4 May 2023
EMADOC-360526170-1417853
Committee for Orphan Medicinal Products

EMA/COMP position on review of criteria for orphan designation

of an orphan medicinal product submitted for marketing authorisation application

Tibsovo (ivosidenib)
Sponsor: Les Laboratoires Servier

Note

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

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1. Introductory note

The approved therapeutic indications:

- 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; and
- Tibsovo monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy.

falls within the scope of the two designated orphan conditions "treatment of acute myeloid leukaemia" and "treatment of biliary tract cancer".

The review of the criteria for the maintenance of the two respective orphan designations is covered in this one document.

2. Tibsovo for treatment of acute myeloid leukaemia - EU/3/16/1802 (EMA/OD/0000115491)

2.1. Product and administrative information

Product	
Designated active substance(s)	Ivosidenib
Other name(s)	--
International Non-Proprietary Name	Ivosidenib
Tradename	Tibsovo
Orphan condition	Treatment of acute myeloid leukaemia
Sponsor's details:	Les Laboratoires Servier 50 Rue Carnot 92284 Suresnes Cedex France
Orphan medicinal product designation procedural history	
Sponsor/applicant	QRC Consultants Ltd
COMP opinion	4 November 2016
EC decision	12 December 2016
EC registration number	EU/3/16/1802
Post-designation procedural history	
Transfer of sponsorship	Transfer from QRC Consultants Ltd, United Kingdom, to Quality Regulatory Clinical Ireland Limited, Ireland – EC decision of 8 June 2018 Transfer from Quality Regulatory Clinical Ireland Limited, Ireland, to FGK Representative Service GmbH, Germany – EC decision of 6 December 2018 Transfer from FGK Representative Service GmbH, Germany, to Agios Netherlands B.V., Netherlands – EC decision of 28 November 2019 Transfer from Agios Netherlands B.V., Netherlands, to Les Laboratoires Servier, France – EC decision of 1 June 2021
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Alexandre Moreau / Blanca Garcia-Ochoa
Applicant	Les Laboratoires Servier
Application submission	3 March 2022
Procedure start	24 March 2022
Procedure number	EMA/H/C/005936
Invented name	Tibsovo

Proposed therapeutic indication	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.
CHMP opinion	23 February 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Frauke Naumann-Winter / Maria Elisabeth Kalland
EMA scientific officer	Janina Karres
Expert	NA
Sponsor's report submission	3 November 2022
COMP discussion and adoption of list of questions	14-16 February 2023
Oral explanation	21 March 2023
COMP opinion	23 March 2023

2.2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2016 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 ivosidenib was considered justified based on preliminary clinical data in patients with the condition showing complete and partial response;
- 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 overall 5-year relative survival with the currently available treatments is approximately 22%;
- 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing ivosidenib will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate a response in relapsed/refractory acute myeloid leukaemia patients. 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 ivosidenib as an orphan medicinal product for the orphan indication: treatment of acute myeloid leukaemia.

2.3. 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, 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 a subset of the AML population, i.e., patients carrying a mutation in the isocitrate dehydrogenase-1 (IDH1) enzyme, which is approximately 6% to 10% of the general AML patient population (Bullinger et al, 2017; Xu et al, 2017). Publications on the prognostic impact of IDH R132 mutations for patients with AML indicate that IDH1 R132 mutations may be associated with inferior responses and worse OS compared with wild-type IDH1 (Feng 2012; Xu et al, 2017; Zhou et al, 2012), although other studies, conducted in newly diagnosed AML, did not find IDH1 to be a molecular prognostic factor (DiNardo et al, 2015, Messina et al, 2022).

The medicinal product Ivosidenib is a small molecule inhibitor of the mutant IDH1 enzyme. Mutant IDH1 converts alpha- ketoglutarate (α-KG) to 2-hydroxyglutarate (2-HG) which blocks cellular differentiation and promotes tumorigenesis in both, hematologic - and non-hematologic malignancies (Dang et al, 2009; Figueroa et al, 2010). The product is intended for oral administration (film-coated tablet).

The approved therapeutic indication is:

> *"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".*

The authorised therapeutic indication 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, see EPAR.

Chronically debilitating and/or life-threatening nature

The sponsor has not identified any significant changes in the seriousness of AML since the orphan designation was granted in 2016. AML remains an aggressive and rapidly progressive malignancy that cannot be cured in most patients (Newell and Cook, 2021; NCCN AML 2022). Although the majority of patients with AML achieve complete remission with induction chemotherapy, relapse after achievement of clinical remission remains the most critical clinical challenge in the treatment of AML (Heuser M. et al. 2020). The 5-year relative survival remains low in Europe at approximately 15-20% for the entire AML population (Kell, 2016), even though survival of patients with AML has generally improved over the last four decades. Furthermore, elderly patients, who account for the majority of new cases, are often unable to tolerate current regimens, especially intensive regimens, and currently carry a particularly poor prognosis (De Kouchkovsky and Abdul-Hay, 2016). Consequently, long-term survival can vary substantially across different age groups, ranging from approximately 35-40% in adults ≤60 years of age to as low as 5-15% in older patients (Editorial, 2019).

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 a few months or less, if left untreated.

Number of people affected or at risk

At the time of the orphan designation in 2016, the prevalence was agreed to be approximately 1.1 per 10,000 persons in the European Union (EU).

For this review report, the sponsor re-calculated the prevalence of AML in Europe based on available data between 01 January 2013 to 01 September 2022. The prevalence presented to the COMP was estimated to be the same as previously, i.e., 1.11 per 10,000. This is based on the following calculation of AML incidence rate (0.37/10,000) and mean duration of disease (3 years): P = (0.37/10,000) x 3 = 1.11/10,000.

The incidence rate of 0.37/10,000 persons is based on the ECIS dataset as published in 2022 (*ECIS: European Cancer Information System. Available at: https://ecis.jrc.ec.europa.eu. 2022*), which comprises the most recent information on the incidence of leukemia and covers all EEA member states except for Liechtenstein. ECIS presents incidence data for all leukaemia (ICD-10 C91 – C95). As AML accounts for 27% of all leukaemia in women and 22% in men (*Krebs in Deutschland für 2017/2018, 2021*), the incidence of AML is approximated as 25% of all leukaemia cases.

As regards the incidence rate, the sponsor also discusses five papers published over the past 10 years, which describe the incidence or prevalence of AML in Europe. These include Hughes et al., 2017, two systematic literature reviews by Lubeck et al, 2016 and Panjabi et al, 2019. The sponsor did however not consider these data as the data collection methods, evaluation and collection periods were not deemed consistent. Additionally, the sponsor discusses a publication by Heuser et al, 2020. However, these data are based on a 2013 representative population (~4 million) of the UK described by Roman et al, 2016. The AML incidence rates reported in these publications ranged between 1.63 – 7.9 per 100,000 persons. Lastly, the sponsor refers to a publication by Polsinelli et al, 2017, reporting prevalence figures agreed by the Committee for Orphan Medicinal Products (COMP) for AML Orphan Designations granted between 2000 to 2015, which range from below 0.5 per 10,000 – approximately 1.4 per 10,000.

International AML clinical practice guidelines have been updated since the granting of the Orphan Designation. The sponsor points out that although it was noted that the rate of AML is generally increasing, no changes to the prevalence of AML in Europe are described.

Survival rates of AML are published by several registries and show similar survival rates as per year for up to 10 years after diagnosis. The sponsor noted that AML is a very aggressive disease characterized by high mortality shortly after diagnosis and relatively stable survival rates among those who survived for more than 2 years, thus indicating that about 20% of patients achieve permanent cure. Data sources included by the sponsor were reports from NORDCAN 2022, Netherlands Cancer Registry (NCR) 2022, Krebs in Deutschland 2021. This comprised AML survival data from the following EU countries: The Netherlands (2011-2022), Germany (2017-2018), Denmark (2012-2016), Finland (2012-2016), Iceland (2012-2016), Norway (2012-2016), Sweden (2012-2016). Based on these data on survival rates, an average disease duration of 3 years was assumed for the purpose of prevalence calculation.

The COMP considered the proposed prevalence estimate of approximately 1.1 per 10,000 persons acceptable and largely in line with previously accepted values in recent designations for AML.

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, there are currently four authorised therapies in the EU: the hypomethylating agents (HMAs) decitabine and azacitidine, Venclyxto (venetoclax, + azacitidine or decitabine), and Daurismo (glasdegib, + low-dose cytarabine [LDAC]).

The target patient population of the product applied for (ivosidenib), consists of newly diagnosed AML patients who are not eligible for standard induction chemotherapy and carrying a mutation in the IDH1 gene. This specific patient subset is also eligible for treatment with the four currently therapies authorised for the overall AML population without molecular selection. A recent pooled post-hoc analysis of two trials with Venclyxto confirmed however that AML patients with IDH1 and IDH2 mutations do respond to treatment with Venclyxto (Pollyea et al., 2022).

More generally, the sponsor 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 standard induction and consolidation chemotherapy or non-intensive treatment, depending on eligibility criteria and patient preference. Therapy for patients in complete remission consists of either consolidation chemotherapy, or autologous or allogeneic hematopoietic stem cell transplantation (HSCT). While eligibility for intensive treatment is critical for the therapeutic approach, there is agreement that there are no objective criteria on which to base the decision of non-eligibility to intensive treatment, thereby increasing the heterogeneity of patient populations with AML in addition to age, ECOG, cytogenetics, molecular markers, de-novo or secondary AML (see also https://onlinelibrary.wiley.com/doi/10.1111/ joim.13293).

The two HMAs azacitidine and decitabine are regarded as having similar activity and no predictive markers are described to choose one HMA over the other. More recently, their use as single agents has been superseded by HMAs in combination with venetoclax (Venclyxto).

Glasdegib in combination with LDAC is not recommended in the ELN guideline in spite of the overall survival (OS) benefit observed in the confirmatory randomized trial. OS was still less than one year and only a marginal improvement of the complete response (CR) rate to what would be expected for LDAC alone was observed.

The ELN guidelines already suggests the use of ivosidenib for patients carrying IDH1 mutations, however, still with reference to the investigational setting at the time of publication of the guideline.

All the above mentioned four authorized products are considered satisfactory methods relevant for a discussion on the significant benefit of ivosidenib in AML since their approved therapeutic indication covers all patients with previously untreated AML who are not eligible for intensive chemotherapy (Table 1).

Table 1. EU approved products for treatment of newly diagnosed AML patients who are not eligible (unfit) for standard induction chemotherapy

EU Centralised number; MA	**Product name (INN)**	**Approved therapeutic indication**	**Significant benefit discussion needed**
EMEA/H/C/000978; 17/12/2008	Vidaza and generics (azacitidine) *parenteral forms*	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, the method is satisfactory as there is a complete overlap with the proposed therapeutic indication for ivosidenib
EMEA/H/C/002221; 20/09/2012	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, the method is satisfactory as there is a complete overlap with the proposed therapeutic indication for ivosidenib

EMEA/H/C/004106; 04/12/2016	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, the method is satisfactory as there is a complete overlap with the proposed therapeutic indication for ivosidenib
EMEA/H/C/004878; 26/06/2020	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, the method is satisfactory as there is a complete overlap with the proposed therapeutic indication for ivosidenib

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

Significant benefit

The sponsor argued that available clinical data have demonstrated that ivosidenib in combination with azacitidine is of significant benefit based on 1) a clinically relevant advantage in terms of improved efficacy in comparison to existing methods of treatment for newly diagnosed, unfit AML patients with an IDH1 mutation who are not eligible to receive intensive chemotherapy and 2) a major contribution to patient care based on the improved health-related quality of life (HRQoL) and transfusion independence over Venclyxto.

Clinically relevant advantage due to improved efficacy

General considerations

For the efficacy comparisons of ivosidenib combination therapy to the authorized azacitidine and decitabine monotherapy, respectively, the sponsor presented 1) the data from the pivotal efficacy data from the randomized pivotal licensing study (AGILE) and 2) data from a systematic review and meta-analysis of randomized controlled trials and retrospective studies comparing the efficacy of decitabine and azacitidine monotherapy in the general, newly diagnosed, unfit AML population.

For the efficacy comparison of ivosidenib combination therapy to the authorized venetoclax + azacitidine/HMA combination treatment (Venclyxto) results from a Network Meta-Analysis (NMA) and from several matching-adjusted indirect comparisons (MAIC) are presented. The efficacy comparison to the authorized glasdegib + LDAC combination treatment (Daurismo), is only supported by a NMA but not a MAIC analysis. The reason for this is not explained by the sponsor.

In brief, the primary data supporting the efficacy of ivosidenib in combination with azacitidine in newly diagnosed AML in the marketing authorization application were obtained from the ongoing, global, multicenter, double-blind, randomized, placebo-controlled phase 3 study AGILE (N=146). The study was designed to evaluate the efficacy and safety of ivosidenib plus azacitidine versus placebo plus azacitidine in adult patients with previously untreated IDH1-mutated AML and who are considered appropriate candidates for non-intensive therapy (i.e., not eligible to receive standard induction chemotherapy). The primary efficacy endpoint was event-free survival (EFS) and key secondary efficacy endpoints included OS, CR rate, CR+CR with partial hematologic recovery (CRh) rate and objective response rate (ORR). Additional secondary endpoints included CR+CR with incomplete hematologic recovery (CRi, including CR with incomplete hematologic [neutrophil and/or platelet]

recovery [CRp]), duration of response (DOR) endpoints (DOCR, DOCRh, DOCRi), time to response (TTR) endpoints (TTR, TTCR, TTCRh, TTCRi), and health-related quality of life (HRQoL) assessments (i.e., by the European Organisation for Research and Treatment of Cancer Core QoL Questionnaire [EORTC QLQ-C30] and EuroQol 5 Dimension 5-Level questionnaire [EQ-5D-5L]).

Before describing the analyses of the indirect treatment comparisons, the tables with key information on the relevant clinical trials and outcomes (Table 4) and on patients' baseline characteristics (Table 2) are displayed. Even though the sponsor lists and discusses overall 6 studies, the main focus lies on the pivotal licensing trials AGILE (ivosidenib + azacitidine), VIALE-A (venetoclax + azacitidine) and BRIGHT-AML 1003 (glasdegib + LDAC). Of further interest is the pooled data selecting patients with IDH1 (and IDH2) mutations from a phase 1b and the pivotal VIALE-A study with venetoclax + azacitidine (Pollyea et al., 2022). All studies included in Table 4 are comparative randomized studies. However, the Pollyea study which describes pooled data from two different studies, did not preserve randomization between study arms and as such is considered observational.

As regards the comparison of baseline patient characteristics between the relevant studies (Table 2), the patient population in the AGILE study appears to be of better ECOG performance status (PS) and a lower proportion of patients have high cytogenetic risk as compared to VIALE-A and BRIGHT-AML 1003. Furthermore, the proportion of primary/ secondary AML varies across the studies. Cortes and colleagues reported a lower proportion of patients with primary AML in BRIGHT-AML 1003 compared with the remaining studies (Cortes et al, 2019a). This creates a potential bias considering that the prognosis for primary and secondary AML are different, with secondary AML having worse outcomes. Of note, only Daurismo is explicitly authorized for patients with secondary AML.

Table 2. Summary of patient characteristics at baseline

Study	AGILE		AZA-AML 001		VIALE-C		VIALE-A		Pooled VIALE-A+ Phase 1b		BRIGHT AML 1003		DACO-016		Mohammed, 2021	
Treatment Arm	IVO+AZA	PBO+AZA	AZA	CCR	VEN+LDAC	PBO+LDAC	VEN+AZA	PBO+AZA	VEN+AZA	PBO+AZA	Glasdegib + LDAC	LDAC	Decitabine	Supportive care or cytarabine	LDAC	BSC
Population for baseline characteristics (N)	72	74	240	245	143	68	286	145	81	28	78	38	242	243	30	30
Median age, years (range)	76.0 (58.0 - 84.0)	75.5 (45.0 - 94.0)	75.0 (64.0 - 91.0)	75.0 (65.0 - 89.0)	76.0 (36.0 - 93.0)	76.0 (41.0 - 88.0)	76.0 (49.0 – 91.0)	76.0 (60.0 – 90.0)	76 (64.0-90.0)	77.5 (62.0-90.0)	77.0 (64.0 – 92.0)	76.0 (58.0 – 83.0)	73.0 (64.0 – 89.0)	73.0 (64.0 – 91.0)	64.0 (60.0 - 71.0)	64.5 (61.0 - 71.0)
Male, n/N (%)	42 (58.3)	38 (51.4)	139 (57.7)	149 (60.3)	78 (55.0)	39 (57.0)	172 (60.1)	87 (60.0)	47 (58.0)	17 (60.7)	59 (76.0)	23 (61.0)	137 (56.6)	151 (62.1)	15 (50.0)	17 (56.7)
ECOG 0-1, n (%)	46 (63.8)	50 (67.6)	NR (NR)	NR (NR)	74 (51.0)	34 (50.0)	157 (54.9)	81 (56.0)	46 (56.8)	19 (67.9)	36 (46.0)	20 (53.0)	184 (76.0)	183 (75.3)	12 (40.0)▪	12 (40.0)▪
ECOG 2, n (%)	26 (36.1)	24 (32.4)	55 (22.8)	58 (23.2)	63 (44.0)	25 (37.0)	129 (45.1) †	64 (44.0) †	35 (43.2)*	9 (32.1)*	41(53.0)	18 (47.0)	58 (24.0)	60 (24.7)	18 (60.0)	18 (60.0)
Primary/ de novo AML, n(%)	54 (75.0)	53 (71.6)	NR (NR)	NR (NR)	85 (59.0)	45 (66.0)	214 (75.0)	110 (76.0)	60 (74.1)	24 (85.7)	38 (49.0)	18 (47.0)	155 (64.0)	157 (64.6)	26 (86.7)	27 (90.0)
Cytogenetic risk: intermediate, n (%)	48 (66.7)	44 (59.5)	155 (64.3)	160 (64.5)	90 (63.0)	43 (63.0)	182 (64.0) ‡	89 (61.0) ‡	62 (76.5)	19 (67.9)	49 (63.0)	29 (37.0)	152 (63.1)	154 (63.6)	NR (NR)	NR (NR)
Cytogenetic risk: poor, n (%)	16 (22.2)	20 (27.0)	85 (35.3)	85 (34.4)	47 (33.0)	20 (29.0)	104 (36.0)	56 (39.0)	19 (23.5)	9 (32.1)	29 (37.0)	17 (45.0)	87 (36.1)	87 (36.1)	NR (NR)	NR (NR)
Median bone marrow blasts (95% CI)	54.0 (32.0 - 75.0)	48.0 (33.0 – 70.0)	70.0 (2.0 - 100.0)	72.0 (2.0 - 100.0)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	NR (NR)	41.5 (16.0 – 99.0)	48.3 (13.0 – 95.0)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
IDH1, n (%)	70 (97.2)	73 (98.7)	NR (NR)	NR (NR)	21 (19.0)	12 (23.0)	61 (25.0)§	28 (22.0)▪	33 (40.7) ɣ	11 (39.3) ‖	19 (24.3)	6 (15.8)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
IDH2, n (%)	NR (NR)	NR (NR)	NR (NR)	NR (NR)					41 (50.61) ɣ	18 (64.3) ‖			NR (NR)	NR (NR)	NR (NR)	NR (NR)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NR, Not reported; NA: Not applicable as inclusion of patients with IDH1m only; IDH, isocitrate dehydrogenase; IVO, Ivosidenib; AZA, Azacitidine; PBO, Placebo; VEN, Venetoclax; LDAC, Low-dose cytarabine; CCR, Combined Conventional Care; AML, Acute Myeloid Leukaemia; CI, Confidence interval.
† Defined as low/intermediate; ‡ Cytogenic risk intermediate is defined as intermediate I and II; ▪ Only includes patients with ECOG 0; * ECOG 2 -3; ɣ total of 81 IDH1/2 patients due to some patients having both IDH1/2 mutations. ‖ total of 28 IDH1/2 patients due to some patients having both IDH1/2 mutations. § Out of 245 patients. Out of 127 patients.

Table 3 below also shows the different definitions of EFS in the pivotal licensing studies AGILE and VIALE-A. The possible implications of this have not been discussed by the sponsor. EFS has been the primary efficacy endpoint in the AGILE study.

Table 3. Definition of Event-free survival (EFS) in the relevant pivotal studies

Study	**EFS**
AGILE (Ivosidenib)	Time to PD, TF, relapse from CR or CRi or death. TF is defined as failure to achieve CR, CRi, or MLFS after at least 24 weeks of study treatment, whichever is earlier.
VIALE-A (Venclyxto)	Time to PD, TF, confirmed relapse, or death. TF is defined as failure to achieve complete remission or <5% bone marrow blasts after at least six cycles of treatment
BRIGHT AML 1003 (Daurismo)	Not assessed

Abbreviations: CR, Complete Remission; CRi, Complete remission with incomplete hematologic recovery; EFS Event Free Survival; OS Overall Survival; PD, progressive disease; TF treatment failure; HR hazard ratio; NA, Not available; PD, Progressive disease; MLFS, Morphologic leukemia-free state.

Table 4. Outcomes of interest in included studies

Study	**Treatments**	**Population, N**	**OS median (months), 95% CI**	**OS HR (95% CI)** **KM curve and NAT available (Yes/No)**	**EFS median (months), 95% CI**	**EFS HR (95% CI)** **KM curve and NAT available (Yes/No)**
AGILE	Ivosidenib + Azacitidine	ITT, 146	24.0 (11.3–34.1)	0.44 (0.27 – 0.73) Yes	22.9 (7.5– NE)	0.39 (0.24 - 0.64) Yes
	Placebo + Azacitidine		7.9 (4.1–11.3)		4.1 (2.7– 6.8)	
VIALE-A	Venetoclax + Azacitidine	ITT, 431	14.7 (11.9–18.7)	0.66 (0.52 – 0.85) Yes	9.8 (8.4– 11.8)	0.63 (0.50 – 0.80) Yes
	Azacitidine		9.6 (7.4–12.7)		7.0 (5.6– 9.5)	
VIALE-A	Venetoclax + Azacitidine	IDH1/2, 53	IDH1 alone: 10.2 (2.3 – -)	0.34 (0.20 – 0.60) IDH1 alone: 0.28 (0.12 – 0.65)	NA	NA
	Azacitidine		IDH1 alone: 2.2 (1.1–5.6)		NA	
VIALE-C	Venetoclax + LDAC	ITT 210	8.4 (5.9–10.1)	0.70 (0.50 – 0.98) Yes	4.9 (3.7–6.4)	0.61 (0.44–0.84) No
	LDAC		4.1 (3.1–8.1)		2.1 (1.5–3.2)	
BRIGHT AML 1003	Glasdegib + LDAC	ITT, 116	8.3 (4.7–12.2)	0.50 (0.325–0.752)[†] Yes	NA	NA No
	LDAC		4.3 (1.9–5.7)		NA	
	Decitabine	ITT, 485	7.7 (6.2–9.2)		NA	NA

DACO-016	Treatment of choice		5.0 (4.3–6.3)	0.82 (0.68 – 0.99) Yes	NA	No
AZA-AML-001	Azacitidine	ITT, 285	10.4 (8.0–12.7)	0.9 (0.7 -1.16) Yes	6.7 (5.0–8.8)	0.87 (0.72 - 1.05) No
	CCR		6.5 (5.0–8.6)		4.8 (3.8–6.0)	
Pollyea 2022	Venetoclax + Azacitidine or decitabine vs Placebo + Azacitidine	IDH1, 44	15.2 (7.0–NE)	0.19 (0.08 – 0.44) Yes	NA	NA
			2.2 (1.1–5.6)		NA	
Pollyea 2022	Venetoclax + Azacitidine or decitabine vs Placebo + Azacitidine	IDH1/2, 108	24.5 (15.2–NE)	0.32 (0.19 – 0.54) Yes	NA	NA No
			6.2 (2.3–12.7)		NA	

Abbreviations: KM, Kaplan-Meier; NE, Not evaluable, NA : Not applicable; OS, Overall survival; ITT, Intention to Treat; EFS, Event-free survival; NAT: Number at risk; CCR, Combined Conventional Care.
† Based on Heuser 2021 estimates with 20 additional months of follow-up from Cortes 2019 (data cut-off date: 11 October 2018)

Significant benefit of ivosidenib plus azacitidine versus azacitidine as monotherapy

The efficacy results of the pivotal study AGILE demonstrated that treatment with ivosidenib plus azacitidine produced statistically significant and clinically relevant improvements in EFS, OS, and CR, CR + CRh and OR rates compared to treatment with azacitidine alone (Table 2).

Table 5. Efficacy of ivosidenib in newly diagnosed IDH1-mutated AML (data cut off: 18 March 2021)

Effect	**Short Description**	**Unit**	**Treatment**	**Control**	**Uncertainties/ Strength of evidence**
EFS	Median of the 3rd quartile	months	23.98 (14.78-NE)	0.03 (0.03, 11.30)	HR = 0.33 95% CI: 0.16, 0.69
OS	Median (95% CI)	months	24.0 (11.3, 34.1)	7.9 (4.1, 11.3)	HR = 0.44 95% CI: 0.27, 0.73
CR	Rate of complete remission	%	47.2 (35.3, 59.3)	14.9 (7.7, 25.0)	OR = 4.76 95% CI: 2.15, 10.50
CR+ CRh	Rate of complete remission + CR with partial hematologic recovery	%	52.8 (40.7, 64.7)	17.6 (9.7, 28.2)	OR = 5.01 95% CI: 2.32, 10.81
ORR	Rate of objective response	%	62.5 (50.3, 73.6)	18.9 (10.7; 29.7)	OR = 7.15 95% CI: 3.31, 15.44.

Abbreviations: CRR: complete remission rate; EFS: event-free survival; HR: hazard-ratio; OR: odds ratio; ORR: objective response rate; OS: overall survival.

COMP conclusion:

The claim of significant benefit over azacitidine is considered demonstrated based on the results from the randomised pivotal study which showed improved efficacy of ivosidenib plus azacitidine in AML.

Significant benefit of ivosidenib plus azacitidine versus decitabine as monotherapy

The sponsor presented a systematic review and meta-analysis of randomized controlled trials and retrospective studies comparing the efficacy of decitabine and azacitidine monotherapy in the general, newly diagnosed, unfit AML population (Saiz-Rodríguez et al, 2021; n=2743). Despite heterogeneity across the clinical studies, similar response rates were observed for azacitidine compared to decitabine (38% [95% CI: 30, 47] versus 40% [95% CI: 32, 48]; p = 0.825) and OS between azacitidine and decitabine was also similar (10.04 months [95% CI: 8.36, 11.72] versus 8.79 months [95% CI: 7.62, 9.96]; p = 0.386).

Since this meta-analysis could not detect any significant differences in efficacy between decitabine and azacitidine, the sponsor concluded that significant benefit over decitabine can be regarded as justified based on the efficacy results from the randomised pivotal study AGILE.

COMP conclusion:

The sponsor's claim of improved efficacy of ivosidenib plus azacitidine vis a vis decitabine monotherapy is supported.

Significant benefit of ivosidenib plus azacitidine versus Venclyxto and Daurismo

Network meta-analysis (NMA)

The conducted analyses consisted of continuous outcomes, i.e., hazard ratios (HRs) for OS and EFS. A normal model with an identity link function was employed. This NMA can be seen as an "anchored" approach, although the "anchor" goes via the azacitidine and LDAC comparison (which add additional uncertainty). Only one study was available per comparison in the network. No underlying assumptions were stated for the Network Meta-Analysis.

NMA for overall survival (OS):

A results matrix (league table) presenting HRs for OS with associated 95% credible intervals (CrI) and a forest plot for OS HRs and associated 95% CrI were produced by the sponsor for comparison of the intervention of interest (ivosidenib + azacitidine) versus all other active comparators. However, for the purpose of this procedure, only the most relevant results are summarized in this report.

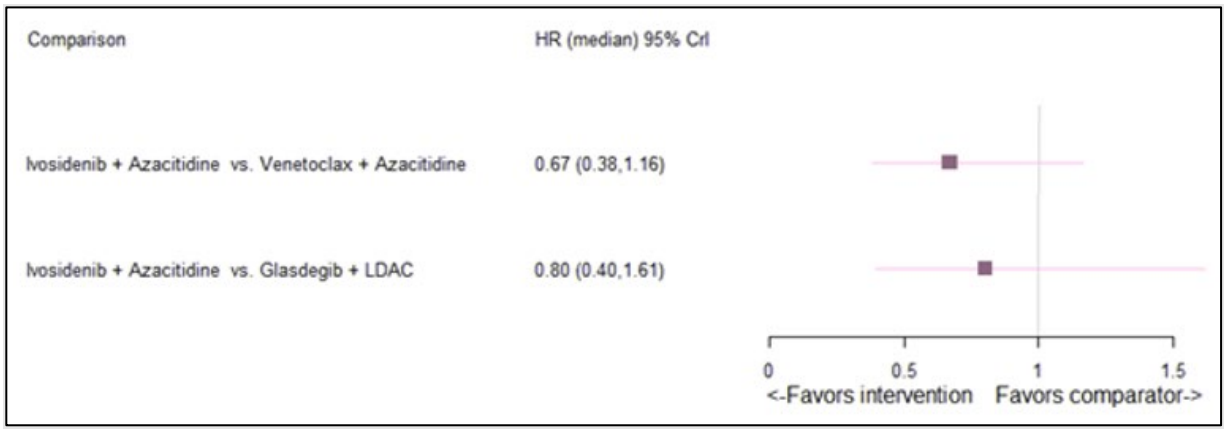
The network for OS consists of six studies reporting estimates for seven interventions. The following studies contributed to the network: VIALE-A with venetoclax plus azacitidine and azacitidine (DiNardo et al., 2020), BRIGHT-AML 1003 with glasdegib plus LDAC and LDAC (Heuser et al., 2021), DACO-016 with decitabine and LDAC (Kantarjian et al., 2012), AZA-AML-001 with azacitidine and LDAC (Dombret et al., 2015), VIALE-C with venetoclax plus LDAC and LDAC (Wei et al., 2021), and the pivotal study AGILE comparing ivosidenib plus azacitidine versus azacitidine

The relevant results, presenting median HRs for OS with associated 95% CrI are described as follows: Ivosidenib + azacitidine was estimated to improve OS against both combination regimens:

- Venclyxto (venetoclax + azacitidine): HR 0.67 (95% CrI: 0.38-1.16), and
- Daurismo (glasdegib + LDAC): HR 0.80 (95% CrI: 0.40-1.61).

Ivosidenib + azacitidine was also estimated to improve OS against the following single combination agents, i.e., versus LDAC (HR 0.40; 95% CrI: 0.23-0.69), azacitidine (HR 0.44; 95% CrI: 0.27-0.72), and decitabine (HR 0.48; 95% CrI: 0.27-0.87).

Figure 1. Forest plot for overall survival from NMA (as adjusted from Figure 9 of sponsor report)



Furthermore, the sponsor presented ranking probabilities for OS (i.e., surface under the cumulative ranking curve, SUCRA), based on the NMA analysis. Results from this SUCRA ranking analysis suggest that ivosidenib ranked highest (93% SUCRA value), followed by Daurismo (glasdegib + LDAC) ranking second highest (81% SUCRA value) and Venclyxto (venetoclax + azacitidine) ranking only third highest (51% SUCRA value).

NMA for event free survival (EFS):

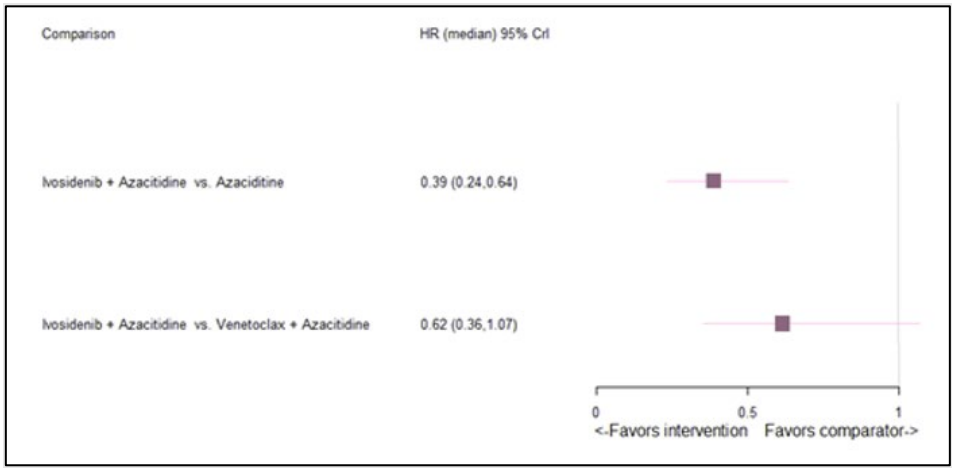
The NMA for EFS consists of four studies reporting estimates for five interventions. A comparison could not be included versus Daurismo (glasdegib + LDAC), as relevant data on EFS were not collected in the pivotal BRIGHT-AML 1003 study with OS as the primary endpoint. The following studies contributed to the network: VIALE-A with venetoclax plus azacitidine and azacitidine (DiNardo et al., 2020), AZA-AML-001 with azacitidine and LDAC (Dombret et al., 2015), VIALE-C with venetoclax plus LDAC and LDAC (Wei et al., 2021), and AGILE with ivosidenib plus azacitidine and azacitidine.

The relevant results, presenting median HRs for EFS with associated 95% credible intervals (CrI) are described as follows: Ivosidenib + azacitidine was estimated to improve EFS against:

Venclyxto (venetoclax + azacitidine): HR 0.62 (95% CrI: 0.36, 1.07).

Ivosidenib + azacitidine was also estimated to improve EFS against the following single combination agent, i.e., versus azacitidine in monotherapy (HR 0.39; 95% CrI: 0.20-0.57).

Figure 2. Forest plot for event free survival from NMA (as adjusted from Figure 12 of sponsor report)



COMP conclusion:

With regards to the NMA, the COMP noted that these results were overall difficult to interpret, as the underlying assumptions of the NMA were not presented by the sponsor and neither was it discussed whether any possible assumptions were met. Considering that the 95% CrI for OS vis-à-vis both satisfactory methods and against Venclyxto for EFS crossed 1 in the NMA and this analysis was the only data to support significant benefit over the authorized product Daurismo (glasdegib + LDAC), no conclusion could be drawn for these efficacy comparisons.

The sponsor noted that although the open-label randomized study showed improved survival for the hedgehog inhibitor glasdegib in combination with LDAC, compared with LDAC alone (Cortes et al, 2019a), the relatively low response rate (CR/CRi 24%) with this regimen does not favour its use as an alternative non-intensive option, and this fact is reflected in the latest version of the ELN guideline (Döhner et al, 2022). Considering this, the COMP questioned the overall validity of the NMA results and SUCRA ranking values, which suggested that Daurismo ranked higher than the currently recommended first line treatment choice Venclyxto, according to current treatment guidelines.

An additional concern is the different definitions of EFS in the AGILE and the VIALE-A studies (see Table 1b, above). Especially *Treatment Failure*, which is part of the EFS definition, is defined differently across these two studies. The possible impact (e.g., over- or under-estimation of a treatment effect) on the efficacy conclusions is not discussed by the sponsor.

Matching-adjusted indirect comparisons (MAIC)

For the indirect comparison of ivosidenib + azacitidine versus venetoclax + azacitidine three MAICs were conducted utilizing either the whole ITT population or the IDH1-mutated subgroup data from the VIALE-A study for matching.

The full list of mutually reported potential effect modifying/prognostic variables was the following: age (as continuous & categorical), sex, AML type, cytogenic risk, ECOG PS, bone marrow blasts, and IDH1 mutation. Three different approaches were used for the selection of covariates and each approach identified different sets of covariates for inclusion in the MAIC analysis per outcome of interest. To ensure the robustness of the results a base case (BC) analysis was included in all three analyses, representing the conservative approach. In here, a matching to all commonly reported covariates was explored before adjusting for smaller sets of covariates in the Scenario 1 and 2 analyses. The three analyses with up to three adjustments each were conducted as follows:

1. An anchored MAIC for OS in which the baseline characteristics for patients in AGILE were matched to reflect the baseline characteristics of the ITT population in the VIALEA study. Besides the BC analysis, only one scenario analysis was explored for OS, adjusting for AML type (Scenario analysis 1).

Table 6. Baseline characteristics in the AGILE trial before and after matching to ITT population for OS (anchored MAIC)

Analysis	Baseline characteristic	AGILE IPD pre-matching	AGILE IPD post-matching	VIALE- A (ITT)
BC	Age (≥75) (%)	56.9	60.6	60.6
	Sex, Male (%)	54.9	60.1	60.1
	ECOG (0 or 1) (%)	65.3	55.2	55.2
	AML type (De novo / Primary) (%)	74.3	75.2	75.2
	AML type (Secondary) (%)	25.0	24.8	24.8
	Cytogenetic risk (Intermediate (%)	63.9	62.9	62.9
	Cytogenetic risk (Poor) (%)	24.3	37.1	37.1
	Bone marrow blasts (<30%) (%)	19.4	29.2	29.2
	Bone marrow blasts (≥30-50%) (%)	26.4	21.8	21.8
SA1	AML type (De novo / Primary) (%)	73.3	75.2	75.2
	AML type (Secondary) (%)	25.3	24.8	24.8

Abbreviations: AML, Acute Myeloid Leukaemia; BC, Base case; ECOG, Eastern Cooperative Oncology Group; IPD, Individual patient data; SA, Scenario analysis

2. An unanchored MAIC for OS in which the baseline characteristics for patients in AGILE were matched to reflect the baseline characteristics of the venetoclax + azacitidine arm in the IDH1/2 post-hoc subgroup in the Pollyea study. For the unanchored MAIC, OS data for venetoclax + azacitidine were obtained from the IDH1 sub-population in the VIALE-A study, however, due to lack of baseline characteristics specifically for IDH1 patients, the baseline characteristics for IDH1/2 patients from the Pollyea study were used instead. Besides the BC, two scenario analyses adjusted for age and the percentage of bone marrow blasts (Scenario analysis 1) and adjusting for age, ECOG status, and the percentage of bone marrow blasts (Scenario analysis 2).

Table 7. Baseline characteristics in the AGILE trial before and after matching to IDH1 population for OS (unanchored MAIC)

Analysis	Baseline characteristic	AGILE IPD pre-matching	AGILE IPD post-matching	Pooled VIALE-A + Phase 1b – (IDH1/2)
BC	Age (≥75) (%)	54.9	65.4	65.4
	Sex, Male (%)	59.2	58.0	58.0
	ECOG (0 or 1) (%)	63.4	56.8	56.8
	AML type (De novo / Primary) (%)	76.1	74.1	74.1
	AML type (Secondary) (%)	22.5	25.9	25.9
	Cytogenetic risk (Intermediate (%)	67.6	76.5	76.5
	Cytogenetic risk (Poor) (%)	22.5	23.5	23.5
	Bone marrow blasts (<30%) (%)	18.3	17.3	17.3
	Bone marrow blasts (≥30-50%) (%)	21.1	24.7	24.7
SA1	Age (≥75) (%)	54.9	65.4	65.4
	Bone marrow blasts (<30%) (%)	18.3	17.3	17.3
	Bone marrow blasts (≥30-50%) (%)	21.1	24.7	24.7
SA2	Age (≥75) (%)	54.9	65.4	65.4
	Bone marrow blasts (<30%) (%)	18.3	17.3	17.3
	Bone marrow blasts (≥30-50%) (%)	21.1	24.7	24.7
	ECOG (0 or 1) (%)	63.4	56.8	56.8

Abbreviations: AML, Acute Myeloid Leukaemia; BC, Base case; ECOG, Eastern Cooperative Oncology Group; IPD, Individual patient data; IDH, isocitrate dehydrogenase; SA, Scenario analysis

3. An anchored MAIC for EFS (with very similar EFS definitions between the two studies) in which baseline characteristics for patients in AGILE were matched to reflect the baseline characteristics of the ITT population in the VIALE-A study. Besides the BC analysis, two scenario analyses were explored adjusting for sex, and ECOG status (Scenario analysis 1) and adjusting for sex, cytogenetic risk, and ECOG status (Scenario analysis 2).

Table 8. Baseline characteristics in the AGILE trial before and after matching to ITT population for EFS (anchored MAIC)

Analysis	Baseline characteristic	AGILE IPD pre-matching	AGILE IPD post-matching	Pooled VIALE-A + Phase 1b – (IDH1/2)
BC	Age (≥75) (%)	56.9	60.6	60.6
	Sex, Male (%)	54.9	60.1	60.1
	ECOG (0 or 1) (%)	65.3	55.2	55.2
	AML type (De novo / Primary) (%)	74.3	75.2	75.2
	AML type (Secondary) (%)	25.0	24.8	24.8
	Cytogenetic risk (Intermediate (%)	63.9	62.9	62.9
	Cytogenetic risk (Poor) (%)	24.3	37.1	37.1
	Bone marrow blasts (<30%) (%)	19.4	29.2	29.2
	Bone marrow blasts (≥30-50%) (%)	26.4	21.8	21.8
SA1	Sex, Male (%)	54.8	60.1	60.1
	ECOG (0 or 1) (%)	65.8	55.2	55.2
SA2	Sex, Male (%)	54.8	60.1	60.1
	Cytogenetic risk (Intermediate (%)	65.8	55.2	55.2
	Cytogenetic risk (Poor) (%)	63.0	62.9	62.9
	ECOG (0 or 1) (%)	24.7	37.1	37.1

Abbreviations: AML, Acute Myeloid Leukaemia; BC, Base case; ECOG, Eastern Cooperative Oncology Group; IPD, Individual patient data; IDH, isocitrate dehydrogenase; SA, Scenario analysis

In all cases, post-matching characteristics were identical to the comparator ones providing grounds for successful matching. The sponsor emphasised that in the unanchored MAIC for OS, despite utilizing the IDH1 mutation-specific data from venetoclax + azacitidine, the matching was conducted against the IDH1/2 baseline characteristics reported in Pollyea (pooled data from VIALE-A and phase Ib study) due to lack of IDH1 mutation-specific baseline characteristics for venetoclax + azacitidine.

Overall survival

Unanchored MAIC for IDH1 population

Only the results from an unanchored indirect treatment comparison were presented, matching the AGILE trial to IDH1 population of the VIALE-A study using the baseline characteristics from pooled VIALE-A and phase Ib study reported in Pollyea. The OS Kaplan Meier (KM) curve from VIALE-A is lower than that reported in the AGILE trial, indicating a lower median OS time for venetoclax + azacitidine compared to the ivosidenib + azacitidine arm before and after population adjustment. Table 8 contains the median OS times (in months) of the AGILE trial before and after matching and also of the pseudo-individual patient data (IPD) of VIALE-A per scenario analysis.

Table 9. Median OS times (in months) of AGILE before and after matching to IDH1 population for OS (unanchored MAIC) and VIALE-A

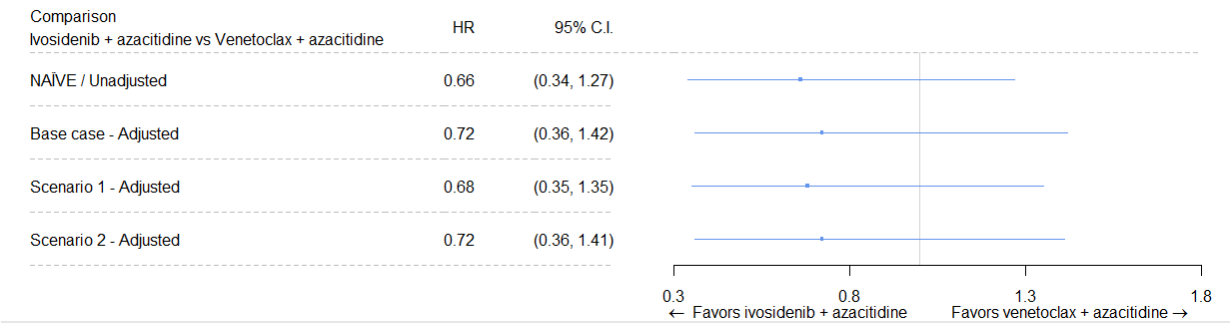
Analysis, N/ESS	Trial	Treatment arm	Median OS times (in months) (95% CI)
-	VIALE-A	venetoclax + azacitidine	10.2 (2.3, NR)
Naïve, N=71	AGILE (unadjusted)	ivosidenib + azacitidine	24.0 (13.3, 34.1)
BC, ESS=58	AGILE (adjusted)	ivosidenib + azacitidine	22.1 (9.03, 34.1)
SA1, ESS=66		ivosidenib + azacitidine	24.0 (11.3, 34.1)
SA2, ESS=65		ivosidenib + azacitidine	22.1 (11.3, 34.1)

Abbreviations: BC, Base case; CI, Confidence interval; ESS, Effective sample size; NR, Not reached; OS, Overall survival; SA, Scenario analysis

The sponsor noted that visual inspection of the plots of log-scaled cumulative hazard and Schoenfeld residuals revealed no strong evidence of non-parallelism, and the null hypothesis that the proportional hazard (PH) assumption holds was not rejected, indicating that PH may be a reasonable assumption.

The HR estimates of OS of the naïve (unadjusted) and matching-adjusted comparisons of ivosidenib + azacitidine versus venetoclax + azacitidine along with the corresponding 95% CIs are presented in Figure 3 per scenario analysis. The MAIC relative effect in the BC was HR: 0.72 (95% CI: 0.36, 1.42) and in scenario analyses 1 and 2, where smaller sets of covariates were included in the matching process, the HR was equal to 0.68 and 0.72, respectively. HR lower than 1 suggested an improvement in OS for ivosidenib + azacitidine compared with venetoclax + azacitidine, but the broad confidence intervals crossing 1 indicate uncertainty in this regard.

Figure 3. Hazard ratio estimates of OS for ivosidenib + azacitidine compared to venetoclax + azacitidine (all scenario analyses)



Abbreviations: CI, Confidence interval; HR, Hazard ratio; OS, Overall survival

The COMP concluded the following:

The impact of IDH1 mutations on survival is still not fully clear, possibly due to the additional influence of co-mutational patterns of IDH-mutated clones (see Uptodate and Pollyea 2022). However, considering that ivosidenib will be especially authorized for patients with confirmed IDH1 mutations, a comparative efficacy analysis in this subpopulation is considered of particular relevance vis a vis the authorized therapies Venclyxto and Daurismo. The sponsor only presents such an analysis against Venclyxto.

The effective sample size (ESS) for the unanchored comparison is relatively high for all scenario analysis that were conducted. In addition, the median OS times are close to the unadjusted AGILE results, which is reassuring. While the results from the unanchored MAIC, which compared OS of ivosidenib treatment with the one of Venclyxto (i.e., IDH1-mutated subgroup of VIALE-A) may suggest better efficacy of ivosidenib, the COMP noted the following weaknesses:

The reported confidence Intervals are rather wide and overlapping with median OS and all confidence intervals of the HRs cross 1.

Furthermore, the stark difference in median OS in the azacitidine-only control arms of 2.2 months (VIALE-A, IDH1-mutated subgroup) versus 7.9 months (AGILE study) raises concerns about the general comparability of the whole IDH1 subgroup in the VIALE-A study (with the ITT population of the AGILE study), not only the azacitidine-only control arms. Therefore, an unanchored MAIC analysis, which disregarded the azacitidine arms from both studies, is not considered to address this issue, also bearing in mind that both trials have a randomised design. As the baseline characteristics for IDH1-mutated patients were not reported in VIALE-A or in Pollyea, it is difficult to know the source of such a potential bias. The sponsor themselves believe that the ITT population of the VIALE-A study is preferable to the subgroup analysis in patients carrying the IDH1 mutation, as the patient number was low in this subgroup, the presence of this mutation was not a stratification factor and the median OS in the azacitidine-only control arm was unexpectedly low. The sponsor believes that there is a risk for bias in this IDH1 subpopulation from VIALE-A and Pollyea also due to non-preserved randomization and different venetoclax dosages being pooled, resulting in an unreliable estimate for the treatment effect. The COMP also noted the following, as baseline characteristics for IDH1 patients were not reported in VIALE-A or in Pollyea the sponsor used the ones for the combined IDH1 and IDH2 patients as per Pollyea in their unanchored MAIC analysis; however, the analysis itself was based on the smaller VIALE-A only IDH1 subpopulation, not the slightly larger pooled IDH1 population as described in Pollyea. The reason for this is not clear.

Anchored MAIC for ITT population

Table 7 summarizes the unadjusted and adjusted median OS times (in months) of the AGILE trial and the VIALE-A study. The KM estimates are very similar between the BC and the scenario analysis which were explored before and after matching due to the overlap in the baseline characteristics within the two studies.

Table 10. Median OS times (in months) of AGILE before and after matching to ITT population for OS (anchored MAIC) and VIALE-A

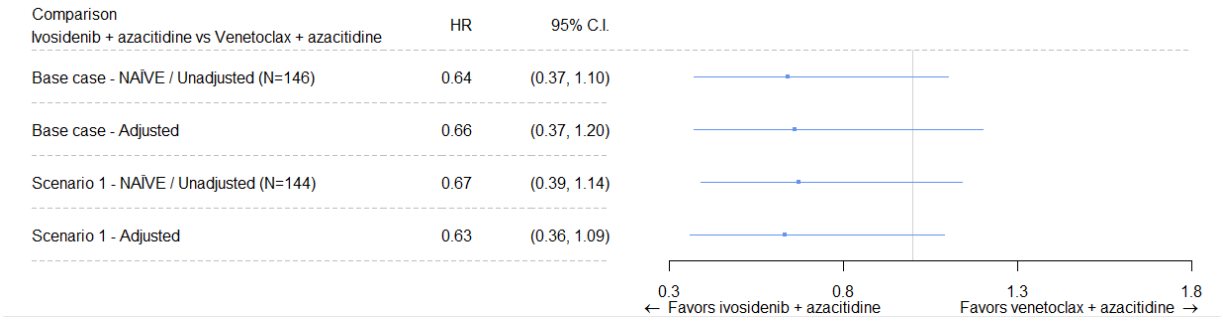
Analysis, N/ESS	Trial	Treatment arm	Median OS times (in months) (95% CI)
-	VIALE-A	venetoclax + azacitidine	14.1 (10.7, 19.3)
		azacitidine	9.6 (6.8, 13.0)
Naïve (for BC), N=144	AGILE (unadjusted)	ivosidenib + azacitidine	24.0 (13.3, 34.1)
		azacitidine	7.9 (4.1, 12.8)
BC, ESS=102	AGILE (adjusted)	ivosidenib + azacitidine	22.1 (8.5, 34.1)
		azacitidine	7.9 (3.1, 11.3)
Naïve (for SA1), N=146	AGILE (unadjusted)	ivosidenib + azacitidine	24.0 (11.3, 34.1)
		azacitidine	7.9 (4.1, 12.8)
SA1, ESS=143	AGILE (adjusted)	ivosidenib + azacitidine	24.0 (11.3, 34.1)
		azacitidine	7.9 (4.1, 12.8)

Abbreviations: BC, Base case; CI, Confidence interval; ESS, Effective sample size; ITT, Intention to treat; OS, Overall survival; SA, Scenario analysis

The sponsor noted that the PH assumption was met. As a result, the relative treatment effect of ivosidenib + azacitidine compared with venetoclax + azacitidine was presented in the form of a constant HR, utilizing both the MAIC relative effect of ivosidenib + azacitidine versus azacitidine and the published HR comparing venetoclax + azacitidine versus azacitidine.

The HR estimates of the naïve (unadjusted) and matching-adjusted comparisons of ivosidenib + azacitidine versus venetoclax + azacitidine along with the corresponding 95% CIs are presented in Figure 4 per scenario analysis. The MAIC relative effect in the BC was HR: 0.66 (95% CI: 0.37, 1.20) and in scenario analyses 1, where only AML type has been included in the matching process, the HR was equal to 0.63. HRs in all scenario analyses suggested an improvement in OS for ivosidenib + azacitidine compared to venetoclax + azacitidine.

Figure 4. Hazard ratio estimates of OS for ivosidenib + azacitidine compared to venetoclax + azacitidine (all scenario analyses)



Abbreviations: CI, Confidence interval; HR, Hazard ratio; OS, Overall survival

The COMP concluded the following:

This second OS comparison is an anchored comparison of the ITT population of VIALE-A. The ESS reduction is substantial with a decrease of around 30% for the BC scenario, but the median OS estimates in the treatment arms for the unadjusted and adjusted analyses are still relatively similar (Table 7). Confidence intervals for the HRs cross 1 for all scenarios and the confidence intervals of the

median OS times are also largely overlapping, indicating uncertainties in the estimated improvement in OS.

While the sponsors view is shared that the comparison to the IDH1 subpopulation of VIALE-A has several weaknesses (as per the above), the anchored MAIC analyses to the ITT population of the VIALE-A study also harbours uncertainty over the comparability of the wider VIALE-A study population (ITT), to the one of AGILE with inclusion of IDH1-mutated patients only. In specific, the patient population in AGILE appears to be younger, with better ECOG PS and lower proportion of high-risk cytogenetics compared to VIALE-A. Since the prognostic impact of IDH1 mutation is still controversial, an impact by otherwise more favourable prognostic factors on this outcome cannot be excluded. This is considered to add an additional layer of uncertainty to the results.

Event-free survival

Anchored MAIC for ITT population

Table 8 summarizes the unadjusted and adjusted median EFS times (in months) of the AGILE trial and the pseudo-IPD for VIALE-A study. The sponsor noted that the KM estimates for the BC and the scenario analyses explored are again very similar before and after population adjustment.

Table 11. Median EFS times (in months) of AGILE before and after matching to ITT population for EFS (anchored MAIC) and VIALE-A

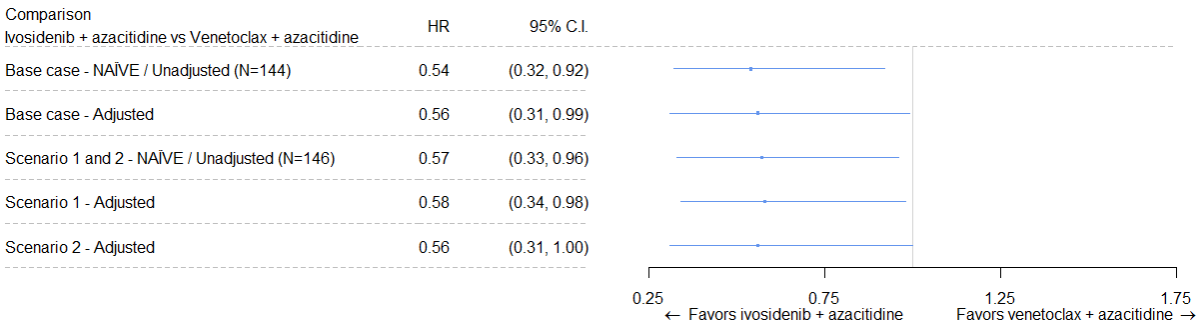
Analysis, N=ESS	**Trial**	**Treatment arm**	**Median EFS times (in months) (95% CI)**
-	VIALE-A	venetoclax + azacitidine	9.8 (8.4, 11.8)
		azacitidine	7.0 (5.6, 9.5)
Naïve (for BC), N=144	AGILE (unadjusted)	ivosidenib + azacitidine	22.9 (7.5, NR)
		azacitidine	4.1 (2.7, 8.6)
BC, ESS=102	AGILE (adjusted)	ivosidenib + azacitidine	14.8 (5.9, NR)
		azacitidine	3.8 (2.1, 6.8)
Naïve (for SA1 and SA2), N=146	AGILE (unadjusted)	ivosidenib + azacitidine	22.9 (7.5, NR)
		azacitidine	4.1 (2.7, 8.6)
SA1, ESS=136	AGILE (adjusted)	ivosidenib + azacitidine	14.8 (6.3, NR)
		azacitidine	4.0 (2.5, 8.6)
SA2, ESS=112	AGILE (adjusted)	ivosidenib + azacitidine	14.8 (6.3, NR)
		azacitidine	3.9 (2.1, 6.8)

Abbreviations: BC, Base case; CI, Confidence interval; EFS, Event-free survival; ESS, Effective sample size; NR, Not reached; SA, Scenario analysis; ITT, Intention to treat.

The PH assumption was met upon visual checks. As a result, the relative treatment effect was expressed in the form of a constant HR along with the 95% CIs.

The HR estimates of the naïve (unadjusted) and matching-adjusted comparisons of ivosidenib + azacitidine versus venetoclax + azacitidine and the corresponding 95% CIs are presented in Figure 5 per scenario analysis. The MAIC relative effect in the BC was HR: 0.56 (95% CI: 0.31, 0.99) and in scenario analyses 1 and 2, where smaller sets of covariates have been included in the matching process, the HR was equal to 0.58 and 0.56, respectively. The reported HRs in all scenario analyses demonstrated an improvement in EFS for ivosidenib + azacitidine compared to venetoclax + azacitidine.

Figure 5. Hazard ratio estimates of EFS for ivosidenib + azacitidine compared to venetoclax + azacitidine (all scenario analyses)



Abbreviations: CI, Confidence interval; EFS, Event free survival; HR, Hazard ratio.

The COMP concluded the following:

The ESS reduction for the anchored EFS comparison, as was also noted for OS, is substantial with a decrease of around 30% for the BC scenario. However, for this comparison, the median EFS for ivosidenib + azacitidine is also substantially reduced by the matching to the VIALE-A trial, from 22.9 months (unadjusted) to 14.8 months (adjusted), implying that there are differences between the trial populations and the adjustment leads to a down-weighting of several patients in the AGILE trial population. This is of concern given that EFS is the primary endpoint of AGILE.

An additional concern are the different definitions of EFS in the AGILE and the VIALE-A studies (see Table 1b, above). Especially *Treatment Failure*, which is part of the EFS definition, is defined differently across studies. The possible impact on the efficacy conclusions is not discussed by the sponsor.

Major Contribution to Patient Care

The sponsor bases significant benefit of ivosidenib plus azacitidine over Venclyxto also on a claim for a major contribution to patient care due to achieving similar relative rates of transfusion independence and reduced fatigue (as evaluated through HRQoL Assessments). No major contribution to patient care claims are made compared to Daurismo due to the lack of inclusion of these endpoints it its pivotal study.

Transfusion Independence

Patients with AML have a severe deficiency in the ability to produce normal blood cells. Transfusions are provided as a supportive care and, though necessary, represent a substantial clinical, economic and patient burden (Cannas et al., 2015). Reduction of transfusion dependence among patients with AML treated with non-intensive therapies has been shown to be associated with significantly better survival and a reduction in costs.

The sponsor's data suggests a similar decrease in transfusion independence achieved within the respective pivotal studies for ivosidenib (AGILE) and Venclyxto (VIALE-A), vis a vis their respective control arm:

- AGILE: Regardless of baseline transfusion status, a greater proportion of subjects in the ivosidenib + azacitidine arm experienced postbaseline RBC and platelet transfusion independence compared with the placebo + azacitidine arm (56.9% vs. 37.8%); these results were statistically significant (1 sided p= 0.0182) (AGILE CSR).
- VIALE-A: Regardless of baseline transfusion status, a greater proportion of subjects in the venetoclax + azacitidine arm experienced post-baseline RBC and platelet transfusion independence

compared with the placebo + azacitidine arm (58.0% vs. 33.8%), although it is not clear if these results were statistically significant (Venclyxto AR, 2021).

The sponsor argues that this still represents a significant benefit, as the results presented for venetoclax + azacitidine are not specific for the IDH1 mutated subpopulation.

Additionally, the sponsor argues that there is a link between incidence of complete remission (CR) + complete remission with incomplete hematologic recovery (CRi) and transfusion independence.

COMP conclusion:

The sponsor's data suggests a similar decrease in transfusion dependence achieved within the respective pivotal studies for ivosidenib (AGILE) and Venclyxto (VIALE-A), vis a vis their respective control arm. The sponsor's view that this still represents a significant benefit, for the IDH1-mutated subpopulation is not shared, considering that also the VIALE-A study included patients with a IDH1 mutation and Venclyxto is also authorized in this patient subset.

Also, the sponsors claim on a link between incidence of complete remission (CR) + complete remission with incomplete hematologic recovery (CRi) and transfusion independence has not been sufficiently substantiated.

Health-Related Quality of Life Assessments

HRQoL data from the pivotal study for ivosidenib (AGILE) using EORTC QLQ-C30, demonstrated that ivosidenib + azacitidine confers clinically meaningful improvements in global health status and fatigue compared to treatment with azacitidine alone.

From C5D1 to C19D1, after an initial decline in both groups consistent with the time to response, subjects in the ivosidenib + azacitidine arm experienced clinically meaningful improvements in the Global Health Status (GHS)/QoL subscale (exceeding the 10-point threshold) at all visits except C17D1. In contrast, subjects in the placebo + azacitidine arm had no clinically meaningful changes compared with baseline at any time. From baseline through C19D1, the difference in GHS/QoL score changes between arms was significant at Cycles 2 (D1, p=0.0126; D15, p=0.0225), 7 (p=0.0261) and 9 (p=0.0002) with clinically meaningful differences for the ivosidenib + azacitidine arm versus the placebo + azacitidine arm at Cycles 2 (D1 and D15), 7, 9, 13, 15 and 19.

Similar trends were observed on the Fatigue subscale. From C5D1 to C19D1, improvements in the ivosidenib + azacitidine arm were clinically meaningful at all visits except for C5D1, whereas Fatigue scores were similar to baseline in the placebo + azacitidine arm. The difference between arms was statistically significant at Cycles 7 (p=0.0482), 9 (p=0.0309) and 13 (p=0.0147) with clinically meaningful differences for the ivosidenib + azacitidine arm versus the placebo + azacitidine arm at Cycles 7, 9, 11, 13, 15 and 19.

In the pivotal licensing study for Venclyxto (VIALE-A), HRQoL was assessed using the EORTC QLQ-C30 GHS/QoL (and PROMIS Cancer Fatigue SF-7a) instruments. There were no differences observed in terms of fatigue and other patient-reported outcomes (PROs) between patients treated with venetoclax + azacitidine and those treated with azacitidine alone (Venclyxto EPAR, 2021).

The sponsor therefore concluded that ivosidenib + azacitidine represents a major contribution to patient care as compared to venetoclax + azacitidine as ivosidenib + azacitidine is associated with clinically meaningful improvements in HRQoL and especially fatigue.

COMP conclusion:

The sponsor claims a major contribution to patient care for the combination treatment with ivosidenib + azacitidine over Venclyxto also based on improvements in HRQoL. In specific, the sponsor refers to the Fatigue Score of QLQ-C30 in AGILE. While clinically relevant improvement may have been observed at isolated timepoints during the pivotal study for ivosidenib, these improvements did not appear to be sustained. A detailed comparison to the VIALE-A Fatigue data has not been presented by the sponsor. It is also not clear whether the baseline characteristics of the azacitidine plus placebo arm of VIALE-A are comparable to the AGILE comparator arm. Moreover, the HRQoL analyses remains exploratory (i.e., not statistically significant) and should be interpreted with caution. Indeed, compliance decreased over the course of treatment cycles (80% at cycle 5 versus 70% at cycle 19 with no data for the placebo + azacitidine group). Overall, a more detailed discussion on the claim of a major contribution to patient care would have been expected, based on all results/parameters from the HRQoL. Furthermore, the COMP would have welcomed a discussion which included the HRQoL data as recently reported by Pratz and colleagues (Pratz et al., 2022, Blood Cancer J. 2022 Apr 20;12(4):71. doi: 10.1038/s41408-022-00668-8).

Overall conclusion COMP:

The significant benefit of ivosidenib vis a vis the authorized products Venclyxto and Daurismo is currently not considered to be established by the COMP, based on the data presented by the sponsor. A more comprehensive discussion on the claim of significant benefit for ivosidenib over Venclyxto and Daurismo in newly diagnosed AML patients with an IDH1 mutation who are unfit for standard induction chemotherapy is therefore needed. The COMP adopted a List of Questions on significant benefit aiming at clarifying the validity, interpretability, robustness, reliability, and consistency of indirect treatment comparisons (NMA and MAIC) of a molecularly selected patient population compared to an unselected or a differently selected one in a heterogeneous disease like AML. A more detailed discussion on the claim of a major contribution to patient care was also requested.

Comments on sponsor's response to the COMP list of issues

In the written response, and during an oral explanation before the Committee on 21 March 2023, the sponsor presented their responses to the COMP's list of questions. The sponsor further justified the claim of significant benefit for ivosidenib plus azacitidine over Venclyxto (venetoclax) plus azacitidine and Daurismo (glasdegib) plus LDAC in newly diagnosed AML as requested.

The sponsor underlines that both types of indirect comparisons, NMA (respecting the randomisation) and the two different MAIC approaches (anchored or unanchored addressing differences in prognostic factors) on the HR of OS are consistent and therefore underpin the significant benefit of the ivosidenib combination compared to the venetoclax combination. The sponsor argues that in view of the consistent results for the NMA and MAICs (also using different matching scenarios), the documented differences in baseline characteristics (age, cytogenetic risk, ECOG) do not seem to drive the relative effect estimates.

Table 12. OS and EFS Hazard Ratios and 95% Confidence Intervals

	NMA **(ITT population)**	**MAIC (anchored)-Base Case** **(ITT population)**	**MAIC (unanchored)-Base Case** **(IDH1 population)**
Overall Survival			
Ivosidenib+azacitidine *vs* Venetoclax+azacitidine	0.67 (0.38, 1.16)	0.66 (0.37, 1.20)	0.72 (0.36, 1.42)

Network meta-analysis on overall survival: lack of statistical significance

Hypothetical NMA scenario analyses for the outcome of OS were performed to evaluate the sample size required in AGILE to reach statistical significance in the NMA, indicating that 330 patients would have been needed in the AGILE study, whereas this study was stopped when half of this number was included further to the recommendation of the Independent Data Monitoring Committee (IDMC) for ethical reasons due to a major difference in the number of deaths between the two treatment arms.

Comparison of results from MAIC and NMA for Venclyxto and Daurismo

The sponsor reiterates the approach of conducting both NMA and MAICs for the comparison of the ivosidenib and venetoclax combinations.

The NMA results suggested that ivosidenib improves both OS and EFS against all other treatments, specifically versus venetoclax plus azacitidine with HRs for OS of 0.67 (95% CrI: 0.38-1.16) and 0.62 (95% CrI: 0.36-1.07) for EFS.

The MAIC analyses of OS were conducted for ivosidenib versus venetoclax using an anchored approach for the analysis with the VIALE-A ITT population, and an unanchored approach for the analysis with the IDH1 mutation subgroup of the trial. The unanchored approach for the IDH1 mutation subgroup was justified with the implausible low treatment effects in the control arm observed in VIALE-A, with a median OS of only 2.2 months. In the literature, median OS in (azacitidine only) control arms have been reported to range from 4.1 months (Wei et al., 2021) to 9.6 months (DiNardo et al., 2020).

All known effect modifying and/or prognostic variables were included (age, sex, AML type, cytogenetic risk, ECOG PS, bone marrow blasts) to balance patient population characteristics prior to reweighting outcomes. The results for OS were closely aligned with the NMA (OS: HR 0.67; 95% CrI: 0.38-1.16) in both the unanchored MAIC comparing to the IDH1 subgroup from VIALE-A (OS HR: 0.72; 95% CI: 0.36-1.42) and the anchored MAIC comparing to the ITT population from VIALE-A (OS HR: 0.66; 95% CI: 0.37-1.20), thus confirming the survival benefit of ivosidenib relative to venetoclax after adjusting for imbalances in population characteristics across the studies. The sponsor concluded that the consistency of these HR's between NMA and MAICs with point estimates ranging only between 0.63 to 0.72, confirms the survival benefit of the ivosidenib relative to the approved venetoclax-combination.

The median OS based on the results obtained from the most recent data cut-offs of AGILE (30 June 2022; median follow-up: 28.6 months) and VIALE-A (01 December 2021; median follow-up: 43.2 months) was also presented. The results of this naïve indirect comparison across the two pivotal studies suggested a survival benefit of ivosidenib versus venetoclax (HR: 0.67; 95%CI: 0.47-0.94; p-value: 0.0226), with a notable difference in the point estimates of the median OS.

Table 13. Median OS and median follow-up for Ivosidenib and Venetoclax in AGILE and VIALE-A studies, respectively

	Ivosidenib + azacitidine (March 2021) IDH1 only	**Ivosidenib + azacitidine (June 2022) IDH1 only**	**Venetoclax + azacitidine (January 2020) Broad population[1]**	**Venetoclax + azacitidine (December 2021) Broad population[2]**
Median Follow-up (months)	15.1	28.6	20.5	43.2
mOS (months)	24.0 (11.3, 34.1)	29.3 (13.2-NE)	14.7 (11.9, 18.7) 10.2 (2.3, -) **only IDH1**	14.7 (12.1, 18.7) 10.2 **only IDH1**[3]

1: Venetoclax, EPAR, EMA/280804/2021
2: Pratz et *al*., 2022, [ASH 2022 Presentation Abstract]
3: All patients included in the IDH1subgroup of VIALE-A treated with venetoclax+azacitidine (n=23), had an event by Month 27, thus mOS is not expected to be different at the most recent data-cut (Venetoclax, EPAR, EMA/280804/2021)

The sponsor provided the proportion of survival after 42 months, also favouring the ivosidenib-combination (35.8% versus less than 20% for venetoclax). These data do not address the impact of the differences in the study populations, but report results directly extracted from the publications.

With respect to the glasdegib combination, the sponsor explained that the difference in study populations limits the interpretation of the indirect treatment comparisons. The MAIC approach is only applicable for addressing between-study differences, but not within-study differences, as noted in the baseline characteristics in BRIGHT-AML 1003. However, the result from the NMA also suggests an OS benefit for the ivosidenib combination versus the glasdegib combination (HR OS of 0.8 with a CrI spanning 1).

Ranking of treatments in the NMA as compared to recommendations from clinical guidelines

The sponsor reviewed the recommendation of both European and US treatment guidelines and highlights their agreement with respect to venetoclax combinations being the standard of care and ivosidenib already recommended for the IDH1-mutated population. Glasdegib is not among the preferred regimens in neither guideline. The sponsor then highlighted the (rudimentary) results posted on clinicaltrials.gov of the recently analysed (and not yet published) BRIGHT-AML 1019 study comparing glasdegib + azacitidine versus placebo + azacitidine. This is apparently a failed study with a HR OS of 1.04 (95% CI: 0.775-1.388; p=0.5955) with a median OS of approximately 10 months in both treatment arms. Taking into account both, the imbalances known for the trial studying glasdegib + LDAC (baseline differences in the study arms) and the apparently negative results in an additional population with patients not eligible for standard induction chemotherapy, the sponsor removed the study from the NMA and from the SUCRA score table instead of discussing the seemingly better ranking of glasdegib compared to venetoclax. The sponsor concluded that by discarding glasdegib + LDAC due to the imbalances in baseline characteristics and subsequent treatment, the ranking results obtained through the ITC are aligned with the most updated guidelines with the two most recommended regimens at the higher level for both OS (ivosidenib + azacitidine 93% vs. venetoclax + azacitidine 67%) and EFS (ivosidenib + azacitidine 98% vs. venetoclax + azacitidine 68%).

Major contribution to patient care based on available results on HRQoL

According to the ELN recommendations, one of the aims of AML treatment is to optimize QoL of the patients (Döhner et al. 2022), which is of major importance in older AML patients (Urbino et al. 2021). Information on HRQoL is thus of interest in the context of the target population for ivosidenib.

In the main publications reporting the primary pivotal study results of the recent products approved in first-line AML for patients non-eligible for intensive chemotherapy, only the one from ivosidenib (Montesinos et al., 2022) reported some improvement in HRQoL (exploratory endpoint). For venetoclax it has been reported that "*No differences were observed between the two treatment groups with respect to quality-of-life measures*" (DiNardo et al., 2020). Evidence on HRQoL has not been reported for glasdegib (Heuser et al., 2021).

The sponsor reviewed the QoL instruments used in the AGILE study (EORTC QLQ-C30 and the EQ-5D-5L) and referred to a publication which defines a threshold of at least 10 points difference in the C30 score as a clinically meaningful change (Osoba et al., 1998). Overall, most curves separated only occasionally and the change from baseline is at most moderate. Of note, no numbers at risk were provided for the subdomains and the confidence intervals tend to broaden notably.

In addition to assessing the impact of treatment on HRQoL using the EORTC questionnaire, the EQ-5D-5L questionnaire (including a visualised analogue scale [VAS]) was utilized in the AGILE study. A difference from baseline of at least 7 points is considered clinically meaningful according to published literature (the VAS rates up to 100). An improvement of more than 7 was observed in the ivosidenib arm at most visits from cycle 5 onwards (excluding C11), while in the placebo-arm, results fluctuated more and included clinically meaningful deterioration on two occasions and only one clinically meaningful improvement at cycle 11 (C11).

COMP discussion

The sponsor has provided additional data to further substantiate the claim of significant benefit for ivosidenib in patients with newly diagnosed AML as requested. The arguments for performing an indirect comparison between ivosidenib, as studied in a molecularly selected population, with venetoclax and glasdegib, studied in molecularly unselected populations, were acceptable to the COMP, given that the prognostic effect of IDH1 status is not yet fully clear. Furthermore, the COMP considered that the number of patients carrying mutations in IDH1 from VIALE was too small to yield reliable results, in view of a heterogeneous disease such as AML.

The COMP took particular note of the updated median OS analyses using data with longer follow-up from both AGILE and VIALE-A. The updated results of this indirect comparison indicated a prolonged survival benefit of ivosidenib versus venetoclax with a median OS of 29.3 months (95% CI: 13.2, NE) versus 14.7 months (95% CI: 11.9, 18.7), respectively, using the broader ITT population of VIALE-A. The COMP considered it unlikely that such a notable numerical difference in median OS could solely relate to the differences in baseline characteristics across the studies. The similar outcomes of the azacitidine control arms in both trials was considered reassuring in this regard (7.9 months for AGILE and 9.6 months in VIALE-A). Moreover, the consistency between the NMA and MAICs on HR of OS supports a minor impact of the differences in population characteristics between the studies on the estimates of the relative treatment effect. Although the consistency of the indirect comparisons is reassuring, the COMP also noted that the wide confidence intervals still highlight an uncertainty associated with the indirect comparisons presented. The sponsor clarified that the minimum total sample size needed to reach the required standard error would be about 330 patients, i.e., more than double of the total sample size in AGILE. The committee also noted that the AGILE study was stopped when 146 patients were included, following the recommendation of the independent data monitoring

committee (IDMC) for ethical reasons due to a major difference in the number of deaths between the two treatment arms.

With regards to the comparative results on EFS, the COMP noted that in the setting of patients not being eligible for standard induction chemotherapy, the value of EFS as an outcome measure is still controversial, therefore the reasoning of the sponsor with respect to EFS is not followed and emphasis is therefore rather put on the OS results. A MAIC comparing the treatment effect of ivosidenib versus glasdegib was not performed. The COMP agreed with the sponsor that glasdegib can be removed from the NMA and the SUCRA ranking and that it is better to base the clinically relevant advantage of glasdegib on the large difference in the OS outcome of patients (more than tripling of the median OS) and the major differences in study populations (secondary AML, LDAC as combination partner).

The sponsor has provided some updated data and additional clarifications to further substantiate the claim of a major contribution to patient care for ivosidenib over venetoclax. These data were overall not considered robust enough to allow a positive conclusion on the grounds of a major contribution to patient care as they were not statistically significant, had methodological shortcomings (only the ivosidenib arm was compared to a null effect) and were exploratory in nature. However, they can be considered generally supportive of the observed clinical benefit of ivosidenib in the target patient population.

COMP conclusion

Considering the totality of the data, the COMP concluded that Tibsovo offers a significant benefit over the satisfactory methods of treatment in AML. The sponsor has provided clinical data demonstrating improved efficacy over the HMAs azacitidine and decitabine, and has conducted indirect comparisons to venetoclax and glasdegib indicating a prolonged OS in newly diagnosed patients with AML unfit for standard induction chemotherapy who were treated with Tibsovo. The COMP considered that this constituted a clinically relevant advantage.

2.4. COMP position adopted on date

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product;
- the prevalence of acute myeloid leukaemia (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 1.1 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to the consequences of bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections. The condition progresses rapidly and is fatal within 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 Tibsovo may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor has provided clinical data demonstrating improved efficacy over the hypomethylating agents azacitidine and decitabine, and has conducted indirect comparisons to venetoclax and glasdegib indicating a prolonged overall survival in newly diagnosed patients with acute myeloid leukaemia who were treated with Tibsovo. 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 Tibsovo, ivosidenib for treatment of acute myeloid leukaemia (EU/3/16/1802) is not removed from the Community Register of Orphan Medicinal Products.

3. Tibsovo for treatment of biliary tract cancer - EU/3/18/1994 (EMA/OD/0000115500)

3.1. Product and administrative information

Product	
Designated active substance(s)	Ivosidenib
Other name(s)	--
International Non-Proprietary Name	Ivosidenib
Tradename	Tibsovo
Orphan condition	Treatment of biliary tract cancer
Sponsor's details:	Les Laboratoires Servier 50 Rue Carnot 92284 Suresnes Cedex France
Orphan medicinal product designation procedural history	
Sponsor/applicant	QRC Consultants Ltd
COMP opinion	15 February 2018
EC decision	21 March 2018
EC registration number	EU/3/18/1994
Post-designation procedural history	
Transfer of sponsorship	Transfer from QRC Consultants Ltd, United Kingdom to Quality Regulatory Clinical Ireland Limited, Ireland – EC decision of 13 August 2018 Transfer from Quality Regulatory Clinical Ireland Limited, Ireland, to Agios Netherlands B.V., Netherlands – EC decision of 14 December 2020 Transfer from Agios Netherlands B.V., Netherlands, to Les Laboratoires Servier, France – EC decision of 1 June 2021
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Alexandre Moreau / Blanca Garcia-Ochoa
Applicant	Les Laboratoires Servier
Application submission	3 March 2022
Procedure start	24 March 2022
Procedure number	EMA/H/C/005936
Invented name	Tibsovo
Proposed therapeutic indication	Tibsovo monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who were previously treated by at least one prior line of systemic therapy
CHMP opinion	23 February 2023

COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Frauke Naumann-Winter / Maria Elisabeth Kalland
Sponsor's report submission	3 November 2022
COMP discussion	14-16 February 2023
COMP opinion (adoption via written procedure)	27 February 2023

3.2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2018 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 ivosidenib was considered justified based on preliminary clinical observations in relapsed/refractory patients, who responded to treatment with the product as a monotherapy;
- the condition is life-threatening and chronically debilitating due to the development of liver insufficiency, cholestasis, cholangitis, weight loss and cachexia. Patients with unresectable tumours die between 6 and 12 months following diagnosis. Death usually occurs from liver failure or infectious complications accompanying the progressive biliary obstruction;
- the condition was estimated to be affecting approximately 1.3 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.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

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 ivosidenib as an orphan medicinal product for the orphan indication: treatment of biliary tract cancer.

3.3. 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

Biliary tract cancer (BTC) is a heterogeneous group of invasive carcinomas arising in the bile duct epithelium (cholangiocytes), the gallbladder and the ampulla of Vater. BTC includes gallbladder cancer

(GBC), cholangiocarcinoma (CCA) and ampullary carcinoma (AC). CCAs, also known as bile duct cancer, comprises all tumours arising from bile duct epithelium where the majority (over 90%) are adenocarcinomas. The classification of CCAs is further divided anatomically as intrahepatic CCA (iCCA) and extrahepatic CCA (eCCA; perihilar- or distal CCA). GBC is classified as extrahepatic biliary cancer and is the most common malignancy of the biliary tract accounting for 80-95% of BTCs.

Biliary tract cancer remains a serious life-threatening disease with limited treatment options. Biliary tract cancers have a poor prognosis, with an estimated 5-year OS rate across all disease stages of <20% (Lamarca et al., 2021). Patients often present with advanced and incurable disease, with up to 90% of patients being ineligible for potentially curative surgical resection at diagnosis (Nathan et al., 2007; Cidon, 2016). Common presentation includes symptoms related to biliary tract obstruction including jaundice, abdominal pain, weight loss, fever, fatigue, and abnormal liver function tests and can swiftly become life-threatening (Lamarca et al., 2021).

In the advanced, non-resectable or metastatic CCA setting, which includes the proposed target population for ivosidenib, the disease is incurable and palliative chemotherapy is the primary treatment option. In this setting, the 5-year survival rates associated with CCA are around 10% and even less for patients with distant metastases (ACS 2021). IDH1 mutations occur globally in approximately 13% of intrahepatic cholangiocarcinomas and approximately 1% of extrahepatic cholangiocarcinomas (Boscoe et al, 2019). Based on the majority of available literature, IDH1 mutations do not have a prognostic impact on clinical outcomes (Boscoe et al, 2019; Goyal et al, 2015).

The active substance in the medicinal product ivosidenib is a small molecule inhibitor of the mutant IDH1 enzyme. Mutant IDH1 converts alpha- ketoglutarate (α-KG) to 2-hydroxyglutarate (2-HG) which blocks cellular differentiation and promotes tumorigenesis in both, hematologic - and non-hematologic malignancies (Dang et al, 2009; Figueroa et al, 2010). The product is intended for oral administration (film-coated tablet).

The approved therapeutic indication is:

> *"Tibsovo monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who were previously treated by at least one prior line of systemic therapy".*

The authorised therapeutic indication falls within the scope of the designated orphan condition "Treatment of biliary tract cancer".

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 disease is often advanced and incurable at the time of diagnosis. Common presentation includes symptoms related to biliary tract obstruction including jaundice, abdominal pain, weight loss, fever, fatigue, and abnormal liver function tests.

BTC is difficult to treat primarily because it is generally diagnosed at an advanced stage (Blechacz et al., 2008; Bridgewater et al., 2014; Valle et al., 2017), a point at which the tumour obstructs the bile ducts or has spread to other organs. Patients with unresectable tumours die between 6-12 months following diagnosis. Death usually occurs from liver failure or infectious complications accompanying the progressive biliary obstruction.

There has been no change in the chronically debilitating and/or life-threatening nature of the condition since the initial orphan designation was granted in 2018.

The COMP considers the condition to be chronically debilitating due to development of hepatic insufficiency, progressive biliary obstruction followed by complications such as infections, and life-threatening with a low overall median survival of less than two year following diagnosis.

Number of people affected or at risk

The sponsor proposes a prevalence estimate of 1.34 per 10,000 persons in the European community.

The proposed estimate is mainly based on incidence data from the European Cancer Information System (ECIS) and survival rates from the German Centre for Cancer Registry Data (ZfKD). ECIS is a Europe-wide data repository using the aggregated output and the results computed from data submitted by population-based European cancer registries. As regards the ZfKD, in Germany, a legal requirement exists to report all diagnoses and cancer related deaths to the registries, ensuring high quality and completeness of the data set covering the entire German population, which accounts for a substantial portion (approx. 18%) of the entire EU population.

Since most cancer registries/publications do not report incidence or prevalence of BTC as a whole but rather only of the different subtypes, the calculation of the overall incidence and prevalence was based on a consolidated approach from different datasets.

The incidence figures for CCA, GBC and AC are presented in Table 1. These data are based on newly diagnosed cases in 2020 in the 27 EU member states (EU-27) plus Norway (NO) and Iceland (IS), as reported in ECIS 2022 and represent the latest reported incidence figures for these cancers in this database. Of note, ECIS reports separate incidence data for GBC, but no figures for CCA are reported. The sponsor noted that approximately 10% of all liver cancer cases are iCCA (Khan et al., 2019), whereas eCCA accounts for approximately 70% of all CCA cases. The latter is based on available data which have reported that eCCA accounts for approximately 70-90% of all CCAs (Khan et al, 2019; Valle et al, 2016; von Hahn et al, 2011; Sarcognato et al, 2021). The incidence of CCA was therefore calculated based on the crude incidence rates of liver cancer reported by ECIS of 1.354 per 10,000 people for the EU-27 plus NO and IS in 2020. In addition, available literature indicated that AC represents approximately 7% of all cases of BTC.

In 2020, the combined population of EU-27 plus Norway and Iceland was 453,216,945 persons (Eurostat, 2022). Based on 2020 ECIS data and assumptions made, as outlined above, the total number of newly diagnosed BTC cases in the EU-27 plus NO and IS was 30,398. This corresponds to a BTC crude incidence rate of 0.67/10,000.

Table 14. Incidence of AC and BTC based on 2020 ECIS data (EU-27 plus NO and IS)

	CCA [cases]	**GBC [cases]**	**AC* [cases]**	**BTC Total§ [cases]**
Incidence [cases]	20,454	7,816	2,128	30,398
Incidence rate per 10,000 persons in EU-27 plus NO and IS	0.45	0.17	0.05	0.67

Abbreviations: AC=ampullary carcinoma; CCA=cholangiocarcinoma; GBC=gallbladder cancer. * Data deduced from incidence for CCA and GBC (=[CCA+GBC]/93 X 7). § = CCA + GBC + AC

Prevalence of biliary tract cancer in the EEA

For the purpose of this application, the calculation of disease duration is based on 10-year survival data from the ZfKD, as this source reports the survival rates in yearly increments (Table 2).

Table 15. Survival rates (5) GBC and biliary tract cancer

Year after diagnosis	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Male (% survivor)	39	24	19	16	14	14	13	12	12	11
Female (% survivor)	48	31	23	19	17	15	14	13	11	11

Source: German Centre for Cancer Registry Data, 2022 (ZfDK)

One year after diagnosis, less than half of the patients (39% for males, 48% for females) are still alive. Only about 20 % for the patients (19% of males, 23% for females) survive until 3 years after diagnosis, and after 5 years, only 14% of male- and 17% of female patients are still alive. After more than 5 years, the survival rate is rather stable, indicating that about 10% of patients have been permanently cured. In recent literature, similar survival rates are reported for populations in Belgium (Gilliaux et al, 2021), Finland (Koppatz et al, 2021) and Sweden (Strijker et al, 2019).

Based on these data, an average survival time and disease duration of 2 years is assumed for the purpose of the prevalence calculation, resulting in the following prevalence calculation:

$$P = (0.67/10{,}000) \times 2 = 1.34/10{,}000$$

The point prevalence of BTC in the EEA (EU-27 plus Norway, Iceland, Liechtenstein) is estimated as 1.34/10,000. For a total population of 452,669,629 in the EEA in 2022, this corresponds to 60,658 BTC patients in the EEA today.

Over the last 2 years, the COMP accepted prevalence estimates for this condition that were similar, though slightly higher than the sponsors proposal of 1.34 per 10,000 persons. Differences in the prevalence calculations include the previous consideration of additional databases (besides ECIS) for deriving incidence values for BTC in the EU, such as Nordic Cancer Registry (NORDCAN). Furthermore, different ratios of iCCA cases among all cases of liver cancer have been reported in the more recent available literature. In newer orphan designations, it has been concluded that iCCA accounts for around 15% and up to 26% of all primary liver tumors based on reported percentages according to the literature (Banales et al., 2020: 15%, ZfKD, 2018: 26%). As regards the value for mean disease duration between 1.5 and 2 years were considered acceptable to the COMP previously.

Considering the above, the COMP considered that a slightly up-rounded prevalence estimate of approximately 1.5 per 10,000 persons in the European community is acceptable.

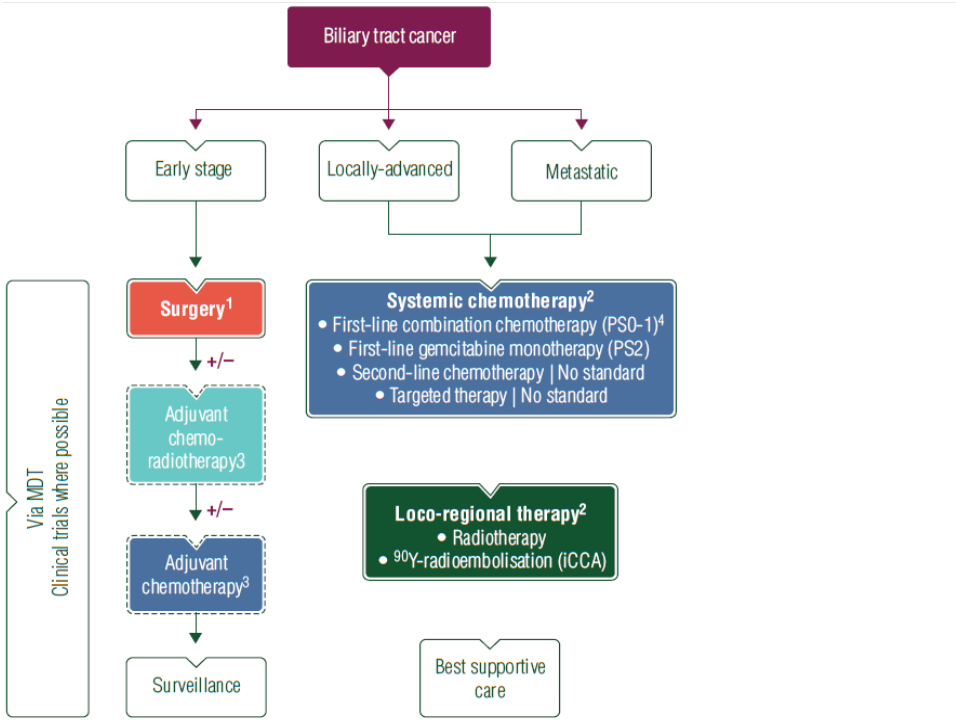
Article 3(1)(b) of Regulation (EC) No 141/2000

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 only authorized medicinal product for the treatment for CCA in the EU is Pemazyre (pemigatinib). This product is however only authorised for a genetically defined subpopulation of patients with locally advanced or metastatic CCA with an FGFR2 fusion or rearrangement that progressed after at least one prior line of systemic therapy (Pemazyre (pemigatinib) tablets SmPC, 2022). FGFR2 alterations occur in only 10% to 15 % of the CCA population and rarely co-occur with IDH1 mutations (co-occurrence in approximately 2% to 5% of patients) (Battaglin et al, 2020; Jain et al, 2018; Valle et al, 2017; Saborowski et al, 2020). Therefore, the vast majority of patients with mutated IDH1 CCA do not have an authorised therapeutic option available in the EU. Even considering treatments used off-label, there is no satisfactory treatment for patients with previously-treated locally advanced or metastatic disease (Valle et al., 2016). Generally, treatment decisions are made according to the algorithm as shown in Figure 1 below.

Figure 6. Algorithm for the management of patients with biliary tract cancer



[1] Special considerations:
- Need for pre-operative biliary drainage
- Avoid percutaneous biopsy in resectable disease
- Assess Future Liver Remnant
- Assess need for Portal Vein Embolisation
- Neoadjuvant approach (selected cases)
- Completion surgery for incidental gallbladder cancer of T-stage T1b and above

[2] Option of salvage surgery should be considered in responding patients with initially inoperable disease
[3] Level of recommendation IV,C
[4] Cisplatin and gemcitabine [category IA], other gemcitabine-based combination [category IIB]

MDT, multidisciplinary team; PS, performance status; iCCA, intrahepatic CCA.
Source: Valle et al., 2016

In conclusion, the COMP considered that the authorized medicinal product Pemazyre (pemigatinib) is not considered to be a satisfactory method, for the purpose of this orphan designation review. The pre-requisite for a satisfactory method is the existence of a full overlap of the therapeutic indication and patient populations between the candidate and the authorised medicinal product. The sponsor's product Tibsovo is intended to treat adult patients with locally advanced or metastatic CCA with an IDH1 R132 mutation who were previously treated by at least one prior line of systemic therapy. Since the overlap between the therapeutic indications for the target patient populations of Pemazyre and Tibsovo is expected to be ≤5% of the whole CCA population, most patients with IDH1-mutated CCA do not have an authorised therapeutic option available in the EU. Thus, the proposed indication for Tibsovo targets a different genetically defined subgroup of patients than the one of the approved product Pemazyre.

In conclusion, there is no approved treatment that qualifies as a satisfactory method of treatment for the purpose of examining the significant benefit compared to Tibsovo, as the only authorised treatment option currently available does not cover the entire patient population for which Tibsovo is intended.

Significant benefit

Tibsovo is intended for a patient population for whom no other satisfactory method is available (see the section about *Existing methods* above for more information). No justification for significant benefit is therefore required.

3.4. COMP position adopted on 27 February 2023

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 biliary tract cancer (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 1.5 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to development of hepatic insufficiency, progressive biliary obstruction followed by complications such as infections, and life-threatening with a low overall survival;
- at present no satisfactory method has been authorised in the European Union for the treatment of the entirety of patients covered by the therapeutic indication of Tibsovo.

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 Tibsovo, ivosidenib for treatment of biliary tract cancer (EU/3/18/1994) is not removed from the Community Register of Orphan Medicinal Products.