EU RISK MANAGEMENT PLAN
for
TIBSOVO (Ivosidenib)

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QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
2-HG	2 hydroxyglutarate
ADR	Adverse Drug Reaction
AE(s)	Adverse Event(s)
AIDS	Acquired Immunodeficiency Syndrome
AML	Acute Myeloid Leukaemia
APL	Acute Promyelocytic Leukaemia
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BP	Blood Pressure
CCA	Cholangiocarcinoma
CHF	Congestive Heart Failure
CI	Confidence Interval
CNS	Central Nervous System
CR	Complete Remission
CRi	Complete remission with incomplete haematologic recovery
CYP	Cytochrome
dCCA	Distal CCA
DLP	Data Lock Point
DLT	Dose-Limiting Toxicity
eCCA	Extrahepatic CCA
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
eGFR	estimated Glomerular Filtration Rate
ELN	European Leukaemia Net
EPAR	European Public Assessment Report
ESMO	European Society for Medical Oncology
EU	European Union
FDA	Food and Drug Administration
FGFR	Fibroblast Growth Factor Receptor
FSFV	First Subject First Visit
GI	Gastrointestinal

Abbreviation	Definition
GLP	Good Laboratory Practice
HBV	Hepatitis B
HCC	Hepatocellular Carcinoma
HCP	Healthcare Professionals
HCV	Hepatitis C
hERG	Human Ether-à-go-go Related Gene
HIV	Human Immunodeficiency Virus
HMA	Hypomethylating Agents
IAT	Intra-Arterial Therapy
ICB	Immune Checkpoint Blockade
iCCA	Intrahepatic CCA
IC	Induction chemotherapy
ICH	International Council for Harmonisation
IDH1	Isocitrate Dehydrogenase-1
IKr	Rapidly activating delayed rectifier potassium current
INN	International Nonproprietary Name
IV	Intravenous
LDAC	Low-dose cytarabine
LSLV	Last Subject Last Visit
LVEF	Left Ventricle Ejection Fraction
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NOAEL	No Observed Adverse Effect Level
ODWG	Organ Dysfunction Working Group
OS	Overall Survival
PAC	Patient Alert Card
pCCA	Perihilar CCA
PD	Pharmacodynamic
PFS	Progression-Free Survival
PK	Pharmacokinetic
PL	Package Leaflet

Abbreviation	Definition
PML	Progressive Multifocal Leukoencephalopathy
PRAC	Pharmacovigilance Risk Assessment Committee
PSC	Primary Sclerosing Cholangitis
QD	Once Daily
QTc	Heart rate corrected QT
RMP	Risk Management Plan
R/R	Relapsed or refractory
SAEs	Serious Adverse Events
SCT	Stem Cell Transplantation
SIRT	Selective Internal Radiation Therapy
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA query
TACE	Trans-Arterial Chemoembolisation
TEAE	Treatment Emergent Averse Events
UC	Ulcerative Colitis
UK	United Kingdom
ULN	Upper Limit Of Normal
US	United States
WBC	White Blood Count/Cell
WHO	World Health Organization
α-KG	Alpha Ketoglutarate

PART I: PRODUCT(S) OVERVIEW

Table 1: Part I: Product Overview

Active substance (INN or common name)	Ivosidenib
Pharmacotherapeutic group (ATC Code)	Antineoplastic agents; other antineoplastic agents (L01XX62)
Marketing Authorisation Applicant	Les Laboratoires Servier
Medicinal products to which this RMP refers	One
Invented name in the European Economic Area (EEA)	Tibsovo
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class**: inhibitor of mutated isocitrate dehydrogenase-1 (IDH1).
	Summary of mode of action: Ivosidenib is a small molecule inhibitor of the mutant IDH1 enzyme. Mutant IDH1 converts alpha-ketoglutarate (α-KG) to 2-hydroxyglutarate (2-HG) which impairs myeloid differentiation, increases proliferation of myeloblasts, and blocks cellular differentiation.
	Important information about its composition: Each film-coated tablet contains: 250 mg of ivosidenib. Excipient with known effect: Each film-coated tablet contains lactose monohydrate equivalent to 9.5 mg lactose.
Hyperlink to the Product Information	Module 1.3.1 Product Information
Indications in the EEA	Current: **Acute Myeloid Leukaemia** Ivosidenib in combination with azacitidine is indicated for the treatment of adult patients with newly diagnosed Acute Myeloid Leukaemia (AML) with an IDH1 R132 mutation who are not eligible to receive standard induction chemotherapy. **Cholangiocarcinoma** Ivosidenib 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.

Dosage in the EEA	Current: The recommended dose is 500 mg ivosidenib (2 x 250 mg tablets) taken orally once daily at about the same time each day.
Pharmaceutical form and strength	Current: Film-coated tablet 250 mg.
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATIONS AND TARGET POPULATIONS

Indication-Acute Myeloid Leukaemia

Ivosidenib 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.

Incidence and Prevalence

Acute myeloid leukaemia is a malignant disorder of haemopoietic stem cells characterised by clonal expansion of abnormally differentiated blasts of myeloid lineage (Short et al, 2018). AML is a rare disease overall, accounting for only about 1% of all cancers (ACS, 2021). AML makes up 31% of all adult leukaemia cases (Cancer.Net, 2021).

Hughes 2017 estimates an EU AML incidence of 4.0/100,000. Two systematic literature reviews by Lubeck et al, 2016 and Panjabi et al, 2019 report the incidence rate between 1.63 – 7.9/100,000 individuals in Europe. Data collection methods, evaluation and collection periods were not consistent between the two papers. Heuser et al, 2020 reports an incidence of 5.06/100,000 in Europe in the ESMO Clinical Practice Guidelines for AML. However, these data are based on a 2013 representative population (~4 million) of the UK described by Roman et al, 2016. National incidence was also reported in several publications ranging from 2.79 - 4.79/100,000 (Nagel et al, 2017; Zatloukalová et al, 2021; AIRTUM, 2015; Dinmohamed et al, 2016). The Surveillance of Rare Cancers in Europe (RARECARE, 2013) was a project based on patients diagnosed from 2000-2007 and predicting incidence in 2013. This was based on data from 94 European population-based registries. This estimated a crude incidence rate of 3.5/100,000. One of the higher incidence rates for AML reported for Europe estimates 6.2 cases per 100.000 (NORDCAN, 2021).

NORDCAN describes a mean prevalence of 18.1 in 100,000 in 2019 (ie, 1.81 in 10,000) equating to 81,530 persons in a European population of 452,948,552 (EEA [EU27 plus Norway, Iceland and Liechtenstein]) (NORDCAN, 2021; Eurostat, 2020).

The overall frequency of IDH1 mutations in AML is approximately 6% to 10% (Bullinger et al, 2017). The age-adjusted incidence rate of AML with IDH1 mutation is <1 per 100,000 individuals per year (Marcucci et al, 2010; Mardis et al, 2009; NCI, 2018); patients having AML with IDH-mutations are a subset of patients with AML, which is a rare disease.

Demographics of the population in the proposed indication - age, gender, racial and/or ethnic origin

Acute myeloid leukaemia is primarily a disease of older adults. The average age of people when they are first diagnosed with AML is about 68 (ACS, 2021). As per European cancer registries from 1995 to 2002, the incidence of AML gradually increases with age, with an incidence rate per 100,000 of 0.7 for the age group of 0-14 years, 0.8 for the group of 15-24 years, 2.4 for the group of 25-64 years, and 13.7 for the oldest age group (65 years or older) (Visser et al, 2012). In the UK, Canada, Australia, and Sweden, the reported median age at AML diagnosis ranges from 63 to 71 years. However, in India, Brazil, and Algeria, the median age at AML diagnosis was 40, 42, and 45 years, respectively, which may be attributable to these countries' overall younger populations or differences in reporting methods which might make the diagnosis of older patients with AML less likely (Shallis et al, 2019). The absolute number of patients with AML is anticipated to increase substantially over the next several decades due to the advancing age of the population.

AML is slightly more common among men than women, but the average lifetime risk of developing AML in both sexes is about one half of 1% (ACS, 2021). European cancer registries from 1995 to 2002 show crude incidence rates of AML to be elevated in males (4.0 per 100,000) compared with females (3.4 per 100,000) (Visser et al, 2012).

Race and ethnicity do not appear to influence disease status to a significant degree with the number of new cases of AML per 100,000 in males and females respectively reported as White (5.4 and 3.7), Black (4.4 and 3.3), Asian /Pacific Islander (4.2 and 2.9), American Indian /Alaska Native (3.2 and 2.1), Hispanic (4.1 and 3.2), Non-Hispanic (5.3 and 3.6) and all races (5.2 and 3.6) (NCI, 2021).

The demographics of patients with AML that harbour an IDH1 mutation are less well known but demographics can be derived from studies that have evaluated this patient population. A study defining the natural history and prognosis of patients with AML and IDH1 or IDH2 mutations found that 20% of 826 AML patients treated from 2010 to 2014 at a single institution in the US had IDH1 (n=59) or IDH2 (n=106) mutations (DiNardo et al, 2015). In this study it was concluded that patients with IDH1 mutation have distinctive clinicopathologic characteristics including older age, increased incidence of FLT3-ITD and NPM1 mutations, intermediate-risk cytogenetics, higher platelet count, and increased bone marrow blast percentage at diagnosis (DiNardo et al, 2015).

Risk factors for the disease

The risk factors for AML are well characterised and include advancing age, male gender, family history (having a first degree relative with AML increases the risk of getting the disease), exposure to benzene, formaldehyde and cigarette smoke, exposure to ionizing radiation, exposure to cytotoxic and/or immunosuppressive agents, alkylating agents (cyclophosphamide, mechlorethamine, procarbazine, chlorambucil, melphalan, busulfan, carmustine, cisplatin, and carboplatin), topoisomerase II inhibitors (etoposide, teniposide, mitoxantrone, epirubicin, and doxorubicin), blood disorders including myelodysplastic syndrome, polycythaemia vera, essential thrombocytosis, and idiopathic myelofibrosis, genetic disorders such as Fanconi anaemia, Bloom syndrome, ataxia-telangiectasia, Diamond-Blackfan anaemia, Shwachman-Diamond syndrome, Li-Fraumeni syndrome, neurofibromatosis type 1, severe congenital neutropenia (Kostmann syndrome), and Down's syndrome and Trisomy 8 (ACS, 2021; Godley and Larson, 2008).

The main existing treatment options

The standard treatment strategy for otherwise fit AML patients includes intensive induction chemotherapy (IC) or less intensive chemotherapy, followed either by post-remission haematopoietic Stem Cell Transplantation (SCT) or consolidation chemotherapy. The initial treatment decisions for newly diagnosed AML are based on patient age, history of prior Myelodysplastic Syndrome (MDS), prior genotoxic therapy, Eastern Cooperative Oncology Group (ECOG) performance status, and presence of serious comorbidities (Heuser et al, 2020).

People with AML have very high numbers of leukaemia cells in their blood when they are first diagnosed, which can cause problems with normal blood circulation. This is called leukostasis (leukapheresis might be used before chemo) (ACS, 2021). In patients with non-Acute Promyelocytic Leukaemia (APL) AML with a white blood count (WBC) >100x10^9/L and signs of leukostasis, the requirement for cytoreduction should be considered. This is achieved with 50-60 mg/kg hydroxycarbamide per day, or, if a patient cannot swallow, either

with intravenous (IV) or subcutaneous cytarabine, or with IV daunorubicin (Heuser et al, 2020).

Approximately 35% to 40% of newly diagnosed AML patients <60 years old with favourable prognostic factors can be cured with intensive induction chemotherapy and, where applicable, haematopoietic SCT (NCCN, 2021; Döhner et al, 2015; Juliusson et al 2009; Juliusson et al 2012). Among individuals >60 years old, the cure rate is only 5% to 15% (Kantarjian et al, 2010; Medeiros et al 2015, and Oran et al, 2012). Population-based epidemiological studies in the US indicated that approximately 60% of patients with newly diagnosed AML who were over age 65 years remained untreated and had a median survival of approximately 2 months (Oran et al, 2012).

Intensive Regimens

In younger patients, such as those under 60 years, induction often involves treatment with 2 chemo drugs cytarabine (Ara-C) and an anthracycline drug such as daunorubicin (daunomycin) or idarubicin. This is sometimes called a 7 + 3 regimen, because it consists of receiving cytarabine continuously for 7 days, along with short infusions of an anthracycline on each of the first 3 days. A third drug (midostaurin, gemtuzumab ozogamicin, or cladribine) might be added to improve the chances of remission (ACS, 2021). These therapies are associated with significant toxicity. Although the mortality rates associated with IC have improved over time, they remain substantial, particularly in older adults and patients with diminished performance status, elevated white blood cell (WBC) count, and thrombocytopenia (Othus et al, 2014).

Non-intensive Regimens

For patients who are not candidates for intensive therapies due to advanced age, history of prior MDS, prior genotoxic therapy, poor ECOG performance status or presence of serious comorbidities, the National Comprehensive Cancer Network (NCCN) guidelines recommend non-intensive therapies such as hypomethylating agents (HMAs), low-dose cytarabine (LDAC), gemtuzumab ozogamicin, glasdegib + LDAC, enasidenib, venetoclax based regimens, or best supportive care (hydroxyurea, transfusions) (NCCN, 2021).

While the treatment options in the first line setting have recently expanded, the HMAs azacitidine and decitabine are still considered options for patients who are not candidates for intensive chemotherapy. Complete remission rates associated with these therapies are low (approximately 10%-20%), and median Overall Survival (OS) ranges from 2 to 10 months (Dombret et al, 2015; Kantarjian et al, 2012). An open-label Phase 3 trial evaluating outcomes in patients with newly diagnosed AML randomised to azacitidine versus conventional care regimens (Dombret et al, 2015) demonstrated that patients who were randomised to receive azacitidine, experienced a Complete Remission (CR) + Complete remission with incomplete haematologic recovery (CRi) rate of 27.8% and a CR rate of 19.5%. The duration of CR + CRi was 10.4 months (range 7.2 to 15.2 months). The median overall survival among patients treated with azacitidine was 10.4 months (95% Confidence Interval (CI) 8.0 to 12.7 months). A retrospective trial describing 107 older patients treated with azacitidine reported a CR + CRi rate of 20%, with CR rate of 11% (Dumas et al, 2017) and a median OS of 10.8 months (inter-quartile range: 4.8 to 26.4). The 30-day and 60-day mortality rates in the azacitidine arm were 6.6% and 16.2%, respectively.

Recently, venetoclax in combination with HMA and glasdegib in combination with LDAC have been approved by the European Medicines Agency (19 May 2021 (venetoclax) and 26 June 2020 (glasdegib)) respectively for adult patients with newly diagnosed AML who were

not eligible for intensive chemotherapy. These regimens displayed superior survival outcomes to HMA and LDAC alone. As per the European Society for Medical Oncology (ESMO) guidelines, patients should be treated for at least 4 cycles and, in case of clinical benefit, should continue until progression or intolerance. Patients responding to initial treatment should be re-evaluated regarding their ability to undergo alloHCT using reduced-intensity conditioning, which may cure a proportion of these patients. The combination of venetoclax plus azacitidine versus azacitidine yielded a CR rate of 36.7% versus 17.9% and a median OS of 14.7 versus 9.6 months, respectively (DiNardo et al, 2020). Despite these recent approvals, there are no molecularly targeted combination therapies approved for patients with newly diagnosed AML with an IDH1 mutation who are not candidates for IC.

Therapeutic options for patients with newly diagnosed AML with an IDH1-mutation

Treatment options for patients with newly diagnosed AML with an IDH1 mutation are the same as those for the general AML population, with no authorised targeted therapies in the EU and no effective standard of care. Patients with AML with an IDH1 mutation represent a rare population with a serious unmet medical need for safe and effective targeted therapies.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Acute myeloid leukaemia is characterised by the presence of ≥20% blasts in bone marrow or peripheral blood (ACS, 2022). These immature precursors, or myeloblasts, accumulate in the bone marrow, peripheral blood, and organs and can result in a wide range of symptoms. The clinical manifestations of AML are attributable to the replacement of normal, functional hematopoietic cells by immature leukemic blasts, causing anaemia, neutropenia, and thrombocytopenia. The most common causes of death are infections and bleeding events.

Acute myeloid leukaemia remains primarily a disease of older adults, with a median age at diagnosis of 67 years AML is fatal without treatment, with a median survival of approximately 2 months if left untreated. Although survival has generally improved since the 1980s, the 5-year relative survival rate remains low, at approximately 15% to 20% in Europe (Kell et al, 2016). The number of AML-related death in males was higher than in females. As for a specific geographical zone, Western Europe, South Asia, and high-income North America zones were the top 3 regions with the most AML-related deaths (Western Europe: 18,220 death cases in 2017) (Yi et al, 2020).Mutations in IDH1 are associated with inferior responses and worse overall survival (OS). Three meta-analyses (Feng et al, 2012; Xu et al, 2017; Zhou et al, 2012) show that the presence of an IDH1 mutation is associated with a worse prognosis compared to wild-type IDH1. The largest and most recent meta-analysis was conducted by Xu et al and included 33 publications encompassing 12,747 AML cases reported across Europe, Asia, Australia, and America. The IDH1 mutation conferred worse OS (P=0.0047) and Event-Free Survival (EFS) (P=0.011), including in patients with normal cytogenetics (OS P=0.039; EFS P=0.0002). In addition, treatment outcome was poorer for patients with an IDH1 mutation than for those without the mutation; complete remission (CR) rates were lower (RR, 1.21; 95% CI, 1.02–1.44, P=0.029) (Xu et al, 2017). In a prospective, randomised Phase 2 clinical study that included patients with newly diagnosed, relapsed, and refractory myeloid malignancies treated with azacitidine, IDH1 mutations were significantly associated with reduced OS in univariable (Hazard Ratio (HR) 1.9; P=0.004) and multivariable (HR 3.6; P=0.001) analyses (Craddock et al, 2017).

Important co-morbidities

As AML is predominantly a disease of the elderly (Visser et al, 2012), patients are more susceptible to treatment complications particularly severe infections than younger patients, with pre-existing medical conditions such as diabetes, coronary heart disease, or chronic pulmonary obstructive disease recognised as contributing to a higher risk of an unfavorable outcome (Fey et al, 2013).

Common pre-treatment co-morbidities of AML include cardiomyopathy, ischaemic heart disease; chronic renal failure, with and without dialysis; hepatitis and cirrhosis; chronic pulmonary insufficiency; cerebral vascular disease; infections; haemorrhages; electrolyte abnormalities and sepsis (Kantarjian et al, 2012; Ofran et al, 2016; Ravandi et al, 2015; Roboz et al, 2014).

Another co-morbidity of AML is tumour lysis syndrome, a group of metabolic abnormalities that result from the rapid release of nucleic acids, proteins, phosphorus and potassium from lysed malignant cells that can potentially cause hyperuricaemia, hyperkalaemia, hyperphosphataemia, with or without hypocalcaemia and uraemia that can lead to renal failure, arrhythmias, seizures and even death (Cairo et al, 2010). These abnormalities may occur spontaneously before the initiation of chemotherapy due to increased catabolism and the turn-over of leukaemia cells but more frequently tumour lysis syndrome is induced by IC (Montesinos et al, 2008).

Indication-Cholangiocarcinoma

Ivosidenib 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.

Incidence and Prevalence

Cholangiocarcinoma (CCA), also known as bile duct cancer, is a diverse group of malignancies arising from the biliary epithelium. CCA is a highly aggressive rare tumour. CCA accounts for approximately 3% of gastrointestinal (GI) malignancies and 10-15% of all hepatobiliary malignancies (Orphanet 2020). CCA has an overall global incidence of 0.3–6/100,000 (Banales et al, 2020). The biliary tree varies in size and morphology. CCA is classified based on anatomical location as intrahepatic, perihilar and distal (Kendall et al, 2019), perihilar and distal being two extrahepatic forms of CCA. Perihilar CCA (pCCA) account for 50%-60% of all CCA, distal CCA (dCCA) 20%-30%; and intrahepatic CCA (iCCA) comprises 10%-20% of all CCA (Banales et al, 2016; Blechacz 2017; Khan et al, 2019). The disease is often advanced and incurable at the time of diagnosis.

In the EU, the incidence of CCA varies across countries from 0.5/100,000 (in Spain) to 3.36/100,000 (in Italy) (Banales et al, 2016). The mean prevalence for CCA is considered to be 1.3/10,000 in the EU (EMA, 2018).

IDH1 mutations occur in up to 13% of iCCA and 1% of extrahepatic CCA (eCCA) (Boscoe et al, 2019). Based on the available literature, IDH1 mutations do not have a prognostic impact on clinical outcomes including Progression-Free Survival (PFS) and OS (Boscoe et al, 2019). Therefore, outcomes in this biomarker-selected population are expected to be comparable to those reported among the general advanced, previously treated CCA population (Boscoe et al, 2019; Goyal et al, 2015).

Southeast Asia has the highest incidence rates of CCA, while Australia has reported the lowest incidence rate. The annual incidence ranges from 0.1/100,000 to 71.3/100,000 within Southeast

Asia, while in the US incidence rates range between 0.6/100,000 to 1.0/100,000 (Khan et al, 2012; Tyson et al, 2014; Witjes et al, 2012; Blechacz 2017).

It has been reported that diagnoses and epidemiological data are not necessarily being recorded uniformly and accurately. Hence, the data may not reflect the true incidence of different types of CCA (Khan et al, 2019).

Epidemiological studies looking at trends in different countries and regions have mostly, but not uniformly, reported a rise in CCA. There are consistent reports of an increasing incidence of iCCA. There was a steady decrease in the incidence of eCCA as per the World Health Organization (WHO) database, from Australian and different European cohorts (Luke et al, 2010; Khan et al, 2019).

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin

Globally, the average age at diagnosis is >50 years (Blechacz 2017). In Western industrialised nations, the median age at presentation is 65 years. CCA is uncommon before the age of 40 years except in patients with Primary Sclerosing Cholangitis (PSC). In most parts of the world, particularly Western countries, the peak age of incidence for CCA is after 70 years-of-age and the disease has a slightly higher incidence in men. Epidemiological studies showed that men have 1.5-fold increased risk of CCA development compared with women (Moazzami et al, 2020; Blechacz 2017; Rizvi et al, 2014; Qureshi et al, 2014). The highest incidence of CCA has been reported in Asians among all ethnic groups and CCA types (iCCA as well as eCCA) (Kirstein and Vogel, 2016). The incidence rates of CCA most likely vary in different geographic regions due to differences in environmental and genetic risk factors (Kirstein and Vogel, 2016).

Risk factors for the disease

CCA encompasses an assorted group of malignancies lacking a stereotyped phenotype and molecular signature. Compelling evidence supports the notion that CCA heterogeneity is the result of a complex interaction between the host-specific genetic background and a different geographical distribution of the risk factors associated with this disease. No predisposing factors are identified in most patients with CCA, although there is evidence that the presence of chronic inflammation, such as PSC, hepatolithiasis, choledochal cysts, and liver fluke infections (*Opisthorchis viverrini* and *Clonorchis sinensis*), might be associated with the disease in some patients (NCCN 2020; Blechacz 2017; Lazaridis and Gores, 2005). Other risk factors for iCCA have been found to include infections with hepatitis C virus and/or hepatitis B virus, obesity, cirrhosis, diabetes, alcohol, nonalcoholic fatty liver disease, tobacco use, biliary enteric drainage procedures, and toxins (dioxins, polyvinyl chloride) (Welzel 2007; Blechacz 2017).

Epidemiological studies suggest that multiple risk factors are involved in cholangiocarcinogenesis, and that some of them are less frequent but associated with a higher risk of CCA, whereas others are more common but associated with a lower risk. The main risk factor for CCA is long-term inflammation of the bile ducts. This may be caused by the same liver disorders that can lead to Hepatocellular Carcinoma (HCC), such as hepatitis and fatty liver disease. Other risk factors include exposure to certain chemicals used in the printing industry or having inflammatory bowel disease (e.g. ulcerative colitis) or liver conditions such as PSC which can cause scar tissue in the bile ducts. (Cancer Council Australia 2020).

The strongest association of CCA in Western populations has been established for PSC, with or without inflammatory bowel diseases, mainly Ulcerative Colitis (UC) (Kirstein and Vogel,

2016). While some risk factors seem to be shared by iCCA and the two extrahepatic forms, others seem more specific for iCCA or eCCAs. This observation is also reinforced by the broad geographic variations in iCCA and eCCA incidence, a phenomenon that suggests a spatial-temporal segregation of the underlying aetiological factors (Kirstein and Vogel, 2016; Khan et al, 2019).

Moreover, despite advancements in the knowledge of CCA aetiology, in Western countries about 50% of cases are still diagnosed without any identifiable risk factor. It is therefore conceivable that other risk factors which are still undefined are responsible for the recent reported increases in CCA (especially iCCA) incidence worldwide. Risk factors may vary depending on the geographical region (Kirstein and Vogel, 2016; Blechacz 2017).

In East Asia, parasite infestation with liver flukes from ingestion of raw, undercooked, or pickled seafood is the most important risk factor for cholangiocarcinogenesis. Other potential risk factors for *O. viverrini*-associated infections are coinfection with *Helicobacter* and diabetes mellitus (Kirstein and Vogel, 2016).

The main existing treatment options

CCA is a serious and life-threatening disease with very limited treatment options and an overall poor prognosis. The only chance for cure is surgical resection, for which only approximately one-third of patients are eligible (Lamarca et al, 2019). The 5-year survival rate for patients with CCA was reported to be less than 10% (Everhart and Ruhl, 2009). For patients who have progressed after first-line treatment, there are even fewer therapeutic options and there remains a significant unmet need for new therapies.Although surgery remains the only curative treatment, chemotherapy can extend survival of patients with CCA. The median survival time is reported to be 3 to 6 months (Li-Ye 2018). For patients with advanced CCA who relapse after first-line therapy, a meta-analysis of available treatments supported a mean OS of 7.2 months with a mean PFS of 3.2 months and mean response rate of 7.7% (Lamarca et al, 2019). Fluoropyrimidine based regimens are most commonly used as the second-line chemotherapy after progression on a gemcitabine-containing regimen (Brieau et al, 2015). Fluorouracil/leucovorin in combination with oxaliplatin (mFOLFOX) is the preferred treatment option in second line setting and this is supported by the prospective randomised control study (ABC-06) comparing mFOLFOX to active symptom control (ASC) with overall response rate of 5% and median survival of 6.2 months (Lamarca et al, 2019).

Systemic chemotherapy has an established, albeit modest, survival benefit. According to the NCCN guidelines, chemotherapy is a recommended treatment option for patients with unresectable iCCA. Several chemotherapeutic drugs may be used to treat bile duct cancer, for example, 5-fluorouracil, gemcitabine, cisplatin, capecitabine and oxaliplatin. The current standard treatment drugs for CCA are 5-fluorouracil, gemcitabine, or their combinations with cisplatin. In certain cases, two or more of these drugs may be combined. However, their treatment efficacy is unsatisfactory with a low clinical response rate (Chujan 2018).

Surgical resection, where possible, is the cornerstone of therapy; is effective in early, completely-resectable stages and also in locally-advanced stages in combination with adjuvant chemotherapy (5-fluoruracil, gemcitabine, oxaliplatin, etc.) or adjuvant radiotherapy (Simile et al, 2019). However, in patients presenting with advanced disease, surgery may not be appropriate (Najran 2017).

Immunotherapeutic strategies such as Immune Checkpoint Blockade (ICB) harness the host immune system to unleash an effective and durable anti-tumour response in a subset of patients

with a variety of malignancies. However, response to ICB monotherapy has been relatively disappointing in CCA.

The use of locoregional therapies in patients with iCCA is becoming more established. Different methods of Intra-Arterial Therapy (IAT) include bland embolisation, Trans-Arterial Chemoembolisation (TACE), the use of drug-eluting beads and radioembolisation (also known as Selective Internal Radiation Therapy (SIRT)) (Cancer Council Australia 2020). Liver IAT is a ubiquitous locoregional therapy used in the treatment of patients with localised HCC, and its use in randomised trials has demonstrated a survival benefit. The use of IAT in CCA is not as well documented; although studies have suggested a survival benefit, this evidence is limited to single-centre or retrospective studies. Additionally, the published studies use variable outcome measures to assess treatment benefit. Therefore, a true comparison of IAT with alternative treatments is limited (Najran 2017). None of these therapies are approved for treatment of CCA in EU.

Pemigatinib, a tyrosine kinase inhibitor of Fibroblast Growth Factor Receptors (FGFRs) 2, received conditional marketing authorisation in the EU for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with a FGFR2 fusion or rearrangement that have progressed after at least one prior line of systemic therapy. FGFR-2 alterations occur in roughly 10%-15% of cholangiocarcinoma and rarely co-occur with IDH1 mutations in cholangiocarcinoma (approximately 2%-5%) (Battaglin et al, 2020; Jain et al, 2018; Valle et al, 2017). There are no targeted therapies authorised in the EU for the treatment of any solid tumour bearing an IDH1 mutation, including cholangiocarcinoma.

Another kinase inhibitor, infigratinib was granted approval by the FDA in the US for the treatment of adults with previously treated, unresectable locally advanced or metastatic CCA with a FGFR2 fusion or other rearrangement (TRUSELTIQ USPI).

Natural history of the indicated condition in the untreated population, including mortality and morbidity

In patients with iCCA, jaundice is the initial symptom only in around 10%-15% of the cases, when biliary obstruction would mainly be related to obstruction of the liver hilum by lymph nodes or migration of detritus and subsequent failure of the correct drainage of the biliary ducts. CCA patients may present with symptoms associated with abdominal pain, malaise, night sweats, asthenia, nausea and weight loss (Forner et al, 2019). Patients with eCCA tend to present with symptoms of obstructive jaundice and sometimes with complications like cholangitis (Ghouri et al, 2015). There is no effective screening for CCA; hence, most patients with CCA are diagnosed at an advanced stage.

With diagnosis at a late stage of disease, CCA prognosis is poor with 5-year survival rates of 20-50% after resection and almost 0% in unresectable tumours (Orphanet 2020). Death is often due to biliary sepsis, cancer cachexia, malnutrition and liver failure.

Approximately, 13% of overall cancer-related mortality is due to hepatobiliary malignancies (Everhart et al, 2009; Tyson and El-Serag 2011; Blechacz 2017; Kirstein and Vogel, 2016; Moazzami et al, 2020). CCA accounts for about 20% of the deaths from hepatobiliary cancers, which cause 13% of the total cancer mortality worldwide. CCA is one of the cancers associated with the highest mortality: although 1-year mortality has improved over time, the 5-year survival is still as low as 10%. The 5-year survival rates associated withintrahepatic and extrahepatic cholangiocarcinoma are poor at 9% and 10%, respectively, and only 2% in patients with distant metastases (ACS, 2021). Survival is generally reported as approximately 6 months

(Brieau et al, 2015; Demols et al, 2020; Kim et al, 2017; Lamarca et al, 2014; Lamarca et al, 2019; Matsuyama et al, 2018; Ying and Chen, 2019).

Epidemiological studies have shown that mortality rates of iCCA are rising, while those of eCCA are falling, globally (Khan et al, 2019). Mortality from iCCA increased by around 9% in both genders from 1990 to 2008, reaching rates of 1.1/100,000 men and 0.75/100,000 women, the highest rates occurring in the UK, Germany and France amongst European countries. Data for Australia was also analysed for comparison, and similar trends were observed (Bragazzi et al, 2011; Khan et al, 2019).

Important co-morbidities

Co-morbidities are known to increase disease mortality and complicate intervention approaches. In the case of CCA, the disease can be a complication of chronic inflammation of the biliary system, or primary sclerosing cholangitis (Suk et al, 2018). Co-morbidities that may be related to CCA include inflammatory bowel disease, obesity, nonalcoholic liver disease, diabetes, and cirrhosis (Suk et al, 2018).

A retrospective analysis of the clinical characteristics of 68 consecutive patients diagnosed with eCCA found that the most common co-morbid conditions in these patients were hypertension (44%), diabetes mellitus (17.6%), chronic obstructive pulmonary disease (16%), coronary heart disease (11.7%), and cerebrovascular disease (8.8%) (Fernández-Ruiz et al, 2009). A history of previous malignancy was identified in 4 of the patients (5.8%).

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Table 2: Part II.1: Key Safety Findings from Non-Clinical Studies and Relevance to Human Usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity	
Single-dose toxicity: A non-GLP single-dose escalation, DRF study of ivosidenib was performed in cynomolgus monkeys (Report AG120-N-040-R1; Module 2.6.7, Section 5). Ivosidenib was well tolerated as a single dose at levels up to 100 mg/kg (calculated AUC_{0-24hr} value 2.5-fold the human AUC_{0-24hr} value) and was tolerated but with gastrointestinal clinical observations at 250 mg/kg (calculated AUC_{0-24hr} value 3.6-fold the human AUC_{0-24hr} value). **Repeat-dose toxicity studies:** Repeat-dose toxicity of ivosidenib was performed on Sprague-Dawley The compound was well tolerated at AUC_{0-24hr} levels that were 0.5- to 1.1-fold (3-month rat) and 2.3-fold (3-month monkey) the C2D1 human AUC_{0-24hr} at the recommended human daily dose of 500 mg/day. In rats, the dosage level of 500 mg/kg/day (highest dosage tested) was tolerated over a 3-month dosing period and did not result in any test article-related moribundity or mortality (Report AG120-N-058-R1; Module 2.6.7, Section 7.B). Target tissues and findings at this dose level in the 3-month rat study included liver and thyroid, and red blood cell parameter alterations and splenic extramedullary haematopoiesis and bone marrow increased haematopoiesis consistent with a red cell regenerative response. Myelostromal proliferation was observed in a single male. Higher urine potassium fractional excretion that correlated with a decreased serum potassium level was also observed. The findings observed in the 3-month rat study are largely consistent with those noted at tolerable doses in the 28-day study (Module 2.6.7, Section 7.A), with the exception of the novel finding of a higher urine potassium fractional excretion. All significant findings at this dose level in both the 28-day and 3-month studies were partially or fully reversible following a 14- and 28-day non-dosing period, respectively. Dose-limiting toxicity (DLT) in the rat occurred at a dosage of 2,000 mg/kg/day in the 28-day study (Report AG120-N-002-R1; Module 2.6.7, Section 7.A). The cause of early DLT (between Days 2 and 6; exposures 3.3- to 3.5-fold the human AUC_{0-24hr}) was centrilobular hepatocellular degeneration and necrosis with additional contributing factors including tubular necrosis in the kidney; cortical and medullary tubular vacuolation in the kidney; atrophy of small intestines; hypocellularity, haemorrhage, and necrosis of the femoral and/or sternal bone marrow; and erosions of the glandular stomach. When DLT occurred later in the dosing period (Days 19 and 20; exposures 1.2- to 1.7-fold the C2D1 human AUC_{0-24hr} at 500 mg/day), it was due to mucosal atrophy of the intestines, erosions and ulcerations of the glandular stomach and/or rectum, and lymphoid depletion and necrosis in lymphoid organs with renal tubular necrosis	Overall nonclinical findings, including hepatic dysfunction, renal dysfunction and gastrointestinal symptoms, in the repeat-dose toxicity studies in the rat and monkey were observed in humans, but they were generally mild in severity. The majority of treatment-related AEs resolved and are not considered important risks of ivosidenib.

Key Safety findings (from non-clinical studies)	Relevance to human usage
as an additional contributing factor. Toxic effects observed on haematologic system, GI system and kidney were reversible whereas the toxic effects observed on liver, spleen and thyroid were still observed at the end of the recovery period. In monkeys, the dosage level of 180 mg/kg/day (highest dosage tested in the 3-month study) was well tolerated over a 3-month dosing period and did not result in any test article-related moribundity or mortality (Report AG120-N-059-R1; Module 2.6.7, Section 7.D). Findings at this dose level included intermittent diarrhoea as well as liver findings. A CV assessment was conducted toward the end of study (Week 12) and possible/probable test article-related QTcB prolongation was noted in individual animals (results discussed in Module 2.6.6, Section 3.1.2.5). All findings were partially or fully reversible following a 28-day nondosing period. The findings observed in the 3-month study in cynomolgus monkeys are largely consistent with those noted at tolerable doses in the 28-day study (Module 2.6.7, Section 7.C). In the GLP 28-day study in cynomolgus monkeys, DLT occurred in male monkeys at a dose of 270 mg/kg/day (Report AG120-N-001-R1; Module 2.6.7, Section 7.C). The cause of DLT was general malaise characterised by poor body condition, gastrointestinal clinical signs leading to emesis, and secondary aspiration. In females at the same dose level, ivosidenib was tolerated. Two 7-day (BID dosing) toxicology and TK studies of ivosidenib were performed in Sprague-Dawley rats and three 7-day (BID dosing) DRF and tolerability studies of ivosidenib were performed in cynomolgus monkeys (Reports AG120-N-041-R1, AG120-N-044-R1, AG120-N-042-R1, AG120-N-043-R1 and AG120-N-007-R; Module 2.6.7, Section 6). Findings were consistent with the longer-term studies.	
Reproductive/developmental toxicity *Fertility and early embryonic development* Per ICH S9 guidance, fertility studies have not been conducted for ivosidenib. Effects on reproductive organs were assessed in the GLP repeat-dose toxicology studies. No effects on reproductive organs were seen in the 3-month rat study (Report AG120-N-058-R1; Module 2.6.7, Section 7.B) or the 28-day monkey study (Report AG120-N-001-R1; Module 2.6.7, Section 7.C) and 3-month monkey study (Report AG120-N-059-R1; Module 2.6.7, Section 7.D). In the 28-day rat study, decreased uterine weights were noted at ≥500 mg/kg/day with microscopic correlate of uterine atrophy at 2,000 mg/kg/day (Report AG120-N-002-R1; Module 2.6.7, Section 7.A). Lower ovary weights were also observed in the 2,000 mg/kg/day group and in the control (vehicle + PVAP) group, which may have correlated with decreased recent corpora lutea. For many females with alterations in uterine and ovarian parameters, the effects were considered to be secondary to stress and occurred in conjunction with persistent diestrous. However, there were females with uterine atrophy, no ovarian findings, and without disruption of the estrous cycle. Lower pituitary weights were noted in females at ≥100 mg/kg/day but were without microscopic correlate. All changes	Ivosidenib has the potential to cause embryo-foetal toxicity. Experience of clinical exposure during pregnancy is currently limited [redacted] To minimise the risk of embryo-foetal toxicity, pregnancy status should be verified before use of ivosidenib and women of childbearing potential and males with female partners

Key Safety findings (from non-clinical studies)	Relevance to human usage
were fully reversible, with the exception of lower pituitary weights at 2,000 mg/kg/day. In male rats in the 28-day GLP toxicology study, degeneration/atrophy of seminiferous tubules with secondary changes in accessory reproductive tissues occurred at 2,000 mg/kg/day only in animals that did not survive to scheduled euthanasia and was considered likely a secondary effect of inanition and/or stress, but an effect of ivosidenib could not be ruled out (Report AG120-N-002-R1; Module 2.6.7, Section 7.A). Testicular effects were not noted in animals that survived to scheduled euthanasia at any dose level. In males that survived to scheduled euthanasia, decreased prostate weights without microscopic correlate was seen at ≥500 mg/kg/day. An increased incidence of pituitary pars distalis vacuolation was seen at ≥500 mg/kg/day. There were no other findings in male reproductive organs. All changes were fully reversible. *Embryo/Foetal Development* In the GLP definitive embryo/foetal development study in pregnant female Sprague-Dawley rats, ivosidenib was administered at oral dosage levels of 20, 100, and 500 mg/kg/day (Report AG120-N-064-R1; Module 2.6.7, Section 13.B). Based on the absence of adverse effects on maternal animals at any dosage level, a dosage level of 500 mg/kg/day was considered to be the No Observed Adverse Effect Level (NOAEL) for maternal toxicity. The maternal calculated plasma $AUC_{0\text{-}24hr}$ at this dosage level was 2.0-fold the human C2D1 $AUC_{0\text{-}24hr}$ at 500 mg/day. Based on lower mean foetal body weights at 500 mg/kg/day, the NOAEL for embryo/foetal development was 100 mg/kg/day. The maternal calculated plasma $AUC_{0\text{-}24hr}$ at this dosage level was 0.4-fold the human C2D1 $AUC_{0\text{-}24hr}$ at 500 mg. Foetal reduced or absent skeletal ossification also occurred at 500 mg/kg/day and was considered to be secondary to reduced foetal body weight. Mean foetal ivosidenib plasma concentrations were 8.1% to 15.6% of the maternal plasma concentration at 2 hours after dosing on GD 17. In the GLP definitive embryo/foetal development study in New Zealand White rabbits, ivosidenib was administered at oral dosage levels of 30, 90, and 180 mg/kg/day (Report AG120-N-067; Module 2.6.7, Section 13.D). Based on moribundity, abortion, clinical findings, and effects on body weight gain and food consumption at 180 mg/kg/day, a dosage of 90 mg/kg/day was considered to be the NOAEL for maternal toxicity. The foetal NOAEL was also considered to be 90 mg/kg/day based on findings at 180 mg/kg/day of decreased foetal weights, with correlating reduced or absent skeletal ossification, and small spleen. The maternal calculated plasma $AUC_{0\text{-}24hr}$ at the 90 mg/kg/day dosage level was 1.4-fold the human C2D1 $AUC_{0\text{-}24hr}$ at 500 mg. Mean foetal ivosidenib plasma concentrations were 3.1% to 20.4% of the maternal plasma concentration 2 hours after dosing on GD 21. *Prenatal and Postnatal Development and Maternal Function* Since ivosidenib is intended for the treatment of patients with cholangiocarcinoma with an IDH1 mutation and for the treatment of patients with newly diagnosed AML with an IDH1 mutation in	of childbearing potential should use effective contraception during treatment and for at least one month after the last dose. Ivosidenib may decrease the systemic concentrations of hormonal contraceptives and, therefore, concomitant use of a barrier method of contraception is recommended. Considering the available data embryo-foetal toxicity is considered an important potential risk of ivosidenib.

Key Safety findings (from non-clinical studies)	Relevance to human usage
combination with azacitidine, studies of pre- and postnatal toxicity and maternal function were not conducted and are not warranted (ICH S9). *Studies in Juvenile Animals* No dedicated toxicology studies in juvenile animals have been conducted, and none is warranted. Ivosidenib is subject to PIP waiver for the treatment of all conditions included in the category of malignant neoplasms (except central nervous system (CNS) tumours, haematopoietic and lymphoid tissue neoplasms) and for the treatment of AML (Module 1, Section 10). No studies in juvenile animals have been considered necessary.	
Genotoxicity Ivosidenib was not mutagenic in in vitro bacterial reverse mutation (Ames) assays. Ivosidenib was not clastogenic in an in vitro human lymphocyte micronucleus assay, or in an in vivo rat bone marrow micronucleus assay.	None.
Carcinogenicity In accordance with ICH S9, carcinogenicity studies have not been performed and are not warranted, as ivosidenib is intended for the treatment of patients with cholangiocarcinoma with an IDH1 mutation and for the treatment of patients with newly diagnosed AML with an IDH1 mutation in combination with azacitidine.	None.
Safety pharmacology	
Cardiovascular system (CVS), including potential effect on the QT interval Multiple studies have been conducted to address the potential CV effects of ivosidenib, including nonGLP automated and manual patch clamp assays for potential inhibition against currents known to be associated with prolonged heart rate-corrected QT interval (QTc) (Reports AG120-N-005-R1; AG120-N-009-R1; AG120-N-054-R1), a nonGLP single-dose CV safety pharmacology study in cynomolgus monkeys (Report AG120-N-053-R1; Module 2.6.3, Section 4), and ECG assessments conducted as part of the 28-day (Report AG120-N-001-R1) and 3-month (Report AG120-N-059-R1) GLP toxicology studies in cynomolgus monkeys (Module 2.6.7, Section 7.C and Section 7.D). Ivosidenib was tested twice in the automated QPatch assay to assess for the potential inhibition of the rapidly activating delayed rectifier potassium current (IKr), encoded by the human ether-à-go-go related gene (hERG). The IC_{50}s were 21,000 nM (equivalent to 12,243 ng/mL) and 10,000 nM (equivalent to 5,830 ng/mL) as compared to the clinical free C_{max} of 550 ng/mL. In the manual patch clamp assay, ivosidenib inhibited the IKr hERG, with a concentration of drug that achieved 20% inhibition (IC_{20}) and IC_{50} of 3,000 nM (equivalent to 1,749 ng/mL) and 12,600 nM (equivalent to 7,346 ng/mL), respectively. The IC_{50} of ivosidenib was >30,000 nM (equivalent to >17,490 ng/mL) against hCaV1.2, hNaV1.5 and hKvLQT1/hminK. The clinical free C_{max} for ivosidenib is 550 ng/mL.	As demonstrated in nonclinical studies ivosidenib is known to cause QT prolongation by virtue of hERG inhibition. Concomitant use of ivosidenib with medications known to prolong the QT interval may increase the risk of QT interval prolongation. Additionally, concomitant administration of moderate or strong CYP3A4 inhibitors may increase ivosidenib plasma concentrations, which may increase the risk of QT interval prolongation. QT prolongation is considered an important identified risk of ivosidenib as it can lead to life-threatening ventricular arrhythmias, which may result in sudden cardiac death.

Key Safety findings (from non-clinical studies)	**Relevance to human usage**
Individual animals with possible (≥30 msec) and probable (≥60 msec) ivosidenib-related prolongation of the QT interval corrected for heart rate using Bazett's formula (QTcB) (Morganroth, 2001) have been noted in both the 28-day (at 30 and 270 mg/kg/day) and 3-month (90 and 180 mg/kg/day) GLP cynomolgus monkey studies with BID dosing at approximately 12-hour intervals. The lowest C_{max} at which prolonged QTcB occurred was 2,120 ng/mL which equates to free C_{max} values ≥0.7 fold the C2D1 500 mg free C_{max} human exposure (recommended human daily dose is 500 mg/day). In addition, prolonged QTcB was observed at the 45 and 135 mg/kg dose levels in a nonGLP single dose monkey CV safety pharmacology study in which group mean C_{max} values were predicted to be similar to that of individual animals in the 28-day and 3-month repeat-dose studies. Reversibility of the prolonged QTcB effect was assessed in a single high-dose male in the 3-month study in cynomolgus monkeys; the QTcB levels returned to baseline following the 28-day recovery period (Module 2.6.7, Section 7.D). Prolonged QTc has been observed previously at drug concentrations that result in as little as 12% to 30% inhibition of hERG (Redfern et al, 2003). For ivosidenib, the hERG IC_{20} is approximately 3,000 nM; thus hERG inhibition is a plausible explanation for the prolonged QTcB observed in cynomolgus monkeys. Electrocardiogram assessments in the 28-day GLP study in cynomolgus monkeys identified ivosidenib-related ventricular bigeminy in 1 high dose male and 1 high-dose female (270 mg/kg/day); there was no histopathologic or electrolytic correlate. Reversibility was not assessed. It is unlikely that the observed ventricular bigeminy is due to hERG inhibition, and the cause of this finding remains unclear. The Day 27 C_{max} values in the male and female were 16 600 ng/mL and 15 900 ng/mL, respectively, which equate to free C_{max} values ≥5-fold the C2D1 500 mg free C_{max} human exposure level (Clinical Study AG120-C-001). Ventricular bigeminy was not observed in the dedicated single-dose CV study or in the 3-month GLP monkey study, despite similar exposures having been achieved.	QT prolongation can be managed in clinical practice through regular ECG monitoring; avoiding concomitant medication with products known to prolong QT interval, or moderate or strong CYP3A4 inhibitors whenever possible; and by interrupting, discontinuing, or reducing the dose of ivosidenib depending on the severity of QT interval prolongation, as advised in the product information.
Central nervous system and respiratory system There were no treatment-related clinical observations related to the CNS or respiratory systems in the GLP rat 28-day study (50, 250, and 1 000 mg/kg/dose BID; Report AG120-N-002-R1; Module 2.6.6, Section 3.1.1.3) or in the GLP rat 3-month study (10, 50, and 250 mg/kg/dose BID; Report AG120-N-058-R1; Module 2.6.6, Section 3.1.1.4). There were no treatment-related clinical observations related to the CNS or the respiratory system in the GLP monkey 28-day (15, 45, and 135 mg/kg/dose BID; Report AG120-N-001-R1; Module 2.6.6, Section 3.1.2.4) or in the GLP monkey 3-month study (15, 45, and 90 mg/kg/dose BID; Report AG120-N-059-R1; Module 2.6.6, Section 3.1.2.5).	None.

Key: AE = Adverse Event, AUC = Area Under Curve, CNS = Central Nervous System, C_{max} = Maximum concentration, CVS = Cardiovascular System, DLT = Dose-limiting Toxicity, DRF = Dose Range Finding, ECG = Electrocardiogram, FDA = Food and Drug Administration, GLP = Good Laboratory Practices, hERG = human ether-à-go-go related gene, IC_{20} = 20% inhibition ICH = International Council For Harmonisation, IDH1 = Isocitrate dehydrogenase-1 inhibitor, IKr = Rapidly activating delayed rectifier potassium current, NOAEL = No Observed Adverse Effect Level, PIP = Paediatric Investigational Plan.

Conclusions from the non-clinical development programme:

The nonclinical studies that evaluated the pharmacological, Pharmacokinetic (PK), and toxicological properties of ivosidenib support the clinical use of ivosidenib for the treatment of newly diagnosed AML (in combination with azacitidine) and CCA.

Nonclinical findings with relevance for use in humans include Electrocardiogram QT prolongation and embryo-foetal toxicity.

Safety concern based on nonclinical findings that has relevance for human usage and has been confirmed by clinical data:

- QT prolongation (Important identified risk).

Safety concern based on nonclinical findings that has relevance for human usage and has not been adequately refuted by clinical data:

- Embryo-foetal toxicity (Important potential risk).

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

The ivosidenib clinical development programme was initiated in 2014, with Development International Birth Date as 17 January 2014, and investigated single-agent and combination therapy for the treatment of subjects with cancers that harbor IDH1 mutations, including solid tumours and haematologic malignancies. All studies of ivosidenib were conducted in accordance with the ethical principles of Good Clinical Practice, according to International Council for Harmonisation (ICH) Harmonised Tripartite Guideline E6.

The AG120-C-009 (AGILE) Study supporting the newly diagnosed AML indication in combination with azacitidine, is a pivotal global, Phase 3, multicenter, double-blind, randomised, placebo-controlled clinical trial to evaluate the efficacy and safety of ivosidenib + azacitidine vs. placebo + azacitidine in adults with newly diagnosed AML with an IDH1 mutation and who are not considered candidates for intensive therapy. Subjects were randomised 1:1 to receive oral ivosidenib or placebo in combination with subcutaneous (SC) or IV azacitidine.

The AG120-C-005 (ClarIDHy) Study supporting the CCA indication, is a pivotal global Phase 3, double-blind, placebo-controlled study evaluating ivosidenib in previously treated subjects with nonresectable or metastatic CCA with an IDH1 mutation, for efficacy, safety, PK, and pharmacodynamic (PD) activity. In addition to this pivotal study, supporting safety data for the CCA indication are provided for ivosidenib at the 500 mg QD (once a day) dosing regimen from the subpopulation of patients with CCA in Study AG120-C-002 (solid tumours).

As the safety profile of ivosidenib differs across the different patient populations, safety data from populations with haematologic malignancies including newly diagnosed AML and solid tumours including cholangiocarcinoma were not pooled and are presented separately.

The following tables summarise the exposure to ivosidenib for patients included in the clinical development programme for the AML and CCA indications respectively. The data cutoff date for the study AG120-C-009 was 01 October 2021, the data cutoff date for the study AG120-C-002 was 16 January 2019, and the final database lock date for study AG120-C-005 was 21 June 2021.

Table 3: Duration of Exposure in AML

Acute Myeloid Leukaemia (AML)		
	Ivosidenib + Azacitidine AML[a] N=72	
Duration of Exposure	**Persons n (%)**	**Total Person Time[b] (Years)**
<1 month	12 (16.7)	0.5
1 to <3 months	10 (13.9)	1.6
3 to <6 months	10 (13.9)	4.2
6 to <12 months	11 (15.3)	8.5
12 to <24 months	22 (30.6)	34.0
>=24 months	7 (9.7)	17.7
Total	72	66.4

[a] Includes all AML subjects in AG120-C-009 who have been exposed to Ivosidenib + Azacitidine.
[b] Total Person Time = sum of person time for each subject in the category. Person time in years: (Date of last dose – Date of first dose + 1)/365.25.
Source: AML RMP Table 17.3-1.1a, Study AG120-C-009 DLP: 01 October 2021.
Study: AG120-C-009, Data Cutoff date: 01 October2021.

Table 4: Duration of Exposure in Cholangiocarcinoma

Cholangiocarcinoma				
	Ivosidenib Cholangiocarcinoma Overall[a] N=239		**Ivosidenib Cholangiocarcinoma 500 mg QD Overall[b] N=228**	
Duration of Exposure (at least)	**Persons n (%)**	**Total Person Time (Years)[c]**	**Persons n (%)**	**Total Person Time (Years)[c]**
< 1 month	28 (11.7)	2.9	27 (11.8)	2.9
1 to < 3 months	91 (38.1)	17.6	86 (37.7)	16.7
3 to < 6 months	34 (14.2)	14.1	34 (14.9)	14.1
6 to < 12 months	44 (18.4)	32.7	42 (18.4)	31.0
12 to < 24 months	28 (11.7)	42.5	25 (11.0)	38.3
>=24 months	14 (5.9)	36.6	14 (6.1)	36.6
Total	239	146.4	228	139.6

Source: CCA RMP Table 18.3.4.1, Study AG120-C-005 DLP: 21 June 2021.
Study AG120-C-002 Data Cutoff: 16 January 2019.

[a]Includes all cholangiocarcinoma subjects in studies AG120-C-005 and AG120-C-002 who have been exposed to ivosidenib.

[b]Includes all cholangiocarcinoma subjects in studies AG120-C-005 and AG120-C-002 who have been exposed to ivosidenib 500mg QD (once a day).

[c]Total Person Time = sum of person time for each subject in the category. Person time in years: (Date of last dose – Date of first dose + 1)/365.25; for subjects who are still on treatment at data cut-off, the date of the last dose will be the last dosing date or a pre-specified data cut-off date, whichever is earlier.

Table 5: Exposure by Dose in AML

Acute Myeloid Leukaemia (AML)		
	Ivosidenib + Azacitidine AML[a] N=72	
Dose Level	**Persons n (%)**	**Total Person Time[b] (Years)**
Ivosidenib 500 mg QD + Azacitidine 75 mg/m ^{2} SC or IV	72 (100)	66.4
Total	72	66.4

[a]Includes all AML subjects in AG120-C-009 who have been exposed to Ivosidenib + Azacitidine.

[b]Total Person Time = sum of person time for each subject in the category. Person time in years: (Date of last dose – Date of first dose + 1)/365.25.

Source: AML RMP Table 17.3-1.3a, Study AG120-C-009 DLP: 01 October 2021.

Study: AG120-C-009, Data cut-off date: 01 October 2021.

Table 6: Exposure by Dose in Cholangiocarcinoma

Cholangiocarcinoma		
	Ivosidenib Cholangiocarcinoma Overall[a] N=239	
Dose Level	**Persons n (%)**	**Total Person Time (Years)[b]**
100 mg BID	2 (0.8)	1.1
300 mg QD	3 (1.3)	1.2
400 mg QD	1 (0.4)	1.7
500 mg QD	228 (95.4)	139.6
800 mg QD	2 (0.8)	1.5
1,200 mg QD	3 (1.3)	1.2
Total	239	146.4

Source: CCA RMP Table 18.3.4.3, Study AG120-C-005 DLP: 21 June 2021.
Study AG120-C-002 Data Cutoff: 16 January 2019.

[a] Includes all cholangiocarcinoma subjects in studies AG120-C-005 and AG120-C-002 who have been exposed to ivosidenib.

[b] Total Person Time = sum of person time for each subject in the category. Person time in years: (Date of last dose – Date of first dose + 1)/365.25; for subjects who are still on treatment at data cut-off, the date of the last dose will be the last dosing date or a pre-specified data cut-off date, whichever is earlier.

Table 7: Age Group and Gender in AML

Acute Myeloid Leukaemia (AML)						
	Ivosidenib + Azacitidine AML[a] N=72					
Age Group	**Persons n (%)**			**Total Person Time[b] (Years)**		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
<60 years	1 (2.4)	0	1 (1.4)	0.4	0	0.4
60 - <65 years	3 (7.3)	0	3 (4.2)	2.7	0	2.7
65 - <75 years	18 (43.9)	12(38.7)	30 (41.7)	21.5	7.2	28.7
75 - <85 years	19 (46.3)	19 (61.3)	38 (52.8)	15.1	19.5	34.6
>= 85 years	0	0	0	0	0	0
Total	41	31	72	39.7	26.7	66.4

[a] Includes all AML subjects in AG120-C-009 who have been exposed to Ivosidenib + Azacitidine.

[b] Total Person Time = sum of person time for each subject in the category. Person time in years: (Date of last dose – Date of first dose + 1)/365.25.

Source: AML RMP Table 17.3-1.2a Study AG120-C-009 DLP: 01 October 2021.

Study: AG120-C-009, Data cut-off date: 01 October 2021.

Table 8: Age Group and Gender in Cholangiocarcinoma

Cholangiocarcinoma								
	Ivosidenib Cholangiocarcinoma Overall[a] N=239				**Ivosidenib Cholangiocarcinoma 500 mg QD Overall[b] N=228**			
	Persons n (%)		**Total Person Time (Years)[c]**		**Persons n (%)**		**Total Person Time (Years) [c]**	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
<60 years	37 (45.7)	67 (42.4)	16.3	43.6	37 (48.1)	64 (42.4)	16.3	41.0
60 - <65 years	13 (16.0)	34 (21.5)	4.9	21.5	12 (15.6)	34 (22.5)	4.7	21.5
65 - <75 years	22 (27.2)	41 (25.9)	8.8	27.6	19 (24.7)	37 (24.5)	8.2	24.1
75 - <85 years	9 (11.1)	16 (10.1)	6.5	17.2	9 (11.7)	16 (10.6)	6.5	17.2
>=85 years	0	0	0	0	0	0	0	0
Total	81	158	36.4	110.0	77	151	35.7	103.9

Source: CCA RMP Table 18.3.4.2, Study AG120-C-005 DLP: 21 June 2021.

Study AG120-C-002 Data Cutoff: 16 January 2019.

[a] Includes all cholangiocarcinoma subjects in studies AG120-C-005 and AG120-C-002 who have been exposed to ivosidenib.

[b] Includes all cholangiocarcinoma subjects in studies AG120-C-005 and AG120-C-002 who have been exposed to ivosidenib 500mg QD.

[c]Total Person Time = sum of person time for each subject in the category. Person time in years: (Date of last dose – Date of first dose + 1)/365.25; for subjects who are still on treatment at data cut-off, the date of the last dose will be the last dosing date or a pre-specified data cut-off date, whichever is earlier.

Table 9: Ethnic Origin in AML

Acute Myeloid Leukaemia (AML)		
	Ivosidenib + Azacitidine AML[a] N=72	
Ethnic Origin	**Persons n (%)**	**Total Person Time[b] (Years)**
White	11 (15.3)	12.2
Other	61 (84.7)	54.3
Black or African American	0	0
Native Hawaiian or Other Pacific Islander	0	0
Asian	15 (20.8)	13.9
American Indian or Alaska Native	0	0
Other[c]	1 (1.4)	0.1
Not Reported	45 (62.5)	40.2
Missing	0	0
Total	72	66.4

[a] Includes all AML subjects in AG120-C-009 who have been exposed to Ivosidenib + Azacitidine.

[b] Total Person Time = sum of person time for each subject in the category. Person time in years: (Date of last dose – Date of first dose + 1)/365.25.

[c] Non-white subjects not otherwise classified

Source: AML RMP Table 17.3-1.4a, Study AG120-C-009 DLP: 01 October 2021.

Study: AG120-C-009, Data cut-off date: 01 October 2021.

Table 10: Ethnic Origin in Cholangiocarcinoma

Cholangiocarcinoma				
	Ivosidenib Cholangiocarcinoma Overall[a] N=239		**Ivosidenib Cholangiocarcinoma 500 mg QD Overall[b] N=228**	
Ethnic Origin	**Persons n (%)**	**Total Person Time (Years)[c]**	**Persons n (%)**	**Total Person Time (Years)[c]**
White	152 (63.6)	99.1	141 (61.8)	92.3
Other	87 (36.4)	47.3	87 (38.2)	47.3
Black or African American	2 (0.8)	0.2	2 (0.9)	0.2
Native Hawaiian or Other Pacific Islander	1 (0.4)	0.2	1 (0.4)	0.2
Asian	24 (10.0)	12.6	24 (10.5)	12.6
American Indian or Alaska Native	1 (0.4)	0.1	1 (0.4)	0.1
Other[d]	2 (0.8)	1.4	2 (0.9)	1.4
Not Reported	11 (4.6)	7.8	11 (4.8)	7.8
Missing	46 (19.2)	25.0	46 (20.2)	25.0
Total	239	146.4	228	139.6

Source: CCA RMP Table 18.3.4.4, Study AG120-C-005 DLP: 21 June 2021.

Study AG120-C-002 Data Cutoff: 16 January 2019.

[a] Includes all cholangiocarcinoma subjects in studies AG120-C-005 and AG120-C-002 who have been exposed to ivosidenib.

[b] Includes all cholangiocarcinoma subjects in studies AG120-C-005 and AG120-C-002 who have been exposed to ivosidenib 500mg QD.

[c] Total Person Time = sum of person time for each subject in the category. Person time in years: (Date of last dose – Date of first dose + 1)/365.25; for subjects who are still on treatment at data cut-off, the date of the last dose will be the last dosing date or a pre-specified data cut-off date, whichever is earlier.

[d] Non-white subjects not otherwise classified

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

The exclusion criteria from the pivotal clinical studies in newly diagnosed AML in combination with azacitidine (AG120-C-009) and in CCA (AG120-C-005) have been presented below.

The exclusion criteria that are related to ongoing or recent conditions, or treatments that may impact the safety and efficacy assessment of ivosidenib in Studies AG120-C-009 and AG120-C-005 are listed below and not discussed further:

If the subject:

- Had received a prior IDH inhibitor.
- Had received systemic anticancer therapy or investigational agent <2 weeks prior to Day 1 (washout from prior immune based anticancer therapy was 4 weeks). In addition, the first dose of study treatment should not have occurred before a period ≥5 half-lives of the investigational agent have elapsed.
- Had previously received treatment for an antecedent haematologic disorder, including investigational agents, were not to be randomised until a washout period of at least 5 half-lives of the investigational agent had elapsed since the last dose of that agent.
- Received radiotherapy to metastatic sites of disease <2 weeks prior to Day 1.
- Was candidate for intensive chemotherapy for their AML.
- Had received any prior treatment for AML with the exception of non-oncolytic treatments to stabilise disease such as hydroxyurea or leukapheresis.
- Underwent hepatic radiation, chemoembolisation, and radiofrequency ablation <4 weeks prior to Day 1.
- Had known symptomatic brain metastases requiring steroids.
- Had a history of another primary cancer, with the exception of: a) curatively resected non-melanoma skin cancer; b) curatively treated cervical carcinoma in situ; or c) other primary solid or liquid tumour with no known active disease present that, in the opinion of the Investigator, did not affect subject outcome in the setting of current CCA diagnosis.
- Had a prior history of malignancy other than MDS or myeloproliferative disorder, unless the subject had been free of the disease for ≥1 year prior to the start of study treatment.
- Had received a hypomethylating agent for MDS.
- Had clinical symptoms suggestive of active CNS leukaemia or known CNS leukaemia. Evaluation of cerebrospinal fluid during Screening was only required if there was a clinical suspicion of CNS involvement by leukaemia during Screening.
- Had immediate, life-threatening, severe complications of leukaemia, such as uncontrolled bleeding, pneumonia with hypoxia or sepsis, and/or disseminated intravascular coagulation.
- Had known medical history of progressive multifocal leukoencephalopathy (PML).

- Had uncontrolled hypertension (systolic blood pressure (BP) >180 mmHg or diastolic BP >100 mmHg).
- Underwent major surgery within 4 weeks of Day 1 or had not recovered from postoperative complications.
- Had an active infection requiring systemic anti-infective therapy or with an unexplained fever >38.5°C within 7 days of Day 1 or active, uncontrolled, systemic fungal, bacterial, or viral infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment.
- Had known active inflammatory gastrointestinal disease, chronic diarrhoea, previous gastric resection or lap band dysphagia, short-gut syndrome, gastroparesis, or other conditions that limit the ingestion or gastrointestinal absorption of drugs administered orally. Gastroesophageal reflux disease under medical treatment was allowed (assuming no drug interaction potential).
- Had significant active cardiac disease within 6 months prior to the start of study treatment, including New York Heart Association Class III or IV Congestive Heart Failure (CHF); myocardial infarction; unstable angina; and/or stroke or had Left Ventricle Ejection Fraction (LVEF) <40% by echocardiography scan (or by other methods according to institutional practice) obtained within 28 days prior to the start of study treatment.

The remaining exclusion criteria from Study AG120-C-009 and AG120-C-005 are presented below:

Subject was pregnant or breastfeeding

Reason for exclusion: To minimise risk to pregnant women and nursing mothers and their offspring. Women of childbearing potential and males with partners of childbearing potential should use effective contraception during treatment with ivosidenib and for at least 1 month after the last dose.

Is it considered to be included as missing information? No

Rationale: The safety of ivosidenib is not known in these populations, and as there is a risk of possible harm during pregnancy based on nonclinical studies, embryo-foetal toxicity is an important potential risk of ivosidenib. This safety concern has adequately been described in the Summary of Product Characteristics (SmPC) section 4.4 'Special warnings and precautions for use' and 4.6 'Fertility, pregnancy and lactation'.

Subjects taking known strong CYP3A4 inducers or sensitive CYP3A4 substrate medications with a narrow therapeutic window, unless they could have been transferred to other medications within ≥5 half-lives prior to dosing.

Reason for exclusion: Ivosidenib is predominantly metabolised by cytochrome (CYP)3A4 isozyme. Subjects taking known strong CYP3A4 inducers or sensitive CYP3A4 substrates were excluded from the clinical development programme for efficacy and safety reasons.

Is it considered to be included as missing information? No

Rationale: Concomitant administration of strong CYP3A4 inducers has been adequately covered in the SmPC (section 4.3 'Contraindications' and section 4.5 'Interaction with other medicinal products and other forms of interaction'). Ivosidenib is contraindicated in patients concomitantly administered strong CYP3A4 inducers as they are expected to decrease plasma concentrations of ivosidenib and may impact efficacy of ivosidenib.

Ivosidenib induces CYP3A4 and may decrease systemic exposure to CYP3A4 substrates. Therefore, the product information recommends that suitable alternatives that are not CYP3A4 substrates with a narrow therapeutic index should be considered during treatment with ivosidenib

Subject with known hypersensitivity to any of the components of ivosidenib, matched placebo or azacitidine.

Reason for exclusion: Subjects with known hypersensitivity to any of the components of ivosidenib, matched placebo or azacitidine were excluded from the clinical development programme for safety reasons. Subjects with a known hypersensitivity would be at a higher risk of subsequent serious systemic hypersensitivity reactions with re-exposure.

Is it considered to be included as missing information? No

Rationale: The hypersensitivity to the medicinal product has been adequately covered in the SmPC (section 4.3 'Contraindications'). Ivosidenib is contraindicated for patients having hypersensitivity to the ivosidenib active substance or to any of the excipients.

CCA or AML subject had a heart-rate corrected QT interval (using Fridericia's formula) (QTcF) ≥450 or ≥470 msec, respectively, or other factors that increased the risk of QT prolongation or arrhythmic events (eg, New York Heart Association Class III or IV CHF, hypokalaemia, family history of long QT interval syndrome) or was taking medications that were known to prolong the QT interval, unless they could have been transferred to other medications within ≥5 half-lives prior to dosing or unless the medications could have been properly monitored during the study. (If equivalent medication was not available, QTcF was to be closely monitored.)

Reason for exclusion: Ivosidenib is known to cause QTc prolongation, also concomitant administration of medicinal products known to prolong the QTc interval may increase the risk of QTc interval prolongation hence were excluded from clinical development programme.

Is it considered to be included as missing information? No

Rationale:QT prolongation is an important identified risk of ivosidenib. This safety concern has adequately been described in the SmPC (Section 4.2 'Posology and method of administration', Section 4.3 'Contraindications', 4.4 'Special warnings and precautions for use', 4.5 'Interaction with other medicinal products and other forms of interaction', 4.8 'Undesirable effects').

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, or adverse reactions with a long latency.

The Adverse Drug Reactions (ADRs) due to prolonged exposure and long latency periods may not have been detected during the Clinical Trial programme of ivosidenib. However, ivosidenib is being developed for the treatment of patients with advanced cancer, who are likely to have a shortened life expectancy.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 11: Exposure of Special Populations Included or not in Clinical Trial Development Programmes

<table>
<tr><th>Type of special population</th><th>Exposure</th></tr>
<tr><td>Pregnant women</td><td rowspan="2">Not included in the clinical development programme.</td></tr>
<tr><td>Breastfeeding women</td></tr>
<tr><td colspan="2">Patients with relevant comorbidities:</td></tr>
<tr><td>• Patients with hepatic impairment</td><td>The clinical development programme for AML and CCA included subjects with mild and moderate hepatic impairment as presented in the tables below:
Table 12: Baseline Liver Function in AML
<table>
<tr><th colspan="3">Baseline Liver Function by NCI ODWG Criteria[a]</th></tr>
<tr><th></th><th colspan="2">Ivosidenib + Azacitidine
AML[b] N=72</th></tr>
<tr><th>Liver Function</th><th>Persons n (%)</th><th>Total Person Time[c] (Years)</th></tr>
<tr><td>Normal</td><td>61 (84.7)</td><td>55.2</td></tr>
<tr><td>Mild</td><td>11 (15.3)</td><td>11.2</td></tr>
<tr><td>Moderate</td><td>0</td><td>0</td></tr>
<tr><td>Severe</td><td>0</td><td>0</td></tr>
<tr><td>Missing</td><td>0</td><td>0</td></tr>
</table>
Source: AML RMP Table 17.3-1.5a, Study AG120-C-009 Data Cutoff: 01 October 2021.
[a]Baseline liver function based on NCI ODWG (National Cancer Institute Organ Dysfunction Working Group) Criteria for hepatic impairment: Normal (total bilirubin <=ULN and SGOT/AST <=ULN); Mild (total bilirubin <=ULN and SGOT/AST>ULN; or total bilirubin >1.0x - 1.5xULN); Moderate (total bilirubin >1.5x - 3x ULN); Severe (total bilirubin >3x ULN).
[b]Includes all AML subjects in AG120-C-009 who have been exposed to Ivosidenib + Azacitidine.
[c]Total Person Time = sum of person time for each subject in the category. Person time in years: (Date of last dose – Date of first dose + 1)/365.25.</td></tr>
</table>

Type of special population	Exposure
• Patients with hepatic impairment	**Table 13: Baseline Liver Function in Cholangiocarcinoma**

Baseline Liver Function by NCI ODWG Criteria[a]

	Ivosidenib Cholangio Overall[b] N=239		Ivosidenib Cholangio 500 mg QD Overall[c] N=228	
Liver Function	**Persons n (%)**	**Total Person Time[d] (Years)**	**Persons n (%)**	**Total Person Time[d] (Years)**
Normal	125 (52.3)	89.1	119 (52.2)	86.4
Mild	109 (45.6)	54.8	104 (45.6)	50.8
Moderate	5 (2.1)	2.5	5 (2.2)	2.5
Severe	0	0	0	0

Source: CCA RMP Table 18.3.4.5, Study AG120-C-005 DLP: 21 June 2021. Study AG120-C-002 Data Cutoff: 16 January 2019.

[a]Baseline liver function based on NCI ODWG (National Cancer Institute Organ Dysfunction Working Group) Criteria for hepatic impairment: Normal (total bilirubin <=ULN and SGOT/AST <=ULN); Mild (total bilirubin <=ULN and SGOT/AST>ULN; or total bilirubin >1.0x - 1.5xULN); Moderate (total bilirubin >1.5x - 3x ULN); Severe (total bilirubin >3x ULN).

[b]Includes all cholangiocarcinoma subjects in studies AG120-C-005 and AG120-C-002 who have been exposed to ivosidenib.

[c]Includes all cholangiocarcinoma subjects in studies AG120-C-005 and AG120-C-002 who have been exposed to ivosidenib 500mg QD.

[d]Total Person Time = sum of person time for each subject in the category. Person time in years: (Date of last dose – Date of first dose + 1)/365.25; for subjects who are still on treatment at data cut-off, the date of the last dose will be the last dosing date or a pre-specified data cut-off date, whichever is earlier.

• Patients with renal impairment

The clinical development programme for AML and CCA included subjects with renal impairment as presented in the tables below:

Table 14: Baseline Renal Function in AML

Baseline Renal Function by Creatinine Clearance (mL/min) and eGFR (mL/min/1.73m^2)

	Ivosidenib + Azacitidine AML[a] N=72	
Creatinine Clearance (mL/min)[b]	**Persons n (%)**	**Total Person Time (Years)[d]**
Normal (>=90)	19 (26.4)	10.8
Mild (60-<90)	31 (43.1)	28.4
Moderate (30-<60)	20 (27.8)	26.8
Severe (15-<30)	2 (2.8)	0.4
Missing	0	0

eGFR (mL/min/1.73m²)[c]	Persons n (%)	Total Person Time (Years)[d]
Normal (>=90)	25 (34.7)	16.7
Mild (60-<90)	33 (45.8)	34.8
Moderate (30-<60)	12 (16.7)	13.2
Severe (15-<30)	2 (2.8)	1.7
Missing	0	0
TOTAL	72 (100)	66.4

Source: AML RMP Table 17.3-1.5a, Study AG120-C-009 Data Cutoff: 01 October 2021.

[a]Includes all AML subjects in AG120-C-009 who have been exposed to Ivosidenib + Azacitidine.

*[b]Baseline creatinine clearance (ml/min) is calculated as: (140-age) * baseline weight (kg) * (0.85 if female)/ (72 * baseline serum creatinine (mg/dL)).*

*[c]eGFR = estimated Glomerular Filtration Rate, which is calculated as: eGFR (ml/min/1.73 m²) = 175 * (Scr /88.4)^(-1.154) * (Age)^(-0.203) * (0.742 if female) * (1.212 if African American), where Scr is serum creatinine in standard unit (umol/L).*

[d]Total Person Time = sum of person time for each subject in the category. Person time in years: (Date of last dose – Date of first dose + 1)/365.25.

Table 15: Baseline Real Function in Cholangiocarcinoma

Baseline Renal Function by Creatinine Clearance (mL/min) and eGFR (mL/min/1.73m²)

	Ivosidenib Cholangio Overall[a] N=239		Ivosidenib Cholangio 500 mg QD Overall[b] N=228	
Creatinine Clearance (mL/min)[c]	**Persons n (%)**	**Total Person Time[d] (Years)**	**Persons n (%)**	**Total Person Time[e] (Years)**
Normal (>=90)	125 (52.3)	65.7	120 (52.6)	64.0
Mild (60-<90)	79 (33.1)	59.5	75 (32.9)	56.3
Moderate (30-<60)	29 (12.1)	17.5	27 (11.8)	15.6
Severe (15-<30)	1 (0.4)	2.0	1 (0.4)	2.0
Missing	5 (2.1)	1.7	5 (2.2)	1.7
eGFR (mL/min/1.73 m²)[d]	**Persons n (%)**	**Total Person Time[d] (Years)**	**Persons n (%)**	**Total Person Time[e] (Years)**
Normal (>=90)	102 (42.7)	51.6	96 (42.1)	49.0
Mild (60-<90)	105 (43.9)	71.4	104 (45.6)	69.7
Moderate (30-<60)	31 (13.0)	21.4	27 (11.8)	18.9

Type of special population	Exposure
	Severe (15-<30) | 1 (0.4) | 2.0 | 1 (0.4) | 2.0 *Source: CCA RMP Table 18.3.4.5, Study AG120-C-005 DLP: 21 June 2021. Study AG120-C-002 Data Cutoff: 16 January 2019.* *[a]Includes all cholangiocarcinoma subjects in studies AG120-C-005 and AG120-C-002 who have been exposed to ivosidenib.* *[b]Includes all cholangiocarcinoma subjects in studies AG120-C-005 and AG120-C-002 who have been exposed to ivosidenib 500mg QD.* *[c]Baseline creatinine clearance (ml/min) is calculated as: (140-age) * baseline weight (kg) * (0.85 if female)/ (72 * baseline serum creatinine (mg/dL)).* *[d]eGFR = estimated Glomerular Filtration Rate, which is calculated as: eGFR (mL/min/1.73 m2) = 175 * (Scr /88.4)^(-1.154) * (Age)^(-0.203) * (0.742 if female) * (1.212 if African American), where Scr is serum creatinine in standard unit (umol/L).* *[e]Total Person Time = sum of person time for each subject in the category. Person time in years: (Date of last dose – Date of first dose + 1)/365.25; for subjects who are still on treatment at data cut-off, the date of the last dose will be the last dosing date or a pre-specified data cut-off date, whichever is earlier.*
• Patients with cardiovascular impairment	Patients with severe cardiovascular impairment were not included in the clinical development programme.
• Immuno-compromised patients	Immunocompromised patients were not specifically excluded from clinical studies unless they had HIV/AIDS. Given the nature of the indications, and the previous treatments that had been administered to both AML patients and CCA patients, some degree of immunosuppression is likely in most study participants. However, the exposure to ivosidenib in these patients cannot be reliably quantified.
• Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable.
Population with relevant different ethnic origin	Table 9 above provides the numbers of patients treated with ivosidenib in the clinical trial development programme studies by ethnicity (AG120-C-009 and AG120-C-005).
Subpopulations carrying relevant genetic polymorphisms	The are no relevant polymorphisms.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

Ivosidenib was authorised in the United States on 20 July 2018 for the treatment of adult patients with relapsed or refractory AML with a susceptible IDH1 mutation as detected by a Food and Drug Administration (FDA)-approved test.

The initial new drug application (NDA) approval was followed by the approval of a supplemental new drug application (sNDA) for the treatment of newly-diagnosed AML with a susceptible IDH1 mutation as detected by an FDA-approved test in adult patients who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy, on 02 May 2019. A second sNDA was approved on 25 August 2021 for the treatment of adult patients with previously treated, locally advanced or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test.

SV.1.1 Method used to calculate exposure

The usual administration schedule of ivosidenib is 500 mg once daily.

The estimated post-authorisation exposure is based on sales volumes, the mean daily dosage of 2 tablets of 250 mg of ivosidenib per day, and months of 30.4 days.

SV.1.2 Exposure

[redacted]

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Given the pharmacological properties of ivosidenib and its indication, the potential for misuse or abuse for illegal purposes is negligible. No potential for drug dependence or drug abuse has been noted for ivosidenib in any of the clinical studies.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

1. Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

Newly diagnosed AML specific risks with minimal clinical impact on patients

- Arthralgia
- Back pain
- Dizziness
- Insomnia
- Leukocytosis
- Leukopenia
- Neutropenia
- Oropharyngeal pain
- Pain in extremity
- Thrombocytopenia

1.

CCA specific risks with minimal clinical impact on patients

- Abdominal pain
- Alanine aminotransferase increased
- Anaemia
- Ascites
- Aspartate aminotransferase increased
- Blood bilirubin increased
- Decreased appetite
- Diarrhoea
- Fall
- Fatigue
- Hyperbilirubinaemia
- Jaundice cholestatic
- Nausea
- White blood cell count decreased
- Platelet count decreased
- Rash

Risks with minimal clinical impact on patients common to both AML and CCA

- Headache
- Vomiting
- Neuropathy peripheral

AML and CCA are diagnoses associated with a significant reduction in life expectancy, in spite of treatment, in many instances. Patients with AML and CCA would be treated in a clinical oncology setting equipped to recognise, and to manage appropriately, the complications of treatment listed in this section.

2. Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

None.

3. Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised):

   The risks associated with ivosidenib that require no further characterisation and are adequately described in the product information are:

   - Hypersensitivity
   - Drug-drug interaction (Concomitant administration of strong CYP3A4 inducers or dabigatran).

4. Known risks that do not impact the risk-benefit profile:

   None.

5. Other reasons for considering the risks not important:

   None.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk: Differentiation Syndrome in patients with AML

Differentiation Syndrome is an important identified risk in ivosidenib-treated patients with haematologic malignancies; it is not a risk in patients with solid tumours; therefore it is an important identified risk in patients with AML and not in patients with cholangiocarcinoma. Differentiation syndrome can be life-threatening or fatal if not treated. The important identified risk is supported by data from the clinical development programme (In Study AG120-C-009, differentiation syndrome was reported among the most common (≥2%) serious adverse reactions.)

Benefit-risk impact: Patients with newly diagnosed AML with an IDH1 mutation who are not eligible to receive standard induction chemotherapy have a poor prognosis with a serious unmet medical need for safe and effective targeted therapies. The benefit of ivosidenib in combination with azacitidine as an effective treatment for newly diagnosed AML with an IDH1 mutation outweighs the risk of differentiation syndrome which can be managed in clinical practice through initiation of medicinal products such as corticosteroids, diuretics, and hydroxycarbamide in conjunction with temporary interruption of ivosidenib treatment as clinically indicated.

Important Identified Risk: QT prolongation

QT prolongation is an important identified risk in patients with AML and CCA as it can lead to life-threatening ventricular arrhythmias which can result in sudden cardiac death. The important identified risk is supported by data from nonclinical findings and the clinical development programme.

Benefit-risk impact: Patients with newly diagnosed AML with an IDH1 mutation who are not eligible to receive standard induction chemotherapy and CCA patients with an IDH1 mutation who were previously treated by at least one prior line of systemic therapy have a poor prognosis with a serious unmet medical need for safe and effective targeted therapies. The benefit of ivosidenib in combination with azacitidine as an effective treatment for newly diagnosed AML with an IDH1 mutation and ivosidenib as a monotherapy for the treatment of CCA with an

IDH1 mutation outweighs the risk of electrocardiogram QT prolonged which can be managed in clinical practice through periodic ECG monitoring in ivosidenib treated patients including those with CHF, electrolyte abnormalities, or those who are taking medications known to prolong the QT interval, or moderate or strong CYP3A4 inhibitors.

Ivosidenib is contraindicated in patients with congenital long QT syndrome, familial history of sudden death or polymorphic ventricular arrhythmia or with QT/QTc interval > 500 msec, regardless of the correction method. Treatment with ivosidenib should be permanently discontinued in patients with QTc interval prolongation with signs or symptoms of life-threatening arrhythmia.

Important Potential Risk: Embryo-foetal toxicity

Embryo-foetal toxicity is an important potential risk of ivosidenib in patients with AML and CCA as there are limited data on ivosidenib exposure in pregnant women. Subjects who were pregnant were excluded from studies for both the indications. [redacted]

The effect of ivosidenib on embryo-foetal development was characterised in rats and rabbits including placental transfer of ivosidenib. Based on animal embryo-foetal toxicity studies, embryo-foetal toxicity is considered an important potential risk of ivosidenib in patients with AML and cholangiocarcinoma.Benefit-risk impact: Patients with newly diagnosed AML with an IDH1 mutation who are not eligible to receive standard induction chemotherapy and patients with CCA with an IDH1 mutation who were previously treated by at least one prior line of systemic therapy have a poor prognosis with a serious unmet medical need for safe and effective targeted therapies. The benefit of ivosidenib in combination with azacitidine as an effective treatment for newly diagnosed AML with an IDH1 mutation and ivosidenib as a monotherapy for the treatment of CCA with an IDH1 mutation may outweigh the potential risk of embryo-foetal toxicity which may be prevented by the use of effective contraception.

Missing Information: Use in patients with moderate and severe hepatic impairment

Use in patients with moderate and severe hepatic impairment is an area of missing information based on limited exposure in this population in clinical trials. Ivosidenib should be used with caution in patients with moderate and severe hepatic impairment in clinical practice and this patient population should be closely monitored.

Benefit-risk impact: Patients with newly diagnosed AML with an IDH1 mutation who are not eligible to receive standard induction chemotherapy and patients with CCA with an IDH1 mutation who were previously treated by at least one prior line of systemic therapy have a poor prognosis with a serious unmet medical need for safe and effective targeted therapies. The benefit of ivosidenib in combination with azacitidine as an effective treatment for newly diagnosed AML with an IDH1 mutation and ivosidenib as a monotherapy for the treatment of CCA with an IDH1 mutation may outweigh safety concerns in patients with moderate and severe hepatic impairment that have yet to be confirmed in clinical practice. Ivosidenib should be used with caution in patients with moderate and severe hepatic impairment and this patient population should be closely monitored.

Use in patients with moderate and severe hepatic impairment will be further characterised in study S095031-218, which replaces the previously planned organ impairment substudy of Study AG120-C-001.

Missing Information: Use in patients with severe renal impairment

Use in patients with severe renal impairment is an area of missing information based on limited exposure in this population in clinical trials. Ivosidenib should be used with caution in patients with severe renal impairment and this patient population should be closely monitored.

Benefit-risk impact: Patients with newly diagnosed AML with an IDH1 mutation who are not eligible to receive standard induction chemotherapy and patients with CCA with an IDH1 mutation who were previously treated by at least one prior line of systemic therapy have a poor prognosis with a serious unmet medical need for safe and effective targeted therapies. The benefit of ivosidenib in combination with azacitidine as an effective treatment for newly diagnosed AML with an IDH1 mutation and ivosidenib as a monotherapy for the treatment of CCA with an IDH1 mutation may outweigh safety concerns in patients with severe renal impairment that have yet to be confirmed in clinical practice. Ivosidenib should be used with caution in patients with severe renal impairment and this patient population should be closely monitored.

Use in patients with severe renal impairment will be further characterised in study S095031-218, which replaces the previously planned organ impairment substudy of Study AG120-C-001.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk: Differentiation Syndrome in patients with AML (defined by MedDRA PT: Differentiation syndrome)

Potential mechanisms:

The mechanism of action of ivosidenib induced differentiation syndrome in patients with AML is not completely understood. Differentiation syndrome was first described in patients with APL treated with all-trans retinoic acid as a potentially fatal complication of effective leukaemia treatment (Frankel et al, 1994). In APL, all-trans retinoic acid and arsenic trioxide are thought to induce release of cytokines from differentiating myeloid cells, leading to excessive inflammatory response and may increase expression of cell-surface integrins, which could increase adhesion of myeloid cells to vascular endothelium, thereby facilitating extravasation. The differentiation syndrome observed in patients treated with mutant IDH inhibitor therapy may be due to similar phenomena when treatment removes the differentiation block in the malignant myeloid clone, leading to a rapid increase in differentiated neutrophils (Birendra and DiNardo, 2016).

Evidence source and strength of evidence:

Differentiation syndrome is a serious side effect that may occur in patients with acute myeloid leukaemia who have been treated with anticancer drugs that are known to induce differentiation of malignant myeloid precursors, including ivosidenib. It is caused by a large, rapid release of cytokines (immune substances) from leukaemia cells that are affected by the anticancer drugs.

Signs and symptoms of differentiation syndrome include fever; cough; trouble breathing; weight gain; swelling of the arms, legs, and neck; build-up of excess fluid around the heart and lungs; low blood pressure; and kidney failure.

In a clinical study of ivosidenib and azacitidine given in combination for the treatment of AML (AG120-C-009), the percentage of subject in whom differentiation syndrome was reported was 13.9%. In the control group treated with azacitidine alone, the percentage of subject in whom differentiation syndrome was reported was 8.1%. Patients treated with ivosidenib were reported to have recovered with appropriate treatment.

The evidence is derived from clinical trials. Evidence from this source is considered to be a reliable predictor of how subjects will respond to treatment in clinical practice, by convention.

Characterisation of the risk:

Table 16: Differentiation Syndrome – Frequency (AML)

	AG120-C-009 Ivosidenib + Azacitidine N=72	**AG120-C-009 Placebo + Azacitidine N=74**
Subjects with TEAEs[a], n (%)	10 (13.9)	6 (8.1)
Total Number of TEAEs	11	6
Incidence Rate - Subjects with AEs/100 Person-years[b]	15.05	17.95
95% CI for Incidence Rate[c]	8.10, 27.97	8.06, 39.94

Source: AML RMP Table: 17.3-2.3a, Study: AG120-C-009, Data Cutoff Date: 01 October 2021.
[a]Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[b]Person-year: (Date of last dose – Date of first dose + 1)/365.25.
[c]The CI of Incidence Rate is assumed to follow exact Poisson confidence interval (CI).

Table 17: Differentiation Syndrome – Seriousness/outcomes (AML)

	AG120-C-009 Ivosidenib + Azacitidine N=72	**AG120-C-009 Placebo + Azacitidine N=74**
Subjects with TEAEs[a], n (%)	10 (13.9)	6 (8.1)
Seriousness[b] n (%)		
Serious	6 (8.3)	1 (1.4)
Non-Serious	4 (5.6)	5 (6.8)
Outcome[c] n (%)		
Unknown	0	0
Recovered/Resolved	9 (12.5)	3 (4.1)
Recovered/Resolved With Sequelae	1 (1.4)	0
Not Recovered/Not Resolved	0	3 (4.1)
Fatal	0	0

Source: AML RMP Table: 17.3-2.3a, Study: AG120-C-009 Data Cutoff Date: 01 October 2021.
[a]Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[b]Only the most serious event is counted - Seriousness: Serious>Non-serious.
[c]Only the most severe outcome is counted - Outcomes: Fatal>Ongoing>Recovered>Unknown.

Table 18: Differentiation Syndrome - Severity and Nature of the risk (AML)

	AG120-C-009 Ivosidenib + Azacitidine N=72	**AG120-C-009 Placebo + Azacitidine N=74**
Subjects with TEAEs[a], n (%)	10 (13.9)	6 (8.1)
Severity[b] n (%)		
Missing	0	0
Grade 1	0	0
Grade 2	7 (9.7)	3 (4.1)
Grade 3	3 (4.2)	2 (2.7)
Grade 4	0	1 (1.4)
Grade 5	0	0

Source: AML RMP Table: 17.3-2.3a, Study: AG120-C-009 Data Cutoff Date: 01 October 2021.
[a]Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[b]Severity is graded based on the NCI CTCAE 4.03. Only the most severe event is counted - Severity: Grade 5>Grade 4>Grade 3>Grade 2>Grade 1>Missing.

Risk factors and risk groups:

All patients treated with ivosidenib for IDH1 mutation-positive AML are potentially at risk of differentiation syndrome. There are no known factors that might predict the risk in these patients.

Preventability:

Differentiation syndrome associated with ivosidenib cannot be prevented; however, the risk can be minimised through awareness of the symptoms of differentiation syndrome detailed in SmPC and Package Leaflet (PL). Detailed guidance regarding monitoring and management of differentiation syndrome is provided in the SmPC sections 4.2, 4.4 and 4.8. Additional guidance is provided in the PL to raise patients awareness on the symptoms and actions to be taken.

Impact on the benefit-risk balance of the product:

Patients with newly diagnosed AML with an IDH1 mutation have a poor prognosis with a serious unmet medical need for safe and effective targeted therapies. The benefit of ivosidenib in combination with azacitidine as an effective treatment for newly diagnosed AML with an IDH1 mutation outweighs the risk of differentiation syndrome. It can be managed in clinical practice through initiating corticosteroid treatment and temporarily interrupting ivosidenib if clinically indicated.

Public health impact:

Differentiation syndrome is a very common adverse reaction of ivosidenib in combination with azacitidine in patients with newly diagnosed AML. As AML with an IDH1 mutation is a rare condition, the overall public health impact is expected to be low. In addition, there is no indication that the frequency or severity will be any different in the postmarketing setting.

Important Identified Risk: QT prolongation (defined as Medical Dictionary for Regulatory Activities (MedDRA) search criteria: Standardised MedDRA query (SMQ) (Broad) of Torsade de Pointes/QT Prolongation)

Potential mechanisms:

Duration of the QT interval is prolonged by hERG inhibition. Prolonged QT is known to occur at drug concentrations that result in as little as 12% to 30% inhibition of hERG channels (Redfern et al, 2003). Ivosidenib inhibited IKr (hERG), with IC_{20} and IC_{50} values of 3,000 and 12,600 nM, respectively and caused prolonged QTcB in cynomolgus monkeys at individual free C_{max} values of ≥388 ng/mL. Prolonged QTcB was found to be reversible in a single high-dose male in the 3-month study in cynomolgus monkeys (only monkey/study in which reversibility was assessed) where the QTcB levels returned to baseline following the 28-day recovery period.

Evidence source and strength of evidence:

QT prolongation may increase the risk of developing abnormal heart rhythms and may rarely lead to sudden cardiac arrest.

Nonclinical evidence indicates that ivosidenib can prolong QT interval in a reversible manner.

In a clinical study of ivosidenib and azacitidine given in combination for the treatment of AML (AG120-C-009), the percentage of subject in whom QT prolongation was reported was 27.8%. In the control group treated with azacitidine alone, the percentage of subject in whom QT prolongation was reported was 12.2%.

In a clinical study of ivosidenib given for the treatment of cholangiocarcinoma (AG120-C-005), the percentage of subject in whom QT prolongation was reported was 9.2%.

The evidence is derived from clinical trials and nonclinical studies. Evidence from these sources is considered to be a reliable predictor of how subjects will respond to treatment in clinical practice, by convention.

Characterisation of the risk:

Table 19: Electrocardiogram QT Prolonged – Frequency (AML)

Acute Myeloid Leukaemia		
	AG120-C-009 Ivosidenib + Azacitidine N=72	**AG120-C-009 Placebo + Azacitidine N=74**
Subjects with TEAEs[a], n (%)	20 (27.8)	9 (12.2)
Total Number of TEAEs	39	12
Incidence Rate - # of Patients with AEs per 100 Person-years[b]	30.10	26.92
95% CI for Incidence Rate[c]	19.42, 46.66	14.01, 51.73

Source: AML RMP Table 17.3-2.1a, Study: AG120-C-009 Data Cutoff date: 01 October 2021.
[a]Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[b]Total Person-year: (Date of last dose – Date of first dose + 1)/365.25.
[c]The CI of Incidence Rate is assumed to follow exact Poisson confidence interval (CI).

Table 20: Electrocardiogram QT Prolonged – Frequency (Cholangiocarcinoma)

Cholangiocarcinoma			
	Ivosidenib Cholangio-carcinoma Overall[b] n=228	**AG120-C-005 Ivosidenib without Crossover[c] n=123**	**AG120-C-005 Placebo Pre-Crossover n=59**
Patients with TEAEs[a], n (%)	21 (9.2)	12 (9.8)	2 (3.4)
Total N of TEAEs	45	28	2
Incidence Rate - # of Patients with AEs per 100 Person-years	15.04	17.47	6.21
95% CI for Incidence Rate	9.81, 23.07	9.92, 30.77	1.55, 24.84

Source: CCA RMP Table 18.3.4.6.1, Study AG120-C-005 DLP: 21 June 2021.
Study AG120-C-002 Data Cutoff: 16 January 2019.
[a]Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[b]Includes all cholangiocarcinoma subjects in studies AG120-C-005 and AG120-C-002 who have been exposed to ivosidenib 500mg QD.
[c]The group 'AG120-C-005 without Crossover' refers to the subjects who were randomised to and received ivosidenib 500mg QD.
The CI of Incidence Rate is assumed to follow exact Poisson confidence interval (CI).

Table 21: Electrocardiogram QT Prolonged – Seriousness/Outcomes (AML)

Acute Myeloid Leukaemia		
	AG120-C-009 Ivosidenib + Azacitidine N=72	**AG120-C-009 Placebo + Azacitidine N=74**
Subjects with TEAEs[a], n (%)	20 (27.8)	9 (12.2)
Seriousness[b] n (%)		
Serious	1 (1.4)	1 (1.4)
Non-Serious	19 (26.4)	8 (10.8)
Outcome[c] n (%)		
Unknown	0	0
Recovered/Resolved	19 (26.4)	8 (10.8)
Recovered/Resolved With Sequelae	0	0
Not Recovered/Not Resolved	1 (1.4)	1 (1.4)
Fatal	0	0

Source: AML RMP Table 17.3-2.1a, Study: AG120-C-009 Data cut-off date: 01 October 2021.
[a]Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[b]Only the most serious event is counted - Seriousness: Serious>Non-serious.
[c]Only the most severe outcome is counted - Outcomes: Fatal>Ongoing>Recovered>Unknown.

Table 22: Electrocardiogram QT Prolonged – Seriousness/Outcomes (Cholangiocarcinoma)

Cholangiocarcinoma			
	Ivosidenib Cholangio-carcinoma Overall[b] n=228	**AG120-C-005 Ivosidenib without Crossover[c] n=123**	**AG120-C-005 Placebo Pre-Crossover n=59**
Patients with TEAEs[a], n (%)	21 (9.2)	12 (9.8)	2 (3.4)
Seriousness[d] n (%)			
Serious	2 (0.9)	1 (0.8)	0
Nonserious	19 (8.3)	11 (8.9)	2 (3.4)
Outcomes[e]			
Unknown	0	0	0
Recovered/Resolved	15 (6.6)	10 (8.1)	2 (3.4)
Recovered/Resolved with Sequelae	2 (0.9)	1 (0.8)	0
Recovering/Resolving	0	0	0
Not Recovered/Not Resolved	4 (1.8)	1 (0.8)	0
Fatal	0	0	0

Source: CCA RMP Table 18.3.4.6.1, Study AG120-C-005 DLP: 21 June 2021.
Study AG120-C-002 Data Cutoff: 16 January 2019.

[a]Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[b]Includes all cholangiocarcinoma subjects in studies AG120-C-005 and AG120-C-002 who have been exposed to ivosidenib 500mg QD.

[c]The group 'AG120-C-005 without Crossover' refers to the subjects who were randomised to and received ivosidenib 500mg QD.

[d] Only the most serious event is counted - Seriousness: Serious>Non-serious.

[e]Only the most severe outcome is counted - Outcomes: Fatal> Not Recovered/Not Resolved> Recovering/Resolving> Recovered/Resolved with Sequelae>Recovered/Resolved>Unknown

Table 23: Electrocardiogram QT Prolonged – Severity and Nature of the risk (AML)

Acute Myeloid Leukaemia		
	AG120-C-009 Ivosidenib + Azacitidine N=72	**AG120-C-009 Placebo + Azacitidine N=74**
Subjects with TEAEs[a], n (%)	20 (27.8)	9 (12.2)
Severity[b] n (%)		
Missing	0	0
Grade 1	2 (2.8)	4 (5.4)
Grade 2	10 (13.9)	2 (2.7)
Grade 3	8 (11.1)	3 (4.1)
Grade 4	0	0
Grade 5	0	0

Source: AML RMP Table 17.3-2.1a, Study: AG120-C-009 Data Cutoff date: 01 October 2021.
[a]Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[b]Severity is graded based on the NCI CTCAE 4.03. Only the most severe event is counted - Severity: Grade 5>Grade 4>Grade 3>Grade 2>Grade 1>Missing.

Table 24: Electrocardiogram QT Prolonged – Severity and Nature of the risk (Cholangiocarcinoma)

Cholangiocarcinoma			
	Ivosidenib Cholangio-carcinoma Overall[b] n=228	**AG120-C-005 Ivosidenib without Crossover[c] n=123**	**AG120-C-005 Placebo Pre-Crossover n=59**
Patients with TEAEs[a], n (%)	21 (9.2)	12 (9.8)	2 (3.4)
Severity[d], n (%)			
Missing	0	0	0
Grade 1	7 (3.1)	4 (3.3)	2 (3.4)
Grade 2	9 (3.9)	6 (4.9)	0
Grade 3	5 (2.2)	2 (1.6)	0
Grade 4	0	0	0
Grade 5	0	0	0

Source: CCA RMP Table 18.3.4.6.1, Study AG120-C-005 DLP: 21 June 2021.
Study AG120-C-002 Data Cutoff: 16 January 2019.
[a]Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.
[b]Includes all cholangiocarcinoma subjects in studies AG120-C-005 and AG120-C-002 who have been exposed to ivosidenib 500mg QD.
[c]The group 'AG120-C-005 without Crossover' refers to the subjects who were randomised to and received ivosidenib 500mg QD.
[d]Severity is graded based on the NCI CTCAE 4.03. Only the most severe event is counted - Severity: Grade 5>Grade 4>Grade 3>Grade 2>Grade 1>Missing

In Study AG120-C-009, 27.8% (20 of 72) of the patients in the ivosidenib + azacitidine arm and 12.2% (9 of 74) of the patients in the placebo + azacitidine arm experienced an AE within the SMQ Torsades de pointes/QT prolongation. Among subjects with AML with at least 1 TEAE within the SMQ Torsades de pointes/QT prolongation one was serious in each treatment arm. Most were low severity grade; 2 (2.8%) subjects had Grade 1, 10 (13.9%) subjects had Grade 2, and 8 (11.1%) had Grade 3 events among subjects treated with ivosidenib + azacitidine. The majority resolved (19 [26.4%] subjects) and 1 (1.4%) subject had not recovered. No life-threatening arrhythmia events were observed, including Torsades de Pointes. No Grade 4 or Grade 5 Treatment Emergent Averse Events (TEAEs) occurred within the SMQ Torsades de Pointes/QT prolonged. AEs reported within SMQ of Torsades de Pointes/QT prolongation by preferred term were Electrocardiogram QT prolonged and Syncope.

During the on-treatment period, a higher proportion of subjects in the ivosidenib + azacitidine arm (N=72) compared with the placebo + azacitidine arm (N=74) had QTcF >450 msec (58.3% vs 34.7%), QTcF >480 msec (26.4% vs 8.3%), and QTcF >500 msec (15.3% vs 2.8%). The incidence of QTcF increase of >60 msec from baseline was 24.3% in the ivosidenib + azacitidine arm and 13.9% in the placebo + azacitidine arm.

In Study AG120-C-005 in patients with CCA, a higher incidence of subjects randomised to and treated with ivosidenib (N=123) experienced an AE within the SMQ Torsades de pointes/QT prolongation compared with the placebo arm (N=59). Of the 228 patients with CCA treated with 500 mg ivosidenib, 21 (9.2%) subjects had at least 1 TEAE within the SMQ Torsades de pointes/QT prolongation. The majority was nonserious; 19 (8.3%) subjects and 2 (0.9%) subjects experienced nonserious AEs and serious AEs, respectively. Most of these AEs were low grade; 7 (3.1%) subjects had Grade 1, 9 (3.9%) had Grade 2, and 5 (2.2%) had Grade 3. None of the AEs within the SMQ Torsades de pointes/QT prolongation was a Grade 4 or Grade 5 AE. Most subjects had an AE that resolved (15 [6.6%] subjects); 4 (1.8%) subjects had an AE that not yet resolved, and 2 (0.9%) subjects had an AE that resolved with sequelae.

Among all subjects with CCA treated with ivosidenib 500 mg QD and evaluated for ECG (N=227), the incidence of QT increase of >60 msec from baseline was 10.1% and the incidence of QT >500 msec was 2.2%; the incidence of QTcF increase of >60 msec from baseline was 5.7% and the incidence of QTcF >500 msec was 2.2%.

Risk factors and risk groups:

The following may increase the risk of developing QT prolongation or its symptoms:

- A history of abrupt loss of consciousness, or of cardiac arrest
- Having a first-degree relative (parent, sibling) with abnormal heart rhythm or fast and chaotic heartbeats (long QT syndrome)
- Concomitant use of other medicines that may cause irregular heart rhythm or rapid heartbeats (prolonged QT intervals)
- Being female and on heart medication
- Excessive vomiting, diarrhoea or other conditions resulting in the loss of electrolytes.

Preventability:

QT interval prolongation cannot be prevented; however it can be managed by adhering to the instructions provided in SmPC. Detailed guidance regarding contraindications, monitoring and management of electrocardiogram QT prolonged is provided in the SmPC sections 4.2, 4.3,

4.4, 4.5 and 4.8. Additional guidance is provided in the PL to raise patients awareness on the symptoms and actions to be taken.

Impact on the benefit-risk balance of the product:

Patients with AML with an IDH1 mutation and CCA with an IDH1 mutation have a poor prognosis with a serious unmet medical need for safe and effective targeted therapies. The benefit of ivosidenib as an effective treatment for AML with an IDH1 mutation and CCA with an IDH1 mutation, outweighs the risk of electrocardiogram QT prolonged which can be managed in clinical practice. Electrocardiogram QT prolonged will be further characterised using routine pharmacovigilance.

Public health impact:

Electrocardiogram QT prolongation is a very common adverse reaction of ivosidenib. Newly diagnosed AML with IDH1 mutation and CCA with IDH1 mutation are rare conditions, the overall public health impact is expected to be low. There is no indication that the frequency or severity will be any different in the postmarketing setting.

Important Potential Risk: Embryo-foetal toxicity (MedDRA search strategy: Maternal drugs affecting foetus and Paternal drugs affecting foetus)

Potential mechanisms:

The mechanism of ivosidenib induced embryo-foetal toxicity is unknown; however, it was shown that placental transfer of ivosidenib occurs in utero in both rats and rabbits. There are limited human data available regarding the potential effect of ivosidenib on pregnancy or development of the embryo or foetus.

Evidence source and strength of evidence:

Embryofoetal toxicity refers to the potential to injure the developing child in the womb.

Evidence for embryofoetal toxicity is based on non-clinical studies, which may be relevant for humans. In the absence of evidence of the effects on the foetus in humans, embryofoetal toxicity is considered an important potential risk for ivosidenib. In non-clinical embryo-foetal toxicity studies, ivosidenib was associated with maternal toxicity and spontaneous abortions, decreased foetal body weights, delayed bone formation and variation in organ development (small spleen). Ivosidenib was also found to cross the placenta. Based on these studies, ivosidenib could cause foetal harm when administered to women during pregnancy.

Characterisation of the risk:

[redacted]

Risk factors and risk groups:

Sexually active women of childbearing potential and male patients whose partners are women of childbearing potential are at risk of the consequences of embryofoetal toxicity. Women of childbearing potential and males with partners of childbearing potential not using effective contraception during treatment with ivosidenib and for at least 1 month after the last dose are at risk. Patients treated with oral contraceptives not using a barrier method of contraception are also at increased risk, as ivosidenib may decrease the effectiveness of oral contraceptives.

Preventability

Ivosidenib is not recommended for use during pregnancy and in women of childbearing potential and males with partners of childbearing potential not using effective contraception. Pregnancy can be prevented; the risk minimisation measures in the product information inform prescribers and patients how to minimise potential exposure in women of childbearing potential and males with female partners of childbearing potential.

Impact on the benefit-risk balance of the product:

The benefit of ivosidenib as an effective treatment for AML with an IDH1 mutation and CCA with an IDH1 mutation, which has an unmet medical need for targeted therapies, outweighs the potential risk of embryo-foetal toxicity that can be managed by adhering to the use of effective contraception as described in the product information. Embryo-foetal toxicity will be further characterised using routine pharmacovigilance which includes the use of a pregnancy follow-up form to gather information on pregnancy outcomes.

Public health impact:

There are limited human data available regarding the potential effect of ivosidenib on pregnancy or development of the foetus, but nonclinical findings suggest a potential risk to the foetus. Both newly diagnosed AML with IDH1 mutation and CCA with IDH1 mutation are rare conditions and therefore the public health impact is expected to be low. There is no indication that the frequency or severity will be any different in the postmarketing setting.

SVII.3.2. Presentation of the missing information

Use in patients with moderate and severe hepatic impairment

Evidence source and strength of evidence:

Ivosidenib is metabolised predominantly by CYP3A4, hence there is the potential for hepatic impairment to affect ivosidenib exposure.

The PK of ivosidenib was evaluated in healthy subjects with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment (Study AG120-C-012). Using the NCI classification, no clinically meaningful effects on the PK of ivosidenib were observed in patients with mild hepatic impairment. The PK of ivosidenib in patients with moderate and severe hepatic impairment (Child-Pugh Class B and C) are unknown in patients with newly diagnosed AML and with cholangiocarcinoma. No PK data in patients with hepatic impairment stratified by the Child Pugh classification are available. Therefore, ivosidenib should only be used with caution in these patients with close monitoring.

In Study AG120-C-012, which was conducted to investigate the effect of mild and moderate hepatic impairment on the PK, safety, and tolerability of ivosidenib, there was no evidence of any increased risk associated with ivosidenib in subjects with mild or moderate hepatic impairment compared to matched subjects with normal hepatic function.

Use in patients with moderate and severe hepatic impairment is missing information for both newly diagnosed AML with IDH1 mutation and CCA with IDH1 mutation due to limited exposure in this population. In study AG120-C-009 patients exposed to ivosidenib + azaciditine had either normal liver function (84.5%) or mild hepatic impairment (15.5%) at baseline. No patient was categorised as having moderate or severe hepatic impairment at baseline as assessed by National Cancer Institute Organ Dysfunction Working Group (NCI ODWG) Criteria. In Study AG120-C-005, among patients randomized and exposed to ivosidenib and placebo, most of the patients had either normal liver function (50.4% vs. 57.6%) or mild hepatic impairment (48.0% vs. 42.4%) at baseline, with only a few patients included with moderate liver impairment (1.6% vs. 0%). No patient was categorised as having severe hepatic impairment at baseline as assessed by NCI ODWG Criteria.

Population in need of further characterisation:

Overall, clinical data suggest that no dose adjustment is required in patients with mild or moderate hepatic impairment. The PK of ivosidenib in patients with moderate and severe hepatic impairment are unknown and therefore a recommended dose has not been determined for these patients.

Use in patients with moderate and severe hepatic impairment will be further characterised in an organ impairment study S095031-218, which replaces the previously planned substudy of Study AG120-C-001 to evaluate the PK, PD, safety and tolerability of ivosidenib in adult subjects with IDH1-mutated malignancies.

Use in patients with severe renal impairment

Evidence source and strength of evidence:

Renal elimination does not play an important role in the excretion of ivosidenib as determined in human AME study AG120-C-003. Since urinary excretion is a minor elimination pathway (approximately 9.9%), renal impairment is unlikely to have a clinically relevant impact on ivosidenib elimination.

Use in patients with severe renal impairment is missing information for both AML with IDH1 mutation and CCA with IDH1 mutation due to the limited exposure in this population in clinical trials.

In Study AG120-C-009, most of the patients exposed to ivosidenib + azaciditine had either normal renal function (33.8%) or mild renal impairment (46.5%) at baseline as assessed by estimated Glomerular Filtration Rate (eGFR), with fewer patients included with moderate renal impairment (16.9%). There were only 2 (2.8%) patients with severe renal impairment.

AEs in these 2 subjects were consistent with the overall safety profile and analysis population. Most commonly occurring AEs by Grade and seriousness differed for each patient. No specific pattern of AEs by System organ class (SOC) was identified and no clinically meaningful differences were observed. Overall, most AEs in both subjects were predominantly nonserious and low grade (Grade 1 or Grade 2). Only one subject experienced an AE from the Renal and urinary disorders SOC (PT: Urinary retention), which was assessed as Grade 1 and nonserious. SAEs reported in one subject with a history of blood creatinine increased, dyspnoea, peripheral oedema, and Sweet's syndrome included Hypoxia, Fibrinogen decrease, Lung infection, and Pulmonary embolism; each was Grade 3. In the second subject, with a history of colon and gastric cancer, intraductal papillary mucinous neoplasm, renal disorder, spinal osteoarthritis, aortic aneurysm, aortic valve incompetence, hypertension, SAEs included Febrile neutropenia and Differentiation syndrome.

In Study AG120-C-005, among patients randomized and exposed to ivosidenib and placebo most of the patients had either normal renal function (43.1% vs. 33.9%) or mild renal impairment (47.2% vs. 39.0%) at baseline as assessed by eGFR, with fewer patients included with moderate renal impairment (9.8% vs. 27.1%). No patients with severe renal impairment were included in this study.

No dose adjustment is required in patients with mild (eGFR ≥60 to <90 mL/min/1.73 m^2) or moderate (eGFR ≥30 to <60 mL/min/1.73 m^2) renal impairment.

Population in need of further characterisation:

The pharmacokinetics of ivosidenib in patients with severe renal impairment or renal impairment requiring dialysis (eGFR <30 mL/min/1.73 m^2) are unknown; therefore, a recommended dose has not been determined for these patients.

Use in patients with severe renal impairment will be further characterised in an organ impairment study S095031-218, which replaces the previously planned substudy of Study AG120-C-001 to evaluate the PK, PD, safety and tolerability of ivosidenib in adult subjects with IDH1-mutated malignancies.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 25: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Differentiation Syndrome in patients with AML
	QT prolongation
Important potential risks	Embryo-foetal toxicity
Missing information	Use in patients with moderate and severe hepatic impairment
	Use in patients with severe renal impairment

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific follow-up forms will be used as routine pharmacovigilance activities beyond adverse reactions reporting and signal detection to collect additional information on post-authorisation cases of differentiation syndrome and on pregnancy outcomes (ANNEX 4).

III.2 Additional pharmacovigilance activities

III.2.1. Organ impairment study:

The use of ivosidenib in patients with moderate and severe hepatic or severe renal impairment will be investigated as part of the organ impairment study S095031-218, which replaces the previously planned organ impairement substudy of AG120-C-001.

Of note, there is no evidence to suggest that the risk of exposure to ivosidenib in patients with renal or hepatic impairment should be any different for patients with haematological malignancies compared with those with solid tumours. The synopsis is presented below:

Study short name and title:

Study S095031-218 is a Phase 1, multicentre, open-label organ impairment study to evaluate the PK, PD, safety and tolerability of ivosidenib in subjects with moderate hepatic impairment, severe hepatic impairment, or severe renal impairment with haematologic malignancies or solid tumors excluding brain tumors with an IDH1 mutation

Study objectives:

The primary objective of the study is: To assess the PK of ivosidenib administered at 500 mg QD in subjects with IDH1-mutated hematologic malignancies or solid tumors excluding brain tumors with moderate hepatic impairment, severe hepatic impairment, or severe renal impairment compared with subjects with IDH1-mutated hematologic malignancies or solid tumors excluding brain tumors with adequate hepatic and/or renal function.

Study design:

Study S095031-218 is a Phase 1, multicentre, open-label, safety, PK, PD and tolerability study of orally administered ivosidenib in patients with advanced haematological malignancies or solid tumors excluding brain tumors that harbour an IDH1 mutation.)

Study population:

Approximately 30 participants will be enrolled into 5 groups (6 participants in each group) and according to their hepatic/renal function. The groups are: moderate hepatic impairment, severe hepatic impairment, severe renal impairment, adequate hepatic function, adequate renal function.

Hepatic/renal impairment study design:

Patients will be treated with ivosidenib 500 mg QD. Assessments for screening, safety and tolerability, and end of treatment/follow-up will follow the same schedule as the initial organ impairment substudy AG120-C-001. Total bilirubin or creatinine clearance, as applicable based on the patient's organ impairment, will be repeated within 24 hours before the first dose of ivosidenib to confirm eligibility.

The NCI ODWG criteria are used to define moderate hepatic impairment and severe hepatic impairment; creatinine clearance (estimated according to the Cockcroft-Gault equation) is used to define severe renal impairment:

- Moderate hepatic impairment is defined as total bilirubin >1.5 to ≤3.0 × ULN and any AST.
- Severe hepatic impairment is defined as total bilirubin >3.0 × ULN and any AST.
- Severe renal impairment is defined as creatinine clearance ≥15 mL/min to ≤29 mL/min.

Milestones:

Milestone	**Planned date**
Final study report	Planned for Q2 2031

III.2.2. Patient survey study to assess the effectiveness of additional risk minimisation measures:

A Patient Alert Card (PAC) is part of an additional risk minimization measure for differentiation syndrome in AML indication, focusing on the key elements to alert patients on the symptoms of differentiation syndrome and the importance of seeking medical advice. The PAC will be distributed inside each pack of ivosidenib.

A dedicated study for measuring effectiveness of additional risk minimisation measures on differentiation syndrome (PAC) will be conducted. This study will be classified as a Post-Authorisation Safety Study (PASS) and will follow the European (EU) Good Pharmacovigilance Practices (GVP) Module XVI and VIII guidelines. The synopsis is presented below:

Study short name and title:

Cross-sectional study to assess the effectiveness of the patients' alert card to inform on risk of differentiation syndrome in AML patients treated with TIBSOVO® (Ivosidenib).

Rational and Study Objectives:

The study will evaluate the effectiveness of the PACs to inform on the risk of differentiation syndrome in AML patients treated with TIBSOVO® (Ivosidenib), using process dimensions for patients' awareness, receipt of the material, reading, utility of the PAC, self-reported behaviour, and knowledge.

Study Design:

This study will be a multi-national, observational cross-sectional survey among adult patients who have recently received TIBSOVO® (Ivosidenib) for treatment of AML, that will be conducted in at least three countries in the European Union (EU).

The survey will be initiated around 12 months after TIBSOVO® launch in each EU selected country. EU countries will be selected based on launch date and the volume of prescriptions in AML indication. The timing of the survey initiation and implementation will vary according to the individual country launch plans and the extent of TIBSOVO® uptake after launch. The survey will be a paper survey.

Study Population:

Patients will be identified through their Healthcare Professionals (HCPs) – (physicians and nurses) and will be included in the study if they are aged ≥18 years at recruitment, have taken Ivosidenib for newly diagnosed AML in the previous 6 months, and are able to understand and complete the consent form and patient survey. Patient selection will be based on systematic sampling, i.e., all consecutive eligible patients are expected to be included in the study, with no selection other than the eligibility criteria and the study period defined.

Physicians will be identified using the lists of AML specialists provided by the Marketing Authorisation Holder. Nurses will be identified through physicians. A pilot step will be conducted to determine the feasibility of recruitment and the patients/Healthcare professionals (HCPs) ratio to be used in the study.

Study Variables:

The survey will collect data resulting from the PAC of TIBSOVO®, referring in particular to the patient's receipt, the understanding of DS risk, the correct identification of these symptoms onset and the knowledge of the right actions to be taken. Additionally, the survey will collect information on demographic characteristics of patients including age, sex, geographical location, the time under TIBSOVO® treatment, the work or retirement status, known cognitive impairment and any concurrent disease that may impact patient's cognitive function.

Data Sources:

Structured, self-administered questionnaire comprising closed-ended questions or statements with multiple response choices will be used to collect the survey data. A user testing evaluation will be conducted prior to the master study.

Study Size:

Considering that around 200-300 patients will have been treated in Europe 12 months after launch in each country, and an expected estimate of 80% of understanding rate of the PACs, 80 evaluable surveys for primary objective are required to allow a precision of 8.8%, i.e. a confidence interval of [71.2%-88.8%], for a confidence level of 95% corresponding to a 0.05 alpha. Surveys will be considered "evaluable for primary objective" when at least 4 questions related to the primary outcome are answered.
As a 60% response rate is expected, 133 patients will have to be recruited to achieve the targeted number of evaluable surveys for primary objective.
The study size will be re-estimated after a pilot step assessment.

Data Analysis:

Data collected from the survey will be reported as descriptive statistics. Frequency distributions will be calculated for items that address the survey objective (excluding demographic questions).

Milestones:

The protocol was submitted to the Pharmacovigilance Risk Assessment Committee (PRAC) within 3 months following European Commission (EC) decision. The final study report is planned in Q2 2027.

III.3 Summary Table of additional Pharmacovigilance activities

Table 26: On-going and Planned Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestone	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Organ impairment S095031-218 Study (in replacement of Organ impairment substudy of AG120-C-001) to evaluate the PK, PD, safety and tolerability of ivosidenib in subjects with moderate hepatic impairment, severe hepatic impairment, or severe renal impairment with malignancies with an IDH1 mutation **Status:** Planned	To evaluate the pharmacokinetics, safety and tolerability of ivosidenib in patients with malignancies with an IDH1 mutation with moderate hepatic impairment, severe hepatic impairment or severe renal impairment.	• Use in patients with moderate and severe hepatic impairment • Use in patients with severe renal impairment	Final report available	Planned for Q2 2031.

Study Status	Summary of objectives	Safety concerns addressed	Milestone	Due dates
Patients survey study to assess the effectiveness of the additional risk minimisation measures. Cross-sectional study to assess the effectiveness of the patients' alert card to inform on risk of differentiation syndrome in AML patients treated with TIBSOVO® (Ivosidenib). **Status:** Ongoing	To evaluate the effectiveness of the PACs to inform on the risk of differentiation syndrome in AML patients treated with TIBSOVO® (Ivosidenib), using process dimensions for patients' awareness, receipt of the material, reading, utility of the PAC, self-reported behaviour, and knowledge.	• Differentiation Syndrome in the AML indication.	Final report available	Planned for Q2 2027

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable, since no post-authorisation efficacy studies are proposed.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 27: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
#1. Differentiation syndrome in patients with AML (Important identified risk)	Routine risk communication: SmPC section 4.8. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Monitoring and management of differentiation syndrome along with its treatment and temporary interruption of ivosidenib is advised in SmPC section 4.2, 4.4 and 4.5. • Warning is given in SmPC section 4.4 and PL section 2 that differentiation syndrome may be life-threatening or fatal if not treated along with description of symptoms. • Advice is given in PL section 4 to seek urgent medical attention if patient experiences side effects/symptoms corresponding to differentiation syndrome. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine. Treatment to be initiated by experienced oncologist.
#2. QT prolongation (Important identified risk)	Routine risk communication: SmPC section 4.8. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Contraindications are listed in SmPC section 4.3 and reflected in the PL section 2. • Guidance on regular, and when required continuous, ECG monitoring and management of QTc interval prolongation is detailed in SmPC section 4.2 and 4.4. Information on regular ECG monitoring is also reflected in the PL section 2. • Monitoring and management of concomitant administration of moderate or strong CYP3A4 inhibitors (leads to increase in plasma concentrations of ivosidenib) and medicines that prolong QT interval is advised in SmPC section 4.2, 4.4 and 4.5. • Warning is given in the SmPC section 4.4 that QTc interval prolongation has been reported following treatment with ivosidenib. Patients with congestive heart failure or electrolyte abnormalities should be monitored closely, with periodic monitoring of ECGs and electrolytes, during treatment with ivosidenib. Ivosidenib should be used with caution in patients with albumin levels below the normal range and underweight patients. • Warning is given in the PL section 2 and 4 that ivosidenib can cause a serious condition known as QTc interval prolongation which can be life threatening. Advice is given to seek urgent medical attention if patient

Safety concern	Routine risk minimisation activities
	experiences side effects/symptoms corresponding to QTc interval prolongation. • The patient should talk to the doctor if the patient has heart problems or have problems with abnormal electrolytes levels or patient is taking any medicines that affects the heart. Furthermore, regular ECG monitoring is advised as per PL section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine. Treatment to be initiated by experienced oncologist.
#3. Embryo-foetal toxicity (Important potential risk)	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Warning is given in the SmPC section 4.4, 4.6 and PL section 2 that the women of childbearing potential should have a pregnancy test prior to start of therapy and should avoid becoming pregnant during therapy. The women of childbearing potential and males with female partners of childbearing potential should use effective contraception during treatment with ivosidenib and for at least 1 month after the last dose. • Caution is advised that ivosidenib may decrease systemic concentrations of hormonal contraceptives. Concomitant use of a barrier method of contraception is recommended as per section 4.4, 4.5 and 4.6 of the SmPC and PL section 2. • Ivosidenib is not recommended for use during pregnancy and in women of childbearing potential and males with partners of childbearing potential not using effective contraception; if a patient (or female partner of a treated male patient) becomes pregnant during treatment or during the one-month period after the last dose, they should be informed of the potential risk to the foetus as advised in section 4.6 of the SmPC. • Ivosidenib is not recommended during pregnancy as it may harm the unborn baby. Furthermore, if the patient is pregnant, thinks she might be pregnant or is planning to have a baby, consultation from doctor before taking ivosidenib is advised as per PL section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine. Treatment to be initiated by experienced oncologist.
#4. Use in patients with moderate and severe hepatic impairment (Missing information)	Routine risk communication: Section 4.8 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Warning is given in SmPC section 4.2 and 4.4 that the safety and efficacy of ivosidenib have not been established in patients with moderate and severe hepatic impairment (Child Pugh classes B and C respectively). Therefore, ivosidenib should be used with caution and this patient population should be closely monitored. • Advice is given in PL section 2 to talk to the doctor if patient has any liver problem before taking ivosidenib.

Safety concern	Routine risk minimisation activities
	Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine. Treatment to be initiated by experienced oncologist
#5. Use in patients with severe renal impairment (Missing information)	Routine risk communication: None. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Warning is given in SmPC section 4.2 and 4.4 that the safety and efficacy of ivosidenib have not been established in patients with severe renal impairment (eGFR < 30 ml/min/1.73 m^2) therefore, ivosidenib should be used with caution and this patient population should be closely monitored. • Advice is given in PL section 2 to talk to the doctor if patient has any kidney problem before taking ivosidenib. Other routine risk minimisation measures beyond the Product Information: Legal status: Prescription only medicine. Treatment to be initiated by experienced oncologist.

V.2. Additional Risk Minimisation Measures

Patient Alert Card

Besides routine risk minimisation activities (SmPC and patient information leaflet), an additional risk minimisation activity, a Patient Alert Card (PAC), is considered to be necessary for the important identified risk of Differentiation Syndrome (DS) in AML indication.

Objective:

To raise awareness of AML patients on differentiation syndrome, focusing on the key elements to alert patients on its symptoms and the importance of seeking medical advice.

Rationale for the additional risk minimisation activity:

Differentiation syndrome may be life-threatening or fatal if not treated.

Target audience and planned distribution path:

The target audience is patients. The PAC will be distributed inside each pack of ivosidenib.

Plans to evaluate the effectiveness of the interventions and criteria for success:

A synopsis of the patients' survey PASS to assess the effectiveness of the additional risk minimisation measures is presented in the above section Part III.2-Additional pharmacovigilance activities. The study will assess process dimensions for patients' receipt, understanding of DS risk and its symptoms, and use resulting from the ivosidenib PAC on DS in AML. No outcome indicators will be estimated due to the absence of a valid comparison to evaluate the reduction of the risk.

MAH considers the additional risk minimisation measure to be successful if the majority of patients understand the key messages being communicated.

A pilot step will be conducted before the conduct of the survey to evaluate its feasibility and identify challenges and barriers. The low incidence of AML and the rarity of the IDH1 mutation allowing for the use of ivosidenib could result in a long period for recruitment of patients and

a low rate of survey response and completeness. In addition to this measure, the PAC will also be assessed by routine pharmacovigilance and reported in the PSURs, including the evaluation of post-marketing reports of differentiation syndrome to assess trends indicating delays in recognizing symptoms or seeking medical attention.

V.3 Summary of risk minimisation measures

Table 28: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Differentiation Syndrome in patients with AML (Important identified risk)	Routine risk minimisation measures: *SmPC section 4.2, 4.4 and 4.5 where advice is given for monitoring and management of differentiation syndrome along with its treatment and temporary interruption of ivosidenib.* *SmPC section 4.4 and PL section 2 where warning is given in that differentiation syndrome may be life-threatening or fatal if not treated along with description of symptoms.* *SmPC section 4.8.* *PL section 4 where advice is given to seek urgent medical attention if patient experiences side effects/symptoms corresponding to differentiation syndrome.* Legal status: Prescription only medicine. Treatment to be initiated by experienced oncologist. Additional risk minimisation measures: Patient Alert Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Differentiation syndrome follow-up questionnaire. Additional pharmacovigilance activities: • Cross-sectional study to assess the effectiveness of the patients' alert card to inform on risk of differentiation syndrome in AML patients treated with TIBSOVO® (Ivosidenib). • Final report due date: Planned for Q2 2027.
QT prolongation (Important identified risk)	Routine risk minimisation measures: *SmPC section 4.3 and PL section 2 where contraindications are listed for patients with increase risk of QTc prolongation* *SmPC section 4.2 and 4.4 where guidance is given on regular, and when required continuous, ECG monitoring and management of QTc interval prolongation, also reflected in the PL section 2.* *SmPC section 4.2, 4.4 and 4.5. where advice is given for monitoring and management of concomitant administration of moderate or strong CYP3A4 inhibitors (leads to increase in plasma concentrations of ivosidenib) and medicines that prolong QT interval.* *SmPC section 4.4 where warning is given that QTc interval prolongation has been reported following treatment with ivosidenib. Patients with congestive heart failure or electrolyte abnormalities should be monitored closely, with periodic*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	monitoring of ECGs and electrolytes, during treatment with ivosidenib.Ivosidenib should be used with caution in patients with albumin levels below the normal range and underweight patients. *SmPC section 4.8.* *PL section 2 and 4 where warning is given that ivosidenib can cause a serious condition known as QTc interval prolongation which can be life threatening. Advice is given to seek urgent medical attention if patient experiences side effects/symptoms corresponding to QTc interval prolongation* *PL section 2 where patient is advised to talk to the doctor if the patient has heart problems or have problems with abnormal electrolytes levels or patient is taking any medicines that affects the heart, along with advice on regular ECG monitoring.* Legal status: Prescription only medicine. Treatment to be initiated by experienced oncologist Additional risk minimisation measures: None	
Embryo-foetal toxicity (Important potential risk)	Routine risk minimisation measures: *SmPC section 4.4, 4.6 and PL section 2 where warning is given that woman of childbearing potential should have a pregnancy test done prior to start of therapy and the women of childbearing potential and males with female partners of childbearing potential should use effective contraception during treatment with ivosidenib and for at least 1 month after the last dose.* *SmPC section 4.4, 4.5, 4.6 and PL section 2 where caution is advised that ivosidenib may decrease the systemic concentrations of hormonal contraceptives and, therefore, concomitant use of a barrier method of contraception is recommended.* *SmPC section 4.6 where advice is given that ivosidenib is not recommended for use during pregnancy and in women of childbearing potential not using effective contraception; if a patient (or female partner of a treated male patient) becomes pregnant during treatment or during the*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Pregnancy follow-up questionnaire. Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	one-month period after the last dose, they should be informed of the potential risk to the foetus. *PL section 2 where advice is given that ivosidenib is not recommended during pregnancy as it may harm the unborn baby. Furthermore, patient should consult doctor if the patient is pregnant, thinks she might be pregnant or is planning to have a baby, before taking ivosidenib.* Legal status: Prescription only medicine. Treatment to be initiated by experienced oncologist Additional risk minimisation measures: None	
Use in patients with moderate and severe hepatic impairment (Missing information)	Routine risk minimisation measures: *SmPC section 4.2 and 4.4 where warning is given that the safety and efficacy of ivosidenib have not been established in patients with moderate and severe hepatic impairment (Child Pugh classes B and C respectively), therefore ivosidenib should be used with caution and this patient population should be closely monitored.* *SmPC section 4.8.* *PL section 2 where advice is given to talk to the doctor if the patient has any liver problem before taking ivosidenib.* Legal status: Prescription only medicine. Treatment to be initiated by experienced oncologist Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • Organ impairment study study S095031-218 in replacement of Organ impairment substudy of AG120-C-001. • Final report due date: Planned for Q2 2031.
Use in patients with severe renal impairment (Missing information)	Routine risk minimisation measures: *SmPC section 4.2 and 4.4 where warning is given that the safety and efficacy of ivosidenib have not been established in patients with severe renal impairment (eGFR < 30 ml/min/1.73 m^2) therefore, ivosidenib should be used with caution and this patient population should be closely monitored.* *PL section 2 where advice is given to talk to the doctor if the patient has any kidney problem before taking ivosidenib.* Legal status: Prescription only medicine.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • Organ impairment study study S095031-218 in replacement of Organ impairment substudy of AG120-C-001.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Treatment to be initiated by experienced oncologist Additional risk minimisation measures: None.	• Final report due date: Planned for Q2 2031.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Tibsovo (ivosidenib)

This is a summary of the risk management plan (RMP) for Tibsovo. The RMP details important risks of Tibsovo, how these risks can be minimised, and how more information will be obtained about Tibsovo's risks and uncertainties (missing information).

Tibsovo's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Tibsovo should be used.

This summary of the RMP for Tibsovo should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

I. THE MEDICINE AND WHAT IT IS USED FOR

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.

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.

It contains ivosidenib as the active substance and it is given orally. The recommended dose is 500 mg (2 tablets of ivosidenib 250 mg) once daily at about the same time each day.

Further information about the evaluation of Tibsovo's benefits can be found in Tibsovo's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage <link to product's EPAR summary landing page on the EMA webpage.>

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Tibsovo, together with measures to minimise such risks and the proposed studies for learning more about risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Tibsovo, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report assessment - so that

immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Tibsovo is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Tibsovo are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Tibsovo. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Differentiation Syndrome in patients with AML
	QT prolongation
Important potential risks	Embryo-foetal toxicity
Missing information	Use in patients with moderate and severe hepatic impairment Use in patients with severe renal impairment

II.B Summary of important risks

Important identified risks: Differentiation Syndrome in patients with AML	
Evidence for linking the risk to medicine	Differentiation syndrome is a serious side effect that may occur in patients with acute myeloid leukaemia who have been treated with certain types of anticancer drugs, including ivosidenib. It is caused by a large, rapid release of cytokines (immune substances) from leukaemia cells that are affected by the anticancer drugs. Signs and symptoms of differentiation syndrome include fever; cough; trouble breathing; weight gain; swelling of the arms, legs, and neck; build-up of excess fluid around the heart and lungs; low blood pressure; and kidney failure. In a clinical study of ivosidenib and azacitidine given in combination for the treatment of AML (AG120-C-009) the percentage of subject in whom differentiation syndrome was reported was 13.9%. In the control group treated with azacitidine alone, the percentage of subject in whom differentiation syndrome was reported was 8.1%. Patients treated with ivosidenib were reported to have recovered with appropriate treatment. The evidence is derived from clinical trials. Evidence from this source is considered to be a reliable predictor of how subjects will respond to treatment in clinical practice, by convention.
Risk factors and risk groups	All patients treated with ivosidenib for IDH1 mutation-positive AML are potentially at risk of differentiation syndrome. There are no known factors that might predict the risk in these patients.

Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.2, 4.4 and 4.5 where advice is given for monitoring and management of differentiation syndrome along with its treatment and temporary interruption of ivosidenib.* *SmPC section 4.4 and PL section 2 where warning is given in that differentiation syndrome may be life-threatening or fatal if not treated along with description of symptoms.* *SmPC section 4.8.* *PL section 4 where advice is given to seek urgent medical attention if patient experiences side effects/symptoms corresponding to differentiation syndrome.* Legal status: Prescription only medicine. Treatment to be initiated by experienced oncologist. Additional risk minimisation measures: Patient Alert Card
Additional pharmacovigilance activity	Additional pharmacovigilance activity: Cross-sectional study to assess the effectiveness of the patients' alert card to inform on risk of differentiation syndrome in AML patients treated with TIBSOVO® (Ivosidenib).
Important identified risks: QT prolongation	
Evidence for linking the risk to medicine	QT prolongation may increase the risk of developing abnormal heart rhythms and may rarely lead to sudden cardiac arrest. Nonclinical evidence indicates that ivosidenib can prolong QT interval in a reversible manner. In a clinical study of ivosidenib and azacitidine given in combination for the treatment of AML (AG120-C-120) the percentage of subject in whom QT prolongation was reported was 27.8%. In the control group treated with azacitidine alone, the percentage of subject in whom QT prolongation was reported was 12.2%. In clinical studies of ivosidenib given for the treatment of cholangiocarcinoma the percentage of subject in whom QT prolongation was reported was 9.2%. The evidence is derived from clinical trials and nonclinical studies. Evidence from these sources is considered to be a reliable predictor of how subjects will respond to treatment in clinical practice, by convention.
Risk factors and risk groups	The following may increase the risk of developing QT prolongation or its symptoms: • A history of abrupt loss of consciousness, or of cardiac arrest • Having a first-degree relative (parent, sibling) with abnormal heart rhythm or fast and chaotic heartbeats (long QT syndrome) • Concomitant use of other medicines that may cause irregular heart rhythm or rapid heartbeats (prolonged QT intervals) • Being female and on heart medication • Excessive vomiting, diarrhoea or other conditions resulting in the loss of electrolytes.

Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.3 and PL section 2 where contraindications are listed for patients with increase risk of QTc prolongation.* *SmPC section 4.2 and 4.4 where guidance is given on regular, and when required continuous, ECG monitoring and management of QTc interval prolongation also reflected in the PL section 2.* *SmPC section 4.2, 4.4 and 4.5. where advice is given for monitoring and management of concomitant administration of moderate or strong CYP3A4 inhibitors (leads to increase in plasma concentrations of ivosidenib) and medicines that prolong QT interval.* *SmPC section 4.4 where warning is given that QTc interval prolongation has been reported following treatment with ivosidenib. Patients with congestive heart failure or electrolyte abnormalities should be monitored closely, with periodic monitoring of ECGs and electrolytes, during treatment with ivosidenib. Ivosidenib should be used with caution in patients with albumin levels below the normal range and underweight patients.* *SmPC section 4.8.* *PL section 2 and 4 where warning is given that ivosidenib can cause a serious condition known as QTc interval prolongation which can be life threatening. Advice is given to seek urgent medical attention if patient experiences side effects/symptoms corresponding to QTc interval prolongation* *PL section 2 where patient is advised to talk to the doctor if the patient has heart problems or have problems with abnormal electrolytes levels or patient is taking any medicines that affects the heart, along with advice on regular ECG monitoring.* Legal status: Prescription only medicine. Treatment to be initiated by experienced oncologist Additional risk minimisation measures: None
Important potential risk: Embryo-foetal toxicity	
Evidence for linking the risk to medicine	Embryo-foetal toxicity refers to the potential to injure the developing child in the womb. Evidence for embryofoetal toxicity is based on non-clinical studies, which may be relevant for humans. In the absence of evidence of the effects on the foetus in humans, embryofoetal toxicity is considered an important potential risk for ivosidenib. In non-clinical embryo-foetal toxicity studies, ivosidenib was associated with maternal toxicity and spontaneous abortions, decreased foetal body weights, delayed bone formation and variation in organ development (small spleen). Ivosidenib was also found to cross the placenta. Based on these studies, ivosidenib could cause foetal harm when administered to women during pregnancy.
Risk factors and risk groups	Sexually active women of childbearing potential and male patients whose partners are women of childbearing potential are at risk of the consequences of embryofoetal toxicity. Women of childbearing potential and males with partners of childbearing potential not using effective contraception during treatment with ivosidenib and for at least 1 month after the last dose are at risk. Patients treated with oral contraceptives not

	using a barrier method of contraception are also at increased risk, as ivosidenib may decrease the effectiveness of oral contraceptives.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4, 4.6 and PL section 2 where warning is given that woman of childbearing potential should have a pregnancy test done prior to start of therapy and the women of childbearing potential and males with female partners of childbearing potential should use effective contraception during treatment with ivosidenib and for at least 1 month after the last dose.* *SmPC section 4.4, 4.5, 4.6 and PL section 2 where caution is advised that ivosidenib may decrease the systemic concentrations of hormonal contraceptives and, therefore, concomitant use of a barrier method of contraception is recommended.* *SmPC section 4.6 where advice is given that ivosidenib is not recommended for use during pregnancy and in women of childbearing potential not using effective contraception; if a patient (or female partner of a treated male patient) becomes pregnant during treatment or during the one-month period after the last dose, they should be informed of the potential risk to the foetus.* *PL section 2 where advice is given that ivosidenib is not recommended during pregnancy as it may harm the unborn baby. Furthermore, patient should consult doctor if the patient is pregnant, thinks she might be pregnant or is planning to have a baby, before taking ivosidenib.* Legal status: Prescription only medicine. Treatment to be initiated by experienced oncologist Additional risk minimisation measures: None
Missing information: Use in patients with moderate and severe hepatic impairment	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.2 and 4.4 where warning is given that the safety and efficacy of ivosidenib have not been established in patients with moderate and severe hepatic impairment (Child Pugh classes B and C respectively) therefore ivosidenib should be used with caution and this patient population should be closely monitored.* *SmPC section 4.8.* *PL section 2 where advice is given to talk to the doctor if the patient has any liver problem before taking ivosidenib.* Legal status: Prescription only medicine. Treatment to be initiated by experienced oncologist Additional risk minimisation measures: None
Additional pharmacovigilance activity	Additional pharmacovigilance activity: Organ impairment study S095031-218 in replacement of Organ impairment substudy of AG120-C-001.
Missing information: Use in patients with severe renal impairment	
Risk minimisation measures	Routine risk minimisation measures:

	SmPC section 4.2 and 4.4 where warning is given that the safety and efficacy of ivosidenib have not been established in patients with severe renal impairment (eGFR < 30 ml/min/1.73 m^2) therefore, ivosidenib should be used with caution and this patient population should be closely monitored. *PL section 2 where advice is given to talk to the doctor if the patient has any kidney problem before taking ivosidenib.* Legal status: Prescription only medicine. Treatment to be initiated by experienced oncologist Additional risk minimisation measures: None.
Additional pharmacovigilance activity	Additional pharmacovigilance activity: Organ impairment study S095031-218 in replacement of Organ impairment substudy of AG120-C-001.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Tibsovo.

II.C.2 Other studies in post-authorisation development plan

II.C.2.1 Organ impairment study S095031-218

There is one organ impairment study S095031-218, planned to investigate the use of ivosidenib in patients with hepatic or renal impairment in replacement of OI substudy of study AG120-C-001.

Purpose of the study:

To evaluate the pharmacokinetics, safety and tolerability of ivosidenib in patients with malignancies with an IDH1 mutation with moderate hepatic impairment, severe hepatic impairment or severe renal impairment.

II.C.2.2 Cross-sectional study to assess the effectiveness of the patients' alert card to inform on risk of differentiation syndrome in AML patients treated with TIBSOVO® (Ivosidenib)

There is one patients survey study planned to assess the effectiveness of the risk minimisation measures.

Purpose of the study:

To evaluate the effectiveness of the PACs to inform on the risk of differentiation syndrome in AML patients treated with TIBSOVO® (Ivosidenib), using process dimensions for patients' awareness, receipt of the material, reading, utility of the PAC, self-reported behaviour, and knowledge.

PART VII: ANNEXES

Table of contents

Annex 4 – Specific adverse drug reaction follow-up forms

Annex 4.1: Ivosidenib follow-up questionnaire – Differentiation syndrome

Annex 4.2: Ivosidenib follow-up questionnaire – Pregnancy

DIFFERENTIATION SYNDROME (DS) POST MARKETING QUESTIONNAIRE

Please complete this form and return with any supporting documentation to:
Email: << >> If you have questions, please call: << >>

Reporter's name:	**Manufacturer Case Number:**	
Patient initials: ____ ____ ____	**Patient DOB/Age:**	**Patient gender:** ☐ **Male** ☐ **Female**

Differentiation Syndrome Event Onset	Date of first symptom onset: (dd/mmm/yyyy)	Date of diagnosis: (dd/mmm/yyyy)

IVOSIDENIB INFORMATION

Lot # & Exp. date:		Indication		
Start Date: (dd/mmm/yyyy)	Stop Date: (dd/mmm/yyyy)	Route	Frequency:	Dose

Action taken with ivosidenib ☐ Ongoing ☐ Temporarily withheld ☐ Restarted ☐ Dose decreased: New dose _____ mg ☐ Withdrawn

Restart Date: (dd/mmm/yyyy)	Stop Date: (dd/mmm/yyyy)	Route	Frequency:	Dose

Did the DS event resolve after the drug was withdrawn, temporarily withheld or decreased? ☐Yes ☐No ☐N/A
If yes, did the event reoccur or worsen after re-introduction? ☐Yes ☐No

Differentiation Syndrome Event: Signs and Symptoms **Check all that apply**

☐High WBC count Highest Value: Units: Date: (dd/mmm/yyyy)

☐New or worsened pulmonary symptoms: ☐Shortness of breath ☐Low blood oxygen content/low oxygen saturation ☐Other

☐New or worsened findings on chest imaging ☐ X ray ☐ CT ☐ Other_____
☐Pulmonary infiltrates ☐Pleural effusion ☐Pericardial effusion ☐Pulmonary Edema
Date and Findings:
_____

☐New or worsened peripheral edema and/or fluid overload. Edema severity: ☐+1 ☐+2 ☐+3 ☐+4
Weight increased by kg/lb

☐Hypotension/Low blood pressure: Lowest BP during event:_____ Date:_____(dd/mmm/yyyy)

☐Fever Highest body temperature during the event: ☐°C ☐°F

☐New or worsened rash: location & description:

☐New or worsened lymph node enlargement

☐New or worsened musculoskeletal pain

Did the patient experience? (check all that apply)
☐Acute Kidney Injury: Please complete the Acute kidney injury section on next page
☐Tumor lysis syndrome: Please complete the Tumor lysis section on the next page
☐New or worsened Pneumonia: Treatment:

Other symptoms experienced by the patient:

Laboratory data: Please complete the following

	Around the start of ivosidenib		**Highest value during DS**		**Value at resolution**	
	Result	Date (dd/mmm/yyyy)	Result	Date (dd/mmm/yyyy)	Result	Date (dd/mmm/yyyy)
Bone marrow myeloblasts						
White blood cell count						
Peripheral myeloblasts						
Neutrophil count						
Platelets						
Monocytes						
Hemoglobin						

Culture results (date, source and result)

Differentiation Syndrome Treatment

DS treatment medication

	Start date (dd/mmm/yyyy)	Stop date (dd/mmm/yyyy)	Dose	Route	Frequency
Hydroxyurea					

DIFFERENTIATION SYNDROME (DS) POST MARKETING QUESTIONNAIRE (page 2)
Manufacturer Case Number:

Systemic steroid (specify):						
Diuretic (specify):						
Other(specify):						
Other treatments such as hospitalization, supplemental O_2, etc.						

Patient Outcome

☐Improved on Steroid treatment Date of improvement_____(dd/mmm/yyyy) Date of recovery_____(dd/mmm/yyyy)
☐Symptoms reoccurred following steroid discontinuation (specify): Other:

Tumor Lysis Syndrome (TLS) (complete only if the patient had TLS)

Date of initial symptoms	(dd/mmm/yyyy)	Date of diagnosis	(dd/mmm/yyyy)
Medical History: check all that apply (Prior to ivosidenib)	☐ Hyperuricemia ☐Renal disease (Specify): ☐ Dehydration ☐Other (specify):		

Laboratory results indicating TLS	Laboratory test	Result and units
	Serum potassium	
	Serum uric acid	
	Serum phosphate	
	Serum calcium	
	Serum creatinine	

Complications of TLS	
Treatment of TLS	
TLS outcome	□ **Complete Recovery** Date of resolution: _____(dd/mmm/yyyy) □ **Ongoing** □ **Unknown** □ **Recovered with sequelae** Describe sequelae: _____Date of resolution:_____(dd/mmm/yyyy) □ **Fatal** Date of death (dd/mmm/yyyy) Autopsy done: □Yes □No (If yes, please attach autopsy report) Cause of death:

Acute Kidney Injury (AKI) (complete only if the subject had AKI)

Date of initial symptoms	(dd/mmm/yyyy)	Date of diagnosis	(dd/mmm/yyyy)
Renal function prior to ivosidenib	☐Normal ☐Abnormal (Specify): Creatinine prior to ivosidenib: _____/_____(units)		

Suspect medications prior to AKI	Dose	Route	Frequency	Start date (dd/mmm/yyyy)	Stop date (dd/mmm/yyyy)	Indication

Complications of TLS	Laboratory test	Result and Units	
	Serum creatinine		
	Serum BUN		
	Serum sodium		
	Serum potassium		
	Serum chloride		
	Serum bicarbonate		
	GFR		
	Arterial Blood Gas		

Complications of AKI	
Treatment of AKI	Did the subject receive dialysis? ☐Yes ☐No
AKI outcome	□ **Complete Recovery** Date of resolution: _____(dd/mmm/yyyy) □ **Ongoing** □ **Unknown** □ **Recovered with sequelae** Describe sequelae: _____Date of resolution: _____(dd/mmm/yyyy) □ **Fatal** Date of death (dd/mmm/yyyy) Autopsy done: □Yes □No (If yes, please attach autopsy report) Cause of death:

Completed by: **Date:**

PREGNANCY FOLLOW-UP (initial form)

A - REPORTER (All Personal data have to be anonymised before sending to PV)

Full name: City: Country:

Phone No.:

B - INFORMATION ABOUT THE PREGNANT WOMAN

Last name: ☐☐☐ First name: ☐ Date of birth:

First 3 letters* First letters (DD-MM-YYYY)

Date of last menstruation (DD-MM-YYYY):

* For patients whose last name or first name consists of only 2 or 3 letters, only the first letter is entered

Exposure to medication

Medication ① :

Daily dosage : Route :

Date of first intake (DD-MM-YYYY): Indication:

Date of last intake (DD-MM-YYYY):

Concomitant medications during pregnancy (including oral contraceptives)

	②	③	④	⑤	⑥
Name					
Daily dosage					
Date first intake					
Date last intake					

Use of recreational substance(s) by the pregnant woman

Tobacco: cigarettes/day: Alcohol:

Illicit drugs:

Obstetrical history

Number of pregnancies : Number of full-term deliveries:

Number of premature deliveries: Number of abortions:

- spontaneous:
- therapeutic:

Previous foetal/neonatal anomalies (specify):

Complications during previous pregnancies(specify):

Medical history of the pregnant woman

Source of the information: (All Personal data have to be anonymised before sending to PV)

Full name
Qualification
Address
Phone / Fax N°

Date of completion: / / Name *:

*All Personal data have to be anonymised before sending to PV

PREGNANCY FOLLOW-UP (final form)

A - REPORTER(All Personal data have to be anonymised before sending to PV)

Full name: City: Country:

Phone No.:

B - PREGNANCY OUTCOME

Complications for the mother linked to the pregnancy

Arterial hypertension: Diabetes:

Infection: Other (specify):

Other medications received during the pregnancy

Name					
Daily dosage					
Date first intake					
Date last intake					

Relevant examinations/biological results (during the pregnancy follow-up)

Outcome

☐ Live birth: proceed with section C (neonatal information)

☐ Spontaneous abortion / stillborn Date (DD-MM-YYYY):

☐ Congenital anomaly detected (specify):

☐ Therapeutic termination Date (DD-MM-YYYY):

Reason for the termination and fœtal test results and:

C - NEONATAL INFORMATION

Date of birth (DD-MM-YYYY): Gestational age at birth: Weeks:

Gender: ☐ M ☐ F Weight: kg Height: cm

Apgar scores: 1min: 5min:

Physical examination at birth:

☐ No dysmorphic features identified

☐ Minor anomaly (specify):

☐ Major malformation (specify):

☐ Syndrome / diagnosis (specify):

☐ Other significant findings (specify):

Date of completion: / / Name* :

*All Personal data have to be anonymised before sending to PV

Annex 6 – Details of proposed additional risk minimisation activities

Key messages of the additional risk minimisation measure (Patient Alert Card):

Prior to the launch of Tibsovo in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at patients with AML prescribed Tibsovo, to further provide information regarding the important identified risk of differentiation syndrome.

The MAH shall ensure that in each Member State where Tibsovo is marketed, all patients who are expected to use Tibsovo are provided with the following educational package:

The patient information pack:

- Patient information leaflet
- Patient alert card:
    - Information for patients with AML that Tibsovo treatment may cause differentiation syndrome.
    - Description of signs or symptoms of the safety concern and when to seek medical care if differentiation syndrome is suspected
    - A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using Tibsovo.
    - Contact details of the treating physician who has prescribed Tibsovo.
    - Needs to be carried all the time and presented to any healthcare professional.

The patient alert card will be integrated in the packaging and the content will be agreed as part of the labelling (Annex III).