reported and calculated complete prevalence (per 100,000 persons) of AML from EU/EEA country registries are presented in Table 1. (all incidence and prevalence data below are presented as per 100,000 persons unless otherwise specified).

Table 1. Reported and calculated complete prevalence of AML from EU/EEA country registries

Registry	Reported 'total' prevalence N=4	Calculated from NL 20-year prevalence N=7	Calculated from NORDCAN total prevalence N=7
ECIS	-	11.7	10.6
RARECARE	13.6	-	-
C in G	-	15.0	13.6
Kraywinkel	-	16.1	14.7
BE crude rate	-	15.5	14.1
NL crude rate	17.7	-	-
NORDCAN	18.8	-	-
REDECAN	-	14.6	13.2
Italian crude rate	-	13.6	12.7
Czech crude rate	10.4	-	-
Total	60.5	86.5	78.9
Prevalence (n/N)	15.1	12.4	11.3
Overall average prevalence†	**13.3**		

† Calculated as the average of the sum of all 19 individual datapoints

The COMP agreed with the proposed prevalence of 1.3 per 10,000 persons which is in line with previous opinions.

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

For newly diagnosed AML patients who are not eligible to intensive induction chemotherapy, the authorised therapies in the EU include: the hypomethylating agents (HMAs) Dacogen (decitabine) and Vidaza (azacytidine), Venclyxto (venetoclax + azacitidine or decitabine), Daurismo (glasdegib + low-dose cytarabine [LDAC]) and Tibsovo (ivosidenib).

The sponsor also refers to the European Society for Medical Oncology (ESMO) clinical practice guidelines and the European LeukemiaNet (ELN) recommendations (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 consists of either consolidation chemotherapy, or autologous or allogeneic HSCT (alloHSCT). In both the ESMO and ELN guidelines, patients are still encouraged to participate in clinical trials whenever possible.

The target patient population of Inaqovi consists of newly diagnosed AML patients who are ineligible for standard induction chemotherapy. Table 2 below includes the medicinal products authorized in EU for the treatment of newly diagnosed AML patients who are not eligible (unfit) for standard induction

chemotherapy. Based on the indication, Vidaza, Dacogen, Venxlycto and Daurismo as considered as satisfactory methods because there is a complete overlap with the indications.

Since Tibsovo is indicated for the treatment of adult patients with newly diagnosed AML who are not eligible to receive standard induction chemotherapy but with a specific mutation isocitrate dehydrogenase-1 (IDH1) R132 mutation the target population covered by Inaqovi is broader therefore Tibsovo is not considered as satisfactory method.

Table 2. EU approved products for treatment of newly diagnosed AML patients who are not eligible (unfit) for standard induction chemotherapy

Product name (INN)	**Approved therapeutic indication**	**Significant benefit discussion needed**
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	Yes
Dacogen (decitabine)	Dacogen is indicated for the treatment of adult patients with newly diagnosed de novo or secondary AML, according to the WHO classification, who are not candidates for standard induction chemotherapy.	Yes
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.	Yes
Daurismo (glasdegib)	Daurismo is indicated, in combination with low-dose cytarabine, for the treatment of newly diagnosed de novo or secondary AML in adult patients who are not candidates for standard induction chemotherapy.	Yes
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

MA: marketing authorisation; HSCT: hematopoietic stem cell transplantation; WHO: World Health Organisation

Significant benefit

The sponsor claimed the significant benefit of Inaqovi, versus the medicinal products considered as satisfactory methods for newly diagnosed AML patients who are not eligible to intensive induction chemotherapy, based on the major contribution to patient care. This is due to orally administered HMA and also argued with indirect comparisons versus the satisfactory methods described above.

In summary, the primary data supporting the efficacy of Inaqovi in newly diagnosed AML in the marketing authorization application were obtained from a phase 3 (ASTX727-02-EU) open-label, randomised, 2-cycle, 2-sequence crossover study that included adult patients with de novo or secondary AML as defined by World Health Organisation (WHO) criteria, who were not candidates for standard induction chemotherapy. A total of 89 patients were randomised 1:1 to receive Inaqovi (35 mg decitabine and 100 mg cedazuridine) orally in cycle 1 and decitabine (20 mg/m^2) intravenously

(IV) in cycle 2 (n=44) or the reverse sequence (n=45). Both Inaqovi and intravenous decitabine were administered once daily on days 1 through 5 of the 28-day cycle. Starting with cycle 3, all patients received Inaqovi orally once daily on days 1 through 5 of each 28-day cycle until disease progression, death, or unacceptable toxicity. The primary outcome measure of the phase 3 study was 5-day cumulative decitabine AUC between Inaqovi and IV decitabine. Inaqovi achieved $AUC_{0\text{-}24hr}$ exposures equivalent to intravenous infusion of decitabine at 20 mg/m^2. Secondary efficacy endpoints included complete response (CR) and the rate of conversion from transfusion dependence to transfusion independence.

ASTX727 demonstrated equivalent decitabine pharmacokinetic (PK) to IV decitabine 20 mg/m^2 when both were administered over 5 days.

After a median follow-up of 7.95 months, the CR rate in patients receiving ASTX727 was 21.8% (95% CI 13.7, 32.0), the median duration of CR was 5.8 months (95% CI 3.3, not estimate) and the median time to first response was 2.87 months (min, max: 1.8, 7.4).

Median duration of treatment (data cut-off date 10 September 2021) was 4.86 months (range 0 to 18 months), with 37.5% of subjects treated for >6 months and 6.3% of subjects treated for >12 months.

- Major contribution to patient care

Treating the elderly unfit AML patient population

The sponsor claimed that AML is largely, but not exclusively, a disease of the elderly (≥ 60 years of age; median age at diagnosis 69-71 years [SEER 2023; Juliusson 2017]) and discussed extensively the challenges with treating the elderly unfit AML patient population including severe comorbidities and hospitalisation required.

Illustrating the scale of the current parenteral HMA treatment burden for elderly unfit AML patients, in three multicentric observational (i.e. real world) studies of decitabine first-line treatment in the elderly (60-<70 years 12%; 70-74 years 34% 75-79 years 35%; ≥ 80 years 19%) unfit population conducted across Italy, the median number of cycles administered was 5, with patients receiving up to 31 cycles overall. This is equivalent to 155 separate IV administration of decitabine across 155 clinic visits over approximately 2.5 years for those patients deriving the most treatment benefit; in other words these maximally benefiting patients likely spent nearly 18% of their days (up to 155 of 868 days) over that period in travelling to clinics/hospitals for treatment (Bocchia 2019). Similarly, data from the expanded international E-ALMA series derived from 5 EU registries codify the frontline azacitidine therapy experience of a large series of 710 older (60-64 years 7.5%; 65-69 years 13%; 70-74 years 25%; ≥75 years 54%) AML patients considered unfit for standard induction chemotherapy (Falantes 2017). Patients received a median of 5 cycles of therapy, but up to 52 cycles in the longest treated individuals. That equates to 364 subcutaneous injection (SC) injections of azacitidine equivalent to a full calendar year of clinic visits and equating to 25% of all days across 4 years partially spent traveling to clinics for treatment for the longest treated patients.

Patient preference for convenient oral chemotherapy

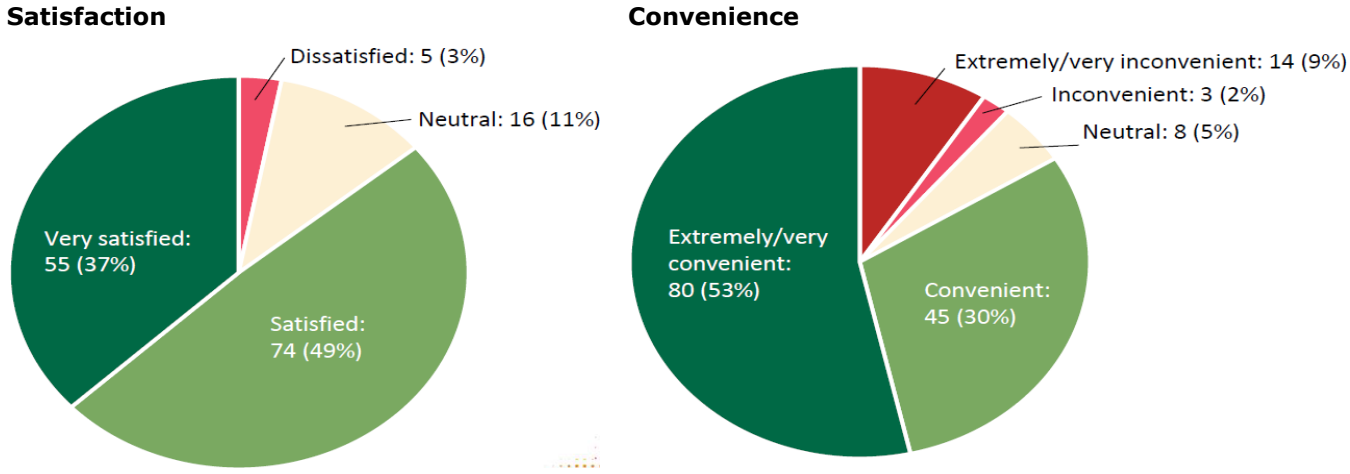
The sponsor discussed several studies that illustrate the aspects of the 'treatment burden' and how oral therapy would significantly improve upon them in a manner that would be a major improvement in patient care.

Furthermore, the sponsor has conducted a small patient preference study in 21 AML patients, median age 51 years (range 33-72 years), who were using/have used HMA or were suitable to be treated with HMA (i.e., unfit for standard induction therapy) (Delmas 2023). Patients were recruited in the UK, Spain, and Germany. The patients had 60-minute interviews conducted by trained interviewers. The

interviews included the following topics: experiences of AML (diagnosis and engagement with healthcare system since), experiences of HMA treatments, perspectives on HMA treatments, perspectives on the profile of oral ASTX727 (presented as a hypothetical treatment), perceived unmet need in the treatment of AML, and factors that determine treatment satisfaction/preferences and relative importance of different treatment-related characteristics. Most patients expressed as preference for the hypothetical oral therapy (76%) over a parenteral HMA (SC or IV) (14%). The primary reasons for this preference were convenience (48% of respondents mentioned this), not wanting to go to the clinic for treatment (e.g. travel and waiting time; 10%), and reduced risk of infection (caught in a clinic, 5%). Amongst characteristics that were important for treatment decisions, respondents mentioned efficacy (86%) and safety (62%) most often. Other important characteristics included daily life impact and therapy duration (each 24%), and time spent in hospital, treatment duration, and financial impact (each 14%) (Delmas 2023).

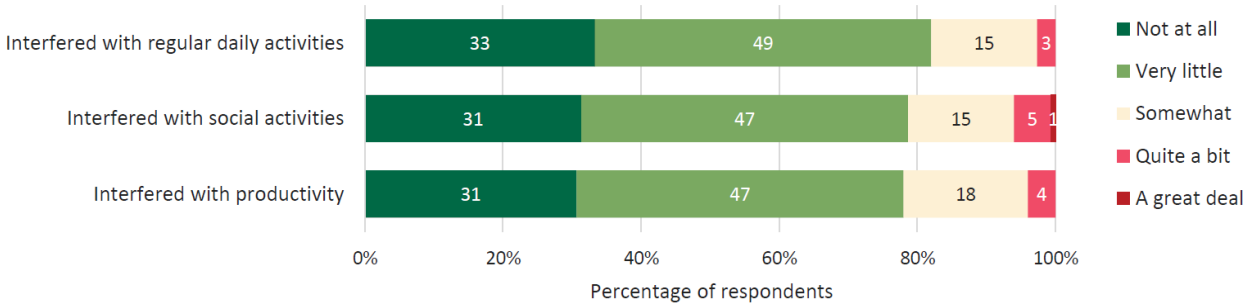
Finally, to illustrate the major contribution to patient care of oral ASTX727, the sponsor has conducted an online survey to evaluate the perspectives of US patients with myelodysplastic syndromes (MDS) receiving ASTX727, as an alternative to IV/SC HMAs (Zeidan 2023). In total, 150 patients completed the survey, 61% of whom were ≥60 years of age, and 63% of whom were male. At the time of the survey, 82% of patients were receiving ASTX727 and 18% had stopped taking that product. Half (50%) of the patients had taken ASTX727 for ≥6 months. Importantly, for the demonstration of a major contribution to patient care of ASTX727, 61% of patients (n=91) had received IV/SC HMA prior to oral ASTX727. As a reminder, these patients are treated comparably to patients with AML as far as that relates to HMA posology. Majorities of patients (n=150) were satisfied (86%) with oral treatment and found it to be convenient (83%) (Figure 1).

Figure 1. Satisfaction with and convenience of oral ASTX727 amongst 150 adult patients with MDS



Most patients reported no or very little interference from oral ASTX727 treatment on regular daily activities (82%), social activities (78%), and productivity (78%) (Figure 2).

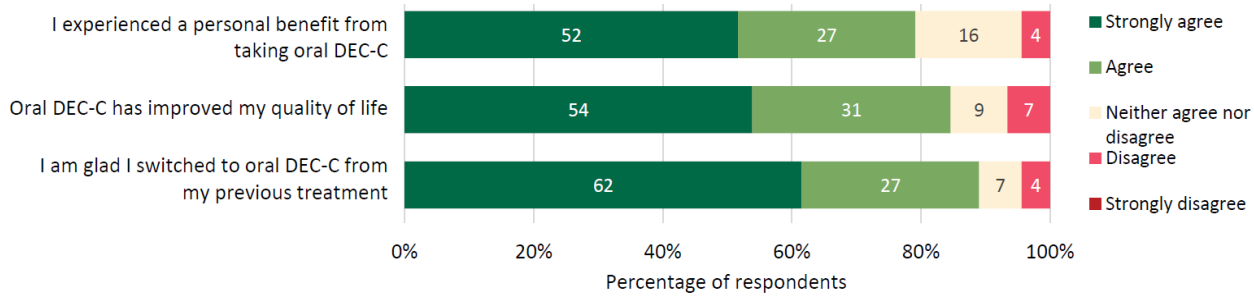
Figure 2. Impact of oral ASTX727 on daily activities amongst 150 adult patients with MDS



source: zeidan 2023

Most respondents felt a personal benefit (79%) and experienced an improvement in quality of life (85%) from oral ASTX727 compared with previous IV/SC treatment (Figure 3).

Figure 3. Patient experience with oral ASTX727 compared with previous IV/SC treatment amongst 91 HMA patients who received both treatment modalities



source: zeidan 2023

These data are from an online survey amongst MDS patients who are somewhat younger on average than the AML population (median 69-70 years at diagnosis) and potentially more motivated (and technologically proficient) due to their ongoing treatment response. For instance, half of all patients had received ≥6 months of treatment (i.e. ≥6 cycles), whereas the median EU AML patient receives approximately 5 cycles of HMA treatment (Bocchia 2019; Falantes 2017). Further, the inclusion criteria did not differentiate between lower-risk MDS and higher-risk, and therefore more 'AML-like' MDS. Nevertheless, that all participants were treated with a HMA implies most were higher-risk.

COMP conclusion

The COMP identified several issues with the preference study. First of all, it is based on a very small sample size (n=21), which may not be representative of the larger AML patient population. Second, the preference study is based on "purely theoretical preferences", meaning it may not reflect real-world experiences or outcomes. There's also a difference between what patients might prefer hypothetically and how they actually respond to a treatment. Furthermore, there may be confounding variables that are not accounted for in the studies, such as the impact of other medications, lifestyle factors, or varying healthcare systems.

In addition, the online survey was not part of a controlled study and participation was optional. This opens up the possibility of selection bias, as those who had positive experiences might be more inclined to participate. Finally, while it's mentioned that elderly/unfit patients have mobility challenges, there isn't enough data showing how Inaqovi specifically addresses this issue compared to traditional treatments.

Based on the above, the COMP concluded that the sponsor should elaborate on the conclusiveness of the results of the preference study for the patients with AML, taking into account: first, the limitations

of the study design and second, the extent to which the results of the preference study demonstrate that Inaqovi ensures a major contribution to patient care in comparison with the satisfactory methods of treatment.

Of particular importance is that a claim of major contribution to patient care may only be assessed once it is established that the candidate product is at the very least equivalent in terms of efficacy (and safety) to the satisfactory methods of treatment (see assessment below).

- Indirect comparisons versus the satisfactory methods

Significant benefit of Inaqovi (cedazuridine, decitabine) versus Dacogen (decitabine)

The sponsor presented an indirect comparison between efficacy results in subjects with AML treated in study ASTX727 02 EU and subjects with AML treated with single agent IV decitabine in the open label, randomised, multicentre, Phase 3 pivotal decitabine AML study (study DACO 016) (Table 3).

Table 3. Summary of response and OS in AML patients not eligible for intensive chemotherapy: ASTX727 vs IV decitabine

	ASTX727	**Decitabine**		
Study ID	**ASTX727-02-C EU**	**DACO-016**	**2012-1017**	
Source	**CSR**	**Kantarjian 2012 / EPAR**	**Short 2019**	
Population	Previously un-Tx AML (≥20% bone marrow blasts) ineligible for standard induction chemotherapy	Newly diagnosed AML in patients ≥65 years	Newly diagnosed AML ineligible for intensive chemotherapy	
			5 d regimen	10 d regimen
N	87	242	28	43
Median OS (95% CI), months	7.9	7.7 (6.2, 9.2) 8.5 (6.5, 9.5)a	5.5 (IQR 2.1, 11.7)	6.0 (IQR 1.9, 11.7)
1-year OS rate, % (95% CI)	36 (22, 50)	NR	25	25
2-year OS rate, % (95% CI)	NR	NR	NR	NR
CR	21.8%	16%	29%	30%
CR + CRp	24.1%	17.8%		
CR + CRi	27.6%	26%	32%	35%
CR + CRh	24.1%	NR	NR	NR
Median age, years (range)	78 (61-92)	73 (64-89)	77 (70-80)	78 (69-82)
≥75 years	64.4%	40%	NR	NR
AML - de novo	63.2%	64%	NR	NR
AML - secondary	36.8%	36%	NR	NR
WHO AML classification With genetic abnormalities With MDS-related changes (MRC) Therapy-related NOS	NR - - - -	 NR 31%c 5%d NR	NR - - - -	NR - - - -

Cytogenetic risk – intermediate	51.7%b	63%	NR	NR
Cytogenetic risk – poor	37.9%	36%	NR	NR
Median BM blast count	35.0%	47%	40%	46%
ECOG PS 0-1	100% (58.6% PS 1)	75%	64%	70%
ECOG PS 2	0	25%	-	-
ECOG-PS 2-3	0	-	36%	30%
Median cycles	5.0	4	2.0	3.0

CR=complete remission; CRh=complete remission with partial hematologic recovery; CRi=complete remission with incomplete hematologic recovery; CRp=complete response with incomplete platelet recovery CSR=clinical study report; ECOG PS=Eastern Cooperative Oncology Group performance status; EPAR=European Public Assessment Report; MDS=myodysplasia; MRC=myodysplasia-related changes; NOS=not otherwise specified; NR=not reported; Tx=treatment/treated

a Sensitivity analysis - patients (38%) who received subsequent disease-modifying therapy were censored.
b A further 10.3% of subjects were either non-evaluable (5.7%) or had a missing (4.6%) cytogenetic risk classification.
c Reported as MDS plus myeloproliferative disorder cases of secondary AML (EPAR).
d Reported as proven leukemogenic exposure (EPAR).

The sponsor concluded that this data supports the equivalence of ASTX727 to IV decitabine in terms of efficacy in the unfit AML population not eligible for induction chemotherapy.

The sponsor also claimed that the mechanism of action of decitabine is DNA demethylation (Yang 2006; Steensma 2009), with the potential for cytotoxic activity, manifested predominantly by myelosuppression (anaemias and cytopenias), neutropenia-related infections, and thrombocytopenia-related bleeding events. These same effects have been consistently reported in the labelled safety information (adverse drug reactions [ADRs]) for IV decitabine and SC azacitidine. A comparison of frequencies of adverse drug reactions for IV Dacogen in AML with those reported for in ASTX727-02 EU, and with overall AML/MDS/CMML Safety Population by CTCAE grade was presented in Table 4.

The sponsor referred to the CHMP assessment that the safety profile of ASTX727 is comparable with that for Dacogen and therefore that the safety information included in the summary of product characteristics (SmPC) for the two products should be identical.

COMP conclusion

The COMP agreed that the efficacy and safety of Inaqovi is equivalent to the efficacy and safety of Dacogen.

Significant benefit of Inaqovi (cedazuridine, decitabine) versus Vidaza (azacitidine)

The sponsor presented an indirect comparison of response and OS for ASTX727 vs azacitidine (Table 4).

Table 4. Summary of response and OS in AML patients not eligible for intensive chemotherapy: ASTX727 vs SC azacitidine

	ASTX727	**Azacitidine**				
Study ID	**ASTX727-02-C EU**	**AG120-C-009 (AGILE)**	**M15-656**	**AZA PH GL 2003 CL 001**	**AZA-AML-001**	
Source	**CSR**	**Montesinos 2022 / EPAR**	**DiNardo 2020 / EPAR**	**Fenaux 2010**	**Dombret 2015/ EPAR**	**Seymour 2017**
Population	Previously un-Tx AML(≥20% bone marrow blasts) ineligible for standard induction chemotherapy	Previously un-Tx IDH1m AML (≥20% bone marrow blasts) ineligible for intensive induction chemotherapy	Newly diagnosed AML ineligible for intensive chemotherapy	AML with 20-30% blasts and multi-lineage dysplasia not eligible for HSCT	AML with >30% bone marrow blasts, aged ≥65 years, not eligible for HSCT	
N	87	74	145	55	241	129
Median OS (95% CI), months	7.9	7.9 (4.1, 11.3) (100% IDH1m population)	9.6 (7.4, 12.7)	24.5 (14,6, Not reached)[a]	10.4 (8.0, 12.7) 12.1 (9.2, 14.2)[b]	8.9 (6.9, 12.9) 10.8 (7.6, 14.7)[b]
1-year OS rate, % (95% CI)	36 (22, 50)	36.9 (24.3, 49.7)	43.8 (35.5, 51.8)	NR	46.5 (40, 53)	44.3
2-year OS rate, % (95% CI)	NR	20.5 (10.0, 33.7)	18.3 (11.1, 27.0)	50.2 (33.8, 64.5)	NR	NR
CR	21.8%	15%	18%	18%	20%	19%
CR + CRi	27.6%	16%	28%	NR	28%	25%
CR + CRh	24.1%	18%	23%	NR	NR	NR
Median age, years (range)	78 (61-92)	76 (45-94)	76 (60-90)	70 (50-80)	75 (64-91)	76 (64-90)
≥75 years	64.4%	58%	60%	22%	57%	60%
AML - de novo	63.2%	72%	76%	NR	NR	NR
AML - secondary	36.8%	28%	24%	NR	NR	NR
WHO AML classification	NR					

With genetic abnormalities	-	32%	NR	NR	2%	0%
With MDS-related changes (MRC)	-	35%	34%	NR	31%[c]	100%
Therapy-related	-	1%	6%	NR	3%	0%
NOS	-	31%	NR	NR	64%	0%
Cytogenetic risk – intermediate	51.7%[d]	60%	61%	69%	64%	49%
Cytogenetic risk – poor	37.9%	27%	39%	26%	35%	51%
Median BM blast count	35.0%	48%	47%	23%	70%	65%
ECOG PS 0-1	100% (58.6% PS 1)	68%	56%	93%	77%	73%
ECOG PS 2	0	32%	41%	7%	23%	27%
ECOG-PS 2-3	0	-	44%	-		-
Median cycles	5.0	2.3	4.5	8	6	5

CR=complete remission; CRh=complete remission with partial hematologic recovery; CRi=complete remission with incomplete hematologic recovery; CSR=clinical study report; ECOG PS=Eastern Cooperative Oncology Group performance status; EPAR=European Public Assessment Report; HSCT=hematopoietic stem cell transplantation; IDH1m=mutated isocitrate dehydrogenase 1 gene; MDS=myodysplasia; MRC=myodysplasia-related changes; NOS=not otherwise specified; NR=not reported; Tx=treatment/treated
a The median OS (16 months) with conventional care in AZA PH GL 2003 CL 001 was atypically high (Fenaux 2010), which suggested bias in the patient selection, particularly the exclusion of patients with proliferative AML (WBCs >10,000/µL), who are known to have worse prognoses (discussed in Kantarjian et al, 2012).
b Pre-planned analysis: 67 azacitidine treated patients censored at the time of starting subsequent treatment in the analysis of Dombret et al, 2015. Unknown number censored in the analysis of Seymour et al, 2017 which was conducted in AML-MRC subset of patients; note the authors report a median OS of 11.4 months in the azacitidine group from the sensitivity analysis in the description of survival results, but a median OS of 10.8 months in the corresponding Kaplan-Meier curve (Figure 2b in the publication).
c As originally reported. Upon post-hoc central review of histological samples (Seymour et al, 2017), it was determined that 53% overall in this arm had AML-MRC
d A further 10.3% of subjects were either non-evaluable (5.7%) or had a missing (4.6%) cytogenetic risk classification.

The sponsor argued that data reported in the literature support that SC azacitidine and IV decitabine are associated with comparable levels of efficacy.

In the absence of a direct, comparative clinical trial, the functional equivalence of the two HMAs is supported by a systematic review and meta-analysis of randomised controlled trials and retrospective studies on the efficacy of decitabine and azacitidine monotherapy in the general, newly diagnosed AML population (Saiz Rodríguez 2021). A total of 2743 patients from 23 cohorts were analysed (10 cohorts of azacitidine and 13 of decitabine). The results are presented below.

Table 5. Summary of response outcomes, OS and mortality during SC azacitidine or IV decitabine treatment as monotherapy

Product	**CR %, 95% CI**	**ORR %, 95% CI**	**1-Year Mortality %, 95% CI**	**OS (Months) 95% CI**
Meta-analysis				
Azacitidine (75 mg/m^2, 7d)	16% (12-20) I^2 = 54.41%	41% (32-50) I^2 = 85.10%	54% (47-61) I^2 = 75.71%	10.83 (9.07-12.59)
Decitabine (20 mg/m^2, 5d)	24% (18-30) I^2 = 63.54%	46% (42-50%) I^2 = 0	72% (67-76)	8.46 (7.00-9.93)
p-value	0.025	0.327	<0.001	0.138
Study ASTX727-02-C EU				
ASTX727 (35 mg/100 mg, 5d)	21.8% (13.7-32.0)	32.1%[a]	64% (50-88)[b]	7.9 (5.9, 13.0)

CR, complete remission; ORR, overall response rate = CR + CRi + PR; OS, overall survival.
a Summation of individually reported CR, CRi and PR rates. 95% CI for ORR not reported.
b Inverse of reported 1-year survival and its 95% CI.
I^2 coefficient >50% suggests substantial heterogeneity.
Source: Saiz Rodríguez 2021 and ASTX727-02-C EU CSR

Separately, Ma et al, 2021 reported the results of a systematic review and network meta-analysis comparison of azacitidine with decitabine in patients with AML or high-risk MDS (HR-MDS). Eight randomised controlled studies (n=2,184) were identified in the network meta-analysis. Four trials compared azacitidine to CCR, and four compared decitabine to CCR. Whilst this analysis therefore includes a second indication, OS results indicate broadly comparable overall survival in the AML populations.

In the real-world setting, previously described US data from Zeidan et al, 2020 support that the clinical outcomes across 2,263 older patients (≥66 years; median 77 years) treated with HMA monotherapy (IV decitabine or SC azacitidine) are clinically comparable in terms of median overall survival (8.2 and 7.1 months, respectively). Albeit, in multivariate analysis a slightly mortality risk was observed for patients treated with azacitidine compared with decitabine (HR, 1.11; 95% CI, 1.01 1.21; P = 0.02).

The sponsor also argues on similar safety of Inaqovi vs Vidaza (azacitidine) and presented an indirect comparison of the adverse reactions reported in the SmPCs including comparisons with Dacogen as well to justify similar safety of Vidaza in comparison to Dacogen.

COMP conclusion

The sponsor should further elaborate on the extent to which the results of the preference study demonstrate that Inaqovi ensures a major contribution to patient care in comparison with Vidaza.

Significant benefit of Inaqovi (cedazuridine, decitabine) versus Venclyxto (venetoclax)

Venetoclax in combination with an HMA is indicated for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

The sponsor claimed that the efficacy of InaqoviSTX727 as monotherapy is inferior to that of venetoclax plus IV decitabine or SC azacitidine (Table 6). Conversely, and intuitively, the cumulative toxicity (ADRs) associated with either doublet must be worse than that of ASTX727. Albeit that point is difficult to prove.

However, the sponsor considers that a comparison of ASTX727 with the venetoclax plus HMA doublet combinations is the wrong comparison for the purposes of demonstrating significant benefit. It follows that the correct comparison is: venetoclax + oral ASTX727 vs venetoclax + IV decitabine/SC azacitidine. In all doublets venetoclax is a daily orally administered product. IV decitabine and SC azacitidine are administered as the same regimens—5 days or 7 days per 28-day cycle, respectively—as when used as monotherapy.

Table 6. Summary of Response and OS in AML patients not eligible for intensive chemotherapy: ASTX727 vs venetoclax (400 mg) + hypomethylating Agent

	ASTX727	**Venetoclax (400 mg) + Azacitidine**		**Venetoclax (400 mg) + Decitabine**
Study	**ASTX727-02-CEU**	**M15-656 / VIALE-A**	**M14-358**	
Source	**CSR**	**DiNardo 2020 / EMEA/H/C/004106/II/0030**	**DiNardo 2018 / Pollyea 2021b / EMEA/H/C/004106/II/0030**	
Population	Previously un-Tx AML (≥20% bone marrow blasts) ineligible for standard induction chemotherapy	Newly diagnosed AML ineligible for intensive chemotherapy	Newly diagnosed AML ineligible for intensive chemotherapy	
N	87	286	84	31
Median OS (95% CI), months	7.9	14.7 (11.9, 18.7)	NR (9.0, NR)[a] 16.4 (11.3, 24.5)[b]	14.2 (7.7, NR)[a] 16.2 (9.1, 27.8)[b]
1-year OS rate, % (95% CI)	36 (22, 50)	55.8 (49.7, 61.5)	Not reported	61.3 (42.0, 75.8)
2-year OS rate, % (95% CI)	NR	36.5 (29.7, 43.4)	Not reported	Not reported
CR	21.8%	37%	44%[b]	55%[b]
CR + CRi	27.6%	66%	71%[b]	74%[b]
CR + CRh	24.1%	65%	Not reported	Not reported
Median age, years (range)	78 (61-92)	76 (49-91)	75 (61-90)	72 (65-86)
≥75 years	64.4%	61%	50%	26%
AML - de novo	63.2%	75%	75%	71%
AML – secondary	36.8%	25%	25%	29%
WHO AML classification	NR		Not reported	Not reported
With genetic abnormalities	-	Not reported	-	-
With MDS-related changes (MRC)	-	32%	-	-
Therapy-related	-	9%	-	-
NOS	-	Not reported	-	-

Cytogenetic risk – intermediate	51.7%[c]	64%	60%		52%	
Cytogenetic risk - poor	37.9%	36%	39%		48%	
Median BM blast count	35.0%	47%	20-30%	29%	20-30%	19%
			30-<50%	33%	30-<50%	45%
			≥50%	37%	≥50%	32%
ECOG PS 0-1	100% (58.6% PS 1)	55%	69%		87%	
ECOG PS 2	0	40%	29%		13%	
ECOG-PS 2-3	0	45%	31%		13%	
Median cycles	5.0	7.0	5[a], 6[b]		5[a], 6[b]	

CR=complete remission; CRh=complete remission with partial hematologic recovery; CRi=complete remission with incomplete hematologic recovery; EPAR=European Public Assessment Report; HSCT=hematopoietic stem cell transplantation; IDH1m=mutated isocitrate dehydrogenase 1 gene; MDS=myodysplasia; MRC=myodysplasia-related changes; NOS=not otherwise specified; NR=not reached; Tx=treatment/treated

a As reported in original publication (DiNardo 2018).

b As reported after long-term follow-up (Pollyea2021; EMEA/H/C/004106/II/0030).

c A further 10.3% of subjects were either non-evaluable (5.7%) or had a missing (4.6%) cytogenetic risk classification.

COMP conclusion

The sponsor is invited to substantiate further whether Inaqovi is at least equivalent in terms of efficacy, safety and benefit/risk balance as compared to Venclyxto (venetoclax) in its authorised indication.

Significant benefit of Inaqovi (cedazuridine, decitabine) versus Daurismo (glasdegib) + LDAC

The sponsor claimed that the combination of glasdegib and LDAC, although notionally considered to be a satisfactory method of treatment of AML in the unfit population unsuited for standard induction chemotherapy, is not recommended for this use in the current ELN treatment guideline (Döhner 2022) and ESMO guideline (Heuser 2020).

Glasdegib is associated with a boxed warning for embryo-foetal toxicity, albeit that is unlikely to be relevant to the generally older unfit AML population. In combination with LDAC, glasdegib is also associated with QT interval prolongation which should be monitored for early in treatment. Glasdegib in combination with LDAC is also associated with muscle-related adverse events, including pain tenderness and weakness. Further, patients with pre-existing renal impairment or risk factors for renal dysfunction, who are more likely to be older patients, require close monitoring. None of these safety issues pertain to the use of ASTX727 in the same AML population.

The sponsor presented an indirect comparison of response and OS of ASTX727 vs glasdegib + LDAC (Table 8). The sponsor concluded that ASTX727 offers a significant benefit over glasdegib and LDAC in terms of improved safety on a background of at least comparable efficacy, and a major contribution to patient care in terms of ease of administration.

Table 7. Summary of response and OS in AML patients not eligible for intensive chemotherapy: ASTX727 vs glasdegib + LDAC

	ASTX727	**Glasdegib**	
		+ LDAC	**+ Azacitidine**
Study ID	**ASTX727-02-C EU**	**B1371003 / BRIGHT AML 1003**	**B1371019 / BRIGHT AML1019**
Source	**CSR**	**Cortes 2019a / Heuser 2021 / EPAR**	**Cortes 2019b**
Population	Previously un-Tx AML (≥20% bone marrow blasts) ineligible for standard induction chemotherapy	AML unsuitable for intensive chemotherapy[a]	AML unsuitable for intensive chemotherapy[c]
N	87	78	163
Median OS (95% CI), months	7.9	8.3 (4.7, 12.2)	10.3 (7.7, 12.4)[e]
1-year OS rate, % (95% CI)	36 (22, 50)	39.4 (28.3, 50.3)	Not reported
2-year OS rate, % (95% CI)	NR	19.0 (11.0, 28.7)	Not reported
CR	21.8%	18%[d]	1.8% / 19.6%[f]
CR + CRi	27.6%	24%[d]	Not reported
CR + CRh	24.1%	Not reported	2.5%
Median age, years (range)	78 (61-92)	77 (64-92)	Mean (SD): 73 ± 7.2
≥75 years	64.4%	62%	≥65 y: 90%
AML - de novo	63.2%	49%	Not reported
AML – secondary	36.8%	51%	Not reported
WHO AML classification	NR	Not reported	Not reported
With genetic abnormalities	-	-	-
With MDS-related changes (MRC)	-	-	-
Therapy-related	-	-	-
NOS	-	-	-
Cytogenetic risk - intermediate	51.7%[b]	63%	Not reported
Cytogenetic risk – poor	37.9%	37%	Not reported
Median BM blast count	35.0%	41%	Not reported
ECOG PS 0-1	100% (58.6% PS 1)	46%	Not reported
ECOG PS 2	0	53%	Not reported

ECOG-PS 2-3	0	-	-
Median cycles	5.0	3[g]	Not reported

CR=complete remission; CRh=complete remission with partial hematologic recovery; CRi=complete remission with incomplete hematologic recovery; CSR=clinical study report; ECOG PS=Eastern Cooperative Oncology Group performance status; EPAR=European Public Assessment Report; HSCT=hematopoietic stem cell transplantation; IDH1m=mutated isocitrate dehydrogenase 1 gene; IDH2m=mutated isocitrate dehydrogenase 2 gene; MDS=myodysplasia; MRC=myodysplasia-related changes; NOS=not otherwise specified; NR=not reached; SD=standard deviation; Tx=treatment/treated

a Study conducted in patients with AML or high-risk myelodysplastic syndrome unsuitable for intensive chemotherapy. Data from the AML subgroup treated glasdegib + LDAC (78 of a total 88 patients), as reported in EPAR, are shown.

b A further 10.3% of subjects were either non-evaluable (5.7%) or had a missing (4.6%) cytogenetic risk classification.

c Data as reported to clinicaltrials.gov and the EU Clinical Trials Register shown.

d Fourteen patients were reported to have achieved CR in Cortes et al, 2019a and the EPAR; a further patient (total 15; 19%) had achieved a CR with long-term follow-up (Heuser et al, 2021).

e A treatment benefit over placebo + azacitidine was not demonstrated. Median OS in the control arm was 10.6 months (8.4 to 13.3).

f Data are from CR without / including negative minimal residual disease.

g Data for combined AML + MDS group treated with glasdegib ozogamicin + LDAC.

COMP conclusion

The COMP agreed that the efficacy and safety of Inaqovi is equivalent to the efficacy of Daurismo (glasdegib) + LDAC. The sponsor should further elaborate on the extent to which the results of the preference study demonstrate that Inaqovi (cedazuridine, decitabine) ensures a major contribution to patient care in comparison with versus Daurismo (glasdegib) + LDAC.

4. COMP list of issues

Significant benefit

The sponsor sought to establish the existence of significant benefit of Inaqovi (cedazuridine, decitabine) vis-à-vis the satisfactory methods of treatment on the basis of the claim of major contribution to patient care.

- It is recalled that a claim of major contribution to patient care may only be assessed once it is established that the candidate product is at the very least equivalent in terms of efficacy (and safety) to the satisfactory methods of treatment. On that basis, the sponsor is invited to substantiate further whether Inaqovi and the satisfactory method of treatment Venclyxto (venetoclax) in its authorised indication are equivalent in terms of efficacy.
- The sponsor is further invited to elaborate on the conclusiveness of the results of the preference study for the patients with AML, taking into account: first, the limitations of the study design; and second, the extent to which the results of the preference study demonstrate that Inaqovi ensures a major contribution to patient care in comparison with the satisfactory methods of treatment.