EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 February 2023
EMA/173654/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tibsovo

International non-proprietary name: ivosidenib

Procedure No. EMEA/H/C/005936/0000

Note

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

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List of abbreviations

2-HG	2-hydroxyglutarate
AE	Adverse event
AESI	AEs of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
API	Active Pharmaceutical Ingredient
aPTT	Activated partial thromboplastin time
AR	Assessment Report
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the plasma concentration-time curve
AZA	Azacitidine
BID	Twice daily
BMI	Body Mass Index
BOR	Best overall response
BP	Blood pressure
BSA	Body surface area
C1D1	Cycle 1, Day 1
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
CFU	Colony Forming Units
CL/F	Steady state apparent clearance
Cmax	Maximum observed plasma concentration
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CoA	Certificate of Analysis
COVID-19	Coronavirus disease 2019
CPP	Critical process parameter
CQA	Critical Quality Attribute
CR	Complete remission
CRh	Complete remission with partial hematologic recovery
CRi	Complete remission with incomplete hematologic recovery
CRF	Case report form
CRp	Complete remission with incomplete platelet recovery
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
CV	Coefficient of variation
D	Day
DCO	Data cut off
DDI	Drug-drug interaction
DLT	Dose-limiting toxicity
DOCR	Duration of complete remission
DOR	Duration of response
DRT	Dose review team
DSC	Differential Scanning Calorimetry

EC	European Commission
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Groupe
eCRF	Electronic case report form
EFS	Event-free survival
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire
EOT	End of treatment
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FT-IR	Fourier Transform Infrared Spectroscopy
GC	Gas Chromatography
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HDPE	High Density Polyethylene
HIV	Human immunodeficiency virus
HMA	Hypomethylating agent
HPLC	High performance liquid chromatography
HR	Hazard ratio
HRQoL	Health-related quality of life
HSCT	Hematopoietic stem cell transplant
IB	Investigator's Brochure
IC	Induction chemotherapy
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IDH	Isocitrate dehydrogenase
IDH1	Isocitrate dehydrogenase 1
IDH1m	Isocitrate dehydrogenase 1 mutation-positive
IDMC	Independent Data Monitoring Committee
IPC	In-process control
ICP-MS	Inductively coupled plasma mass spectrometry
IR	Infrared
IRT	Interactive response technologies
IV	Intravenous
IWG	International Working Group
IWRS	Interactive Web Response System
Ka	Absorption rate
KF	Karl Fischer titration
KM	Kaplan-Meier
LDAC	Low-dose cytarabine
LDPE	Low Density Polyethylene
LOD	Loss on drying
LT	Less than
LVEF	Left ventricular ejection fraction
MA	Marketing Authorisation
MAA	Marketing Authorisation application
MAH	Marketing Authorisation holder
MC	Mutation clearance

MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	Morphologic leukemia-free state
MS	Mass Spectrometry
MTD	Maximum tolerated dose
MTBE	Methyl ter-butyl ether
NADP	Nicotinamide adenine dinucleotide phosphate
NADPH	Adenine dinucleotide phosphate
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ND	Not detected
NE	Not estimable
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NOR	Normal Operating Range
NYHA	New York Heart Association
OAT	Organic anion transporter
OOS	Out of Specifications
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PAR	Proven Acceptable Range
PBPK	Physiologically based pharmacokinetic
PCR	Polymerase chain reaction
PD	Progressive disease
PE	Polyethylene
PGI	Potential genotoxic impurity
PH	Proportional hazards
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic
PML	Progressive multifocal leukoencephalopathy
PO	Oral
PP	Polypropylene
PPS	Per-Protocol Set
PR	Partial remission
PRO	Patient-reported outcome
PS	Performance status
PT	Preferred Term
Q1	First quartile
Q3	Third quartile
QC	Quality Control
QD	Once daily
QoL	Quality of life
QP	Qualified person
QTc	Corrected QT interval
QTcF	QT interval was calculated using Fridericia's formula
QWP	Quality Working Party
R/R	Relapsed/refractory
$RaccAUC_{0-4}$	Accumulation ratio based on AUC_{0-4}
$RaccAUC_{max}$	Accumulation ratio based on C_{max}

RBC	Red blood cell
RH	Relative Humidity
RMST	Restricted Mean Survival Time
ROW	Rest of World
RRT	Relative retention time
RSD	Relative standard deviation
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SC	Subcutaneous
SD	Standard deviation
SDI	solid dispersion intermediate
SDV	Source data verification
SE	Standard error
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
$t_{1/2}$	Elimination half-life at steady state
TAMC	Total aerobic microbial count
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TF	Treatment failure
TFE	Trifluoroethanol
TGA	Thermo-Gravimetric Analysis
THF	Tetrahydrofurane
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of toxicological concern
TTCR	Time to CR
TTCRh	Time to CR + CRh
TTCRi	Time to CR + CRi (including CRp)
TTR	Time to first response
TYMC	total yeasts and molds count
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
VAF	Variant allele frequency
VAS	Visual analog scale
Vc/F	Central volume of distribution
W	Week
WBC	White blood cell
WHO	World Health Organization
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Les Laboratoires Servier submitted on 3 March 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Tibsovo, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 May 2021.

Tibsovo was designated as an orphan medicinal product EU/3/18/1994 on 21 March 2018 in the following condition: treatment of biliary tract cancer.

The applicant applied for the following indication:

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

Tibsovo was designated as an orphan medicinal product EU/3/16/1802 on 12 December 2016 in the following condition: treatment of acute myeloid leukaemia.

The applicant applied for the following indication:

Tibsovo in combination with azacitidine is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) mutation who are not eligible to receive intensive induction chemotherapy.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Tibsovo as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/tibsovo.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Cholangiocarcinoma

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Acute myeloid leukaemia

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

1.3. Information on Paediatric requirements

Cholangiocarcinoma

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0406/2019, on the granting of a product-specific waiver.

Acute myeloid leukaemia

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0280/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0280/2018 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.4.2. New active Substance status

The applicant requested the active substance ivosidenib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Protocol assistance

Cholangiocarcinoma

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
13/10/2016	EMEA/H/SA/3403/1/2016/SME/II	Jan Sjöberg and Paolo Foggi

The scientific advice pertained to the following clinical aspects:

- the design of the Phase 3 pivotal study, a multicenter, randomized, double-blind, placebo-controlled study of AG-120 in previously-treated patients with non-resectable or metastatic cholangiocarcinoma with an IDH1 mutation, including the choice of patient population, primary and secondary efficacy endpoints, the use of placebo as a comparator and allowance of crossover from placebo to active treatment at the time of progression, the dose selection strategy, the statistical design and analysis methods, the safety monitoring plan;

Acute myeloid leukaemia

The applicant received the following scientific advice on the development relevant for the indication

subject to the present application:

Date	Reference	SAWP co-ordinators
10/11/2016	EMEA/H/SA/3403/2/2016/SME/III	Pierre Démolis and Jan Sjöberg
31/05/2018	EMEA/H/SA/3403/3/2018/PA/II	Martin Mengel and Odoardo Olimpieri

The scientific advice pertained to the following non-clinical, and clinical aspects:

- the toxicology data package for Marketing Authorisation Application, in particular to support the non-clinical safety of the combined administration of AG-120 plus azacytidine;
- the design of the Phase 3 study AG-120-C-009, a multicenter, double-blind, randomized, placebo-controlled clinical trial to evaluate the efficacy and safety of AG-120 + azacitidine versus placebo + azacitidine in subjects with previously untreated IDH1-mutated AML or subjects with AML in first relapse after a remission duration of at least 12 months whose AML harbors a mutation in IDH1 and who are considered appropriate candidates for non-intensive induction therapy;
- the clinical pharmacology of ivosidenib to support a MAA in the treatment of patients with IDH1 mutation-positive positive relapse of refractory AML;
- the design of the phase I study AG120-C-001, including the patient population, the primary and secondary endpoints, the efficacy and safety analysis to support a conditional marketing application in the treatment of patients with IDH1 mutation-positive relapse of refractory AML;
- the plan for obtaining external historical control data to contextualise the data from the phase 1 study AG120-C-001 for the benefit-risk assessment;
- the criteria (in terms of molecular structure, mechanism of action and therapeutic indication) to demonstrate non-similarity in the context of the CHMP assessment for MAA.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau Co-Rapporteur: Blanca Garcia-Ochoa

The application was received by the EMA on	3 March 2022
The procedure started on	24 March 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	13 June 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	27 June 2022
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	1 July 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	21 July 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 October 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP	24 November 2022

and PRAC members on	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	1 December 2022
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	15 December 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	23 January 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	8 February 2023
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tibsovo on	23 February 2023
The CHMP adopted a report on similarity of Tibsovo with Pemazyre, Dacogen, Rydapt, Mylotarg, Vyxeos liposomal, Xospata and Daurismo on	23 February 2023
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product on	23 February 2023

2. Scientific discussion

Cholangiocarcinoma

2.1. Problem statement

2.1.1. Disease or condition

The applicant was initially seeking a marketing authorisation for the following indication:

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

The recommended dose is 500 mg ivosidenib (2 x 250 mg tablets) taken orally once daily.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Cholangiocarcinomas are rare cancers that arise from intrahepatic or extrahepatic biliary epithelium. In the European Union (EU), the incidence varies across countries from 0.5/100,000 (in Spain) to 3.36/100,000 (in Italy) (Banales et al, 2016). Incidence and mortality are increasing, indicating a medical need. Incidence and mortality are highest in South East Asia. The mean prevalence for biliary tract cancer is considered to be approximately 1.3/10,000 in the EU (EMA, 2018a); based on a population of 512,600,000 in 28 member states (EUROSTAT, 2018), this approximates to 66,638 persons affected in the EU.

IDH1 mutations occur globally in approximately 16%, up to 29% in some reports, of intrahepatic cholangiocarcinomas and approximately 0-7% of extrahepatic cholangiocarcinomas. Using a maximum incidence of 14% (13% for intrahepatic + 1% for extrahepatic) for IDH1 mutations in cholangiocarcinoma indicates an overall prevalence of 0.182 in 10,000 people. The 5-year survival rates associated with intrahepatic and extrahepatic cholangiocarcinoma are 9% and 10%, respectively, and only 2% for patients with distant metastases (ACS 2021).

2.1.3. Biologic features, aetiology and pathogenesis

IDH1 mutations continue to be identified in a variety of solid tumor subtypes, including glioma, chondrosarcoma, and intrahepatic cholangiocarcinoma. Mutations in IDH1 have been found in approximately 70% of Grade 2 to 3 gliomas (Yan et al, 2009), 50% of chondrosarcomas (Amary et al, 2011), and approximately 13% of intrahepatic cholangiocarcinomas (Boscoe et al, 2019).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The classification of cholangiocarcinomas is divided anatomically as extrahepatic, intrahepatic, and perihilar (Saha et al, 2016; Van Dyke et al, 2019). The disease is often advanced and incurable at the time of diagnosis. Common presentation includes symptoms related to biliary tract obstruction including jaundice, abdominal pain, weight loss, fever, fatigue, and abnormal liver function tests. The prognosis for cholangiocarcinoma is generally poor owing to the aggressive nature of the disease, and the late stage at which the disease is typically diagnosed. The prognosis for patients with cholangiocarcinoma is poor; regardless of stage at diagnosis, the 5-year survival rates associated with both intrahepatic and extrahepatic cholangiocarcinoma are 9% to 10% and only 2% in patients with distant metastases (ACS 2021). Median overall survival for unresectable disease with active palliative treatment is 10.6 months (https://pubmed.ncbi.nlm.nih.gov/35167909/).

IDH1/2 mutations are found in 10% to 23% of intrahepatic cholangiocarcinomas. The prognostic effect of this mutation in intrahepatic cholangiocarcinoma is uncertain, but the IDH1 mutation, which accounts for 0.8% (95% CI, 0.4%–1.5%) of patients with extrahepatic cholangiocarcinoma, is associated with poor prognosis in these patients (Goyal et al, 2015).

2.1.5. Management

Cholangiocarcinoma is a lethal disease for which there is significant unmet need. The first-line, standard-of-care treatment for patients with cholangiocarcinoma, including patients with IDH1 mutation-positive cholangiocarcinoma, in the locally advanced or metastatic setting is gemcitabine and platinum based chemotherapy (ESMO 2016). Combination chemotherapy with gemcitabine and cisplatin has shown a PFS HR of 0.63, mPFS 8.0 vs. 5.0 months, P<0.001, and OS HR: 0.64, mOS 11.7 vs. 8.1 months, P<0.001, compared with gemcitabine alone, making this combination the preferred standard option in the first-line setting for patients with locally advanced nonresectable disease (Valle et al, 2010).

The prognosis for previously treated cholangiocarcinoma patients, is poor, and treatment options depend on several factors, including site of reoccurrence, prior treatment regimens, and individual patient status (Khan et al, 2002). For patients with good PS and lack of potentially actionable molecular targets, 5-FU regimens, including mFOLFOX regimen, are typically considered after progression on a gemcitabine-containing regimen. mFOLFOX afforded an incremental advantage over active symptom control (ASC), with an ORR of 5% and mOS of 6.2 months compared with 5.3 months in the ASC arm (HR 0.69, p=0.031). Median PFS with second line mFOLFOX in this study was 4 months. However, there is some hesitation to use this regimen in patients progressing after a treatment regimen already containing a platinum in first line (gemcitabine+cisplatin), which makes this a suitable treatment option but cannot be considered the standard of care in clinical practice (Lamarca et al, 2021).

There are no targeted therapies authorized by the EMA for the treatment of any solid tumor bearing an IDH1 mutation, including in cholangiocarcinoma. Approved targeted treatments for cholangiocarcinoma are limited to pemigatinib (approved in the EU in March 2021) for the treatment of adults with locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion or rearrangement that have progressed after at least one prior line of systemic therapy. While FGFR2 alterations occur in roughly 10% to 15% of cholangiocarcinoma, they rarely co-occur with IDH1 mutations (co-occurrence in approximately 2% to 5%) (Battaglin et al, 2020; Jain et al, 2018; Valle et al, 2017; Saborowski et al, 2020).

2.2. About the product

Ivosidenib is a small molecule inhibitor of the mutant IDH1 enzyme. Inhibition of mutant IDH1 by ivosidenib in vitro led to reduction of 2-HG levels and the induction of differentiation of hepatoblasts.

The initially proposed indication for ivosidenib was for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 mutation, who were previously treated by at least one prior line of systemic therapy.

The CHMP adopted a positive opinion for the following indication:

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.

Before taking ivosidenib, patients must have confirmation of an IDH1 mutation using an appropriate diagnostic test.

The recommended dose of ivosidenib is 500 mg (2 x 250 mg tablets) taken orally once daily. Treatment should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

2.3. Type of Application and aspects on development

The ivosidenib clinical development program was initiated in 2014 and is investigating ivosidenib as single-agent and combination therapy for the treatment of subjects with cancers that harbor IDH1 mutations, including solid tumors and hematologic malignancies. The basis of the evidence for use of ivosidenib monotherapy in the cholangiocarcinoma indication comprises the efficacy and safety results from the Phase 3 Study AG120-C-005 (pivotal study) and the Phase 1 Study AG120-C-002 (supportive study).

A total of 10 clinical studies have contributed to the characterization of the clinical pharmacology of ivosidenib in the application. Four studies have been conducted in healthy subjects, 1 study has been conducted in subjects with mild or moderate hepatic impairment. Three studies have been conducted with ivosidenib monotherapy in subjects with advanced malignancies including 2 studies in subjects with cholangiocarcinoma (AG120-C-002 and AG120-C-005). Two studies have been conducted in subjects with newly diagnosed AML (AG120-C-009 and AG-221-AML-005) with ivosidenib in combination with azacitidine.

Two Scientific Advices and one Protocol Assistance were provided by the EMA with regard to the development of Tibsovo. A pre-submission meeting with the EMA was held on 24 September 2021. Pre-submission meeting with the CHMP Rapporteur and Co-rapporteur took place with France (ANSM) and Spain (AEMPS) on the 14 January 2022. For the cholangiocarcinoma indication, SA was sought from the CHMP on the design of Study AG120-C-005 and the adequacy of the overall clinical program to support registration (EMA/CHMP/SAWP/646225/2016). Specific advice was sought on the appropriateness of the primary and secondary efficacy endpoints; the use of placebo as a comparator and allowance of crossover from placebo to active treatment at the time of progression; dose selection strategy; and appropriateness of the statistical design and analysis methods.

In this CHMP scientific advice, the applicant was recommended to consider OS as the primary endpoint instead of PFS. It was also suggested that a control arm consisting of investigator's choice would be "more clinically relevant and may ease recruitment, and further remove the need for crossover, making OS a possible primary endpoint." This recommendation, with implications on sample size and other statistical considerations, was not followed by the applicant.

Acute myeloid leukaemia

2.4. Problem statement

2.4.1. Disease or condition

The applicant was initially seeking a marketing authorisation for the following indication:

"Tibsovo in combination with azacitidine is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) mutation who are not eligible to receive intensive induction chemotherapy."

Acute myeloid leukemia is an aggressive, rapidly progressive malignancy characterized by the clonal proliferation of myeloid precursors in the peripheral blood, bone marrow and/or other tissues (Estey and Döhner, 2006; Licht and Sternberg, 2005; Shipley and Butera, 2009).

A number of studies have examined the prognostic impact of isocitrate dehydrogenase 1 (IDH1) mutation in AML. These studies have included meta-analyses, cooperative group subset analyses, and single-institution studies and overall, the results demonstrate that an IDH1 mutation confers an adverse prognosis in the newly diagnosed and relapsed/refractory setting (Feng et al, 2012; Zhou et al, 2012; DiNardo et al, 2015; Bertoli et al, 2016; Paschka et al, 2016; Wattad et al, 2017; Xu et al, 2017; Hills et al, 2018).

2.4.2. Epidemiology and risk factors, screening tools/prevention

The prevalence information from the NORDCAN database was used to calculate the prevalence of AML (18.1 in 100,000), ie, 1.8 in 10,000, equating to 81,531 persons in a European population of 452,948,552 (European Economic Area [EU27 plus Norway, Iceland and Liechtenstein, excluding the United Kingdom]) (NORDCAN, 2019a; NORDCAN, 2019b; Eurostat 2020). Acute myeloid leukemia remains primarily a disease of older adults, with a median age at diagnosis of 67 years. Although survival has generally improved since the 1980s, the 5-year relative survival rate remains low, at approximately 15% to 20% in Europe (Kell, 2016).

The overall frequency of IDH1 mutations in AML is approximately 6% to 10% (Bullinger et al, 2017). The age-adjusted incidence rate of IDH1-mutated AML is <1 per 100,000 individuals per year (Marcucci et al, 2010; Mardis et al, 2009; NCI, 2018). As stated before, mutations in IDH1 are associated with inferior responses and worse OS and therefore with a worse prognosis compared to wild-type IDH1. In addition, treatment outcome was poor for patients with an IDH1 mutation (Xu et al, 2017).

The risk factors for AML are well characterised and include advancing age, male gender, family history, exposure to benzene, formaldehyde and cigarette smoke, exposure to ionizing radiation, exposure to cytotoxic and/or immunosuppressive agents, alkylating agents, topoisomerase II inhibitors, blood disorders including myelodysplasia, polycythaemia vera, thrombocythaemia 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).

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).

2.4.3. Biologic features, aetiology and pathogenesis

AML is a heterogeneous hematologic malignancy that is characterized by clonal expansion of myeloid blasts in the bone marrow and frequently also in the peripheral blood and/or other tissues. It is characterized by clonal heterogeneity at the time of diagnosis, with the presence of both a founding clone and at least 1 subclone.

The IDH family of proteins comprises 3 isoforms: IDH1, IDH2, and IDH3. Cancer-associated mutations have been identified in IDH1 and IDH2 (Yen et al, 2010).

Isocitrate dehydrogenase mutations confer a gain of function, permitting the mutant enzyme to catalyze the reduction of alpha-ketoglutarate (α-KG) to R(-)2-hydroxyglutarate (2-HG) (Dang et al, 2009). 2-HG exerts its metabolic effects via a number of mechanisms, including the competitive inhibition of α-KG–dependent dioxygenases such as DNA and histone demethylases, which modulate transcription of many genes important in cell differentiation (Chowdhury et al, 2011; Koivunen et al, 2012; Xu et al, 2011).

The hallmark of IDH1 mutation in cancer is overproduction of 2-HG, a metabolite that impairs differentiation of hematopoietic stem cells into mature blood cells, contributing to oncogenesis (Dang et al, 2009; Figueroa et al, 2010).

2.4.4. Clinical presentation, diagnosis and stage/prognosis

Acute myeloid leukemia is characterized by uncontrolled proliferation of clonal neoplastic hematopoietic precursor cells and impaired hematopoiesis, leading to neutropenia, anemia, and thrombocytopenia. If untreated, patients die of infection or bleeding usually in a matter of weeks (Tallman et al, 2005; Fey et al, 2013). Clinical manifestations of AML result either from the proliferation of leukaemic cells or from bone marrow failure that leads to decrease in normal cells. Leukaemic cells can infiltrate tissues, leading to hepatomegaly, splenomegaly, skin infiltrates and swollen gums. As an indirect effect of the leukaemic proliferation leading to high cell destruction, hyperuricaemia and occasionally renal failure may occur. The haematopoiesis suppression leads to clinical features of anaemia, neutropenia and thrombocytopenia. Signs and symptoms that signal the onset of AML include pallor, fatigue, weakness, palpitations, and dyspnea on exertion.

According to European Society for Medical Oncology (ESMO) guidelines, the diagnosis of AML requires the examination of peripheral blood and bone marrow specimens. The work-up of these specimens should include morphology, cytochemistry, immunophenotyping, cytogenetics and molecular genetics [chiefly polymerase chain reaction (PCR) and fluorescence in situ hybridisation (FISH) techniques]. As AML is characterized by the accumulation of immature precursors, or myeloblasts, in the bone marrow, peripheral blood, and organs and disrupt the production of normal blood cells; the diagnosis is based on the presence of ≥20% blasts in bone marrow or peripheral blood in accordance with the 2016 World Health Organization (WHO) classification (Redaelli et al, 2003).

A number of publications have assessed outcomes in adults with mutated IDH1 AML. Overall, these studies conclude that an IDH1 mutation is associated with worse outcomes.

2.4.5. Management

The standard treatment strategy for newly diagnosed AML includes the option of standard IC and consolidation chemotherapy, or non-intensive treatment. Consolidation therapy for patients in complete response after IC consists of either chemotherapy, autologous hematopoietic stem cell transplantation (HSCT) or allogeneic HSCT. Patients are encouraged to participate in clinical trials whenever possible. The initial treatment decisions for newly diagnosed AML are based on patient age, history of prior myelodysplastic syndrome, prior genotoxic therapy, genetic classification of AML, Eastern Cooperative

Oncology Group performance status (ECOG PS), and presence of serious comorbidities (Heuser et al, 2020).

Approximately 35% to 40% of younger (<60 years) newly diagnosed AML patients with favorable prognostic factors can be cured with intensive IC and, and where applicable, HSCT (Döhner et al, 2015; Juliusson et al, 2009; Juliusson et al, 2012; NCCN, 2021). Among older individuals, the cure rate is only 5% to 15% (Medeiros et al, 2015; Oran and Weisdorf, 2012). Population-based epidemiologic studies in the United States (US) indicated that approximately 60% of patients with newly diagnosed AML who were over age 65 years remained untreated after being diagnosed, as they cannot tolerate intensive therapies (Oran and Weisdorf, 2012). They had a short median survival of approximately 2 months. For these patients, the ESMO guidelines recommend non-intensive therapies including hypomethylating agents (HMAs), low-dose cytarabine (LDAC) and best supportive care with either 6-mercaptopurine or low-dose melphalan or hydroxycarbamide (Heuser et al, 2020).

Supportive care measures are used to address the underlying comorbidities associated with AML and include hydroxyurea (also called hydroxycarbamide) to control leukocytosis, blood product transfusions, hematopoietic growth factors, and antimicrobials. Transfusions place a substantial medical burden on the patient. In addition, none of these supportive measures modify the course of the leukemia and patients ultimately die from their disease.

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 OS ranges from 2 to 10 months (Dombret et al, 2015; Kantarjian et al, 2012).

Recently, venetoclax in combination with HMA and glasdegib in combination with LDAC have been approved in the EU (on 19 May 2021 and 26 June 2020, respectively) as first line treatment for adult patients with newly diagnosed AML who were not eligible for intensive chemotherapy.

In the pivotal Phase 3, double-blind, randomized trial in subjects with newly diagnosed AML ineligible for IC, median OS was 14.7 months (95% CI 11.9, 18.7) in the venetoclax + azacitidine arm compared with 9.6 months (95% CI 7.4, 12.7) in the placebo + azacitidine arm (HR = 0.662; P<0.001) (DiNardo et al, 2020). In the pivotal Phase 2, open-label, randomized trial in subjects with newly diagnosed AML ineligible for IC, median OS was 8.3 months (80% CI 6.6, 9.5) in the glasdegib + LDAC arm compared with 4.3 months (80% CI 2.9, 4.9) with LDAC alone (HR=0.46; P=0.0002) (Cortes et al, 2019). As per the 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 allogeneic HSCT using reduced-intensity conditioning, which may cure a portion of these patients (Heuser et al, 2020).

Despite the recent approvals of new therapies, there are no molecularly targeted combination therapies approved for patients with newly diagnosed IDH1-mutated AML who are not eligible for intensive IC.

2.5. About the product

Ivosidenib is a small molecule inhibitor of the mutant IDH1 enzyme. Mutant IDH1 converts alpha-ketoglutarate (α-KG) to 2-hydroxyglutarate (2-HG) which impairs myeloid differentiation, increases proliferation of myeloblasts and blocks cellular differentiation.

Ivosidenib targets the mutant IDH1 variant R132. Inhibition of the mutant IDH1 enzyme by ivosidenib led to decreased 2-HG levels and induced myeloid differentiation in vitro and in vivo in mouse xenograft models of IDH1mutated AML. In blood samples from patients with AML with mutated IDH1, ivosidenib decreased 2-HG levels, reduced blast counts and increased percentages of mature myeloid cells.

The initially proposed indication for ivosidenib was for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) mutation who are not eligible to receive intensive induction chemotherapy.

The CHMP adopted a positive opinion for the following indication:

Tibsovo in combination with azacitidine is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy.

Ivosidenib drug product is presented as film coated tablets containing 250 mg of ivosidenib.

The recommended dose of ivosidenib is 500 mg taken orally QD in combination with azacitidine until disease progression or unacceptable toxicity.

2.6. Type of Application and aspects on development

The ivosidenib clinical development program was initiated in 2014 and is investigating ivosidenib as single-agent and combination therapy for the treatment of subjects with cancers that harbor IDH1 mutations, including solid tumors and hematologic malignancies.

The basis of evidence for use of ivosidenib combination therapy with azacitidine as first-line treatment in the AML indication comprises the results from:

- the AGILE Phase 3 Study AG120-C-009 (pivotal study).
- the Phase 1b/2 Study AG-221-AML-005 (supportive data)

Study AG120-C-001 provides additional data on the safety of monotherapy with ivosidenib at the 500 mg QD dosing regimen in N=228 subjects with newly diagnosed and relapsed/refractory (R/R) advanced hematologic malignancies with an IDH1 mutation.

Additional safety data of ivosidenib in combination with induction and consolidation chemotherapy in subjects with newly diagnosed AML is provided from Study AG120-221-C-001.

The applicant sought general scientific advice twice from the EMA: first on the design of the Phase 3 registration study, AGILE Study and the adequacy of the overall clinical program to support a MAA (10 November 2016; EMA/CHMP/SAWP/713016/2016) and then on the protocol revision that modified the primary endpoint of the AGILE Study from OS to EFS (with OS as a key secondary endpoint – Protocol Assistance; EMA/CHMP/SAWP/300933/2018).

The Agency found the justification assessment of ivosidenib plus azaciditine in IDH1-mutant AML to be acceptable. As recommended, the final design of the pivotal study limited enrolment to patients with previously untreated AML who were not candidates for intensive induction chemotherapy (IC), including allogeneic stem cell transplantation.

Although not endorsed by the Agency, the primary endpoint was modified from OS to EFS as the feasibility of the study was limited due to recruitment challenges: the rarity of the population and the anticipated approval of venetoclax in combination with azacitidine making randomization to the azacitidine monotherapy control arm of the AGILE study less desirable. Also, no early interim analysis for futility were planned while doubts about the efficacy of the selected dose were raised.

2.7. General comments on compliance with GMP, GLP, GCP

GMP

- Batch release site:

Les Laboratoires Servier Industrie (LSI), 905 Route de Saran, 45520 Gidy, France

A copy of the manufacturer's authorisation from Eudra GMP dated 25 September 2020 and a GMP certificate dated 18 October 2021 based on an inspection performed by the French authority on the 27 November 2015, confirming that this site is authorized for the batch certification of imported non-sterile medicinal products, were provided.

All sites involved in the manufacturing, quality control, batch release and packaging have been inspected by the relevant Competent Authority. Certificates of inspection and licenses for all the named sites have been provided. No additional inspection prior to grant of a marketing authorisation is required. The manufacturing sites comply with the European GMP.

GLP

No additional GLP study was submitted in this new MAA procedure (EMEA/H/C/005936) compared to the previous one for ivosidenib (EMEA/H/C/005056). The GLP studies submitted in this application are identical to the ones submitted in the previous application. The pivotal toxicology and safety pharmacology studies were conducted in accordance with GLP regulations and ICH guidelines, i.e. supported by an adequate quality assurance system including in study audits. No reasons to trigger a GLP inspection were observed.

GCP

The applicant confirms that all of the clinical trials within this Marketing Authorisation Application (MAA) meet the ethical requirements of Directive 2001/20/EC (involving countries outside and inside EEA). All studies were conducted with respect for the individual participants according to the respective protocol, the World Medical Association Declaration of Helsinki and Good Clinical Practice (GCP) as per the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline (ICH E6).

2.8. Quality aspects

2.8.1. Introduction

The finished product is presented as film coated tablets containing 250 mg of ivosidenib.

Other ingredients are:

For the tablet core: microcrystalline cellulose, croscarmellose sodium, hypromellose acetate succinate, colloidal silica, anhydrous, magnesium stearate, sodium lauryl sulfate (E487).

For the film-coating: hypromellose, titanium dioxide (E171), lactose monohydrate, triacetin, indigo carmine aluminium lake (E132).

The product is available in white, high density polyethylene (HDPE) bottle with polypropylene (PP) child-resistant closure and polyethylene (PE)-faced induction heat seal liner as described in section 6.5 of the SmPC.

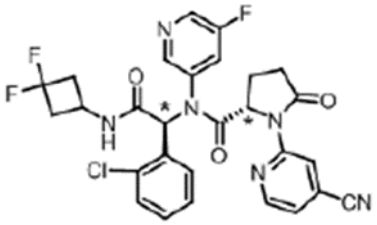
2.8.2. Active Substance

2.8.2.1. General information

The chemical name of Ivosidenib is (2S)-N-{(1S)-1-(2-chlorophenyl)-2-[(3,3-difluorocyclobutyl)amino]-2-oxoethyl}-1-(4-cyanopyridin-2-yl)-N-(5-fluoropyridin-3-yl)-5-

oxopyrrolidine-2-carboxamide corresponding to the molecular formula $C_{28}H_{22}ClF_3N_6O_3$. It has a relative molecular mass 583.0 g/mol and the following structure:

Figure 1. Active substance structure



The chemical structure of Ivosidenib was elucidated by a combination of elemental analysis, IR and UV spectrum, Proton (^{1}H), Carbon (^{13}C) and Fluorine (^{19}F) Nuclear Magnetic Resonance Spectroscopy and High Resolution Mass Spectrometry. The solid state properties of the active substance were measured by X-Ray Powder Diffraction, Differential Scanning Calorimetry and Thermal Gravimetric Analysis.

The active substance is a crystalline white to light yellow solid, sparsely hygroscopic, practically insoluble in aqueous solutions, freely soluble in dichloromethane, methanol and methyl tert-butyl ether (MTBE), soluble in isopropyl acetate and ethanol, and insoluble in n-heptane.

The active substance exhibits stereoisomerism due to the presence of two chiral centres; the isomer with S configuration at both centers is the active substance. Correct configurations of the stereocentres are established by the synthetic process and the specifications of one starting material. Enantiomeric purity is also controlled routinely on the active substance by chiral HPLC.

Polymorphism has been observed for the active substance. Polymorph screenings were performed by generating solid ivosidenib under a variety of conditions and characterizing the samples obtained by x-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), and Nuclear magnetic resonance spectroscopy (NMR).

The active substance is not the subject of a monograph in the Ph. Eur.

The applicant has performed comparative structural analysis to show that ivosidenib is to be regarded as a new active substance (NAS) in itself and that it is not a salt, complex, derivative or isomer (nor mixture of isomers) of a previously authorised substance.

2.8.2.2. Manufacture, characterisation and process controls

The active substance intended for the proposed commercial process is obtained from a single manufacturer, which also performs the quality control testing. A valid QP declaration was provided. The quality control testing of the active substance could be also performed by other sites.

The active substance is synthesized by a four-stage process involving several starting materials .

A detailed description of the manufacturing process and process controls is provided and is considered satisfactory.

The selection and control of starting materials is discussed.

The choice of starting materials is considered well justified in compliance with the Decision tree of ICH Q11 Guideline Q&A.

The manufacturing process development has been well documented. While a traditional drug development approach was used to define the commercial manufacturing process for ivosidenib, some elements of an enhanced approach under Quality by Design were employed to define the process criticality and process parameters. Over the course of development, the synthetic route, starting materials, and intermediates have remained the same. However, changes to reagents, catalysts, solvents, specifications (for starting materials, intermediates and active substance), and process parameters have been made. In general changes introduced have been presented in sufficient detail and have been well justified.

Description of the CQAs for the active substance along with the points of control for each of them is provided. Design space is not claimed. Process development studies performed for process understanding and criticality assessment of each stage chosen for commercial manufacture are described.

The characterization of the active substance and its impurities are in accordance with the EMA Guideline on the chemistry of active substances. Potential and actual impurities were in general well discussed with regards to their origin and characterisation. The discussion on impurities covers starting materials, intermediates, identified process impurities and degradation products, elemental impurities and residual solvents.

The mutagenic potential of impurities is also addressed; the discussion and related controls proposed are in general considered sufficient taking into account the proposed indications.

The active substance is packaged in double low-density polyethylene (LDPE) bags. The bags are closed with ties and subsequently placed inside an aluminium foil bag. The aluminium foil bag is placed into a high-density polyethylene (HDPE) drum and closed. LDPE used for the bag complies with Ph. Eur. Requirements and the EU Regulation 10/2011 as amended.

2.8.2.3. Specification

The active substance specification includes tests for: appearance, identity (FT-IR), assay (HPLC), related impurities (HPLC), chiral impurity (HPLC), residual solvents (GC), water content (KF), residue on ignition (Ph. Eur.) and elemental impurities (ICP-MS).

The proposed specifications are satisfactory. In particular, related substance specifications are in compliance with the GL ICH Topic Q3A (R2) Impurities in new Drug Substances. Enantiomeric purity is also controlled routinely on the active substance by chiral HPLC.Specifications for residual solvents are in compliance with ICH guideline Q3C (R7) on impurities: guideline for residual solvents. Specification for elemental impurities are in compliance with ICH guideline Q3D (R1) on elemental impurities. The crystallinity of the active substance is not critical to the bioavailability of the finished product. Hence the absence of polymorphism control in the active substance specifications is considered justified in compliance with ICH Topic Q 6 A Note for guidance specifications: test procedures and acceptance criteria for new drug substances and new drug products and its decision tree #4 (when the drug product safety, performance or efficacy is not affected by the active substance polymorphic form, no further test or acceptance criterion for polymorph content is needed for the drug substance).

The analytical methods used have been in general adequately described. Non-compendial methods were appropriately validated in accordance with the ICH guidelines.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on 5 commercial size batches of ivosidenib active substance, manufactured at the commercial site according to the proposed commercial route and process are provided. The results are within the specifications and consistent from batch to batch. In addition batch analyses of primary stability batches, of batches used in clinical and non-clinical safety studies are also provided.

2.8.2.4. Stability

Stability data on 3 pilot scale batches of active substance from the proposed manufacturer using the proposed commercial process except for minor process variations, stored in a container closure system representative of that intended for the market for 60 months under long term conditions at 30ºC /65% RH and for up to 6 months under accelerated conditions at 40ºC /75% RH according to the ICH guidelines were provided.

Stability data through 60 months are provided on 3 commercial size batches under long-term conditions (30°C/65% RH).

Results on stress conditions were also provided. The analytical methods were stability indicating.

Photostability testing following the ICH guideline Q1B option 2 was performed.

The stability results obtained for long term and accelerated conditions justify the proposed retest period of 60 months when stored at not more than 30°C in the proposed container.

2.8.3. Finished Medicinal Product

2.8.3.1. Description of the product and pharmaceutical development

The finished product is a film-coated tablet for oral administration. The film-coated tablets are oval, blue, film-coated, debossed with 'IVO' on one side and '250' on the other side. The approximate tablet dimensions are length of 18.0 mm and width of 8.4 mm.

The finished product is packed in HDPE bottles with polypropylene child-resistant closures. Each bottle contains 60 tablets and 1.0 g silica gel desiccant.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The information provided on the composition of the tablets is adequate. No overages are used in the composition of the finished product.

Ivosidenib tablets are manufactured using a 2-stage process: the manufacture of the finished product intermediate and the manufactrure of the finished product using typical pharmaceutical excipients and standard tablet manufacturing processes.

Elements of Quality by Design were used in the pharmaceutical development of the manufacturing process, target levels and operating ranges as well as proved acceptable ranges were stated for the critical process parameters.

The ivosidenib 250 film-coated, debossed tablet is the only tablet presentation intended for commercial use. The commercial tablet presentation is the same as the clinical tablet presentation, differing only in use of a non-functional film coat and debossing. Adequate bridging of the tablets used in clinical studies and the proposed commercial image tablets has been achieved through in vitro dissolution profile comparisons using the optimized and validated dissolution method, therefore no formal bioequivalence studies have been conducted in humans.

The overall manufacturing process for finished product has remained the same since the beginning of ivosidenib clinical development. The primary packaging is HDPE bottles closed with polypropylene child resistant closures with a polyethylene film bonded to aluminium foil. A silica gel desiccant (in a canister) is included in the bottle. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

This type of container is often use for this type of product. The container used for the finished product is acceptable, materials specifications and examples CoA were provided. The confirmation of compliance of the child resistant packaging with the US regulations was provided. The applicant has committed to test the child resistant container according to International Standard (EN ISO 8317) **(Recommendation 1)**.

2.8.3.2. Manufacture of the product and process controls

The finished product manufacturing process is relatively standard, and consists of two main steps: the manufacture of the intermediateand the manufacture of the finished product.

The tablets are packed in double polyethylene lined HDPE containers, then shipped to the primary packaging site.

The controls applied during the manufacturing process were presented under two categories, i.e. critical controls and in-process controls.

The controls considered critical during the different steps of the manufacturing process were listed with acceptance limits (target and range), as well as details on the control strategy. Similarly, in-process controls were provided, with acceptance limits (target and range), as well as a short description of the method used.
Although ranges were provided for the control of the critical parameters, no design space was claimed.

The validation of the finished product manufacturing process was conducted on 5 batches of the intermediate and 3 batches of the tablets. Results at release were provided for the batches manufactured for the validation (including results from in-process controls).

2.8.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identity (HPLC/UV, HPLC/DAD), assay (HPLC), impurities (HPLC), uniformity of dosage units (Eur. Ph.), dissolution (HPLC), water content (KF) and microbiological quality (Eur. Ph.).

The specification proposed for the control of the finished product covers the essential parameters for this type of pharmaceutical form. The control of the microbiological quality of the finished product is performed on one in ten batches, with a minimum of one batch controlled per year. The limits based on the results obtained at batch release and the results of the stability study (i.e. water content, related impurities) are acceptable.

A risk-based assessment of potential sources of elemental impurities based on ICH Guideline for Elemental Impurities Q3D has been performed. This risk assessment involved an evaluation of the individual components of the finished product, manufacturing equipment, packaging materials, and an evaluation of the materials used during manufacture of the finished product. Based on the risk

assessment, no testing of elemental impurities of the finished product is warranted, and elemental impurities are suitably controlled in the finished substance specification.

A risk assessment for nitrosamine formation and contamination was performed and the applicant considered the risk to be negligible for the product. This was not accepted due to the methodology applied and as the information was incomplete. Taking into account known root-causes, the presence of secondary/tertiary amines and the potential presence of nitrite/nitrosating agents, a Major Objection was raised. In the responses and subsequent assessment, the limits for potential nitrosamines were defined as per ICH S9 which outlines that ICH Q3A/B limits can be applied. Potential content of nitrosamines in the active substance and the finished product was estimatedbased on a theoretical study. However the data to support the model proposed was not available, and this approach could not be accepted during the procedure. The applicant also performed a worst case theoretical calculation of potential nitrosamine content in the productBatch analysis results for two nitrosamines impurities on batches of active substance and finished product were presented.As contents are below 10% of the limit, the absence of regular control is considered acceptable. With regards to potential nitrosamine impurities related to the active substance structure, no confirmatory testing was initially available. For these impurities, the hypothetical results obtained cannot be taken into accountThe results for small molecule nitrosamines could also not be extrapolated to these compounds. The issue was discussed at QWP–CT on 07/12/2022, where it was agreed further information would be requested. To resolve the concern related to potential nitrosamine drug substance related impurities, results of confirmatory testing demonstrated that for active substance batches the potential precursors of these and the impurities themselves were below 10% of the acceptable limit. The description and validation of the analytical method(s) used were provided. It was therefore also concluded that no routine test was required for this type of potential nitrosamine impurities. The nitrosamine impurity assessment was therefore considered acceptable.

The in-house analytical methods have been adequately described and validated. The compendial methods (uniformity of mass of the tablets, test of the water content and microbial examination test) were also described.

The in-house analytical methods (the HPLC method used for the identification, assay and analysis of the degradation products and the HPLC method used for the control of the dissolution) have been described and validated.

The two alternative methods for water content according to general chapters Ph.Eur. 2.5.12 (volumetric Karl Fischer method) and 2.5.32 (coulometric oven Karl Fischer method) were briefly described and their verification was performed.

Batch results were provided on three finished product production batches and on three pilot scale batches used for primary registration stability. The product was tested in line with the proposed specification and all the results were compliant with the proposed acceptance criteria and were similar between the batches.

2.8.3.4. Stability of the product

A shelf life of 48 months was initially proposed for the finished product, with no particular storage conditions. It is proposed that the labelling indicates that the bottle should be tightly closed in order to protect from moisture. A in use shelf-life of 30 days after first opening was proposed.

It was proposed to calculate the shelf life of the finished product using as the starting time the moment when theintermediate is mixed with the excipientsData to support a separate holding time of for the intermediate was presented. The main stability study (longest) was performed on three pilot scale batches), and data up to 60 months from the storage under long term conditions (30±2°C/65±5%RH)

and 6 months under accelerated conditions (40±2°C/75±5%RH) was provided. The analytical procedures used are stability indicating.

A stability study was performed on three batches of ivosidenib tablets manufactured with intermediate batches that have been held for 12, 18 and 24 months prior to the use in the manufacture of the finished product. Results up to 36 months (with 18 and 24 months aged Intermediate) and 48 months (with 12 months aged Intermediate) were provided for this study.

Additionally, stability data on three production scale batches up to 30 months were presented.

The data provided shows that the finished product is very stable, no changes/variations of the product's quality are observed under long term stability conditions and accelerated stability conditions.

Results and discussions from several supporting studies performed with the intermediate and the finished product not packed in the final packaging were included in this section: open dish study, photostability, and holding time study. The results of these studies show that the finished product is stable in the majority of the conditions, and support the choice of the selected packaging and the proposed labelling statements about keeping the product in the original container.

A stability study was performed on one pilot batch (for 18 months) and on one production batch (for 13 months) of the bulk tablets, to support a holding time of 12 months.

A 3 months open dish study following a long term storage period of resp. 0, 9, 21, 33 and 45 months in commercial packaging was done. an in-use stability study on two batches including one batch after 60 months stability at 30°C/65% RH was performed. These data support an in-use period of 30 days after first opening of the HDPE bottle.

The initially proposed shelf life of 48 months for the finished product is acceptable with the following storage conditions "This medicinal product does not require any special temperature storage conditions. Keep the bottle tightly closed in order to protect from moisture".

2.8.3.5. Adventitious agents

Lactose monohydrate is used in the film-coat excipient Opadry II, Blue, used in the manufacture of Ivosidenib Tablets, 250 mg. The lactose monohydrate component of Opadry II Blue is sourced from bovine milk. Lactose monohydrate does not pose a BSE/TSE risk, since the excipient is Category C material as defined in EMA/410/01, which indicates no detected infectivity. The manufacturer of Opadry II, Blue has provided the BSE/TSE Statement.

2.8.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertain to the child proof safety of the finished product container closure system. This point is put forward and agreed as a recommendation for future quality development.

2.8.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions

defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.8.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1.- The applicant should test the child resistance of the container closure system according to the International Standard (EN ISO 8317) before the distribution for the EU market.

2.9. Non-clinical aspects

2.9.1. Introduction

The non-clinical development program has relied on applicable regulatory guidelines, including ICH guideline S9.

2.9.2. Pharmacology

2.9.2.1. Primary pharmacodynamic studies

In some tumours IDH1 carries a point mutation, altering its amino acid position 132. This mutation does not inactivate the enzyme but leads to a novel catalytic activity which gives rise to the formation of 2-hydroxyglutarate (2-HG) from alpha-ketoglutarate (KG). It is thought that 2-HG contributes to tumour proliferation by inhibition of DNA and histone demethylation. The degree and the sites of DNA and histone methylation govern gene expression and silencing so that inhibiting demethylation alters the gene expression pattern.

Binding affinity of ivosidenib was studied in IDH biochemical system. Ivosidenib is a potent inhibitor against IDH1 mutant isoforms (R132H/G/H/S/L/C, IC_{50} = 2-17 nM) and IDH1wt (IC_{50} = 24-71 nM). Indeed, when incubation was prolonged (1 to 16h with NADP), the affinity towards IDH1wt markedly increased (71 nM after 1h vs 24 nM after 16h). Thus, after repeated administration of ivosidenib in animals or humans, inhibition of wt and mutated IDH1 is most likely similar. Moreover, ivosidenib inhibited IDHwt in HCT-116 cells (human colorectal carcinoma) when treated with ivosidenib for 3 or 48h (IC_{50} of around 10 µM). Plasma concentrations achieved in toxicology studies and in patients in clinical trials could inhibit wt IDH1 so that some adverse findings could be due to this inhibition. Ivosidenib presented selectivity for IDH1 *versus* IDH2 enzyme.

Acute myeloid leukaemia

Cell differentiation induced by ivosidenib *in vitro* was studied using the permanent human erythroleukemia cell line TF-1 transfected with mutant IDH1 or control. Expression of haemoglobin (HBG) and Krueppel-like factor 1 (KLF-1) served as differentiation markers. Ivosidenib (200 nM and 1 µM) dose-dependently increased expression of the differentiation markers HBG and KLF1. TF-1 cells transfected with mutant (R132H) IDH1 produced 2-HG, and this production was strongly inhibited with ascending concentrations of ivosidenib. Proliferation was reduced with 1 µM ivosidenib but not with 200 nM. 2-HG inhibition was studied in several additional cell lines in addition to TF-1 cells. Part of these cell lines express mutated IDH1 spontaneously, and the other were transfected with the respective expression vector. For comparison, cell lines expressing IDH2 were also included. The IC50 range of ivosidenib for 2-HG inhibition in cells expressing endogenous or overexpressed R132C, R132H or R132S was 2 to 20 nM and no inhibition of 2-HG production in cells expressing IDH2 mutations was confirmed.

Ex-vivo experiments were performed. First, ivosidenib effects on 2-HG production and proliferation were assessed in primary tumour cells obtained from two AML patients. Cells from one patient carried an IDH1 mutation, the other had wt IDH1. A clear difference between AML cells carrying mutated IDH1 and cells carrying wt IDH1 was observed; ivosidenib markedly suppressed 2-HG production in cells of patient IDH1 R132C and increased proliferation of cells harbouring mutated IDH1 but not in cells of patient IDH wt. There was a marked difference in proliferation rate between the cells already in the absence of ivosidenib. Cells carrying the mutated enzyme virtually did not proliferate at all in the absence of ivosidenib whereas in the wt IDH1 cells displayed a fast proliferation. In addition, *ex-vivo* differentiation of AML cells was studied with cells sampled form six patients (two carrying wt IDH1). Nearly complete suppression of 2-HG production was achieved with ivosidenib in the four patient cell preparations carrying mutated IDH1 and ivosdenib (5 µM) markedly increased the number of colonies formed in the mutated cells.

No study to support the pharmacologic rational for the combination ivosidenib+azacitidine was performed by the applicant. The data submitted are reported from a poster (Yen and al, 2018). Measures of cell differentiation, growth, and death were evaluated in TF-1-IDH1 R132H cells. The increases of CD235a, HBG RNA and KLF-1 RNA expression were higher when cells were treated with the combination compared than those observed when single agent is used. However, no additional or synergic effect of the combination is observed on proliferation rate. Likewise, even if a potentiation effect on apoptosis is observed when cells were treated with the combination ivosidenib (100 and 300 nM) + azacitidine (1000 nM), this effect was not observed at the highest doses (ivosidenib, 1000 nM).

The applicant submitted an array of five similar *in vivo* studies investigating the effect of oral ivosidenib administration on 2-HG levels in blood, brain and tumour tissue in mice bearing xenograft tumours formed from injected human fibrosarcoma HT1080 cells. HT1080 cells bear a native IDH1 R132C mutation (permanent tumour cell line). The results demonstrated that also in vivo ivosidenib markedly suppresses 2-HG production. The biological consequences of this suppression were not investigated. In addition, studies with mice were inoculated with AML cells from a patient to produce a xenograft leukaemia were also used to study the effect observed with ivosidenib in vivo. First, study was performed in female tumor-bearing NOG mice (Human IDH1 (R132C) AML xenograft mouse model), ivosidenib was administrated by oral dosing BID (50 and 150 mg/kg) in different dose groups for 14 days. This study also demonstrated an inhibition of 2-HG production *in vivo*. Beside 2-HG reduction, the effect of ivosidenib on the number of human AML cells in the animals was tested. No effect of ivosidenib on AML cell count in blood, spleen and bone marrow was observed after 14 days of treatment. In addition, a similar model was used to study *in vivo* effect of ivosidenib for 43 days (50 and 150 mg/kg) in human IDH1 (R132H) AML xenograft mouse model. The main endpoint was survival of the animals after treatment with ivosidenib or vehicle. The level of 2-HG and number of human CD45+ cells in peripheral blood of the mice were also determined. Inhibition of 2-HG production was observed (data not shown). Survival time of the animals was markedly reduced by ivosidenib treatment (data not shown). The number of circulating AML cells was increased at study end in the ivosidenib-treated animals as compared to vehicle controls (data not shown). Ivosidenib was not able to reduce proliferation of the patient AML cells used for creating the xenograft animal model.

Cholangiocarcinoma

To support cholangiocarcinoma indication, the pharmacology non-clinical package has been completed with one *in vivo* study. Mice were inoculated with patient-derived IDH1 (R132C) intrahepatic cholangiocarcinoma tumor fragments to produce a xenograft intrahepatic cholangiocarcinoma xenograft mouse model. Ivosidenib was administrated at 150 mg/kg by oral gavage 3 times at 12-hour intervals. 2-HG levels in tumor homogenates were quantified. This studies also demonstrated an inhibition of 2-HG production *in vivo (data not shown)*; however the biological consequences of this suppression were not investigated in this study.

2.9.2.2. Secondary pharmacodynamic studies

Secondary pharmacodynamics were conducted to evaluate the potential inhibition on several receptors, enzymes or ion channels. Ivosidenib showed no cross reactivity against a panel of 80 receptors, ion channels, transporters and enzymes at a concentration of 10 µM (equivalent to 5 830 ng/mL). The concentration tested (10 µM) is close to the Cmax value expected in the clinical exposure.

2.9.2.3. Safety pharmacology programme

During the safety pharmacology programme, ivosidenib inhibits the cardiac potassium channel *hERG in vitro* at concentrations (10 to 20 µM) which are in the range of therapeutic human plasma levels. Accordingly, prolongation of the QTc interval in the ECG of telemetered monkeys was observed at Tmax of ivosidenib. Marked QTc prolongation was also seen in humans at therapeutic doses of ivosidenib (see safety clinical AR and related questions). The applicant also tested cardiac sodium and calcium channels *in vitro* as well as another potassium channel (beside hERG). None of these channels was affected by ivosidenib. The effects on QTc interval and related exposure levels are incorporated into SmPC.

There were no clinical observation or detailed physical examination findings attributed to ivosidenib in the respiratory or central nervous system, except for the 28-day rat study, in which respiratory system findings were observed in rats at non-tolerated dose levels (data not shown).

2.9.2.4. Pharmacodynamic drug interactions

No PD assessments were conducted during the drug-drug interaction PK studies. The lack of any PD drug interactions studies is acceptable.

2.9.3. Pharmacokinetics

Absorption, distribution, metabolism, and excretion studies of ivosidenib were performed in Sprague-Dawley rats, beagle dogs, and cynomolgus monkeys. The analytical methods were adequately validated for quantitative determination of ivosidenib in the plasma of all animal species.

Ivosidenib PK profile is characterized by rapid oral absorption; low total body plasma clearance; low to moderate volume of distribution; and moderate to long apparent terminal elimination half-life. Several formulations of ivosidenib were tested in animals, and oral bioavailability strongly depended on the kind of formulation. Ivosidenib polyvinyl acetate phthalate (PVAP) solid dispersion showed higher oral exposures compared to its free form or ivosidenib Hydroxypropyl methylcellulose (hypromellose) acetate succinate (HPMCAS) solid dispersion in rats. The excipient PVAP was shown to be toxic in cynomolgus monkeys (see toxicity part below) and was excluded from use in subsequent toxicology studies in monkeys; the excipient HPMCAS was well tolerated and provided acceptable ivosidenib oral exposures in cynomolgus monkeys. HPMCAS was also used in rabbits. With suitable formulations oral availability is around 30% to 40% in the tested species. Plasma half live ($t_{1/2}$) is around 8 hours in rats and monkeys. A solid dispersion which yielded a rather good oral availability was used for the main toxicology studies. Exposures in rats and in monkeys were lower at the end of the treatment when compared to the first administration (except at the highest dose used in monkeys). No gender differences were observed in monkeys; in rats, exposures to ivosidenib were higher in females.

Plasma protein binding of ivosidenib was high, ivosidenib showed low RBC/plasma partitioning. Ivosidenib was mainly distributed to liver and adipose tissue; this is in line with the lipophilic property of the ivosidenib molecule. No retention, accumulation, or affinity observed for any tissue and there was no affinity for tissues containing melanin or for any other tissue. Ivosidenib distribution in brain were low (4%). No dedicated studies for placental transfer and milk excretion studies in animals were performed

for ivosidenib. However, placental transfer of ivosidenib was shown in the pivotal studies on embryo-fetal development in rats and rabbits (as reflected in section 5.3 of the SmPC).

Ivosidenib extensively becomes metabolised, mainly by oxidation by CYP3A4 (minor CYP2B6 and CYP2C8) and other CYP enzymes but also by N-dealkylation and conjugation with glutathione, cysteine or glucuronic acid. However, no circulation major metabolites were identified. In plasma the predominant compound is unchanged ivosidenib. In monkeys and rats but not in humans, small amounts of M1 and M2 were detected in plasma. Ivosidenib is excreted after metabolisation via bile and kidney. Five metabolites, M39 to M44 were reported in humans only (urine, feces). These do not appear in plasma so that potential systemic toxicity is not of concern. Liver toxicity cannot be excluded. However, these metabolites are not formed by unique chemical modifications but constitute a new combination of reactions which also occur to form the other metabolites; therefore, it is not expected that their liver toxicity is markedly different from the other metabolites.

Liver effects were consistently observed in the repeated-dose toxicity studies (see toxicology section below), mostly hepatocellular hyperplasia but also signs of liver damage (at the level of histopathology and of serum markers). It is not known whether this is related to ivosidenib metabolism, but the accompanying alterations in serum chemistry would also be detectable in humans.

2.9.4. Toxicology

To support the proposed treatment of patients with cholangiocarcinoma and AML with an IDH1 mutation, ivosidenib was evaluated in non-clinical toxicology studies that meet requirements as defined in ICH S9. Repeat-dose toxicity studies included up to 3 months in duration in rats and monkeys. The choice of the species used in toxicity studies is adequately justified. The potential genetic toxicity of ivosidenib was determined in a bacterial reverse mutation assay, *in vitro* micronucleus assay in human peripheral blood lymphocytes, and *in vivo* micronucleus study in rats. Potential embryofetal developmental toxicity was evaluated in rats and rabbits. Phototoxicity was investigated in an in vitro neutral red uptake study in BALB/c 3T3 mouse fibroblasts. Starting materials, potential process impurities, and process intermediates were evaluated in silico for potential mutagenicity using Derek Nexus and Sarah Nexus statistical-based software for the prediction of mutagenicity. No carcinogenicity, fertility and pre- and post natal developmental toxicity (PPND) studies were performed. Oral route was used in animal studies, ivosidenib was administered twice a day as intended in clinical population. The formulations used for the repeat-dose toxicity studies in rats (ivosidenib PVAP solid dispersion) and monkeys (ivosidenib HPMCAS solid dispersion) were selected to optimize tolerability and exposure in order to evaluate ivosidenib in two species. In AML patients, ivosidenib is indicated to administrate in combination with azacitidine (MA since 2008); no non-clinical studies to evaluate the toxicity of the combination were conducted, this is acceptable according to ICH guideline S9 requirements.

2.9.4.1. Single dose toxicity

After single administration of ivosidenib free form in monkeys, gastrointestinal toxicity (soft faeces and emesis) was found from 100 mg/kg. No maximum tolerated single oral doses were determined.

2.9.4.2. Repeat dose toxicity

In repeated dose toxicity studies in rats, the main findings were liver hypertrophy, accompanied by increase of liver enzymes in serum, and increased and extramedullar haematopoiesis combined with decreased red cell count and related parameters as well as increased reticulocyte count. The results were fairly consistent across the studies. Soft or otherwise abnormal faeces were only observed at very high doses (2000 mg/kg). Two pivotal studies were performed in rats (28 day and 3-month duration). Rats (15 animals/sex/group) were dosed for 28 days at 0, 100, 500 and 2000 mg/kg/day (0, 50, 250 and

1000 mg/kg/dose BID) and 14 days recovery was added. There was early mortality in the high-dose group. Besides effects on liver and haematopoiesis, decreased weight of several organs was observed. Further effects were decreased body weight gain, prolonged coagulation time, reduced serum potassium and glucose, kidney alterations and, at the highest dose, diarrhoea or soft faeces. Thyroid hyperplasia may be related to the hepatocellular hypertrophy (faster degradation of thyroid hormones). Effects on reproductive organs were seen in female and male rats that were reversible only in the case of females (see details in reproductive section). There were findings even in the low-dose group so that a NOAEL could not be defined. The exposure margins compared to human therapeutic exposure were not high, up to 3.5-fold in the high-dose group. The doses used in the 3-month study were lower than in the 28-day study, rats (15 animals/sex/group) were dosed for 92 days at 0, 20, 100, 500 mg/kg/day (10, 50, 250 mg/kg/dose BID) and 28-day recovery was added. The toxicological findings were similar. Main target structures were again liver (hypertrophy, but also liver cell necrosis and increased serum liver enzymes) and haematopoiesis (decreased red blood cell parameters, increased and extramedullar haematopoiesis). Regarding organ weights, increase was only seen in liver and thyroid. No NOAEL could be determined. Exposure margins relative to human therapeutic exposure were rather low and decreased during the study because of decreasing exposure of the animals. It is noted that in the chronic study, at the end of the 4-week recovery period, some findings were not recovered: incisors whiter than normal at 500 mg/kg/day, decreased mean corpuscular hemoglobin concentration (MCHC) at 500 mg/kg/day, higher serum Sorbitol dehydrogenase (SDH) and Alanine aminotransferase (ALT) at 500 mg/kg/day (hepatocellular hypertrophy had partially recovered and the secondary hepatic necrosis had fully recovered), increased thyroid weights and colloid alteration at ≥100 mg/kg/day, and splenic brown pigment at ≥100 mg/kg/day (see discussion in the clinical part).

Two pivotal studies were performed in monkeys (28 day and 3-month duration). Monkeys (5 animals/sex/group) were dosed for 28 days at 30, 90, and 270 mg/kg/day (15, 45, and 135 mg/kg/dose BID) and 14 days recovery was added. Gastrointestinal symptoms (swollen abdomen, emesis, soft faeces, and diarrhoea) and liver cell hypertrophy were the most prominent findings in this study. The liver findings were accompanied by altered serum parameters in the high dose group (increased bilirubin in males and decreased albumin in females). Red blood cell parameters were reduced (Hb, Hct) in the high dose group, but – in contrast to rats – no increased haematopoiesis was reported. Furthermore, QTc prolongation and bigeminy was observed in the ECG. This is most likely due to hERG channel inhibition. A NOAEL level could not be determined since toxicological findings were observed already at the lowest dose. The exposure margins to human therapeutic exposure were low and decreased during the study since AUC0-12h and – to a lesser extent – Cmax decreased from Day 0 to Day 27 in the animals (except for high dose males). Monkeys (6 animals/sex/group) were dosed for 92 days at same dose than used in 28-d study: 30, 90, and 270 mg/kg/day (15, 45, and 135 mg/kg/dose BID) and 28 days recovery was added. The results were similar to the 28-day study with gastrointestinal, liver and ECG findings. No alterations in haematological parameters were reported in this 3-month study.

The mechanism of liver cell hyperplasia is not clearly identified. It is not possible to conclude that hepatocellular damage is only due to enzyme induction.

Haematological changes results mainly to gastrointestinal (GI) bleeding, resulting in anaemia and increased blood regeneration in the bone marrow. GI bleeding and perhaps haemolysis obviously contributed to the observed haematological changes. The mechanisms underlying GI bleeding or haemolysis has not been demonstrated. The effects were observed in monkeys mostly at high doses which led to supratherapeutic exposure. Haematological findings were observed in patients, and are mentioned in SmPC (see clinical report).

Although no histologic alterations of the gut mucosa were observed in the 3-month monkey study, pronounced gastrointestinal effects in monkeys (soft faeces, diarrhoea) were observed. At higher doses (in the 7-day study), damage of the intestinal mucosa was observed.

2.9.4.3. Genotoxicity

Ivosidenibdid not show any evidence for a relevant genotoxic potential.

2.9.4.4. Carcinogenicity

No carcinogenicity studies were conducted with ivosidenib, in compliance with ICH guideline S9.

2.9.4.5. Reproductive and developmental toxicity

Fertility and pre-post-natal toxicity studies were not conducted, in line with recommendations of ICH S9 guideline. In the 28-day rat toxicity study, a reversible decrease in prostate weight was noted at 0.5-fold the clinical AUC-based exposure, with additional testicular degeneration observed only in animals euthanized prematurely at the high dose level (1.2-fold the clinical AUC). In females, a decrease in the weight of uterus was observed at 1.0-fold the clinical exposure (based on AUC) with estrous cycle changes, uterine atrophy and ovarian (decreased number of corpora lutea) findings at 1.7-fold the clinical AUC. These changes in females were reversible. Adverse findings on reproductive organs were not observed in the 3-month rat toxicity study at up to 500 mg/kg/day, or in 28-day and 3-month monkey studies at up to 270 mg/kg/day and 180 mg/kg/day, respectively (0.8-, 3.0-, and 2.3-fold human exposure). The clinical relevance of uterine atrophy and testicular degeneration observed in rats is not known; these findings are reported in SPC 5.3.

Embryo-fetal development studies were performed in rats and rabbits. In rats, a decrease in fetal weight and subsequent delayed skeletal ossification were observed at the non-maternotoxic high dose level of 500 mg/kg/day (2-fold clinical exposure based on AUC levels). In rabbits, the high dose level of 180 mg/kg/day (2-fold clinical exposure based on AUC levels) caused maternal toxicity as shown by body weight loss and decreased food consumption over the treatment period, premature euthanasia of one dam on GD19, and abortion of another dam on GD21. At this dose level, embryo-foetal toxicity was evidenced by the reports of increased post-implantation loss, decrease in fetal weights, visceral variations (small spleen), and delayed skeletal ossification. The developmental NOAELs of 100 mg/kg/day rats and 90 mg/kg/day in rabbits corresponded to 0.4- and 1.4-fold, respectively, the clinical exposure based on AUC levels.

2.9.4.6. Toxicokinetic data

The exposure margins vs. human therapeutic exposure in the high-dose groups of the repeated-dose studies were rather low (up to around four). The exposure margins markedly decreased over time, i.e. from study start to study end. At study end, the margins were close to one at the highest dose. This was due to decreasing exposure of the animals over time. A clear no-effect level could not be determined from the repeated-dose studies.

2.9.4.7. Local Tolerance

The intended route of administration is oral. The gastrointestinal tract was evaluated in all repeat-dose toxicology studies in Sprague-Dawley rats and cynomolgus monkeys. No dedicated local tolerance testing was conducted.

2.9.4.8. Other toxicity studies

The qualification and specification of impurities is considered acceptable. Ivosidenib did not show any phototoxic potential.

2.9.5. Ecotoxicity/environmental risk assessment

Ivosidenib PEC_{SW} value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5.

Table 1. Summary of main study results

Substance (INN/Invented Name): Ivosidenib			
CAS-number (if available): 1448347-49-6			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	Log Pow at pH 5 = 3.2 Log Pow at pH 7 = 3.2 Log Pow at pH 9 = 3.1	Potential PBT (No)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	AML with IDH mutation: 0.00450 CCA with IDH mutation: 0.00455 Overall: 0.00905	µg/L	> 0.01 threshold (No)

2.9.6. Discussion on non-clinical aspects

In vivo PD experiments confirmed that ivosidenib caused an inhibition of 2-HG production *in vivo*, however, biological consequences remain unclear. The data obtained from human mutated IDH1 AML xenografted mice demonstrated that ivosidenib was not able to reduce proliferation and more importantly, survival time of the animals was markedly reduced by ivosidenib treatment. Non-clinical proof-of-concept to use ivosidenib in AML or cholangiocarcinoma patients was insufficiently demonstrated. The mechanism of action of ivosidenib is not well characterized as it is not yet clear whether decrease of 2-HG levels always leads to cellular differentiation. The presented non-clinical data (*in vitro*, *ex-vivo* and *in vivo*) do not allow unambiguous conclusions. The poor growth in vitro may indicate that the mutant IDH1 cells were highly differentiated. Therefore, it will not be possible to conclude that ivosidenib has induced differentiation in these cells. However, it is not clear whether colony formation in ex vivo experiments indeed reflects cell differentiation; histology or differentiation markers were not determined. Improved ability to grow in vitro can also be a sign of increased malignancy. Evaluation of differentiation markers revealed that AML cells from different patients react in different ways on ivosidenib. Ivosidenib not always increased expression of differentiation markers but also decreased expression occurred. This is physiologically plausible because ivosidenib does not target specific genes. Rather, it changes the pattern of DNA and histone methylation so that the resulting alterations in gene expression depend on the methylation pattern which existed before ivosidenib treatment. Thus, it may happen that ivosidenib increases the malignancy of tumour cells instead of decreasing it. Therefore, although it seems clear that ivosidenib inhibited production of 2-HG, as a first step, the events resulting from this 2-HG inhibition and particularly the effect of ivosidenib on differentiation of AML cells is considered not characterized. Therefore, the use of 2-HG level as PD biomarker in patients is questionable. Ivosidenib clinical efficacy in both indications was assessed in clinical trials; the uncertainties of the ivosidenib mechanism of action raised in non-clinical part are superseded by clinical efficacy data. In the SmPC section 5.1 it is stated that the mechanism of action is not clearly understood. The secondary pharmacodynamic data support that ivosidenib is a selective molecule with no significant off-target activity observed; however, proteins more closely related to IDH1 with higher chance of being off-targets were not specifically tested. Uncertainties of the ivosidenib mechanism of action raised during the previous procedure are similar for both indications – however, these uncertainties are superseded as clinical efficacy is satisfactorily demonstrated (see discussion on clinical efficacy).

The *in vitro* data presented to support the combination ivosidenib+azacitidine in the AML indication is not robust. Moreover, as mentioned above, uncertainties of ivosidenib mechanism of action in preventing or reducing tumor cell proliferation make it difficult to appreciate a combination effect. At this stage, no convincing non-clinical arguments were presented to support the combination ivosidenib and azacitidine. Efficacy of the combination ivosidenib+azacitidine was studied in humans and results are discussed in clinical AR.

ADME studies did not reveal a cause for concern. Ivosidenib extensively becomes metabolised in animal at the difference of human where no circulating metabolites were observed in plasma, metabolites were found only in urine and feces. Liver effects were consistently observed in the repeated-dose toxicity studies, mostly hepatocellular hyperplasia but also signs of liver damage (at the level of histopathology and of serum markers). It is not known whether this is related to ivosidenib metabolism, but the accompanying alterations in serum chemistry would also be detectable in humans.

Toxicity studies revealed that the main findings in rats were liver hypertrophy, accompanied by increase of liver enzymes in serum, and increased and extramedullar haematopoiesis combined with decreased red cell count and related parameters as well as increased reticulocyte count. The main findings in the monkey studies were soft faeces/diarrhoea, decreased red cell count and related parameters, liver hypertrophy associated with increased liver weight and ECG changes (particularly QTc prolongation).

In animal studies at clinically relevant exposures, ivosidenib induced haematologic abnormalities (bone marrow hypocellularity, lymphoid depletion, decreased red cell mass together with extramedullary haematopoiesis in the spleen), gastrointestinal toxicity, thyroid findings (follicular cell hypertrophy/hyperplasia in rats), liver toxicity (elevated transaminases, increased weights, hepatocellular hypertrophy and necrosis in rats and hepatocellular hypertrophy associated with increased liver weights in monkeys) and kidney findings (tubular vacuolation and necrosis in rats). 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 regards to gastro intestinal effects, it is difficult to distinguish between functional and cytotoxic effects because cytotoxicity not leading to overt cell death would indeed lead to disturbance of the normal cellular function. The possibility that the GI effects could be related to IDH1 wt inhibition in the gut mucosa could not be excluded. Moreover, plasma concentrations achieved in toxicology studies could inhibit wt IDH1 so that some toxicological findings could be due to wt IDH1 inhibition. In regards to IDH1 inhibition leading to undesired effects in patients, IDH1 wild-type inhibition in the clinical setting cannot be ruled out at the recommended dose level. Indeed, the difference in plasma protein binding between humans and animals was low and it is not known whether plasma protein binding plays a major role at all when the affinity of the target structure of a drug substance (IDH1 in this case) has a markedly higher affinity to the drug than albumin. Therefore, the argument that plasma protein binding of ivosidenib is higher in humans than in animals so that even higher plasma levels of total ivosidenib would be required to achieve wt IDH1is not agreed. Potential inhibition of wt IDH inhibition and potential consequences are discussed in clinical part.
Hepatic dysfunction, renal dysfunction and gastrointestinal symptoms, in the repeat-dose toxicity studies in the rat and monkey were observed in humans.
Finally, QT prolongation observed in vitro (hERG inhibition) and *in vivo* in animals and in humans at clinically relevant plasma levels. ECG QT prolonged is classified as an important identified risks in the RMP.

NOAEL levels could not be determined since toxicological findings were observed already at the lowest dose and some of them with were not recovered. Exposure margins relative to human therapeutic exposure were rather low or absent. The reason for this observation could be induction of CYP enzymes by ivosidenib which are responsible for ivosidenib metabolism. It could not be clearly established in the

PK studies whether ivosidenib indeed induces its own metabolism, but the TK data are a clear hint for it. For calculation of the exposure margins a human exposure value taken from population PK analysis was used which represents the situation after repeated administration (Day 1 of Cycle 2). Thus, the (lower) exposure margin calculated from the animal exposure at study end appears more relevant.
The mechanism of liver cell hyperplasia is not clearly identified. It is not possible to conclude that hepatocellular damage is only due to enzyme induction. Haematological changes results mainly to gastrointestinal (GI) bleeding, resulting in anaemia and increased blood regeneration in the bone marrow. GI bleeding and perhaps haemolysis obviously contributed to the observed haematological changes. The mechanisms underlying GI bleeding or haemolysis has not been demonstrated. The effects were observed in monkeys mostly at high doses which led to a limited margin of exposure (about 2-fold human exposure). Haematological findings were observed in patients and are mentioned in SmPC.

Ivosidenib was not mutagenic or clastogenic in conventional *in vitro* and *in vivo* genotoxicity assays. Carcinogenicity studies have not been conducted with ivosidenib.

Fertility studies have not been conducted with ivosidenib. In the 28-day repeat dose toxicity study in rats, uterine atrophy was observed in females at non-tolerated dose levels approximately 1.7-fold the clinical exposure (based on AUC) and was reversible after a 14-day recovery period. Testicular degeneration was observed in males at non-tolerated dose levels approximately 1.2-fold the clinical exposure (based on AUC) in animals prematurely euthanized.

In embryofoetal development studies in rats, lower foetal body weights and delayed skeletal ossification occurred in the absence of maternal toxicity. In rabbits, maternal toxicity, spontaneous abortions, decreased foetal body weights, increased post implantation loss, delayed skeletal ossification and visceral development variation (small spleen) were observed. Animal studies indicate that ivosidenib crosses the placenta and is found in foetal plasma. In rats and rabbits, the no adverse effect levels for embryofoetal development were 0.4-fold and 1.4-fold the clinical exposure (based on AUC), respectively.

Finally, ivosidenib is not expected to pose a risk to the environment. Regarding the 2018 draft of the ERA Guideline (EMEA/CHMP/SWP/4447/00 Rev.1), it would be prudent to analyse potential secondary poisoning since log Kow has been reported to be over 3. As this guideline is not currently on force, it is acceptable not to have conducted the Bioconcentration factor in fish "BCF (fish) but, it should be considered for future applications of Ivosidenib in order to assure that secondary poisoning is not a risk to the environment.

2.9.7. Conclusion on the non-clinical aspects

Overall the presented non-clinical data are considered acknowledged and no major issues for concerns are raised. Information on relevant non-clinical aspects has been included in the SmPC section 5.3.

Ivosidenib is not expected to pose a risk to the environment.

2.10. Clinical aspects

2.10.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 2. Clinical Studies Contributing to Clinical Pharmacology with Ivosidenib in Healthy Subjects, Special Populations and Patients

Study Number	Study Design	N	Report date/ analysis cute-off date
Healthy Subjects			
AG120-C-004 Bioavailability-availability, food effect Complete	A Phase 1, open-label, 2 part study: Part 1: randomized 2 period crossover (fed & fasted) to determine food effect on PK of a single 500 mg dose of ivosidenib Part 2: single period safety & PK of a single 1,000 mg dose of ivosidenib	36	Report date: 17 June 2016
AG120-C-003 PK, absorption, metabolism, excretion (AME) Complete	A Phase 1, open-label, non-randomized, single-dose (500 mg [^{14}C]-ivosidenib), mass balance AME study in healthy male subjects	8	Report date: 23 March 2016
AG120-C-006 PK, Japanese vs Caucasian subjects Complete	A Phase 1, open-label, single-dose, PK study in healthy male Japanese & Caucasian subjects after single oral ivosidenib doses (250, 500 or 1,000 mg)	60	Report date: 06 September 2017
AG120-C-007 Drug-drug Interaction, itraconazole Complete	A Phase 1, open-label, 2 period, fixed sequence, drug-drug interaction study to evaluate the effect of multiple doses of itraconazole on the PK of a single 250 mg dose of ivosidenib in healthy subjects	21	Report Date: 04 April 2017
Special Populations			
AG120-C-012 PK, hepatic impairment Complete	A Phase 1, open-label, single-dose (500 mg ivosidenib) study to compare the PK in subjects with mild or moderate hepatic impairment to that in matched subjects with normal hepatic function	32	Report Date: 23 August 2018
Patients with Cholangiocarcinoma			
AG120-C-005 Pivotal for cholangiocarcinoma Complete	(see Table 3 for main Phase 3 study design) Pharmacology objectives: To characterize the PK of ivosidenib in subjects with advanced cholangiocarcinoma. To evaluate the PK/pharmacodynamic relationship of ivosidenib and 2-HG.	156 Population PK analysis: N=166	Cut-off date: 31 January 2019 Population PK and E-R analyses cut-off: 31 May 2020
Patients with Cholangiocarcinoma and Other solid Tumors			
AG120-C-002[2] Supportive for cholangiocarcinoma Ongoing	(see Table 3 for main Phase 1 study design) Pharmacology objectives: To characterize the PK of ivosidenib in subjects with advanced solid tumors. To evaluate the PK/pharmacodynamic relationship of ivosidenib and 2-HG. To monitor plasma cholesterol and 4β-OH-cholesterol as a potential CYP3A4 induction marker (dose escalation).	168[1] Population PK analysis: N=73[3]	Cut-off date: 16 January 2019 (relevant for PK and pharmacodynamic data) Population PK and E-R analyses cut-off: 31 May 2020

Patients with Hematologic Malignancies			
AG120-C-009 Pivotal for newly diagnosed AML Ongoing	(see Table 5 for main Phase 3 study design) Pharmacology objectives: To characterize the PK of ivosidenib in combination with azacitidine in subjects with newly diagnosed AML. To evaluate the PK/pharmacodynamic relationship of ivosidenib and 2-HG.	71[1] Population PK analysis: N=64	Cut-off date: 18 March 2021

Study Number	**Study Design**	**N**	**Report date/ analysis cute-off date**
AG-221-AML-005 Supportive for newly diagnosed AML Ongoing	(see Table 5 for main Phase 1b/2 study design) Pharmacology objectives: To evaluate the efficacy and safety of 2 combinations of IDH mutant targeted therapies plus azacitidine: Oral ivosidenib + SC azacitidine, and oral AG 221 + SC azacitidine in adult subjects with newly diagnosed IDH1 mutation-positive AML and who were not candidates for intensive induction chemotherapy	23[1]	Cut-off date: 19 August 2019
Patients with Advanced Hematologic Malignancies			
AG120-C-001[1] Additional safety Ongoing	(see Table 5 for main Phase 1 study design) Pharmacology objectives: To characterize the PK of ivosidenib in subjects with advanced hematologic malignancies. To evaluate the PK/pharmacodynamic relationship of ivosidenib and 2-HG. To monitor plasma cholesterol and 4β-OH-cholesterol as a potential CYP3A4 induction marker (dose escalation).	258[1] Population PK analysis: N=253	Cut-off date (relevant for PK and pharmacodynamic data): 12 May 2017 Population PK analysis cut-off: 12 May 2017

2.10.2. Clinical pharmacology

2.10.2.1. Pharmacokinetics

Methods

Pharmacokinetic analyses

Standard non-compartmental (model-independent) pharmacokinetic methods were used to calculate PK parameters using Phoenix® WinNonlin version 8.3 or higher (Certara, Princeton, NJ).

Additionally, population PK (PPK) and PK/PD, E-R analyses were conducted based on the non-linear mixed effects modeling. The PPK estimation was performed using the first-order conditional estimation with interaction (FOCEI) method implemented in NONMEM 7, version 7.3.0 or 7.4.3.

Statistical analysis

Generally, standard summary statistics (e.g. mean, median, standard deviation [SD], and coefficient of variation [CV]) have been generated. For comparison, in most cases the 90 % confidence intervals (CI) were calculated in case of equivalence testing. In addition, in case significance levels were used, the significance level in most trials was 5%.

Absorption

Biopharmaceutical Classification System (BCS) Classification

The drug substance is practically insoluble (solubility of 38 to 66 µg/mL) in aqueous solutions between pH 1.1 and 7.5. At the highest solubility (66 µg/mL), 16.5 mg of ivosidenib drug substance can dissolve in 250 mL of aqueous solution, which is less than the proposed commercial dose. Ivosidenib drug substance has moderate permeability across Caco-2 cells at therapeutic concentration (1 to 10 µM). Therefore, ivosidenib can be classified as a BCS class IV (low solubility/low permeability).

Healthy volunteers

Following single dose of ivosidenib as a film-coated tablet formulation in healthy volunteers (studies **AG120-C-004**, **AG120-C-006** and **AG120-C-012**), absorption was relatively rapid with Cmax approximately achieved at Tmax of 3 h for dose of 500 mg.

At 500 mg geometric mean Cmax ranged from 2270 to 2850 ng/mL and AUCinf from 143000 to 222000 ng.h/mL.

Patients

Advanced Hematologic malignancies

Following single dose of ivosidenib 500 mg QD as film coated tablet in patients (Study **AG120-C-001**), Tmax was achieved at 2.37h. Geometric mean Cmax was 4481 ng/mL and AUC_{0-24h} was 61135 ng.h/mL. Following multiple dose of 500 mg QD, Tmax was achieved approximately at 3h, with a geometric mean Cmax of 6710 ng/mL and an AUC0-tau of 123150 ng.h/mL.

AML

Following multiple dose of ivosidenib 500 mg QD as film coated tablet in patients (Study **AG120-C-009**), Tmax was achieved at 2.22h. Geometric mean Cmax was 6145 ng/mL and AUC_{0-24h} was 106326 ng.h/mL.

Cholangiocarcinoma

Following single dose of ivosidenib 500 mg QD as film coated tablet in patients (Study **AG120-C-002**), Tmax was achieved at 3h. Geometric mean Cmax was 3666 ng/mL (Cmax arithmetic mean was 4060 ng/mL) and AUC_{0-24h} was 50109 ng.h/mL. Following multiple dose of 500 mg QD, Tmax was achieved approximately at 2h, with a geometric mean Cmax of 4547 ng/mL and an AUC0-tau of 74956 ng.h/mL.

Similar PK parameters were observed for Study **AG120-C-005**, after multiple dose with Tmax achieved at 2h, with a geometric mean Cmax of 4799 ng/mL and an AUC0-24h of 86382 ng.h/mL.

Absolute bioavailability

The absolute bioavailability of ivosidenib has not been investigated.

Relative bioavailability/ Bioequivalence

Two tablet formulations of ivosidenib were developed and evaluated during the clinical development program:

- Uncoated tablets at three strengths 50, 200, and 250 mg used in the Phase 1 studies in patients (Study **AG120-C-001** and **AG120-C-002**).
- Blue non-debossed film coated tablet at 250 mg used for the Phase 1 studies in HV and Phase 3 studies.

The commercial tablet formulation is the same as the 250 mg clinical tablet formulation used in the Phase 3 studies, differing only in the debossing, wherein mentions as "IVO" on one side and "250" on

the other, serves as a product identifier and does not impact the performance, exposure, or stability of the drug product.

Influence of food

The effect of a standardized high fat meal on ivosidenib PK was investigated in 30 healthy subjects who were administered a single oral dose of 500 mg ivosidenib in the fast and fed states, as Part 1 of study **AG120-C-004**.

PK Results indicated that administration of a high fat meal increased moderately geometric mean AUC0-inf by 25.6%, while doubling the Cmax (increase of 98%). Tmax was not affected by food and remains unchanged at around 3h under both conditions.

It is recommended that food should not be ingested for 2 hours before and for 1 hour after taking ivosidenib film-coated tablets.

Influence of gastric modifier

Ivosidenib does not contain ionisable groups under physiological condition and its aqueous solubility is pH independent. Therefore, plasma exposure of ivosidenib should be expected to be unchanged when co-administered with pH modulators such as antiacids, PPI or H2 receptor antagonists.

Distribution

Ivosidenib has a moderate protein binding (92 to 96%), with greater affinity for AAG, a B/P less than 1 and is extensively distributed in tissue with Vc/F of 3.20 L/kg in patients with newly diagnosed AML and 2.97 L/kg in patients with cholangiocarcinoma.

Elimination

Healthy volunteers

Across clinical studies in healthy volunteers, after single dose of ivosidenib as film coated tablet mean half-life at a 500 mg dose ranged from 55.4 to 75.5 h. In healthy volunteers, CL/F ranged from 2.25 to 2.74 L/h.

Patients

In patients with hematological malignancies (Study **AG120-C-001**), mean half-life ranged from 71.8 to 138h, CLss/F generally increased with increasing dose levels after single and multiple doses and ranged from 2.68 to 6.09 L/h on C2D1 of dose escalation across the 100 mg BID and 300 to 1,200 mg QD dose range.

Based on PPK modelling, the CLss/F of ivosidenib was estimated at 5.39 L/h after multiple dose of 500 mg QD.

Cholangiocarcinoma

In patients with cholangiocarcinoma, the mean apparent clearance of ivosidenib at steady state was 6.1 L/hour with a mean terminal half-life of 129 hours.

Newly diagnosed AML

In patients with newly diagnosed AML (Study **AG120-C-009**), based on post-hoc estimates CLss/F was estimated at 4.6L/h with a mean terminal half-life of 98h.

- Mass balance

A formal and dedicated PK study **AG120-C-003** investigated the excretion and biotransformation of a Ivosidenib (^{14}C-radiolabeled) after a suspension oral dose in 6 healthy subjects.

Following a single oral dose of ivosidenib (500 mg), the overall mean recovery of radioactivity was high about 94.3% (± 6.8), with 77.4 and 16.9% recovered in feces and urine respectively. Unchanged ivosidenib accounted for approximately 67.4% and 9.92% of the total administered dose in feces and urine, respectively.

The arithmetic mean renal clearance was 0.537 L/h.

- Metabolism

Metabolite profiling was performed and up to 13 metabolites were identified (10 in urine and 7 in feces). The primary metabolic processes for [^{14}C]ivosidenib were oxidations at the chlorobenzyl-N-5-fluoropyridinyl (M1), cyanopyridinyl-pyrrolidone (M3), and difluorocyclo butyl (M4) moieties, N-dealkylation of the difluorocyclobutyl moiety (M30), N-dearylation of the cyanopyridine (M44), and amide hydrolysis (M49). Other metabolites were the result of combinations of these primary pathways and glucuronide conjugation.

Ivosidenib was the predominant circulating component (approximately 92.4% of plasma radioactivity). Ivosidenib is slowly metabolized in humans. Elimination of absorbed ivosidenib occurred largely by oxidative metabolism (M1, M3 and M4 metabolites) with minor contributions by N-dealkylation and hydrolytic metabolism. In vitro investigations suggested that ivosidenib is mainly metabolized by CYP3A4, with minor contributions from CYP2B6 and CYP2C8.

- Interconversion

Ivosidenib is chiral with two centers suggesting 4 stereoisomers. A dedicated non-GLP method to quantify ivosidenib stereoisomers was developed in human plasma and applied on selected clinical samples to confirm the lack of chiral inversion in vivo following ivosidenib administration. No indication of chiral inversion of ivosidenib was observed.

- Pharmacokinetic of metabolites

No major metabolites were detected in plasma.

- Consequences of possible genetic polymorphism

As part of Study **AG120-C-003**, subjects were genotyped for CYP2D6 metabolizer status and the effect of a poor metabolizer (PM) genotype on PKs of ivosidenib was investigated. Two of the eight subjects were identified as PM.

Following single oral 500 mg dose, geometric mean Cmax values were similar between PMs and non-PMs (1000 and 986 ng/mL, respectively), while a moderate 30% decrease was observed on AUClast in PM subjects (52100 versus 80800 ng*h/mL) compared to non PMs reference subjects. Overall, even no clear evidence that CYP2D6 metabolizer status affected ivosidenib PK, no formal conclusion could be drawn taken into account the very small number of subjects (n=2) and the high variability observed in the study.

Dose proportionality and time dependencies

Based on PK data from patients (patients with hematological malignancies [Study **AG120-C-001**] and patients with cholangiocarcinoma [**AG120-C-002**]) following ascending single or multiple doses, ivosidenib exposures PK parameters exhibit a less than dose proportional increase across the dose range of 100 to 1200 mg (single dosing) and from 100 mg BID to 1200 mg.

Based on the results from study **AG120-C-001** (patients with hematological malignancies), studies **AG120-C-002**, **AG120-C-005** (patients with cholangiocarcinoma) and studies **AG221-AML-005**, **AG120-C-009** (newly diagnosed AML) after the recommended 500 mg QD regimen in patients, steady

state is claimed to be reached by Day 15 and low to moderate accumulation (Racc ≤ 2 for both AUCtau and Cmax) was observed in C2D1.

Intra-and inter-individual variability

Across studies in patients and using noncompartmental analysis (NCA) approach, the between-patient variability in ivosidenib was moderate to high ranging from 33.8% to 63.3% for Cmax, and ranging from 28.6 to 55 % for AUCs (variability shown as CV%).

Data from PPK analyses showed very high between-patient variability for the absorption rate constant ka (CV= 108%). A lower IIV was estimated for Vc/F (CV = 26 to 47%) and CL/F (CV= 33 to 35%). The magnitude of the proportional errors was moderate (CV = 20 to 27%).

Pharmacokinetics in target population

The PKs of ivosidenib in patients was investigated after single and repeated administration in two Phase 1 (Study **AG120-C-001**: patients with hematological malignancies and **AG120-C-002**: patients with cholangiocarcinoma), one Phase 1b/2 (Study **AG221-AML-005** : patients with newly diagnosed AML) and two Phase 3 studies (Study **AG120-C-005** :patients with cholangiocarcinoma and **AG120-C-009** : patients with newly diagnosed AML), covering thus the two claimed indications for patients with new diagnosed AML and patients with cholangiocarcinoma.

Pivotal Phase 3 studies

*Study **AG120-C-005***

Study **AG120-C-005** was a Phase 3, multicentre, randomized, double-blind, placebo-controlled, safety and efficacy study in previously treated subjects with non-resectable or metastatic cholangiocarcinoma with an IDH1 mutation.

Eligible subjects were randomized 2:1 to receive oral ivosidenib 500 mg QD or matched-placebo QD in continuous 28-day cycles.

PK parameter estimates of patients receiving ivosidenib 500 mg QD from Study **AG120-C-005** are presented in Table 7 and compared to those observed in subjects with cholangiocarcinoma from study **AG120-C-002**.

Table 3. Summary of ivosidenib plasma PK parameters after SD or MD administration dose of ivosidenib 500 mg for studies AG120-C-002 and AG120-C-005

Plasma PK Parameters	Geometric Mean (GeoCV%); n		
	Study 002	Study 005	002 and 005 Combined
500 mg QD, Cycle 1, Day 1			
N	53	142	195
$AUC_{0\text{-}24hr}$ (hr•ng/mL)	NC	NC	NC
C_{max} (ng/mL)	3,666 (37.8); 53	4,060 (45.4); 142	3,949 (43.6); 195
T_{max}[1] (hr)	3.00 (1.00, 6.00); 53	2.63 (0.50, 4.87); 142	3.00 (0.50, 3.00); 195
500 mg QD, Cycle 2, Day 1			
N	59	107	166
$AUC_{0\text{-}24hr}$ (hr•ng/mL)	74,956 (33.4); 58	86,382 (33.8); 107	82,180 (34.3); 165
C_{max} (ng/mL)	4,547 (28.6); 59	4,799 (32.9); 107	4,708 (31.5); 166
T_{max}[1] (hr)	2.15 (0.87, 6.17); 59	2.07 (0.50, 4.08); 107	2.08 (0.50, 6.17); 166
$R_{acc(AUC)}$	1.52 (32.3); 49	1.54 (42.9); 98	1.53 (39.5); 147
$R_{acc(Cmax)}$	1.28 (29.7); 50	1.16 (37.2); 101	1.20 (35.1); 150

*Study **AG120-C-009***

Study **AG120-C-009** was a Phase 3, multicenter, double-blind, randomized, placebo-controlled clinical study to evaluate the efficacy and safety of ivosidenib + azacitidine vs placebo + azacitidine in adult subjects with newly diagnosed AML with an IDH1 mutation and who are considered appropriate candidates for non-intensive therapy.

Eligible subjects were randomized 1:1 to receive oral ivosidenib 500 mg QD plus 75 mg/m2/day SC or IV azacitidine or ivosidenib matched-placebo orally QD plus 75 mg/m2/day SC or IV azacitidine.

PK parameter estimates of patients receiving ivosidenib 500 mg QD from Study **AG120-C-009** are presented in Table 8 and compared to other subjects with AML observed in studies **AG221-AML-005** and **AG120-C-001**.

Table 4. Summary of ivosidenib plasma PK parameters after SD or MD administration dose of ivosidenib 500 mg for studies AG120-C-001, AG221-AML-005 and AG120-C-009.

Plasma PK Parameters	Geometric Mean (GeoCV%); n					
	500 mg QD, Cycle 1, Day 1			500 mg QD, Cycle 2, Day 1		
	Study AG120-C-001	Study AG-221-AML-005	Study AG120-C-009	Study AG120-C-001	Study AG-221-AML-005	Study AG120-C-009
$AUC_{0\text{-}4hr}$ (hr•ng/mL)	NC	27,844.8 (63.32); 12[1]	12,683 (54.9); 50	NC	41,029.8 (42.04); 12[1]	20,111 (36.9); 34
$AUC_{0\text{-}24hr}$ (hr•ng/mL)	61,135 (33.2); 12	NC	NC	117,348 (50.1); 170	NC	106,326 (40.9); 32
C_{max} (ng/mL)	4,503 (37.9); 186	5,407.0 (56.19); 15	4,820 (38.7); 59	6,551 (44.2); 173	5,662.5 (52.82); 14	6,145 (33.8); 34
T_{max}[2] (hr)	2.97 (1.83-8.12); 186	3.0 (0.5-8.1); 15	2.57 (0.50-4.25); 59	3.00 (1.00-8.02); 173	2.5 (0.5-7.9); 14	2.22 (0.52-4.67); 34
R_{acc} C_{max}	NC	NC	NC	1.90 (53.9); 135	1.0 (38.57); 14	1.58 (86.4); 29
R_{acc} $AUC_{0\text{-}4}$	NC	NC	NC	1.46 (48.1); 142	1.2 (39.42); 9[1]	1.22 (57.4); 33

Population PK modelling and simulation

One population PK (PPK) analysis using PK data from Study **AG120-C-001** in order to describe the PK and identify the source of variability of ivosidenib was developed. This PPK model was subsequently updated with additional PK data.

Using this population information in combination with observed PK data from patients from study **AG120-C-009**, individual PK parameters were estimated using a MAP approach and used as input for ER analysis.

Using structure of the PK model described in Report AG120-C-001-PPK, as a starting point, a new PPK model was developed for patients with cholangiocarcinoma with PK data from studies **AG120-C-002** /**AG120-C-005** from which individual PK parameters were used as input for ER analysis .

Report AG120-C-001-PPK

Ivosidenib plasma concentration from study **AG120-C-001** (cutoff date of 12 May 2017) were included in this PPK model. The PK data set consisted of 253 patients with 4656 observations.

The potential effect of baseline continuous (Age, weight, BSA, CrCL, ALB, ALT, AST, BILI), categorical covariates (gender, race, NCI hepatic impairment, Cancer type, ECOG) and concomitant drug administration (antifungals, PPI, Anti-H2 …) were investigated on ivosidenib PK.

Ivosidenib oral PK in these patients was described by a 2-compartment model with a sequential zero-order release (Tlag) and first-order absorption (Ka) and a time-varying elimination. The apparent clearance (CL/F) of ivosidenib was estimated to be 1.63 L/hr on the first day and 5.39 L/hr at steady-state (CLss/F) at 500 mg QD. The change from Day 1 to steady-state was modeled as a 2-fold decrease in relative bioavailability and a 1.66-fold increase in clearance.

Relative bioavailability (Frel) of ivosidenib was found to increase in a less than dose-proportional manner. The dose-nonlinearity exponent on Frel is -0.49, thus a doubling of dose translates approximately only to a 40% increase in exposure. Moderate to high IIV was observed with %CVs of 35% (CLss/F), 47% (Vc/F) to 108% (Ka) respectively, with the highest variability estimated on the absorption parameter. The magnitude of the residual log-additive errors was moderate (CV= 26%).

Final model PK parameter estimates are presented in Table 9, GOF on Figure 2 and sensitivity effects of covariates on steady-state ivosidenib AUC in Figure 3.

Table 5. Final population PK parameter estimates

Parameter	Fixed Effect		BSV		Shrinkage
	Estimate	RSE	CV%	RSE	
Steady-State CL/F (L/h)	5.39	4%	35%	6%	5%
Steady-State Vc/F (L)	234	7%	47%	6%	11%
Steady-State Q/F (L/h)	15.8	19%	--	--	--
Steady-State Vp/F (L)	151	22%	--	--	--
First-Dose CL/F (L/h)	1.63	--	--	--	--
First-Dose V/F (L)	71	--	--	--	--
First-Dose Q/F (L/h)	4.8	--	--	--	--
First-Dose Vp/F (L)	46	--	--	--	--
ka (1/h)	1.38	10%	108%	7%	32%
Tlag (h)	0.27	11%	--	--	--
Steady-state fold-change in Frel	0.50	7%	--	--	--
Steady-state fold-change in CL	1.66	11%	--	--	--
Dose-Frel exponent	-0.49	19%	--	--	--
Wt-Vc/F exponent	0.92	13%	--	--	--
Baseline Alb-CL/F exponent	0.82	20%	--	--	--
Time-varying Alb-CL/F exponent	0.99	19%	--	--	--
Baseline Alb-Vc/F exponent	0.73	28%	--	--	--
Time-varying Alb-Vc/F exponent	1.1	38%	--	--	--
Fold-Change in CL with voriconazole	0.64	6%	--	--	--
Fold-Change in CL with fluconazole	0.59	6%	--	--	--
Fold-Change in CL with posaconazole	0.65	12%	--	--	--
Fold-change in CL with other moderate/strong Cyp3A inhibitors	0.92	17%	--	--	--
Fold-change in CL with mild Cyp3A inhibitors	1.04	6%	--	--	--
Log-additive CV%	26	3%	--	--	6%

Alb = time-varying albumin; BSV: between-subject variability; CL/F: apparent clearance; CV: coefficient of variation (=square root of variance / mean × 100%); F: relative bioavailability; ka: first-order absorption rate constant; Q/F: apparent distribution clearance; RSE: relative standard error (standard error/estimate × 100%, RSE on standard deviation terms = RSE of variance/2); SD: standard deviation; SS: steady-state; Tlag: zero-order release duration (lag-time); Vc/F: apparent central volume of distribution; Vp/F: apparent peripheral volume of distribution; Wt = baseline body weight. Note that first-dose parameters do not have standard-errors, because they are derived from steady-state parameters and fold-changes in Frel and/or CL.

Figure 2: GOF plots for the final population PK model

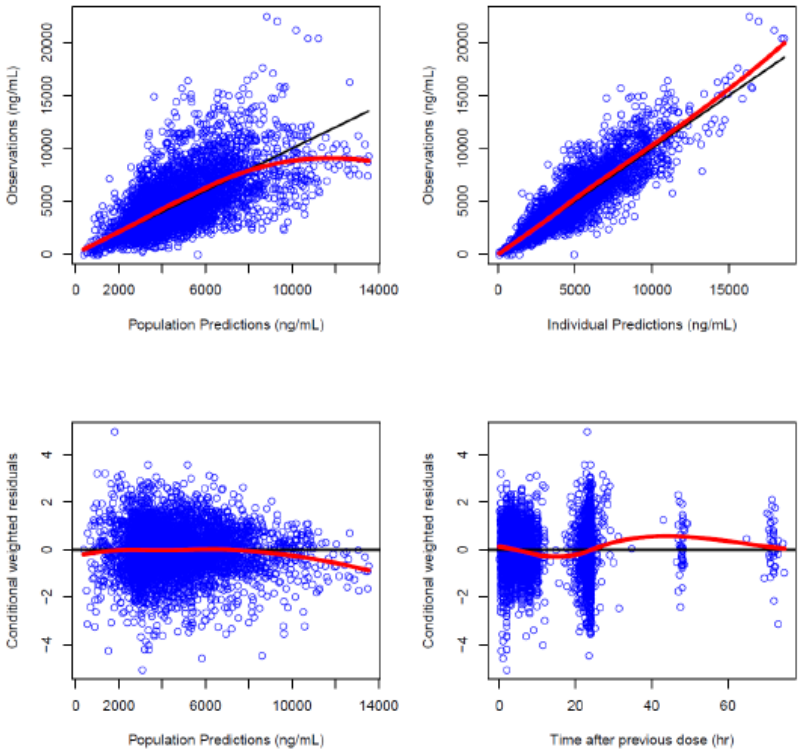
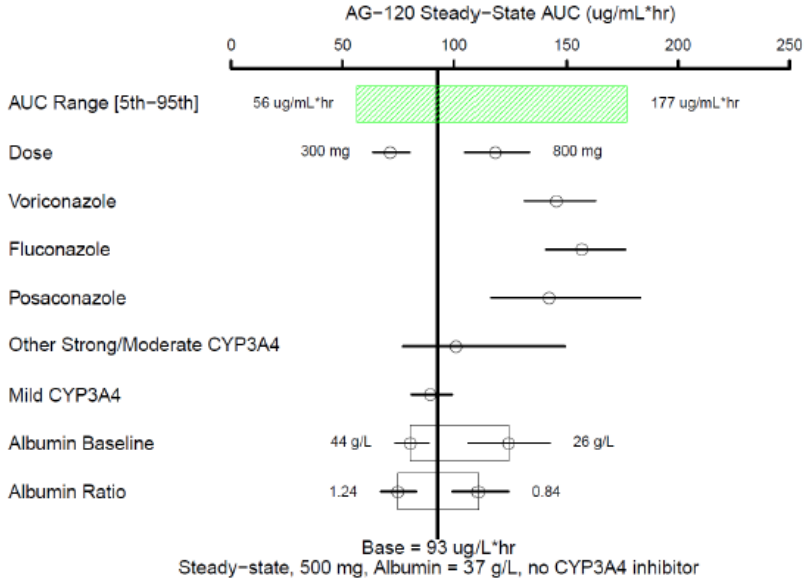


Figure 3. Sensitivity of steady-state AUC to covariates and dose



Report AG120-C-001-untreated AML-PPK

The aim of this analysis was to update the Pop-PK model previously developed in subjects with advanced hematologic malignancies using additional data as of the 11 May 2018 data cutoff date (Study **AG120-C-001**). The PK dataset for this analysis included 5034 observations from a total n= 254 patients. Of these subjects, 36 (14%) had untreated AML and 224 (88%) received the recommended ivosidenib 500 mg QD regimen.

Overall, ivosidenib oral PK in patients with hematologic malignancies was described by the same structural 2-compartment model (Tlag, Ka and a time-varying elimination) with nearly identical estimates of main PK parameters. In fact, CLss/F of ivosidenib was estimated to be 5.44 L/hr

(CV=36%) in this analysis versus 5.39 L/hr (CV=35%). In addition, the dose-exponent for relative bioavailability (-0.50 versus -0.49) and the magnitude of the covariates for CLss/F, including the effects voriconazole, fluconazole, and posaconazole, were very close between the two models. Because the updated data set has only one additional patient and only approximately 10% more samples, these similarities were expected.

Based on the updated model, steady state systemic exposure metrics (AUC_{tau}, $Cmax_{ss}$, $Cmin_{ss}$) for patients receiving the recommended ivosidenib 500 mg QD dosing regimen were derived per disease type and exposures were found to be similar across subjects with R/R AML (AUC_{tau} = 124178 ng.h/mL and Cmax = 6171 ng/mL) and subjects with untreated AML (AUC_{tau} = 115556 ng.h/mL and Cmax = 5857 ng/mL).

Report AG120-C-009-PPK

The objectives of this analysis were to use the previously developed ivosidenib PPK model (Report AG120-C-001-PK-untreated AML), in order to derive posterior Bayes PK parameter estimates and ivosidenib systemic exposure metrics for patients from study **AG120-C-009** and compare these metrics to those from study **AG120-C-001**.

The PK dataset for ivosidenib included 943 evaluable observations (after exclusion of 35 BLQ) from a total of n= 64 patients.

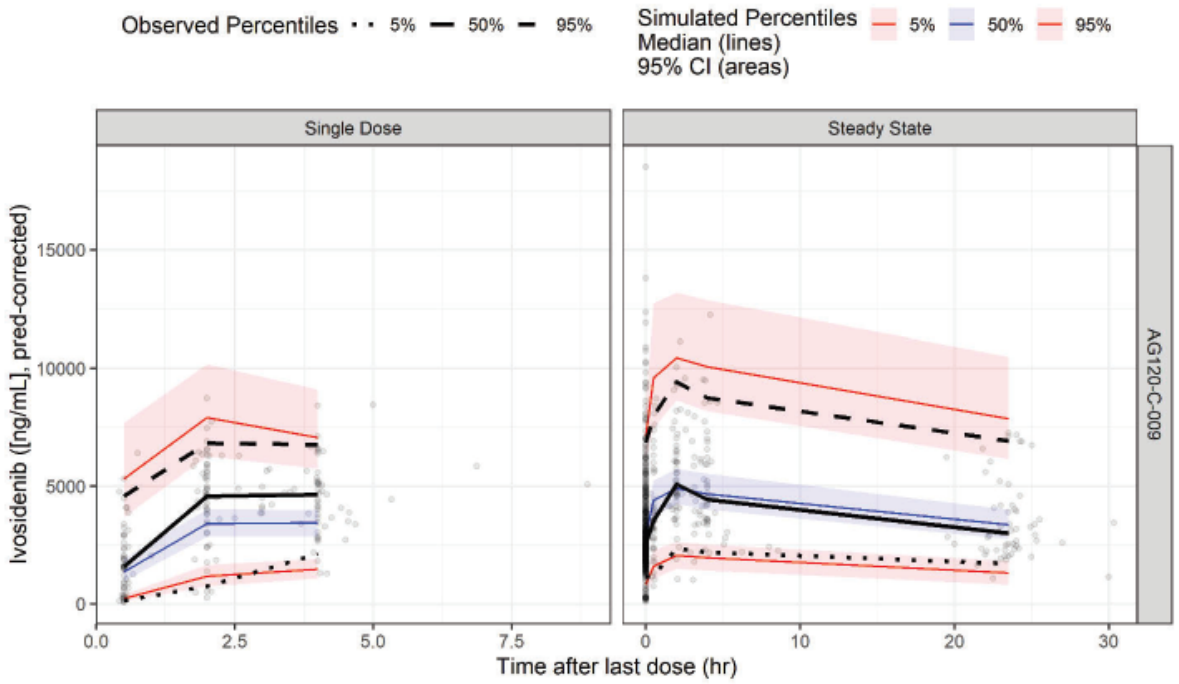
Post-hoc parameter estimates are presented in Table 10.

Table 6: Summary statistics of post hoc parameter estimates from studies AG120-C-009 and AG120-C-001

	AG120-C-001 (N = 254)	AG120-C-009 (N = 64)
CL/F (L/h)		
Mean (CV%)	4.57 (44.0)	4.56 (34.9)
Median [min, max]	4.23 [0.851, 12.3]	4.53 [1.50, 9.59]
Geometric mean (GeoCV%)	4.15 (46.8)	4.27 (38.9)
Vc/F (L)		
Mean (CV%)	279 (51.9)	232 (48.0)
Median [min, max]	248 [60.8, 1050]	205 [86.8, 746]
Geometric mean (GeoCV%)	249 (49.8)	213 (41.5)
ka (1/h)		
Mean (CV%)	1.67 (62.0)	1.95 (90.6)
Median [min, max]	1.60 [0.0564, 10.0]	1.51 [0.106, 8.49]
Geometric mean (GeoCV%)	1.35 (84.9)	1.28 (133.8)

In general, the diagnostic plots (population and individual predicted versus observed data, cwres and iwres weighted residuals graphs) showed no major bias, which confirm consistency between observed and predicted ivosidenib concentration data for Study **AG120-C-009**. In addition, the VPCs (corresponding in this case to an external validation of the previous final Pop- PK model with the data from **Study AG120-C-009** as the model parameters were fixed) indicated that the model adequately describe the observed steady state data (median and 5 and 95 percentiles levels), while observations after single dose were under-predicted at the median level (Figure 4).

Figure 4. pcVPC of ivosidenib concentrations vs Time since last dose



The derived exposures metrics (Table 11) indicated that the systemic ivosidenib exposures at steady state using the recommended oral 500 mg QD regimen were comparable between the two studies AG120-C-009 and AG120-C-001. In fact, geometric means of AUCtau, Cmaxss, or Cminss were calculated to be 117000 ng.h/mL, 5960 ng/mL, 4040 ng/mL, respectively for Study AG120-C-009 (n=64 patients untreated AML) versus 120000 ng.h/mL, 5990 ng/mL and 4250 ng/mL, respectively for AG120-C-001 (n= 254); with GMRs ratio not significantly different from 1.

Table 7. Summary exposure metrics calculated with a dose of 500 mg for subjects from studies AG120-C-001 and AG120-C-009

	AG120-C-001 (N = 254)	AG120-C-009 (N = 64)
AUC (ng•h/mL)		
Mean (CV%)	133000 (48.9)	126000 (43.0)
Median [min, max]	118000 [40600, 587000]	110000 [52100, 333000]
Geometric mean (GeoCV%)	120000 (46.8)	117000 (38.9)
Cmax (ng/mL)		
Mean (CV%)	6510 (44.9)	6310 (37.4)
Median [min, max]	5770 [2350, 26700]	5740 [2820, 14900]
Geometric mean (GeoCV%)	5990 (41.7)	5960 (33.8)
Cmin (ng/mL)		
Mean (CV%)	4820 (53.9)	4470 (49.8)
Median [min, max]	4270 [1160, 23100]	3730 [1570, 13100]
Geometric mean (GeoCV%)	4250 (53.7)	4040 (46.5)
t1/2 (h)		
Mean (CV%)	107 (42.1)	97.8 (41.6)
Median [min, max]	98.7 [43.0, 371]	83.3 [48.6, 247]
Geometric mean (GeoCV%)	99.6 (39.6)	91.2 (37.8)

Report AG120-C-002-005-PPK

Ivosidenib plasma concentration from study **AG120-C-002** and **AG120-C-005** (cutoff date of 31 May 2020) were included in this PPK model. The final PK dataset for ivosidenib included 3363 concentrations (after exclusion of n = 65 BLQ observations, around 1.9% of data) from 239 patients with cholangiocarcinoma, comprised of 73 subjects (30.3%) from Study AG120-C-002 and 166 (69.7%) from Study AG120-C-005.

The potential effect of baseline continuous (Age, weight, BSA, CrCL, ALB, ALT, AST, BILI), categorical covariates (gender, race, NCI hepatic impairment, Renal impairment, ECOG) and concomitant drug administration (moderate/weak CYP3A4 inhibitor/inducer, PPI, Anti-H2 …) were investigated on ivosidenib PK.

Ivosidenib oral PK was described by the same PPK model developed previously (new diagnosed AML). As per the provided results, the estimates for structural model parameters were similar in both populations (patients with cholangiocarcinoma versus advanced hematologic malignancies), with the exception of Vp/F: estimated to be 428 L in this analysis versus 272 L previously.

The apparent clearance (CL/F) of ivosidenib was estimated to be 1.55 L/hr on the first day and 5.82 L/hr at steady-state (CLss/F) at 500 mg QD. The change from Day 1 to steady-state was modeled as a 2-fold decrease in relative bioavailability and a 1.88-fold increase in clearance.

Vc/F was dependent on weight, with a power model exponent of 0.801. Overall, Moderate to high IIV was observed with %CVs of 33.4% (CLss/F), 25% (Vc/F) to 122% (Ka) respectively, again similar to those estimated in the previous analysis.

Despite the similarities in typical values PK parameters, the observed ivosidenib steady state systemic exposure in patients with cholangiocarcinoma were lower than that in patients with advanced hematological malignancies.

Final model PK parameter estimates are presented in Table 12, GOF on Figure 5 and effects of covariates on steady-state ivosidenib AUC in Table 13.

Table 8: Final population PK model parameter estimates for the update and previous analysis

Parameter	Updated Analysis		Previous Analysis	
	Fixed Effect			
	Value	RSE	Value	RSE
Steady-state CL/F (L/hr)	5.82	0.4%	5.86	2.7%
Steady-state Vc/F (L)	220	0.4%	222	5.2%
Steady-state Q/F (L/hr)	13.4	0.1%	14.4	15.6%
BSV correlation (CL/F,Q/F)	--	--	--	--
BSV correlation (Vc/F,Q/F)	--	--	--	--
Steady-state Vp/F (L)	428	0.1%	420	10.4%
First dose CL/F (L/hr)	1.55	--	1.56	--
ka (1/hr)	1.24	15.6%	1.25	10%
Tlag (hr)	0.33	1.4%	0.330	0.8%
Steady-state fold-change in FRel	0.5	0.6%	0.496	5.0%
Steady-state fold-change in CL	1.88	0.6%	1.86	17.9%
Dose-FRel exponent	-0.535	9.1%	-0.535	9.2%
CL ~ Ranitidine fractional change	-0.197	30.1%	-0.190	42.1%
CL ~ Other CYP3A4 inhibitors fractional change	-0.198	35.2%	-0.225	29.7%
CL ~ Prednisone fractional change	0.206	38.4%	0.282	29.7%
Baseline Wt-Vc/F exponent	0.801	0.9%	0.845	13.6%
Log additive residual error CV% Study 002	19.9%	2.1%	19.9%	5.5%
Log additive residual error CV% Study 005	25.9%	5.5%	26.8%	5.2%
	BSV			
	CV%	RSE	CV%	RSE
Steady-state CL/F (L/hr)	33.4%	0.1%	33.60%	6.4%
Steady-state Vc/F (L)	25.5%	0.1%	25.90%	16.2%
Steady-state Q/F (L/hr)	126%	0.1%	118%	11.9%
BSV correlation (CL/F, Q/F)	0.809[a]	0.04%	0.808[a]	8.5%
BSV correlation (Vc/F, Q/F)	0.585[a]	0.1%	0.588[a]	7.6%
Steady-state Vp/F (L)	75%	0.002%	74.9%	12.3%
ka (1/hr)	122%	0.2%	122%	6.2%
	Shrinkage			
	Value		Value	
Steady-state CL/F (L/hr)	6.9%		7.5%	
Steady-state Vc/F (L)	18%		19.1%	
Steady-state Q/F (L/hr)	8%		8.6%	
Steady-state Vp/F (L)	41.2%		42.8%	
ka (1/hr)	12.8%		13.3%	
Log additive residual error CV% Study 002	7.9%		7.9%	
Log additive residual error CV% Study 005	11.4%		13.4%	

Note that first-dose parameters do not have standard errors, because they are derived from steady-state parameters and fold changes in FRel and/or CL/F.

Figure 5. GOF plots for the final Population PK model

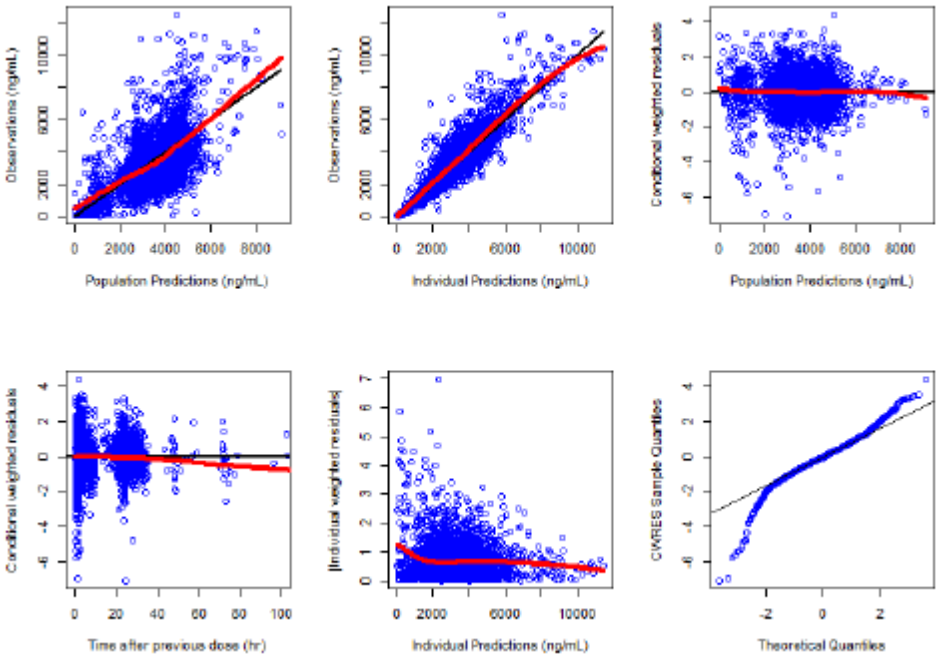


Table 9: Factors explaining variability in steady-state AUC0-24h

Covariate Values		$AUC_{0\text{-}24}$ Estimate (µg·hr)/mL	Covariate Effect (% of the Typical Value)
Typical subject receiving 500 mg QD with no concomitant CYP3A4 inhibitors or inducers		86	--
Clearance (L/hr)	5^{th} percentile (3.44 L/hr)	145	+69%
	95^{th} percentile (9.61 L/hr)	55	-36%
CYP3A4 inhibitor	Ranitidine	107	+24%
	Others	107	+25%
CYP3A4 inducer	Prednisone	71	-17%
Dose of ivosidenib	300 mg	68	-21%
	800 mg	107	+24%

Special populations

- Renal impairment

No formal dedicated PK study was performed to investigate the effect of renal impairment on ivosidenib PK, as the result from the human AME study **AG120-C-003** suggest that less than 9% (8.82%) of unchanged ivosidenib was recovered in urine (TRA of 16.9%). Therefore, investigations of the effect of renal impairment on ivosidenib PK could be retrieved from several clinical studies performed in patients (studies **AG120-C-001/002/005/009**) or following the results from the PPK models.

In studies **AG120-C-001** and **AG120-C-002**, the potential impact of baseline renal function (determined by two criteria, baseline creatinine clearance [CrCL] or estimated glomerular filtration rate [eGFR] by MDRD) was investigated in a subset of patients as patients with a mild or moderate impairment function at study entry were permitted.

From Study **AG120-C-001**, following multiple dose of ivosidenib 500 mg, a comparison between normal renal function vs mild or moderate renal impairment at baseline (eGFR) was conducted and showed no significant difference between both populations (Table 14). Similar results are observed for Study **AG120-C-002.**

Table 10. Geometric LS means ratios and 95% CIs of AG120 CLss/F following administration of AG-120 at steady-state (C2D1), effect of baseline eGFR

Renal Impairment (eGFR)		Geometric LS Mean			Adjusted ^*	
Test	Reference	Test	Reference	Ratio*	p-Value	95% C.I.**
Mild (n=74)	Normal (n=60)	4.31	4.27	100.9	0.991	(83.93, 121.39)
Moderate (n=36)	Normal (n=60)	3.81	4.27	89.2	0.422	(71.38, 111.50)

In studies **AG120-C-001** and **AG120-C-002**, there was only 1 subject with severe renal impairment based on eGFR (3 subjects with severe renal impairment based on CrCL; data cutoff 12 May 2017) and hence the safety and PK data are too limited to be able to draw meaningful conclusions in this population. There is limited clinical experience in subjects with severe renal impairment.

Based on the PPK analysis CrCL was not identified as a covariate of interest in all the developed PPK models.

- Hepatic impairment

A formal PK study study investigating the effect of impaired hepatic function on the PK of ivosidenib has been performed in Study **AG120-C-012**, in subjects with normal, or mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment.

Results from the formal PK dedicated study indicated a clear systemic underexposure of ivosidenib associated with increased CL/F. In fact, a pronounced decrease in AUC_{0-t} and C_{max} by 34% and 44% respectively was observed in the moderate HI group.

Statistical summary of the effect of hepatic impairment on ivosidenib PK and free concentration presented in Table 15 and Table 16, respectively.

Table 11: Statistical summary of the effect of hepatic impairment on ivosidenib PK

Comparison	Parameter	Geometric Mean Ratio (%)	90% Confidence Intervals (%)
Mild hepatic impairment (test) versus matched normal hepatic function (reference)	AUC_{0-t}	0.819	0.596, 1.12
	$AUC_{0-\infty}$	0.847	0.624, 1.15
	C_{max}	0.933	0.715, 1.22
Moderate hepatic impairment (test) versus matched normal hepatic function (reference)	AUC_{0-t}	0.659	0.435, 0.998
	$AUC_{0-\infty}$	0.716	0.479, 1.07
	C_{max}	0.565	0.419, 0.763

Table 12. ANOVA for unbound plasma ivosidenib PK parameters by Child-Pugh classification

Comparison	Parameter	Geometric Mean Ratio (%)	90% Confidence Intervals (%)
Mild hepatic impairment (test) versus matched normal hepatic function (reference)	C_{max_free}	1.40	0.987, 1.97
Moderate hepatic impairment (test) versus matched normal hepatic function (reference)		1.29	1.00, 1.66

An evaluation of hepatic impairment status using NCI-ODWG criteria was performed for patients with either advanced hematologic malignancies (AG120-C-001 and AG120-C-009), or with cholangiocarcinoma/chondrosarcoma (AG120-C-002 and AG120-C-005). The observed steady-state PK parameters at Cycle 2 Day 1 (C2D1) for ivosidenib following 500 mg QD regimen by study is provided in Table 17.

Table 13. Summary of Plasma Pharmacokinetic Parameters at Steady-State (C2D1) of ivosidenib after Oral Administration of ivosidenib 500 mg QD Stratified by Baseline Hepatic Impairment NCI Classification - by Study.

Study	PK parameter	Normal	Mild	Moderate
AG120-C-001 (R/R AML)	AUC0-24 (ng*h/mL)	119000 (48.6); 146	94000 (62.8); 27	93200 (44.1); 2
	AUC0-t (ng*h/mL)	45300 (47); 148	39200 (60.4); 28	40000 (60.7); 2
	Cmax (ng/mL)	6590 (42.7); 148	5840 (54.1); 28	5700 (43.8); 2
	Ctrough (ng/mL)	4200 (71); 149	2750 (149); 29	2430 (3.2); 2
AG120-C-002 (CCA)	AUC0-24 (ng*h/mL)	69400 (28.5); 30	81400 (36.7); 28	
	AUC0-t (ng*h/mL)	28200 (26.3); 30	32100 (36.4); 29	
	Cmax (ng/mL)	4390 (21.5); 30	4720 (34.6); 29	
	Ctrough (ng/mL)	2370 (36.2); 30	2870 (39.1); 28	
AG120-C-005 (CCA)	AUC0-24 (ng*h/mL)	84500 (29.8); 49	90500 (36.2); 35	
	AUC0-t (ng*h/mL)	16000 (29.7); 49	16600 (38.2); 35	
	Cmax (ng/mL)	4760 (30.7); 49	4940 (36.7); 35	
	Ctrough (ng/mL)	2800 (40.8); 72	2590 (74.3); 48	
AG120-C-009 (ND AML)	AUC0-24 (ng*h/mL)	102000 (42.7); 25	111000 (40.3); 7	
	AUC0-t (ng*h/mL)	104000 (43.3); 25	113000 (40.7); 7	
	Cmax (ng/mL)	5920 (35.4); 25	6260 (30.5); 7	
	Ctrough (ng/mL)	3510 (49.1); 27	3960 (39.4); 7	

Based on PPK analysis, the NCI Hepatic impairment covariate (categorical at 4 levels, normal, mild, moderate and severe) was not found to have a significant effect on ivosidenib PK.

- Race

A formal dedicated investigating the effect of ethnicity on the PK of ivosidenib has been performed in Study **AG120-C-006**. Subjects were randomized to 1 of 3 cohorts where ivosidenib was administered at doses of 250, 500, and 1000 mg in fasted state. Ten subjects per race and dose cohorts were enrolled.

Concentration-time profiles for ivosidenib are presented in Figure 6 and associated PK parameters in Table 18, statistical analysis in Table 19.

Table 14. Summary of PK parameters in Japanese vs Caucasians subjects

Parameter	Summary Statistic [1]					
	250 mg Ivosidenib		500 mg Ivosidenib		1000 mg Ivosidenib	
	Japanese (N=10)	Caucasian (N=10)	Japanese (N=10)	Caucasian (N=10)	Japanese (N=10)	Caucasian (N=10)
AUC_{0-t} (hr•ng/mL)	55,100 (23.9)	69,300 (31.5)	102,000 (24.0)	176,000 (43.4)	125,000 (46.0)	174,000 (46.0)
$AUC_{0-\infty}$ (hr•ng/mL)	60,800 (21.4)	75,500 (29.0)	108,000 (22.9)	185,000 (42.4)	130,000 (44.9)	180,000 (46.4)
C_{max} (ng/mL)	1340 (34.0)	1390 (24.0)	2020 (22.0)	2850 (16.0)	2440 (35.0)	2930 (19.0)
T_{max} (hr)[2]	3.50 (3.00, 18.10)	3.00 (2.00, 12.00)	3.00 (2.00, 6.00)	3.02 (1.00, 9.00)	3.00 (2.00, 9.00)	4.00 (2.00, 24.18)
$t_{½}$ (hr)[3]	40.9 (11.6)	45.8 (7.02)	46.0 (15.9)	64.0 (22.5)	41.7 (15.2)	48.3 (26.2)
CL/F (L/hr)	4.12 (21.4)	3.31 (29.4)	4.65 (22.9)	2.71 (42.4)	7.68 (44.9)	5.55 (46.4)

Figure 6. Mean (SD) plasma ivosidenib concentration-time profiles in Japanese and Caucasian subjects

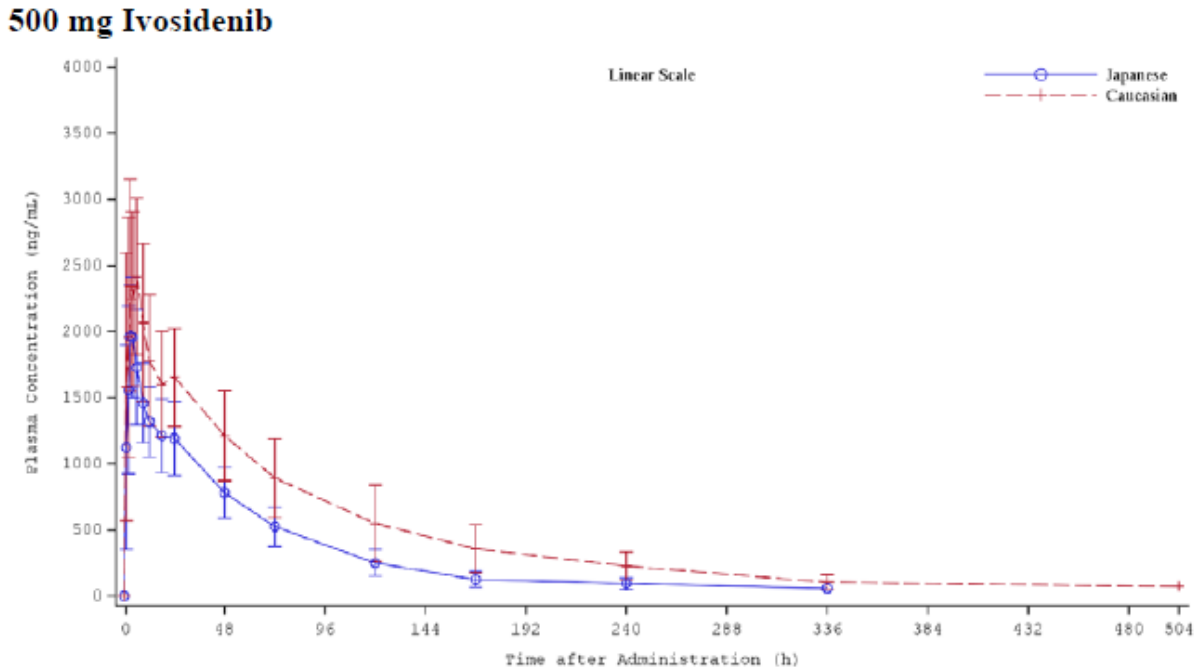


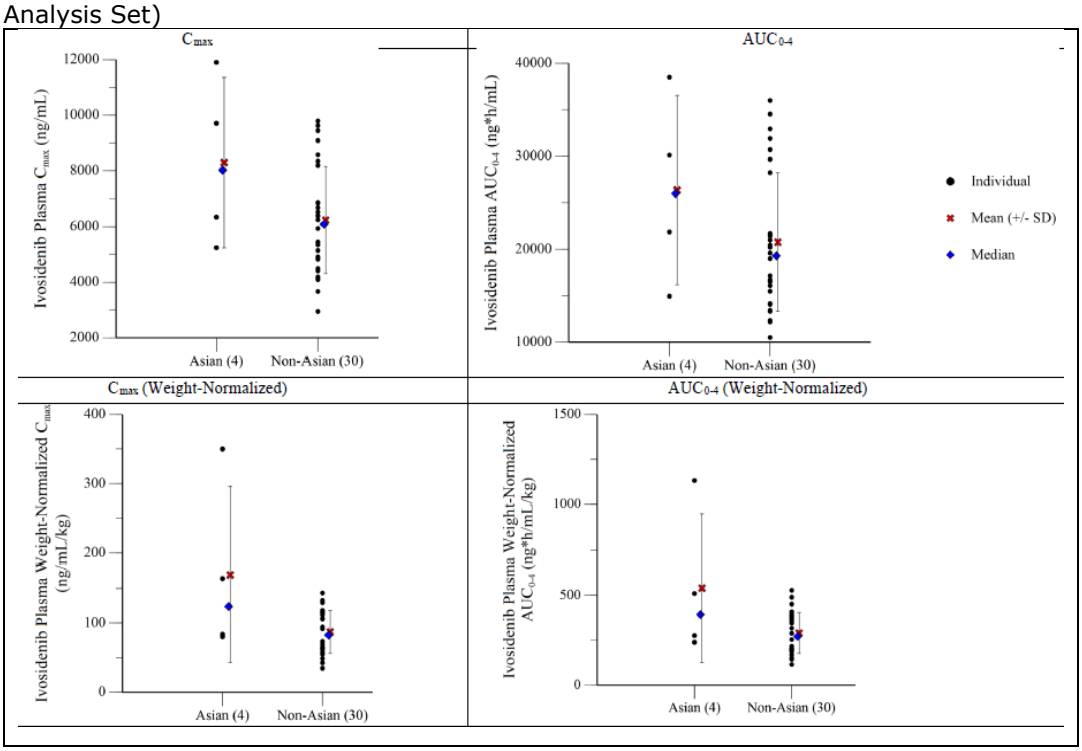
Table 15. Statistical summary of the effect of race (Japanese vs Caucasian) on ivosidenib PK

Parameter	Ivosidenib Dose	Geometric Mean Ratio	90% Confidence Intervals
AUC_{0-t}	250 mg	0.80	0.61, 1.04
	500 mg	0.58	0.44, 0.75
	1000 mg	0.72	0.55, 0.94
	Overall	0.69	0.59, 0.81
$AUC_{0-\infty}$	250 mg	0.80	0.62, 1.04
	500 mg	0.58	0.45, 0.75
	1000 mg	0.72	0.56, 0.94
	Overall	0.70	0.60, 0.81
C_{max}	250 mg	0.97	0.80, 1.17
	500 mg	0.71	0.59, 0.86
	1000 mg	0.83	0.69, 1.01
	Overall	0.83	0.74, 0.93

The overall geometric mean ratios (90% CI) for AUC0-t, AUC0-∞, and Cmax were 0.69 (0.59, 0.81), 0.70 (0.60, 0.81), and 0.83 (0.74, 0.93), respectively. This reflects an average exposure that was lower overall in the Japanese subjects compared with the Caucasian subjects by approximately 30 to 31% (AUC parameters), and 17% (Cmax). The distribution of AUC and Cmax values for Japanese subjects generally fell within the range of values for Caucasian subjects.

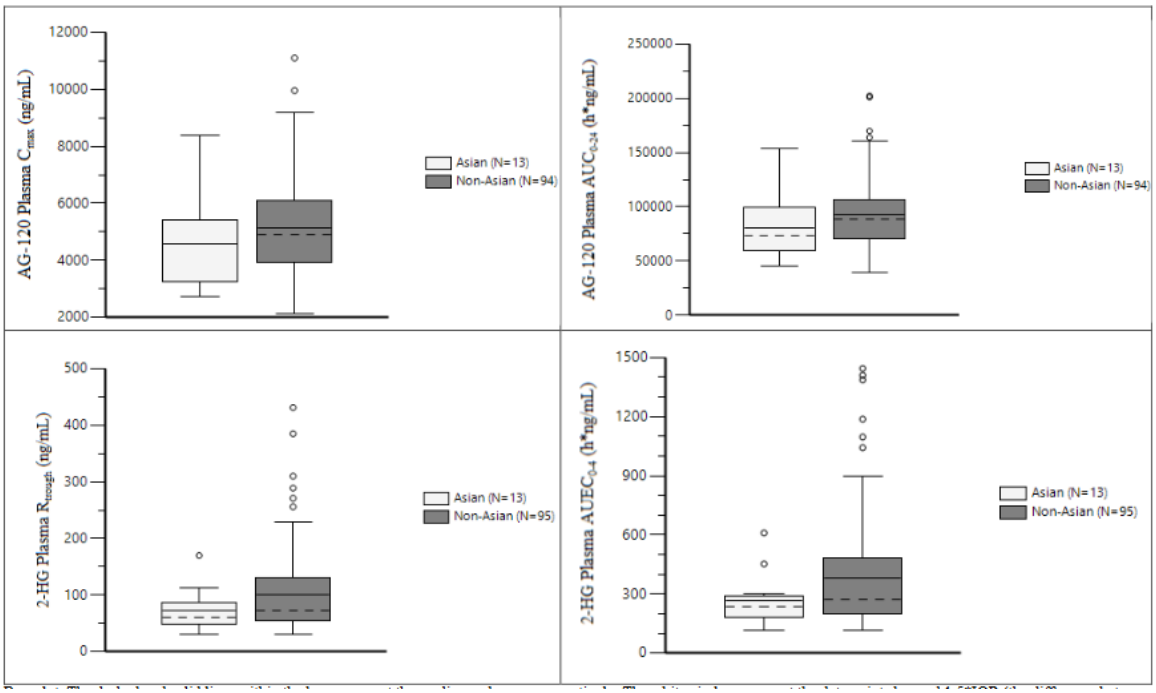
Besides Study AG120-C-006, an exploratory assessment of ivosidenib PK in Asian (Japanese, Taiwanese and Korean) vs non-Asian (Caucasian) subjects was performed in the pivotal phase 3 Study AG120-C-009 in adult subjects with newly diagnosed AML with an IDH1 mutation. Strip charts with and without weight-normalized ivosidenib PK parameters for Asians vs non-Asians after oral administration of ivosidenib 500 mg QD on C2D1 (repeat dose) are presented in Figure 7.

Figure 7. Strip Charts of Plasma Ivosidenib AUC0-4, and Cmax – Asians vs. Non-Asians – C2D1 (PK Analysis Set)



An exploratory assessment of ivosidenib PK in Asian vs non-Asian (Caucasian) subjects was also performed in the pivotal phase 3 Study AG120-C-005 in adult subjects with cholangiocarcinoma with an IDH1 mutation. Box plots of ivosidenib PK and 2-HG PD parameters for Asians vs non-Asians for Cycle 2 Day 1 after oral administration of ivosidenib 500 mg QD are presented in Figure 8.

Figure 8. Box plots of AG-120 Pharmacokinetic and 2-HG Pharmacodynamic Parameters by Race for Cycle 2 Day 1 after Oral Administration of AG-120 500 mg QD (Study AG120-C-005)



Based on PPK analysis, race was not found to have a statistically significant effect on ivosidenib PK of patients with cholangiocarcinoma or new diagnosed AML.

- Gender

Based on the PPK analysis, sex was not found to have a statistically significant effect on ivosidenib PK

- Weight

Based on the PPK analysis, weight was found to have a significant effect on Vc/F.

- Elderly

A summary of ivosidenib PK parameters (AUC_{0-8}, AUC_{0-24}, AUC_{0-T}, C_{max}, C_{trough}) estimated on Cycle 2 Day 1 following 500 mg OD ivosidenibdosing is presented by study (AG120-C-001, AG120-C-002, AG120-C-005, AG120-C-009, and AG-221-AML-005) and age group (< 65, 65 to 74, 75 to 84, 85 years of age or older) in Table 20.

Table 16. Summary PK Parameters of Ivosidenib Following Multiple Once-Daily Oral Administrations of 500 mg Ivosidenib (C2D1) by Study

		Age Group (years)			
		less than 65 (N=230/460 total)	65 to 74 (N=136/460 total)	75 to 84 (N=87/460 total)	more or equal to 85 (N=7/460 total)
Study	PK Parameter	Geometric Mean (Geometric CV%); N			
AG120-C-001	AUC_{0-8} (ng*h/mL)	44356 (54.7);55	40711 (46.4);69	44666 (45.3);44	37247 (42.7);6
	AUC_{0-24} (ng*h/mL)	119473 (57.5);5:	109097 (50.6);71	122143 (44.5);4:	91152 (51.2);5
	AUC_{0-t} (ng*h/mL)	45631 (54.4);57	42414 (47.4);71	46000 (46.2);45	40158 (49.3);6
	C_{max} (ng/mL)	6774 (49.4);57	6055 (41.9);71	6839 (43.3);45	5767 (30.3);6
	C_{trough} (ng/mL)[c]	4946 (64.3);55	4549 (54.9);73	4868 (47.8);46	4709 (72.2);7
AG120-C-002	AUC_{0-8} (ng*h/mL)	25767 (34.2);93	30408 (25.5);17	25958 (5.2);5	NA
	AUC_{0-24} (ng*h/mL)	66021 (36);92	79739 (26.1);17	71058 (8.8);5	NA
	AUC_{0-t} (ng*h/mL)	26554 (34.2);94	31802 (29.2);17	26960 (11.7);5	NA
	C_{max} (ng/mL)	4095 (32.5);94	4657 (25.6);17	4400 (10.6);5	NA
	C_{trough} (ng/mL)[c]	2414 (46.9);93	2944 (23.4);17	2432 (18.3);5	NA
AG120-C-005	AUC_{0-24} (ng*h/mL)	87483 (34.7);59	86812 (24.6);17	83539 (35.7);8	NA
	AUC_{0-t} (ng*h/mL)	16325 (35.4);59	16257 (26.8);17	15606 (33.6);8	NA
	C_{max} (ng/mL)	4827 (35.6);59	5052 (23.2);17	4448 (34.6);8	NA
	C_{trough} (ng/mL)[c]	3021 (49.1);79	2811 (39.3);29	2972 (43.1);14	NA
AG120-C-009[d]	AUC_{0-24} (ng*h/mL)	89690 (NC);1	95668 (40.8);11	112474 (42.4);1	NA
	C_{max} (ng/mL)	5350 (NC);1	5612 (36.2);11	6333 (34.2);19	NA
	C_{trough} (ng/mL)[c]	NC	3586 (52.3);12	4355 (45.7);17	NA
AG-221-AML-005	AUC_{0-8} (ng*h/mL)	60806 (38.2);2	40686 (48.3);5	38489 (29.5);4	NA
	C_{max} (ng/mL)	9797 (21.7);2	5642 (55.3);6	6183 (18.5);4	NA
	C_{trough} (ng/mL)[c]	5183 (70.5);3	3610 (69.5);5	3196 (63.6);5	NA

Based on the PPK analysis, age was not found to have a statistically significant effect on ivosidenib PK

- Children

Ivosidenib PK has not been investigated in children.

Pharmacokinetic interaction studies

As supportive data for SmPC recommendation, PBPK model was used for DDI predictions. In general, with the evidence provided, the PBPK framework is considered valid for DDI prediction of CYP3A4 substrates in AML patients, but further improvement in terms of bioavailability and oral absorption of ivosidenib are required before conducting any extrapolation in special sub-groups of patients for dose selection.

Ivosidenib as victim drug

Ivosidenib was shown to be both CYP3A4, and P-gp substrates.

The DDI study conducted with itraconazole –AG120-C-007 following ivosidenib 250 mg administration which is half therapeutic dose, showed a 2.69 fold exposure increase (GMR AUC 0-inf = 268.69 % with

90% CI [244.90 – 294.78]) without affecting Cmax (GMR Cmax = 102.41 % with 90% CI [52.71 – 113.13]). These results could not be extrapolated to the therapeutic dose of 500 mg due to ivosidenib auto-induction. PBPK modelling approach was thus used to support the expected magnitude of interactions between ivosidenib and strong CYP3A4 inhibitors. The PBPK framework is considered valid for DDI prediction of CYP3A4 substrates in AML patients. Collectively, the performed in vivo study, although not conducted at the therapeutic dose, and the PBPK model results provide some weight of evidence that interaction of ivosidenib at 500 mg with strong CYP3A4 inhibition is expected to increase ivosedenib exposure by two to three-fold.

No formal interaction study of ivosidenib with moderate CYP3A4 inhibitor was conducted. However, the PBPK model predicted an AUC ratio of 1.90, and in addition to PBPK model, PPK model showed fluconazole, moderate inhibitor of CYP3A4 was a significant covariate associated with an AUC ratio of 1.69. In absence of formal DDI study conducted with fluconazole, as a conservative measure, and also taking into consideration the safety profile of ivosidenib, in case of concomitant treatment with moderate CYP3A4 inhibitor, ivosidenib exposure increase is considered to be within two-fold. Therefore the SmPC proposed posology to be reduced by two fold with safety monitoring is supported in case of concomitant treatment with a moderate or strong CYP3A4 inhibitor.

Ivosidenib concentrations, as CYP3A substrate, is expected to be decreased in case of co-administration with CYP3A4 inducer. Ivosidenib is thus contraindicated with strong CYP3A4 inducers.

Ivosidenib as perpetrator

In vitro, ivosidenib was shown to be both inhibitor and inducer of CYP3A4. No clinical study was conducted to assess the net effect of ivosidenib on CYP3A4 substrates. However, PBPK simulations of ivosidenib effects on midazolam (CYP3A4 substrate drug) based on CYP3A4 inhibition alone, on CYP3A4 both inhibition and induction, and CYP3A4 induction, alone suggest the net effect was CYP3A4 induction. Therefore, caution of use in case of concomitant treatment with CYP3A4 substrate is recommended as ivosidenib is expected to decrease the drug concentrations, altering thereby the drug efficacy. Of note, ivosidenib auto-induced its own metabolism at steady-state.

Ivosidenib was also shown in vitro to be inducer of CYP2B6, 2C8, 2C9, and may induce 2C19 and UGT. No clinical study was performed but the induction potentials are reported in SmPC. Ivosidenib was also shown to be inhibitor of P-gp and has the potential to induce P-gp. Therefore, the SmPc mentions that concomitant treatment of dabigatran is contraindicated.

Ivosidenib was also shown to be inhibitor of OATP1B1/3 and OAT3. Therefore SmPc mentioned that concomitant treatment with these transporters substrates should be avoided and careful monitoring for safety of these drugs should be performed if avoidance is not possible.

2.10.2.2. Pharmacodynamics

Mechanism of action

Ivosidenib is a potent, selective inhibitor of mutated IDH1.

The IDH family of proteins comprises 3 isoforms: IDH1, IDH2, and IDH3. Cancer-associated mutations have been identified in IDH1 and IDH2. Isocitrate dehydrogenase converts isocitrate to alpha-ketoglutarate (α-KG) through oxidative carboxylation and results in the production of nicotinamide adenine dinucleotide phosphate (NADPH). IDH mutations confer neomorphic enzymatic activity resulting in the reduction of α-KG to form 2-HG, which consumes NADPH and renders the cell vulnerable to oxidative stress. High levels of 2-HG inhibit α-KG-dependent enzymes involved in DNA and histone methylation. These impairments have been linked to a block in cellular differentiation promoting tumorigenesis in both hematologic and nonhematologic malignancies.

Direct inhibition of mutated IDH1 suppresses production of 2-HG, restoring differentiation and reducing proliferation of the cancerous cells.

Primary pharmacology: Cholangiocarcinoma (CCA)

Study AG120-C-005

Data Sets Analyzed

A total of 60 subjects received the placebo treatment and data from these subjects was not analysed.

Table 17. NCA PK and PD Analysis (Number of Subjects)

Visit	PK and PD		
	Active	Crossover	Total
Cycle 1 Day 1	121	35	156
Cycle 2 Day 1	99	27	126

Concentrations of 2-HG in Plasma

Mean (+SD) plasma 2-HG concentrations and percent inhibition following single and multiple daily oral doses of AG-120 and Box plots of 2-HG (observed concentrations and percent inhibition) vs time and vs visit are presented in Figures below.

Figure 9. Mean (+SD) 2-HG (Observed Concentrations and Percent Inhibition) vs. Time after Oral Administration of AG-120 500 mg QD (Linear Scale)

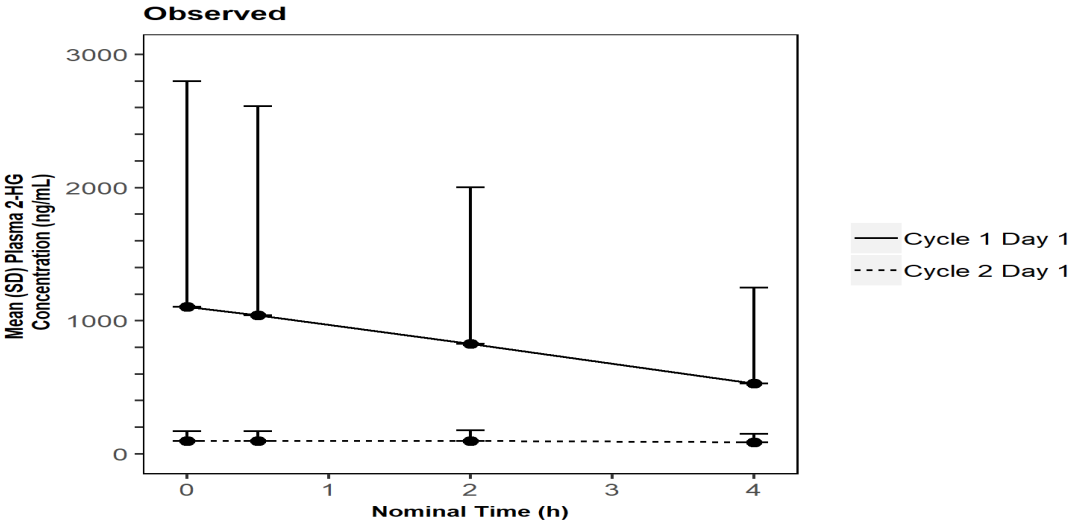


Figure 10. Plasma 2-HG Concentrations vs. Visit at Pre-dose (Trough) after Oral Administration of AG-120 500 mg QD (Linear Scale)

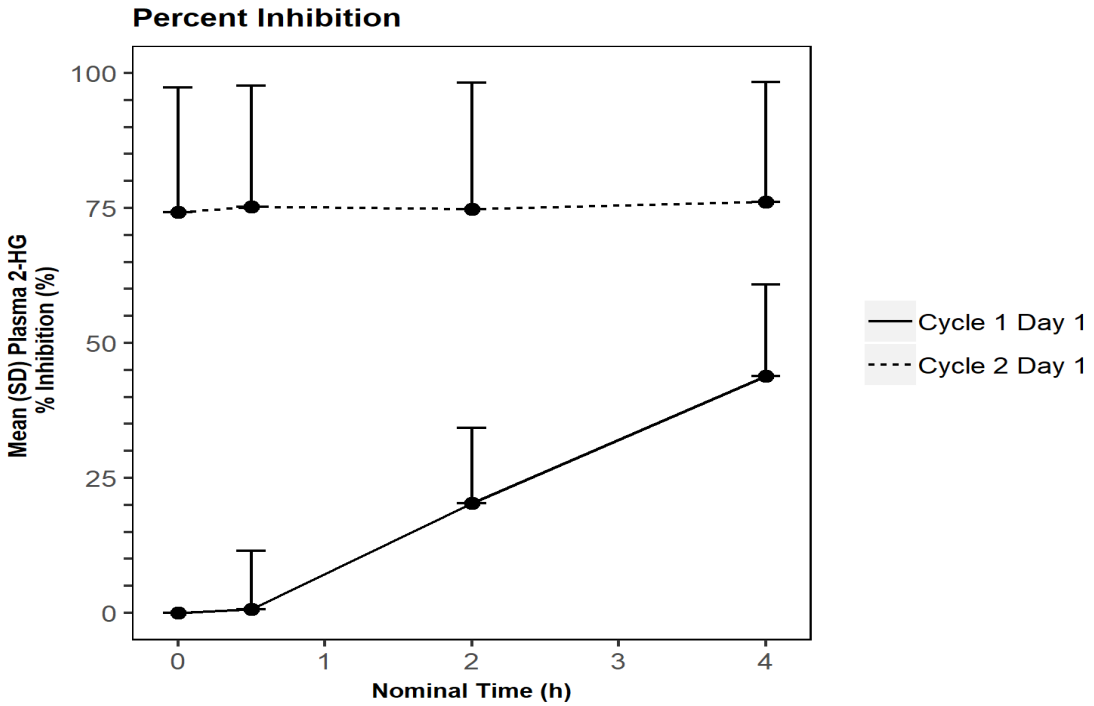
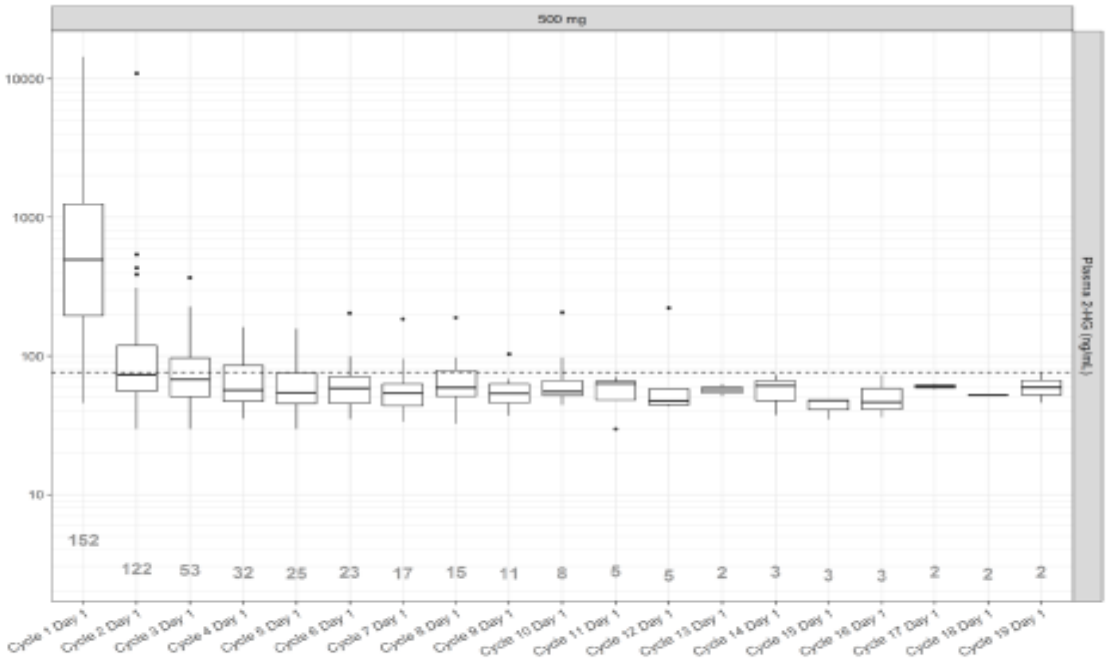
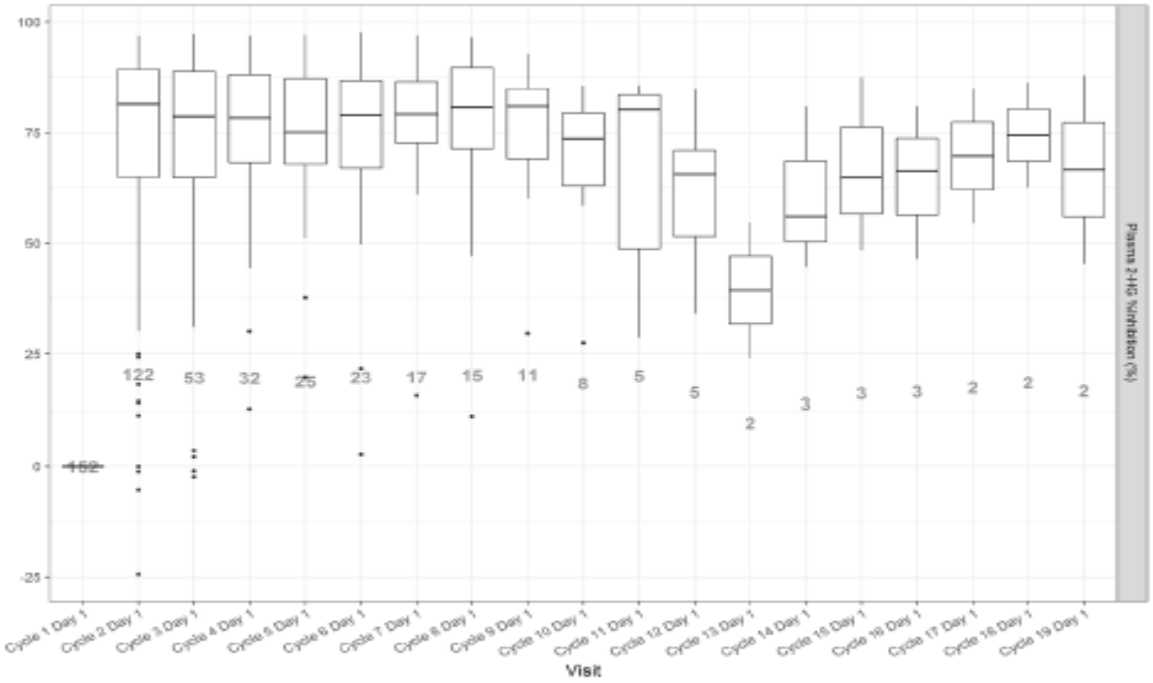


Figure 11. Percent Inhibition of 2-HG Concentrations vs. Visit at Pre-dose (Trough) after Oral Administration of AG-120 500 mg QD (Linear Scale)



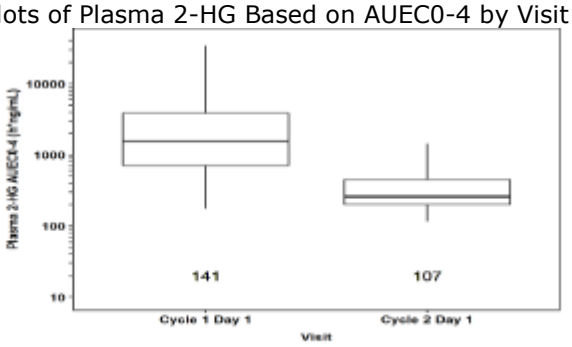
Box plots: The dotted line represent 2-HG level in healthy subjects (72.6 ng/mL). The solid black circles represent the data points beyond 1.5*IQR, a version of the 25th and 75th quartiles in R software. Gray numbers below the box plot presents data count at each Visit. Data not presented for visits where n=1.
Source: Table 14.5.3.2.



Box plot: The solid black circles represent the data points beyond 1.5*IQR, a version of the 25th and 75th quantiles in R software.
Gray numbers below the box plot presents data count at each Visit. Data not presented for visits where n=1.
Source: Table 14.5.3.2.

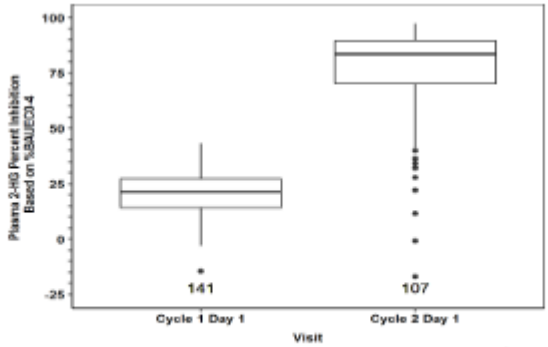
PD Parameters of AG-120 in Plasma after a Single Dose (C1D1) and Multiple Doses (C2D1) Administration of AG-120 500 mg QD

Figure 12. Box plots of Plasma 2-HG Based on AUEC0-4 by Visit - AG-120 500 mg QD



Box plot: Numbers below the box plot presents data count at each Visit.
Source: Table 14.5.4.1.

Figure 13. Box plots of Plasma 2-HG Percent Inhibition Based on %BAUEC0-4 by Visit - AG-120 500 mg QD



Box plot: The solid black circles represent the data points beyond 1.5*IQR, a version of the 25th and 75th quantiles in R software.
Numbers below the box plot presents data count at each Visit.
Source: Table 14.5.4.1

Table 18. Mean Plasma Pharmacodynamic Parameters of 2-HG Following Oral Administration of AG-120 500 mg QD

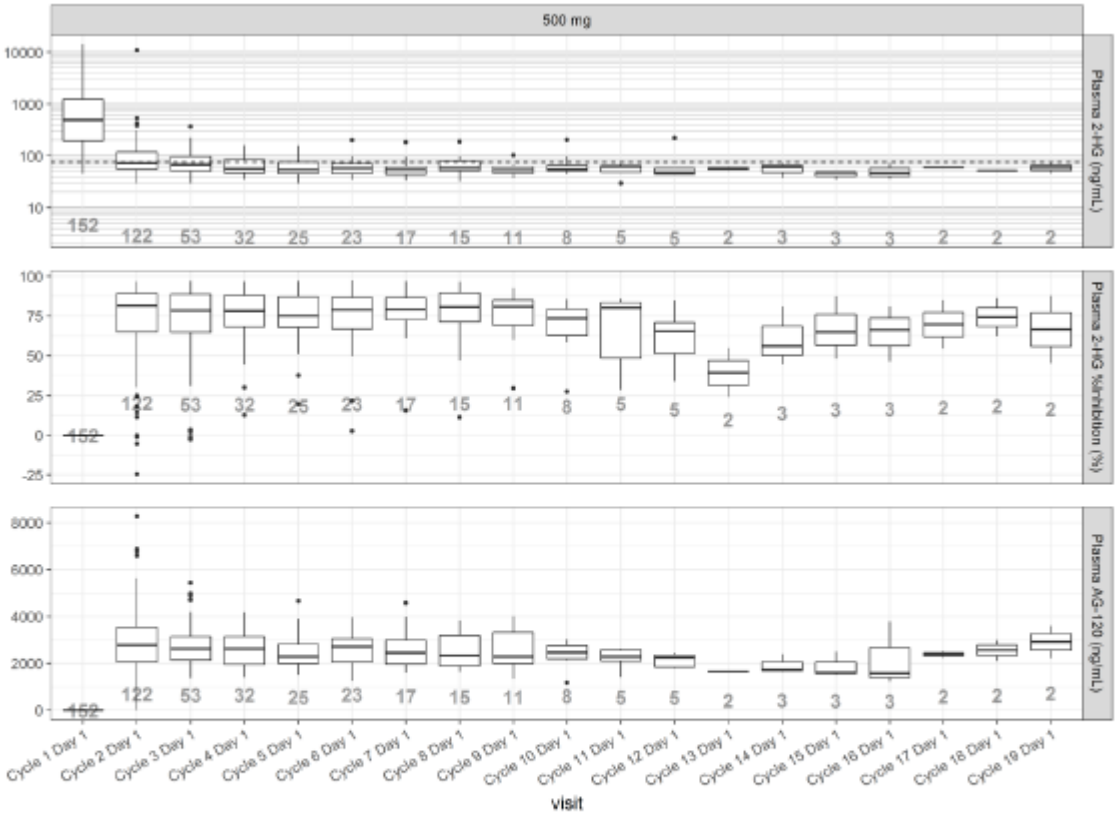
VISIT	PD Parameters	N	Mean	CV%
C1D1	B (ng/mL)	142	1108	154.4
	$AUEC_{0-4}$ (h*ng/mL)	141	3334	143.5
	$\%BAUEC_{0-4}$ (%)	141	20.2	50.1
C2D1	$AUEC_{0-4}$ (h*ng/mL)	107	368	75.7
	$\%BAUEC_{0-4}$ (%)	107	75.0	30.1
	R_{trough} (ng/mL)	108	97.7	74.6
	$\%BR_{trough}$ (%)	108	73.7	31.6

$\%BAUEC_{0-4}$ = Percent Inhibition for $AUEC_{0-4}$; $\%BR_{trough}$ = Percent Inhibition for R_{trough}; $AUEC_{0-4}$ = Area of the response curve from time point zero (pre-dose) up to 4 hr post-dose; B = Baseline effect value; CxDy = Cycle x Day y; CV% = coefficient of variation; N = number of subjects; R_{trough} = Observed response value at the end of a dosing interval

Longitudinal PK/PD Correlations

The longitudinal assessment revealed that 2-HG inhibition was robust and persistent from C2D1 through C19D1.

Figure 14. Longitudinal PK/PD Profiles: Box Plots of Pre-dose (Trough) Plasma AG-120 and Pre-dose (Trough) Plasma 2-HG over Time - AG-120 500 mg QD



Source: Figure 14.4.4.1.

Box plot: The solid black circles represent the data points beyond 1.5*IQR, a version of the 25th and 75th quantiles in R software.

Gray numbers below the box plot presents data count at each Visit. Data not presented for visits where n=1.

The dash line represent the mean 2-HG baseline in healthy subjects (72.6 ng/mL).

Combined AG-120 PK and 2-HG PD Summaries for Subjects with Cholangiocarcinoma from Study AG120-C-005 and Study AG120-C-002

Table 19. AG-120 Pharmacokinetic and 2-HG Pharmacodynamic Parameters Summaries for Study AG120-C-005 and Study AG120-C-002 after Single and Multiple Oral Administration of AG-120 500 mg QD

Plasma PK and PD Parameters	Geometric Mean (GeoCV%); n					
	500 mg QD, Cycle 1, Day 1			500 mg QD, Cycle 2, Day 1		
	Study AG120-C-002	Study AG120-C-005	Both Studies Combined	Study AG120-C-002	Study AG120-C-005	Both Studies Combined
N	53	142	195	59	107	166
AUC_{0-24} (h*ng/mL)	NC	NC	NC	74956 (33.4); 58	86382 (33.8); 107	82180 (34.3); 165
C_{max} (ng/mL)	3666 (37.8); 53	4060 (45.4); 142	3949 (43.6); 195	4547 (28.6); 59	4799 (32.9); 107	4708 (31.5);166
T_{max}[a] (h)	3.00 (1.00, 6.00); 53	2.63 (0.50, 4.87); 142	3.00 (0.50, 3.00); 195	2.15 (0.87, 6.17); 59	2.07 (0.50, 4.08); 107	2.08 (0.50, 6.17); 166
Racc(AUC)	NC	NC	NC	1.52 (32.3); 49	1.54 (42.9); 98	1.53 (39.5); 147
Racc(C_{max})	NC	NC	NC	1.28 (29.7); 50	1.16 (37.2); 100	1.20 (35.1); 150
	Arithmetic Mean (CV%); n					
$AUEC_{0-4}$ (Study AG120-C-005) or $AUEC_{0-8}$ (Study AG120-C-002) (h*ng/mL)	4129 (127.5); 50	3334 (143.5); 141	NC	692 (79.7); 60	368 (75.7); 107	NC
%$AUEC_{0-4}$ (Study AG120-C-005) or %$AUEC_{0-8}$ (Study AG120-C-002) (h*ng/mL)	41.5 (36.7); 50	20.2 (50.1);141	NC	77.5 (33.3); 53	75.0 (30.1); 107	NC

[a] Median (min, max); n; NC=Not calculated
Data from Study AG120-C-002 are only from cholangiocarcinoma subjects.
Accumulation ratio (based on AUC), calculated as AUC_{0-tau} (C2D1)/AUC_{0-24} (Day -3 or C1D1) for Study AG120-C-002 (NCA PK/PD Report AG120-C-001-PKPD-Addendum for R/R AML subjects) and calculated as AUC_{0-4} (C2D1)/AUC_{0-4} (C1D1) for Study AG120-C-005.

AG120-C-002 (DCO of 16-January-2019)

Pharmacodynamics

As of 16-Jan-2019 data cutoff date, the PD analysis of 2-HG in plasma was also evaluated in 60 subjects in the dose escalation portion and 108 subjects in the expansion portion of Study AG120-C-002**.**

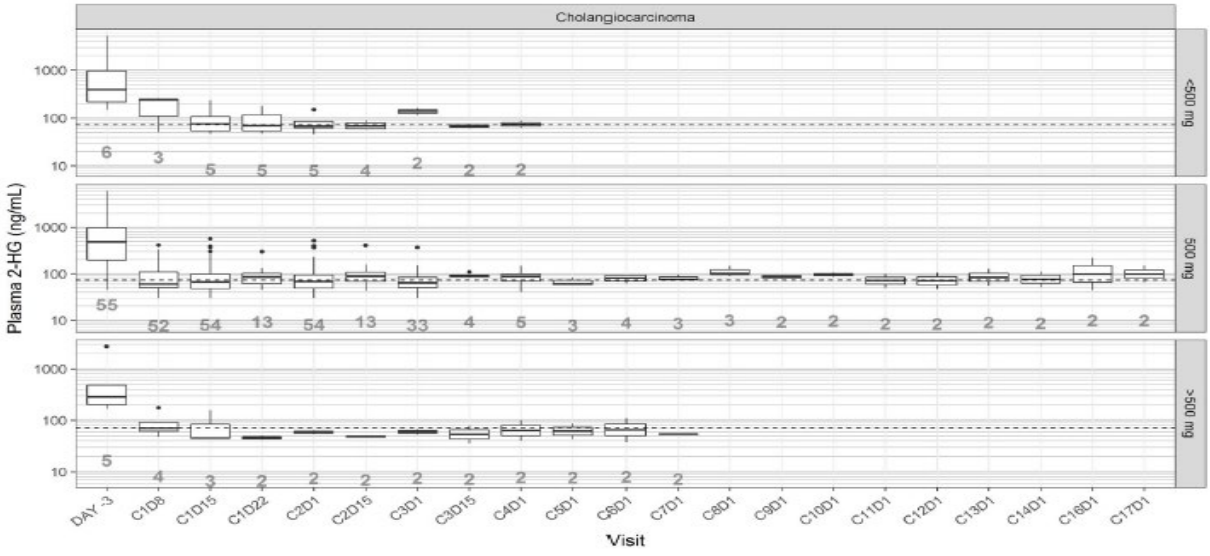
Table 20. PK and PD Analysis Populations (Number of Subjects)

AG-120 Dose (mg)	AG-120 Dose Levels							
	100 mg BID	300 mg QD	400 mg QD	500 mg QD	600 mg QD	800 mg QD	900 mg QD	1200 mg QD
Dose Escalation								
Day -3	4	8[c]	5	15[f]	5	6	4	5
Cycle 1 Day 15	3[a]	8[d]	5	22	5	6	4	5
Cycle 2 Day 1	2[b]	8[e]	5	22	5	5	4	5
Expansion								
Cycle 1 Day 1				104[g]				
Cycle 2 Day 1				96[h]				

[a] 1 subject (N206-001) did not have a profile at Cycle 1, Day 15.
[b] Two subjects are missing due to the following: 1 subject (N208-001) was given an increased dose of 300 mg QD at Cycle 2, Day 1, while he was dosed at 100 mg BID at Day -3 and Cycle 1, Day 15. One subject (N206-001) did not have a profile at Cycle 2, Day 1.
[c] One subject (N202-003) did not have a profile at this visit
[d] One subject (N208-002) did not have a profile at this visit.
[e] Two subjects (N204-003 and N208-002) did not have a profile at this visit, while 1 subject (N208-001) who started at 100 mg BID was given an increased dose of 300 mg QD at Cycle 2, Day 1.
[f] 7 subjects did not have Day -3 profile.
[g] 4 subjects did not have Cycle 1, Day 1 profile.
[h] 12 subjects did not have Cycle 2, Day 1 profile.

Concentrations of 2-HG in Plasma – Dose Escalation

Figure 15. Box Plots of Plasma Pre-Dose Concentrations of 2-HG vs. Time after Multiple Oral Administrations of AG-120 in Subjects with Cholangiocarcinoma – Dose Escalation and Expansion – By Dose Group (Semi-Log Scale)



Plasma 2-HG LLOQ = 30.0 ng/mL.
Note: The solid black circles represent the data points beyond 1.5*IQR, a version of the 25th and 75th quantiles in R software. Gray numbers below the boxplot presents data count at each visit. Visit data were not presented when N =1.
The dashed line represents plasma 2-HG levels in healthy subjects (72.6 ng/mL).
Source: Table 14.5.3.1

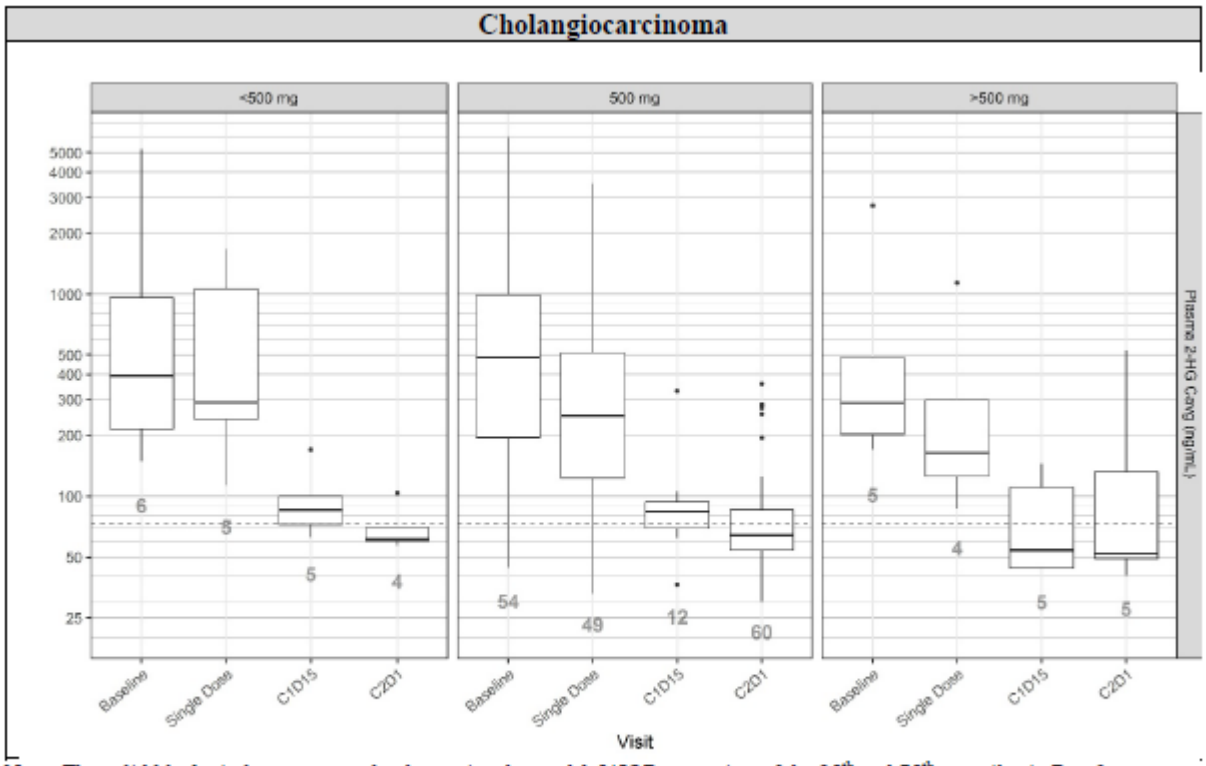
Table 21. Mean (RSD%) Plasma Pharmacodynamic Parameters of 2-HG Following Oral Administration of AG-120 500 mg QD – Dose Escalation and Expansion

Plasma PD Parameters	Mean (RSD%); n	
	Cholangiocarcinoma	Chondrosarcoma
	Day -3 and C1D1	
N	50	9
B (ng/mL)	976 (125.9);50	390 (169.6);9
$AUEC_{0-s}$ (ng*h/mL)	4129 (127.5);50	1888 (143.4);9
$\%BAUEC_{0-s}$ (%)	41.5 (36.7);50	20.4 (83.4);9
C_{avg} (ng/mL)	508 (126.3);49	233 (142.3);9
$\%BC_{avg}$ (%)	42.5 (36.6);49	20.9 (82.6);9
	C1D15	
N	12	2
B (ng/mL)	953 (108.3);10	129 (NC);1
$AUEC_{0-s}$ (ng*h/mL)	766 (78.2);13	571 (26.1);2
$\%BAUEC_{0-s}$ (%)	78.4 (21.3);10	54.7 (NC);1
C_{avg} (ng/mL)	99.8 (75.7);12	74.8 (28.2);2
$\%BC_{avg}$ (%)	78.8 (22.2);9	53.5 (NC);1
	C2D1	
N	60	8
B (ng/mL)	948 (126.9);53	346 (200.4);8
$AUEC_{0-s}$ (ng*h/mL)	692 (79.7);60	596 (33.3);8
$\%BAUEC_{0-s}$ (%)	77.5 (33.3);53	42.8 (64.2);7
C_{avg} (ng/mL)	86.6 (78.7);60	74.7 (32.4);8
$\%BC_{avg}$ (%)	77.4 (33.3);53	42.8 (64.2);7

Note: $AUEC_{0-s}$: Area under the effect concentration time curve from time point zero (pre-dose) up to 8 h; $\%BAUEC_{0-s}$: Percent inhibition based on area under the effect concentration time curve from time point zero (pre-dose) up to 8 h; $\%BC_{avg}$: Percent inhibition based on C_{avg}; B: Baseline; C_{avg}: Average 2-HG concentration over the observed post-dose period; NC: Not calculated; N: Total number of observations per dose group; n: Total number of observations per sub-category for each dose group; RSD%: relative standard deviation, which is equal to the absolute value of the coefficient of variation.
Mean (±SD) plasma 2-HG concentrations in healthy subjects is 72.6 ±21.8 ng/mL.[25,26]
Source: Tables 14.5.4.1 to 14.5.4.3

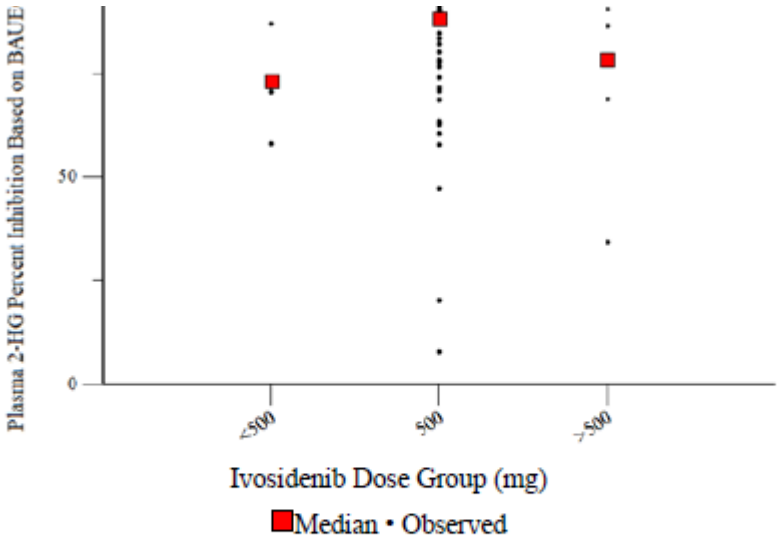
Assessment of the Dose Effect on Plasma 2-HG Dose Escalation and Expansion Combined

Figure 16. Box Plots of Plasma 2-HG Cavg vs. Visit after Oral Administration of AG-120 (Semi- Log Scale) – By Tumor Type and Dose Group (Dose Escalation and Expansion Combined)



Note: The solid black circles represent the data points beyond 1.5*IQR, a version of the 25th and 75th quantiles in R software.
Gray numbers below the boxplot present data count at each Visit. Visit data were not presented when n=1.
The dashed line represents plasma 2-HG levels in healthy subjects (72.6 ng/mL).
Source: Listings 16.2.6.5 and 16.2.6.6

Figure 17. Strip Chart of 2-HG Percent Inhibition After Multiple Oral Administration of Ivosidenib in Subjects With Cholangiocarcinoma (AG120-C-002: C2D1 Dose Escalation and Expansion)



Source: Report AG120-C-002-PKPD Addendum, Figure 7. Data cutoff date: 16 Jan 2019.
Abbreviations: 2-HG = 2-hydroxyglutarate; %BAUEC$_{0\text{-}8hr}$ = percent inhibition based on area under the effect concentration time curve from time point zero (predose) up to 8 hours; CxDy = Cycle x Day y; n = number of subjects in group; QD = once daily.
Note: <500 mg (n=5), 500 mg (n=53), and >500 mg (n=5)
Not presented on the plot: 2 subjects who received ivosidenib 500 mg QD showed an increase in 2-HG compared to baseline (ie, %BAUEC$_{0\text{-}8hr}$ of -23.7 and -6.5%).

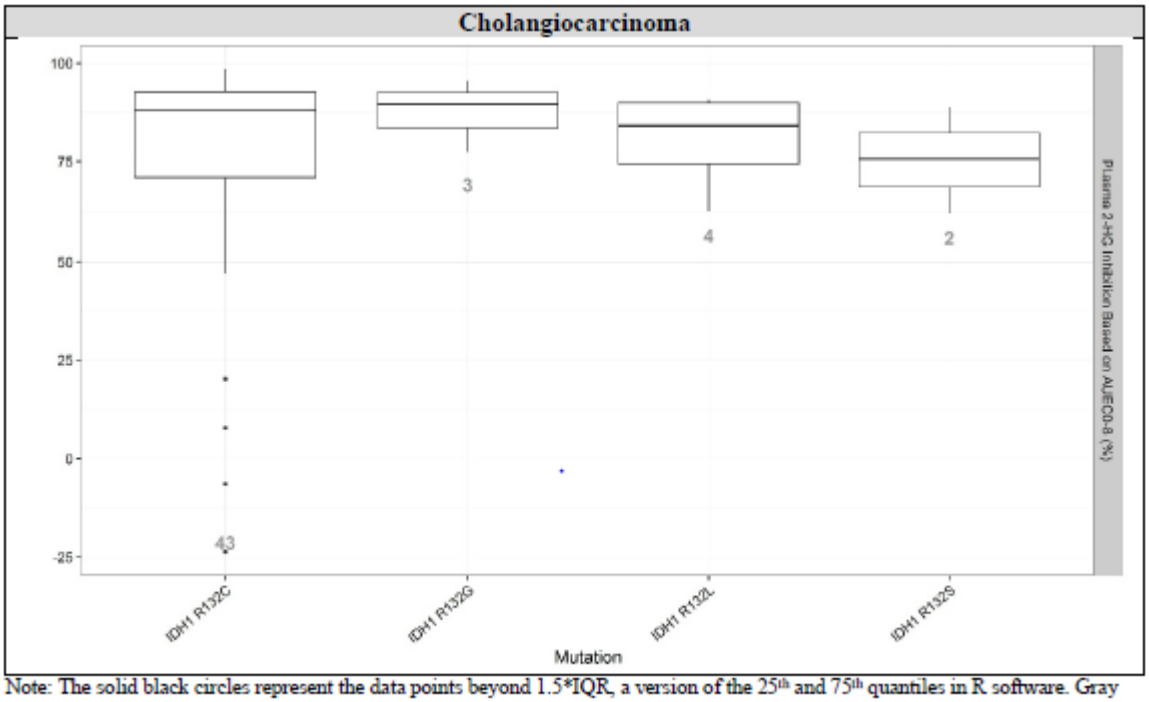
Table 22. Summary of 2-HG Percent Inhibition Based on AUEC0-8 After Oral Administration of AG-120 at Cycle 2, Day 1

Dose Group (mg)	Cholangiocarcinoma					
	N	Mean	SD	Min	Median	Max
< 500	5	77.2	15.5	58.0	72.7	98.0
500	53	77.5	25.8	-23.7	87.9	98.4
> 500	5	71.5	22.4	34.3	78.1	90.4

Notes: Min= Minimum;, Max=Maximum; N: Total number of observations per dose group; SD= Standard deviation; 20 out of 53 subjects (38%) at 500 mg QD, with percent inhibition based on $AUEC_{0-8}$ (%) ≥ 90%; 33 out of 53 subjects (62%) at 500 mg QD, with percent inhibition based on $AUEC_{0-8}$ (%) ≥ 80%.
Source: Listings 16.2.6.5 and 16.2.6.6

Effect of IDH1 Mutation Type on Plasma 2-HG AUEC0-8 – 500 mg QD –Dose Escalation and Expansion Combined

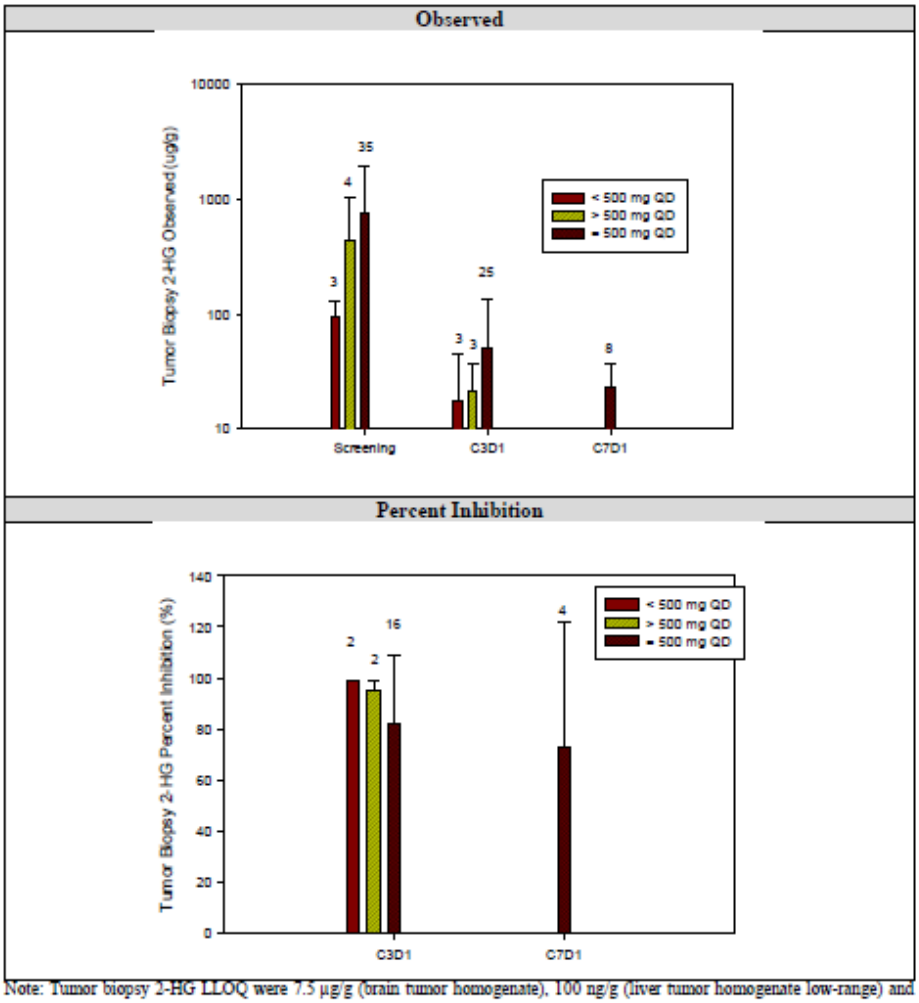
Figure 18. Plasma 2-HG Percent Inhibition Based on AUEC0-8 vs. IDH1 Mutation (Specific Mutation Type) for AG-120 500 mg QD – Cycle 2, Day 1 (Dose Escalation and Expansion Combined)



Note: The solid black circles represent the data points beyond 1.5*IQR, a version of the 25th and 75th quantiles in R software. Gray numbers below the boxplot presents data count at each visit. Visit data were not presented when n=1.
Source: Figure 14.4.5.1

Concentrations of 2-HG in Tumor Biopsy – Dose Escalation and Expansion

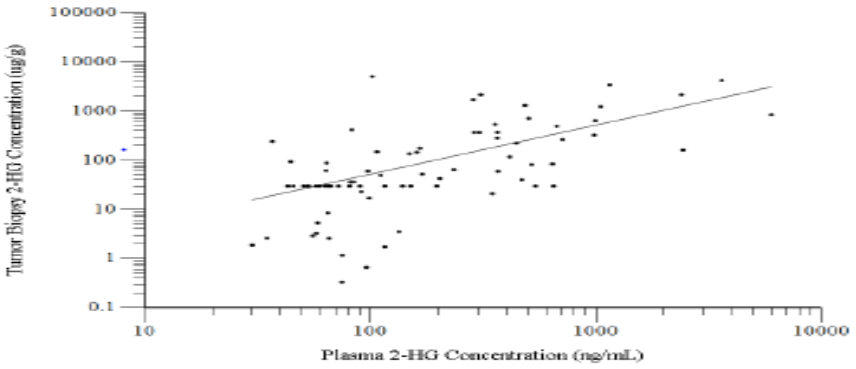
Figure 19. Column Chart of Mean (+SD) 2-HG in Tumor Biopsy vs. Visit after Oral Administration of AG-120 by Dose Group (Semi-Log and Linear Scales) – Dose Escalation and Expansion



Note: Tumor biopsy 2-HG LLOQ were 7.5 µg/g (brain tumor homogenate), 100 ng/g (liver tumor homogenate low-range) and 30 µg/g (liver tumor homogenate high-range), depending on the tumor types. Numbers above the bars presents data count at each visit.
Source: Tables 14.5.5.1 to 14.5.5.2

PD/PD Correlations

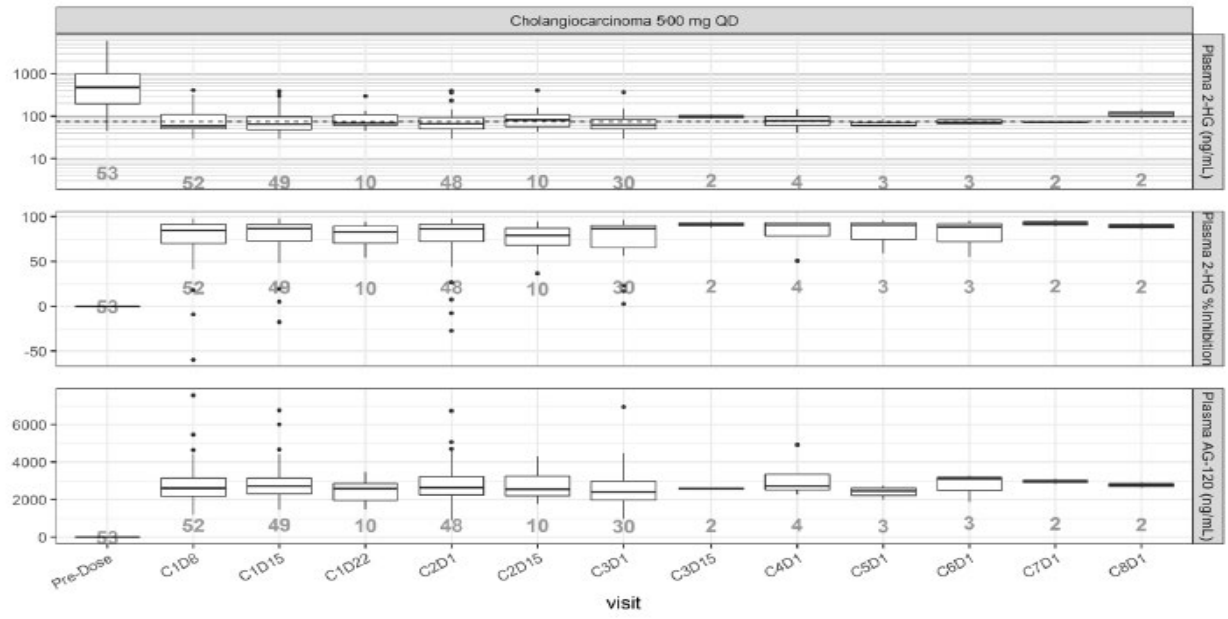
Figure 20. Tumor Biopsy 2-HG Concentrations vs. Plasma 2-HG Concentrations (Time- Matched) – All Tumor Types Combined – Dose Escalation and Expansion (Log-Log Scale) DCO 16-Jan-2019



Note: Linear regression fixed at 0,0 at the y-intercept.
Source: Figure 14.4.7.1

Longitudinal PK/PD Correlations

Figure 21. Longitudinal PK and PD Plot of Plasma AG-120 vs. Plasma 2-HG (Percent Inhibition) after Oral Administration of AG-120 500 mg QD in Subjects with Cholangiocarcinoma– Dose Escalation and Expansion Combined

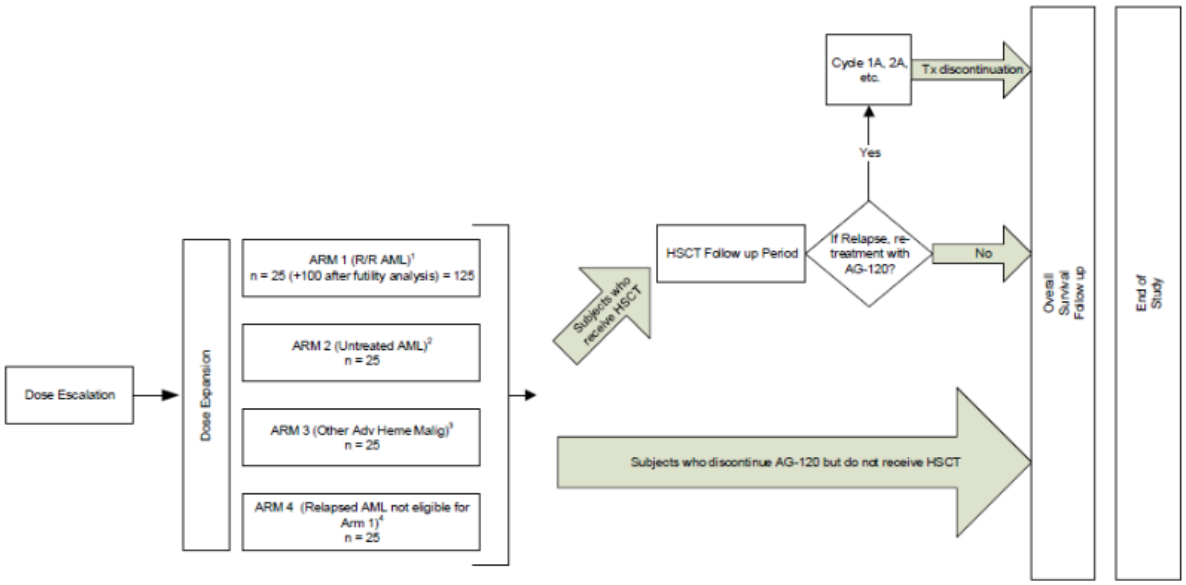


Primary Pharmacology: Acute myeloid leukaemia (AML)

AG120-C-001: advanced hematologic malignancies

Study AG120-C-001 is an ongoing Phase 1, multicenter, open-label, dose escalation and expansion, safety, PK/pharmacodynamic, and clinical activity evaluation of orally administered ivosidenib in subjects with advanced hematologic malignancies with an IDH1 mutation. The study included a dose escalation portion to determine MTD and/or RP2D and an expansion portion to further evaluate the safety, tolerability, and clinical activity of ivosidenib.

Figure 22. Overall study schema of Study AG120-C-001



Abbreviations: AML = acute myeloid leukemia; HSCT = hematopoietic stem cell transplant; R/R = relapsed or refractory; Tx = treatment.

[1] R/R AML defined as: subjects who relapsed after transplantation; subjects in second or later relapse; subjects who were refractory to initial induction or reinduction treatment; subjects who relapsed within 1 year of initial treatment, excluding subjects with favorable-risk status according to NCCN Guidelines, version 1.2015 (NCCN 2015).

[2] Untreated AML who were not candidates for standard therapy due to comorbid condition, performance status, and/or adverse risk factors, according to the Investigator and with approval of the Medical Monitor.

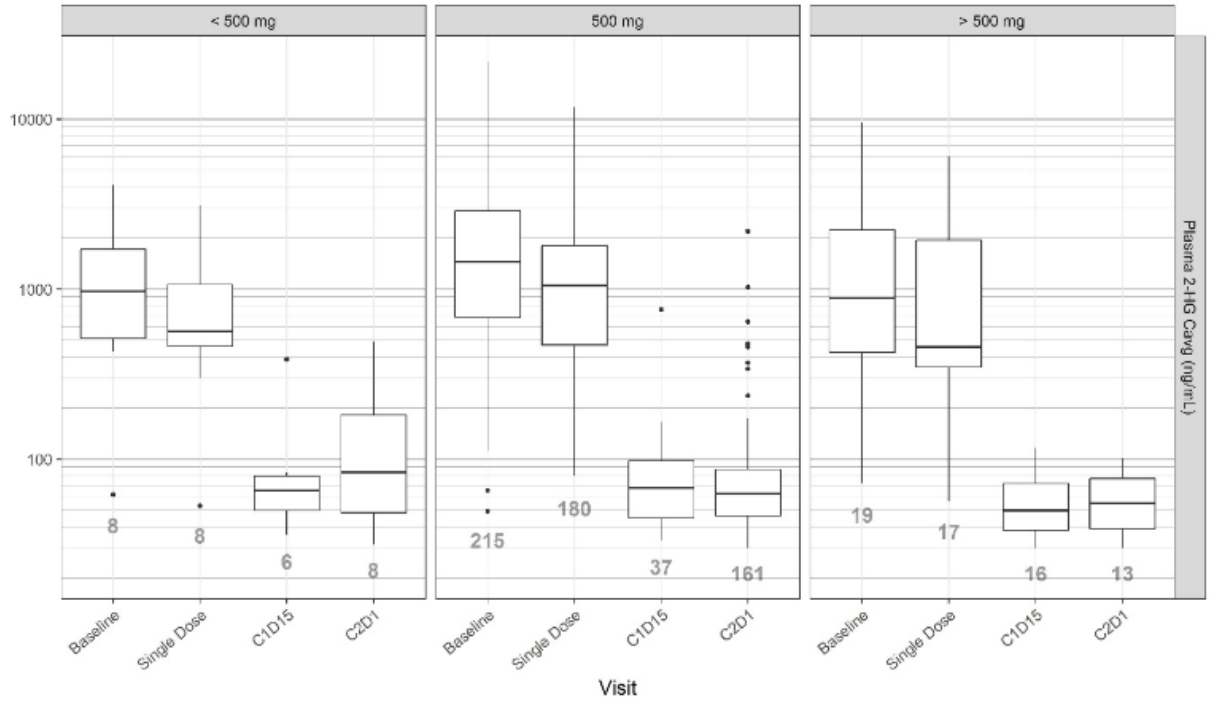
[3] Other non-AML IDH1-mutated R/R advanced hematologic malignancies, where no standard of care treatment option was available; such as: MDS that was recurrent or refractory after having failed hypomethylating agent(s) and with the approval of Medical Monitor; relapsed and/or primary refractory CMML with the approval of Medical Monitor; other non-AML IDH1-mutated R/R advanced hematologic malignancy, that had failed standard of care or no standard of care treatment option was available according to the Investigator and with the approval of the Medical Monitor.

[4] Relapsed AML subjects not eligible for Arm 1 that have failed available standard of care or are unable to receive standard of care due to age, comorbid condition, performance status, and/or adverse risk factors, according to the Investigator and with approval of the Medical Monitor.

Subjects in the dose escalation portion were enrolled into sequential cohorts and received either 100 mg BID, 300, 500, 800 or 1,200 mg QD ivosidenib in continuous 28-day cycles. At least 3 subjects in each cohort also received a single dose of 100, 300, 500, 800 or 1,200 mg ivosidenib 3 days prior to the start of multiple dosing (ie, Day -3).

Box plots of average plasma 2-HG concentration versus time for each dose category in the dose escalation and expansion portions combined are presented in the figure below.

Figure 23. Box Plots of Plasma 2-HG Cavg vs. Visit after Oral Administration of Ivosidenib, by Dose Category – All Hematologic Malignancy Types (Dose Escalation and Expansion Combined)



The suppression of 2-HG concentrations was comparable across expansion arms, by R/R AML subgroup, and between different IDH1 mutation subtypes. Furthermore, 2-HG inhibition among subjects with R/R AML dosed at 500 mg QD was robust and persisted from C1D8 through Cycle 13, with no apparent decrease in 2-HG inhibition over time. Greater than 90% median reduction of 2-HG in bone marrow was also observed in subjects receiving 500 mg QD. The concentrations of 2-HG in plasma and bone marrow were correlated, as depicted in the table below.

Table 23. Summary of Plasma 2-HG Pharmacodynamic Parameters of Ivosidenib After Multiple Oral Administration of 500 mg QD Ivosidenib at C2D1 in Subjects With Relapsed or Refractory AML (AG120-C-001)

Pharmacodynamic Parameters	Mean (RSD%); n		
	Arm 1	Arm 1^{+}	R/R AML at 500 mg QD
n	87	113	127
Baseline (ng/mL)	1,998 (90.3); 87	2,128 (100.4); 112	2,115 (109.3); 126
$AUEC_{0\text{-}8hr}$ (hr•ng/mL)	898 (239.8); 87	1,036 (247.2); 113	997 (243.5); 127
$\%BAUEC_{0\text{-}8hr}$ (%)	91.9 (12.2); 87	90.4 (15.5); 112	89.7 (15.5); 126
C_{avg} (ng/mL)	110 (234.8); 87	129 (241.0); 109	124 (237.3); 123
$\%BC_{avg}$ (%)	91.9 (12.2); 87	91.0 (13.7); 108	90.2 (13.9); 122

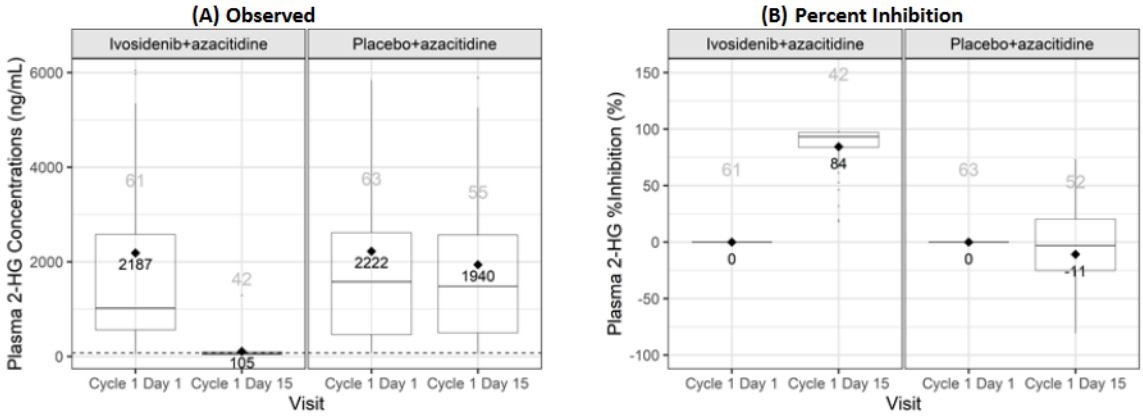
Source: Report AG120-C-001-PKPD Table 33, Table 34, and Table 35. Data cutoff date: 12 May 2017.
Abbreviations: $AUEC_{0\text{-}8hr}$ = area under the effect concentration-time curve from time 0 (predose) through 8 hours; $\%BAUEC_{0\text{-}10hr}$ = percent inhibition for $AUEC_{0\text{-}8hr}$; $\%BC_{avg}$ = percent inhibition for C_{avg}; C_{avg} = average 2-HG concentration over the observed postdose period; R/R AML = relapsed/refractory acute myeloid leukemia; RSD% = relative standard deviation, which is equal to the absolute value of the coefficient of variation.
Note: Arm 1^{+} combines R/R AML subjects in Arm 1 of the expansion and R/R AML subjects in the dose escalation whose starting dose was 500 mg QD and who were eligible for Arm 1 as determined by Investigators. R/R AML includes all subjects with R/R AML regardless in dose escalation and expansion arms 1 and 4.

AG120-C-009: Subjects with Newly Diagnosed AML

Study AG120-C-009 is an ongoing Phase 3, multicenter, double-blind, randomized, placebo-controlled clinical study to evaluate the efficacy and safety of ivosidenib + azacitidine vs placebo + azacitidine in adult subjects with newly diagnosed AML with an IDH1 mutation and who are considered appropriate candidates for non-intensive therapy. Subjects who met all study eligibility criteria were randomly assigned in a 1:1 ratio to receive ivosidenib 500 mg orally QD plus 75 mg/m2/day SC or IV azacitidine or ivosidenib-matched placebo orally QD plus 75 mg/m2/day SC or IV azacitidine. Randomization was stratified by de novo status (de novo AML and secondary AML) and geographic region (United States and Canada; Western Europe, Israel, and Australia; Japan; and rest of world).

Box plots of observed plasma 2-HG trough concentrations and percent inhibition for each treatment are presented in the figure below.

Figure 24. Box Plots of Plasma Predose (Trough) of 2-HG Concentrations (Observed and Percent Inhibition) Versus Visit After Oral Administration of Ivosidenib or Placebo with Azacitidine (AG120-C-009)



Source: AG120-C-009-PK, Figure 2.
Abbreviations: 2-HG = 2-hydroxygluturate; CxDy = Cycle x, Day y; IQR = interquartile range.
Box plots: The dotted horizontal line represents 2-HG concentrations in healthy subjects (72.6 ng/mL). The solid horizontal line in the box represents the median. The diamond and the text label in the box represent the mean. The solid gray circles represent the data points beyond 1.5*IQR, a version of the 25th and 75th quantiles in R software. Gray numbers at the top of each box plot present data count at each visit. Data not presented for an unscheduled visit where n=1.
Note: 4 outlier 2-HG concentrations at C1D1 for ivosidenib + azacitidine data are above the y-axis upper limit and were not presented. 2 and 1 outlier 2-HG concentrations at C1D1 and C1D15, respectively, for placebo + azacitidine are above the y-axis upper limit and were not presented. 2 outlier 2-HG percent inhibition at C1D15 for placebo + azacitidine data are below the y-axis lower limit and were not presented.

It is concluded that azacitidine did not affect the PK or pharmacodynamics of ivosidenib.

Secondary pharmacology (CCA and AML)

Ivosidenib has the potential to prolong the QTc interval.

In previous modelling compared with the original dataset, the number of patients who experienced QTCF>500 ms varied from 8.9% and 1.2% to 4.6% and 0% and the augmentation from baseline >60ms from 14.3% and 5.4% to 3.5% and 0.9% respectively in the modelled conditions. The dose-exposure relation was also very variable, so that Cmax values ranged from 2390 – 22500 ng/ml (9-fold range) in study AG120-C-001 and from 1900 – 9860 ng/ml (5-fold range) in study AG120-C-002. Therefore, it is concluded that a large proportion of patients will be exposed to potentially critical concentrations with respect to QT-interval prolongation and a close clinical ECG monitoring was considered necessary.

Further cardiac safety data with regards to the chosen dose suggested that both, efficacy and cardiac safety considerations/findings triggered the selection of the 500 mg QD dose.

Additional data from a concentration-QTc analysis report assessing ivosidenib monotherapy in solid tumours (AG120-C-002-005-CQT dated 20 September 2019) as well as additional data from clinical studies AG120-C-009 (ivosidenib in combination with azacitidine in newly diagnosed AML) were provided.

In clinical studies provided in newly diagnosed AML and cholangiocarcinoma indication, events of QT prolongation were also reported as frequent (19.7% in AML indication and 9.2 % in cholangiocarcinoma pool (N=228) with respectively 9.9 % and 2.2% of grade ≥ 3).

Ivosidenib has the potential to inhibit wt IDH1.

Previously submitted non- clinical data suggest that wt IDH could be partially inhibited by ivosidenib, thus contributing to the observed safety profile of ivosidenib.

Relationship between plasma concentration and response

For both indications no evidence of a clear relationship between a PK exposure parameter (presently AUC) and any of the investigated efficacy/safety endpoints was found.

2.10.3. Discussion on clinical pharmacology

Pharmacokinetics

Generally, the used methods for the determination of ivosidenib in plasma or urine appear to be adequate and comply with acceptance criteria of the bioanalytical method validation EMA Guideline. Description and validation reports were provided with satisfactory results regarding specificity, sensitivity, precision, accuracy, dilution factor linearity, matrix effect. Short and long-term stability of the analytes in biological matrix were tested and shown to be satisfactory. ISR for each clinical study were provided with satisfactory results.

Absorption

Formal clinical investigation (mass balance study AG120-C-003) does not support a fairly high degree (≥85%) of absorption of ivosidenib in humans. The overall mean recovery of radioactivity was high (94.3% over 360 h post dose), with 77.4% and 16.9% of the dose recovered in feces and in urine, respectively. However, approximately 67.4% of [^{14}C] Ivosidenib was recovered unchanged in feces and according to the applicant this amount was unabsorbed and is explained by the used formulation (oral suspension) and the solubility limited absorption. The fact that an increase in ivosidenib rate and extent of absorption (Cmax and AUC) was observed in the fed state does not necessarily imply that ivosidenib is a high permeable drug (> 85%).

The drug substance is practically insoluble (solubility of 38 to 66 µg/mL) in aqueous solutions between pH 1.1 and 7.5. At the highest solubility (66 µg/mL), 16.5 mg of ivosidenib drug substance can dissolve in 250 mL of aqueous solution, which is less than the proposed commercial dose (500 mg). Therefore given the doubt on the claimed high fraction absorbed (only an in vitro high permeability comparable to propranolol at a supratherapeutic level was observed in Study AG120-N-100), ivosidenib can be classified as a BCS class IV compound.

Food effect

There is a significant increase on Cmax level (almost doubling) after single 500 mg ivosidenib taken with high-fat meal food and there are remaining uncertainty about the extent of increase in Cmax after a low fat meal on ivosidenib PK. As well, a clear concentration-dependent QTc prolongation is established: results of both C-QTc analyses in AML and CCA patients (despite their limitations with regards to the available data) clearly show that the upper limit of the 90% CI of the geometric mean steady state Cmax predicted a mean ΔQTcF largely above the clinically relevant threshold of 10 msec. Taking into account the above and considering that a relationship between ivosidenib Cmax and efficacy has not been identified a recommendation, that food should not be ingested 2 hours before and for 1 hour after taking ivosidenib FCT, has been included in the product information.

Population PK modelling

The clinical pharmacology properties of ivosidenib in patients with advanced hematological malignancies have been characterized through a population PK model including experimental evidence gathered from Study AG120-C-0001 (Phase 1) in 253 subjects and 4656 samples. The strategy of conducting a population PK model only including patients from one indication can be questioned, since the amount of PK evidence limits the evaluation of covariate effects and it is not expected based on the non-compartmental analysis that major differences between patients with advanced hematological

malignancies, acute myeloid leukemia, and cholangiocarcinoma could affect the PK parameters of ivosidenib. The use of a parallel strategy for each indication selection was justified when developing the population PK model in order to accurately identify the PK parameters and covariate effects for each separate indication. Although it seems that less power and more bias can be incorporated in parameter estimation, it is also agreed that sufficient experimental evidence was collected in terms of number of patients, dose levels, dosing regimens that allow the identification of the main PK mechanisms of ivosidenib on each indication.

The final population PK model (addendum report) developed in patients with advanced hematological malignancies includes different structural PK parameters (CL/F, Vc/F, Q/F, and Vp/F) between first dose and steady-state conditions, which is unexpected because time-dependent factors should be explained using structural functions able to address and explain the behavior observed. A time-varying function to describe the change over time of CL/F was statistically significant (a reduction of the OFV value of 65 units). A rate of change to steady-state conditions was estimated with a half-life of 18 hours, which is in line with the step-change set at 96-h. Therefore, the continuous function of time-varying and the step-change model at 96h provide similar conclusions. The selection of the step-change model over the time-varying CL was justified by the lack of sufficient experimental evidence during the induction phase, which is accepted. Even though further clinical evidence during the induction phase would be needed to be incorporated to the model to finally update the time-varying function of CL, based on the current limitations and the lack of appropriate experimental evidence to mechanistically describe the observed effects, the current population PK model is considered purely descriptive and no extrapolation analysis should be conducted.

Regarding the impact of covariates on ivosidenib exposure in AML patients as well, the model seems quite empirical, and no relevant implications can be derived based on the limited structural mechanisms included that allow to understand the clinical relevance on special populations or drug-drug interaction studies.

The strategy to evaluate the PK properties of ivosidenib in combination with azacitidine in subjects with previously untreated acute myeloid leukemia with an IDH1 mutation (study AG120-C-009) includes the estimation of individual parameters through a Bayesian approach using the previously developed population PK model in patients with advanced hematological malignancies.

A population PK model has been developed in 229 subjects and 2939 samples from Study AG120-C-002 and Study AG120-C-005, which includes similar structural elements as described for patients with advanced hematological malignancies. An updated version of the population PK model has been presented including 424 new samples from 10 new individuals.

The clinical evaluation of the impact of covariates on ivosidenib exposure in CCA patients was not adequately established due to the lack of sufficient evidence collected and overall, minor effects were predicted due to coadministration of ranitidine, predinosone, other CYP3A4 inhibitors and baseline body weight. The current analysis, although not fully confirmatory, did not suggest any clinically relevant change on ivosidenib exposure in CCA patients.

Special Populations

Hepatic impairment

Given the claimed major role for the hepatic metabolism of ivosidenib, hepatic impairment (HI) is expected to result on significant systemic overexposure (associated with decreased CL/F) with increasing severity of HI.

PK data in healthy volunteers - Study AG120-C-012

Overall, PK results from the dedicated HI study in healthy volunteers appear inconclusive and should be regarded with caution. Thus, dosing recommendations (if any) in hepatic impaired group should rely on available PK data observed in patients with hepatic impairment.

PK results in patients with hepatic impairment

The requested steady state C2D1 PK parameters (AUCs, Cmax and Cmin) in patients with mild and moderate HI for either advanced hematologic malignancies or cholangiocarcinoma was provided. However, the hepatic function was graded using the National Cancer Institute (NCI) classification. The conversion from NCI-ODWG scores to the recommended Child-Pugh classification was not possible since all clinical measures required for grouping subjects based on the Child-Pugh (CP) score were not available. For both the claimed patient populations: newly diagnosed AML patients (AG120-C-009) and with cholangiocarcinoma (AG120-C-002 and AG120-C-005), a representative PK data were available in the mild hepatic impairment group. Besides, no data were available in the moderate and severe HI subgroups of patients.

Overall, in patients (both ND AML and CCA) with mild hepatic impairment, a modest increase (up to 17% at maximum) in the ivosidenib systemic exposure was observed compared to reference normo-hepatic subjects. Thus, it is agreed that no major difference in PK between normal and mild hepatic function population are seen. Hence, no dose adjustment for ivosidenib in subjects with mild hepatic impairment is recommended.

Very few data (n=2) were available in the moderate HI group in patients with R/R AML (AG120-C-001). No reliable conclusion could be drawn from such limited data. Moreover, patients with R/R AML are not in the scope of the claimed / target populations. The lack of PK data in these patients has been reflected in the SmpC. As the two hepatic function classifications (NCI versus CP) are discordant and as PK data are only available with the NCI classification, the text in the SmpC indicates clearly the classification used together with the information on the lack of PK data using the recommended Child Pugh classification. No PK data are available in patients with severe HI and this is reflected in the SmpC (see SmPC section 4.2). An organ impairment substudy of AG120-C-001 will evaluate the pharmacokinetics, safety and tolerability of ivosidenib in patients with haematologic malignancies with an IDH1 mutation with moderate hepatic impairment, severe hepatic impairment or severe renal impairment as a category 3 post authorisation study (see RMP).

Race

In patients with newly diagnosed AML (Phase 3 Study AG120-C-009), exploratory assessment of steady state ivosidenib PK C2D1 after oral administration of ivosidenib 500 mg QD in Asian (Japanese, Taiwanese and Korean) vs Caucasian indicated a tendency of an increase on the systemic exposure in Asian compared to Caucasian patients. However, such comparison should be regarded with caution given the very few data (n=4) available in Asian patients.

In patients with cholangiocarcinoma (Phase 3 Study AG120-C-005), exploratory assessment of steady state ivosidenib PK C2D1 after oral administration of ivosidenib 500 mg QD in Asian vs Caucasian indicated a tendency of a lower systemic exposure (Cmax and AUC24h) in Asian compared to Caucasian patients was observed. Even, more rich data in Asian patients were available (n= 13) for the comparison, this result should be interpreted with caution.

To summarize, PK data in AML patients appear inconsistent / conflicting with those in patients with cholangiocarcinoma and in healthy volunteers. In fact, even a decrease on the systemic exposure was observed in healthy volunteers and in patients with cholangiocarcinoma, a tendency of overexposure is observed in NL AML patients. This preclude drawing a formal conclusion regarding the impact of race on the PKs of ivosidenib. However, it is important to note that in both patient populations, ivosidenib systemic exposure (C_{max} and AUC_{0-24}) in Asians largely overlapped those observed in non-Asians. Overall,

taken all data together, the tendency of lower systemic exposure in Asian (PK data in patients with AML are very immature), the flat exposure- efficacy relationships, this do not suggest a clinically significant impact on ivosidenib PK between Asian and Caucasian patients. Thus, no dose adjustment for ivosidenib based on race is needed.

Weight

Baseline body weight (BW) was included as a continuous covariate in the different Pop-PK analyses. BW was found to be a statistically significant covariate on the Vc/F of ivosidenib in both claimed patients with cholangiocarcinoma and patients with newly AML with similar exponents of 0.81. Therefore, an impact on Cmax is expected, especially in the obese and underweighted patients. In AML patients, approximately a 30% higher mean steady state AUCtau, Cmax and Cmin were observed for underweight AML patients (n=8) when compared to AML patients with BMI in the healthy weight range. Based on the results from the C-QTc analysis and the mean Cmax of 6780 ng/mL or median Cmax (min max) of 6520 (4090-11100) ng/mL, a QTc prolongation of 17.8 msec (for mean Cmax) and 28.9 msec (max Cmax) was predicted.

In CCA subjects, a 8.8% increase in mean steady state Cmax was observed for underweight patients (n=12) compared to healthy weight range. Based on the results from the C-QTc analysis and the mean Cmax of 5440 ng/mL or median Cmax (min max) of 4830 (3390-8690) ng/mL, a QTc prolongation of 19.8 msec (for mean Cmax) and 31.3 msec (max Cmax) was predicted.

All together in underweight patients there is a high risk of QT prolongation whatever the indications, therefore cautions should be taken in this subpopulation and this is reflected in the SmPC.

Elderly

Sufficient and representative sample size of patients in age groups [65-74 y] and [75-84 y] are available. However, no PK data in patients > 85 years old are available for the claimed patient populations (patients newly diagnosed AML and with cholangiocarcinoma). Limited data exist for this subgroup in R/R AML patients but this population is not in the scope of claimed indications.

As per the provided data, the mean steady state PK parameters in age groups [65-74 years] and [75-84 years] appear to be overall comparable to those observed in patients <65 years old. Hence, the recommendation for a flat dosing scheme in these two specific subgroups of age is supported. For patients, >85 years old, the lack of PK data is clearly implemented in the SmpC.

Exposure-Response (ER)

For both indications no evidence of a clear relationship between a PK exposure parameter and any of the investigated efficacy/safety endpoints was found.

The exposure-efficacy evaluation did not identify any relevant relationship between AUCss and the efficacy endpoints selected in patients with advanced hematological malignancies, acute myeloid leukemia and cholangiocarcinoma. Model-predicted AUCss were simulated based on the final population PK model for each indication considering nominal dose (scenario 1). This simplification (nominal dose) attenuates changes in AUCss due to dose modifications or time-varying covariates, which could increase the AUCss range in order to identify any likely exposure-efficacy relationship. Additional logistic regressions were conducted using observed and model predicted probability of response versus AUC at cycle 1, suggesting no significant and positive trend of higher probability of response with higher AUC. A minor deviation (14.1% in cycle 1) from the actual dose was observed for newly diagnosed AML, suggesting no relevant differences between the actual and predicted AUC at cycle 1, which reinforces the conclusions gathered from the current analysis. Based on the results available, no clinically relevant exposure-efficacy relationship was established in patients with advanced hematological malignancies,

acute myeloid leukemia and cholangiocarcinoma, which may impact the identification of an optimal dose selection.

Regarding exposure-safety relationship, exposure metric (AUCss) was selected based on exposure correlation plots that suggest direct and linear relationship between AUC,ss and Cmax,ss.

Regarding exposure-safety analysis in CCA patients, the analyses did not identify any positive relationship across the 13 safety endpoints considered (p-values>0.05).

Regarding the exposure-safety analysis in newly diagnosed AML patients who received ivosidenib in combination with azacitidine did not identify any positive relationship across the adverse events selected. A relevant increase AST probability with increasing Cmax exposure was detected (probability of T1 around 20% and probability at T3 around 55%).

The exposure-safety analysis for hematological endpoints in AML patients who received ivosidenib monotherapy, patients with newly diagnosed AML who received ivosidenib in combination with azacitidine, and patients with CCA who received ivosidenib monotherapy revealed no statistically significant relationship between AUC or Cmax and the 4 selected heamotological AE (anaemia, cytopenia, leukopenia/neutropenia and thrombocytopenia). Therefore, based on the evidence provided, no exposure-safety relationship was identified between ivosidenib exposure and the AE's selected.

PK interactions

The use of new boundaries for model evaluation of PBPK predictions, which are derived from Guest et al. 2011 was clarified and considered acceptable. Prediction accuracy of PBPK modelling with respect to the induction of CYP3A4-mediated DDIs in the Simcyp Simulator (V15) was assessed considering twenty clinical studies. In these studies, the inducers of CYP3A4 were rifampicin, carbamazepine, phenobarbital, efavirenz and rifabutin and the substrates of CYP3A4 were midazolam, nifedipine, triazolam, and alfentanil. In 100% and 75% of the cases, the predicted mean AUC and Cmax ratios were within the criteria described by Guest et al. (2011). This result suggests that the PBPK platform is unable to accurately address Cmax ratios in 25% of the cases of the Drug-Drug-Interaction mediated by CYP3A4 induction. The adequate prediction of Cmax is highly relevant based on its clinical impact in terms of QTc prolongation and prospective assessment of clinical relevance for dose selection in special sub-groups of population. In addition, concerns regarding the prediction ability of Cmax have been highlighted in the population PK analysis that would suggest that several factors may be responsible of Cmax misspecification.

Additional evidence demonstrates the ability of the PBPK model to capture the proposed dosing regimen of ivosidenib (500 mg QD) after multiple dosing regimens and the model misspecification identified in AUC prediction in healthy volunteers with itraconazole (1.26-fold change) was justified by the fact that metabolism of ivosidenib was entirely assigned to CYP3A4 and no other metabolic routes were imputed. However, differences were observed between healthy volunteers and patients that could not be scientifically justified by any intrinsic or extrinsic factor, since the population PK model did not conclude any relevant impact of disease status nor age. Although the fm and fe between healthy volunteers and patients were very similar, differences in oral clearance are present, which represents a major limitation of the PBPK framework due to its inconsistency with the population PK model. The applicant provided an explanation of the differences in oral clearance between PBPK and PPK model as well as the limitations in terms of bioavailability and oral absorption of ivosidenib. Therefore, with the evidence provided, the PBPK framework is considered valid for DDI prediction of CYP3A4 substrates in AML patients, but further improvement in terms of bioavailability and oral absorption of ivosidenib are required before conducting any extrapolation in special sub-groups of patients for dose selection.

Pharmacodynamics

CCA

Pharmacodynamic data for ivosidenib 500 mg QD were consistent between studies AG120-C-002 and AG120-C-005. Mean plasma 2-HG percent inhibition (%BAUEC) for the 500 mg QD dose level on C2D1 was 77.5% (range up to 98.4%) and 75% (range up to 97.3%) for subjects with cholangiocarcinoma in AG120-C-002 and AG120-C-005, respectively. Mean plasma 2-HG concentrations in subjects with cholangiocarcinoma decreased from baseline to levels observed in healthy subjects (72.6 ±21.8 ng/mL) after treatment for one cycle. This decrease generally persisted through the treatment period with continued dosing of ivosidenib.

Although limited, data suggested that no additional 2-HG inhibition was observed at doses >500 mg QD compared with 500 mg QD, while doses <500 mg QD are associated with lower levels of inhibition.

Based on limited sample sizes from tumour biopsies, multiple administration of AG-120 at 500 mg QD up to C3D1 resulted in 82% inhibition of 2-HG concentration in tumour biopsy.

Pharmacodynamic data for 500 mg QD ivosidenib appeared consistent by IDH1 mutation type. Median values of percent inhibition 2-HG based on AUEC0-8 at C2D1 were comparable between the different IDH1 mutation type (R132C, R132G, R132L, R132S). These results are however limited by the small number of subjects in some subtypes.

AML

The pharmacodynamics parameters of ivosidenib in patients with hematologic malignancies, mainly based on 2-HG Concentrations, were evaluated using serial blood sampling in two studies.

Based on PD results from study AG120-C-001, ivosidenib was shown to decrease the levels of the 2-HG in plasma in patients. The mean plasma 2-HG inhibition were comparable between C1D15 and C2D1. The maximum effect was observed at 500mg QD (more than 90% inhibition) with no additional 2-HG decrease was observed at higher doses.

Based on PD results from study AG120-C-009, the observed plasma 2-HG concentrations for subjects in the placebo + azacitidine arm remained unchanged after multiple doses of placebo + azacitidine on C1D15, raising no impact of azacitidine on ivosidenib PD parameters. In ivosidenib + azacitidine arm, plasma 2-HG concentrations at baseline was comparable to the placebo + azacitidine arm, and then sharply decreased after multiple doses of ivosidenib + azacitidine treatment, raising more than 80% of inhibition at C1D15.

Overall, the PD results from both studies confirmed the inhibitory effect of ivosidenib on IDH1 mutation and subsequent decrease in 2-HG concentrations in AML patients, after multiple dosing of 500 mg QD, with or without concomitant treatment with azacitidine.

Secondary PD

Overall, the risk of QT prolongation with ivosidenib was supported by non-clinical findings and were further observed in clinical studies. The concentration-QTc relationship has been evaluated in healthy volunteers, patients with advanced hematological malignancies, acute myeloid leukemia and cholangiocarcinoma. The results suggest a moderate relationship (10-20 msec) of ivosidenib exposure after 500 mg QD dose on QTc prolongation based on the mean Cmax concentration at the proposed schedule. The upper limit of the 90% prediction interval on QTc prolongation for a typical patient (mean Cmax) with hematological malignancies, acute myeloid leukemia and cholangiocarcinoma were 19.7, 18.9, and 20.6 msec. Therefore, roughly half of the patients with higher concentrations that the typical (mean) patient are in a high risk of QTc prolongation greater than 20 msec, suggesting the proposed schedule could lead to QTc prolongation in a relevant proportion of patients of the overall population.

Therefore, based on all available data, ivosidenib significantly prolongs the QTc interval duration. In clinical studies, in a selected population (QT <450ms, no cardiac disease) no sudden deaths were retrieved and only one case of ventricular fibrillation was reported. However, in real life conditions, it is more than likely that events will be more frequent and potentially more serious. This is also reinforced by the fact that dose-exposure relationship is highly variable, with a large proportion of patients exposed to potentially critical concentration with respect to QT interval prolongation.

Overall, relevant information has been reflected in sections 4.2, 4.3, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC along with relevant measures to mitigate the risk associated with QT prolongation (See also Clinical Safety discussion and RMP).

Considering that ivosidenib at concentration reached in patients has the potential to inhibit wt IDH1 and that the clinical relevance of potential wt IDH1 inhibition is unknown at the present time, however although a high variability of Cmax values were observed in clinical studies those values remains below the concentration determined to maintained 50% inhibition of WT IDH1.

2.10.4. Conclusions on clinical pharmacology

The PK of ivosidenib was thoroughly investigated using the non-compartmental and nonlinear-mixed effects modelling approaches. Data from 7 Phase 1 studies in healthy volunteers and patients, one Phase 1b/2 and 2 Phase 3 studies in the claimed patients with newly diagnosed AML and Cholangiocarcinoma were used for analyses. Overall, the PK properties of ivosidenib product to be administered by oral route are considered as sufficiently characterized.

Ivosidenib is a small molecule inhibitor of the mutant IDH1 enzyme. In PD studies, the suppression of production of 2-HG was the explored PD biomarker for ivosidenib activity. Ivosidenib suppresses production of 2-HG, restoring differentiation and reducing proliferation of the cancerous cells. For ivosidenib doses of 500 mg, plasma 2-HG inhibition was observed in subjects with hematologic malignancies such as AML and subjects with cholangiocarcinoma as early as following single dose administration. This level of 2-HG inhibition was maintained throughout with continued dosing of ivosidenib. Nevertheless, the correlation of antitumour activity (tumour shrinkage) with 2-HG concentrations has not been established. So the relevance of this result as a biomarker is unclear so far.

The applicant will submit the results of an Organ impairment substudy of AG120-C-001 with the aim to evaluate the PK, safety and tolerability, PD, and clinical activity of ivosidenib in subjects with moderate hepatic impairment, severe hepatic impairment, or severe renal impairment with haematologic malignancies with an IDH1 mutation.

Cholangiocarcinoma

2.10.5. Clinical efficacy

2.10.5.1. Dose response study

Study AG120-C-002 is an ongoing phase 1, multicenter, open-label, dose escalation and expansion, safety, PK, pharmacodynamic, and clinical activity study of orally administered AG-120 in subjects with advanced solid tumors, including glioma, with an IDH1 mutation.

The primary objectives of this study were to assess the safety and tolerability of treatment with ivosidenib administered continuously as a single agent dosed orally on days 1 to 28 of 28-day cycles and to

determine the MTDs and/or the RP2Ds in subjects with advanced solid tumors, including glioma. The initial dosing regimen was BID (approximately every 12 hours). The study design followed a standard 3 + 3 design to assess ascending, multiple doses of ivosidenib.

For dose escalation, the initial starting dose was 100 mg administered orally twice daily (BID; 200 mg/daily) in continuous 28-day cycles. Based on the observed PK profile, a QD dosing schedule was initiated after Cohort 1. Eight dosing cohorts (100 mg BID, and 300 mg, 400 mg, 500 mg, 600 mg, 800 mg, 900 mg, and 1,200 mg QD) were enrolled and the MTD was not reached.

The starting dose recommended for the expansion portion of the study was 500 mg QD. This was based on the PK/PD, safety, and clinical activity associated with ivosidenib from the dose escalation portion of this study. Plasma exposure increased as dose levels increased from 100 mg BID to 1,200 mg QD dose in a less than proportional manner. PK data generated above 800 mg QD suggested ivosidenib exposure likely reached a plateau after 500 mg QD. Evaluation of the 2-HG response demonstrated sustained 2-HG reduction in tumor and plasma after multiple administrations and up to 98% inhibition at all doses by C2D1. Maximal inhibition of 2-HG was observed at 500 mg QD. No further significant increases in 2-HG inhibition were observed at doses >500 mg QD.

The selection of the 500 mg QD dose of ivosidenib was also supported by data from patients with hematologic malignancies. DLTs of Grade 3 rash and Grade 3 QT prolongation were observed in the 1200 mg QD and 800 mg QD cohorts respectively in patients with advanced hematologic malignancies (Study AG120-C-001); however, expansion of these dose cohorts did not result in identification of the MTD.

The study AG120-C-002 allowed as well to assess the efficacy of ivosidenib based upon ORR and PFS.

2.10.5.2. Main study

AG120-C-005: A phase 3 multicenter, randomized double blind placebo controlled study of AG-120 in previously treated subjects with nonresectable or metastatic cholangiocarcinoma with an IDH1 mutation.

Methods

Subjects were randomized in a 2:1 ratio to receive ivosidenib orally at a dose of 500 mg QD or ivosidenib-matched oral placebo QD, respectively. Randomization was stratified by number of prior therapies (1 vs. 2). All subjects continued to receive best supportive care according to institutional practice throughout the study, regardless of treatment arm. Subjects randomized to the placebo arm could cross over to the active treatment arm upon disease progression (as assessed by the Investigator).

- **Study Participants**

Inclusion Criteria

1. ≥18 years of age.

2. Had a histopathological diagnosis (fresh or banked tumor biopsy sample, preferably collected within the last 3 years) consistent with nonresectable or metastatic cholangiocarcinoma and were not eligible for curative resection, transplantation, or ablative therapies.

3. Had documented IDH1 gene-mutated disease (from a fresh tumor biopsy or the most recent banked tumor tissue available) based on central laboratory testing (R132C/L/G/H/S mutation variants tested).

4. Had an ECOG PS score of 0 or 1

5. Had an expected survival of ≥3 months.

6. Had at least one evaluable and measurable lesion as defined by RECIST v1.1. Subjects who had received prior local therapy (including but not limited to embolization, chemoembolization, radiofrequency ablation, or radiation therapy) were eligible provided measurable disease fell outside of the treatment field or within the field and had shown ≥20% growth in size since post-treatment assessment.

7. Had documented disease progression following at least 1 and no more than 2 prior systemic regimens for advanced disease (nonresectable or metastatic). Subjects had to receive at least 1 gemcitabine- or 5-FU-containing regimen for advanced cholangiocarcinoma. Systemic adjuvant chemotherapy was considered a line of treatment if there was documented disease progression during or within 6 months of completing the therapy.

8. Had recovered from toxicities associated with prior anticancer therapy to baseline unless stabilized under medical management.

9. Had adequate bone marrow function as evidenced by:

a. Absolute neutrophil count ≥1,500/mm3 or 1.5 ×109/L

b. Hemoglobin ≥8 g/dL

c. Platelets ≥100,000/mm3 or 100 × 109/L

10. Had adequate hepatic function as evidenced by:

a. Serum total bilirubin ≤2 × upper limit of normal (ULN), unless considered due to Gilbert's disease

b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤5 × ULN

11. Had adequate renal function as evidenced by:

a. Serum creatinine <1.5 × ULN

OR

b. Creatinine clearance ≥50 mL/min based on the Cockcroft-Gault glomerular filtration rate estimation

Exclusion Criteria

1. Received a prior IDH inhibitor.

2. Received systemic anticancer therapy or investigational agent <2 weeks prior to Day 1 (washout from prior 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 has elapsed.

3. Received radiotherapy to metastatic sites of disease <2 weeks prior to Day 1.

4. Underwent hepatic radiation, chemoembolization, and radiofrequency ablation <4 weeks prior to Day 1.

5. Had known symptomatic brain metastases requiring steroids. Subjects with previously diagnosed brain metastases were eligible if they had completed their treatment and had recovered from the acute effects of radiation therapy or surgery prior to study entry, had discontinued corticosteroid treatment for these metastases for at least 4 weeks and had radiographically stable disease for at least 3 months prior to study entry. Note: up to 10 mg per day of prednisone equivalent was allowed.

6. 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 tumor with no known active disease present that, in the opinion of the Investigator, did not affect subject outcome in the setting of current cholangiocarcinoma diagnosis.

7. Underwent major surgery within 4 weeks of Day 1 or had not recovered from post-surgery toxicities.

8. Were pregnant or breastfeeding.

9. Were 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.

10. Had an active infection requiring systemic anti-infective therapy or with an unexplained fever >38.5°C within 7 days of Day 1 (at the discretion of the Investigator, subjects with tumor fever may have been enrolled).

13. 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; myocardial infarction; unstable angina; and/or stroke.

14. Had LVEF <40% by echocardiography (ECHO) scan (or by other methods according to institutional practice) obtained within 28 days prior to the start of study treatment.

15. Had a heart-rate corrected QT interval (using Fridericia's formula) (QTcF) ≥450 msec or other factors that increased the risk of QT prolongation or arrhythmic events (eg, heart failure, hypokalemia, family history of long QT interval syndrome). Bundle branch block and prolonged QTcF interval were permitted with approval of the Medical Monitor.

16. Were 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.)

17. Had known active hepatitis B (HBV) or hepatitis C (HCV) infections, known positive human immunodeficiency virus antibody results, or acquired immunodeficiency syndrome related illness. Subjects with a sustained viral response to HCV or immunity to prior HBV infection were permitted. Subjects with chronic HBV that was adequately suppressed per institutional practice were permitted.

18. Had any other acute or chronic medical or psychiatric condition, including recent (within 12 months of Day 1) or active suicidal ideation or behavior, or a laboratory abnormality that could increase the risk associated with study participation or investigational product administration or could interfere with the interpretation of study results and, in the judgment of the Investigator, made the subject inappropriate for entry into this study.

19. Had known active inflammatory gastrointestinal disease, chronic diarrhea, 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).

- **Treatments**

Ivosidenib was administered orally once daily continuously at a dose of 500 mg. Placebo was supplied as matched tablets to be administered orally (250 mg strength tablets). Dosing was continuous; there were no planned inter-cycle rest periods. Subjects were instructed to take their QD dose at approximately the same time each day. In the event of radiographic progression per RECIST v1.1 but in the absence of clinical deterioration, worsening ECOG performance status, or disease progression that may have compromised organ function, the subject could have continued to receive study treatment with ivosidenib at the discretion of the treating physician in consultation with the Medical Monitor.

- **Objectives**

The primary objective of the study was to demonstrate the efficacy of ivosidenib based on PFS per Independent RadiologyCenter (IRC) assessment compared to placebo in subjects with nonresectable or metastatic cholangiocarcinoma with an IDH1 mutation.

The secondary objectives of the study were mainly to compare the efficacy of ivosidenib with placebo based on overall survival (OS), objective response rate (ORR), duration of response (DOR), and time to response (TTR), with response assessed per Investigator and by the IRC.

- **Outcomes/endpoints**

Primary Endpoint

• The primary endpoint was PFS, defined as the time from date of randomization to date of first documented disease progression (as assessed by the IRC per RECIST v1.1), or date of death due to any cause.

• Secondary efficacy endpoints included:

-OS, defined as the time from date of randomization to date of death.

-ORR, defined as the proportion of subjects with a best overall response defined as complete response (CR) or PR, as assessed by the Investigator and by the IRC per RECIST v1.1.

-DOR, defined as the time from date of first documented CR or PR to date of first documented disease progression or death due to any cause, as assessed by the Investigator and by the IRC per RECIST v1.1.

-TTR, defined as the time from date of randomization to date of first documented CR or PR for responders, as assessed by the Investigator and by the IRC per RECIST v1.1.

-PFS as determined by the Investigator.

• HRQOL as assessed by validated instruments (EORTC QLQ-C30, EORTC QLQBIL21, PGI-C, and PGI-S).

Radiographic assessments (CT or MRI) were conducted at screening, every 6 weeks for the first 8 assessments (ie, through week 48), and every 8 weeks thereafter (±5 days). A central review of collected images and response assessment per RECIST v1.1 was conducted by the IRC. No interim analysis was conducted. Scans after crossover were not read by the IRC.

- **Sample size**

A total of approximately 186 subjects (124 ivosidenib, 62 placebo) were planned for enrolment in the study.

Assuming a HR of 0.5 for PFS (equivalent to a median PFS of 3 months in the placebo arm versus 6 months in the ivosidenib arm, assuming an exponential distribution), a total of 131 PFS events were required to provide 96% power at a 1-sided alpha of 0.025 level of significance to reject the null hypothesis using a stratified log-rank test. Based on this, a total of approximately 186 subjects were required to be randomized in a 2:1 ratio to the ivosidenib and placebo arms, respectively, assuming approximately a 22% dropout rate, an approximate 26-month randomization period, and an additional 6-month follow-up for PFS after the last subject was randomized. Therefore, the primary analysis of PFS was to occur at approximately 6 months after the last subject was randomized.

Overall survival was to be analysed twice, once at the time of the final analysis for PFS and once at the occurrence of 150 OS events (final analysis for OS). Assuming an HR of 0.67 for OS (median OS of 8 months in the placebo arm vs. 12 months in the ivosidenib arm, assuming an exponential distribution), a total of 150 OS events would provide 64% power at a 1-sided alpha of 0.025.

Interim analysis

The study report states that there was no formal analysis of the data. However, it is also described that two analyses were planned for OS: 1) an interim analysis at the projected time of the final analysis for PFS (provided PFS was significant); 2) a final analysis for OS when 150 deaths were observed. Overall survival at the interim was tested with the alpha being determined using the gamma spending function (gamma=-8), and the overall type I error rate was controlled at the 1-sided 0.025 level.

- **Randomisation and Blinding (masking)**

Subjects who met all study eligibility criteria were randomly assigned in a 2:1 ratio, stratified by number of prior systemic treatment regimens for advanced disease (1 or 2), to receive ivosidenib orally QD or ivosidenib-matched placebo orally QD.

The randomization schedule was generated by an independent statistical group. The randomization assignment was implemented by an IWRS.

The subjects, Investigators, the clinical research unit staff who dealt directly with subjects, and the Sponsor were blinded to study treatment assignment until documented disease progression. The IWRS assigned each subject specific Medication ID-labelled study drug containers. Ivosidenib and placebo were packaged and labelled identically so that the study pharmacist remained blinded to treatment assignment.

The subjects, clinical research unit staff, and Sponsor remained blinded for the duration of the study unless emergency unblinding was required. Upon request by the Investigator, subjects and staff were unblinded at the time of disease progression as confirmed by study sponsor.

An IDMC reviewed unblinded safety and other clinical data at scheduled meetings; the unblinded summaries were prepared by an independent statistical centre.

- **Statistical methods**

Analysis populations

The following analysis populations were used.

- Intent-To-Treat Set (ITT): All subjects who were randomized, with the treatment group designated according to the randomization. The ITT was the primary analysis set for all analyses except for safety.
- Safety Analysis Set (SAS): All subjects who received at least one dose of study drug (ivosidenib or placebo). Subjects were analysed according to the actual treatment received. The SAS was the primary analysis set for all safety analyses.
- Per-Protocol Set (PPS): All subjects in ITT who did not violate the terms of the protocol in a way that would significantly affect the study outcome, with treatment group designated according to the randomization. In general, subjects who met the following criteria were excluded from this analysis set:
    - Did not have histopathologically diagnosed nonresectable or metastatic cholangiocarcinoma
    - Did not have documented IDH1 gene-mutated disease based on central laboratory testing
    - Did not have any measurable lesion as defined by RECIST v1.1 as determined by IRC
    - 3 or more prior systemic therapy in an advanced setting (nonresectable or metastatic) as defined in the protocol

    - Had received a prior IDH inhibitor

- Crossover Set (COS): A subset of placebo subjects who crossed over and receive ivosidenib upon the radiographic progressive disease (PD). The COS was the analysis set for analyzing post-crossover data.

Multiplicity adjustment

Of the secondary endpoints, OS and ORR were designated as key secondary efficacy endpoints. The primary and key secondary endpoints were tested at an overall one-sided Type I error rate at 2.5% level based on the fixed sequence testing procedure (Westfall and Krishen, 2001) at the time of primary analysis. These endpoints were tested in the following order:

- PFS based on IRC
- OS
- ORR based on IRC

In addition, a hierarchical testing procedure was adopted for OS analyses only if the primary efficacy endpoint PFS was statistically significant. Two analyses were planned for OS: 1) an interim analysis at the projected time of the final analysis for PFS (provided PFS was significant); 2) a final analysis for OS when 150 deaths were observed. Overall survival at the interim was tested with the alpha being determined using the gamma spending function (gamma=-8), and the overall type I error rate was controlled at the 1-sided 0.025 level. The log-rank test stratified by randomization stratification factor was used to compare OS between the 2 treatment arms.

Primary endpoint

The primary analysis of PFS was based on IRC assessment for the ITT set. PFS was defined as the time in months from the randomization date to the date of the first documentation of disease progression as determined by the IRC per RECIST v1.1 or death due to any cause, whichever occurred first.

PFS = (Earliest Date of Disease Progression or Death – Randomization Date + 1) / 30.4375.

As suspected in the review of PFS results, it was confirmed that the primary definition of PFS included in the SAP was incomplete. The full censoring scheme was provided during the procedure and is presented below.

Table 24. Handling of Missing Response Assessment and Censoring for the Primary Analysis of PFS per Independent Radiology Center (IRC)

Situation [1]	Date of Censoring
No baseline assessment and no death.	Date of the randomization
Crossover started before documented PD per IRC or death.	**Date of last adequate IRC assessment prior to the start of crossover[2]**
Investigator assessed PD before documented PD per IRC	**Date of last adequate IRC assessment prior to or on investigator assessed PD[3]**
Alternate anticancer systemic treatment started before documented progression (PD) per IRC or death.	Date of last adequate IRC assessment prior to the start of anticancer treatment[1]
No adequate post-baseline assessment and no death.	Date of the randomization
Documented PD or death following a long gap from the previous adequate assessment (eg, 2 or more consecutive missed scheduled disease status assessments). If no adequate assessment prior to minimum of (PD, death), the long gap is calculated from the randomization date.	Date of last adequate IRC assessment prior to the first occurrence of 2 or more consecutive missing scheduled assessments
No documented PD or death before data cutoff date.	Date of last adequate IRC assessment[1]

[1] The censoring rules are presented in a hierarchical order
[2] Adequate disease assessment is defined as a response assessment other than"not assessed or"not evaluable." If there is no adequate response assessment prior to the start of anticancer treatment, it will be censored at the randomization date.The long gap is defined as ≥95 days (ie, 12 weeks + 10 days per the protocol defined visit window).
[3] Per study design, after unblinding at PD per Investigator assessment, subjects on ivosidenib are allowed to stay on ivosidenib if the treating Investigator deems they are clinically benefiting. The IRC will read all scans up to the discontinuation of ivosidenib. Subjects on placebo will no longer stay on placebo after radiographic disease progression and unblinding, hence no further scans will be read by IRC beyond the initial locally assessed disease progression imaging time point. Because of that, there is a potential systematic bias that subjects on the ivosidenib arm could have PD called by IRC later than the locally assessed PD date; however, subjects on the placebo arm would systematically be censored by IRC analysis at the time of local PD if not concordant with local PD. To alleviate the potential imbalance between two arms, IRC assessments after the local PD from both arms will be excluded from the primary analysis of scan-related endpoints per IRC read.

A stratified log-rank test (1-sided) was used to compare PFS of the ivosidenib arm against the placebo arm at the time when 131 investigator-assessed events had occurred, with the one-sided significance level controlled at 0.025. The HR (ivosidenib/placebo) and the corresponding 2-sided 95% confidence interval were estimated using a stratified Cox regression model. For both the stratified log-rank test and stratified Cox regression model, the strata were to be those used for stratified randomization.

Number of subjects with events, types of events (progression or death), and number of subjects censored, number of subjects for each reason of censoring, Kaplan-Meier estimates and 95% confidence intervals for the 25th percentile, median, and the 75th percentile for PFS were presented by treatment group. Probabilities of event free at selected time points, such as 3-month, 6-month, 9-month and 12-month, were presented by treatment arms. Kaplan-Meier curves of PFS were provided for each treatment arm, with the number of subjects at risk over time included.

Secondary endpoints

Overall Survival

The OS analysis was based on ITT set and included all OS data, including data after crossover. Overall survival was defined as the time in months from the randomization date to the date of death due to any cause. Subjects without documentation of death at the time of the data cutoff for analysis were censored at the date the subject was last known to be alive, or the data cutoff date, whichever was earlier. The last known alive date was the last record in the study database. For example, this date may have been the maximum of the last visit date or last contact date, including telephone follow-up where the subject was known to be alive.

A stratified one-sided log-rank test was used to compare OS between the 2 treatment groups, with the one-sided significance level controlled at 0.025. The HR along with the 95% CI was estimated using a stratified Cox model. For both the stratified log-rank test and the stratified Cox model, the strata were those at randomization. A Kaplan-Meier plot for OS was presented by treatment arm. Estimates and 95% confidence intervals for the 25th percentile, median, and 75th percentile for OS were presented by treatment arm (if estimable). Probabilities of survival at selected time points (3 months, 6 months, 9 months, and 12 months) may have also been presented.

Overall Response Rate

ORR was derived from BOR. BOR was defined as the best time point response that a subject achieved during the course of the study, with the response ranked according to the following order (from best to worst): CR>PR> stable disease (SD)>PD>UNK> Other (including Not Estimable and Not Assessed). The number and proportion of ITT subjects with each category of BOR were presented by treatment arms.

Per RECIST v1.1, SD that occurred within <38 days from the randomization date was assigned as unknown (6 weeks minus 5 days per protocol allowed visit window). In addition, the BOR of CR or PR required a confirmation scan. The estimated ORR (percent of subjects with a BOR of CR or PR) and a 2-sided 95% CI (via exact binomial) were provided by treatment arms. All subjects in the analysis set were included in the denominator in the calculation of the percentage for each response category or ORR. The subject without any response assessment was treated as a non-responder in the analyses.

ORR was analyzed using a Fisher's exact test to compare the 2 treatment arms. The odds ratio and its 95% CI were estimated.

In addition, the ORR (and BOR) without confirmation per IRC as well as per Investigator assessments was analyzed similarly.

Time to Response

TTR was defined as the time (in months) from the randomization date to the date of first occurrence of confirmed/unconfirmed response per RECIST v1.1.

Duration of Response

Among responders (subjects who had a best response of confirmed PR or CR), DOR in months was calculated as the date of the first confirmed PR or CR to the date of the first PD or death, whichever was earlier. The censoring rule was the same as that for the PFS analysis.

Health-Related Quality of Life

For the prespecified key subscale scores of EORTC QLQ-C30 (Physical Functioning, Pain, and Appetite Loss) and QLQ-BIL21 (Eating and Pain) as well as other subscales, change from baseline across visits were analyzed using a mixed-effect model with repeated measurements (MMRM) assuming missing data occur at random. The model includes baseline score, treatment arms, visit, visit by treatment interaction as fixed effects, and subject as random effects.

<u>Sensitivity analyses</u>

Sensitivity analyses were performed to assess the robustness of the primary analysis results for PFS based on IRC as follows:

- Stratified analysis based on all available scans read by IRC prior to crossover (including the scans after investigator-assessed progressive disease [PD] for subjects randomized to ivosidenib who continued treatment after investigator-assessed PD).
- Stratified analysis based on PPS.

- Unstratified analysis.

PFS per Investigator Assessment was analyzed similarly as the primary analysis based on PFS per IRC.

Per the protocol, subjects randomized to placebo were allowed to cross over to ivosidenib upon radiographic disease progression provided the eligibility criteria continue being met. To adjust for the crossover effect, sensitivity analysis was also performed for OS based on the Rank Preserving Structural Failure Time (RPSFT) method (Robins and Tsiatis, 1991; White et al, 1997 & 1999).

Subgroup analyses

Subgroup analyses were performed for both PFS and OS. The subgroups included:

- The actual number of prior line of therapies in advanced setting (1 vs. ≥2)
- Gender (female vs. male)
- Extent of disease at screening (locally advanced vs. metastatic)
- Intrahepatic vs. extrahepatic
- ECOG at baseline (0 vs. ≥1)
- Regions (North America vs. Europe vs. Asia)

Changes to planned analyses

Several clarifications were made regarding the primary / secondary endpoints, the statistical assumptions and the sample size as part of protocol amendment 1 (05 October 2016), however no subjects were enrolled under the original protocol.

The PGI-C and PGI-S were added as additional HRQOL measures with protocol amendment 3 (01 September 2017).

Physical examination data were not listed, as any abnormal findings were to be reported as AEs and therefore data collection on the eCRF was limited to whether the assessment was performed. An exploratory analysis of TEAEs adjusted by treatment duration per person years was conducted to assess the frequency of TEAEs in relation to treatment exposure. Exploratory analyses were also performed for the EORTC QLQ-C30 Emotional Functioning subscale, the EORTC QLQ-BIL21 Anxiety symptom subscale, and the EQ-5D-5L Anxiety/Depression dimension. Extent of exposure was to be summarized in a separate table for placebo subjects who crossed over and received ivosidenib based; however, this information was added as a column in the table of exposure for all other treatment arms. Number of subjects with at least 1 prior local or regional therapy was added among the baseline characteristics to be summarized.

No other changes occurred between the final SAP (version 1.0 dated 01 April 2019) and the clinical study report (CSR).

Results

- **Participant flow**

Table 25. Summary of Subject Disposition (Intent-To-Treat Set) (DCO 31 May 2020)

	Placebo N=61 n (%)	AG-120 N=126 n (%)	Total N=187 n (%)
Randomized subjects			
Treated	59 (96.7)	123 (97.6)	182 (97.3)
Not treated	2 (3.3)	3 (2.4)	5 (2.7)
Treatment status			
On treatment	0	8 (6.5)	8 (4.4)
Discontinued treatment	59 (100.0)	115 (93.5)	174 (95.6)
Adverse event	4 (6.8)	8 (6.5)	12 (6.6)
Death	0	5 (4.1)	5 (2.7)
Progressive disease	51 (86.4)	92 (74.8)	143 (78.6)
Withdrawal by subject	2 (3.4)	6 (4.9)	8 (4.4)
Withdrawal of consent	1 (1.7)	2 (1.6)	3 (1.6)
Other	1 (1.7)	2 (1.6)	3 (1.6)
Crossed over to receive AG-120			
On AG-120	5 (11.6)	0	5 (11.6)
Discontinued AG-120	38 (88.4)	0	38 (88.4)
Adverse event	2 (4.7)	0	2 (4.7)
Physician decision	2 (4.7)	0	2 (4.7)
Progressive disease	32 (74.4)	0	32 (74.4)
Withdrawal of consent	2 (4.7)	0	2 (4.7)
Study status			
On study	9 (14.8)	24 (19.0)	33 (17.6)
Discontinued study	52 (85.2)	102 (81.0)	154 (82.4)
Death	43 (70.5)	93 (73.8)	136 (72.7)
Lost to follow-up	0	1 (0.8)	1 (0.5)
Withdrawal of consent	9 (14.8)	8 (6.3)	17 (9.1)

Source: Table 14.1.2. Data cutoff date: 31 May 2020.
Percentages under treatment status are based on Safety Analysis Set in each column (denominator). Percentages under crossed over status are based on COS in each column (denominator). All the other percentages are based on ITT Set in each column (denominator).'Progressive Disease' includes both radiographic and clinical PD.

- **Recruitment**

A total of 49 study sites participated in this study, with 26 sites in the United States (US), 6 sites in South Korea, 5 sites in the United Kingdom (UK), 5 sites in Spain, 4 sites in France, and 3 sites in Italy.

First subject enrolled: 20 February 2017

Last subject completed: As of the final database lock date (21 June 2021), all subjects had discontinued study treatment and all subjects had discontinued the study.

Data cutoff date: 31 January 2019 for the final analysis of PFS and other tumour response endpoints.

31 May 2020 for the final analysis of OS;

- **Conduct of the study**

The original protocol (08 August 2016) was amended 5 times.

No subjects were enrolled under the original protocol. One subject was enrolled under Amendment 1, 65 subjects were enrolled under Amendment 2, 55 subjects were enrolled under Amendment 3, and 64 subjects were enrolled under Amendment 4.

Table 26. Changes to the Study Protocol

Amendment	Date Amendment	Change
Amendment 1, Version 2.0	05 October 2016	• Clarified that the primary endpoint of PFS was based on Independent Radiology center assessment instead of Investigator assessment. • The secondary endpoint of PFS was adjusted to be assessed by the Investigator versus the IRC, and the secondary
Amendment	Date Amendment	Change
		response endpoints were assessed by the Investigator and IRC. • The adjustment of statistical assumptions resulted in an increase in the number of subjects were to be enrolled, and an increase in the statistical power to detect a significant difference. The number of study centers was slightly increased to account for the increase in the sample size. • The exact IDH1 mutation variants to be tested for eligibility were listed to account for assay specifications. • The screening window for baseline scans was shortened from within 28 days to within 21 days prior to C1D1. • Clarified that after 54 weeks (approximately 1 year), scans were to be performed every 8 weeks instead of every 9 weeks, which was the schedule for PFS and QOL assessments in follow-up as well.
Amendment 2, Version 3.0	07 November 2016	• Per FDA feedback, dose re-escalation was not permitted in the event of life-threatening Grade 4 ivosidenib- related toxicities. • Added clarification around qualifications for subjects who continue study treatment beyond disease progression, also per FDA feedback.
Amendment 2, Version 3.1 (UK only)	28 April 2017	• Removed abstinence as a form of contraception. • Removed "highly" from the phrase "use a highly effective form of contraception" and clarified what forms of contraception fit the definition of "effective forms of contraception." • Replaced the details of potential reasons for why unblinding might need to occur with a suggestion that Investigators discuss the plan for breaking the blinding code with the Medical Monitor. • Emphasized skin examinations for assessing rash to be consistent with the recommendation in the ivosidenib IB that "Patients should be routinely monitored for rash during clinical trials."
Amendment 3, Version 4.0	01 September 2017	• Added the Patient Global Impression of Change (PGI-C) and the Patient Global Impression of Severity (PGI-S) as additional HRQOL measures throughout the protocol, per FDA's request to ask some anchor-based questions in addition to the European Organization for Research and Treatment of Cancer - Quality Of Life Questionnaire – Core Questionnaire (EORTC-QLQ-C30) and the European

Amendment	Date Amendment	Change
		Organisation for Research and Treatment of Cancer - Quality Of Life Questionnaire - Cholangiocarcinoma and Gallbladder Cancer Module (EORTC-QLQ-BIL21). • Removed abstinence as a form of contraception; removed "highly" from the phrase, "use a highly effective form of contraception;" and clarified what forms of contraception fit the definition of "effective forms of contraception," per UK requests. • Removed "or inhibitors" and "or unless the medications can be properly monitored during the study" and added "with narrow therapeutic indices" to exclusion criteria 9 and 10 because that language was in conflict with calling something an exclusion (ie, one cannot exclude and "monitor" at the same time). • Added the following caveat to exclusion criterion 17 per the Agios Clinical Science Department: "Subjects with chronic HBV that is adequately suppressed per institutional practice will be permitted." • Added exclusion criterion 20 per Germany's request: "The exclusion of persons who have been committed to an institution by virtue of an order issued either by the judicial or the administrative authorities is missing, cf. § 40 par. 1 cl. 3 no. 4 of the AMG." • Added exclusion criterion 21 per Germany's request: "The exclusion of persons dependent on the sponsor, investigator, or study site is missing, cf. § 40 par. 1 cl. 3 no. 3 b) and c) of the AMG in conjunction with section 1.61 of the ICH/GCP guideline topic E6." • Updated text about taking the tablets with food per Agios' updated, approved food language. • Changed "Consider holding" to "Hold" per France's request: "Please amend Table 1 (Management of Adverse Events) in the protocol for this trial in Section 9.8.1 (Study Treatment Dose Modification and Stopping Criteria) Dose Modifications and Delays, in the event of grade 3 adverse events linked to the trial treatment, to allow for the stopping of the trial treatment (AG120/placebo) until return to baseline or grade 1. The indication, 'consider holding dose of AG-120/placebo,' does not seem specific enough." • Emphasized skin examinations for assessing rash to be consistent with the recommendation in the ivosidenib IB

Amendment	Date Amendment	Change
		that: "Patients should be routinely monitored for rash during clinical trials."
Amendment 4, Version 5.0	04 April 2018	• Palliative radiotherapy to treat symptomatic non-target lesions that could not otherwise be medically managed was permitted after disease progression had been verified and unblinding had occurred, and in the setting of continuation of ivosidenib beyond disease progression, with Medical Monitor approval. • Information on drug-drug interactions was revised, consistent with the ivosidenib IB, Version 7.0. • The exclusion criterion 10, excluding subjects who are taking P-gp transporter-sensitive substrate medications with a narrow therapeutic window, unless they can be transferred to other medications within ≥5 half-lives prior to administration of study treatment, was removed. • Hematology, serum chemistry, circulating tumor DNA, and exploratory biomarker assessments were required at both the end of treatment (EOT) visit and at the cross over Cycle 1 Day 1 (C1D1) visit. Clarified that if the cross over C1D1 visit occurred within 3 days of the EOT visit, these laboratory assessments were not required to be repeated. • The list of medications known to prolong the QT interval was expanded and updated.
Amendment 4, Version 5.1 (South Korea only)	20 June 2018	• Added the Patient Global Impression of Change (PGI-C) and the Patient Global Impression of Severity (PGI-S) as additional HRQOL measures throughout the protocol, per Food and Drug Administration's (FDA's) request to include anchor-based questions in addition to the European Organisation for Research and Treatment of Cancer - Quality of Life Questionnaire – Core Questionnaire (EORTC-QLQ-C30) and the European Organisation for Research and Treatment of Cancer - Quality of Life Questionnaire - Cholangiocarcinoma and Gallbladder Cancer Module (EORTC-QLQ-BIL21). • Removed abstinence as a form of contraception; removed "highly" from the phrase, "use a highly effective form of contraception;" and clarified what forms of contraception fit the definition of "effective forms of contraception," per UK requests. • Added the following caveat to Exclusion Criterion 17 per the Agios Clinical Science Department: "Subjects with chronic

Amendment	Date Amendment	Change
		HBV that is adequately suppressed per institutional practice will be permitted." • Added Exclusion Criterion 20 per Germany's request: "The exclusion of persons who have been committed to an institution by virtue of an order issued either by the judicial or the administrative authorities is missing, cf. § 40 par. 1 cl. 3 no. 4 of the AMG." • Added Exclusion Criterion 21 per Germany's request: "The exclusion of persons dependent on the sponsor, investigator, or study site is missing, cf. § 40 par. 1 cl. 3 no. 3 b) and c) of the AMG in conjunction with section 1.61 of the ICH/GCP guideline topic E6." • Updated text about taking the tablets with food per Agios' updated, approved food language. • Changed "Consider holding" to "Hold" per France's request: "Please amend Table 1 (Management of Adverse Events) in the protocol for this trial in Section 9.8.1 (Study Treatment Dose Modification and Stopping Criteria) Dose Modifications and Delays, in the event of grade 3 adverse events linked to the trial treatment, to allow for the stopping of the trial treatment (AG120/placebo) until return to baseline or grade 1. The indication, 'consider holding dose of AG-120/placebo,' does not seem specific enough." • Palliative radiotherapy to treat symptomatic non-target lesions that cannot otherwise be medically managed will be permitted after disease progression has been verified and unblinding has occurred, with Medical Monitor approval. • Information on drug-drug interactions (DDIs) has been revised, consistent with the ivosidenib IB, Version 7.0. • Hematology, serum chemistry, circulating tumor DNA, and exploratory biomarker assessments are required at both the end of treatment (EOT) visit and at the cross over Cycle 1 Day 1 (C1D1) visit. If the cross over C1D1 visit occurs within 3 days of the EOT visit, these laboratory assessments need not be repeated. • Emphasized skin examinations for assessing rash to be consistent with the recommendation in the ivosidenib IB that: "Patients should be routinely monitored for rash during clinical trials." • The list of medications known to prolong the QT interval was expanded and updated.

Amendment	Date Amendment	Change
Amendment 4, Version 5.2 (France only)	10 August 2018	• Added a new exclusion criterion to exclude subjects with a known medical history of progressive multifocal leukoencephalopathy. • Added a new Section 9.8.1.2 (Dose Suspension Criteria). • Added a new Section 9.10 (Other Potential Risks).

The protocol was amended twice (1 global version, 1 country-specific version) between the primary CSR data cutoff date and the CSR addendum data cutoff date of 31 May 2020; substantial changes are summarized below. No subjects were enrolled under this amendment.

Table 27. Changes to the Study Protocol (Amendment 5)

Amendment	Date Amendment	Change
Amendment 5, version 6.0*	01 Mar 2019	Added language to outline the management of subjects following study unblinding to proactively convey the post-unblinding plan to Investigators and study teams. Added an exclusion criterion to exclude subjects with a known medical history of progressive multifocal leukoencephalopathy per health authority request. Added a new Section, 11.3 (Other Potential Risks), describing leukoencephalopathy and sensorimotor neuropathy/polyneuropathy as other potential risks associated with ivosidenib for consistency with the safety language in other ivosidenib clinical study protocols.
Amendment 5, version 6.1 (South Korea only)		

*Note that country-specific protocol version for France (was version 5.2 under Amendment 4) was unified with the global protocol version in Amendment 5 (version 6.0).

Protocol deviations

A total of 27 of 187 (14.4%) subjects had at least 1 major protocol deviation during the study. No subject had more than 1 major protocol deviation. The most common deviations were informed consent deviations (5.3% subjects) and SAE-related deviations (4.8% subjects).

Table 28. Summary of subject-level Major Protocol Deviations (ITT)

	Placebo N=61 n (%)	AG-120 N=126 n (%)	Total N=187 n (%)
Subjects with at Least 1 Major Protocol Deviation	8 (13.1)	19 (15.1)	27 (14.4)
Subjects by Number of Major Protocol Deviations			
1	8 (13.1)	16 (12.7)	24 (12.8)
2	0	2 (1.6)	2 (1.1)
>=3	0	1 (0.8)	1 (0.5)
Major Protocol Deviation			
PROTOCOL DEVIATION	4 (6.6)	14 (11.1)	18 (9.6)
SAE-RELATED DEVIATIONS	3 (4.9)	6 (4.8)	9 (4.8)
Related to COVID-19	0	0	0
STUDY TREATMENT DEVIATION	0	4 (3.2)	4 (2.1)
Related to COVID-19	0	0	0
OTHER DEVIATION	1 (1.6)	1 (0.8)	2 (1.1)
Related to COVID-19	0	0	0
GCP-RELATED DEVIATION	0	1 (0.8)	1 (0.5)
Related to COVID-19	0	0	0
SELECTION CRITERIA NOT MET	0	1 (0.8)	1 (0.5)
Related to COVID-19	0	0	0
PROTOCOL DEVIATION (Continued)			
VISIT OR ASSESSMENT PERFORMED OUT OF WINDOW	0	1 (0.8)	1 (0.5)
Related to COVID-19	0	0	0
ICH/GCP DEVIATION	4 (6.6)	7 (5.6)	11 (5.9)
INFORMED CONSENT	4 (6.6)	6 (4.8)	10 (5.3)
Related to COVID-19	0	0	0
REGULATORY OR ETHICS OR IRB	0	1 (0.8)	1 (0.5)
Related to COVID-19	0	0	0

ITT: All subjects who are randomized, with the treatment group designated according to the randomization.
Percentages are calculated with the number of subjects in the ITT Set in each column as the denominator.
Major Protocol Deviations are sorted in descending frequency in Total column.

- **Baseline data**

Table 29. Demographics (ITT)

	Placebo N=61	AG-120 N=124	Total N=185
Age (years)			
N	61	124	185
Mean (Std Dev)	62.9 (10.38)	60.3 (10.95)	61.2 (10.81)
Median	63.0	61.0	62.0
Min, Max	40, 83	33, 80	33, 83
Age Category (years), n (%)			
<45	3 (4.9)	11 (8.9)	14 (7.6)
45-<65	33 (54.1)	67 (54.0)	100 (54.1)
≥65	25 (41.0)	46 (37.1)	71 (38.4)

	Placebo N=61	AG-120 N=124	Total N=185
Sex, n (%)			
Male	24 (39.3)	44 (35.5)	68 (36.8)
Female	37 (60.7)	80 (64.5)	117 (63.2)
Ethnicity, n (%)			
Hispanic or Latino	2 (3.3)	7 (5.6)	9 (4.9)
Not Hispanic or Latino	40 (65.6)	83 (66.9)	123 (66.5)
Not Reported	2 (3.3)	0	2 (1.1)
Missing	17 (27.9)	34 (27.4)	51 (27.6)
Race, n (%)			
American Indian or Alaska Native	0	1 (0.8)	1 (0.5)
Asian	8 (13.1)	15 (12.1)	23 (12.4)
Black or African American	1 (1.6)	1 (0.8)	2 (1.1)
Native Hawaiian or Other Pacific Islander	0	1 (0.8)	1 (0.5)
White	35 (57.4)	70 (56.5)	105 (56.8)
Other	0	1 (0.8)	1 (0.5)
Not Reported	0	1 (0.8)	1 (0.5)
Missing	17 (27.9)	34 (27.4)	51 (27.6)
Regions			
Asia	5 (8.2)	7 (5.6)	12 (6.5)
Europe	16 (26.2)	33 (26.6)	49 (26.5)
North America	40 (65.6)	84 (67.7)	124 (67.0)
Height (cm)			
N	58	118	176
Mean (Std Dev)	167.9 (9.21)	165.3 (9.72)	166.2 (9.61)
Median	168.2	164.0	165.1
Min, Max	148.0, 188.0	145.0, 193.0	145.0, 193.0
Weight (kg)			
N	61	119	180
Mean (Std Dev)	74.6 (18.03)	73.9 (19.37)	74.2 (18.88)
Median	73.0	71.9	72.5
Min, Max	44.0, 113.0	39.0, 135.5	39.0, 135.5

	Placebo N=61	AG-120 N=124	Total N=185
BMI (kg/m^2)			
N	58	118	176
Mean (Std Dev)	26.3 (5.38)	26.9 (6.44)	26.7 (6.10)
Median	26.0	25.5	25.6
Min, Max	15.2, 41.5	15.2, 51.0	15.2, 51.0

Source: Table 14.1.5. Data cutoff date: 31 January 2019.
Abbreviations: BMI = body mass index; EU = European Union; ITT = intention-to-treat; Std Dev = standard deviation.
Note: ITT was defined as all subjects who are randomized, with the treatment group designated according to the randomization. Percentages are calculated with the number of subjects in the ITT Set in each column (N) as the denominator. Race/Ethnicity are not permitted to collect in the EU.

Table 30. Baseline Characteristics (Intent-to-Treat Set)

	Placebo N=61 n (%)	AG-120 N=124 n (%)	Total N=185 n (%)
Randomization Strata			
1 Prior Line of Therapy	33 (54.1)	66 (53.2)	99 (53.5)
2 Prior Lines of Therapy	28 (45.9)	58 (46.8)	86 (46.5)
IDH Allele Types[1]			
R132C	45 (73.8)	84 (67.7)	129 (69.7)
R132G	6 (9.8)	17 (13.7)	23 (12.4)
R132H	2 (3.3)	0	2 (1.1)
R132L	7 (11.5)	21 (16.9)	28 (15.1)
R132S	1 (1.6)	2 (1.6)	3 (1.6)
ECOG at Baseline			
0	19 (31.1)	49 (39.5)	68 (36.8)
1	41 (67.2)	74 (59.7)	115 (62.2)
2[2]	1 (1.6)	0	1 (0.5)
3[2]	0	1 (0.8)	1 (0.5)
Cholangiocarcinoma Type at Diagnosis			
Intrahepatic	58 (95.1)	111 (89.5)	169 (91.4)
Extrahepatic	1 (1.6)	1 (0.8)	2 (1.1)
Perihilar	0	4 (3.2)	4 (2.2)
Unknown	2 (3.3)	8 (6.5)	10 (5.4)
T (Tumor) Stage at Initial Diagnosis			
T0	1 (1.6)	0	1 (0.5)
T1	9 (14.8)	13 (10.5)	22 (11.9)
T2	25 (41.0)	54 (43.5)	79 (42.7)
T3	11 (18.0)	13 (10.5)	24 (13.0)
T4	5 (8.2)	13 (10.5)	18 (9.7)
Tx	8 (13.1)	25 (20.2)	33 (17.8)
Missing	2 (3.3)	6 (4.8)	8 (4.3)
N (Lymph node) Stage at Initial Diagnosis			
N0	23 (37.7)	40 (32.3)	63 (34.1)
N1	19 (31.1)	45 (36.3)	64 (34.6)
N2	1 (1.6)	1 (0.8)	2 (1.1)
Nx	16 (26.2)	31 (25.0)	47 (25.4)
Missing	2 (3.3)	7 (5.6)	9 (4.9)
M (Metastasis) Stage at Initial Diagnosis			
M0	33 (54.1)	47 (37.9)	80 (43.2)
M1	23 (37.7)	63 (50.8)	86 (46.5)
Mx	4 (6.6)	9 (7.3)	13 (7.0)
Missing	1 (1.6)	5 (4.0)	6 (3.2)

	Placebo N=61 n (%)	AG-120 N=124 n (%)	Total N=185 n (%)
Grade at Initial Diagnosis			
Well Differentiated	4 (6.6)	8 (6.5)	12 (6.5)
Moderately Differentiated	28 (45.9)	45 (36.3)	73 (39.5)
Poorly Differentiated	16 (26.2)	39 (31.5)	55 (29.7)
Undifferentiated	0	1 (0.8)	1 (0.5)
Unknown	13 (21.3)	31 (25.0)	44 (23.8)
Extent of Disease at Screening			
Local/Regional	5 (8.2)	9 (7.3)	14 (7.6)
Metastatic	56 (91.8)	115 (92.7)	171 (92.4)
Liver Cirrhosis at Screening			
Yes	3 (4.9)	6 (4.8)	9 (4.9)
Hepatitis B	0	1 (0.8)	1 (0.5)
Hepatitis C	1 (1.6)	0	1 (0.5)
Alcohol	0	1 (0.8)	1 (0.5)
Other	2 (3.3)	4 (3.2)	6 (3.2)
No	58 (95.1)	118 (95.2)	176 (95.1)
Presence of Biliary Stent at Screening			
Yes	7 (11.5)	14 (11.3)	21 (11.4)
No	54 (88.5)	110 (88.7)	164 (88.6)
Presence of Ascites at Screening			
Yes	13 (21.3)	34 (27.4)	47 (25.4)
No	48 (78.7)	90 (72.6)	138 (74.6)
Ascites Related to Cholangiocarcinoma Within the Past 3 Months			
Yes	13 (21.3)	37 (29.8)	50 (27.0)
No	48 (78.7)	87 (70.2)	135 (73.0)
Paracentesis Within the Past 3 Months	5 (8.2)	11 (8.9)	16 (8.6)
Pleural Effusion Related to Cholangiocarcinoma Within the Past 3 Months			
Yes	7 (11.5)	13 (10.5)	20 (10.8)
No	54 (88.5)	111 (89.5)	165 (89.2)
Thoracentesis Within the Past 3 Months	1 (1.6)	2 (1.6)	3 (1.6)
Subjects With at Least 1 Prior Local or Regional Therapy	**20 (32.8)**	**43 (34.7)**	**63 (34.1)**

Source: Table 14.1.6. Data cutoff date: 31 January 2019.

- **Numbers analysed**

The following data sets were analysed at the DCO of 31 January 2019.

- 185 (100%) subjects were included in the ITT population.
- 184 (99.5%) subjects were included in the PPS.
- 180 (97.3%) subjects were included in the SAS.
- 35 (18.9%) subjects were included in the COS.

Table 31. Summary of Analysis Datasets at the DCO of 31 May 2020 and 21 June 2021

	Placebo N=61 n (%)	AG-120 N=126 n (%)	Total N=187 n (%)
Intent-To-Treat Set (ITT)[1]	61 (100.0)	126 (100.0)	187 (100.0)
Safety Analysis Set (SAS)[2]	59 (96.7)	123 (97.6)	182 (97.3)
Crossover Set (COS)[3]	43 (70.5)	0	43 (23.0)

Source: Table 14.1.1. Database lock date: 21 June 2021.
Abbreviations: COS = crossover set; PD = progressive disease.
Refer to the primary AG120-C-005 CSR for a complete description of the analysis populations.
[1] All subjects who were randomized, with the treatment arm designated according to the randomization.
[2] All subjects who received at least one dose of study drug (ivosidenib or placebo). Subjects were analyzed according to the actual treatment received.
[3] A subset of placebo subjects who crossed over and received ivosidenib upon Investigator assessment of radiographic PD. The COS was the analysis set for analyzing post-crossover data.

- **Outcomes and estimation**

Progression-Free Survival (DCO: 31 January 2019)

PFS by Independent Review Committee Assessment

Primary Analysis

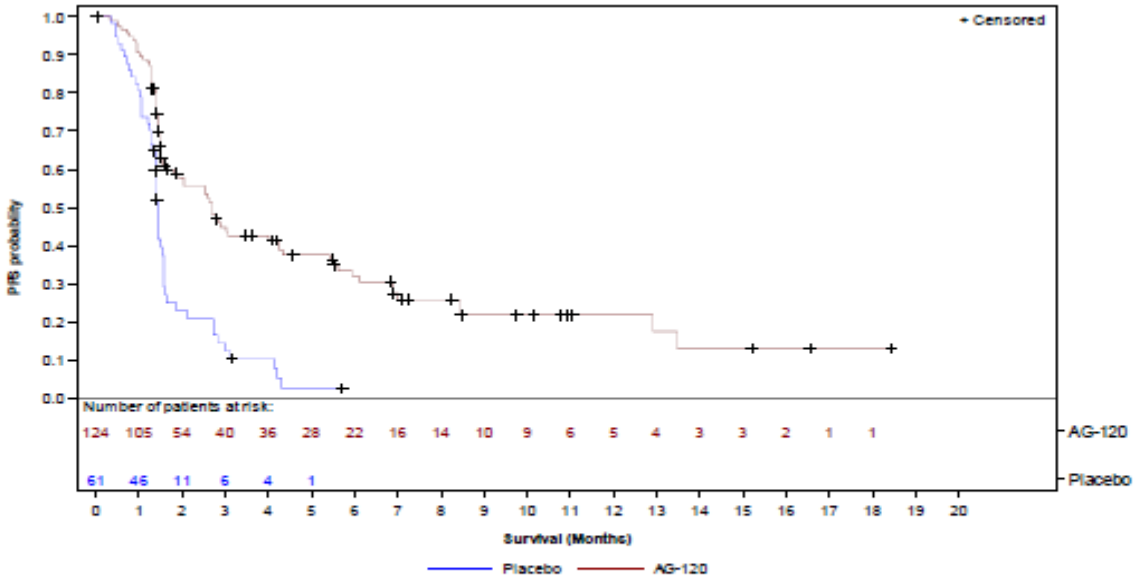
Table 32. Summary of Progression-Free Survival per Independent Review Committee - Before Crossover (Intent-To-Treat Set)

	Placebo N=61	AG-120 N=124
Number of Subjects, n (%)		
Event	50 (82.0)	76 (61.3)
Progressive Disease	44 (72.1)	64 (51.6)
Death	6 (9.8)	12 (9.7)
Censored[1]	11 (18.0)	48 (38.7)
No documented progression or death before data cutoff date	6 (9.8)	32 (25.8)
Documented progression or death following a long gap between adequate disease status assessments	1 (1.6)	5 (4.0)
New anticancer therapy started before documented progression or death	0	5 (4.0)
No post-baseline assessment and no death	3 (4.9)	5 (4.0)
No documented progression or death before permanently discontinued from the study	1 (1.6)	1 (0.8)
Progression-Free Survival (months)[2]		
25th Percentile (95% CI)[3]	1.1 (0.8, 1.4)	1.4 (1.3, 1.5)
Median (95% CI)	1.4 (1.4, 1.6)	2.7 (1.6, 4.2)
75th Percentile (95% CI)	1.6 (1.5, 3.0)	8.4 (5.6, NE)
Hazard Ratio (95% CI)[4]		0.37 (0.25, 0.54)
P-value[5]		<0.001
Kaplan-Meier Survival Rate (%)[6]		
3 months	12.5	44.8
6 months	NE	32.0
9 months	NE	21.9

	Placebo N=61	AG-120 N=124
12 months	NE	21.9

Source: Table 14.2.1.1.
Abbreviations: CI = confidence interval; IRC = independent review committee; ITT = intent to treat; NE = not estimable; PD = progressive disease.
Scans after local PD per Investigator assessment are excluded from this analysis.
ITT: All subjects who are randomized, with the treatment group designated according to the randomization.
Percentages are based on the number of subjects in ITT Set in each column (denominator).
[1] Subjects with no baseline are censored at randomization date; new anticancer therapy started before progression/death are censored at the last adequate assessment prior to the new anticancer therapy; no post-baseline assessment and no death are censored at randomization date; no progression/death by data cutoff date are censored at the last adequate assessment date; progression/death following a long gap (≥2 consecutive scheduled assessments missing) are censored at date of last adequate assessment prior to the gap.
[2] Progression free survival (PFS) = (Earliest Date of PD or Death – Randomization Date + 1) / 30.4375.
[3] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[4] Hazard ratio is calculated from stratified Cox regression model with placebo as the denominator, with two-sided 95% CI. Stratification factor is the number of prior line of therapies at randomization.

Figure 25. Kaplan-Meier Plot of Progression-Free Survival per Independent Review Committee – Before Crossover (Intent-To-Treat Set)



Source: Figure 14.2.3a
Abbreviations: PFS = progression-free survival.
ITT: All subjects who are randomized, with the treatment group designated according to the randomization. Scans after local PD per Investigator assessment are excluded from this analysis.
Progression free survival (PFS) = (Earliest Date of PD or Death – Randomization Date + 1) / 30.4375.

Overall Response Rate (DCO 31 January 2019)

- Overall Response Rate by IRC Assessment

Table 33. Summary of Best Overall Response per Independent Review Committee – Before Crossover (Intent-To-Treat Set)

	Placebo N=61	AG-120 N=124
Confirmed Best Overall Response, n (%)		
Partial Response (PR)	0	3 (2.4)
Stable Disease (SD)	17 (27.9)	63 (50.8)
Progressive Disease (PD)	35 (57.4)	41 (33.1)
Unknown (UNK)	0	2 (1.6)
Not Estimable (NE)	1 (1.6)	1 (0.8)
Confirmed Objective Response Rate (CR or PR), n (%)	0	3 (2.4)
95% CI of Response Rate[1]	(0.0, 5.9)	(0.5, 6.9)
Odds Ratio (95% CI)[2]		NE (0.29, NE)
P-value[3]		0.299
Confirmed + Unconfirmed PR, n (%)	0	6 (4.8)

Source: Table 14.2.2.1.
Abbreviations: CI = confidence interval; CR = complete response; IRC = independent review committee; ITT = intent to treat; NE = not estimable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; UNK = unknown.

Table 34. Characteristics of Subjects Achieving a Confirmed Partial Response by Independent Review Committee Assessment with Ivosidenib Treatment – Before Crossover (Intent-To-Treat Set)

Subject	Assigned Treatment	Prior Systemic Therapies	Duration of Last Prior Line of Systemic Therapy (mo)	Sum of Target Lesions at Baseline (mm)	Maximum Change in Sum of Target Lesions from Baseline (%)	Duration of Treatment (mo)	TTR (mo)	DOR (mo)	PFS (mo)
101-1049	AG-120	Capecitabine, cisplatin, gemcitabine	1.41	33.38	-37.8	11.04	8.28	2.79+	11.04+
103-1030	AG-120	Floxuridine, gemcitabine, oxaliplatin, floxuridine, irinotecan	10.81	26.20	-44.4	5.98	2.79	2.73+	5.49+
113-1042	AG-120	Gemcitabine, oxaliplatin	0.95	63.89	-81.6	17.05+	5.52	11.07+	16.56+

Source: Table 14.2.4.
Abbreviations: DOR = duration of response; PFS = progression-free survival; TTR = time to response.
+ Indicates that PFS was censored at the time of data cut; + in Duration of Treatment indicates that subjects were still on treatment.

A sensitivity analysis based on all scans before crossover read by IRC, including the ones after local PD from subjects who were assigned to ivosidenib, was conducted. Results of this sensitivity analysis were similar to the results observed in the primary analysis of BOR in the ITT population.

Table 35. Sensitivity analysis of best overall response per IRC - before crossover

	Placebo N=61	AG-120 N=124
Confirmed Best Overall Response, n (%)		
Partial Response (PR)	0	3 (2.4)
Stable Disease (SD)	17 (27.9)	63 (50.8)
Progressive Disease (PD)	35 (57.4)	41 (33.1)
Unknown (UNK)	0	2 (1.6)
Not Evaluable (NE)	1 (1.6)	1 (0.8)
Confirmed Objective Response Rate (CR or PR), n (%)	0	3 (2.4)
95% CI of Response Rate [1]	(0.0, 5.9)	(0.5, 6.9)
Odds Ratio (95% CI) [2]		NE (0.29, NE)
P-value [3]		0.299
Confirmed + Unconfirmed PR, n (%)	0	6 (4.8)

ITT: All subjects who are randomized, with the treatment group designated according to the randomization.
This sensitivity analysis includes all scans read by IRC, including scans after local PD. Scans after crossover are not considered.
CR and PR need confirmation. The confirmation rule is determined per RECIST v1.1.
Percentages are calculated with the number of subjects in ITT Set in each column as the denominator.
[1] 2-sided 95% CI is calculated via exact binomial method .
[2] Odds ratio is calculated with placebo as the control (denominator). CI: exact confident interval.
[3] P-value is calculated from 1-sided Fisher exact test.

At the time of the primary analysis, the maximum treatment duration for subjects randomized to ivosidenib was approximately 22.5 months, with the majority of subjects experiencing a durable SD. The maximum treatment duration on placebo before crossover was only 6.9 months, with the majority of subjects experiencing only PD per RECIST v1.1.

Overall Response Rate by Investigator Assessment

Table 36. Summary of best overall response per investigator - before crossover (ITT)

	Placebo N=61	AG-120 N=124
Confirmed Best Overall Response, n (%)		
Partial Response (PR)	1 (1.6)	4 (3.2)
Stable Disease (SD)	23 (37.7)	59 (47.6)
Progressive Disease (PD)	27 (44.3)	44 (35.5)
Unknown (UNK)	2 (3.3)	3 (2.4)
Confirmed Objective Response Rate (CR or PR), n (%)	1 (1.6)	4 (3.2)
95% CI of Response Rate [1]	(0.0, 8.8)	(0.9, 8.1)
Odds Ratio (95% CI) [2]		2.00 (0.19, 100.11)
P-value [3]		0.466
Confirmed + Unconfirmed PR, n (%)	1 (1.6)	5 (4.0)

ITT: All subjects who are randomized, with the treatment group designated according to the randomization.
CR and PR need confirmation. The confirmation rule is determined per RECIST v1.1.
Percentages are calculated with the number of subjects in ITT Set in each column as the denominator.
[1] 2-sided 95% CI is calculated via exact binomial method.
[2] Odds ratio is calculated with placebo as the control (denominator). CI: exact confident interval.
[3] P-value is calculated from 1-sided Fisher exact test.

Table 37. Characteristics of subjects achieving a confirmed partial response per INV - before crossover (ITT)

Subject	Assigned Treatment	Prior Systemic Therapies	Duration of Last Prior Line of Systemic Therapy (mo)	Sum of Target Lesions at Baseline (mm)	Maximum Change in Sum of Target Lesions from Baseline (%)	Duration of Treatment (mo)	TTR (mo)	DOR (mo)	PFS (mo)
602-1107	Placebo	CISPLATIN, CISPLATIN, GEMCITABINE, GEMCITABINE, GEMCITABINE, CAPECITABINE, OXALIPLATIN	4.44	67.00	-56.7	5.49	1.25	4.30	5.52
101-1003	AG-120	CISPLATIN, GEMCITABINE	6.51	60.00	-46.7	22.54+	13.47	7.69	21.13
101-1049	AG-120	CAPECITABINE, CISPLATIN, GEMCITABINE	1.41	70.00	-34.3	11.04	6.80	4.27	11.04
113-1042	AG-120	GEMCITABINE, OXALIPLATIN	0.95	122.00	-44.3	17.05+	8.51	8.08+	16.56+
603-1127	AG-120	FLUOROURACIL, FLUOROURACIL, FOLINIC ACID, OXALIPLATIN, CISPLATIN, GEMCITABINE	6.05	18.00	-35.0	14.06+	4.17	8.77+	12.91+

Table 38. Summary of best overall response per investigator - after crossover (COS)

	AG-120 N=35
Confirmed Best Overall Response, n (%)	
Stable Disease (SD)	15 (42.9)
Progressive Disease (PD)	15 (42.9)
Not Evaluable (NE)	1 (2.9)
Confirmed Objective Response Rate (CR or PR), n (%)	0
95% CI of Response Rate [1]	(0.0, 10.0)
Confirmed + Unconfirmed PR, n (%)	0

COS: A subset of placebo subjects who crossed over and received AG-120 upon the radiographic PD.
CR and PR need confirmation. The confirmation rule is determined per RECIST v1.1.
Percentages are calculated with the number of subjects in COS.
[1] 2-sided 95% CI is calculated via exact binomial method.

Time to Response

The time to response (TTR) by IRC for each of these 3 subjects in the ivosidenib arm was 8.28, 2.79, and 5.52 months, respectively.

The TTR per investigator for each of these 4 subjects in the ivosidenib arm (before crossover) was 13.47, 6.80, 8.51, and 4.17 months, respectively, and 1.25 months for the responder in the placebo arm.

No subjects had a confirmed response after crossover per investigator assessment.

Duration of Response

The duration of response (DOR) by IRC assessment for each of these 3 subjects in the ivosidenib arm was 2.79, 2.73, and 11.07 months, respectively.

The DOR per investigator for each of these 4 subjects in the ivosidenib arm (before crossover) was 7.69, 4.27, 8.08, and 8.77 months, respectively, and 4.30 months for the responder in the placebo arm.

No subjects had a confirmed response after crossover per investigator assessment.

Overall Survival (Interim Analysis DCO 31 January 2019)

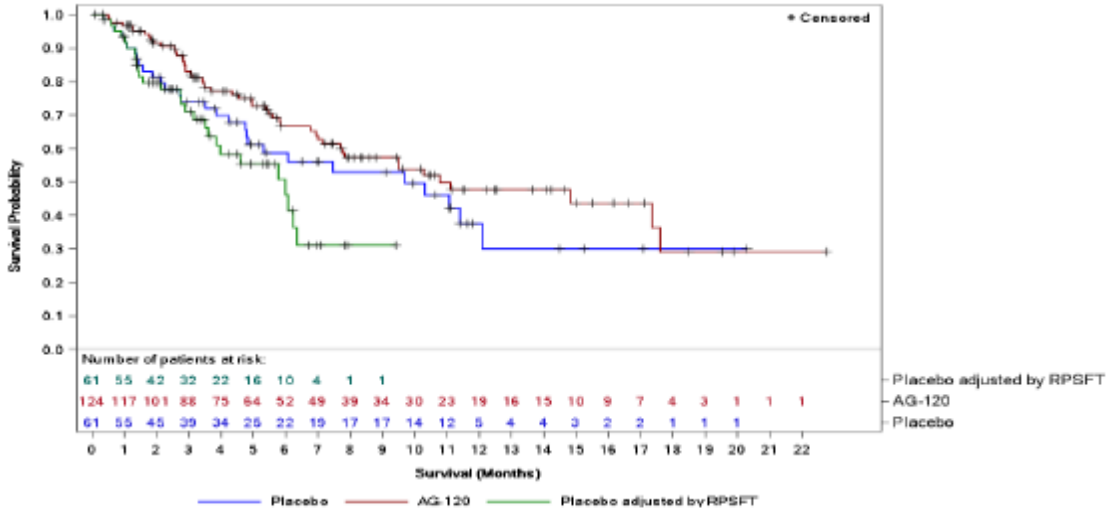
Table 39. Summary of Overall Survival (Intent-To-Treat Set)

	Placebo N=61	AG-120 N=124
Number of Subjects, n (%)		
Event	29 (47.5)	49 (39.5)
Censored[1]	32 (52.5)	75 (60.5)
Overall Survival (months)[2]		
25th Percentile (95% CI)[3]	2.8 (1.4, 4.8)	4.5 (2.9, 5.8)
Median (95% CI)	9.7 (4.8, 12.1)	10.8 (7.7, 17.6)
75th Percentile (95% CI)	NE (11.4, NE)	NE (17.3, NE)
Hazard Ratio (95% CI)[4]		0.69 (0.44, 1.10)
P-value[5]		0.060
Kaplan-Meier Survival Rate (%)[6]		
3 months	73.9	83.1
6 months	58.7	66.6
9 months	52.9	57.3
12 months	37.5	47.6

Source: Table 14.2.6.1.
Abbreviations: CI = confidence interval; NE = not estimable; OS = overall survival.
ITT: All subjects who are randomized, with the treatment group designated according to the randomization.
Percentages are based on the number of subjects in ITT Set in each column (denominator).
[1] Subjects without documentation of death at the time of the data cutoff date will be censored at the date the subject was last known to be alive, or the data cutoff date, whichever is earlier.
[2] Overall survival (OS) = (Date of Death – Randomization Date + 1) / 30.4375.
[3] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[4] Hazard ratio is calculated from the stratified Cox regression model with placebo as the denominator, with 2-sided 95% CI. Stratification factor is the number of prior line of therapies at randomization.
[5] P-value is calculated from the one-sided stratified log-rank test. Stratification factor is the number of prior line of therapies at randomization.

To adjust for the impact of crossover from placebo to ivosidenib, the Rank Preserving Structural Failure Time (RPSFT) model was explored to reconstruct the survival curve for the placebo subjects as if they had never crossed over to ivosidenib. When applying this model, the median OS for the placebo arm was 6.0 months (95% CI: 3.6-6.3). The 6-month OS rate was 46.2% and the 12-month OS rate was not estimable (ie, no subjects in the placebo arm had OS of 12 months or greater as of the data cutoff date).

Figure 26. Kaplan-Meir Plot of overall survival (ITT)



Source: Figure 14.2.10.1
Abbreviations: RPSFT = Rank Preserving Structural Failure Time.
[1] OS = (Date of Death – Randomization Date + 1) / 30.4375.
[2] All subjects who are randomized, with the treatment group designated according to the randomization.

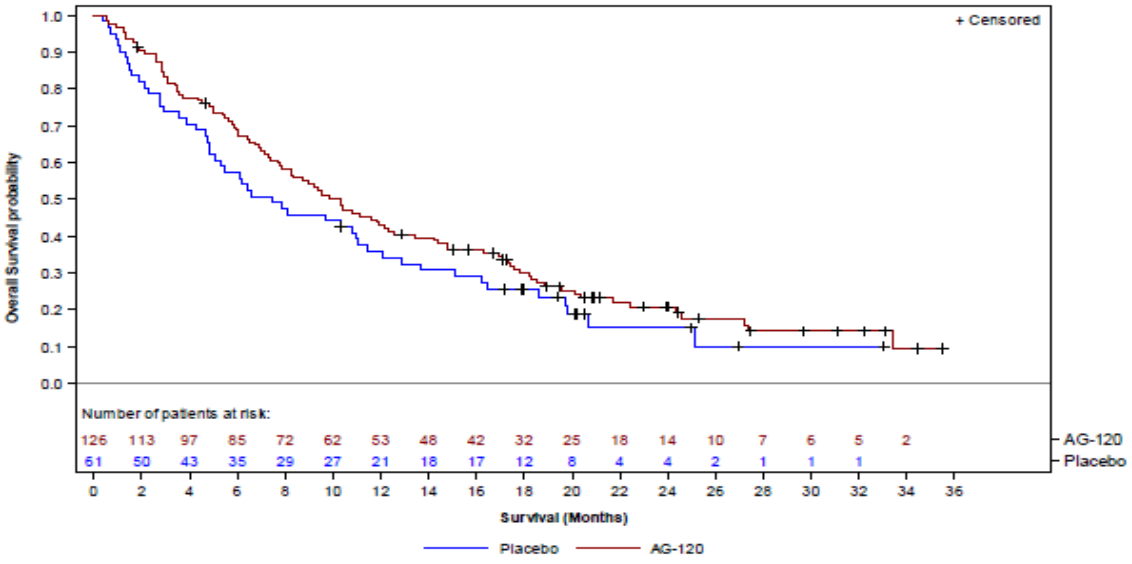
Final analysis of OS (DCO 31 May 2020)

Table 40. Summary of Overall Survival (Intent-to-Treat Set)

	Placebo (N=61)	Ivosidenib (N=126)
Number of subjects, n (%)		
Events, n (%)	50 (82.0)	100 (79.4)
Censored[1], n (%)	11 (18.0)	26 (20.6)
Overall survival (months)[2]		
25th percentile (95% CI)[3]	2.9 (1.4, 4.8)	5.0 (3.1, 6.0)
Median (95% CI)[3]	7.5 (4.8, 11.1)	10.3 (7.8, 12.4)
75th percentile (95% CI)[3]	18.6 (11.4, 25.1)	20.1 (17.3, 27.2)
Hazard ratio[4] (95% CI)	0.79 (0.56, 1.12)	
P-value[5]	0.093	
Kaplan-Meier survival rate[6] (%)		
3 months	73.8	83.3
6 months	57.4	68.8
9 months	45.9	54.2
12 months	35.8	42.9
18 months	25.6	29.9
24 months	15.0	20.7

Source: Table 14.2.6.1. Data cutoff date: 31 May 2020.
Abbreviations: CI = confidence interval; ITT = Intent-to-treat set; NE = not estimable; OS = overall survival.
Note: Percentages are based on the number of subjects in ITT Set in each column (denominator).
[1] Subjects without documentation of death at the time of the data cutoff date were censored at the date the subject was last known to be alive, or the data cutoff date, whichever was earlier.
[2] Overall survival (OS) = (Date of Death – Randomization Date + 1) / 30.4375.
[3] Quartile estimates from product-limit (Kaplan-Meier) method. CIs from Brookmeyer and Crowley method with log-log transformation.
[4] Hazard ratio is calculated from the stratified Cox-regression model with placebo as the comparator, with 2-sided 95% CI. Stratification factor is the number of prior line of therapies at randomization.
[5] P-value is calculated from the 1-sided stratified log-rank test. Stratification factor is the number of prior lines of therapy at randomization.
[6] Based on Survival Distribution Function estimates from product-limit method.

Figure 27. Kaplan-Meier plot of OS (ITT)



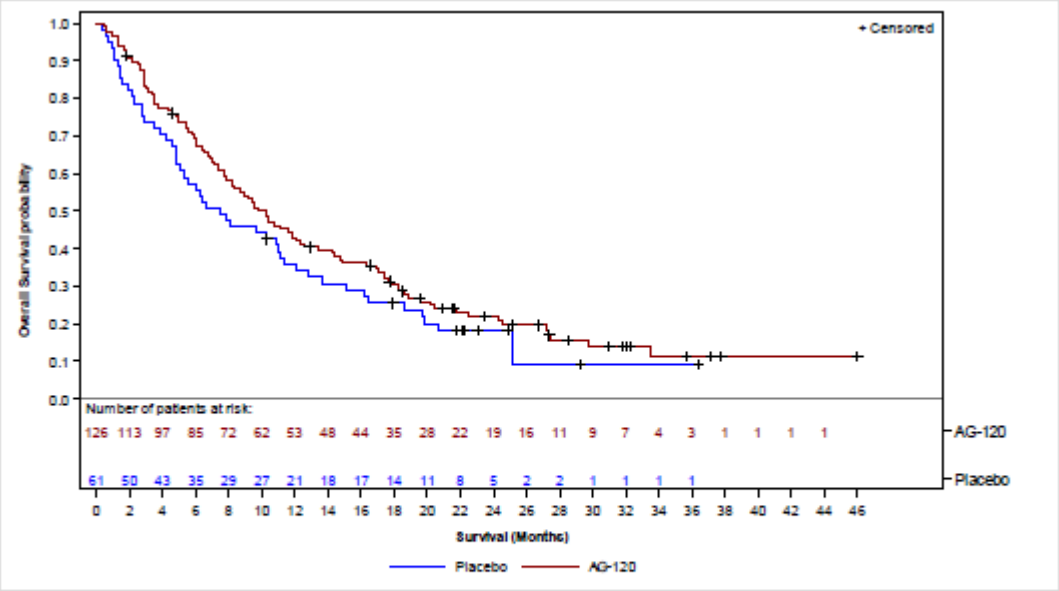
Final analysis of OS (DCO 21 June 2021)

Table 41. Summary of Overall Survival in Study AG120-C-005 (Intent-To-Treat Set as of 21 June 2021)

	Placebo (N=61)	Placebo (RPSFT) (N=61)	Ivosidenib (N=126)
Number of Subjects, n (%)			
Event	51 (83.6)	51 (83.6)	102 (81.0)
Censored[1]	10 (16.4)	10 (16.4)	24 (19.0)
Study Endpoint Met	7 (11.5)		20 (15.9)
Withdrawal of Consent	3 (4.9)		2 (1.6)
Lost to Follow-Up	0		1 (0.8)
Other*	0		1 (0.8)
Overall Survival[2] (months)			
25th Percentile[3] (95% CI)	2.9 (1.4, 4.8)	2.8 (1.4, 3.8)	5.0 (3.1, 6.0)
Median[3] (95% CI)	7.5 (4.8, 11.1)	5.1 (3.8, 7.7)	10.3 (7.8, 12.4)
75th Percentile[3] (95% CI)	18.6 (11.4, 25.2)	11.4 (7.8, 16.7)	20.4 (17.3, 27.2)
Hazard Ratio[4] (95% CI)	Ivosidenib vs. placebo (ITT): 0.82 (0.58, 1.14)		
Hazard Ratio[4](95% CI)	Ivosidenib vs. placebo (RPSFT) 0.52 (0.36, 0.74)		
p-value[5]	Ivosidenib vs. placebo (ITT): 0.118		
p-value[5]	Ivosidenib vs. placebo (RPSFT) <0.0001		
Kaplan-Meier Survival Rate[6] (%)			
3 months	73.8 (60.8, 83.0)	73.8 (60.8, 83.0)	83.3 (75.5, 88.8)
6 months	57.4 (44.0, 68.6)	47.5 (34.6, 59.4)	68.8 (59.8, 76.1)
9 months	45.9 (33.1, 57.8)	32.6 (21.3, 44.5)	54.2 (45.1, 62.5)
12 months	35.8 (24.0, 47.7)	22.1 (12.5, 33.3)	42.9 (34.1, 51.4)
18 months	25.6 (15.4, 37.1)	10.2 (2.8, 23.4)	30.4 (22.5, 38.7)
24 months	18.3 (9.6, 29.1)	NE	22.0 (15.0, 29.9)

Source: AG120-C-005, Table 66.5.3 and Table 66.5.4. Database lock date: 21 June 2021.
Abbreviations: CI = confidence interval; ITT = intent-to-treat; NE = not estimable; OS = overall survival; RPSFT = Rank Preserving Structural Failure Time.
* The patient on the ivosidenib arm was censored due to 'Other: occurrence of 150 OS events.
[1] Subjects without documentation of death at the time of the data cutoff date will be censored at the date the subject was last known to be alive, or the data cutoff date, whichever is earlier.
[2] Overall survival (OS) = (Date of Death – Randomization Date + 1) / 30.4375.
[3] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.

Figure 28. Kaplan-Meier Plot of Overall Survival (Intent-To-Treat Set as of 21 June 2021)



Source: AG120-C-005 Figure 66.5.3. Database lock date: 21 June 2021.
Abbreviations: ITT = Intent-to-Treat; OS = overall survival.
Notes: ITT Set is defined as all subjects who are randomized, with the treatment group designated according to the randomization. OS was calculated as (Date of Death – Randomization Date + 1) / 30.4375. Subjects without documentation of death at the time of the data cutoff date will be censored at the date the subject was last known to be alive, or the data cutoff date, whichever is earlier.

The final prespecified analysis of OS (data cutoff date 31 May 2020) favoured the ivosidenib arm despite the large proportion (70.5%) of subjects in the placebo arm who crossed over early in the study to receive ivosidenib following radiographic: HR= 0.79; 95% CI: 0.56-1.12, 1-sided p-value = 0.093 with a median OS of 10.3 months for ivosidenib and 7.5 months for placebo; The 12 months survival estimate was 43% in the ivosidenib arm and 36% in the placebo arm.

The prespecified adjusted OS analysis, rank preserving structural failure time (RPSFT), was used to account for 70.5% crossover, suggests a clinically meaningful improvement in OS: -HR= 0.49; 95% CI: 0.34-0.70, 1-sided p-value <0.0001.

An updated OS analysis was provided during the procedure, with OS data updated through the final database lock date of 21 June 2021. The updated analysis of OS is consistent with the final analysis of OS (data cutoff date: 31 May 2020): HR= 0.82; 95% CI: 0.58, 1.14; a 1-sided p-value = 0.093.

The median OS of 10.3 for ivosidenib and 7.5 months for placebo were unchanged. The survival rates at 6 and 12 months were also unchanged.

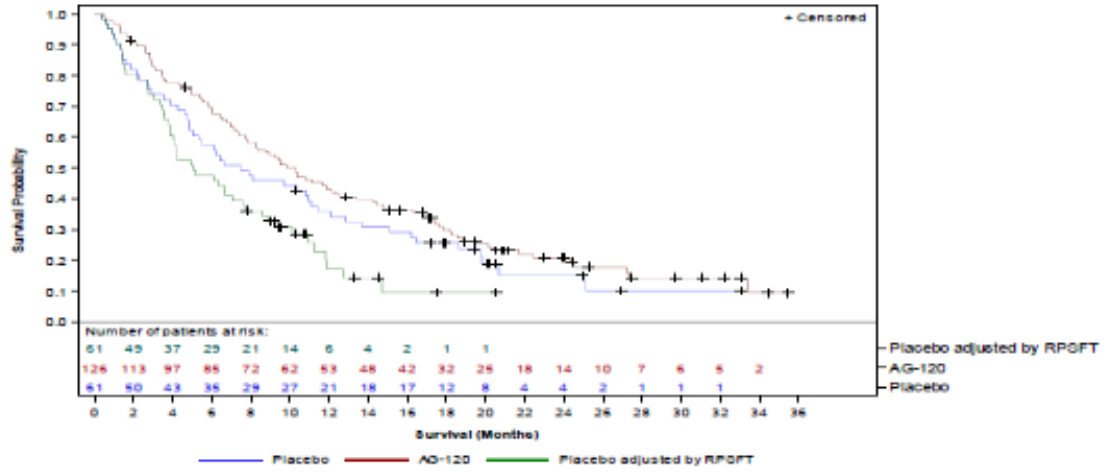
The Rank Preserving Structural Failure Time (RPSFT) model was implemented, as prespecified in the statistical analysis plan, to adjust for the effect of crossover from the placebo arm to ivosidenib arm, suggesting an improvement in OS for ivosidenib compared to placebo with an HR=0.52 (95% CI: 0.36, 0.77) and a 1-sided p-value <0.0001. The median OS for placebo after adjusting for the effect of crossover was 5.1 months.

Table 42. Summary of Overall Survival by Adjusting Crossover for Placebo via Rank Preserving Structural Failure Time in Study AG120-C-005 (Intent-to-Treat)

	Placebo (N=61)	Placebo (RPSFT) (N=61)	Ivosidenib (N=126)
Number of subjects, n (%)			
Events, n (%)	50 (82.0)	49 (80.3)	100 (79.4)
Censored[1], n (%)	11 (18.0)	12 (19.7)	26 (20.6)
Overall survival (months)[2]			
25th percentile (95% CI)[3]	2.9 (1.4, 4.8)	2.8 (1.4, 3.8)	5.0 (3.1, 6.0)
Median (95% CI)[3]	7.5 (4.8, 11.1)	5.1 (3.8, 7.6)	10.3 (7.8, 12.4)
75th percentile[3] (95% CI)[3]	18.6 (11.4, 25.1)	11.2 (7.7, 14.7)	20.1 (17.3, 27.2)
Hazard Ratio (95% CI)[4]	0.49 (0.34, 0.70)		
p-value[5]	<0.0001		
Kaplan-Meier survival rate[6] (%)			
3 months	73.8	73.8	83.3
6 months	57.4	47.5	68.8
9 months	45.9	32.6	54.2
12 months	35.8	17.1	42.9
18 months	25.6	9.5	29.9
24 months	15.0	NE	20.7

Source: Table 14.2.6.9.1. Data cutoff date: 31 May 2020.
Abbreviations: CI = confidence interval; ITT = intent-to-treat; NE = not estimable; OS = overall survival; RPSFT = rank preserving structural failure time.
Note: Percentages are based on the number of subjects in ITT Set in each column (denominator).
[1] Subjects without documentation of death at the time of the data cutoff date were censored at the date the subject was last known to be alive, or the data cutoff date, whichever was earlier.
[2] Overall survival (OS) = (Date of Death – Randomization Date + 1) / 30.4375.
[3] Quartile estimates from product-limit (Kaplan-Meier) method. CIs from Brookmeyer and Crowley method with log-log transformation.

Figure 29. Kaplan-Meier Plot of Overall Survival by Adjusting Crossover for Placebo via RPSFT (Study AG120-C-005 - ITT)



Source: Figure 14.2.10.1. Data cutoff date: 31 May 2020.
Abbreviations: RPSFT = Rank Preserving Structural Failure Time.
[1] OS = (Date of Death – Randomization Date + 1) / 30.4375.
[2] All subjects who were randomized, with the treatment arm designated according to the randomization. Subjects without documentation of death at the time of the data cutoff date were censored at the date the subject was last known to be alive, or the data cutoff date, whichever was earlier.

Health-Related Quality of Life (database lock date of 21 June 2021)

Tables and figures below present the MMRM analysis results, as of the final database lock date of 21 June 2021, from 3 subscales of the EORTC QLQ-C30 (Physical Functioning, Pain, and Appetite Loss) and 2 subscales of the QLQ-BIL21 (Eating and Pain).

Table 43. EORTC QLQ-C30: Change from Baseline for Prespecified Subscale Scores from Mixed Effect Modeling1 in Study AG120-C-005 (Intent-To-Treat Set as of 21 June 2021)

Visit	Placebo N=61	Ivosidenib N=126
Subscale: Physical Functioning (higher scores denote better functioning)		
Cycle 2, Day 1		
n	21	67
Least Square Mean (SE)	-13.4 (2.95)	-2.4 (1.75)
Difference of Least Square Mean (95% CI), ivosidenib vs. placebo		11.0 (4.23, 17.71)
p-value[2]		0.001
Cycle 3, Day 1		
n	9	50
Least Square Mean (SE)	-12.6 (3.86)	-0.3 (1.89)
Difference of Least Square Mean (95% CI)		12.3 (3.88, 20.76)
p-value[2]		0.004
Subscale: Pain (higher scores denote worse symptoms)		
Cycle 2, Day 1		
n	21	67
Least Square Mean (SE)	12.5 (4.37)	2.1 (2.49)
Difference of Least Square Mean (95% CI)		-10.4 (-20.27, -0.53)
p-value[2]		0.039
Cycle 3, Day 1		
n	9	50
Least Square Mean (SE)	-5.3 (5.99)	-1.3 (2.74)
Difference of Least Square Mean (95% CI), ivosidenib vs. placebo		4.0 (-8.92, 16.96)
p-value[2]		0.542
Subscale: Appetite Loss (higher scores denote worse symptoms)		
Cycle 2, Day 1		
N	21	67
Least Square Mean (SE)	4.3 (4.58)	7.9 (2.61)
Difference of Least Square Mean (95% CI), ivosidenib vs. placebo		3.6 (-6.76, 13.93)
p-value[2]		0.496

Visit	Placebo N=61	Ivosidenib N=126
Cycle 3, Day 1		
n	9	50
Least Square Mean (SE)	3.2 (6.45)	-0.5 (2.91)
Difference of Least Square Mean (95% CI)		-3.7 (-17.55, 10.22)
p-value[2]		0.604

Source: CSR AG120-C-005 Addendum 2, Table 14.2.7.9.1.
Abbreviations: CI = confidence interval; EORTC= European Organization for Research and Treatment of Cancer; QLQ-C30 = Quality of Life Questionnaire Core 30; SE = standard error.
[1] A mixed effect model with repeated measurements on the change from baseline scale score for each key domain was applied, with baseline score, treatment, visit, treatment-by-visit as fixed effects, and subject as random effect. Visit was treated as a categorical variable. Compound symmetry covariance matrix was used.
[2] 2-sided p-value is reported.

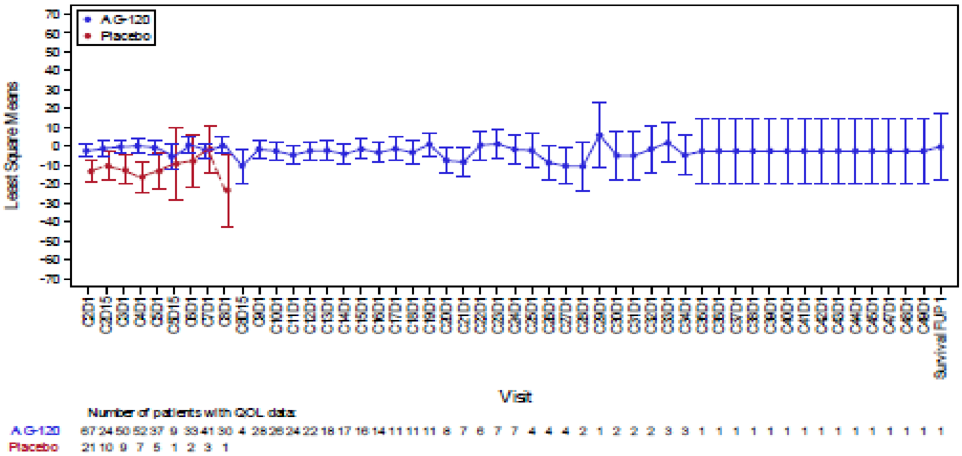
Table 44. EORTC QLQ-BIL21: Change from Baseline for Prespecified Subscale Scores from Mixed Effect Modeling1 Categorized by Visit in Study AG120-C-005 (Intent-To-Treat Set as of 21 June 2021)

Visit	Placebo N=61	Ivosidenib N=126
Subscale: Eating (higher scores denote worse symptoms)		
Cycle 2, Day 1		
n	20	65
Least Square Mean (SE)	3.6 (3.18)	4.3 (1.84)
Difference of Least Square Mean (95% CI), ivosidenib vs. placebo		0.7 (-6.57, 7.87)
p-value[2]		0.859
Cycle 3, Day 1		
n	9	48
Least Square Mean (SE)	4.1 (4.23)	-2.0 (2.02)
Difference of Least Square Mean (95% CI)		-6.1 (-15.33, 3.10)
p-value[2]		0.193
Subscale: Pain (higher scores denote worse symptoms)		
Cycle 2, Day 1		
n	20	65
Least Square Mean (SE)	10.1 (3.50)	5.0 (1.95)
Difference of Least Square Mean (95% CI), ivosidenib vs. placebo		-5.1 (-12.99, 2.80)
p-value[2]		0.205

Visit	Placebo N=61	Ivosidenib N=126
Cycle 3, Day 1		
n	9	48
Least Square Mean (SE)	-2.1 (4.72)	2.3 (2.17)
Difference of Least Square Mean (95% CI)		4.3 (-5.89, 14.56)
p-value[2]		0.406

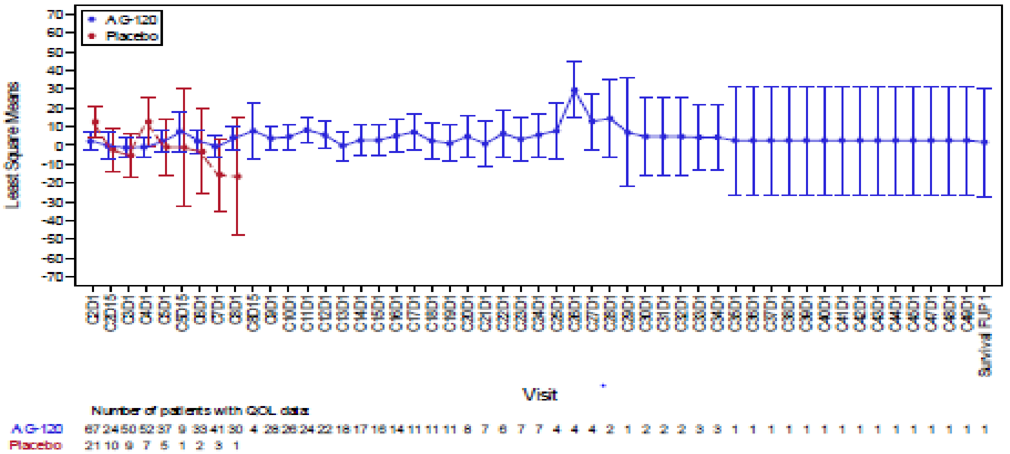
Source: CSR AG120-C-005 Addendum 2, Table 14.2.7.9.2.
Abbreviations: CI = confidence interval; EORTC = European Organization for Research and Treatment of Cancer; QLQ-BIL21 = Quality of Life Questionnaire Cholangiocarcinoma and Gallbladder Cancer; SE = standard error.
[1] A mixed effect model with repeated measurements on the change from baseline scale score for each key domain was applied, with baseline score, treatment, visit, treatment-by-visit as fixed effects, and subject as random effect. Visit was treated as a categorical variable. Compound symmetry covariance matrix was used.
[2] 2-sided p-value is reported.

Figure 30. EORTC QLQ-C30: Least Square Means of Change from Baseline for Physical Functioning Subscale Scores Over Time Before Crossover in Study AG120-C-005 (Subjects with Assessments from Intent-To-Treat Set as of 21 June 2021)



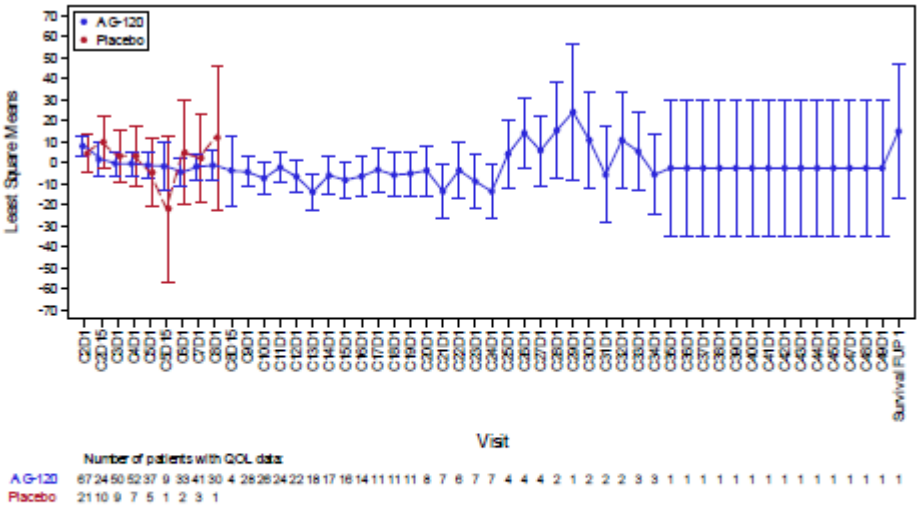
Source: CSR AG120-C-005 Addendum 2, Figure 14.2.7.
Abbreviations: C = cycle; D = day; EORTC = European Organization for Research and Treatment of Cancer; FUP = follow-up; QLQ-C30 = Quality of Life Questionnaire-Core 30.
Notes:
End of Treatment 1 and Safety Follow-up visit were not included in the plot.
95% confidence intervals are plotted.
Higher scores denote better functioning.

Figure 31. EORTC QLQ-C30: Least Square Means of Change from Baseline for Pain Subscale Scores Over Time Before Crossover in Study AG120-C-005 (Subjects with Assessments from Intent-To-Treat Set as of 21 June 2021)



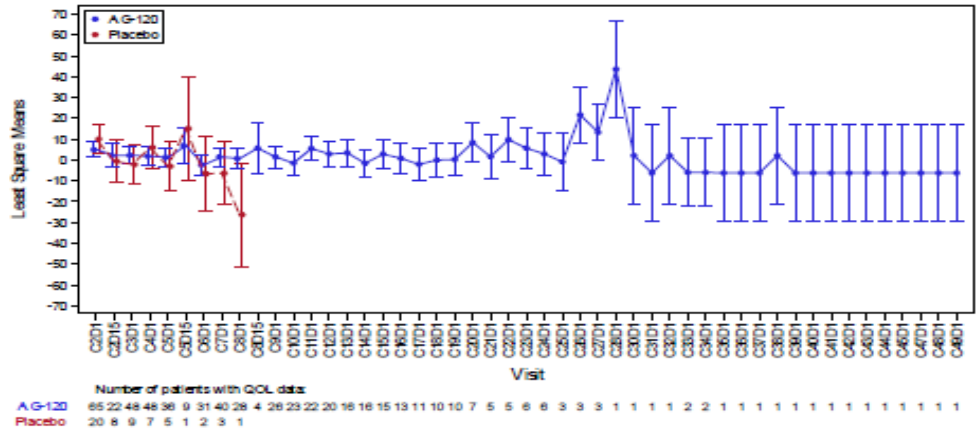
Source: CSR AG120-C-005 Addendum 2, Figure 14.2.7.
Abbreviations: C = cycle; D = day; EORTC = European Organization for Research and Treatment of Cancer; FUP = follow-up; QLQ-C30 = Quality of Life Questionnaire-Core 30.
Notes:
End of Treatment 1 and Safety Follow-up visit were not included in the plot.
95% confidence intervals are plotted.
Higher scores denote worse symptoms.

Figure 32. EORTC QLQ-C30: Least Square Means of Change from Baseline for Appetite Loss Subscale Scores Over Time Before Crossover in Study AG120-C-005 (Subjects with Assessments from Intent-To-Treat Set as of 21 June 2021)



Source: CSR AG120-C-005 Addendum 2, Figure 14.2.7.
Abbreviations: C = cycle; D = day; EORTC = European Organization for Research and Treatment of Cancer; FUP = follow-up; QLQ-C30 = Quality of Life Questionnaire-Core 30.
Notes:
End of Treatment 1 and Safety Follow-up visit were not included in the plot.
95% confidence intervals are plotted.
Higher scores denote worse symptoms.

Figure 33. EORTC QLQ-BIL21: Least Square Means of Change from Baseline for Pain Subscale Scores Over Time Before Crossover in Study AG120-C-005 (Subjects with Assessments from Intent-To-Treat Set as of 21 June 2021)



Source CSR AG120-C-005 Addendum 2, Figure 14.2.8.
Abbreviations: C = cycle; D = day; EORTC = European Organization for Research and Treatment of Cancer; QLQ-BIL21 = Quality of Life Questionnaire-Cholangiocarcinoma and Gallbladder Cancer.

- **Ancillary analyses**

Progression-Free Survival (DCO: 31 January 2019)

PFS by Independent Review Committee Assessment

Sensitivity Analyses

A sensitivity analysis using a stratified log-rank test and Cox regression based on all scans before crossover read by IRC, including the ones after local PD from subjects who were assigned to ivosidenib, was conducted.

Table 45. Summary of sensitivity analysis of PFS per IRC - before crossover (ITT)

	Placebo N=61	AG-120 N=124
Number of Subjects, n (%)		
Event	50 (82.0)	82 (66.1)
Progressive Disease	44 (72.1)	70 (56.5)
Death	6 (9.8)	12 (9.7)
Censored [1]	11 (18.0)	42 (33.9)
No documented progression or death before data cutoff date	6 (9.8)	28 (22.6)
New anticancer therapy started before documented progression or death	0	5 (4.0)
No post-baseline assessment and no death	3 (4.9)	5 (4.0)
Documented progression or death following a long gap between adequate disease status assessments	1 (1.6)	3 (2.4)
No documented progression or death before permanently discontinued from the study	1 (1.6)	1 (0.8)
Progression-Free Survival (months) [2]		
25th Percentile (95% CI) [3]	1.1 (0.8, 1.4)	1.4 (1.3, 1.5)
Median (95% CI)	1.4 (1.4, 1.6)	2.7 (1.9, 3.1)
75th Percentile (95% CI)	1.6 (1.5, 3.0)	7.0 (5.5, 13.5)
Hazard Ratio (95% CI) [4]		0.38 (0.26, 0.55)
P-value [5]		<0.001
Kaplan-Meier Survival Rate (%) [6]		
3 months	12.5	42.1
6 months	NE	30.7
9 months	NE	20.6
12 months	NE	20.6

This sensitivity analysis includes all scans read by IRC, including scans after local PD. Scans after crossover are not considered.
ITT: All subjects who are randomized, with the treatment group designated according to the randomization.
Percentages are based on the number of subjects in ITT Set in each column (denominator).
[1] Subjects with no baseline are censored at randomization date; new anticancer therapy started before progression/death are censored at the last adequate assessment prior to the new anticancer therapy; no post-baseline assessment and no death are censored at randomization date; no progression/death by data cutoff date are censored at the last adequate assessment date; progression/death following a long gap (>=2 consecutive scheduled assessments missing) are censored at date of last adequate assessment prior to the gap.
[2] Progression free survival (PFS) = (Earliest Date of PD or Death - Randomization Date + 1) / 30.4375.
[3] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[4] Hazard ratio is calculated from the stratified Cox regression model with placebo as the denominator, with two-sided 95% CI. Stratification factor is the number of prior line of therapies at randomization.
[5] P-value is calculated from the one-sided stratified log-rank test. Stratification factor is the number of prior line of therapies at randomization.
[6] Based on Survival Distribution Function estimates from product-limit method.

An unstratified log-rank test (1-sided) was used to compare PFS in the 2 treatment arms.

Table 46. Summary of sensitivity analysis of PFS per IRC from unstratified test - before crossover (ITT)

	Placebo N=61	AG-120 N=124
Number of Subjects, n (%)		
Event	50 (82.0)	76 (61.3)
Progressive Disease	44 (72.1)	64 (51.6)
Death	6 (9.8)	12 (9.7)
Censored [1]	11 (18.0)	48 (38.7)
No documented progression or death before data cutoff date	6 (9.8)	32 (25.8)
Documented progression or death following a long gap between adequate disease status assessments	1 (1.6)	5 (4.0)
New anticancer therapy started before documented progression or death	0	5 (4.0)
No post-baseline assessment and no death	3 (4.9)	5 (4.0)
No documented progression or death before permanently discontinued from the study	1 (1.6)	1 (0.8)

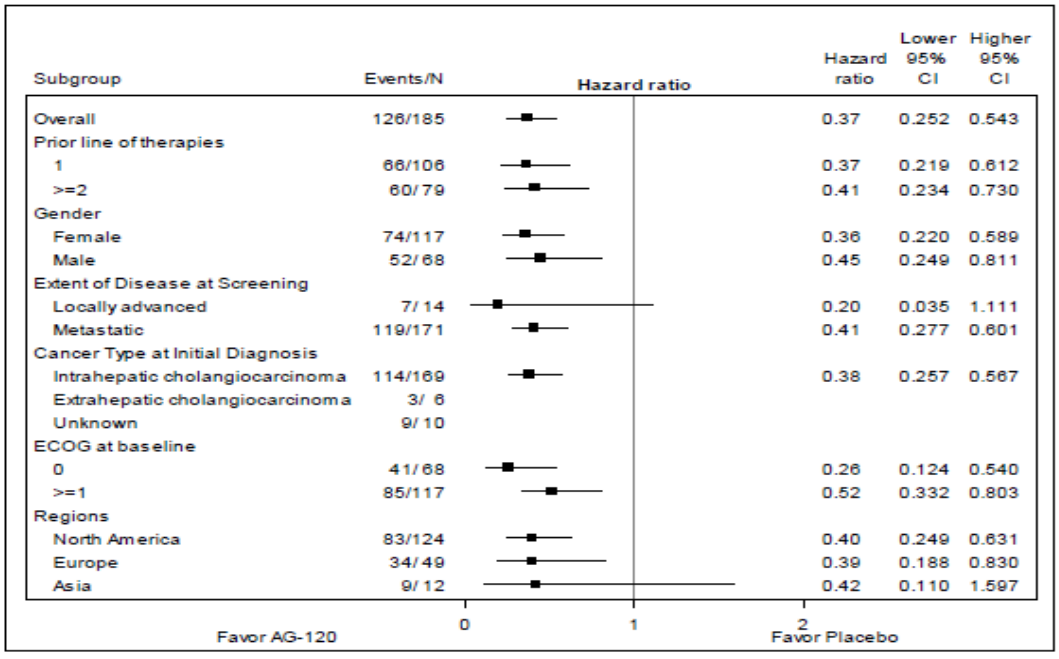
Progression-Free Survival (months) [2]		
25th Percentile (95% CI) [3]	1.1 (0.8, 1.4)	1.4 (1.3, 1.5)
Median (95% CI)	1.4 (1.4, 1.6)	2.7 (1.6, 4.2)
75th Percentile (95% CI)	1.6 (1.5, 3.0)	8.4 (5.6, NE)
Hazard Ratio (95% CI) [4]		0.39 (0.27, 0.57)
P-value [5]		<0.001
Kaplan-Meier Survival Rate (%) [6]		
3 months	12.5	44.8
6 months	NE	32.0
9 months	NE	21.9
12 months	NE	21.9

Scans after local PD per Investigator assessment are excluded from this analysis.
ITT: All subjects who are randomized, with the treatment group designated according to the randomization.
Percentages are based on the number of subjects in ITT Set in each column (denominator).
[1] Subjects with no baseline are censored at randomization date; new anticancer therapy started before progression/death are censored at the last adequate assessment prior to the new anticancer therapy; no post-baseline assessment and no death are censored at randomization date; no progression/death by data cutoff date are censored at the last adequate assessment date; progression/death following a long gap (>=2 consecutive scheduled assessments missing) are censored at date of last adequate assessment prior to the gap.
[2] Progression free survival (PFS) = (Earliest Date of PD or Death - Randomization Date + 1) / 30.4375.
[3] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[4] Hazard ratio is calculated from the unstratified Cox regression model with placebo as the denominator, with two-sided 95% CI.
[5] P-value is calculated from the one-sided unstratified log-rank test.
[6] Based on Survival Distribution Function estimates from product-limit method.

A stratified log-rank test and Cox regression analysis of PFS were conducted based on the PPS set. Results of this analysis provided further support for the PFS improvement observed in the primary analysis on the ITT population (HR: 0.37 [95% CI: 0.25-0.54]; P<0.001).

A subgroup analysis of PFS was conducted with unstratified log-rank test and unstratified Cox regression model.

Figure 34: Forest Plot of Progression-Free Survival by Subgroup per Independent Review Committee – Before Crossover (Intent-To-Treat Set)



Source: Figure 14.2.4.
Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group.
ITT: All subjects who are randomized, with the treatment group designated according to the randomization.
Scans after local PD per Investigator assessment are excluded from this analysis.
Hazard ratio for 'Overall' is calculated from the stratified Cox regression model with placebo as the denominator.
Hazard ratio for each subgroup is calculated from the unstratified Cox regression model. Two-sided 95% CI is displayed.

Exploratory Sensitivity Analysis of Progression-Free Survival without Early Progressors

Table 47. Sensitivity Analysis of Progression-Free Survival (PFS) without Early Progressors - Before Crossover (ITT)

	Placebo N=27	AG-120 N=81
Number of Subjects, n (%)		
Event	16 (59.3)	33 (40.7)
Progressive Disease	14 (51.9)	26 (32.1)
Death	2 (7.4)	7 (8.6)
Censored [1]	11 (40.7)	48 (59.3)
No documented progression or death before data cutoff date	6 (22.2)	32 (39.5)
Documented progression or death following a long gap between adequate disease status assessments	1 (3.7)	5 (6.2)
New anticancer therapy started before documented progression or death	0	5 (6.2)
No post-baseline assessment and no death	3 (11.1)	5 (6.2)
No documented progression or death before permanently discontinued from the study	1 (3.7)	1 (1.2)
Progression-Free Survival (months) [2]		
25th Percentile (95% CI) [3]	1.6 (1.6, 2.1)	2.9 (2.6, 4.3)
Median (95% CI)	2.7 (1.6, 3.1)	6.9 (4.2, 12.9)
75th Percentile (95% CI)	4.1 (2.7, NE)	13.5 (8.4, NE)
Hazard Ratio (95% CI) [4]		0.20 (0.10, 0.41)
P-value [5]		<0.001
Kaplan-Meier Survival Rate (%) [6]		
3 months	33.3	73.6
6 months	NE	52.5
9 months	NE	35.9
12 months	NE	35.9

Source: Table 14.2.1.13.
Note: Early progressors are defined as those subjects who have progressed within 47 days of the randomization date. This is the first post-baseline scan scheduled at 6 weeks + 5-day visit window. Scans after local PD per Investigator

Progression-Free Survival by Investigator Assessment

Table 48. Summary of sensitivity analysis of PFS per Investigator - before crossover (ITT)

	Placebo N=61	AG-120 N=124
Number of Subjects, n (%)		
Event	52 (85.2)	90 (72.6)
Progressive Disease	42 (68.9)	75 (60.5)
Death	10 (16.4)	15 (12.1)
Censored [1]	9 (14.8)	34 (27.4)
No documented progression or death before data cutoff date	4 (6.6)	24 (19.4)
No post-baseline assessment and no death	3 (4.9)	5 (4.0)
Documented progression or death following a long gap between adequate disease status assessments	1 (1.6)	3 (2.4)
New anticancer therapy started before documented progression or death	0	1 (0.8)
No documented progression or death before permanently discontinued from the study	1 (1.6)	1 (0.8)
Progression-Free Survival (months) [2]		
25th Percentile (95% CI) [3]	1.2 (0.9, 1.4)	1.4 (1.3, 1.5)
Median (95% CI)	1.4 (1.4, 2.5)	2.7 (1.6, 3.6)
75th Percentile (95% CI)	2.7 (2.5, 4.2)	7.0 (5.5, 10.9)
Hazard Ratio (95% CI) [4]		0.47 (0.33, 0.68)
P-value [5]		<0.001
Kaplan-Meier Survival Rate (%) [6]		
3 months	21.1	41.0
6 months	4.2	32.1
9 months	0	21.7
12 months	0	10.2

ITT: All subjects who are randomized, with the treatment group designated according to the randomization.
Percentages are based on the number of subjects in the ITT Set in each column (denominator).
[1] Subjects with no baseline are censored at randomization date; new anticancer therapy started before progression/death are censored at the last adequate assessment prior to the new anticancer therapy; no post-baseline assessment and no death are censored at randomization date; no progression/death by data cutoff date are censored at the last adequate assessment date; progression/death following a long gap (>=2 consecutive scheduled assessments missing) are censored at date of last adequate assessment prior to the gap.
[2] Progression free survival (PFS) = (Earliest Date of PD or Death - Randomization Date + 1) / 30.4375.
[3] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[4] Hazard ratio is calculated from the stratified Cox regression model with placebo as the denominator, with two-sided 95% CI. Stratification factor is the number of prior line of therapies at randomization.
[5] P-value is calculated from the one-sided stratified log-rank test. Stratification factor is the number of prior line of therapies at randomization.
[6] Based on Survival Distribution Function estimates from product-limit method.

Figure 35. Kaplan-Meier plot of PFS per investigator - Before Crossover (ITT)

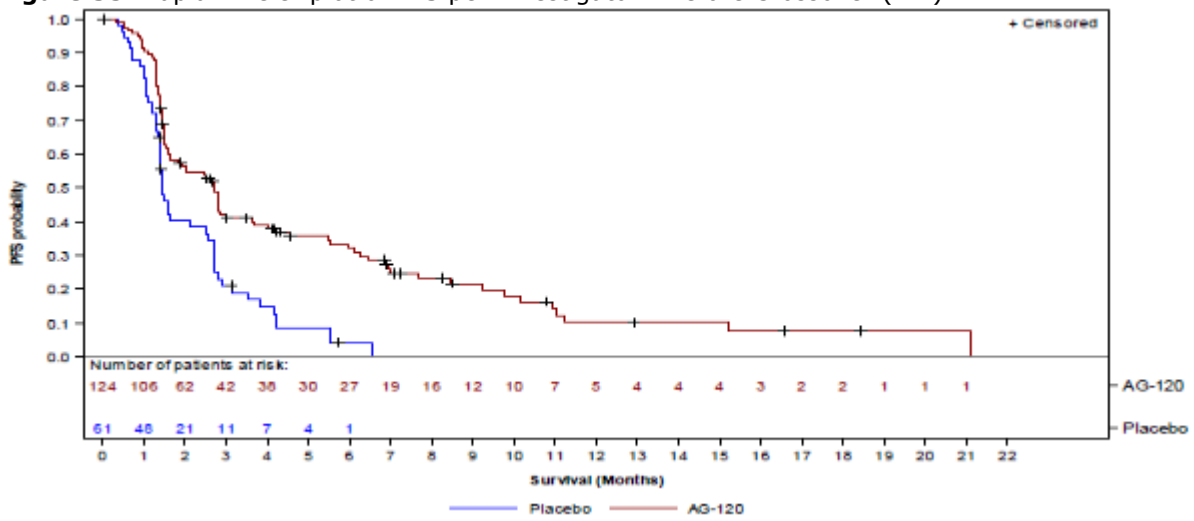
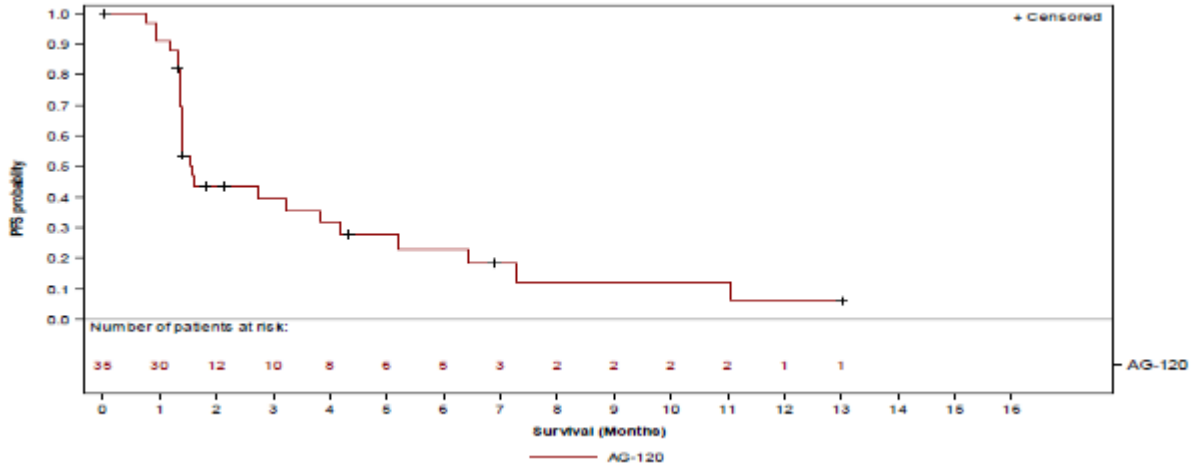


Figure 36. Kaplan-Meier plot of PFS per investigator - After Crossover (ITT)



Concordance between IRC and Investigator Assessments

An analysis of the number of PFS events (progressive disease or death) by IRC assessment and by investigator assessment showed a concordance for PFS of 77.3%.

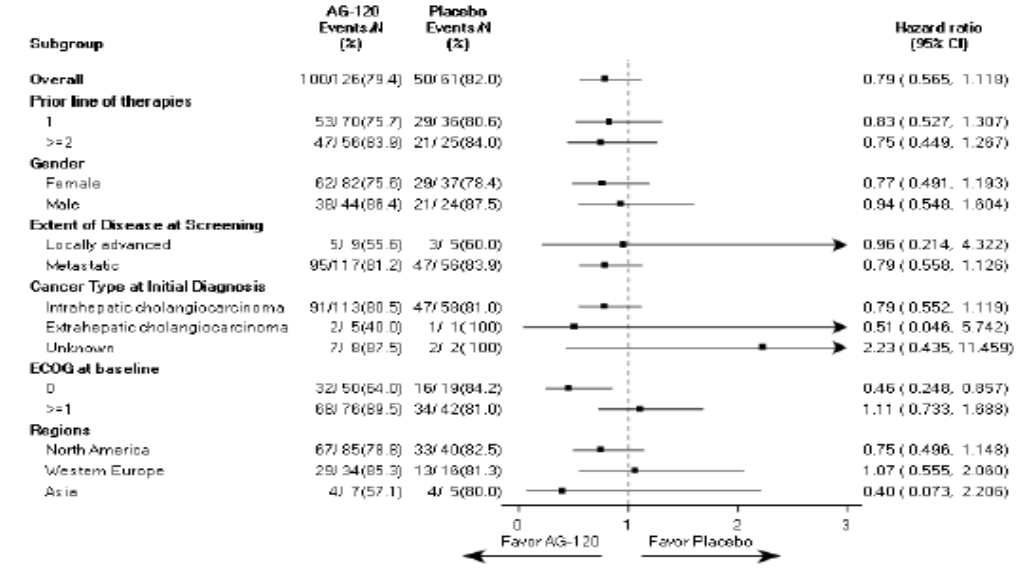
Table 49. Summary of concordance of PFS between IRC and investigator - before crossover (ITT)

		Total - IRC N=185	
		Events, n(%)	Censored, n(%)
Total - Investigator N=185	Events, n(%)	113 (61.1)	29 (15.7)
	Censored, n(%)	13 (7.0)	30 (16.2)

ITT: All subjects who are randomised, with the treatment group designated according to the randomization.
Scans after local PD per Investigator assessment are excluded from IRC reads in this analysis.
Percentages are based on the number of subjects in the ITT Set by treatment groups.
[1] PFS events presented are after applying the censoring rule, that is, subjects with no baseline and no death are censored at randomization date; no post-baseline assessment and no death are censored at randomization date; no progression/death by data cutoff date are censored at the last adequate assessment date; new anticancer therapy started before progression/death are censored at the last adequate assessment prior to the new anticancer therapy; progression/death following a long gap (>=2 consecutive scheduled assessments missing) are censored at date of last adequate assessment prior to the gap.

Subgroup Analyses of OS (DCO 31 May 2020)

Figure 37. Forest Plot of Overall Survival by Subgroup (Intent-To-Treat Set)



Source: Figure 14.2.6. Data cutoff date: 31 May 2020.
Abbreviations: CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; ITT = intent-to-treat.
ITT: All subjects who were randomized, with the treatment arm designated according to the randomization.
Hazard ratio for 'Overall' was calculated from the stratified Cox-regression model with placebo as the denominator.
Hazard ratio for each subgroup was calculated from the unstratified Cox-regression model. Two-sided 95% CI is displayed.
Prior line of therapies was based on the actual prior lines that subjects received per eligibility, reviewed by the Sponsor medical monitor.
If subjects had both local and metastatic status, it was considered as metastatic.
Perihilar was considered as extrahepatic.
Baseline was defined as the most recent measurement prior to the first dose of study drug. In case subjects were not dosed, the latest assessment was considered as baseline.

Table 50. Summary of Overall Survival by Age Subgroups (ITT)

	Age <65 years		Age ≥65 years	
	Placebo (N=36)	Ivosidenib (N=79)	Placebo (N=25)	Ivosidenib (N=47)
Number of subjects, n (%)				
Event	27 (75.0)	65 (82.3)	23 (92.0)	35 (74.5)
Censored[1], n (%)	9 (25.0)	14 (17.7)	2 (8.0)	12 (25.5)
Reason for censoring				
Ongoing	7 (19.4)	13 (16.5)	2 (8.0)	11 (23.4)
Withdrawal of Consent	2 (5.6)	1 (1.3)	0	1 (2.1)
Overall Survival (months)[2]				
25th Percentile (95% CI)[3]	3.1 (1.4, 5.3)	5.0 (2.9, 6.4)	2.9 (0.6, 4.8)	4.3 (1.8, 8.2)
Median (95% CI)	10.6 (4.8, 13.7)	9.8 (7.1, 14.3)	6.4 (3.8, 12.8)	10.4 (6.8, 16.9)
75th Percentile (95% CI)	19.7 (11.4, NE)	20.1 (16.3, 27.4)	15.1 (6.6, 25.1)	18.9 (14.8, NE)
Hazard Ratio (95% CI)[4]	0.93 (0.59, 1.47)		0.64 (0.38, 1.08)	
p-value[5]	0.384		0.046	
Kaplan-Meier Survival Rate (%)[6]				
3 months	75.0 (57.5, 86.1)	84.8 (74.8, 91.1)	72.0 (50.1, 85.5)	80.7 (66.2, 89.5)
6 months	58.3 (40.7, 72.4)	68.2 (56.7, 77.3)	56.0 (34.8, 72.7)	69.8 (54.4, 80.9)
9 months	52.8 (35.5, 67.4)	52.8 (41.2, 63.1)	36.0 (18.2, 54.2)	56.7 (41.3, 69.5)
12 months	38.2 (22.6, 53.7)	42.5 (31.4, 53.1)	32.0 (15.2, 50.2)	43.6 (29.1, 57.2)
18 months	32.4 (17.8, 47.8)	29.0 (19.3, 39.4)	16.0 (5.0, 32.5)	31.7 (18.7, 45.6)
24 months	16.4 (4.3, 35.6)	19.3 (11.0, 29.4)	10.7 (2.2, 27.0)	22.7 (11.2, 36.7)

Source: AG120-C-005, Table 14.2.6.9. Data cutoff date: 31 May 2020.
Abbreviations: CI = confidence interval; ITT = intent-to-treat; OS = overall survival.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 51. Summary of efficacy for trial AG120-C-005

Title: A phase 3 multicenter, randomized double blind placebo controlled study of AG-120 in previously treated subjects with nonresectable or metastatic cholangiocarcinoma with an IDH1 mutation.		
Study identifier	Study AG120-C-005	
Design	randomized double blind placebo controlled	
	Duration of main phase:	20 February 2017 to 31 May 2020 (ongoing)
Hypothesis	Superiority	

Title: A phase 3 multicenter, randomized double blind placebo controlled study of AG-120 in previously treated subjects with nonresectable or metastatic cholangiocarcinoma with an IDH1 mutation.			
Study identifier	Study AG120-C-005		
Treatments groups	Placebo		N=61 500 mg QD Until unacceptable toxicity or documented disease progression.
	Ivosidenib		N=124 500 mg QD Until unacceptable toxicity or documented disease progression.
Endpoints and definitions	Primary endpoint	PFS by IRC	First dose to progressive disease or death
	Key secondary endpoint	OS	First dose to death due to any cause
	Secondary endpoint	DOR	Time from the date of CR or PR until disease progression or death.
	Secondary endpoint	ORR	complete response (CR) or PR.
Database lock	DCO for PFS: 31 January 2019 DCO for OS: 31 May 2020		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Ivosidenib	Placebo
	Number of subjects	124	61
	Median PFS months (95% CI)	2.7 months (95% CI: 1.6, 4.2)	1.4 months (95% CI: 1.4, 1.6)
	Median OS months (95% CI)	10.3 months (95% CI: 7.8, 12.4)	7.5 months (95% CI: 4.8, 11.1)
	ORR (%) (95% CI)	2.4% (0.5, 6.9)	0% (0.0, 5.9)
Effect estimate per comparison	Primary endpoint PFS	Comparison groups	Ivosidenib/placebo
		HR	0.37
		95% CI	0.25, 0.54
		P-value 1-sided	<0.0001
	Secondary endpoint OS	Comparison groups	Ivosidenib/placebo
		HR	0.79
		95% CI	0.56, 1.12
		1 sided P-value	0.093
Notes			

Clinical studies in special populations

Table 52. Elderly patients (≥65 years) included in study AG120-C-005, Full analysis set

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trial - AG120-C-005 Study			
Placebo (N=61) n (%)/N	15 (24.6)/61	10 (16.4)/61	0 (0)/61
Ivosidenib (N=126) n (%)/N	33 (26.2)/126	14 (11.1)/126	0 (0)/126
After Crossover to Ivosidenib (N=43) n (%)/N	11 (25.6)/43	8 (18.6)/43	0 (0)/43
Total (N=187) n (%)/N	48 (25.7)/187	24 (12.8)/187	0(0)/187
Non Controlled Trial – AG120-C-002 Study (Cholangiocarcinoma N=73)			
<500mg QD (N=6) n (%)/N	5 (83.3)/6	0 (0)/6	0 (0)/6
500mg QD (N=62) n (%)/N	14 (22.6)/62	4 (6.5)/62	0 (0)/62
>500mg QD (N=5) n (%)/N	2 (40.0)/5	0 (0)/5	0 (0)/5
Total (N=73) n (%)/N	21 (28.8)/73	4 (5.5)/73	0 (0)/73
Total all Studies			
Total (N=260) n (%)/N	**69 (26.5)/260**	**28 (10.8)/260**	**0 (0)/260**

Source: Table 66.1.11, Listing 16.2.6.3. (AG120-C-005), Listing 16.2.6.3. (AG120-C-002)
Abbreviations: QD = once daily
*115 patients in AG120-C-005 (79 and 36 patients randomized to the ivosidenib and placebo arms, respectively) and 48 cholangiocarcinoma patients in AG120-C-002 were < 65-year-old.

2.10.5.3. In vitro biomarker test for patient selection for efficacy

Enrolment in study AG120-C-005 was restricted to subjects with documented IDH1 gene-mutated disease (from a fresh tumor biopsy or the most recent banked tumor tissue available) based on central laboratory testing (R132C/L/G/H/S mutation variants tested). The applicant submitted a bridging report for the investigational test used in the study with the validated test (Oncomine DxTM Target Test) to provide reassurance that the test used in the pivotal phase 3 was validated, and to provide proof that the patients had their IDH1m status correctly confirmed with the test.

This clinical validation study was conducted to determine concordance between the ODxT Test and both Orthogonal Assay and CTA using retrospective clinical samples provided from trial AG120-C-005 enrolled with the CTA.

The Oncomine Dx Target Test demonstrated agreement to the CTA method used to enrol subjects in the clinical trial and the clinical efficacy assessed as the improvement in PFS by IRC assessment was similar for patients determined by the Oncomine Dx Target Test compared to the CTA method.

Table 53. Percentage of agreement of the Oncomine Dx Target Test compared to the CTA method

Performance	ODxT vs. CTA			
	Agreed N	Total N	Percent	95% Exact CIs
PPA	174	175	99.4%	96.9%, 100.0%
NPA	166	166	100.0%	97.8%, 100.0%
OPA	340	341	99.7%	98.4%, 100.0%

PFS determined in the ODxT+ population (N=115 treatment vs. 57 placebo) showed a HR=0.37 with 95% CI of (0.25, 0.55), and is similar to the ODxT+ plus unevaluable population (N=123 treatment vs. 61 placebo; HR=0.38; 95% CI: 0.26, 0.55) and the overall CTA+ population (primary endpoint of the AG120-C-005 study) (N=124 treatment vs. 61 placebo; HR = 0.37; 95% CI: 0.25, 0.54). These results suggest that no efficacy bias was introduced into the ODxT+ population.

2.10.5.4. Analysis performed across trials (pooled analyses and meta-analysis)

Due to differences in the study design, primarily since only Study AG120-C-005 is placebo-controlled, pooling of efficacy data from Studies AG120-C-002 and AG120-C-005 was not considered appropriate for statistical analysis. Thus, efficacy data are presented separately for each study (refer to sections 3.3.4.2 and 3.3.4.7).

The demographics and baseline disease characteristics for subjects in AG120-C-005 were generally similar to those of subjects in AG120-C-002 who had cholangiocarcinoma and were treated with ivosidenib 500 mg.

An overview of the efficacy results from the 2 studies is presented in Table 58.

Table 54. Comparison of Efficacy of Ivosidenib: Study AG120-C-005 and Study AG120-C-002

Efficacy Analysis	AG120-C-005	AG120-C-002 (500 mg QD)
mPFS by Investigator Assessment	2.7 months (Table 10)	3.7 months (Table 11)
mOS	10.3 months (Table 12)	11.9 months (Table 13)
ORR by Investigator Assessment	PR: 3.2% (n=4) SD: 47.6% (n=59) PD: 35.5% (n=44) (Table 16)	PR: 4.8% (n=3) SD: 58.1% (n=36) PD: 33.9% (n=21) (Table 18)
TTR by Investigator Assessment (min, max)	4.17-13.47 (Section 3.2.4.1.2)	3.7-7.4 months (Section 3.2.4.2.1)
DOR by Investigator Assessment (min, max)	4.27-8.77 months (Section 3.2.5.1.2)	7.3-27.6 months (Section 3.2.5.2.1)

Abbreviations: DOR = duration of response; max = maximum; min = minimum; mOS = median overall survival; mPFS = median progression-free survival; ORR = objective response rate; PD = progressive disease; PR = partial response; QD = once daily; SD = stable disease; TTR = time to response.

2.10.5.5. Supportive study

AG120-C-002: A phase 1 multicenter, open-label dose escalation and expansion, safety, pharmacokinetic, pharmacodynamics, and clinical activity study of orally administered AG-120 in subjects with advanced solid tumors including glioma with an IDH1 mutation.

A total of 168 subjects received at least 1 dose of AG-120 across 8 dose cohorts. A total of 22 (13.1%) subjects remain on treatment and 146 (86.9%) subjects have discontinued treatment. Median treatment duration for these 168 subjects was 3.7 months (range: 0.4-50.5 months).

Table 55. Subject Enrollment and Disposition by Dose Level and Overall for All Disease Types Combined (FAS)

Disposition, n (%)	100 mg BID (N=4)	300 mg QD (N=9)	400 mg QD (N=5)	500 mg QD (N=130)	600 mg QD (N=5)	800 mg QD (N=6)	900 mg QD (N=4)	1,200 mg QD (N=5)	Overall (N=168)
Treatment Status									
On Treatment	0	0	0	17 (13.1)	0	1 (16.7)	2 (50)	2 (40)	22 (13.1)
Discontinued Treatment	4 (100)	9 (100)	5 (100)	113 (86.9)	5 (100)	5 (83.3)	2 (50)	3 (60)	146 (86.9)
Primary Reason for Treatment Discontinuation, n (%)									
Progression of Disease	3 (75)	8 (88.9)	3 (60)	97 (74.6)	5 (100)	3 (50)	2 (50)	2 (40)	123 (73.2)
Clinical Progression[1]	0	0	0	8 (6.2)	0	2 (33.3)	0	1 (20)	11 (6.5)
Adverse Event	0	1 (11.1)	1 (20)	1 (0.8)	0	0	0	0	3 (1.8)
Death	0	0	0	3 (2.3)	0	0	0	0	3 (1.8)
Withdrawal by Subject	1 (25)	0	1 (20)	1 (0.8)	0	0	0	0	3 (1.8)
Other	0	0	0	3 (2.3)	0	0	0	0	3 (1.8)

Source: Table 14.1.1.1. Data cutoff date: 16 January 2019.
Abbreviations: BID = twice daily; FAS = Full Analysis Set; PD = progressive disease; QD = once daily.
Note: Percentages were based on the number of subjects in the FAS in each column (denominator).
[1] Clinically deteriorating, but no radiographic PD.

A total of 73 cholangiocarcinoma subjects were treated (24 in escalation and 49 in expansion phases), of which 62 received the 500 mg dose level (13 in escalation and 49 in expansion phases). Three (4.8%) cholangiocarcinoma subjects at the 500 mg dose level remain on treatment as of 16 January 2019. The most common reason for discontinuation of study treatment across the 59 (95.2%) cholangiocarcinoma subjects at the 500 mg dose level were progression of disease in 50 (80.6%) subjects, clinical progression (defined as clinically deteriorating without evidence of radiographic PD) in 7 (11.3%) subjects, and withdrawal by subject and death in 1 (1.6%) subject each. The median treatment duration was 3.70 months (range: 0.6-36.9 months) for cholangiocarcinoma subjects at the 500 mg QD level, 37.1% of whom received ivosidenib for ≥ 6 months.

Table 56. Subject Enrollment and Disposition by 500 mg Dose Level and Overall for Cholangiocarcinoma – Study AG120-C-002 (Full Analysis Set)

Disposition, n (%)	500 mg QD (N=62)	Overall (N=73)
Treatment Status		
On Treatment	3 (4.8)	3 (4.1)
Discontinued Treatment	59 (95.2)	70 (95.9)
Primary Reason for Treatment Discontinuation, n (%)		
Progression of Disease	50 (80.6)	57 (78.1)
Clinical Progression[1]	7 (11.3)	9 (12.3)
Withdrawal by Subject	1 (1.6)	2 (2.7)
Adverse Event	0	1 (1.4)
Death	1 (1.6)	1 (1.4)

Source: CSR AG120-C-002 Addendum Table 14.1.1.1. Data cutoff date: 16 January 2019.
Abbreviations: PD = progressive disease.
[1] Clinical progression is defined as clinically deteriorating, without evidence of radiographic PD.

The analysis sets used for describing the efficacy and safety of AG-120 are presented in the table below.

Table 57. Analysis Datasets by Dose Level and Overall for All Disease Types Combined

Analysis Datasets, n (%)	100 mg BID (N=4)	300 mg QD (N=9)	400 mg QD (N=5)	500 mg QD (N=130)	600 mg QD (N=5)	800 mg QD (N=6)	900 mg QD (N=4)	1,200 mg QD (N=5)	Overall (N=168)
FAS[1]	4 (100)	9 (100)	5 (100)	130 (100)	5 (100)	6 (100)	4 (100)	5 (100)	168 (100)
SAS[2]	4 (100)	9 (100)	5 (100)	130 (100)	5 (100)	6 (100)	4 (100)	5 (100)	168 (100)
DDS[3]	4 (100)	9 (100)	5 (100)	22 (16.9)	5 (100)	6 (100)	4 (100)	5 (100)	60 (35.7)
PP[4]	3 (75)	9 (100)	5 (100)	123 (94.6)	5 (100)	5 (83.3)	4 (100)	4 (80)	158 (94)

Source: Table 14.1.1.1. Data cutoff date: 16 January 2019.
Abbreviations: BID = twice daily; CST = Clinical Study Team; DDS = Dose Determining Set; DLT = dose-limiting toxicity; FAS = Full Analysis Set; PP = Per Protocol Set; QD = once daily; SAS = Safety Analysis Set.
Note: Percentages were based on the number of subjects in the FAS in each column (denominator).
[1] FAS: all subjects who were enrolled and received at least 1 dose of study treatment, classified to dose assigned.
[2] SAS: all subjects who were enrolled and received at least 1 dose of study treatment, classified to the dose received.
[3] DDS: all subjects who either had a DLT in Cycle 1, or completed ≥75% of their planned Cycle 1 doses (21 of 28 days), and were considered by CST to have had sufficient safety data available to conclude that a DLT did not occur during Cycle 1.
[4] PP: subset of FAS subjects who were compliant with requirements of the study protocol and had no major protocol violations and for whom the baseline scan and at least 1 post baseline scan were available and evaluable.

Best Overall Response

A summary of disease response by dose group and overall for subjects with cholangiocarcinoma (dose escalation and expansion combined) in the FAS is presented below.

Table 58. Summary of Disease Response by Dose Group and Overall for Subjects with Cholangiocarcinoma (FAS)

Parameter	<500 mg (N=6)	500 mg (N=62)	>500 mg (N=5)	Overall (N=73)
Best Overall Response, n (%)[1]				
Complete Response	0	0	0	0
Partial Response	1 (16.7)	3 (4.8)	0	4 (5.5)
Stable Disease	3 (50)	36 (58.1)	2 (40)	41 (56.2)
Progressive Disease	1 (16.7)	21 (33.9)	2 (40)	24 (32.9)
Unknown	0	0	0	0
Other (NE or NA)	1 (16.7)	2 (3.2)	1 (20)	4 (5.5)
Overall Response Rate (CR or PR) [95% CI]	**1 (16.7) [0.4, 64.1]**	**3 (4.8) [1.0, 13.5]**	**0 [NE, NE]**	**4 (5.5) [1.5, 13.4]**

Source: Table 14.2.1.1A. Data cutoff date: 16 January 2019.
Abbreviations: CI = confidence interval; CR = complete response; FAS = Full Analysis Set; NA = not assessed; NE = not evaluable; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.
Note: FAS was defined as all subjects who were enrolled and received at least 1 dose of study treatment, classified to dose assigned. Percentages were based on the number of subjects in the FAS in each column (denominator). CR and PR required confirmation by a subsequent scan.
[1] Best overall response was determined using RECIST (version 1.1). As per RECIST, SD occurred within 42 days of the first dose was assigned as 'unknown.'

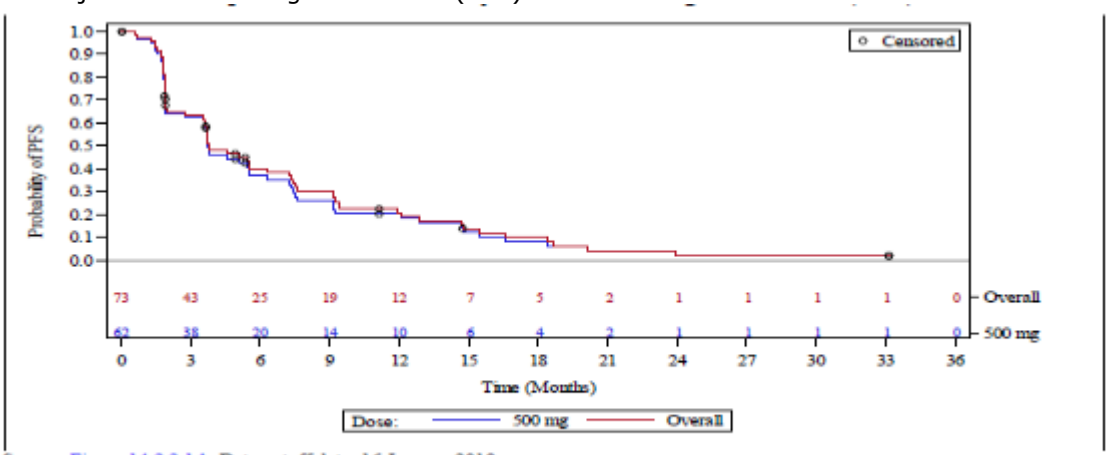
Progression-Free Survival

Table 59. Kaplan-Meier Analysis of Progression-Free Survival by Dose Group and Overall for Subjects with Cholangiocarcinoma (FAS)

Parameter	<500 mg (N=6)	500 mg (N=62)	>500 mg (N=5)	Overall (N=73)
Progression-Free Survival (months)[1]				
Number of Events (%)	4 (66.7)	56 (90.3)	3 (60)	63 (86.3)
Number of Censored (%)[2]	2 (33.3)	6 (9.7)	2 (40)	10 (13.7)
25th Percentile (median) [95% CI][3]	9.4 [1.9, 11.9]	1.9 [1.8, 1.9]	2 [1.9, 9.4]	1.9 [1.8, 2]
50th Percentile (median) [95% CI][3]	11.9 [1.9, 18.6]	3.7 [2.8, 5.6]	5.7 [1.9, NE]	3.8 [3.6, 7.3]
75th Percentile (median) [95% CI][3]	18.6 [1.9, 18.6]	9.2 [5.6, 14.7]	NE [1.9, NE]	9.4 [7.3, 14.8]
Min, Max	(0.0, 18.6)	(0.6, 33.1)	(0.0, 14.8)	(0.0, 33.1)
Kaplan-Meier Survival Rate (%)[4]				
3 Months	80	62.8	50	63.1
6 Months	80	36.9	50	40.2
9 Months	80	25.8	50	30.6
12 Months	26.7	20.3	25	20.8

Source: Table 14.2.2.1A. Data cutoff date 16 January 2019.
Abbreviations: CI = confidence interval; FAS = Full Analysis Set; Max = maximum; Min = minimum; NE = not evaluable; PFS = progression-free survival.
Note: FAS was defined as all subjects who were enrolled and received at least 1 dose of study treatment, classified to dose assigned. Percentages were based on the number of subjects in the FAS in each column (denominator).
[1] PFS = (earliest date of progressive disease or death, whichever was earlier – first dose start date +1)/30.4375.
[2] Subjects with no post-baseline assessment were censored at first dose date; no progression/death by data cutoff date were censored at the last adequate assessment date; alternative anticancer therapy started before progression/death were censored at the last adequate assessment prior to the alternative anticancer therapy; progression/death following a long gap (≥2 consecutive scheduled assessments missing) were censored at date of last adequate assessment prior to the gap.
[3] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals from Brookmeyer and Crowley method with log-log transformation.
[4] Based on Survival Distribution Function estimates from product-limit method.

Figure 38. Kaplan-Meier Curve of Progression-Free Survival in the 500 mg QD Dose Group and Overall for Subjects with Cholangiocarcinoma (FAS)



Source: Figure 14.2.2.1A. Data cutoff date: 16 January 2019.
Abbreviations: FAS = Full Analysis Set; PFS = progression-free survival; QD = once daily.
Note: FAS was defined as all subjects who were enrolled and received at least 1 dose of study treatment, classified to dose assigned.

Overall Survival

Table 60. Kaplan-Meier Analysis of Overall Survival by Dose Group and Overall for Subjects with Cholangiocarcinoma (FAS)

Parameter	<500 mg (N=6)	500 mg (N=62)	>500 mg (N=5)	Overall (N=73)
Overall Survival (months)[1]				
Number of Events, n (%)	4 (66.7)	43 (69.4)	4 (80)	51 (69.9)
Number of Censored[2], n (%)	2 (33.3)	19 (30.6)	1 (20)	22 (30.1)
25th Percentile (median) [95% CI][3]	9.5 [5.3, 13.8]	6.8 [4.3, 8.3]	7.3 [3.3, 14.3]	6.8 [4.3, 8.3]
50th Percentile (median) [95% CI][3]	13.8 [5.3, 29.3]	11.9 [8.3, 20.6]	12.8 [3.3, 29.1]	12.2 [9.2, 20]
75th Percentile (median) [95% CI][3]	21.6 [5.3, 29.3]	29.6 [20.6, NE]	21.7 [3.3, 29.1]	29.1 [20, 40.3]
Min, Max	(1.0, 29.3)	(1.0, 41.1)	(1.5, 29.1)	(1.0, 41.1)
Kaplan-Meier Survival Rate (%)[4]				
3 Months	100	93.5	100	94.4
6 Months	75	75	75	75.1
9 Months	75	62.4	75	64.1
12 Months	75	48.8	50	50.6

Source: Table 14.2.3.1. Data cutoff date: 16 January 2019.
Abbreviations: CI = confidence interval; FAS = Full Analysis Set; Max = maximum; Min = minimum; NE = not evaluable; OS = overall survival.
Note: FAS was defined as all subjects who were enrolled and received at least 1 dose of study treatment, classified to dose assigned. Percentages were based on the number of subjects in the FAS in each column (denominator).
[1] OS = months from the date of the first dose start date to the date of death due to any cause.
[2] Subjects without documentation of death at the time of the data cutoff for analysis were censored at the date the subject was last known to be alive, or the data cutoff date, whichever was earlier.
[3] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence Intervals from Brookmeyer and Crowley method with log-log transformation.
[4] Based on Survival Distribution Function estimates from product-limit method.

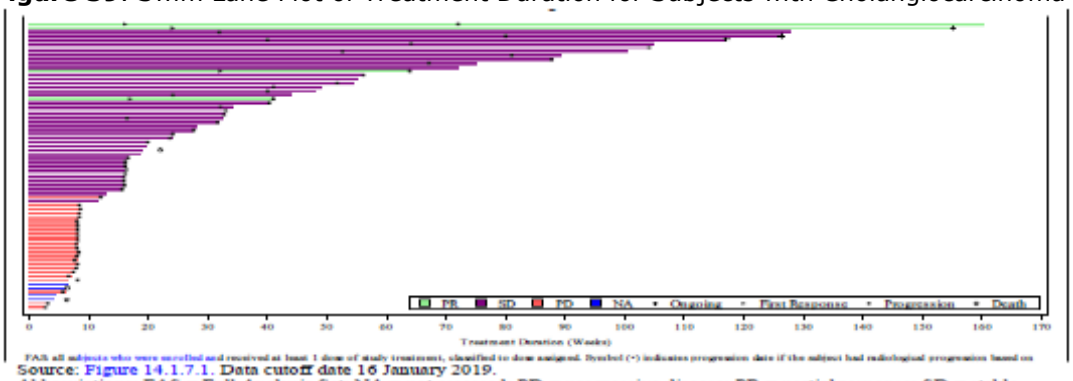
Table 61. Characteristics of Subjects with Cholangiocarcinoma Achieving a Partial Response with AG-120 Treatment

Subject Number	Prior Systemic Therapies[1]	Duration of Last Prior Systemic Therapy[2] (month)	AG-120 Treatment Period					
			Sum of Longest Target Lesion at Baseline[3] (mm)	Maximum Change in Target Lesion from Baseline[3] (%)	Duration of Treatment (month)	TTR[4] (month)	DOR[5] (month)	PFS[6] (month)
300 mg QD AG-120								
N207-003	Cisplatin, gemcitabine hydrochloride, gemcitabine hydrochloride, oxaliplatin, cisplatin, and docetaxel	1.1	99	-45.5	9.4	3.9	5.6	9.4
500 mg QD AG-120								
N202-502	Gemcitabine, cisplatin, fluorouracil, fluorouracil, folinic acid, irinotecan, paclitaxel, and investigational antineoplastic agents	2.1	161	-50.9	14.7	7.4	7.3	14.7
N204-503	Cyclophosphamide, docetaxel, doxorubicin, tamoxifen, letrozole, cisplatin, gemcitabine, carboplatin, and gemcitabine*	2.7	136	-89.7	36.9	3.7	12.9	16.6
N212-506[7]	Gemcitabine and cisplatin	1.4	117	-59	35.7	5.6	27.6	33.1

Source: Listing 16.2.6.9. Data cutoff date: 16 January 2019.
Abbreviations: BOR = best overall response; CR = complete response; DOR = duration of response; mR = minor response; PD = progressive disease; PFS = progression-free survival; PR = partial response; QD = once daily; TTR = time to response.
* Note: Subject N204-503 received letrozole, tamoxifen, cyclophosphamide, and docetaxel as systemic treatment for breast cancer (from 2003 to 2009) prior to being diagnosed with cholangiocarcinoma in February 2014.
[1] Medications were coded using the World Health Organization Drug Dictionary, March 2018.
[2] Duration of last prior systemic therapy was calculated based on Latest End Date-Earliest Start Date)+1/30.4375 in the last prior systemic therapy.
[3] Response Evaluation Criteria in Solid Tumors (version 1.1) was used.
[4] TTR = days from the first dose to the first documentation of response (PR or CR or mR).
[5] DOR (month) = (earliest date of death/PD – date of first mR/PR/CR+1)/30.4375 for subjects who had a BOR of mR, PR or CR).
[6] PFS (month) = (earliest date of PD or death – first dose start date +1)/30.4375.
[7] As of the data cutoff date, Subject N212-506 was continuing to receive treatment with AG-120.

As of the data cutoff date, the maximum treatment duration was approximately 37 months. Subjects tended to continue to receive treatment with AG-120 even if they did not achieve PR or CR.

Figure 39. Swim Lane Plot of Treatment Duration for Subjects with Cholangiocarcinoma (FAS)



Source: Figure 14.1.7.1. Data cutoff date 16 January 2019.
Abbreviations: FAS = Full Analysis Set; NA = not assessed; PD = progressive disease; PR = partial response; SD = stable disease.
Note: FAS was defined as all subjects who were enrolled and received at least 1 dose of study treatment, classified to dose assigned.
Symbol (•) indicates disease progression date if the subject had radiological progression based on the indication-specific response criteria.
Symbol (o) indicates subjects who did not have disease progression at the date of on-treatment death.

2.10.6. Discussion on clinical efficacy

In this procedure, ivosidenib applies for a marketing authorisation in the following revised indication: 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.

The basis of evidence for use of ivosidenib monotherapy in the cholangiocarcinoma indication comprises the efficacy and safety results from the pivotal phase 3 Study AG120-C-005 (ClarIDHy study) and the phase 1 Study AG120-C-002 (supporting study).

Design and conduct of clinical studies

Study AG120-C-005 was a phase 3, multicenter, randomized, double-blind, placebo-controlled efficacy and safety study of orally administered ivosidenib in subjects with advanced cholangiocarcinoma (non-resectable or metastatic).

Subjects were randomized in a 2:1 ratio to receive ivosidenib orally at a dose of 500 mg QD or placebo QD, respectively. Dosing evaluation and selection in the cholangiocarcinoma population were based on the phase 1 AG120-C-002 data. Randomization was stratified by number of prior therapies (1 vs. 2). Radiographic assessments (CT or MRI) were conducted at screening, every 6 weeks for the first 8 assessments (ie, through week 48), and every 8 weeks thereafter. A central review of collected images and response assessment per RECIST v1.1 was conducted by the IRC. No interim analysis was conducted. Scans after crossover were not read by the IRC. Upon progression, patients in the placebo arm were able to crossover to receive ivosidenib. OS analysis is thus diluted by cross-over and multiple subsequent lines of therapy. Patients in the ivosidenib arm may continue treatment with ivosidenib upon progression, provided the subject was clinically benefitting and there was no contraindication to continuing treatment beyond progression. All subjects continued to receive best supportive care according to institutional practice throughout the study, regardless of treatment arm.

In general, inclusion/exclusion criteria are acceptable to reflect the target population. The population enrolled in the study included pre-treated patients ≥18 years with an histopathological diagnosis of non-resectable or metastatic cholangiocarcinoma not eligible for curative resection, transplantation, or ablative therapies, harbouring documented IDH1 gene-mutated disease based on central laboratory testing and measurable disease as per RECIST v1.1. Mutations in IDH1 most commonly lead to alterations affecting arginine-132 (R132H or R132C/L/G/S), and this results in a gain-of-function, and catalyzing the reduction of α-KG to 2-HG. The final indication reflects the population studied in the pivotal trial which is the population with R132 IDH1 mutation given the lack of confirming data on the potential efficacy of ivosidenib in patients with non-R132 mutations.

The number of lines of prior chemotherapy was restricted to 1 or 2 to maintain a relatively homogeneous population. Taking into account the rare disease setting and the current lack of standard treatment beyond first and second line, mutated patients could potentially benefit from a targeted agent after more than 2 systemic treatments. Patients with brain metastasis were excluded from the pivotal trial because of the low survival expectancy. Survival expectancy of ≥ 3 months was an inclusion criteria in the study. Additionally, the available non-clinical data at the time of the pivotal study 005 suggested low brain penetrance. Nevertheless, recent preliminary clinical data suggested a potential activity in patients with low grade gliomas, implying that CCA patients with brain metastases could derive benefit from treatment, however there is no clinical evidence.

PFS by IRC was the primary endpoint supported by OS (key secondary endpoint), TTR, DOR, ORR and PROs as secondary endpoints. The choice of the design "placebo-controlled" and the primary endpoint "PFS" is not in line with the CHMP Scientific Advice (EMA/CHMP/SAWP/646225/2016). During the SA procedure the CHMP was of the opinion to "carefully consider an actively controlled design without cross-over and with OS as the primary endpoint. If, nevertheless, PFS is maintained as the preferred primary outcome, an active comparator, e.g. investigator's choice, is still recommended in order to avoid cross-over and enable robust data on OS". Even considering PFS as a primary endpoint accepted, the choice of placebo instead of active arm is not fully supported, more particularly in the second line setting.

Overall, survival would have been the preferred primary endpoint in this setting given the lack of effective treatment options, the poor prognosis of the condition, and the uncertainties on the actual toxicity of ivosidenib, as it is a first in class medicinal product, however, measures have been put in place in order to increase the reliability of the primary endpoint. The assessment is based on the IRC criteria in order to reduce bias, time between scheduled evaluations is relatively short (every 15 days during the first 3

cycles, and every month thereafter) in consideration of the high rate of disease progression of this condition to increase the accuracy of the evaluation of disease progression.

EORTC-QLQ-C30 and EORTC-QLQ-BIL21 for cholangiocarcinoma are validated QoL instruments and are considered appropriate. However, as no hypotheses are pre-specified, results were not reflected in the PL.

The sample size calculations can be accepted based on the information provided.

The randomisation process is deemed appropriate. The blinding procedures are considered adequate in the context of a trial allowing for crossover.

The primary set for efficacy analyses includes all randomised subjects, which is agreed.

The multiplicity adjustment procedure, as described by the applicant for PFS, OS and ORR, should ensure an adequate control of the study type I error. The boundaries for OS testing, based on gamma spending function (gamma=-8) have been provided during the procedure and confirmed, as expected, the non-significance of OS results at both timepoints.

The primary definition of PFS in the SAP was incomplete. Indeed, the full censoring scheme provided in the applicant's response included two additional situations leading to PFS censoring: 1) Crossover started before documented PD per IRC or death (placebo group only): censored at date of last adequate IRC assessment prior to the start of crossover, and 2) Investigator assessed PD before documented PD per IRC: censored at date of last adequate IRC assessment prior to or on investigator assessed PD. A rationale is provided for the censoring after local PD: subjects on ivosidenib were allowed to stay on treatment after PD whereas subjects no longer stayed on placebo after PD/unblinding, and IRC assessments were not continued after treatment discontinuation. Nevertheless, the sensitivity analyses including all scans after local PD as well as in the requested additional analysis based on the ITT principle both provided similar results in comparison with the primary PFS analysis, for this reason this issue was not pursued further.

Moreover, the censoring rules for the primary PFS analysis do not appear in line with the Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/27994/2008/Rev.1), as the censoring of PFS after the start of subsequent anticancer therapy, after a gap since the previous disease assessment, after crossover or after local PD does not follow the ITT principle. As requested, the applicant provided an additional analysis of PFS including all PFS events regardless of subsequent anticancer therapy, gap since previous assessment, crossover or local PD. The results were consistent with the primary PFS analysis results.

The statistical methods for tests that are part of the fixed sequence procedure (stratified log-rank tests for PFS and OS, Fisher's exact test for ORR) are deemed appropriate, as well as the primary set used for efficacy analyses (all randomised subjects).

A supplemental analysis has been performed for OS based on the Rank Preserving Structural Failure Time (RPSFT) method, in an effort to account for the confounding effect of crossover. It is a different estimand than for the primary analysis, as it follows a hypothetical strategy for the intercurrent event of crossover (the primary estimand had a treatment policy strategy) and could provide supportive contextualisation of the treatment effect. However, as pointed out in the EMA Q&A on adjustment for cross-over in oncology trials (EMA/845963/2018), it can be questioned whether this hypothetical treatment effect is a relevant one. An RPSFT analysis does not account for subsequent anticancer therapies that would have been started in the placebo group in the absence of crossover. Indeed, the only period contributing to the placebo data is before the patient crossing over, which is not expected to include much data (if any) after the start of subsequent anticancer therapies. In addition, despite the

assumption validity checks provided, some degree of bias cannot be excluded. This analysis, which was not part of the fixed sequence testing procedure, is described as a "sensitivity analysis".

The supportive study AG120-C-002 was a phase 1 multicenter, open-label dose escalation and expansion, safety, pharmacokinetic, pharmacodynamics, and clinical activity study of orally administered AG-120 in subjects with advanced solid tumors including glioma with an IDH1 mutation.

Efficacy data and additional analyses

Study AG120-C-005 started recruitment in February 2017, and enrollment was completed on 01 March 2019. The DCO date for the final analysis of the primary endpoint (PFS by IRC) and all other tumor-response endpoints was 31 January 2019 and the DCO date for the final analysis of the key secondary endpoint (OS) was 21 June 2021.

As of the DCO date of 31 May 2020, of the 231 subjects who underwent screening, 44 (19.0%) failed screening; the remaining 187 were enrolled: 126 subjects to ivosidenib and 61 subjects to placebo. 5 subjects did not receive treatment due to deterioration of their health status (2 subjects) and failure to continue to meet eligibility criteria (3 subjects). At the DCO date, 174 (95.6%) subjects had discontinued treatment, with 8 (4.4%) remaining on treatment. Among subjects who received ivosidenib or placebo, the most common reason for treatment discontinuation was progression of disease in 74.8% and 86.4%, respectively. Of the 61 subjects randomized to placebo, 43 (70.5%) subjects crossed over to receive ivosidenib upon progression. At the DCO date, 5 of these subjects (11.6%) remained on treatment and 38 (88.4%) subjects had discontinued treatment (progression of disease in 74.4% of subjects). As of the final database lock date, 21 June 2021, all subjects had discontinued study treatment and all subjects had discontinued the study.

A total of 19 of 185 (10.3%) subjects had at least 1 major protocol deviation during the study. Major deviations were overall equally distributed between both arms. These protocol deviations are not considered likely to affect the study results.

The demographics and baseline characteristics were overall similar between ivosidenib and placebo arms. Overall, most subjects were female (63.2%) and were 45 to <65 years old (54.1%), with a median age of 62 years (range: 33-83 years). Most subjects were White (56.8%), not Hispanic or Latino (66.5%) and had ECOG performance status of 0 (36.8%) or 1 (62.2%). Sixty-seven percent of the total subjects were enrolled in centers in North America (the US), 27% in centers in Western Europe (the UK, Spain, Italy, and France), and 6% in centers in Asia (South Korea). The high representation of non-Asiatic subjects is well noted. Most patients had intrahepatic cholangiocarcinoma (91%) at diagnosis and 92% had metastatic disease. 4.9% of subjects had evidence of underlying liver cirrhosis and 11.4% had a biliary stent. Approximately one-quarter (27%) of subjects had a history of ascites related to cholangiocarcinoma and 20 (10.8%) subjects had a history of pleural effusion related to cholangiocarcinoma within the past 3 months prior to screening. IDH1 mutated alleles were IDH1 R132C in 131 subjects (70.1%), R132L in 28 subjects (15.0%), R132G in 23 subjects (12.3%), R132S in 3 subjects (1.6%), and R132H in 2 subjects (1.1%)

Before entering the study, 52.9% of subjects had progressed after receiving 1 prior line of therapy and 47.1% of subjects had progressed after receiving 2 lines of therapy. Overall, the studied population is considered representative of the intended target population. Both demographics and baseline disease characteristics are evenly distributed among study groups, except for the ECOG PS, with a numerical minor imbalance favouring ivosidenib (PS of 1 in placebo vs ivosidenib at baseline were 67.1% and 59.6%, respectively).

The efficacy analysis was by intention to treat. 99.5% of the subjects randomised were included in the PPS for sensitivity analysis.

Study AG120-C-005 met its primary endpoint demonstrating a statistically significant improvement in PFS per IRC assessment for subjects randomized to ivosidenib versus subjects randomized to placebo (HR = 0.37; 95% CI: 0.25, 0.54; 1-sided p-value <0.0001). At the time of DCO of 31 January 2019, 61.3% (76/124) of the patients in the ivosidenib arm had progressed compared to 82.0% (50/61) of the patients in the placebo arm. The median of PFS showed a difference of 1.3 months favouring ivosidenib arm (2.7 months (95% CI: 1.6, 4.2) vs 1.4 months (95% CI: 1.4, 1.6)). Nevertheless, median PFS in both treatment arms were substantially lower than those anticipated for the sample size calculation (median PFS of 3 months in the placebo arm versus 6 months in the ivosidenib arm). Indeed, it is underlined that only 12.5% of patients in placebo had not progressed at 3 months follow up, and all patients had progressed before 6 months. The inclusion of patients progressing to two prior treatment lines of therapy might explain these results. Indeed, median PFS in placebo was 1.4 months (6 weeks), reflecting a population with a progressive and poor prognosis condition, what makes it difficult conducting any external comparisons given that most studies have tested patients in first- or second-line treatment, and considering also the heterogeneity of the CC population.

From the KM curves it is noted that the curves do not separate until 2 months, suggesting little benefit for rapidly progressing patients. Based on the available evidence, it is not possible to identify a population of previously treated patients with IDH1m CCA for whom an alternative treatment should be considered and that treatment decisions need to be individualised, mostly in patients with poor prognostic factors.

PFS results for sensitivity analyses (unstratified analysis, PPS set analysis and analysis based on all scans before crossover, including the ones after local PD) were in line with PFS by IRC assessment. Sensitivity analysis of PFS by investigator assessment showed similar results with a HR of 0.47 (95% CI: 0.33-0.68; 1-sided P<0.001)). The median PFS were of 2.7 months (95% CI: 1.6-3.6) vs 1.4 months (95% CI: 1.4-2.5) for ivosidenib vs placebo. The concordance rate between IRC and inv assessment was of 77.3%.

An exploratory analysis excluding early progressors (subjects who have had a PFS event within the first 47 days from randomization which corresponded to the first post-baseline imaging timepoint at 6 weeks by IRC), was conducted. The median PFS was 6.9 months among subjects in the ivosidenib arm versus 2.7 months among subjects in the placebo arm (HR 0.20; 95%CI (0.10, 0.41)).

Among subjects who were randomized to placebo and who crossed over to receive ivosidenib following initial progression (N= 43), the median PFS after crossover by inv was 1.6 months (95% CI: 1.4-3.8).

The ORR based on IRC was 2.4%, 95%CI (0.5, 6.9) in the ivosidenib arm (3 subjects with PR), compared with 0% (95%CI (0.0, 5.9)) in the placebo arm (p-value= 0.299). The maximum treatment duration was approximately 22.5 months in the ivosidenib arm and 6.9 months in the placebo arm. The TTR for each of these 3 subjects in the ivosidenib arm was 8.28, 2.79, and 5.52 months, respectively. The DOR was 2.79, 2.73, and 11.07 months, respectively.

Approximately half (50.8%) of subjects in the ivosidenib arm had a BOR of SD, while 17 (27.9%) subjects in the placebo arm had a BOR of SD before crossover. Approximately 40% of subjects with SD experienced a ≥10% reduction in the sum of target lesions that did not meet the criteria for a PR or CR. The median duration of SD was 6.5 months in subjects randomized to ivosidenib, 6.4 months in subjects after crossover to ivosidenib, and 3.0 months in the placebo arm before crossover.

The ORR as assessed by the inv was of 3.2% in the ivosidenib arm (4 subjects with PR), compared with 1.6% in the placebo arm (1 subject with PR). Approximately half (47.6%) of subjects in the ivosidenib arm had a BOR of SD by inv, while 23 (37.7%) subjects in the placebo arm had a BOR of SD before crossover. Furthermore, 15 of 35 (42.9%) subjects in the placebo arm who crossed over to receive ivosidenib following initial progression achieved an investigator-assessed BOR of SD.

As of the 21 June 2021 DCO date, the mOS was 10.3 months (95% CI: 7.8-12.4) for subjects randomized to ivosidenib versus 7.5 months (95% CI: 4.8-11.1) for subjects randomized to placebo (HR=0.82; 95% CI: 0.58-1.14; 1-sided p=0.093). These results were confounded by the crossover of placebo subjects (70.5%) to ivosidenib arm following radiographic progression. The Rank Preserving Structural Failure Time (RPSFT) analysis, adjusting for the effect of crossover, suggested an improvement in OS for ivosidenib compared to placebo with an HR=0.52 (95% CI: 0.36, 0.77). The median OS for placebo after adjusting for the effect of crossover was 5.1 months. These results are however of exploratory nature and bias could not be excluded.

Treatment effect for PFS and OS seems consistent across the pre-specified subgroups. The effect on OS appeared higher and significant in patients with ECOG PS score of 0 (HR=0.46, 95%CI: 0.25; 0.85) compared to ECOG score of 1 (HR=1.11, 95%CI: 0.733; 1.68). PFS and OS subgroup analyses based on age groups, race and mutation type were provided and overall, results were reassuring. When analysed by age subgroup, OS benefit was statistically and clinically significant in subjects ≥65 years of age, the HR was 0.64 (95% CI: 0.38-1.08; 1-sided p-value = 0.046) while the magnitude of OS gain is much reduced or inexistent in patients<65 years of age (HR=0.93, 95% CI: (0.59, 1.47) p=0.384). OS and PFS results by mutation type, are difficult to interpret given limited sample sizes within the subtypes R132G, R132L, R132S and R132H.

The analyses of HRQOL data are exploratory. Because of missing data, results are limited on change from baseline to Cycle 2, Day 1 and to Cycle 3, Day 1 for the EORTC QLQ-C30 and EORTC QLQ-BIL21 analyses.

As of the DCO date of 31 May 2020, the decline on the EORTC QLQ-C30 Physical Functioning and Emotional Functioning subscales in the placebo arm was clinically meaningful, while the ivosidenib arm showed no clinically meaningful worsening. At Cycle 2, Day 1 the difference of least square means for ivosidenib vs. placebo change from baseline in EORTC QLQ-C30 PF and EORTC QLQ-C30 EF subscale was of 11.0 (95% CI: 4.23, 17.73; 2-sided P=0.002) and of 13.8 (95% CI: 6.12, 21.40; 2-sided P<0.001), respectively. For the EORTC QLQ-BIL21 Anxiety subscale, the least square mean change from baseline at Cycle 2, Day 1 was -1.9 among ivosidenib subjects (SE: 2.23) compared with 9.8 for placebo subjects (SE: 3.84) (2-sided P=0.009).

Subjects in the placebo arm experienced more worsening of pain symptoms at Cycle 2, Day 1 based on the EORTC QLQ-C30 pain subscale with a difference of least square means for ivosidenib vs. placebo change from baseline of -10.4 (95% CI: -20.18, -0.52; 2-sided P=0.039).

The applicant has provided a quantitative benefit-risk assessment (BRA) of ivosidenib versus placebo using the pivotal phase 3 study as the source for efficacy and safety data. This quantitative BR assessment is based on the multi-criteria decision analysis (MCDA) framework. The MCDA framework, together with its elicitation process and analysis, can be helpful in transforming multiple aspects of the data into a loss or utility score. Several models were investigated to assess the robustness of the main analysis results, and the uncertainty in weight elicitation was explored by performing sensitivity analyses with Dirichlet SLoS, linear or product models. Nevertheless, the results of this quantitative BRA heavily relies on the choice of the analysis model as well as on the elicitation process. The elicited criteria and corresponding weights and values are dependent on a panel of 7 KOLs, and different panels may have provided different recommendations, leading to some natural variability in the selections and therefore require some careful considerations, and need to be taken into account when interpreting the analysis results.

Supportive data:

Overall, of the 73 subjects with cholangiocarcinoma (dose escalation and expansion combined) in the FAS of the study AG120-C-002, 3 (4.1%) subjects were continuing to receive treatment as of the cutoff date of 16 January 2019, with a median treatment duration of 3.68 months (range: 0.6-36.9 months). More than half (56.2%) of subjects experienced a BOR of SD. The ORR (CR or PR) was 5.5%, with 4 subjects achieved PR (1 subject who received 300 mg QD and 3 subjects who received 500 mg QD). The median PFS was 3.8 months (95% CI: 3.6-7.3). The 6-month and 12-month PFS rates were 40.2% and 20.8%, respectively. The median OS was 12.2 months (95% CI: 9.2-20). The TTR for the 4 subjects who achieved a PR were 3.9, 7.4, 3.7, and 5.6 months, respectively. The DOR for each of these subjects were 5.6, 7.3, 12.9, and 27.6 months, respectively. These results are supportive of the pivotal study results.

Indirect comparisons of available results (DCR, KM estimates of PFS and OS) with ivosidenib against those reported with mFolfox (ABC-06 study) and regorafenib (REACHIN study) for all comer advanced biliary tract cancers seem reassuring keeping in mind the limitations and uncertainties inherent to this comparison.

In overall, the provided results from study AG120-C-005 have shown efficacy for Tibsovo monotherapy in term of reduction in risk of disease progression or death and durability of stable disease in 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. Before taking Tibsovo, patients must have confirmation of an IDH1 R132 mutation using an appropriate diagnostic test.

The recommended dose is 500 mg ivosidenib (2 x 250 mg tablets) taken orally once daily. Treatment should be continued until disease progression or until treatment is no longer tolerated by the patient.

Efficacy results are reflected in the product information (see SmPC section 5.1).

Additional expert consultation

N/A

Assessment of paediatric data on clinical efficacy

The European Medicines Agency has waived the obligation to submit the results of studies with Tibsovo in all subsets of the paediatric population in the treatment of all conditions included in the category of malignant neoplasms (except central nervous system tumours, haematopoietic and lymphoid tissue neoplasms) and in the treatment of malignant neoplasms of the central nervous system (see SmPC section 4.2 for information on paediatric use).

2.10.7. Conclusions on the clinical efficacy

The provided results from study AG120-C-005 support the efficacy of Tibsovo monotherapy in 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.

2.10.8. Clinical safety

The applicant has considered that the safety profile of ivosidenib for the 2 requested indications (CCA and AML) is different and presented safety data separately for each indication.

2.10.8.1. Patient exposure

The safety profile of ivosidenib as monotherapy in the cholangiocarcinoma indication is issued from the pivotal study AG120-C-005, a phase 3 double-blind, placebo-controlled study in previously treated subjects with nonresectable or metastatic cholangiocarcinoma with an IDH1 mutation. After documented disease progression subjects randomized to the placebo arm were given the opportunity to cross over to the active treatment arm and receive ivosidenib. This study's data cutoff date for the original CSR was 31 January 2019 and for the CSR Addendum 1 was 31 May 2020. Subject enrollment was completed by the 31 May 2020 data cut off. The database lock for the analyses of data from Study AG120-C-005 included in CSR Addendum 2 was 21 June 2021.

This study includes safety data from:

- 166 subjects treated with ivosidenib 500 mg QD including exposed to ivosidenib 500 mg QD: 123 subjects exposed in ivosidenib arm and 43 subjects randomized to placebo who received ivosidenib post cross over,

- 59 subjects who received placebo.

In addition to this pivotal study, supporting safety data are provided for ivosidenib monotherapy at the same posology (500 mg QD) from the subpopulation of patients with cholangiocarcinoma (N=62 exposed to ivosidenib) in the open label multicenter, dose-escalation and expansion, Phase 1 Study AG120-C-002. This study also includes N=68 subjects with glioma, chondrosarcoma, or other solid tumors. The study's data cutoff date for the original CSR was 12 May 2017; for the CSR addendum and for this MAA it was 16 January 2019. Enrollment was completed before the data cutoff date for the original CSR (12 May 2017). The expansion phase of the study was still ongoing at date of 16 January 2021.

Additional safety data following exposure to ivosidenib monotherapy at the 500 mg QD dosing regimen are available from another ongoing Phase 1 Study AG120-881-C-001 (N=14) subjects with glioma. The enrollment was completed in April 2019.

The presentation of safety data includes a comparative analysis of safety from ivosidenib arm (N=123) versus placebo arm (N=59) from the pivotal study AG120-C-005 and analysis of safety from 2 Pooled population exposed at the same dosing regimen (ivosidenib 500 mg QD):

- the pooled cholangiocarcinoma population (N=228) of subjects from the AG120-C-005 and AG120-C-002 studies, to complete the safety profile seen in pivotal study AG120-C-005 alone and enable an assessment of the overall safety profile of ivosidenib 500 mg QD as treatment for subjects with cholangiocarcinoma

- the pooled population of subjects with solid tumors, including cholangiocarcinoma combining subjects from Studies AG120-C-005, AG120-C-002, and AG120-881-C-001 integrated as a larger pool for potential signal detection purposes (N=310)

Table 62. Overall Extent of Exposure – Cholangiocarcinoma Population (Safety Analysis Set)

	Ivosidenib 500 mg QD				Placebo
	AG120-C-005 Without Crossover N=123	AG120-C-005 Post-Crossover N=43	AG120-C-002 N=62	Overall[1] N=228	AG120-C-005 Pre-Crossover N=59
Treatment Duration (months)[2]					
n	123	43	62	228	59
Mean (SD)	6.7 (8.20)	5.6 (6.74)	7.9 (9.16)	6.8 (8.23)	2.2 (1.60)
Median	2.8	2.7	3.7	3.6	1.6
Min, Max	0.1, 45.1	0.3, 32.2	0.6, 36.9	0.1, 45.1	0.0[3], 6.9
Relative Dose Intensity (%)[4]					
n	123	43	62	228	59
Mean (SD)	95.7 (9.89)	96.1 (9.19)	96.2 (9.77)	95.9 (9.69)	98.4 (8.31)
Median	100.0	100.0	100.0	100.0	100.0
Min, Max	46.1, 100.5	47.2, 100.0	51.9, 100.0	46.1, 100.5	37.5, 101.9
Subjects by Treatment Duration, n (%)					
≥1 month	107 (87.0)	35 (81.4)	59 (95.2)	201 (88.2)	48 (81.4)
≥3 months	59 (48.0)	18 (41.9)	38 (61.3)	115 (50.4)	10 (16.9)
≥6 months	46 (37.4)	12 (27.9)	23 (37.1)	81 (35.5)	2 (3.4)
≥9 months	29 (23.6)	9 (20.9)	16 (25.8)	54 (23.7)	0
≥12 months	19 (15.4)	7 (16.3)	13 (21.0)	39 (17.1)	0

Source: ISS Table 18.3.1.1. Data cutoff date: 16 January 2019 (AG120-C-002); ; Database lock date: 21 June 2021 (AG120-C-005).
Abbreviations: Max = maximum; Min = minimum; QD = once daily; SD = standard deviation.
[1] Includes all cholangiocarcinoma subjects in Studies AG120-C-005 and AG120-C-002 who have been exposed to ivosidenib 500 mg QD.
[2] Treatment duration (months) = (date of last dose - date of first dose + 1) / 30.4375. For subjects who were still on treatment at data cutoff, the date of the last dose was the last dosing date or a pre-specified data cutoff date, whichever was earlier.
[3] Minimum treatment duration in Placebo AG120-C-005 Pre-Crossover arm is 0.03 months.
[4] Relative Dose Intensity (%) = [Actual Cumulative Dose] / [Planned Cumulative Dose] × 100%.

In subjects with solid tumors including cholangiocarcinoma who received ivosidenib 500 mg QD (N=310), subjects were exposed to ivosidenib up to 45.1 months (median 3.7 months), including 21.3% of subjects with ≥12 months of exposure. Median relative dose intensity of ivosidenib was 100%.

In Study AG120-C-005, the median exposure in ivosidenib arm was 2.8 months. This exposure was longer than the placebo arm (median exposure of 1.6 months). In ivosidenib arm, half of patients were exposed for more than 3 months and only 15.4% of subjects were exposed for more than 12 months.

Median ivosidenib exposure in subjects who crossed over from placebo to active treatment was similar to the randomized active treatment arm (2.7 months; N=43).

The overall cholangiocarcinoma population (N=228) allows to collect data from a slightly longer exposure to ivosidenib (median duration of 3.6 months and exposure ≥12 months in 17.1% of subjects).

In Study AG120-C-005 the main reason for treatment discontinuations was disease progression in both arms (79.7% in the ivosidenib arm and 86.4% in the placebo arm). This explains the short ivosidenib exposure which do not allow to collect long-term safety data.

The proportion of patients who discontinued treatment due to adverse events was small and similar in both arms (6.5% and 6.8%).

Similar results were observed in the cholangiocarcinoma population treated with ivosidenib 500 mg QD (N=228) with a proportion of treatment discontinuation of 98.7%, most of them related to progressive disease (83.8% of the subjects). The proportion of treatment discontinuations due to "Adverse Event" was almost similar (4.4% of the subjects).

2.10.8.2. Adverse events

In Study AG120-C-005, despite a slight difference of treatment duration between the arms of treatment among subjects randomized and exposed to ivosidenib (N=123) and placebo (N=59), the incidences of subjects with TEAEs were almost similar in both arms (97.6% vs 96.0%).

However, the incidence of Grade ≥3 TEAEs was higher in the ivosidenib arm when compared with the placebo arm (51.2% vs 37.3%).

The incidence of SAEs was also higher in the ivosidenib arm when compared with placebo (35.0% and 23.7%, respectively).

About one-third (30.1%) of ivosidenib-treated subjects experienced TEAEs leading to study treatment interruption, and the incidence was 18.6% in the placebo arm, with TEAEs leading to study treatment interruption assessed by the Investigator as treatment related more frequent in ivosidenib arm (4.1% vs 0%).

Frequencies of treatment discontinuations due to TEAEs were similar in the ivosidenib arm compared with placebo (7.3% and 8.5%, respectively), but incidence of related TEAEs leading to study treatment discontinuation was higher in the ivosidenib arm when compared with placebo (1.6% vs 0%).

Of note, there were 6 unrelated fatal TEAEs in subjects randomized and exposed to ivosidenib and 2 unrelated fatal TEAEs in subjects who crossed over to ivosidenib. None of the fatal TEAEs was assessed as treatment-related by the Investigator.

A similar trend is observed in the overall cholangiocarcinoma population (N=228) treated with 500 mg ivosidenib QD with 97.8% of subjects experienced a TEAE (any grade) and half (50.0%) of the subjects with Grade ≥3 TEAEs.

About one-third (31.1%) of subjects treated with ivosidenib experienced SAEs, including 1.3% of subjects with SAEs assessed by the investigator as related to study treatment.

Few subjects experienced TEAEs leading to death (4.4%), dose reduction (3.1%), or study treatment discontinuation (4.8%). No TEAEs leading to death were assessed by the Investigator as related to study treatment.

Treatment-emergent AEs leading to study treatment interruption were experienced by 28.5% of subjects, including 6.1% of subjects with AEs leading to study treatment interruption assessed by the Investigator as related to study treatment.

Table 63.Overall Summary of Treatment-emergent Adverse Events – Cholangiocarcinoma Population (Safety Analysis Set)

	Ivosidenib 500 mg QD, n (%)				Placebo, n (%)
	AG120-C-005 Without Crossover N=123	AG120-C-005 Post-Crossover N=43	AG120-C-002 N=62	Overall[1] N=228	AG120-C-005 Pre-Crossover N=59
Subjects with Any TEAE	120 (97.6)	41 (95.3)	62 (100.0)	223 (97.8)	57 (96.6)
Subjects with Grade ≥3 TEAE	63 (51.2)	26 (60.5)	25 (40.3)	114 (50.0)	22 (37.3)
Subjects with Related TEAE	81 (65.9)	23 (53.5)	40 (64.5)	144 (63.2)	23 (39.0)
Subjects with Grade ≥3 Related TEAE	8 (6.5)	3 (7.0)	3 (4.8)	14 (6.1)	0
Subjects with SAE	43 (35.0)	12 (27.9)	16 (25.8)	71 (31.1)	14 (23.7)
Subjects with Related SAE	3 (2.4)	0	0	3 (1.3)	0
Subjects with TEAE Leading to Study Treatment Reduction	5 (4.1)	0	2 (3.2)	7 (3.1)	0
Subjects with Related TEAE Leading to Study Treatment Reduction	5 (4.1)	0	2 (3.2)	7 (3.1)	0
Subjects with TEAE Leading to Study Treatment Interrupted	37 (30.1)	14 (32.6)	14 (22.6)	65 (28.5)	11 (18.6)
Subjects with Related TEAE Leading to Study Treatment Interrupted	5 (4.1)	5 (11.6)	4 (6.5)	14 (6.1)	0
Subjects with TEAE Leading to Study Treatment Discontinuation	9 (7.3)	2 (4.7)	0	11 (4.8)	5 (8.5)
Subjects with Related TEAE Leading to Study Treatment Discontinuation	2 (1.6)	0	0	2 (0.9)	0
Subjects with TEAE Leading to Death	6 (4.9)	2 (4.7)	2 (3.2)	10 (4.4)	0
Subjects with Related TEAE Leading to Death	0	0	0	0	0

Source: ISS Table 18.4.1. Data cutoff date: 16 January 2019 (AG120-C-002); Database lock date: 21 June 2021 (AG120-C-005).
Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; QD = once daily; SAE = serious adverse event; TEAE = treatment-related adverse event.
Note: Death was defined as any death that occurred between first dose and 28 days after last dose of study treatment.
Percentages were calculated based on N in each column.
A subject with multiple occurrences of a TEAE (PT using MedDRA version 23.1) was counted only once in the TEAE category.
Related refers to study treatment-related. A TEAE with relationship missing (unknown) was counted as Related.
Subject 114-1209 took only placebo after crossover, thus TEAEs after crossover were not summarized in the 'AG120-C-005 Post Crossover' column and were not included in this table.
[1] Includes all cholangiocarcinoma subjects in Studies AG120-C-005 and AG120-C-002 who had been exposed to ivosidenib 500 mg QD.

Common Adverse Events

Table 64. Summary of Treatment-Emergent Adverse Events that Occurred in ≥10% of Subjects by Preferred Term – Cholangiocarcinoma Population (Safety Analysis Set)

	Ivosidenib 500 mg QD, n (%)				Placebo, n (%)
Preferred Term	AG120-C-005 Without Crossover N=123	AG120-C-005 Post-Crossover N=43	AG120-C-002 N=62	Overall[1] N=228	AG120-C-005 Pre-Crossover N=59
Subjects with Any TEAE	**120 (97.6)**	**41 (95.3)**	**62 (100.0)**	**223 (97.8)**	**57 (96.6)**
Nausea	52 (42.3)	12 (27.9)	22 (35.5)	86 (37.7)	17 (28.8)
Fatigue	38 (30.9)	10 (23.3)	29 (46.8)	77 (33.8)	10 (16.9)
Diarrhoea	43 (35.0)	12 (27.9)	20 (32.3)	75 (32.9)	10 (16.9)
Abdominal pain	30 (24.4)	7 (16.3)	19 (30.6)	56 (24.6)	9 (15.3)
Decreased appetite	30 (24.4)	6 (14.0)	20 (32.3)	56 (24.6)	11 (18.6)
Vomiting	28 (22.8)	6 (14.0)	15 (24.2)	49 (21.5)	11 (18.6)
Cough	31 (25.2)	5 (11.6)	10 (16.1)	46 (20.2)	5 (8.5)
Ascites	28 (22.8)	5 (11.6)	10 (16.1)	43 (18.9)	9 (15.3)
Anaemia	23 (18.7)	8 (18.6)	9 (14.5)	40 (17.5)	3 (5.1)
Oedema peripheral	17 (13.8)	9 (20.9)	13 (21.0)	39 (17.1)	6 (10.2)
Constipation	20 (16.3)	5 (11.6)	8 (12.9)	33 (14.5)	11 (18.6)
Back pain	16 (13.0)	3 (7.0)	13 (21.0)	32 (14.0)	7 (11.9)
Arthralgia	14 (11.4)	5 (11.6)	12 (19.4)	31 (13.6)	6 (10.2)
Pyrexia	18 (14.6)	2 (4.7)	11 (17.7)	31 (13.6)	6 (10.2)
Aspartate aminotransferase increased	14 (11.4)	3 (7.0)	8 (12.9)	25 (11.0)	3 (5.1)
Asthenia	17 (13.8)	5 (11.6)	3 (4.8)	25 (11.0)	8 (13.6)
Abdominal distension	14 (11.4)	2 (4.7)	8 (12.9)	24 (10.5)	5 (8.5)
Dyspnoea	13 (10.6)	4 (9.3)	6 (9.7)	23 (10.1)	10 (16.9)
Insomnia	12 (9.8)	3 (7.0)	8 (12.9)	23 (10.1)	3 (5.1)
Electrocardiogram QT prolonged	12 (9.8)	1 (2.3)	8 (12.9)	21 (9.2)	2 (3.4)
Headache	16 (13.0)	2 (4.7)	3 (4.8)	21 (9.2)	4 (6.8)
Hypokalaemia	10 (8.1)	2 (4.7)	9 (14.5)	21 (9.2)	4 (6.8)
Blood alkaline phosphatase increased	11 (8.9)	4 (9.3)	5 (8.1)	20 (8.8)	6 (10.2)
Weight decreased	10 (8.1)	6 (14.0)	4 (6.5)	20 (8.8)	3 (5.1)
Blood bilirubin increased	13 (10.6)	3 (7.0)	3 (4.8)	19 (8.3)	4 (6.8)
Hyponatraemia	14 (11.4)	1 (2.3)	4 (6.5)	19 (8.3)	7 (11.9)
Hypomagnesaemia	9 (7.3)	1 (2.3)	7 (11.3)	17 (7.5)	3 (5.1)
Myalgia	6 (4.9)	0	7 (11.3)	13 (5.7)	0
Hypercalcaemia	3 (2.4)	2 (4.7)	5 (8.1)	10 (4.4)	7 (11.9)

Source: ISS Table 18.18.1 and ISS Table 18.4.1. Data cutoff date: 16 January 2019 (AG120-C-002); Database lock date: 21 June 2021 (AG120-C-005).
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; QD = once daily; TEAE = treatment-emergent adverse event.
Note: The summary includes TEAEs that occurred in ≥10% of subjects in any column at the PT level; "Subjects with Any TEAE" are summarized for all TEAEs. PTs are sorted in descending frequency of the Overall column. A subject with multiple occurrences of a TEAE under 1 treatment was counted only once in the PT for that treatment. PTs were coded from MedDRA version 23.1. Percentages were calculated based on N in each column.
[1] Includes all cholangiocarcinoma subjects in Studies AG120-C-005 and AG120-C-002 who had been exposed to ivosidenib 500 mg QD.

Among subjects randomized and exposed to ivosidenib (N=123) and placebo (N=59), AEs where there was a ≥5% difference in incidence in the ivosidenib arm compared with the placebo arm included: gastrointestinal TEAEs (Ascites, Nausea, Diarrhoea, Abdominal pain), Anaemia, Fatigue, Cough, Hypertension (8.9% vs 3.4%), Decreased appetite, Headache, Electrocardiogram QT prolongation (9.8% vs 3.4%), Hyperbilirubinaemia, Neuropathy peripheral (6.5% vs 0%), Rash (8.1% vs 0%), Hyperglycaemia (7.3% vs 1.7%), and laboratory abnormalities (Aspartate aminotransferase increased, Alanine aminotransferase increased, White blood cell count decreased).

Of note all the following TEAE were mild in severity (grade 1 or 2): cough, diarrhoea, neuropathy peripheral and headache.

A similar trend was retrieved in the overall cholangiocarcinoma population treated with ivosidenib 500 mg QD (N=228) with the most frequent TEAEs (≥20%) of Nausea, Fatigue, Diarrhoea, Decreased appetite, Abdominal Pain, Vomiting, and Cough. Of note TEAE "Electrocardiogram QT prolonged" which is an adverse event of special interest was reported in 9.2% of the subjects.

Regarding hyperglycaemia, a higher incidence was reported in ivosidenib arm compared to placebo in study AG120-C-005 (7.3% vs 1.7%), but Treatment-emergent AEs of Hyperglycaemia were confounded by baseline laboratory data, medical history, and intercurrent illness. Converging data were retrieved from literature data (Costa et al, 2006 and Pant et al, 2020) found a possible association of cholangiocarcinoma and impaired glucose homeostasis. However, as indicated in the Study AG120-C-002, it seems that Hyperglycemia TEAEs were also reported in patients with solid tumors others than cholangiocarcinoma treated with ivosidenib 500 mg QD (7.7%).

Regarding hypertension all grade, a higher incidence was reported in ivosidenib arm compared to placebo in study AG120-C-005 (8.9% vs 3.4%) while it appears that at screening the proportion of patients with a medical history of hypertension was lower in the ivosidenib arm than in the placebo arm (39.7% vs 52.5%). An additional analysis of treatment-emergent adverse events (TEAEs) of hypertension in Study AG120-C-005 was performed, which includes a comprehensive search of grouped terms including the following preferred terms (PTs): Hypertension, Blood pressure increased, Blood pressure ambulatory increased, Blood pressure diastolic increased, Blood pressure systolic increased, Diastolic hypertension, Mean arterial pressure increased, and Systolic hypertension. Based on the additional analysis of TEAEs of hypertension (grouped terms), the incidence of hypertension in the ivosidenib and placebo arms only included 1 additional TEAE of the PT Blood pressure increased in the ivosidenib arm, which was classified as Grade 2. Thus, the incidence of TEAEs of hypertension was 12 (9.8%) subjects in the ivosidenib arm vs. 2 (3.4%) subjects in the placebo arm. In Study AG120-C-005, the incidence of the PT Hypertension Grade ⩾3 TEAEs was similar in subjects in the ivosidenib (N=123) and in the placebo (N=59) arms (2 [1.6%] vs. 1 [1.7%], respectively). There was no Grade 4 or Grade 5 TEAE or any SAE of the PT Hypertension reported in either the ivosidenib or placebo arm. Based on the additional analysis of Grade ⩾3 TEAEs of hypertension (grouped terms) there was no change in the incidence of Grade ⩾3 TEAEs as compared to the incidence of the PT Hypertension.

A difference of incidence between ivisodenib and placebo arm was also reported for PT Myalgia (4.9% versus 0%). The incidence in the pool of cholangiocarcinoma population treated with ivosidenib 500 mg was 5.7%.. In Study AG120-C-005 (database lock 21June2021), a total of 8 TEAEs of PT Myalgia were reported in 6 subjects (4.9%). All 8 TEAEs were considered nonserious and low-grade with all 8 events reported as Grade 1. Three out of 8 events were considered as related to ivosidenib by the Investigator. The review of PT Myalgia demonstrates all subjects had multiple confounding factors to otherwise explain the events including underlying medical history and/or intercurrent illness. Of note in Study AG120-C-005, as clinical laboratory assessments did not include creatinine kinase, creatinine kinase levels are not available for analysis for these subjects who presented myalgia.

In Study AG120-C-005, TEAEs assessed by the Investigator as related to study treatment occurred at 65.9% in the ivosidenib arm vs 39.0% in the placebo arm.

Among subjects randomized and exposed to ivosidenib, the most common treatment-emergent AEs assessed by the Investigator as related to study treatment (≥5% of subjects) were: nausea (22.8%), fatigue (17.1%), diarrhoea (9.8%), vomiting (9.8%), decreased appetite (9.8%), Electrocardiogram QT prolonged (6.5%) and Headache (8.1%) and the TEAES with differences in incidence ≥5% between the ivosidenib arm compared to the placebo arm included Nausea, Fatigue, Diarrhoea and Headache.

In the overall cholangiocarcinoma population treated with ivosidenib 500 mg QD (N=228), TEAEs assessed by the Investigator as treatment-related that occurred in >10% of subjects included Nausea, Fatigue, Diarrhoea and Vomiting.

Common Grade ≥3 Adverse Events

Table 65. Summary of Grade ≥3 Treatment-Emergent Adverse Events that Occurred in ≥5% of Subjects by Preferred Term – Cholangiocarcinoma Population (Safety Analysis Set)

	Ivosidenib 500 mg QD, n (%)				Placebo, n (%)
Preferred Term	AG120-C-005 Without Crossover N=123	AG120-C-005 Post-Crossover N=43	AG120-C-002 N=62	Overall[1] N=228	AG120-C-005 Pre-Crossover N=59
Subjects with Grade ≥3 TEAE	**63 (51.2)**	**26 (60.5)**	**25 (40.3)**	**114 (50.0)**	**22 (37.3)**
Ascites	11 (8.9)	4 (9.3)	3 (4.8)	18 (7.9)	4 (6.8)
Anaemia	9 (7.3)	4 (9.3)	2 (3.2)	15 (6.6)	0
Blood bilirubin increased	7 (5.7)	3 (7.0)	1 (1.6)	11 (4.8)	1 (1.7)
Hyponatraemia	7 (5.7)	1 (2.3)	2 (3.2)	10 (4.4)	6 (10.2)
Hypophosphataemia	4 (3.3)	2 (4.7)	2 (3.2)	8 (3.5)	3 (5.1)
Hypertension	2 (1.6)	3 (7.0)	0	5 (2.2)	1 (1.7)
Blood alkaline phosphatase increased	3 (2.4)	0	1 (1.6)	4 (1.8)	3 (5.1)

Source: ISS Table 18.19.1 and ISS Table 18.4.1. Data cutoff date: 16 January 2019 (AG120-C-002); ; Database lock date: 21 June 2021 (AG120-C-005).
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; QD = once daily; TEAE = treatment-emergent adverse event.
Note: The table includes TEAEs that occurred in ≥5% of subjects in any column at the PT level; "Subjects with Any Grade ≥3 TEAE" are summarized for all TEAEs. PTs are sorted in descending frequency of the Overall column. A subject with multiple occurrences of an TEAE under 1 treatment was counted only once in the PT for that treatment. PTs were coded from MedDRA version 23.1. Percentages were calculated based on N in each column.
[1] Includes all cholangiocarcinoma subjects in Studies AG120-C-005 and AG120-C-002 who have been exposed to ivosidenib 500 mg QD.

Table 66. Summary of Treatment-Related Grade ≥3 Adverse Events by Preferred Term – Cholangiocarcinoma Population (Safety Analysis Set)

Preferred Term	Ivosidenib 500 mg QD, n (%)				Placebo, n (%)
	AG120-C-005 Without Crossover N=123	AG120-C-005 Post-Crossover N=43	AG120-C-002 N=62	Overall[1] N=228	AG120-C-005 Pre-Crossover N=59
Subjects with Any Grade ≥3 Related TEAE	**8 (6.5)**	**3 (7.0)**	**3 (4.8)**	**14 (6.1)**	**0**
Fatigue	2 (1.6)	0	1 (1.6)	3 (1.3)	0
Anaemia	2 (1.6)	1 (2.3)	0	3 (1.3)	0
Blood alkaline phosphatase increased	1 (0.8)	0	1 (1.6)	2 (0.9)	0
Hypophosphataemia	2 (1.6)	0	0	2 (0.9)	0
Abdominal pain	0	0	1 (1.6)	1 (0.4)	0
Stomatitis	0	1 (2.3)	0	1 (0.4)	0
Bile duct stenosis	0	1 (2.3)	0	1 (0.4)	0
Cholestasis	0	1 (2.3)	0	1 (0.4)	0
Hyperbilirubinaemia	1 (0.8)	0	0	1 (0.4)	0
Jaundice cholestatic	1 (0.8)	0	0	1 (0.4)	0
Aspartate aminotransferase increased	1 (0.8)	0	0	1 (0.4)	0
Blood bilirubin increased	1 (0.8)	0	0	1 (0.4)	0
Electrocardiogram QT prolonged	0	0	1 (1.6)	1 (0.4)	0
Lymphocyte count decreased	1 (0.8)	0	0	1 (0.4)	0
Neutrophil count decreased	1 (0.8)	0	0	1 (0.4)	0
White blood cell count decreased	1 (0.8)	0	0	1 (0.4)	0
Hyponatraemia	1 (0.8)	0	0	1 (0.4)	0
Pleural effusion	1 (0.8)	0	0	1 (0.4)	0
Rash pruritic	0	1 (2.3)	0	1 (0.4)	0

Source: ISS Table 18.9.1. Data cutoff date: 16 January 2019 (AG120-C-002); Database lock date: 21 June 2021 (AG120-C-005).
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; QD = once daily; TEAE = treatment-emergent adverse event.
Note: PTs are sorted in descending frequency of the Overall column. A subject with multiple occurrences of a TEAE under 1 treatment was counted only once in the PT for that treatment. PTs were coded from MedDRA version 23.1. Percentages were calculated based on N in each column.
Related refers to study treatment-related. A TEAE with relationship missing (unknown) was counted as related.
[1] Includes all cholangiocarcinoma subjects in Studies AG120-C-005 and AG120-C-002 who had been exposed to ivosidenib 500 mg QD.

In Study AG120-C-005, the commonly reported Grade ≥3 TEAEs in ivosidenib-treated subjects with an incidence ≥2% greater than placebo were: Anaemia, Ascites, Vomiting, Hyperbilirubinaemia, Fall, Jaundice cholestatic, Cholangitis, and laboratory abnormalities (Aspartate aminotransferase increased, Platelet count decreased, and Blood bilirubin increased).

Treatment related Grade ≥3 TEAEs that occurred in >1.0% of subjects in ivosidenib arm included Fatigue, Anaemia, and Hypophosphataemia.

In Study AG120-C-005, the incidence of TEAE anemia was higher in the ivosidisenib arm compared to the placebo arm (18.7% vs 5.1%) with more frequent grade ≥ 3 anemia in the ivosidenib arm (7.3% vs 0%) including 2 patients (1.6%) with related grade ≥ 3 anemia.

Moreover, it appears that despite almost similar incidence of platelet count decreased (5.7% vs 5.1%) the incidence of Grade ≥3 Platelet count decreased or Grade ≥3 thrombopenia was slightly higher in the ivosidenib arm compared with the placebo arm (2.4% [3 cases] vs 0% and 0.8% [1 case] vs 0%, respectively) and that Platelet count decreased and thrombocytopenia leading to treatment interruption occurred each in 1 subject (1.6%) in ivosidenib arm. Platelet count decreased has been listed as ADR in the product information.

In addition, it was reported a greater difference in incidence (≥10%) between the ivosidenib arm and placebo arm for White blood cell count decreased with higher incidence of Grade ≥3 neutrophil decreased in the ivosidenib arm with 2 cases (1.6% vs 0%) and that 1 subject in the ivosidenib arm presented with an ivosidenib related Neutrophil count decreased leading to treatment interruption.

Finally, regarding hematology laboratory abnormalities in Study AG120-C-005, it appears that the incidence of newly occurring or worsening hematology abnormalities was higher (between arm difference ≥5% for all grades or ≥2% for Grade ≥3) in subjects randomized and exposed to ivosidenib than placebo for the following parameters: lymphocytes (low), hemoglobin (low), platelets (low), and leukocytes (low). Recommendations on frequency of monitoring (blood laboratory testing) given the manageability of these ADRs was added to the SmPC Section 4.2: complete blood count should be assessed prior to the initiation of Tibsovo, at least once weekly for the first month of treatment, once every other week for the second month, and at each medical visit for the duration of therapy as clinically indicated.

In Study AG120-C-005, the incidence of rash is higher in the ivosidenib arm compared to the placebo arm (8.1% vs 0%). Almost all rash cases were grade 1 or 2, however, a case of rash grade >3 (maculopapular rash) which did not resolve following topical treatment and a case of "dermatitis exfoliative generalized" which resolved without corrective treatment were reported.

Regarding Treatment-Related Grade ≥3 Adverse Events in Study AG120-C-005 there were more treatment related Grade ≥3 TEAEs in the ivosidenib arm (6.5%) than in the placebo arm (0%). In the ivosidenib arm, each of the Grade ≥3 TEAEs assessed by the Investigator as related to ivosidenib occurred in ≤1.6% of subjects.

Treatment related Grade ≥3 TEAEs that occurred in >1.0% of subjects in ivosidenib arm included Fatigue, Anaemia, and Hypophosphataemia.

In Study AG120-C-005 the incidences of hypophosphatemia were similar in both arms (4.9% vs 5.1%) but Treatment related Grade ≥3 Hypophosphataemia TEAEs occurred in >1.6% (2) of subjects in ivosidenib arm. Hypophosphataemia in the 2 subjects was confounded by underlying index disease, including underlying metastases, medical history irritable bowel syndrome (IBS), ALP increases, hypercalcaemia, decreased appetite, and intercurrent illness including hypoalbuminemia, gastrointestinal symptoms (diarrhoea, constipation), electrolyte imbalances (hypokalaemia, hyperglycaemia), ascites, and sepsis.

In the overall population of subjects with cholangiocarcinoma each of the Grade ≥3 TEAEs assessed by the Investigator as related to ivosidenib occurred in <1.5% of subjects and Grade ≥3 TEAEs assessed by the Investigator as related to ivosidenib that occurred in >1.0% of subjects included Fatigue and Anaemia. It should be noted that in study Study AG120-C-002 1 subject with cholangiocarcinoma presented with a Treatment-Related Grade ≥3 Electrocardiogram QT prolonged.

2.10.8.3. Serious adverse event, deaths, other significant events

On-treatment death AE

Table 67. Summary of Adverse Events Leading to On-Treatment Deaths by Preferred Term – Cholangiocarcinoma Population (Safety Analysis Set)

Preferred Term	Ivosidenib 500 mg QD, n (%)				Placebo, n (%)
	AG120-C-005 Without Crossover N=123	AG120-C-005 Post-Crossover N=43	AG120-C-002 N=62	Overall[1] N=228	AG120-C-005 Pre-Crossover N=59
Subjects With Any TEAE Leading to On-Treatment Death	**6 (4.9)**	**2 (4.7)**	**2 (3.2)**	**10 (4.4)**	**0**
Intestinal obstruction	1 (0.8)	0	0	1 (0.4)	0
Intestinal pseudo-obstruction	0	1 (2.3)	0	1 (0.4)	0
Hepatic cirrhosis	0	1 (2.3)	0	1 (0.4)	0
Clostridium difficile infection	0	0	1 (1.6)	1 (0.4)	0
Pneumonia	1 (0.8)	0	0	1 (0.4)	0
Sepsis	2 (1.6)	0	0	2 (0.9)	0
Procedural haemorrhage	0	0	1 (1.6)	1 (0.4)	0
Hepatic encephalopathy	1 (0.8)	0	0	1 (0.4)	0
Pulmonary embolism	1 (0.8)	0	0	1 (0.4)	0

Source: ISS Table 18.16.1. Data cutoff date: 16 January 2019 (AG120-C-002); Database lock date: 21 June 2021 (AG120-C-005).
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; QD = once daily; TEAE = treatment-emergent adverse event.
Note: A subject with multiple occurrences of a TEAE under 1 treatment was counted only once in the PT for that treatment. PTs were coded from MedDRA version 23.1. Percentages were calculated based on N in each column.
[1] Includes all cholangiocarcinoma subjects in Studies AG120-C-005 and AG120-C-002 who had been exposed to ivosidenib 500 mg QD.

In Study AG120-C-005, 6 subjects (4.9%) experienced a TEAE leading to on-treatment death in the ivosidenib arm. None (0%) was reported in the placebo arm. Of note, the median time on treatment with ivosidenib was 2.8 months compared with 1.6 months with placebo.

Among the overall cholangiocarcinoma population who received ivosidenib 500 mg, the same trend is observed with on-treatment deaths in 32 (14.0%) subjects and progressive disease that was the most common reason for on-treatment death (9.2%), followed by TEAE (4.4%).

None of the TEAEs leading to on-treatment deaths among the overall cholangiocarcinoma population was assessed by the Investigator as treatment-related.

Serious adverse events

Table 68. Serious Adverse Events that Occurred in ≥2 Subjects by Preferred Term – Cholangiocarcinoma Population (Safety Analysis Set)

Preferred Term	Ivosidenib 500 mg QD, n (%)				Placebo, n (%)
	AG120-C-005 Without Crossover N=123	AG120-C-005 Post-Crossover N=43	AG120-C-002 N=62	Overall[1] N=228	AG120-C-005 Pre-Crossover N=59
Subjects with Any SAE	**43 (35.0)**	**12 (27.9)**	**16 (25.8)**	**71 (31.1)**	**14 (23.7)**
Ascites	3 (2.4)	1 (2.3)	2 (3.2)	6 (2.6)	2 (3.4)
Cholangitis	3 (2.4)	1 (2.3)	2 (3.2)	6 (2.6)	0
Pyrexia	2 (1.6)	1 (2.3)	3 (4.8)	6 (2.6)	0
Sepsis	4 (3.3)	0	1 (1.6)	5 (2.2)	2 (3.4)
Pleural effusion	2 (1.6)	0	2 (3.2)	4 (1.8)	0
Pneumonia	4 (3.3)	0	0	4 (1.8)	1 (1.7)
Hip fracture	2 (1.6)	1 (2.3)	1 (1.6)	4 (1.8)	0
Blood bilirubin increased	2 (1.6)	1 (2.3)	1 (1.6)	4 (1.8)	0
Vomiting	2 (1.6)	1 (2.3)	0	3 (1.3)	0
Jaundice cholestatic	3 (2.4)	0	0	3 (1.3)	0
Hyperbilirubinaemia	3 (2.4)	0	0	3 (1.3)	0
Escherichia bacteraemia	2 (1.6)	1 (2.3)	0	3 (1.3)	0
Anaemia	1 (0.8)	1 (2.3)	0	2 (0.9)	0
Biliary obstruction	1 (0.8)	1 (2.3)	0	2 (0.9)	0
Biliary tract infection	1 (0.8)	0	1 (1.6)	2 (0.9)	0
Gastrointestinal haemorrhage	1 (0.8)	1 (2.3)	0	2 (0.9)	0
Intestinal obstruction	2 (1.6)	0	0	2 (0.9)	0
Nausea	1 (0.8)	0	1 (1.6)	2 (0.9)	0
Upper gastrointestinal haemorrhage	1 (0.8)	1 (2.3)	0	2 (0.9)	0
Clostridium difficile infection	0	0	2 (3.2)	2 (0.9)	0
Hepatic encephalopathy	1 (0.8)	0	1 (1.6)	2 (0.9)	0
Dehydration	1 (0.8)	0	1 (1.6)	2 (0.9)	0
Dyspnoea	1 (0.8)	0	1 (1.6)	2 (0.9)	1 (1.7)
Hypercalcaemia	1 (0.8)	1 (2.3)	0	2 (0.9)	2 (3.4)
Back pain	0	1 (2.3)	0	1 (0.4)	2 (3.4)
Hyperkalaemia	1 (0.8)	0	0	1 (0.4)	2 (3.4)

Source: ISS Table 18.10.1. Data cutoff date: 16 January 2019 (AG120-C-002); Database lock date: 21 June 2021 (AG120-C-005).
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; QD = once daily
SAE = serious adverse event;.
Note: The table includes SAEs that occurred in ≥2 subjects in any column. PTs are sorted in descending frequency of the Overall column. A subject with multiple occurrences of an SAE under 1 treatment was counted only once in the PT for that treatment. PTs were coded from MedDRA version 23.1. Percentages were calculated based on N in each column.
[1] Includes all cholangiocarcinoma subjects in Studies AG120-C-005 and AG120-C-002 who had been exposed to ivosidenib 500 mg QD.

Table 69. Treatment-Related Serious Adverse Events by Preferred Term – Cholangiocarcinoma Population (Safety Analysis Set)

Preferred Term	Ivosidenib 500 mg QD, n (%)				Placebo, n (%)
	AG120-C-005 Without Crossover N=123	AG120-C-005 Post-Crossover N=43	AG120-C-002 N=62	Overall[1] N=228	AG120-C-005 Pre-Crossover N=59
Subjects With Any Related SAE	3 (2.4)	0	0	3 (1.3)	0
Hyperbilirubinaemia	1 (0.8)	0	0	1 (0.4)	0
Jaundice cholestatic	1 (0.8)	0	0	1 (0.4)	0
Electrocardiogram QT prolonged	1 (0.8)	0	0	1 (0.4)	0
Pleural effusion	1 (0.8)	0	0	1 (0.4)	0

Source: ISS Table 18.11.1. Data cutoff date: 16 January 2019 (AG120-C-002); Database lock date: 21 June 2021 (AG120-C-005).
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; QD = once daily; SAE = serious adverse event;.
Note: A subject with multiple occurrences of an SAE under 1 treatment was counted only once in the PT for that treatment.
PTs were coded from MedDRA version 23.1. Percentages were calculated based on N in each column.
Related refers to study treatment-related. An SAE with relationship missing (unknown) was counted as related.
[1] Includes all cholangiocarcinoma subjects in Studies AG120-C-005 and AG120-C-002 who had been exposed to ivosidenib 500 mg QD.

Among subjects randomized and exposed to ivosidenib, SAEs assessed by the Investigator as treatment-related occurred in 2.4% of subjects and included Hyperbilirubinaemia, Jaundice cholestatic, Electrocardiogram QT prolonged, and Pleural effusion (with each event in no more than 1 subject all in <1.0%).

In the overall cholangiocarcinoma population treated with ivosidenib 500 mg QD, serious adverse events assessed by the Investigator as treatment-related occurred in 1.3% of subjects and included Hyperbilirubinaemia, Jaundice cholestatic, Electrocardiogram QT prolonged, and Pleural effusion (all in <1.0%).

However, 4 SAE of Gastrointestinal haemorrhage or upper gastrointestinal haemorrhage were reported.

Among the non-GI haemorrhagic events with ivosidenib, the majority were low grade and subjects were able to maintain study treatment without any dose modifications. The applicant will continue to monitor events of haemorrhage as part of routine pharmacovigilance activities.

The infections reported in study AG120-C005 did not appear to be associated with other factor that could increase their likelihood, such us haematological/lab disorders, with very few infections leading to treatment discontinuations, which provides some reassurance.

Adverse Events of Special Interest

For the cholangiocarcinoma indication, Electrocardiogram QT prolonged was the only AESI;

Electrocardiogram QT prolonged is an important identified risk 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 program. Drug-drug interactions with moderate or strong CYP3A4 inhibitors and/or concomitant use of drugs known to prolong the QT interval is part of the risk associated with QT prolongation.

Table 70. Overall Summary of Adverse Events From SMQ (Broad) of Torsades de Pointes/QT Prolongation – Cholangiocarcinoma Population (Safety Analysis Set)

	Ivosidenib 500 mg QD, n (%)				Placebo, n (%)
	AG120-C-005 Without Crossover N=123	AG120-C-005 Post-Crossover N=43	AG120-C-002 N=62	Overall[1] N=228	AG120-C-005 Pre-Crossover N=59
Subjects with Any TEAE	12 (9.8)	1 (2.3)	8 (12.9)	21 (9.2)	2 (3.4)
Subjects with Grade ≥3 TEAE	2 (1.6)	1 (2.3)	2 (3.2)	5 (2.2)	0
Subjects with Related TEAE	8 (6.5)	1 (2.3)	4 (6.5)	13 (5.7)	1 (1.7)
Subjects with Grade ≥3 Related TEAE	0	0	1 (1.6)	1 (0.4)	0
Subjects with SAE	1 (0.8)	1 (2.3)	0	2 (0.9)	0
Subjects with Related SAE	1 (0.8)	0	0	1 (0.4)	0
Subjects with TEAE Leading to Study Treatment Reduction	4 (3.3)	0	0	4 (1.8)	0
Subjects with Related TEAE Leading to Study Treatment Reduction	4 (3.3)	0	0	4 (1.8)	0
Subjects with TEAE Leading to Study Treatment Interrupted	1 (0.8)	0	1 (1.6)	2 (0.9)	0
Subjects with Related TEAE Leading to Study Treatment Interrupted	0	0	0	0	0
Subjects with TEAE Leading to Study Treatment Discontinuation	0	0	0	0	0
Subjects with Related TEAE Leading to Study Treatment Discontinuation	0	0	0	0	0
Subjects with TEAE Leading to Death	0	0	0	0	0
Subjects with Related TEAE Leading to Death	0	0	0	0	0

Source: ISS Table 18.23.1.1. Data cutoff date: 16 January 2019 (AG120-C-002); Database lock date: 21 June 2021 (AG120-C-005).
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; QD = once daily; SMQ = Standardised MedDRA Query; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Note: QT prolongation TEAE equates to any TEAE that falls under the SMQ (Broad) of Torsades de Pointes/QT prolongation.
Death was defined as any death that occurred between first dose and 28 days after last dose of study medication.
Percentages were calculated based on N in each column.
A subject with multiple occurrences of a TEAE (PT using MedDRA version 23.1) was counted only once in the TEAE category.
Related refers to study treatment-related. A TEAE with relationship missing (unknown) was counted as Related.
[1] Includes all cholangiocarcinoma subjects in Studies AG120-C-005 and AG120-C-002 who had been exposed to ivosidenib 500 mg QD.

In Study AG120-C-005, among subjects randomized and exposed to ivosidenib (N=123) and placebo (N=59), 9.8% of subjects in the ivosidenib arm experienced QT prolongation (any Grade) compared with 3.4% of subjects in the placebo arm.

Among subjects with overall cholangiocarcinoma population with ivosidenib 500 mg QD (N=228), 9.2% of subjects had at least 1 TEAE within the SMQ of Torsades de Pointes/QT prolongation (any Grade); 5.7% of subjects had TEAEs assessed by the Investigator as ivosidenib-related. Grade ≥3 TEAEs, SAEs, TEAEs leading to ivosidenib treatment reduction, and TEAEs leading to ivosidenib treatment interruption occurred in ≤ 5 subjects. No subject had TEAEs leading to study treatment discontinuation or TEAEs leading to death. Treatment-related AEs reported within the SMQ of Torsades de Pointes/QT prolongation were Electrocardiogram QT prolonged and Syncope. There were no events of fatal arrhythmia or Torsades de Pointes.

In Study AG120-C-005, among subjects randomized and exposed to ivosidenib (N=123) and placebo (N=59), the median time to onset of QT prolongation (any Grade) within the SMQ was longer in the ivosidenib arm (28 days, range: 1 to 698 days) compared with the placebo arm (22 days; range: 15 to 29 days). In at least 75% of subjects with events in both the ivosidenib and placebo arms, time to first event onset was within the first 30 days. Electrocardiogram QT prolonged occurred as early as 1 day and up to 23 months after treatment initiation.

Among subjects in the overall cholangiocarcinoma population treated with ivosidenib 500 mg QD (N=228), the median time to the first event of any grade was 29 days (range: 1-698). In 16 (76.2%) of the 21 subjects treated with ivosidenib 500 mg QD who experienced these events, time to the first event was ≤30 days. The median time to the first event of Grade 2 or 3 for subjects who experienced a TEAE from the SMQ (N=14) was 22.5 days (range: 1-698). Of note, no Grade 4 or 5 TEAEs within the SMQ were observed.

Hepatotoxicity:

Events that could occur in the context of hepatotoxicity (e.g., ascites, peripheral oedema, AST increased, abdominal distension, blood bilirubin increased) were reported more frequently in ivosidenib-treated patients than in placebo (pre-cross over). Other potential events that could occur in the context of hepatotoxicity or worsening of the liver function (e.g., upper/rectal GI haemorrhages) were reported in ivosidenib-treated patients. Further, some non-clinical findings were observed in two different species.

Hepatic disorders with a ≥5% greater incidence in the ivosidenib compared with placebo included: ascites, aspartate aminotransferase increased, alanine aminotransferase, and hyperbilirubinaemia.

No subjects met Hy's Law criteria.

In the CGC population, which often presents/develops liver function abnormalities during the course of the disease, any potential to induce hepatotoxicity is considered as a matter of concern. Thus, the applicant agreed to set up a closely monitoring in PSUR of "Drug-related hepatic disorder" cases.

Additional Adverse Events of Clinical Importance

Guillain-Barré syndrome

No cases of Guillain-Barré syndrome were reported in clinical trials in subjects with solid tumors, including cholangiocarcinoma to date. However, 2 cases of Guillain–Barré syndrome were reported in clinical trials with ivosidenib administered at the same regimen in patients with hematologic malignancies. Neuropathy peripheral has been identified as an ADR of ivosidenib in patients treated for cholangiocarcinome based on studies AG120-C-005 and 002.

Cases of Guillain-Barré syndrome will be systematically presented and evaluated in PSURs.

Leukoencephalopathy, including Progressive Multifocal Leukoencephalopathy (PML) and Posterior Reversible Encephalopathy Syndrome (PRES)

No cases of PML or PRES were reported in any subject with solid tumors, including cholangiocarcinoma to date.

2.10.8.4. Laboratory findings

In Study AG120-C-005, hematology laboratory abnormalities were expected given the reported TEAE.

Hematology laboratory abnormalities reported in the ivosidenib arm (N=123) as Grade ≥3 TEAEs included anaemia (7.5 %), platelet count decreased (2.4%), neutrophil count decreased and white blood cell count decreased (each 1.6%), lymphocyte count decreased and thrombocytopenia (each 0.8%) among

subjects. The incidence of newly occurring or worsening hematology abnormalities was higher (between arm difference ≥5% for all grades or ≥2% for Grade ≥3) in subjects randomized and exposed to ivosidenib than placebo for the following parameters: lymphocytes (low), hemoglobin (low), platelets (low), and leukocytes (low).

In Study AG120-C-005, serum chemistry laboratory abnormalities reported as Grade ≥3 TEAEs among subjects in the ivosidenib arm (N=123) included blood bilirubin increased and hyponatraemia (each 5.7%); aspartate aminotransferase increased (4.9%); hypophosphataemia, hyperbilirubinaemia (each 3.3%); hyperkalaemia, blood alkaline phosphatase increased (2.4%); alanine aminotransferase increased, hypoalbuminaemia (each 1.6%); and gamma-glutamyltransferase increased, hypercalcaemia, hyperuricaemia, hypokalaemia, and transaminases increased (each 0.8%)

The incidence of newly occurring or worsening clinical chemistry abnormalities was higher (between arm difference ≥5% for all grades or ≥2% for Grade 3-4) in subjects in the ivosidenib arm (than in placebo for the following parameters high serum glucose, high ALP, high AST, high bilirubin, and high ALT.

In Study AG120-C-005, no unexpected safety finding was raised from vital signs. Pyrexia was the most common TEAE reported. It should be noted that the incidence of subjects with hypertension was higher in the ivosidenib arm (8.9% vs 3.4%).

Electrocardiograms

In Study AG120-C-005, among subjects in the ivosidenib arm (N=123), 8 (6.6%) had a QTcF (QT interval corrected for heart rate using Fridericia's formula) value >480 msec and 3 (2.5%) had a QTcF value >500 msec post baseline. No subject in the placebo arm had a QTcF value >480 msec before crossover; however, after crossover to ivosidenib, 1 (2.3%) subject had a QTcF value >480 to ≤500 msec. No subject in the placebo arm had a QTcF value >500 msec.

Among subjects with cholangiocarcinoma 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%.

Table 71. Summary of Notable ECG values During the On-treatment Period – Cholangiocarcinoma Population (Safety Analysis Set)

ECG Parameter Criteria	Ivosidenib 500 mg QD				Placebo
	AG120-C-005 without Crossover N=123 n/N1 (%)	AG120-C-005 Post-Crossover N=43 n/N1 (%)	AG120-C-002 N=62 n/N1 (%)	Overall[1] N=228 n/N1 (%)	AG120-C-005 N=59 n/N1 (%)
QT (msec)					
>30 increase from baseline	60/122 (49.2)	23/43 (53.5)	38/62 (61.3)	121/227 (53.3)	14/58 (24.1)
>60 increase from baseline	8/122 (6.6)	6/43 (14.0)	9/62 (14.5)	23/227 (10.1)	2/58 (3.4)
>450	31/122 (25.4)	8/43 (18.6)	12/62 (19.4)	51/227 (22.5)	7/58 (12.1)
>480	6/122 (4.9)	3/43 (7.0)	5/62 (8.1)	14/227 (6.2)	1/58 (1.7)
>500	2/122 (1.6)	1/43 (2.3)	2/62 (3.2)	5/227 (2.2)	0/58
QTcF (msec)					
>30 increase from baseline	53/122 (43.4)	18/43 (41.9)	33/62 (53.2)	104/227 (45.8)	10/58 (17.2)
>60 increase from baseline	6/122 (4.9)	1/43 (2.3)	6/62 (9.7)	13/227 (5.7)	0/58
>450	53/122 (43.4)	14/43 (32.6)	32/62 (51.6)	99/227 (43.6)	11/58 (19.0)
>480	8/122 (6.6)	1/43 (2.3)	5/62 (8.1)	14/227 (6.2)	0/58
>500	3/122 (2.5)	0/43	2/62 (3.2)	5/227 (2.2)	0/58

Source: ISS Table 18.38.1. Data cutoff date: 16 January 2019 (AG120-C-002); Database lock date: 21 June 2021 (AG120-C-005).
Abbreviations: ECG = electrocardiogram; QD = once daily; QTcF = QT interval corrected for heart rate using Fridericia's formula.
Note: The denominator used to calculate percentages is N1, the number of subjects in the safety analysis set within each treatment arm with at least 1 post-baseline assessment during the on-treatment period or (for changes from baseline only) both baseline and at least 1 post-baseline assessment during the on-treatment period. Baseline was defined as the last assessment before start of study treatment. Triplicate ECGs were collected in Study AG120-881-C-001 and certain visits in Study AG120-C-002. The classification of notable values was based on the average of the triplicate values at each scheduled assessment.
[1] Includes all cholangiocarcinoma subjects in Studies AG120-C-005 and AG120-C-002 who had been exposed to ivosidenib 500 mg QD.

No unexpected safety findings were raised from ECOG PS score.

2.10.8.5. In vitro biomarker test for patient selection for safety

NA

2.10.8.6. Safety in special populations

Age

In Study AG120-C-005, the incidence of TEAE was similar between the ivosidenib and placebo arms for subjects <65 years of age (97.5% vs 97.1%); however higher for subjects 65-<75 years of age (100% vs 93.3% [14 of 15 subjects]) but lower for subjects ≥75 years of age (92.3% [12 of 13 subjects] vs 100% [10 subjects]).

Given the small number of subjects in some subgroups (>75 years), the comparison is challenging.

Accidents/injuries, vascular disorders, infections/infestations and sum of postural hypotension/falls/blackout/syncope/dizziness/ataxia/fracture AEs appeared more frequently in 75 and older than those > 65. These data need to be taken cautiously due to the small size of some of the age subgroups. Overall, no new concerns are identified regarding the elderly population.

Gender

Based on data available, overall no clinically meaningful differences in the incidence of TEAEs between the gender groups were observed suggesting that there is no increased risk for ivosidenib induced undesirable effects due to gender.

Race

In Study AG120-C-005, among subjects randomized and exposed to ivosidenib (N=123) and placebo (N=59), the incidence of TEAE was similar in the ivosidenib and placebo arms for White subjects (98.6% vs 97.0%); however higher for Asian subjects (100% [15 subjects] vs 87.5% [7 of 8 subjects]). Given the small size of the Asian population, the comparison is challenging.

Adverse Events by Baseline Renal Function

Adverse events by baseline renal function were evaluated based on creatinine clearance and on Estimated Glomerular Filtration Rate (eGFR).

Table 72. Overall Summary of Treatment-Emergent Adverse Events by Baseline Renal Function Based on Creatinine Clearance (SAS)

Preferred Term	Ivosidenib 500 mg QD, Overall[1] (N=228), n (%)			Placebo (N=59), n (%)		
	Baseline Renal Function (CrCl)[1]			Baseline Renal Function (CrCl)		
	Normal (N=120)	Mild Impairment (N=75)	Moderate Impairment (N=27)	Normal (N=25)	Mild Impairment (N=17)	Moderate Impairment (N=17)
Subjects With Any TEAE	**118 (98.3)**	**74 (98.7)**	**25 (92.6)**	**24 (96.0)**	**16 (94.1)**	**17 (100.0)**
Subjects with Grade ≥3 TEAE	63 (52.5)	34 (45.3)	13 (48.1)	6 (24.0)	5 (29.4)	11 (64.7)
Subjects with Related TEAE	71 (59.2)	56 (74.7)	15 (55.6)	11 (44.0)	6 (35.3)	6 (35.3)
Subjects with Grade ≥3 Related TEAE	5 (4.2)	7 (9.3)	2 (7.4)	0	0	0
Subjects with SAE	39 (32.5)	20 (26.7)	8 (29.6)	6 (24.0)	1 (5.9)	7 (41.2)
Subjects with Related SAE	2 (1.7)	1 (1.3)	0	0	0	0
Subjects with TEAE Leading to Study Treatment Reduction	2 (1.7)	4 (5.3)	1 (3.7)	0	0	0
Subjects with Related TEAE Leading to Study Treatment Reduction	2 (1.7)	4 (5.3)	1 (3.7)	0	0	0
Subjects with TEAE Leading to Study Treatment Interrupted	35 (29.2)	22 (29.3)	5 (18.5)	2 (8.0)	3 (17.6)	6 (35.3)
Subjects with Related TEAE Leading to Study Treatment Interrupted	5 (4.2)	9 (12.0)	0	0	0	0
Subjects with TEAE Leading to Study Treatment Discontinuation	7 (5.8)	4 (.3)	0	2 (8.0)	2 (11.8)	1 (5.9)
Subjects with Related TEAE Leading to Study Treatment Discontinuation	1 (0.8)	1 (1.3)	0	0	0	0
Subjects with TEAE Leading to Death	4 (3.3)	4 (5.3)	1 (3.7)	0	0	0

Source: ISS Table 18.31.1.1. Data cutoff date: 16 January 2019 (AG120-C-002); Database lock date: 21 June 2021 (AG120-C-005).
Abbreviations: CrCl = creatinine clearance; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; QD = once daily; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Note: Baseline renal function based on creatinine clearance (mL/min): Normal (≥90); Mild Impairment (60 - <90); Moderate Impairment (30 - <60).
[1] Five subjects were missing values for baseline renal function based on creatinine clearance and are not included in this summary table.

Table 73. Overall Summary of Treatment-Emergent Adverse Events by Baseline Renal Function Based on eGFR – Cholangiocarcinoma Population (Safety Analysis Set)

Preferred Term	Ivosidenib 500 mg QD, Overall[1] (N=228), n (%)			Placebo (N=59), n (%)		
	Baseline Renal Function (eGFR)			Baseline Renal Function (eGFR)		
	Normal (N=96)	Mild Impairment (N=104)	Moderate Impairment (N=27)	Normal (N=20)	Mild Impairment (N=23)	Moderate Impairment (N=16)
Subjects With Any TEAE	**94 (97.9)**	**103 (99.0)**	**25 (92.6)**	**19 (95.0)**	**22 (95.7)**	**16 (100.0)**
Subjects with Grade ≥3 TEAE	51 (53.1)	47 (45.2)	16 (59.3)	6 (30.0)	7 (30.4)	9 (56.3)
Subjects with Related TEAE	59 (61.5)	68 (65.4)	16 (59.3)	7 (35.0)	10 (43.5)	6 (37.5)
Subjects with Grade ≥3 Related TEAE	5 (5.2)	6 (5.8)	3 (11.1)	0	0	0
Subjects with SAE	29 (30.2)	32 (30.8)	10 (37.0)	4 (20.0)	5 (21.7)	5 (31.3)
Subjects with Related SAE	2 (2.1)	1 (1.0)	0	0	0	0
Subjects with TEAE Leading to Study Treatment Reduction	2 (2.1)	3 (2.9)	2 (7.4)	0	0	0
Subjects with Related TEAE Leading to Study Treatment Reduction	2 (2.1)	3 (2.9)	2 (7.4)	0	0	0
Subjects with TEAE Leading to Study Treatment Interrupted	30 (31.3)	27 (26.0)	8 (29.6)	1 (5.0)	5 (21.7)	5 (31.3)
Subjects with Related TEAE Leading to Study Treatment Interrupted	7 (7.3)	5 (4.8)	2 (7.4)	0	0	0
Subjects with TEAE Leading to Study Treatment Discontinuation	6 (6.3)	3 (2.9)	2 (7.4)	2 (10.0)	1 (4.3)	2 (12.5)
Subjects with Related TEAE Leading to Study Treatment Discontinuation	1 (1.0)	1 (1.0)	0	0	0	0
Subjects with TEAE Leading to Death	5(5.2)	3 (2.9)	2 (7.4)	0	0	0

Source: ISS Table 18.32.1.1. Data cutoff date: 16 January 2019 (AG120-C-002); Database lock date: 21 June 2021 (AG120-C-005).
Abbreviations: eGFR = estimated glomerular filtration rate; QD = once daily; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Note: Baseline renal function based on eGFR (mL/min/1.73 m²): Normal (≥90); Mild Impairment (60 - <90); and Moderate Impairment (30 - <60).

In Study AG120-C-005, among subjects randomized and exposed to ivosidenib (N=123) and placebo (N=59), the incidence of TEAEs were similar between arms for subjects with mild renal impairment (97.6% [40 of 41 subjects] vs 94.1% [16 of 17 subjects]), and moderate renal impairment (100% [13 subjects] vs 100% [17 subjects]). Considering subgroups with limited numbers of patients, comparisons are challenging.

However it could be noted that in subjects with moderate renal impairment evaluated based on eGFR at baseline, it was reported in the ivosidenib arm (N=12 subjects) versus the placebo arm (N=16 subjects) a slightly higher incidence of gastrointestinal events (Diarrhoea, Nausea, Gastrooesophageal reflux disease), Anaemia, Decreased appetite, Hyperglycaemia, Hypermagnesaemia, Blood creatinine

increased, Electrocardiogram QT prolonged, Back pain, Cough, Oropharyngeal pain, Pruritus, Chills, Pyrexia, Pneumonia, Platelet count decreased, Weight decreased, Weight increased, White blood cell count decreased, Arthralgia, Muscle spasms, and Hypertension.

In the pool of cholangiocarcinoma subjects treated with ivosidenib 500 mg QD (N=228) based on creatinine clearance, the percentage of subjects with at least 1 TEAE was similar between subjects with normal renal function (98.3%) and subjects with mild (98.7%) or moderate (92.6%) impairment. Converging data were retrieved when the renal function is based on evaluate eGFR for subjects with normal renal function (97.9%) and subjects with mild (99.0%) or moderate (92.6%) impairment.

In the overall cholangiocarcinoma population (N=228) treated with ivosidenib 500 mg QD, only 1 subject had severe renal impairment at baseline based on creatinine clearance and eGFR and experienced the following AEs: Anaemia, Diarrhoea, Asthenia, Seasonal allergy, and Myalgia.

Adverse Events by Baseline Hepatic Function

Table 74. Overall Summary of Treatment-Emergent Adverse Events by Baseline Hepatic Function – Cholangiocarcinoma Population (Safety Analysis Set)

Preferred Term	Ivosidenib 500 mg QD, Overall[1] (N=228), n (%)			Placebo (N=59), n (%)		
	Baseline Hepatic Function			Baseline Hepatic Function		
	Normal (N=119)	Mild Impairment (N=104)	Moderate Impairment (N=5)	Normal (N=34)	Mild Impairment (N=25)	Moderate Impairment (N=0)
Subjects With Any TEAE	**116 (97.5)**	**102 (98.1)**	**5 (100.0)**	**32 (94.1)**	**25 (100.0)**	**0**
Subjects with Grade ≥3 TEAE	51 (42.9)	60 (57.7)	3 (60.0)	10 (29.4)	12 (48.0)	0
Subjects with Related TEAE	76 (63.9)	67 (64.4)	1 (20.0)	12 (35.3)	11 (44.0)	0
Subjects with Grade ≥3 Related TEAE	4 (3.4)	10 (9.6)	0	0	0	0
Subjects with SAE	27 (22.7)	42 (40.4)	2 (40.0)	7 (20.6)	7 (28.0)	0
Subjects with Related SAE	0	3 (2.9)	0	0	0	0
Subjects with TEAE Leading to Study Treatment Reduction	3 (2.5)	4 (3.8)	0	0	0	0
Subjects with Related TEAE Leading to Study Treatment Reduction	3 (2.5)	4 (3.8)	0	0	0	0
Subjects with TEAE Leading to Study Treatment Interrupted	26 (21.8)	38 (36.5)	1 (20.0)	5 (14.7)	6 (24.0)	0
Subjects with Related TEAE Leading to Study Treatment Interrupted	9 (7.6)	5 (4.8)	0	0	0	0
Subjects with TEAE Leading to Study Treatment Discontinuation	5 (4.2)	6 (5.8)	0	1 (2.9)	4 (16.0)	0
Subjects with Related TEAE Leading to Study Treatment Discontinuation	0	2 (1.9)	0	0	0	0
Subjects with TEAE Leading to Death	6 (5.0)	3 (2.9)	1 (20.0)	0	0	0

Source: ISS Table 18.33.1.1. Data cutoff date: 16 January 2019 (AG120-C-002); Database lock date: 21 June 2021 (AG120-C-005).
Abbreviations: eGFR = estimated glomerular filtration rate; QD = once daily; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Note: Baseline liver function based on NCI ODWG Criteria for hepatic impairment: Normal (total bilirubin ≤ULN and AST ≤ULN); Mild Impairment (total bilirubin ≤ULN and AST>ULN; or total bilirubin >1.0 × – 1.5 × ULN); Moderate Impairment (total bilirubin >1.5 × – 3 × ULN).
[1] Includes all cholangiocarcinoma subjects in Studies AG120-C-005 and AG120-C-002 who had been exposed to ivosidenib 500 mg QD.

Ivosidenib is metabolized predominantly by CYP3A4, and hence there is the potential for hepatic impairment to affect ivosidenib exposure. The potential impact of baseline hepatic function on ivosidenib safety was evaluated based on the NCI Organ Dysfunction Working Group criteria.

In Study AG120-C-005, most subjects in the ivosidenib and placebo arms had either normal (62 vs 34 subjects) or mild (59 vs 25 subjects) hepatic impairment at baseline, respectively. Only 2 subjects in the ivosidenib arm had moderate liver impairment at baseline and no subject had severe hepatic impairment at baseline.

Among subjects with cholangiocarcinoma, a majority of the subjects had normal hepatic function (N=119) or mild hepatic impairment (N=104) at baseline. Only 5 subjects had moderate hepatic impairment and no subjects had severe hepatic impairment at baseline. The percentage of subjects with at least 1 TEAE was similar between subjects with normal hepatic function (97.5%) and mild (98.1%) and moderate (100.0%) hepatic impairment.

Among all TEAEs across both treatment arms in Study AG120-C-005, there was a trend of higher frequency TEAEs in subjects with mild hepatic impairment compared to subjects with normal hepatic function. The TEAEs of anaemia and QT prolongation were reported at higher incidence in subjects with mild hepatic impairment; these are known ADRs in subjects with cholangiocarcinoma, described in the Section 4.8 of the SmPC. Section 4.8 of the SmPC reflects the trend of higher ADR incidence observed in patients with mild hepatic impairment with the information:" *Trend to a higher incidence of adverse reactions was observed in patients with mild hepatic impairment (Child-Pugh class A)".* Section 4.4 of the SmPC indicates that Ivosidenib should be used with caution in patients with mild hepatic impairment (Child-Pugh class A).

As for the overall cholangiocarcinoma population, very few subjects (5) had moderate hepatic function at the baseline and no subjects had severe hepatic impairment, no conclusion can be drawn on the safety of ivosidenib in these situations.

Extrinsic Factors

Adverse Events by Geographic Region

In Study AG120-C-005, the incidence of TEAEs were similar between the ivosidenib and placebo arms for subjects from North America (97.6% [81 of 83 subjects] vs 97.4% [37 of 38 subjects]) and for subjects from Western Europe (97.0% [32 of 33 subjects] vs 100.0% [16 subjects]).

2.10.8.7. Immunological events

NA

2.10.8.8. Safety related to drug-drug interactions and other interactions

Please refer to section Pharmacology-PK for drug-drug interactions and other interactions.

2.10.8.9. Discontinuation due to adverse events

Discontinuation

In Study AG120-C-005, similar incidences of subjects in the ivosidenib arm had a TEAE leading to treatment discontinuation as compared with the placebo arm (7.3% vs 8.5%).

Adverse events leading to study treatment discontinuation in the ivosidenib arm were Acute kidney injury, Ascites, Intestinal obstruction, Generalised oedema, Hyperbilirubinaemia, Abdominal infection, Sepsis, and Hepatic encephalopathy.

Among overall cholangiocarcinoma population, TEAEs leading to study treatment discontinuation occurred in a slightly lower incidence (4.8%) and were quite similar: Acute kidney injury, Ascites, Intestinal obstruction, Intestinal pseudo-obstruction, Generalised oedema, Hepatic cirrhosis, Hyperbilirubinaemia, Abdominal infection, Sepsis, and Hepatic encephalopathy. Treatment related-AEs leading to study treatment discontinuation were Generalised oedema (Subject 107-1808) and Hyperbilirubinaemia (Subject 113-1084).

Generalized oedema in this subject was confounded by pre-existing conditions, co-occurring illness and TEAEs, concomitant therapy, and negative dechallenge of ivosidenib.

In patients treated with ivosidenib, the frequency of treatment discontinuation due to adverse reactions was 2%. Adverse reactions leading to discontinuation were ascites (1%) and hyperbilirubinemia (1%).

Dose interruptions

In Study AG120-C-005, as expected, a higher incidence of subjects in the ivosidenib arm (30.1%) had a TEAE leading to treatment interruption as compared with the placebo arm (18.6%).

The most frequent TEAE leading to study treatment interruption (>2% of subjects) in the ivosidenib arm were Aspartate aminotransferase increased, Cholangitis, Alanine aminotransferase increased, ascites, hyperbilirubinaemia and sepsis.

Treatment related AEs leading to treatment interruption were Fatigue in 4 ivosidenib-treated subjects, and the following TEAEs were assessed as treatment-related by the Investigator (each in 1 ivosidenib-treated subject): Nausea, Stomatitis, Oedema peripheral, Jaundice cholestatic, Neutrophil count decreased, Dizziness, Pleural effusion, and Rash pruritus.

Among overall cholangiocarcinoma population treated with ivosidenib 500 mg QD, the trend was similar as 28.5% of subjects had treatment interruptions. No individual TEAE leading to study treatment interruption occurred in more than 3% of subjects. The most frequent TEAE leading to study treatment interruption (>2% of subjects) were Pyrexia and Aspartate aminotransferase increased, Fatigue, Cholangitis, and Alanine aminotransferase increased.

It should be noted that 2 subjects had Electrocardiogram QT prolonged leading to ivosidenib treatment interruption.

The frequency of dose interruption of ivosidenib due to adverse reactions was 16%. The most common adverse reactions leading to dose interruption were hyperbilirubinemia (3%), alanine aminotransferase increased (3%), aspartate aminotransferase increased (3%), ascites (2%) and fatigue (2%).

Dose reduction

In Study AG120-C-005, as expected, a higher incidence of TEAE leading to treatment dose reduction was observed in the ivosidenib arm (4.1%) compared with the placebo arm (0%). The TEAEs that led to ivosidenib reduction included Electrocardiogram QT prolonged (3.3%) and Neuropathy peripheral (0.8%).

Among subjects with cholangiocarcinoma treated with ivosidenib 500 mg QD (N=228), TEAEs leading to study treatment reduction occurred in 3.1% of subjects and included: Electrocardiogram QT prolonged, Fatigue, Blood bilirubin increased, and Neuropathy peripheral. All these events were assessed by the Investigator as related to study treatment.

The frequency of dose reduction of ivosidenib due to adverse reactions was 4%. Adverse reactions leading to dose reduction were electrocardiogram QT prolonged (3%) and neuropathy peripheral (1%).

2.10.8.10. Post marketing experience

At 16 January 2021 no new safety information were identified through post-marketing use.

2.10.9. Discussion on clinical safety

The safety profile of ivosidenib as monotherapy in the cholangiocarcinoma indication is based on the pivotal study AG120-C-005, a phase 3 double-blind, placebo-controlled study which included 225 previously treated subjects with nonresectable or metastatic cholangiocarcinoma with an IDH1 mutation (123 treated with ivosidenib and 59 with placebo). After documented disease progression, 43 subjects randomized to the placebo arm were given the opportunity to cross over to the active treatment arm and receive ivosidenib.

In addition, supporting safety data were provided for ivosidenib monotherapy at the same posology from the subpopulation of patients with cholangiocarcinoma (N=62) in the open label multicentre Phase 1 Study AG120-C-002 which also includes subjects with other solid tumors.

Additional safety data were also provided from another ongoing Phase 1 Study AG120-881-C-001 with 14 subjects with glioma.

The methodology based on comparative data versus placebo and also a pooled population strategy with patients with cholangiocarcinoma from studies AG120-C-005, AG120-C-002, and AG120-881-C-001 (n=228 patients), is acceptable for characterisation of the drug safety profile for the claimed indication in its general aspects.

Patient exposure

In the pivotal study, the median exposure in ivosidenib arm was 2.8 months with half of patients in ivosidenib arm, exposed for more than 3 months and only 15.4% of subjects exposed for more than 12 months. Median exposure in placebo arm was slightly shorter (1.6 months). The overall cholangiocarcinoma population (N=228), allows to collect data from a slightly longer exposure to ivosidenib (median duration of 3.6 months and exposure ≥12 months in 17.1% of subjects).

The limited long-term exposure available and the differences in exposure duration between the ivosidenib and placebo groups were identified as key safety concerns. In order to reduce the potential impact of these aspects on the characterisation of the safety profile in the intended indication, exposure-adjusted data was provided. Data have been presented according to the original treatment assignment, with 123 and 59 patients in the ivosidenib and placebo groups, respectively. For the placebo subjects, data before their cross-over was considered. Overall, the exposure-adjusted data showed similar or even lower frequencies for the ivosidenib group, which is reassuring. The only SOCs with AEs more frequent for ivosidenib than for placebo were in the ear/labyrinth disorders (0.12 person-years, CI95% (0.06-0.23) vs. 0.09 person-years, CI95% (0.01-0.66)), eye disorders (0.10 person-years, CI95% (0.05-0.21) vs. 0.09 person-years, CI95% (0.01-0.66)) and immune disorders (0.104 person-years, CI95% (0.061-0.14) vs. (0 person-years).

Other key safety data broken down over time by month were provided, which is considered informative and did not show any worrisome differences.

Per AG120-C-005 study design, once placebo patients progressed, they were allowed to cross-over to active treatment. The applicant has provided safety data broken down into "pre-crossover" and "post-crossover" information. Due to the crossover, the exposure in each treatment group is uneven/unbalanced, which is considered a limitation for the assessment of the comparative safety.

In the pivotal study, the main reason for treatment discontinuations was disease progression in both arms. This explains the short ivosidenib exposure, which do not allow to collect long-term data. The proportion of patients who discontinued treatment due to adverse event was small and similar in both arms (6.5% and 6.8%).

A high relative dose intensitiy (>95%) was observed across groups. This fact added to the observed small number of discontinuations due to AEs in both arms, suggests that ivosidenib toxicities are manageable and the tolerability appears to be acceptable.

Globally, the pivotal study there were no meaningful differences in the demographics characteristics across the treatment arms and the baseline characteristics appear balanced between the treatment arms. The median age was 61.0 years in ivosidenib arm with 10.6% of subjects over 75 years. Study AG120-C-005 and Study AG120-C-002 permitted cholangiocarcinoma subjects with 1 or 2 prior lines of therapy, and Study AG120-C-002 also permitted more heavily pretreated patients (>2 prior lines of therapy).

Regarding demographics, although no large differences were observed, it was noted that study AG120-C-002 was mainly conducted in North America (n=60, 96.8% of subjects) with minimal representation of EU patients (n=2, 3.2%), which rises concerns about representability. It was clarified that the representation of European population in the main study is approximately 27%, with clinical sites in Spain, Italy, France and UK. The subgroup analyses did not show differences in safety profile based on the region (data from previous round, not shown here). No alarming data were identified in the 2 EU patients in study AG120-C-002.

Adverse events

In the pivotal study, despite a slight difference of treatment duration between ivosidenib and placebo arms, the incidences of subjects with TEAEs were similar in both arms (97.6% vs 96.0%). However, the incidence of Grade ≥3 TEAEs, was higher in the ivosidenib arm (51.2% vs 37.3%). The incidence of SAEs was also higher in the ivosidenib arm when compared with placebo (35.0% vs 23.7%).

A similar trend is observed in the overall cholangiocarcinoma population treated with 500 mg ivosidenib QD.

In order to be able to cross-over, treatment assignment was unblinded for those patients who had progressed. As a result, the causality assessment in crossed over patients need to be taken cautiously.

Common Adverse Events

Many of the adverse events could represent manifestations of advanced cholangiocarcinoma, intercurrent illness, tumor burden, and/or residual toxicity in this heavily pre-treated (eg, gemcitabine, cisplatin, and oxaliplatin) population.

The most frequent TEAEs by SOC in the overall cholangiocarcinoma population were in SOC Gastrointestinal disorders (74.1%) which might be explained by the targeted disease (cholangiocarcinoma).

As there are confounding factors associated with the events of cough, the "cough" event is not considered an ADR. This will continue to be monitored as part of routine pharmacovigilance activities.

The applicant provided further discussions on the three following TEAE: hyperglycaemia, hypertension and myalgia. These are not considered as ADRs in the SmPC. The applicant will continue to monitor these events as part of routine pharmacovigilance activities.

Common Grade ≥3 Adverse Events

As identified from non-clinical data, hematotoxicity is retrieved in clinical data with frequent and severe AE of anaemia, platelet count and neutrophil decreased. The applicant has provided additional analysis on haematotoxicity events in CCA and added to the SmPC Section 4.2 recommendations on frequency of monitoring (blood laboratory testing) given the manageability of these ADRs.

TEAE leading to on-treatment death

An imbalance in the number of AEs leading to death is noted between ivosidenib-treated patients and placebo. Some of these AEs leading to death could occur in the context of hepatotoxicity (e.g., hepatic encephalopathy, hepatic cirrhosis). The applicant discussed any potential reasons behind this imbalance. A total of 10 patients, 8 from study AG120-C005 and 2 study AG120-C002, had a TEAE leading to death. The SOCs of these AEs were infections/infestations (4), hepato-biliary disorders (2), GI disorders (2), vascular disorders (1) and injury/procedural complications (1). None of these AEs were considered as treatment-related by the investigator. These deaths were attributed to complications of the underlying disease and a pattern/trend among these AEs was no identified.

Adverse Events of Special Interest

From their prior knowledge of the product in their haematological development, the applicant has identified QT interval prolongation, Guillain Barré Syndrome and Leukoencephalopathy as AESIs for ivosidenib. Electrocardiogram QT prolonged was the only AESI proposed for the cholangiocarcinoma indication.

Cases of Guillain-Barré syndrome will be systematically presented and evaluated in PSURs. No additional information is added in the Section 4.4 of the SmPC as the peripheral neuropathy TEAEs reported across studies AG120-C-005 and AG120-C-002 in cholangiocarcinoma subjects were all low grade, non-serious and manageable.

Overall, no clear mechanism has been identified to suggest that the development of PML or PRES resulted from ivosidenib treatment. Cumulatively, these data support the Sponsor's assessment that PML and PRES are not safety concerns or potential risks with ivosidenib use in the indications proposed in this MAA. Despite absence of reported cases of PML and PRES in any subject with solid tumors, including cholangiocarcinoma to date, few cases were reported in other indications. Events of PML and of PRES will be closely monitor throughout PSUR by reviewing and discussing of each reported case in each PSUR.

QT interval prolongation

For cholangiocarcinoma, concentration-QTc interval analyses were conducted with data from studies AG120-C-002 and AG120-C-005 and demonstrated that the risk of QT interval prolongation increases with increases in plasma Cmax.

ECG QT prolonged is listed in section 4.8 of the SmPC, and currently, to mitigate the risk, it is recommended to monitor ECG prior initiation of the treatment, at least weekly for the first 3 weeks and then monthly. Recommendation to avoid concomitant treatment known to prolong the QTc interval or moderate or strong CYP3A4 inhibitors is also provided. Dose modifications are further recommended in case of grade 2, 3 and 4 ECG QT prolongation and in case administration of a strong CYP3A4 inhibitor is unavoidable (section 4.2 of the SmPC). In addition, a warning regarding QT prolongation is provided in section 4.4 with the recommendation to closely monitor patients with congenital long QTc syndrome, congestive heart failure or electrolyte abnormalities.

Even though the measures provided in the SmPC seem restrictive, ECG QT prolonged was a frequent TEAE including frequent grade 3 events which are a risk factor associated with polymorphic ventricular arrhythmias. Considering that patients were carefully selected (QT <450 msec, no cardiac disease) in clinical studies, considering furthermore that dose-exposure relationship is highly variable, with a large proportion of patients exposed to potentially critical concentration with respect to QT prolongation, implementation of additional mitigation measures were considered needed.

Laboratory abnormalities

The incidence of newly occurring or worsening clinical chemistry abnormalities was higher (between arm difference ≥5% for all grades or ≥2% for Grade 3-4) in subjects in the ivosidenib arm (than in placebo for the following parameters high serum glucose, high ALP, high AST, high bilirubin, and high ALT. Aspartate aminotransferase increased, alanine aminotransferase increased and blood bilirubin increased are listed in section 4.8 of the proposed SmPC.

Safety in special populations

Overall, no meaningful differences were retrieved for intrinsic Factors such as age, gender and race. Comparisons were challenging for some subgroups considering the small sample size.

Renal impairment

According to PK data, mild or moderate renal impairment do not affect ivosidenib exposure. In Study the pivotal study, the incidence of TEAEs were similar between arms for subjects with mild renal impairment (97.6% vs 94.1%), and moderate renal impairment (100% vs 100%), but, considering limited numbers of patients with moderate renal impairment, comparisons are challenging. Since no patient with severe renal impairment was included in the pivotal study (only one was retrieved in the pooled cholangiocarcinoma population), this population has been listed by the applicant in the RMP as a missing information and a PK study is planned (see RMP and Discussion on Clinical Pharmacology).

Hepatic impairment

The safety of ivosidenib have not been established in patients with moderate and severe hepatic impairment (Child-Pugh classes B and C). Tibsovo should be used with caution in patients with moderate and severe hepatic impairment and this patient population should be closely monitored. A trend to a higher incidence of adverse reactions was observed in patients with mild hepatic impairment (Child-Pugh class A) (See SmPC sections 4.2, 4.8 and 5.2.).

Use in patients with severe hepatic impairment has thus been listed in the RMP as a missing information in the RMP and a PK study is planned (see RMP and Discussion on Clinical Pharmacology).

Discontinuation due to adverse events

In the pivotal study, the incidence of TEAE leading to treatment discontinuation was similar between the ivosidenib and placebo (7.3% vs 8.5%) with 1.6% of subjects with related TEAE leading to study treatment discontinuation in the ivosidenib arm and none in the placebo arm. Among overall cholangiocarcinoma population the incidence was 4.8% and TEAE leading to treatment discontinuation were: Acute kidney injury, Ascites, Intestinal obstruction, Intestinal pseudo-obstruction, Generalised oedema, Hepatic cirrhosis, Hyperbilirubinaemia, Abdominal infection, Sepsis, and Hepatic encephalopathy. Treatment related-AEs leading to study treatment discontinuation were Generalised oedema and Hyperbilirubinaemia. The treatment related-AEs "Generalised oedema" will continue to be monitored via routine pharmacovigilance activities.

Dose modifications due to adverse events

In the pivotal study, the incidence of a TEAE leading to treatment interruption was higher in the ivosidenib arm compared to placebo arm (30.1% vs 18.6%). The most frequent TEAE leading to study treatment interruption (>2%) in the ivosidenib arm were Aspartate aminotransferase increased, Cholangitis, Alanine aminotransferase increased, ascites, hyperbilirubinaemia and sepsis. Treatment related AEs leading to treatment interruption were Fatigue in 4 ivosidenib-treated subjects, and the following TEAEs (each in 1 ivosidenib-treated subject): Nausea, Stomatitis, Oedema peripheral, Jaundice cholestatic, neutrophil count decreased, Dizziness, Pleural effusion, and Rash pruritus. Similar trend was observed in overall cholangiocarcinoma population.

In the pivotal study, a higher incidence of TEAE leading to treatment reduction was observed in the ivosidenib arm (4.1%). The TEAEs that led to ivosidenib reduction included Electrocardiogram QT prolonged (3.3%) and Neuropathy peripheral (0.8%). Similar trend was observed in overall cholangiocarcinoma population.

2.10.10. Conclusions on the clinical safety

The safety profile of ivosidenib as monotherapy in patients with previously treated locally advanced or metastatic cholangiocarcinoma with an IDH1 mutation is mainly characterised by gastrointestinal disorders (Nausea, Vomiting, Diarrhoea, Abdominal Pain, and Ascites), Fatigue, Decreased appetite, Cough, and anaemia and appears clinically manageable with an acceptable rate of treatment discontinuations due to AEs. Appropriate wording in the product information, most notably for QT prolongation which is contraindicated in patients with relevant medical history and detailed warnings on precautions to be taken prior to administration, monitoring and management of this risk, are sufficient.

Acute myeloid leukaemia

2.10.11. Clinical efficacy

2.10.11.1. Dose response study

There was no dedicated dose-response study. Exposure-response analyses for safety and efficacy were conducted using data from 64 subjects with newly diagnosed AML receiving ivosidenib (500 mg QD) + azacitidine from the pivotal Study AG120-C-009 (hereafter AGILE Study or Study 009).

Four efficacy endpoints were selected for evaluation of potential exposure-efficacy relationships for ivosidenib + azacitidine response: complete remission (CR), CR with partial hematologic recovery (CR + CRh), objective response (OR), and event-free survival (EFS).

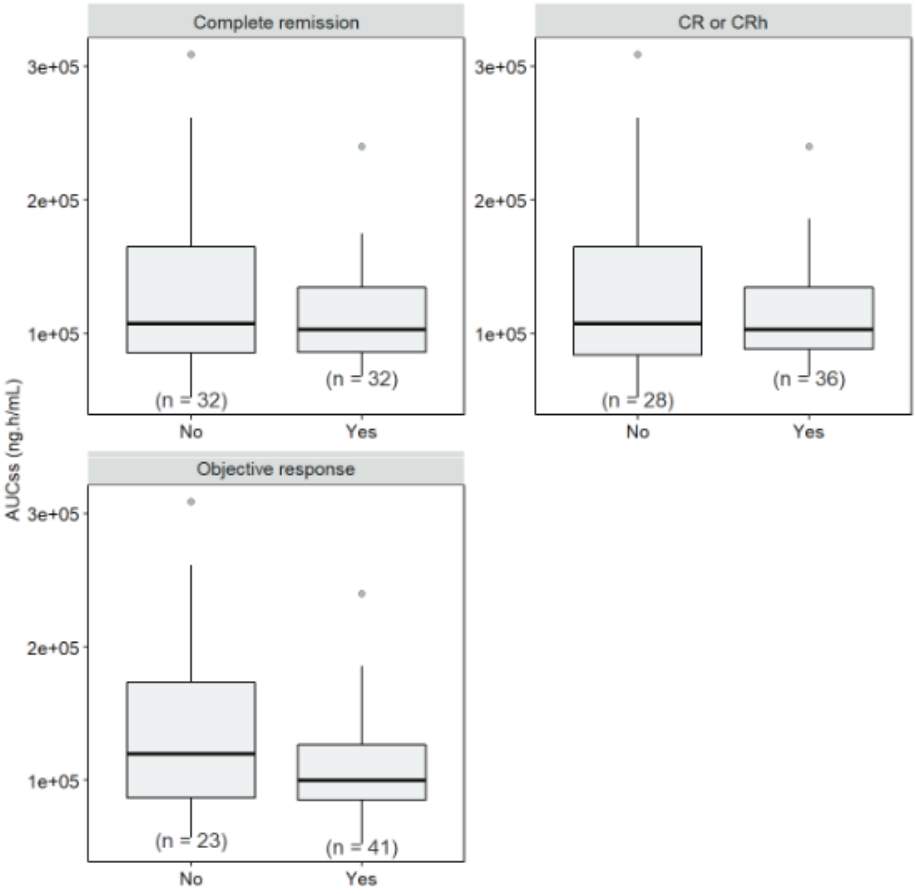
The E-R analyses of these endpoints were impacted by the fact that subjects who achieved an efficacy response (responders based on CR, CR + CRh and OR) stayed longer on treatment than subjects who did not achieve efficacy response (non-responders) and dropped out early from the study. Because the likelihood of dose modifications was correlated with treatment duration, responders received a lower average daily dose than non-responders due to dose reductions and dose interruptions during the course of treatment. As a result, exposure was confounded with treatment duration and as such with clinical response, and results from the analysis should be interpreted with care.

The difference in average daily dose between responders and non-responders was less pronounced when the average daily dose in Cycle 1 was considered.

These observations advocate the use of exposure metrics based on the average daily dose in Cycle 1 to reduce the effect of dose reductions associated with efficacy response.

Exposure distributions were explored with boxplots for responders and non-responders for CR, CR + CRh, and OR, as depicted in the figure below.

Figure 40. Exposure Distributions in Responders and Nonresponders for the Binary Efficacy Endpoints CR, CR + CRh, and OR



Source: exploratory-er-analysis.docx
Notes: The solid line represents the median, the box represents the IQR, the whiskers represent the 1.5× IQR, and the dots represent the data points ("outliers") beyond the end of the whiskers.
Abbreviations: AUCss=area under the concentration-time curve at steady state for the average daily dose in first treatment cycle; CR=complete remission; CRh=complete remission with partial hematologic recovery; n=number of subjects; IQR=interquartile range

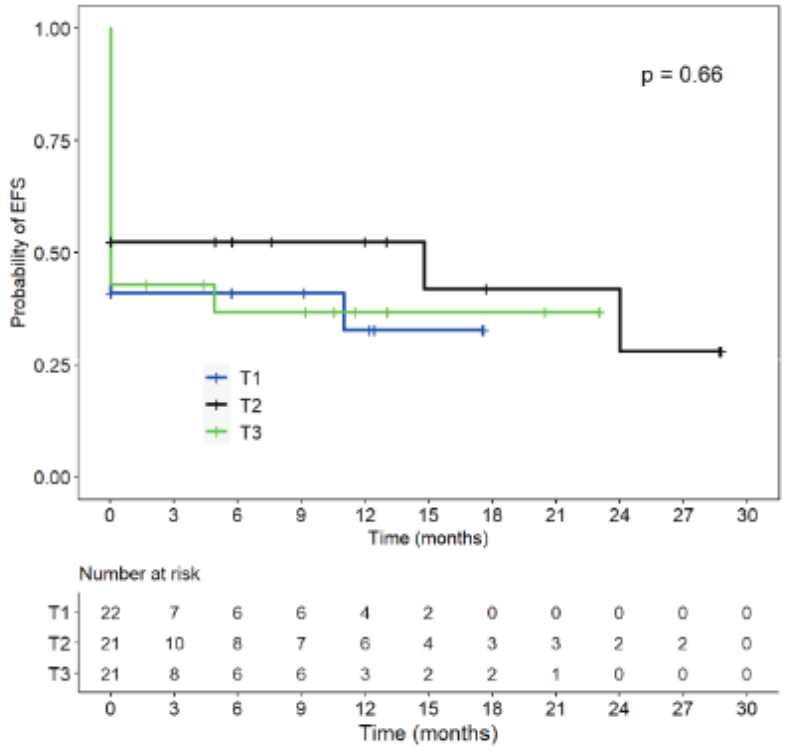
In general, the distributions for both subject groups were overlapping. The AUCs distribution for responders were narrower than for nonresponders for the 3 endpoints. The median AUCs and the distributions were overlapping for CR and CR + CRh. The median AUCs appeared to be lower for responders compared to nonresponders for OR.

Logistic regression was applied to further quantify exposure effects. For all 3 endpoints, an inverse relationship with lower efficacy with increasing exposure was observed. This effect reached statistical significance for OR (p = 0.03): increase in exposure was associated with a decrease in probability of achieving OR. The inverse E-R relationship for OR was still observed when adjusted for baseline covariates (age, body weight, sex, AML nature, ECOG PS score, cytogenetic risk, and geographical region, respectively). No statistically significant relationship between exposure and the probability of response was observed for the other 2 endpoints (CR and CR + CRh).

Similar but somewhat more pronounced trends were observed using the exposure estimates based on the average daily dose in the whole treatment.

Kaplan-Meier Estimation and Cox PH Regression of Event-Free Survival

Figure 41. Kaplan-Meier Curves for Event-Free Survival as a Function of Tertiles of AUCss



Source: exploratory-er-analysis.docx
Notes: The p-value in the upper right corner in the plot represents the p-value of no difference between the exposure tertiles based on the log-rank test.
Abbreviations: AUCss=area under the concentration-time curve at steady state for the average daily dose in first treatment cycle; EFS=event-free survival. T1-T3=first (T1), second (T2), and third (T3) tertiles of the AUCss distribution

The figure above shows KM estimates of the proportion of subjects with EFS for tertiles of AUCss distribution. The KM curves for the 3 exposure tertiles were overlapping and showed no apparent E-R relationship (log-rank test: p = 0.66). A Cox PH model was applied to quantify the exposure effect on EFS. The estimated AUCss effect on EFS from the Cox PH model was not statistically significant (p = 0.44). Similar results were found using the exposure estimates based on the average daily dose in the whole treatment period.

2.10.11.2. Main study

Study AG120-C-009 (AGILE): a Phase 3, multicenter, double-blind, randomized, placebo-controlled clinical trial to evaluate the efficacy and safety of ivosidenib + azacitidine vs placebo + azacitidine in adult subjects with previously untreated IDH1-mutated AML and who are considered appropriate candidates for non-intensive therapy.

Methods

- **Study Participants**

Main inclusion criteria

1. Were ≥ 18 years of age and met at least 1 of the following criteria defining ineligibility for intensive IC:
    a. ≥ 75 years old
    b. ECOG PS = 2

c. Severe cardiac disorder (e.g., congestive heart failure requiring treatment, LVEF≤50% or chronic stable angina)
d. Severe pulmonary disorder (e.g., diffusing capacity of the lungs for carbon monoxide ≤ 65% or forced expiratory volume in 1 second ≤ 65%)
e. Creatinine clearance <45 mL/minute
f. Bilirubin >1.5 times the upper limit of normal (× ULN)
g. Any other comorbidity that the Investigator judged to be incompatible with intensive IC
h. Had previously untreated AML, defined according to WHO criteria. Subjects with extramedullary disease alone (i.e., no detectable bone marrow and no detectable peripheral blood AML) were not eligible for the study.

2. Had an IDH1 mutation resulting in an R132C, R132G, R132H, R132L, or R132S substitution, as determined by central laboratory testing (using an investigational polymerase chain reaction [PCR] assay) in their bone marrow aspirate (or peripheral blood sample if bone marrow aspirate was not available).

3. Local testing for eligibility and randomization was permitted; however, results had to state an IDH1 mutation resulting in an R132C, R132G, R132H, R132L, or R132S substitution.

4. Had an ECOG PS score of 0 to 2

5. Had adequate hepatic function, as evidenced by:

    a. Serum total bilirubin ≤2 × upper limit of normal (ULN), unless considered to be due to Gilbert's disease or underlying leukemia, where it had to be <3 x ULN.
    b. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) ≤3×ULN, unless considered to be due to underlying leukemia.

6. Had adequate renal function, as evidenced by serum creatinine ≤2.0 x ULN or creatinine clearance >30 mL/min based on the Cockcroft-Gault glomerular filtration rate.

7. Agreed to undergo serial blood and bone marrow sampling.

8. If female with reproductive potential, must have had a negative serum pregnancy test prior to the start of study therapy. Females of reproductive potential, as well as fertile men with female partners of reproductive potential, were required to use 2 effective forms of contraception (including at least 1 barrier form) as per study protocol, from the time of giving informed consent throughout the study and for 90 days following the last dose of study drug(s).

<u>Main exclusion criteria</u>

1. Were candidates for intensive IC for their AML.

2. Had received any prior treatment for AML with the exception of non-oncolytic treatments to stabilize disease such as hydroxyurea or leukapheresis.

3. Had received a hypomethylating agent for MDS.

4. Subjects who had previously received treatment for an antecedent hematologic disorder, including investigational agents, were not to be randomized until a washout period of at least 5 half-lives of the investigational agent had elapsed since the last dose of that agent.

5. Had received prior treatment with an IDH1 inhibitor.

6. Had a known hypersensitivity to any of the components of ivosidenib, matched placebo, or azacitidine.

7. Were female and pregnant or breastfeeding.
8. Were taking known strong cytochrome P450 (CYP)3A4 inducers or sensitive CYP3A4 substrate medications with a narrow therapeutic window, unless they could be transferred to other medications within ≥5 half-lives prior to dosing.
9. Had an active, uncontrolled, systemic fungal, bacterial, or viral infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment.
10. 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. However, subjects with the following history/concurrent conditions or similar indolent cancer were allowed to participate in the study:
    a. Basal or squamous cell carcinoma of the skin
    b. Carcinoma in situ of the cervix
    c. Carcinoma in situ of the breast
    d. Incidental histologic finding of prostate cancer
11. Had significant active cardiac disease within 6 months prior to the start of study treatment, including New York Heart Association (NYHA) Class III or IV congestive heart failure, myocardial infarction, unstable angina, and/or stroke.
12. Had a heart-rate corrected QT interval using Fridericia's method (QTcF) ≥470 msec or any other factor that increases the risk of QT prolongation or arrhythmic events. Subjects with prolonged QTcF interval in the setting of bundle branch block could participate in the study.
13. Had a known infection caused by human immunodeficiency virus (HIV) or active hepatitis B virus or hepatitis C virus that cannot be controlled by treatment.
14. Had uncontrolled hypertension (systolic blood pressure [BP] >180mmHg or diastolic BP >100mmHg).
15. Had clinical symptoms suggestive of active central nervous system (CNS) leukemia or known CNS leukemia. Evaluation of cerebrospinal fluid during Screening was only required if there was a clinical suspicion of CNS involvement by leukemia during Screening.
16. Had immediate, life-threatening, severe complications of leukemia, such as uncontrolled bleeding, pneumonia with hypoxia or sepsis, and/or disseminated intravascular coagulation.
17. Had any other medical or psychological condition deemed by the Investigator to be likely to interfere with the subject's ability to give informed consent or participate in the study.
18. Were taking medications that are known to prolong the QT interval unless they could be transferred to other medications within ≥5 half-lives prior to dosing, or unless the medications could be properly monitored during the study.
19. Subjects with a known medical history of progressive multifocal leukoencephalopathy (PML).

- **Treatments**

Treatment was administered as follows:

AG-120 Arm: azacitidine 75 mg/m²/day SC or IV for the first week (7 days) (or on a 5-2-2 schedule) of each 4-week (28-day) cycle in combination with 500 mg ivosidenib PO QD on each day of the 4-week cycle.

Placebo Arm: azacitidine 75 mg/m²/day SC or IV for the first week (7 days) (or on a 5-2-2 schedule) of each 4-week (28-day) cycle in combination with placebo PO QD on each day of the 4-week cycle.

The same schedule was to be used for each subject throughout the duration of treatment, when possible.

Subjects were instructed to take their ivosidenib QD dose at approximately the same time each day. Subjects were to continue to receive therapy with ivosidenib or placebo + azacitidine until death, disease relapse, disease progression, development of unacceptable toxicity (adverse event), confirmed pregnancy, withdrawal by subject, protocol violation, or end of study.

On days when both ivosidenib or placebo and azacitidine were given, ivosidenib or placebo were to be given prior to azacitidine.

- **Objectives**

The primary objective of the study was to compare EFS between ivosidenib + azacitidine and placebo + azacitidine.

The key secondary objectives of the study were:

- To compare the complete remission (CR) rate between ivosidenib + azacitidine and placebo + azacitidine.
- To compare OS between ivosidenib + azacitidine and placebo + azacitidine.
- To compare the CR + complete remission with partial hematologic recovery (CRh) rate between ivosidenib + azacitidine and placebo + azacitidine; CRh will be derived by the Sponsor.
- To compare the objective response rate (ORR) between ivosidenib + azacitidine and placebo + azacitidine.

- **Outcomes/endpoints**

The primary endpoint of the study was EFS, which was defined as the time from randomization until treatment failure (TF), relapse from remission, or death from any cause, whichever occurred first. TF was defined as failure to achieve CR by Week 24.

The key secondary endpoints were:

- CR rate, defined as the proportion of subjects who achieved a CR; CR was defined as bone marrow blasts <5% and no Auer rods; absence of extramedullary disease; ANC $\geq 1.0 \times 109/L$ (1000/μL); platelet count $\geq 100 \times 109/L$ (100,000/μL); and independence of RBC transfusions.
- OS, defined as the time from date of randomization to the date of death due to any cause.
- CR + CRh rate, defined as the proportion of subjects who achieved a CR or CRh. CRh was defined as a CR with partial recovery of peripheral blood counts (<5% bone marrow blasts, platelets >50,000/μL, and ANC >500/μL). CRh was derived by the Sponsor since it was not part of International Working Group criteria.
- ORR, defined as the rate of CR, CRi (including CRp), partial remission (PR), and morphologic leukemia-free state (MLFS). The best response was calculated using the following order: 1) CR; 2) CRi (including CRp); 3) PR, and 4) MLFS.
- CR + CRi rate, defined as the proportion of subjects who achieved a CR or CRi (including CRp).

Additional secondary endpoints focused on HRQoL assessments and assessment of disease response to treatment through the evaluation of bone marrow biopsies and/or aspirates, along with complete blood counts and examination of peripheral blood films.

- **Sample size**

In the original protocol (6 January 2017)

A total of approximately 392 subjects with previously untreated IDH1m AML were planned to be randomised in this study, with OS as the primary endpoint.

In a previous randomised Phase 3 study of azacitidine in older subjects with newly diagnosed AML with > 30% blasts, median OS of 10.4 months was observed for the azacitidine arm (Dombret, et al. 2015). This was used as the modelling assumption for the control arm in the current study. Assuming an HR of 0.71 for OS (equivalent to a median OS of 10.4 months in the placebo arm vs 14.6 months in the AG-120 arm, assuming an exponential distribution), a total of 278 OS events were required to provide 80% power at a 1-sided alpha of 0.025 level of significance to reject the null hypothesis using a stratified log-rank test.

Assuming a recruitment period of approximately 44 months, with an accrual rate of 5 subjects/month during the first 5 months and 9.6 subjects/month afterwards, along with an assumed 10% dropout rate, approximately 392 subjects were to be randomized to the 2 treatment arms in a 1:1 ratio. Given the above assumptions, it was estimated that the primary analysis of OS would occur approximately 54 months after the first subject was randomised.

From protocol amendment 5 (9 January 2020)

A total of approximately 200 subjects with previously untreated IDH1m AML were planned to participate in this study.

Assumptions for the placebo + azacitidine arm in this study were based on results from Study AZA-AML-001 in newly diagnosed AML patients who are ineligible for intensive IC receiving ivosidenib in combination with azacitidine. Based on results from a retrospective analysis of these data, the CR rate at 24 weeks was assumed to be 20% for the placebo + azacitidine arm. For subjects who achieve CR by 24 weeks, the median EFS is assumed to be 14.6 months.

Assumptions for the ivosidenib + azacitidine arm in this study were based on results from Study AG-221-AML-005 in newly diagnosed AML patients who are ineligible for intensive IC receiving ivosidenib in combination with azacitidine. The CR rate by 24 weeks was assumed to be 40%. For subjects who achieve CR by 24 weeks, a target HR of 0.76 for EFS (equivalent to a median EFS among responders of 14.6 months in the placebo + azacitidine arm vs 19.2 months in the ivosidenib + azacitidine arm, assuming an exponential distribution) was assumed. Based on simulation results, the average overall HR over 10,000 simulations for the entire population was 0.641. Given that the assumption of proportional hazards was not met based on the EFS definition, the overall HR is less meaningful in this context. Therefore, the overall HR for the entire population was not part of the study design assumptions. Under these assumptions, a total of 173 EFS events were required to provide 80% power at a 1-sided alpha of 0.025 level of significance to reject the null hypothesis using a stratified log-rank test. Assuming a recruitment period of approximately 44 months, with an accrual rate of 3 subjects per month during the first 10 months and 5 subjects per month thereafter, along with an assumed 5% overall dropout rate, approximately 200 subjects were planned to be randomized to the 2 treatment arms in a 1:1 ratio. Given the above assumptions, it was estimated that the analysis of the primary endpoint for EFS will occur approximately 52 months after the first subject was randomised.

- **Randomisation and Blinding (masking)**

This was double-blind randomised trial. Randomisation was stratified by de novo status (de novo AML and secondary AML) and geographic region (United States and Canada; Western Europe, Israel, and Australia; Japan; and rest of world).

- **Statistical methods**

Primary endpoint

EFS was defined as the time from randomisation until TF, relapse from remission, or death from any cause, whichever occurred first. Subjects who did not achieve CR by Week 24 were considered to have had an EFS event at Day 1 of randomisation. For subjects who achieved CR by Week 24 (responders), the EFS time was the time from randomisation to relapse or death, whichever occurred first.

EFS was tested using the log-rank test stratified by the randomization stratification factors.

Kaplan-Meier estimates (product-limit estimates) were presented by treatment arm together with a summary of associated statistics.

The HR was estimated using a Cox's proportional hazards (PH) model stratified by the randomization strata. The treatment effect between the treatment arm and the control arm was also assessed based on the difference in Restricted Mean Survival Time (RMST).

Determination of relapse date

Only disease assessments performed on or before the start date of subsequent anticancer therapies were considered in the determination of relapse.

Confirmation was required for relapse. Assessments which were not done or were not evaluable were ignored in the derivation of relapse confirmation. A subject was considered to have relapsed if either of the following criteria were met:

- Relapse in 2 consecutive assessments that were at least 4 weeks apart
- Relapse with no further evaluable disease assessments before discontinuation from study or initiation of subsequent anticancer therapy

The date of relapse considered in the analyses was the date when the first relapse, that was subsequently confirmed, was observed.

Determination of CR by 24 weeks

CR was assessed until the date of relapse (that was subsequently confirmed). Only assessments performed on or before the start date of subsequent anticancer therapies were considered in the determination of CR.

The protocol allowed a 1-week window for disease assessments. Therefore, a subject was considered to have achieved "CR by 24 weeks" if the date of first CR was within 25 weeks (24 weeks target+1-week window) after the date of randomization.

Secondary endpoints

The key secondary efficacy endpoints were CR, OS, CR+CRh, and OR rate. CR, CR+CRh and OR were assessed until the date of relapse (that was subsequently confirmed). Only assessments performed on or before the start date of subsequent anticancer therapies were considered in the determination of these response endpoints.

Multiplicity adjustment

To control the overall Type 1 error rate, the fixed sequence testing procedure was to be used to adjust for multiple statistical testing of the primary and key secondary efficacy endpoints.

These endpoints were tested in the following order:

- EFS
- CR rate
- OS
- CR + complete remission with partial hematologic recovery (CRh) rate
- ORR

No control of the alpha level was made for the other analyses.

Interim analysis

In the original protocol (6 January 2017) there were 2 planned interim analyses for OS:

The first interim analysis was a futility analysis that was to be performed when approximately 33% of the required deaths (93 deaths) had occurred (projected to occur approximately 26 months after the first subject was randomized). Consideration to terminate the study was to be based on the evaluation of the overall safety and efficacy data available at that time by the IDMC, including an observed HR of OS is > 1.05 (in favour of the placebo + azacitidine arm), based on the gamma (-2) error spending function as implemented in East 6.4 (Hwang, et al. 1990). Besides OS, other efficacy data may also have been evaluated by the IDMC.

The second efficacy interim analysis for superiority was to be performed when approximately 67% of the required deaths (185 deaths) had occurred (approximately 39 months after first subject was randomized). At this interim analysis, the study could have stopped for efficacy reasons if the observed HR of OS was ≤ 0.691 (one-sided p-value ≤ 0.006) in favour of the AG-120 + azacitidine arm based on the O' Brien-Fleming alpha spending function, the Lan-DeMets method (Lan and DeMets 1983). These 2 interim analyses were to be conducted by the IDMC with the assistance of an independent biostatistician. Based on the rules above, the IDMC was to make recommendation to the Sponsor regarding continuation of the study.

There were no planned interim analyses for efficacy in this study following protocol amendment 5 (9 January 2020.

The protocol was amended 9 times (See also Conduct of the study). Some key changes were made to the statistical methods as part of the protocol amendments, as summarised in Table *79*.

Table 75. Key changes to statistical methods

Protocol version	Changes to statistical methods
Amendment 5, Version 6.0 (09 January 2020)	**Changed the primary endpoint from OS to EFS**, and added OS to the key secondary endpoints Updated the corresponding statistical analyses and multiplicity adjustment procedure Removed the interim analyses for efficacy

	Reduced the number of subjects who will participate in this study from 392 to 200 based on updated sample size estimations, and increased the number of study centres and countries.
Amendment 7, Version 8.0 (16 December 2020)	Continued efficacy follow-up of subjects in the study for EFS after initiation of subsequent anticancer therapy for subjects who did not have an EFS event. Incorporated a sensitivity analysis for the primary endpoint supporting the continued efficacy follow-up for EFS after initiation of subsequent anticancer therapy for subjects who did not have an EFS event.

Changes from the protocol-specified analysis to the SAP included the following: a) the Intent-to-treat Analysis Set in the protocol was referred to as the FAS in the SAP and b) the estimation of the treatment effect in terms of odds ratio utilized the Mantel-Haenszel estimate of odds ratio (the 95% CI provided directly from the CMH option in SAS PROC FREQ) instead of using the logistic regression model.

Changes introduced after the final SAP

- *IDMC unplanned analysis and recommendation to discontinue treatment*

On 04 November 2020, the IDMC met to review the safety data as part of their semi-annual monitoring of the study. During the closed meeting session, when unblinded data was reviewed, the IDMC observed that more deaths were occurring in the placebo + azacitidine arm vs. the ivosidenib + azacitidine arm. The IDMC recommended the sponsor continue the study as planned and in closed session requested additional unblinded efficacy analyses (EFS and OS). These analyses were reviewed at an ad-hoc IDMC meeting on 08 December 2020; no significant difference between the treatment arms could be concluded. At the subsequent IDMC meeting held on 12 May 2021, the IDMC reviewed the safety data based on the 146 subjects enrolled in the study at the 18 March 2021 data cut date. A greater number of deaths in the placebo + azacitidine arm vs. the ivosidenib + azacitidine arm continued to be observed. This prompted another unblinded analysis for efficacy, which included OS, EFS, and clinical response, and led to the IDMC recommendation to halt recruitment to the study on 12 May 2021. The applicant maintained the blind for the critical study team members directly involved with study conduct, while segregating a small unblinded group to address the IDMC recommendation. On 24 May 2021, unblinded the applicant team members, in consultation with the sponsor, obtained FDA input regarding the IDMC recommendation to halt recruitment; on 27 May 2021 the applicant instructed investigators to discontinue recruitment to the study. At that time, 148 subjects had been randomised (2 additional from the18 March 2021 data cut date). The database for the study was locked on 15 July 2021. On 30 July 2021, investigators were informed that the study met its primary endpoint and all key secondary endpoints and they were given instructions on how to unblind the subjects' treatment assignments. Subjects on the placebo + azacitidine arm were given the opportunity to cross over to the ivosidenib + azacitidine arm if additional safety inclusion and exclusion criteria were met.

This change in study conduct (i.e. allowance of cross over) was detailed in AG120-C-009 protocol, Version 9.0 dated 01 July 2021. The p-value boundaries for the primary and key secondary efficacy endpoints were adjusted to account for the IDMC's unplanned analysis as described below.

Due to the changes of the study, in addition to the fixed sequence testing procedure pre-specified in the SAP, an individual set of group-sequential boundaries were applied separately to each of the primary and key secondary efficacy endpoints to account for this unplanned analysis and subsequent recommendation to stop enrollment in the study. Specifically, the O'Brien-Fleming alpha spending function (the Lan-DeMets method) was used for each of the primary and key secondary efficacy

endpoints. At the time of the analysis, for each of the primary and key secondary endpoints, the p-value calculated based on methodologies pre-specified in the SAP were compared to the p-value boundary calculated from the alpha spending function, respectively. EAST Version 6.5 and R Version 4.0.5 were used for the calculation. For EFS, CR, OS, CR+CRh, and ORR, the 1-sided p-value boundaries are 0.0046, 0.0087, 0.0017, 0.0087, and 0.0087, respectively.

The SAP specified that the CSR would include all data up to the data cut-off date that would be determined on the number of events required for the final analysis of the primary endpoint and a minimum follow-up of 24 weeks for all subjects randomized, but this changed due to the IDMC recommendation.

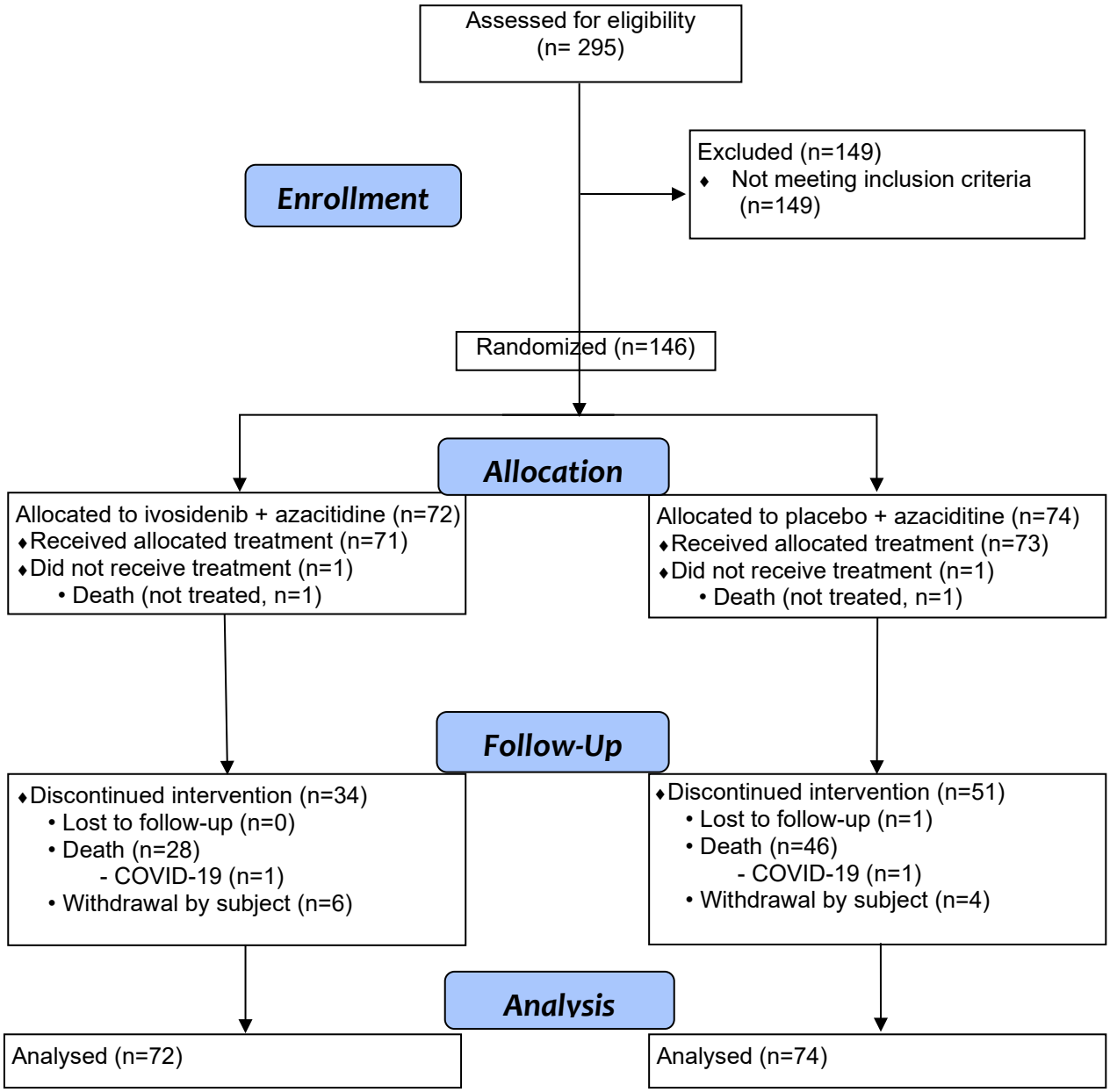
As of the data cutoff date, 10 subjects remained on treatment with less than or equal to 24 weeks who had not yet achieved CR. These subjects could not be evaluated for TF and were censored at the date of randomization. These scenarios were not outlined in the SAP.

Results

- **Participant flow**

Figure 42. Participant flow in study AG120-C-009

- **Recruitment**



- First subject enrolled: 19 March 2018
- Last subject completed: N/A - study ongoing
- Data cut off-date: 18 March 2021

- **Conduct of the study**

Protocol amendments

The original global protocol dated 06 January 2017 was amended nine times. No subjects were enrolled under the original protocol, or Amendments 1, 2, 8 and 9. Ten subjects were enrolled under Amendment 3, 107 subjects were enrolled under Amendment 4, 3 subjects were enrolled under Amendment 5, 25 subjects were enrolled under Amendment 6, 3 subjects were enrolled under Amendment 7.

The key changes to protocol are outlined in the table below. Country-specific amendments are not listed.

Table 76. Main protocol amendments # for study AG120-C-009

Amendment 3, Version 4.0 (14 April 2017)	Removed the optional safety run-in portion of the study based on preliminary safety results for the combination of ivosidenib and azacitidine in Study AG221-AML-005. Revised the section on unblinding to clarify that the responsibility for breaking the treatment code in emergency situations resides solely with the Investigator and that rapid unblinding is possible when necessary. Replaced "treatment failure" with "failure to achieve CR or CR with CRi (including CRp) at 24 weeks" for clarity. Added secondary objectives of rate, duration, and time to CR + CRi (including CRp) to align with the revised definition of EFS, with corresponding endpoints and analyses. Adjusted the timing of response assessments Week 9 and every eighth week thereafter (Weeks 17, 25, etc) to ensure response assessment after 24 weeks (6 months) of treatment. Quality of life assessments were aligned with response assessments from Week 9 onward. Clarified the conditions under which subjects may continue to receive AG-120/placebo after discontinuing azacitidine to mitigate the potential for subjects without CR or CRi (including CRp) to continue on single-agent placebo. Subjects may continue to receive AG-120/placebo following discontinuation of azacitidine, provided they are in CR or CRi (including CRp) and need to discontinue azacitidine due to protocol-specified azacitidine-related toxicity (eg, delayed bone marrow recovery). In response to FDA feedback, removed the attainment of a > 30% reduction in bone marrow blast count percentage as a potential indicator for continued treatment in subjects with a response less than CR or CRi (including CRp) at 24 weeks or beyond. For consistency with the ivosidenib IB, Version 5.0, added that systemic administration of a moderate or strong CYP3A4 inhibitor requires careful QTcF monitoring and that subjects should be routinely monitored for rash. Removed abstinence as an acceptable form of contraception.
Amendment 4, Version 5.0 (31 October 2017) Global	Allowed randomization based on local IDH1 mutation testing (central testing is still required however, and blood and bone marrow samples must be received centrally prior to randomization). Clarified permitted pre-randomization therapies for disease stabilization. Added an exclusion criterion for subjects taking medications that prolong the QT interval, with certain exceptions. Allowed baseline exploratory biomarker samples to be collected as part of Pre-screening.

	Changed disease assessment schedule including: frequency of bone marrow aspirate collection, submission of bone marrow aspirate, and peripheral blood samples for exploratory biomarker analyses. Added an ECG on Day 1 of each treatment cycle. Added pregnancy testing for females of reproductive age on Day 1 of each cycle and at the end of treatment
Amendment 5, Version 6.0 (09 January 2020)	Changed the primary endpoint from OS to EFS and added OS to the key secondary endpoints, and updated the corresponding statistical analyses. Updated the additional secondary endpoint evaluating IDH1 mutation clearance (MC) and the corresponding statistical analyses. Updated the inclusion criterion to more narrowly define a population of patients who are ineligible for intensive IC, and aligned the associated liver and renal function criteria. For consistency with the current edition of the ivosidenib IB, removed the criterion excluding subjects taking P-gp transporter sensitive substrate medications; added a criterion excluding subjects with a medical history of PML as PML is a potential risk of treatment with AG-120; and revised information on drug-drug interactions. Removed the interim analyses for efficacy. Reduced the number of subjects who will participate in this study from 392 to 200 based on updated sample size estimations, and increased the number of study centers and countries
Amendment 7, Version 8.0 (16 December 2020)	Added a section describing temporary protocol modifications to ensure subject safety, maintain compliance with GCP, and minimize risks to study integrity during a COVID-19 public health emergency. Continued efficacy follow-up of subjects in the study for EFS after initiation of subsequent anticancer therapy for subjects who did not have an EFS event. Incorporated a sensitivity analysis for the primary endpoint supporting the continued efficacy follow-up for EFS after initiation of subsequent anticancer therapy for subjects who did not have an EFS event

Protocol deviations

A total of 74 (50.7%) subjects had a major deviation, with similar rates of subjects with major deviations reported in the ivosidenib + azacitidine (37 [51.4%] subjects) and placebo + azacitidine (37 [50.0%] subjects) arms.

Fifty (34.2%) subjects had an ICH/GCP deviation. Rates of subjects with ICH/GCP deviations were similar between the ivosidenib + azacitidine (27 [37.5%] subjects) and placebo + azacitidine (23 [31.1%] subjects) arms; most of these subjects (39 [26.7%]) had deviations related to informed consent.

Overall rates of subjects with other protocol deviations were also similar between the treatment arms (24 [33.3%] in the experimental arm and 25 [33.8%] in the control arm); the most common deviations were SAE reporting deviations and missed visits or assessments.

No protocol deviation was judged to have impacted the overall conduct of the study, data analyses, or study conclusions.

- **Baseline data**

Baseline demographic and disease characteristics are summarised in Table 81 and Table 82 respectively.

Table 77. Demographics of subjects in study AG120-C-009, Full analysis set

	AG-120 + azacitidine (N=72)	Placebo + azacitidine (N=74)	Total (N=146)
Age (years)			
n	72	74	146
Mean (SD)	74.5 (6.18)	75.2 (7.39)	74.8 (6.81)
Median (Q1, Q3)	76.0 (70.5, 79.5)	75.5 (70.0, 80.0)	76.0 (70.0, 80.0)
Min, Max	58, 84	45, 94	45, 94
Age Category I (years), n (%)			
<65	4 (5.6)	4 (5.4)	8 (5.5)
≥ 65	68 (94.4)	70 (94.6)	138 (94.5)
Age Category II (years), n (%)			
<75	33 (45.8)	31 (41.9)	64 (43.8)
≥ 75	39 (54.2)	43 (58.1)	82 (56.2)
Sex, n (%)			
Male	42 (58.3)	38 (51.4)	80 (54.8)
Female	30 (41.7)	36 (48.6)	66 (45.2)
Ethnicity, n (%)			
Hispanic or Latino	6 (8.3)	1 (1.4)	7 (4.8)
Not Hispanic or Latino	21 (29.2)	32 (43.2)	53 (36.3)
Not Reported	45 (62.5)	41 (55.4)	86 (58.9)
Race, n (%)			
Asian	15 (20.8)	19 (25.7)	34 (23.3)
White	12 (16.7)	12 (16.2)	24 (16.4)
Black or African American	0	2 (2.7)	2 (1.4)
Other	1 (1.4)	1 (1.4)	2 (1.4)
Not Reported	44 (61.1)	40 (54.1)	84 (57.5)
Height (cm)			
n	71	74	145
Mean (SD)	166.84 (10.103)	163.50 (9.422)	165.14 (9.870)
Median (Q1, Q3)	167.00 (158.00, 176.00)	162.40 (156.00, 170.00)	163.00 (158.00, 173.00)
Min, Max	143.0, 188.0	145.0, 184.0	143.0, 188.0
Weight (kg)			
n	71	74	145
Mean (SD)	73.22 (12.005)	69.20 (16.170)	71.17 (14.376)
Median (Q1, Q3)	73.00 (65.00, 78.90)	65.35 (56.00, 81.40)	69.00 (61.00, 80.00)
Min, Max	34.0, 105.0	38.0, 116.0	34.0, 116.0
BMI (kg/m^2)			
n	71	74	145
Mean (SD)	26.36 (4.418)	25.77 (5.034)	26.06 (4.735)
Median (Q1, Q3)	25.39 (23.41, 28.99)	25.28 (22.44, 28.40)	25.32 (23.07, 28.40)
Min, Max	16.6, 42.0	16.4, 41.1	16.4, 42.0
BSA (m^2)			
n	71	73	144
Mean (SD)	1.824 (0.1738)	1.745 (0.2210)	1.784 (0.2023)
Median (Q1, Q3)	1.830 (1.720, 1.940)	1.710 (1.580, 1.880)	1.770 (1.635, 1.930)
Min, Max	1.17, 2.20	1.27, 2.36	1.17, 2.36

Table 78. Baseline Disease Characteristics of subjects in study AG120-C-009, Full analysis set

	AG-120 + azacitidine (N=72)	Placebo + azacitidine (N=74)	Total (N=146)
Disease Type, n (%)			
Nature of AML per Investigator			
De Novo	54 (75.0)	53 (71.6)	107 (73.3)
Secondary	18 (25.0)	21 (28.4)	39 (26.7)
Treatment-Related AML	2 (2.8)	1 (1.4)	3 (2.1)
History of MDS	10 (13.9)	12 (16.2)	22 (15.1)
History of MPD	4 (5.6)	8 (10.8)	12 (8.2)
Other	2 (2.8)	0	2 (1.4)
Nature of AML per IWRS			
De Novo	56 (77.8)	55 (74.3)	111 (76.0)
Secondary	16 (22.2)	19 (25.7)	35 (24.0)
WHO classification of AML, n(%)			
AML with Genetic Abnormalities	16 (22.2)	24 (32.4)	40 (27.4)
AML with Myelodysplasia-related Changes	28 (38.9)	26 (35.1)	54 (37.0)
Therapy-Related Myeloid Neoplasms	1 (1.4)	1 (1.4)	2 (1.4)
AML Not Otherwise Specified	27 (37.5)	23 (31.1)	50 (34.2)
ECOG performance status, n (%)			
0	14 (19.4)	10 (13.5)	24 (16.4)
1	32 (44.4)	40 (54.1)	72 (49.3)
2	26 (36.1)	24 (32.4)	50 (34.2)
IDH1 mutation type based on central testing, n(%)			
R132C	45 (62.5)	51 (68.9)	96 (65.8)
R132G	6 (8.3)	4 (5.4)	10 (6.8)
R132H	14 (19.4)	12 (16.2)	26 (17.8)
R132L	3 (4.2)	0	3 (2.1)
R132S	2 (2.8)	6 (8.1)	8 (5.5)
Wild type	1 (1.4)	0	1 (0.7) [5]
Missing	1 (1.4)	1 (1.4)	2 (1.4) [5]
IDH1 mutation status based on local testing, n(%)			
Positive	39 (54.2)	40 (54.1)	79 (54.1)
Negative	1 (1.4)	2 (2.7)	3 (2.1) [6]
Missing	32 (44.4)	32 (43.2)	64 (43.8)
Cytogenetic results based on local testing, n(%)			
Normal karyotype	32 (44.4)	31 (41.9)	63 (43.2)
Abnormal karyotype	26 (36.1)	30 (40.5)	56 (38.4)

	AG-120 + azacitidine (N=72)	Placebo + azacitidine (N=74)	Total (N=146)
Missing	14 (19.4)	13 (17.6)	27 (18.5)
Cytogenetic risk status by Investigator, n(%)			
Favorable	3 (4.2)	7 (9.5)	10 (6.8)
Intermediate	48 (66.7)	44 (59.5)	92 (63.0)
Poor	16 (22.2)	20 (27.0)	36 (24.7)
Other	3 (4.2)	1 (1.4)	4 (2.7)
Missing	2 (2.8)	2 (2.7)	4 (2.7)
Bone marrow blasts (%) [1]			
n	71	73	144
Mean (SD)	55.2 (23.30)	53.3 (23.45)	54.2 (23.31)
Median (Q1, Q3)	54.0 (32.0, 75.0)	48.0 (33.0, 70.0)	52.5 (32.5, 74.5)
Min, Max	20, 95	17, 100	17, 100
Bone marrow aspirate blasts (%)			
n	71	72	143
Mean (SD)	55.2 (23.30)	53.7 (23.37)	54.4 (23.27)
Median (Q1, Q3)	54.0 (32.0, 75.0)	48.5 (33.5, 71.0)	53.0 (33.0, 75.0)
Min, Max	20, 95	17, 100	17, 100
Bone marrow biopsy blasts (%)			
n	7	13	20
Mean (SD)	56.9 (22.97)	50.8 (24.14)	53.0 (23.31)
Median (Q1, Q3)	60.0 (40.0, 80.0)	50.0 (30.0, 59.0)	50.0 (32.5, 72.5)
Min, Max	25, 88	20, 90	20, 90
Peripheral blood blasts (%)			
n	57	59	116
Mean (SD)	33.49 (31.344)	28.14 (30.970)	30.77 (31.135)
Median (Q1, Q3)	23.00 (4.00, 61.40)	15.00 (0.50, 50.00)	20.00 (2.00, 54.85)
Min, Max	0.0, 94.0	0.0, 98.0	0.0, 98.0
WBC (10^9/L) [2]			
n	72	74	146
Mean (SD)	6.971 (15.1384)	9.421 (15.9593)	8.213 (15.5548)
Median (Q1, Q3)	2.055 (1.300, 7.165)	2.315 (1.340, 7.260)	2.245 (1.300, 7.260)
Min, Max	0.42, 118.40	0.50, 83.58	0.42, 118.40
WBC category (10^9/L), n(%)			
< 15	65 (90.3)	60 (81.1)	125 (85.6)
15 - < 30	4 (5.6)	5 (6.8)	9 (6.2)
≥ 30	3 (4.2)	9 (12.2)	12 (8.2)

	AG-120 + azacitidine (N=72)	Placebo + azacitidine (N=74)	Total (N=146)
ANC (10^9/L) [3]			
n	70	71	141
Mean (SD)	0.983 (2.2419)	1.491 (3.6897)	1.239 (3.0576)
Median (Q1, Q3)	0.210 (0.060, 0.630)	0.224 (0.090, 0.970)	0.210 (0.090, 0.780)
Min, Max	0.00, 12.90	0.00, 23.73	0.00, 23.73
ANC category (10^9/L), n(%)			
< 0.5	49 (68.1)	44 (59.5)	93 (63.7)
0.5 - < 1	8 (11.1)	10 (13.5)	18 (12.3)
≥ 1	13 (18.1)	17 (23.0)	30 (20.5)
Missing	2 (2.8)	3 (4.1)	5 (3.4)
Hemoglobin (g/L)			
n	72	74	146
Mean (SD)	88.63 (14.924)	91.96 (15.419)	90.32 (15.216)
Median (Q1, Q3)	87.00 (79.10, 99.50)	90.00 (82.00, 101.00)	89.00 (80.00, 100.00)
Min, Max	59.0, 131.0	63.0, 143.0	59.0, 143.0
Hemoglobin category (g/L), n(%)			
< 80	19 (26.4)	14 (18.9)	33 (22.6)
≥ 80	53 (73.6)	60 (81.1)	113 (77.4)
Platelet count (10^9/L)			
n	72	74	146
Mean (SD)	71.511 (86.4417)	92.656 (100.7111)	82.228 (94.2213)
Median (Q1, Q3)	39.000 (21.000, 95.500)	68.000 (32.000, 129.000)	56.800 (22.000, 108.000)
Min, Max	2.00, 583.00	9.00, 646.00	2.00, 646.00
Platelet count category (10^9/L), n(%)			
< 50	42 (58.3)	27 (36.5)	69 (47.3)
50 - < 100	14 (19.4)	20 (27.0)	34 (23.3)
≥ 100	16 (22.2)	27 (36.5)	43 (29.5)
Lactate dehydrogenase (LDH) (U/L)			
n	72	73	145
Mean (SD)	328.67 (214.486)	356.15 (239.976)	342.50 (227.303)
Median (Q1, Q3)	264.50 (203.00, 405.50)	301.00 (188.00, 421.00)	272.00 (189.00, 416.00)
Min, Max	116.0, 1320.0	65.0, 1397.0	65.0, 1397.0

	AG-120 + azacitidine (N=72)	Placebo + azacitidine (N=74)	Total (N=146)
Creatinine clearance (mL/min) [4]			
n	71	74	145
Mean (SD)	75.91 (27.424)	69.45 (23.807)	72.61 (25.757)
Median (Q1, Q3)	71.84 (58.39, 91.11)	67.17 (54.05, 80.81)	69.92 (55.57, 85.09)
Min, Max	26.9, 174.1	24.8, 140.4	24.8, 174.1
Creatinine clearance category I (mL/min), n(%)			
15 - < 40	4 (5.6)	7 (9.5)	11 (7.5)
40 - < 60	18 (25.0)	20 (27.0)	38 (26.0)
60 - < 90	30 (41.7)	34 (45.9)	64 (43.8)
≥ 90	19 (26.4)	13 (17.6)	32 (21.9)
Missing	1 (1.4)	0	1 (0.7)
Creatinine clearance category II (mL/min), n(%)			
<30	2 (2.8)	3 (4.1)	5 (3.4)
30 - < 45	3 (4.2)	7 (9.5)	10 (6.8)
≥ 45	66 (91.7)	64 (86.5)	130 (89.0)
Missing	1 (1.4)	0	1 (0.7)
Extramedullary disease, n(%)			
Yes	4 (5.6)	2 (2.7)	6 (4.1)
No	59 (81.9)	65 (87.8)	124 (84.9)
Unknown	5 (6.9)	6 (8.1)	11 (7.5)
Not Assessed	4 (5.6)	1 (1.4)	5 (3.4)

Source: Table 14.1-6.1; Listing 16.1-6.1. Data cutoff date: 18 March 2021
Abbreviations: AML = acute myeloid leukemia; ECOG = Eastern Cooperative Oncology Group; FAS = full analysis set; IDH1 =Isocitrate dehydrogenase 1; IWRS = Interactive Web Response System; MDS = Myelodysplastic syndrome; MPD = myeloproliferative disease; SD = standard deviation
The denominator used to calculate percentages is N, the number of subjects in the full analysis set within each column.
[1] For bone marrow blasts, bone marrow aspirate will be used as the primary source. If a bone marrow aspirate assessment is not available, a bone marrow biopsy assessment will be used.
[2] WBC: White blood cell.
[3] ANC: Absolute neutrophil count.
[4] Creatinine Clearance (mL/min) = (140 - age)x baseline weight (kg)x (0.85 if female)/ (72xbaseline serum creatinine [mg/dL]).
[5] IDH1 mutation for these subjects was confirmed with local testing.
[6] IDH1 mutation for these subjects was confirmed with central testing.

Baseline demographics were generally similar for subjects enrolled before and after Protocol Amendment 5 (data not shown). In the overall subject population, the proportion of male subjects (56.0% and 52.7%, respectively) and the proportion of subjects over the age of 75 years (53.8% and 60.0%) were similar among subjects enrolled before and after Protocol Amendment 5, respectively. The proportion of subjects enrolled in Western Europe, Israel, and Australia was somewhat higher before versus after Protocol Amendment 5 (70.3% and 52.7%, respectively); this was due to the change of the number of active sites globally during the evolution of the study.

Baseline disease characteristics were also generally similar for subjects enrolled before and after Protocol Amendment 5 (data not shown). The majority of subjects had de novo AML at initial diagnosis both before Protocol Amendment 5 (70.3% per Investigator and 74.7% per IWRS) and after Protocol

Amendment 5 (78.2% per Investigator and 78.2% per IWRS). Per the WHO classification of AML, among subjects enrolled before and after Protocol Amendment 5, respectively, 22.0% and 36.4% of subjects had AML with genetic abnormalities, 38.5% and 34.5% had AML with myelodysplasia-related changes, and 38.5% and 27.3% had AML not otherwise specified. Approximately one third of subjects had an ECOG PS of 2 (33.0% and 36.4% of subjects, respectively). Cytogenetic risk status as assessed by the Investigators based on the 2017 NCCN guidelines was intermediate (63.7% and 61.8% of subjects enrolled before and after Protocol Amendment 5, respectively) or poor (26.4% and 21.8%, respectively) for most subjects at baseline. Most subjects did not have extramedullary disease (84.6% and 85.5% of subjects enrolled before and after Protocol Amendment 5, respectively).

- **Numbers analysed**

As of the 18 March 2021 data cut-off, 146 subjects have been randomized. The study is ongoing. The following data sets were analysed:

- 146 subjects were included in the FAS (all randomized subjects)
    - 141 (96.6%) subjects were included in the per-protocol set (PPS), a subset of the FAS Subjects who meet any of the following criteria will be excluded from the PPS:
        - Do not receive at least 1 dose of the randomized treatment
        - Eligible for intensive chemotherapy (IC)
        - Do not have an IDH1 mutation as determined by central laboratory testing
        - Have an ECOG PS score >2
        - Have received any prior treatment for AML with the exception of non-oncolytic treatments to stabilize disease such as hydroxyurea or leukapheresis
        - Have received any prior hypomethylating agent
        - Have received any prior IDH1 inhibitor
    - 77 (52.7%) subjects were included in the Biomarker Analysis Set, a subset of the safety analysis set that includes all subjects who have at least 1 on-treatment biomarker sample providing valid IDH1m variant allele frequency (VAF) data.
- 144 subjects were included in the Safety Analysis Set (SAS): all subjects who received at least 1 dose of study treatment (71 in the ivosidenib/azacytidine arm and 73 in the placebo/azacitidine arm).

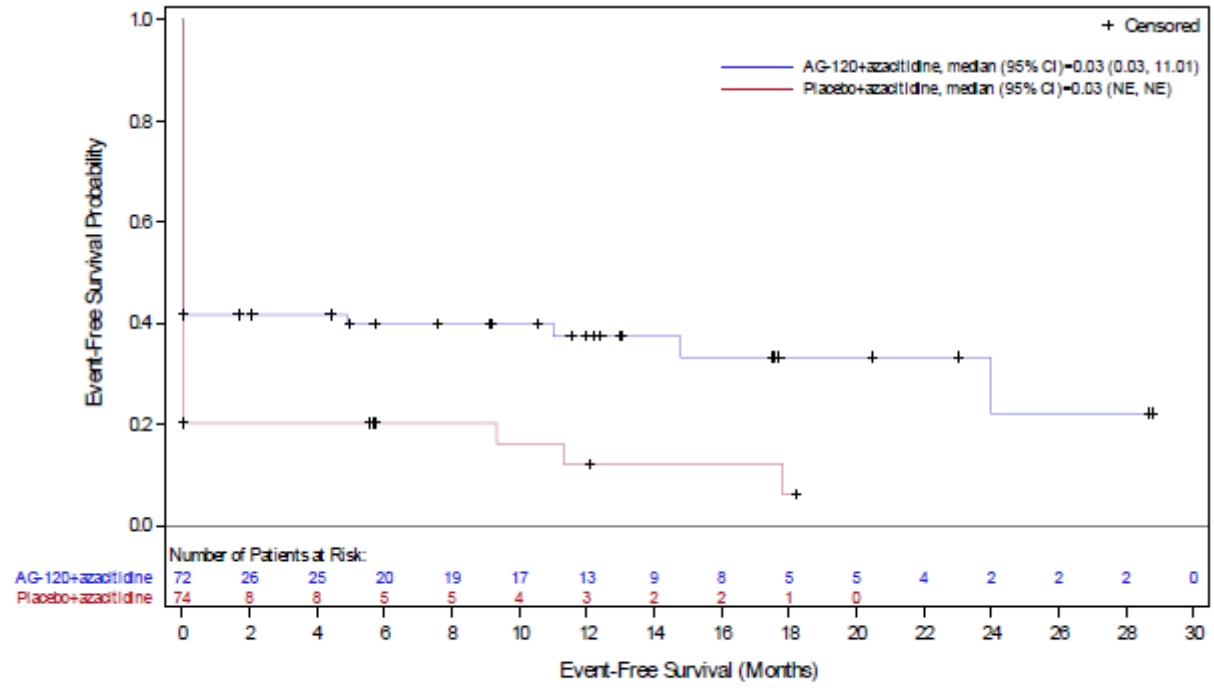
- **Outcomes and estimation**

<u>Event-free Survival (EFS)</u>

Table 79. Summary of Event-free Survival in study AG120-C-009, Full analysis set

	AG-120 + azacitidine (N=72)	Placebo + azacitidine (N=74)
Event-free survival(months) [1]		
Number (%) of Events	46 (63.9)	62 (83.8)
Treatment failure	42 (58.3)	59 (79.7)
TF, on treatment >24 weeks without CR	16 (22.2)	11 (14.9)
TF, treatment discontinuation ≤ 24 weeks without CR	26 (36.1)	48 (64.9)
Relapse	3 (4.2)	2 (2.7)
Death	1 (1.4)	1 (1.4)
Number (%) Censored [2]	26 (36.1)	12 (16.2)
CR by 24 weeks, start subsequent anticancer therapy	1 (1.4)	0
CR by 24 weeks, relapse/death documented after 2 or more missing disease assessments	0	0
CR by 24 weeks, lost to follow-up	0	0
CR by 24 weeks, withdrawal by subject	2 (2.8)	0
CR by 24 weeks, ongoing without relapse or death	20 (27.8)	5 (6.8)
On treatment ≤ 24 weeks, ongoing, have not achieved CR yet	3 (4.2)	7 (9.5)
Percentiles (95% CI) [3]		
25th	0.03 (NE, NE)	0.03 (NE, NE)
50th (median)	0.03 (0.03, 11.01)	0.03 (NE, NE)
75th	23.98 (14.78, NE)	0.03 (0.03, 11.30)
Hazard Ratio (95% CI) [4]		0.33 (0.16, 0.69)
1-sided p-value [5]		0.0011
Event-free survival rate (%) (95% CI) [6]		
1 Day	41.7 (30.2, 52.7)	20.3 (12.0, 30.0)
3 Months	41.7 (30.2, 52.7)	20.3 (12.0, 30.0)
6 Months	39.9 (28.6, 51.0)	20.3 (12.0, 30.0)
9 Months	39.9 (28.6, 51.0)	20.3 (12.0, 30.0)
12 Months	37.4 (25.9, 48.9)	12.2 (4.3, 24.4)
18 Months	33.3 (20.9, 46.2)	6.1 (0.7, 20.9)
24 Months	22.2 (6.6, 43.4)	NE
36 Months	NE	NE

Figure 43. Kaplan-Meier Plot of Event-Free Survival in study AG120-C-009, Full analysis set



Source: Figure 14.2.1-1.1; Listing 16.2.1-1.1; Data cutoff date: 18 March 2021
Abbreviations: CI = confidence interval; NE = not estimable

Complete Remission

Table 80. Summary of Complete Remission Rate in the FAS

	AG-120 + azacitidine (N=72)	Placebo+azacitidine (N=74)
CR Rate, n (%)	34 (47.2)	11 (14.9)
95% CI [1]	(35.3, 59.3)	(7.7, 25.0)
Odds Ratio (95% CI) [2]		4.76 (2.15, 10.50)
1-sided p-value [3]		<0.0001

Source: Table 14.2.1-2.3a, Listing 16.2.1-2.3. Data cutoff date: 18 March 2021
Abbreviations: CR = complete remission
[1] CI: confidence interval. CI of percentage is calculated with the Clopper and Pearson (exact Binomial) method.
[2] Cochran-Mantel-Haenszel (CMH) estimate for odds ratio is calculated with placebo + azacitidine as the control (denominator). CI: confidence interval.
[3] If the primary analysis of EFS is significant, a stratified Cochran-Mantel-Haenszel (CMH) test will be used to compare CR between the 2 treatment arms. 1-sided p-value is calculated from CMH test stratified by the randomization stratification factors (AML status and geographic region).

Overall Survival

The tables below present the summary of OS and OS follow-up time in the FAS, along with the OS KM plot.

Table 81. Summary of Overall Survival in study AG120-C-009, Full analysis set

	AG-120 + azacitidine (N=72)	Placebo + azacitidine (N=74)
Overall Survival (months)		
Number (%) of Events	28 (38.9)	46 (62.2)
Number (%) Censored	44 (61.1)	28 (37.8)
Alive	38 (52.8)	23 (31.1)
Lost to Follow-up	0	1 (1.4)
Withdrawal of consent	6 (8.3)	4 (5.4)
Percentiles (95% CI) [1]		
25th	5.7 (2.1, 11.3)	2.0 (1.1, 3.1)
50th (median)	24.0 (11.3, 34.1)	7.9 (4.1, 11.3)
75th	34.1 (NE, NE)	18.1 (11.3, NE)
Hazard Ratio (95% CI) [2]		0.44 (0.27, 0.73)
1-sided p-value [3]		0.0005
Overall Survival Rate (%) (95% CI) [4]		
3 Months	84.2 (73.3, 91.0)	66.6 (54.4, 76.2)
6 Months	72.9 (60.4, 82.0)	56.3 (43.6, 67.3)
9 Months	67.5 (54.4, 77.6)	43.9 (30.9, 56.1)
12 Months	63.4 (49.8, 74.2)	36.9 (24.3, 49.7)
18 Months	60.9 (47.1, 72.2)	26.4 (14.7, 39.6)
24 Months	45.4 (26.8, 62.2)	20.5 (10.0, 33.7)
36 Months	0	NE

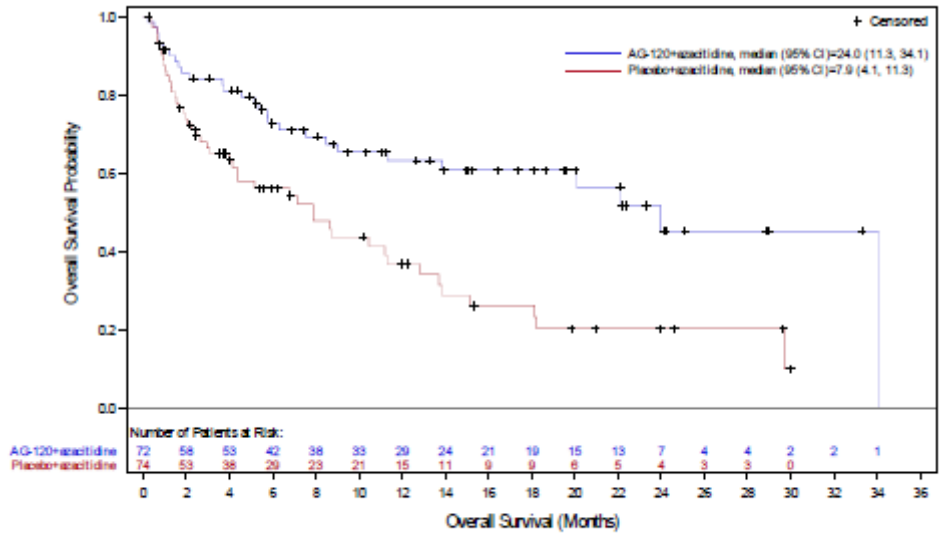
Source: Table 14.2.1-2.1; Listing 16.2.1-2.1. Data cutoff date: 18 March 2021
Abbreviations: CI = confidence interval; NE = not estimable
Percentages are calculated with the number of subjects in each column as the denominator.
[1] Percentiles are estimated from product-limit (Kaplan-Meier) method. Confidence intervals are calculated from Brookmeyer and Crowley method with log-log transformation.
[2] Hazard ratio is estimated using a Cox's proportional hazards model stratified by the randomization stratification factors (AML status and geographic region) with placebo + azacitidine as the denominator.
[3] P-value is calculated from the one-sided log-rank test stratified by the randomization stratification factors (AML status and geographic region).
[4] Overall survival rate is the estimated probability that a subject will remain alive to the specified time point. Overall survival rates are obtained from the Kaplan-Meier survival estimates. Confidence intervals are calculated using Greenwood's formula and log-log transformation.

Table 82. Summary of Overall Survival Follow-up Time in the FAS

	AG-120 + azacitidine (N=72)	Placebo + azacitidine (N=74)
Overall Survival Follow-up Time (months) [1]		
25th Percentile (95% CI) [2]	8.1 (4.9, 11.2)	5.4 (3.5, 10.2)
Median (95% CI)	15.2 (11.2, 19.6)	15.3 (6.8, 24.0)
75th Percentile (95% CI)	22.3 (19.5, 25.1)	24.6 (19.8, 30.0)
Min, Max	0.2, 34.1	0.3, 30.0

Source: Table 14.2.1-2.2; Listing 16.2.1-2.1. Data cutoff date: 18 March 2021
Abbreviation: CI = confidence interval
[1] Overall Survival Follow-up Time is estimated based on reverse Kaplan-Meier method.
[2] Percentiles are estimated from product-limit (Kaplan-Meier) method. Confidence intervals are calculated from Brookmeyer and Crowley method with log-log transformation.

Figure 44. Kaplan-Meier Plot of Overall Survival in study AG120-C-009, Full analysis set



Source: Figure 14.2.1-2.1, Listing 16.2.1-2.1. Data cutoff date: 18 March 2021

CR+CRh

Table 83. Summary of CR+CRh rates (FAS)

	AG-120 + azacitidine (N=72)	Placebo + azacitidine (N=74)
CR+CRh Rate, n (%) [1]	38 (52.8)	13 (17.6)
95% CI [2]	(40.7, 64.7)	(9.7, 28.2)
Odds Ratio (95% CI) [3]		5.01 (2.32, 10.81)
1-sided p-value [4]		<0.0001

Source: Table 14.2.1-2.3a; Listing 16.2.1-2.3. Data cutoff date: 18 March 2021

Abbreviations: CI = confidence interval; CR = complete remission; CRh = complete remission with partial hematologic recovery

[1] CRh is defined as a CR with partial hematologic recovery and is derived.

[2] CI: confidence interval. CI of percentage is calculated with the Clopper and Pearson (exact Binomial) method.

[3] Cochran-Mantel-Haenszel (CMH) estimate for odds ratio is calculated with placebo + azacitidine as the control (denominator). CI: confidence interval.

[4] If the primary analyses of EFS, CR and OS are significant, a stratified Cochran-Mantel-Haenszel (CMH) test will be used to compare CR+CRh between the 2 treatment arms. 1-sided p-value is calculated from CMH test stratified by the randomization stratification factors (AML status and geographic region).

ORR

Table 84. Summary of ORR in study AG120-C-009, Full analysis set

	AG-120 + azacitidine (N=72)	Placebo + azacitidine (N=74)
OR Rate, n (%)	45 (62.5)	14 (18.9)
95% CI [1]	(50.3, 73.6)	(10.7, 29.7)
Odds Ratio (95% CI) [2]		7.15 (3.31, 15.44)
1-sided p-value [3]		<0.0001

Source: Table 14.2.1-2.3a; Listing 16.2.1-2.3. Data cutoff date: 18 March 2021
[1] CI: confidence interval. CI of percentage is calculated with the Clopper and Pearson (exact Binomial) method.
[2] Cochran-Mantel-Haenszel (CMH) estimate for odds ratio is calculated with placebo + azacitidine as the control (denominator). CI: confidence interval.
[3] If the primary analyses of EFS, CR, OS and CR+CRh are significant, a stratified Cochran-Mantel-Haenszel (CMH) test will be used to compare ORR between the 2 treatment arms. 1-sided p-value is calculated from CMH test stratified by the randomization stratification factors (AML status and geographic region).

CR + CRi

The CR + CRi parameters are presented in the table below.

Table 85. Summary of CR+CRi Rate in study AG120-C-009, Full analysis set

	AG-120 + azacitidine (N=72)	Placebo + azacitidine (N=74)
CR+CRi Rate, n (%)	39 (54.2)	12 (16.2)
95% CI [1]	(42.0, 66.0)	(8.7, 26.6)
Odds Ratio (95% CI) [2]		5.90 (2.69, 12.97)
1-sided p-value [3]		<0.0001

Source: Table 14.2.1-2.3a; Listing 16.2.1-2.3. Data cutoff date: 18 March 2021
Abbreviations: CI = confidence interval; NE = not estimable
[1] CI: confidence interval. CI of percentage is calculated with the Clopper and Pearson (exact Binomial) method.
[2] Cochran-Mantel-Haenszel (CMH) estimate for odds ratio is calculated with placebo + azacitidine as the control (denominator). CI: confidence interval.
[3] 1-sided p-value is calculated from CMH test stratified by the randomization stratification factors (AML status and geographic region).

Duration of Response

DOCR

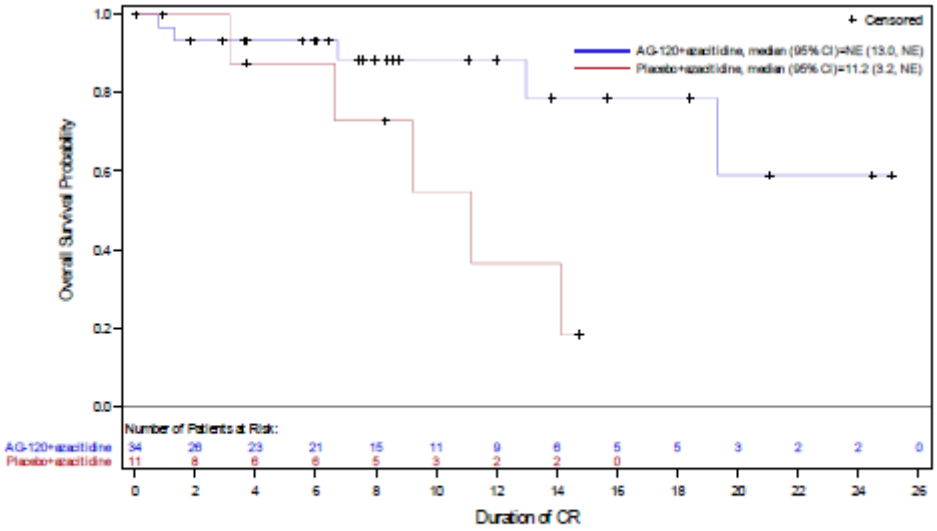
Duration of complete remission (DOCR) is summarized in the table below. The corresponding KM plot of DOCR is also provided.

Table 86. Summary of Duration of Complete Remission (DOCR) in study AG120-C-009, Full analysis set

	AG-120 + azacitidine (N=72)	Placebo + azacitidine (N=74)
Number of Subjects who achieved CR	34	11
Duration of CR (months) [1]		
Number (%) of Events	5 (14.7)	5 (45.5)
Number (%) Censored	29 (85.3)	6 (54.5)
Start subsequent anticancer therapy	2 (5.9)	0
Relapse/death documented after 2 or more missing disease assessments	0	0
Lost to Follow-up	0	0
Withdrawal by subject	2 (5.9)	0
Ongoing without relapse or death	25 (73.5)	6 (54.5)
Percentiles (95% CI) [2]		
25th	19.4 (6.7, NE)	6.6 (3.2, 11.2)
50th (median)	NE (13.0, NE)	11.2 (3.2, NE)
75th	NE (19.4, NE)	14.1 (9.2, NE)
Duration of CR Rate (%) (95% CI) [3]		
3 Months	93.3 (75.9, 98.3)	100
6 Months	93.3 (75.9, 98.3)	87.5 (38.7, 98.1)
9 Months	88.4 (67.5, 96.2)	72.9 (27.6, 92.5)
12 Months	88.4 (67.5, 96.2)	36.5 (5.3, 70.6)
18 Months	78.6 (47.5, 92.5)	NE
24 Months	58.9 (17.7, 85.1)	NE
36 Months	NE	NE

Source: Table 14.2.1-3.1a; Listing 16.2.1-3.1. Data cutoff date: 18 March 2021
Abbreviations: CI = confidence interval; CR = complete remission; NE = not estimable
Percentages are calculated with the number of subjects who achieved CR in each column as the denominator.
[1] Duration of CR is defined, for subjects who achieved CR, as the time from the first occurrence of CR to confirmed relapse or death due to any cause. DOCR (months)=(Date of event or censoring – first date of CR + 1)/30.4375.
[2] Percentiles are estimated from product-limit (Kaplan-Meier) method. Confidence intervals are calculated from Brookmeyer and Crowley method with log-log transformation.
[3] Duration of CR rate is the estimated probability that a subject will remain CR up to the specified time point. Duration of CR rates are obtained from the Kaplan-Meier survival estimates. Confidence intervals are calculated using Greenwood's formula and log-log transformation.

Figure 45. Kaplan-Meier Plot of Duration of Complete Remission (DOCR) in study AG120-C-009, Full analysis set



Source: Figure 14.2.1-3.1; Listing 16.2.1-3.1. Data cutoff date: 18 March 2021
Abbreviations: CR = Complete remission; DOCR = duration of complete remission
DOCR was defined, for subjects who achieved CR, as the time from the first occurrence of CR to confirmed relapse or death due to any cause.

Time to Response

Time to response, defined as TTCR, TTCRh and TTCRi, is reported in the table below.

Table 87. Summary of Time to CR, CR + CRh, First Response and CR + CRi (TTCR, TTCRh, TTR, TTCRi) in study AG120-C-009, Full analysis set

	AG-120 + azacitidine (N=72)	Placebo + azacitidine (N=74)
Time to CR (months) [1]		
n	34	11
Mean (SD)	4.53 (1.934)	4.76 (2.294)
Median	4.25	3.81
Min, Max	1.7, 9.2	1.9, 8.5
Time to CR + CRh (months) [2]		
n	38	13
Mean (SD)	4.11 (1.889)	4.22 (1.548)
Median	4.02	3.91
Min, Max	1.7, 8.6	1.9, 7.2
Time to first response (months) [3]		
n	45	14
Mean (SD)	2.77 (1.320)	3.86 (1.985)
Median	2.07	3.68
Min, Max	1.7, 7.5	1.9, 9.4
Time to CR + CRi (months) [4]		
n	39	12
Mean (SD)	3.36 (1.569)	3.95 (1.483)
Median	2.79	3.76
Min, Max	1.7, 7.2	1.9, 7.2

Source: Table 14.2.1-3.5a; Listing 16.2.1-3.1; Listing 16.2.1-3.2;Listing 16.2.1-3.3;Listing 16.2.1-3.4. Data cutoff date: 18 March 2021

Abbreviations: CI = confidence interval; CR = complete remission; CRh = complete remission with partial hematologic recovery; CRi = complete remission with incomplete recovery; NE = not estimable

[1] Time to CR is defined, for subjects who achieved CR, as the time from randomization to first occurrence of CR. TTCR (months)=(first date of CR - date of randomization + 1)/30.4375.

[2] Time to CR+CRh is defined, for subjects who achieved CR or CRh, as the time from randomization to first occurrence of CR or CRh. TTCRh (months)=(first date of CR or CRh - date of randomization + 1)/30.4375.

[3] Time to first response is defined, for subjects who achieved CR, CRi(including CRp), PR or MLFS, as the time from randomization to first occurrence of CR, CRi(including CRp), PR or MLFS. TTR (months)=(first date of CR, CRi(including CRp), PR or MLFS - date of randomization + 1)/30.4375.

[4] Time to CR+CRi is defined, for subjects who achieved CR or CRi(including CRp), as the time from randomization to first occurrence of CR or CRi(including CRp). TTCR (months)=(first date of CR or CRi(including CRp) - date of randomization + 1)/30.4375.

Health-related Quality of Life Assessments

Table 88. Summary of EORTC QLQ-C30 Global Health Status/QoL and Fatigue Score Change from Baseline in study AG120-C-009, Full analysis set

Visit	Ivosidenib + Azacitidine Arm Least Square Mean (95% CI)	Placebo + Azacitidine Arm Least Square Mean (95% CI)	Difference of Least Square Mean (95% CI)	p-value [1]
Global Health Status/QoL (Higher score indicates better status/HRQoL)				
C1D15	-8.0 (-16.41, 0.37)	-10.4 (-18.78, -1.93)	2.3 (-5.50, 10.18)	0.5580
C2D1	1.3 (-7.24, 9.90)	-8.9 (-17.37, -0.46)	10.2 (2.21, 18.27)	0.0126
C2D15	-4.8 (-13.50, 3.97)	-14.8 (-23.75, -5.89)	10.1 (1.43, 18.69)	0.0225
C3D1	4.1 (-4.55, 12.80)	-3.5 (-12.72, 5.66)	7.7 (-1.14, 16.45)	0.0879
C5D1	11.4 (2.43, 20.36)	4.5 (-5.38, 14.41)	6.9 (-2.88, 16.64)	0.1664
C7D1	10.6 (1.23, 19.97)	-2.0 (-12.80, 8.84)	12.6 (1.51, 23.65)	0.0261
C9D1	15.5 (5.71, 25.32)	-7.1 (-18.48, 4.36)	22.6 (10.59, 34.57)	0.0002
C11D1	12.3 (2.29, 22.22)	4.5 (-8.14, 17.08)	7.8 (-5.51, 21.09)	0.2505
C13D1	19.1 (8.51, 29.72)	4.2 (-11.94, 20.28)	14.9 (-2.09, 31.97)	0.0854
C15D1	15.0 (4.53, 25.48)	-0.4 (-16.53, 15.72)	15.4 (-1.52, 32.34)	0.0744
C17D1	4.1 (-7.24, 15.45)	2.5 (-17.34, 22.26)	1.6 (-19.27, 22.57)	0.8772
C19D1	18.5 (6.29, 30.64)	-0.7 (-24.31, 22.89)	19.2 (-5.77, 44.12)	0.1316

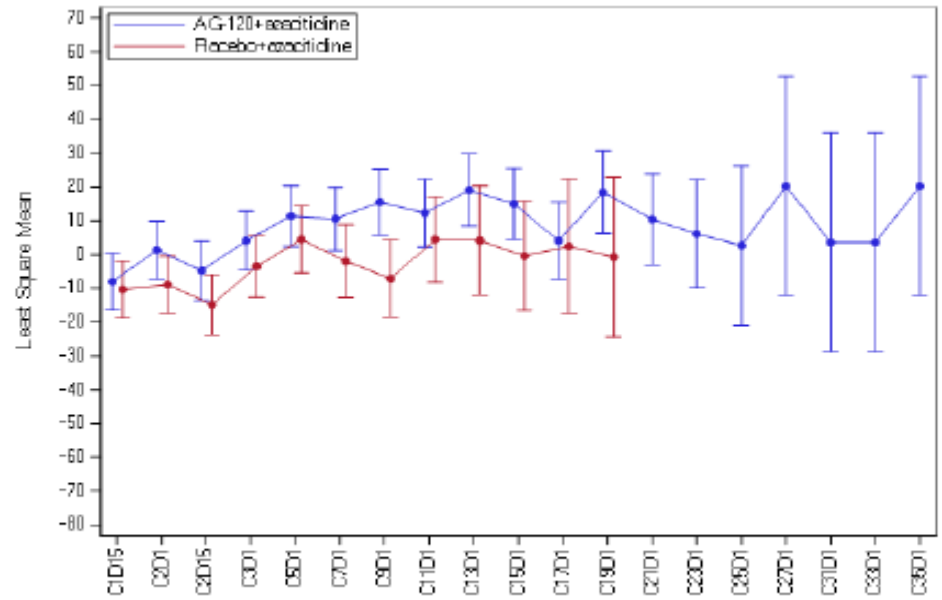
Visit	Ivosidenib + Azacitidine Arm Least Square Mean (95% CI)	Placebo + Azacitidine Arm Least Square Mean (95% CI)	Difference of Least Square Mean (95% CI)	p-value [1]
Fatigue (Higher score indicates worse symptoms/HRQoL)				
C1D15	7.8 (-1.66, 17.26)	10.6 (1.21, 20.03)	-2.8 (-11.68, 6.04)	0.5319
C2D1	5.4 (-4.21, 15.11)	9.5 (0.06, 18.92)	-4.0 (-13.11, 5.04)	0.3824
C2D15	8.6 (-1.20, 18.49)	16.1 (6.13, 26.10)	-7.5 (-17.23, 2.29)	0.1332
C3D1	0.5 (-9.31, 10.26)	2.9 (-7.36, 13.19)	-2.4 (-12.40, 7.52)	0.6301
C5D1	-9.9 (-19.97, 0.27)	-1.8 (-12.92, 9.28)	-8.0 (-19.09, 3.03)	0.1543
C7D1	-13.9 (-24.45, -3.28)	-1.2 (-13.38, 11.00)	-12.7 (-25.24, -0.10)	0.0482
C9D1	-12.8 (-23.91, -1.75)	2.2 (-10.69, 15.04)	-15.0 (-28.63, -1.38)	0.0309
C11D1	-11.8 (-23.04, -0.50)	-0.7 (-14.94, 13.55)	-11.1 (-26.19, 4.04)	0.1506
C13D1	-18.3 (-30.29, -6.28)	5.9 (-12.40, 24.13)	-24.1 (-43.54, -4.76)	0.0147
C15D1	-13.2 (-25.03, -1.32)	-0.1 (-18.41, 18.17)	-13.1 (-32.33, 6.23)	0.1842
C17D1	-11.1 (-23.98, 1.73)	-3.4 (-25.93, 19.08)	-7.7 (-31.54, 16.15)	0.5264
C19D1	-12.4 (-26.22, 1.40)	0.7 (-26.13, 27.58)	-13.1 (-41.57, 15.29)	0.3646

Source: Table 14.2.1-4.2; Listing 16.2.1-4.1. Data cutoff date: 18 March 2021

Abbreviations: C1D# = Cycle 1, Day #; FAS = full analysis set [1] Two-sided nominal p-value is reported. P-values were not adjusted for multiplicity.

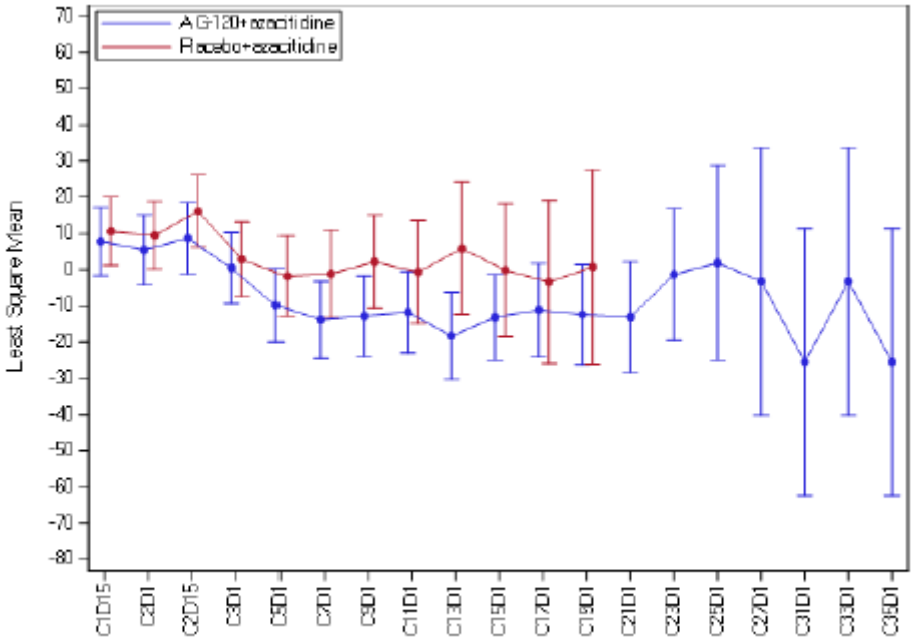
The least square mean and 95% CI are estimated from the mixed effect model on the change from baseline across visits for all scales with baseline score, treatment arm, time, randomization stratification factors (AML status and geographic region) and an interaction between treatment arm and time as fixed effect, and subject as random effects. The unstructured covariance structure is used to define covariance between random effects. Unscheduled visits are excluded from the analysis.

Figure 46. Least Square Means for Global Health Status/QoL Over Time in study AG120-C-009, Full analysis set



Source: Figure 14.2.1-4.1; Table 14.2.1-4.2. Data cutoff date: 18 March 2021

Figure 47. Least Square Means for Fatigue Over Time, in study AG120-C-009, Full analysis set



Source: Figure 14.2.1-4.1; Table 14.2.1-4.2. Data cutoff date: 18 March 2021

Follow-up medications and procedures

Subsequent stem cell transplants for AML

Four (5.6%) subjects in the ivosidenib + azacitidine arm (N=71) and 1 (1.4%) subject in the placebo + azacitidine arm (N=73) had an allogeneic HSCT.

- **Ancillary analyses**

Lan-DeMets O'Brien-Fleming boundaries considering all past IDMC meetings as additional interim analyses

At the time of the final analysis and to account for the IDMC's unplanned analysis and subsequent recommendation to stop enrollment in the study, the p-value boundaries for the primary and key secondary efficacy endpoints were adjusted. Specifically, the O'Brien-Fleming alpha spending function (the Lan and DeMets method) was used for each of the primary and key secondary efficacy endpoints (O'Brien and Fleming, 1979; Lan and DeMets, 1983). For the final analyses, for each of the primary and key secondary endpoints, the p-values were calculated based on the methodologies specified in the SAP (version 1.0 dated 22 June 2020) and they were compared to these adjusted p-value boundaries.

At the request of the CHMP, the Lan-DeMets O'Brien-Fleming boundaries were updated to account for all past IDMC meetings as additional interim analyses in the sequence of tests. The 1-sided p-value boundaries calculated as a result of this update are provided in Table 93.

Table 89. Original and updated Lan-DeMets O'Brien-Fleming boundaries and calculated P-values for primary and key secondary endpoints

Endpoint	1-sided P-value Boundary Used in Final Analysis in AG120-C-009 CSR	Updated 1-sided P-value Boundary, per Assessor Request	Calculated 1-sided P-value
EFS	0.0046	0.0039	0.0011
CR rate	0.0087	0.0073	<0.0001
OS	0.0017	0.0016	0.0005
CR + CRh rate	0.0087	0.0073	<0.0001
ORR	0.0087	0.0073	<0.0001

Abbreviations: CR = complete remission; CRh = CR with incomplete hematologic recovery; EFS = event-free survival; ORR = overall response rate; OS = overall survival.

Analyses of EFS and OS

Event-Free Survival

As of the effective date for Protocol Amendment 5 (09 January 2020), an EFS benefit was observed favoring the ivosidenib + azacitidine arm relative to the placebo + azacitidine arm (HR=0.23; 95% CI, 0.08, 0.66; 1-sided P=0.0022). A total of 25 subjects (55.6%) in the ivosidenib + azacitidine arm and 38 subjects (82.6%) in the placebo + azacitidine arm had experienced treatment failure (TF), defined as not achieving a CR by 24 weeks, and therefore were considered to have had an EFS event at Day 1 of randomization. Data were censored for 19 (42.2%) subjects in the ivosidenib + azacitidine arm and 8 (17.4%) subjects in the placebo + azacitidine arm. The EFS rate at 12 months was 33.3% in the ivosidenib + azacitidine arm versus 17.4% in the placebo + azacitidine arm.

Restricted Mean Survival Time Analysis for Event-Free Survival

The Restricted Mean Survival Time (RMST) is a robust and clinically interpretable summary measure of the survival time distribution (Royston and Parmar, 2011; Zhang, 2013; Uno et al, 2014) and was prespecified to explore the robustness of the EFS analyses and to provide a supplementary efficacy measure to the median survival time and HR.

As of the effective date for Protocol Amendment 5 (09 January 2020), the RMST calculated up to 12.0 months was 5.2 months in the ivosidenib + azacitidine arm and 2.1 months in the placebo + azacitidine arm (AG120-C-009). Difference in RMST, calculated by RMST (ivosidenib + azacitidine) – RMST (placebo + azacitidine), was 3.1 months (95% CI, 1.0 to 5.3 months; 1-sided P=0.0022) (AG120-C-009).

The RMST analysis was consistent with the result of the primary EFS analysis.

Sensitivity Analyses for Event-Free Survival

As of the effective date for Protocol Amendment 5 (09 January 2020), the results of all sensitivity analyses as specified in SAP Version 1 (dated 22 Jun 2020) are summarized below:

- Sensitivity Analysis #1 (EFS tested using the log-rank test stratified by the interactive response technology [IRT] randomization stratification factors and based on the FAS, with time of relapse or death determined using the actual date of relapse or death, even in situations where relapse or death was observed after 2 or more missing disease assessments or start of subsequent anticancer therapy): HR=0.23; 95% CI, 0.08, 0.66; 1-sided P=0.0022 (AG120-C-009)
- Sensitivity Analysis #2 (EFS tested using the unstratified log-rank test and based on the FAS): HR=0.30; 95% CI, 0.12, 0.75; 1-sided P=0.0041 (AG120-C-009)

- Sensitivity Analysis #3 (EFS tested using the log-rank test stratified by the IRT randomization stratification factors and based on the PPS): HR=0.21; 95% CI, 0.07, 0.64; 1-sided P=0.0020 (AG120-C-009)
- Sensitivity Analysis #4 (EFS tested using the log-rank test stratified by the randomization stratification factors derived based on data provided by the Investigator in the eCRF and based on the FAS): HR=0.25; 95% CI, 0.09, 0.70; 1-sided P=0.0030 (AG120-C-009)
- Sensitivity Analysis #5 (EFS tested using the log-rank test stratified by the IRT randomization stratification factors and based on the FAS; for subjects who did not achieve CR by week 24, instead of being considered to have had an EFS event at Day 1 of randomization, the event time was either 24 weeks or EOT, whichever was earlier): HR=0.54; 95% CI, 0.30, 0.98; 1-sided P=0.0197 (AG120-C-009)

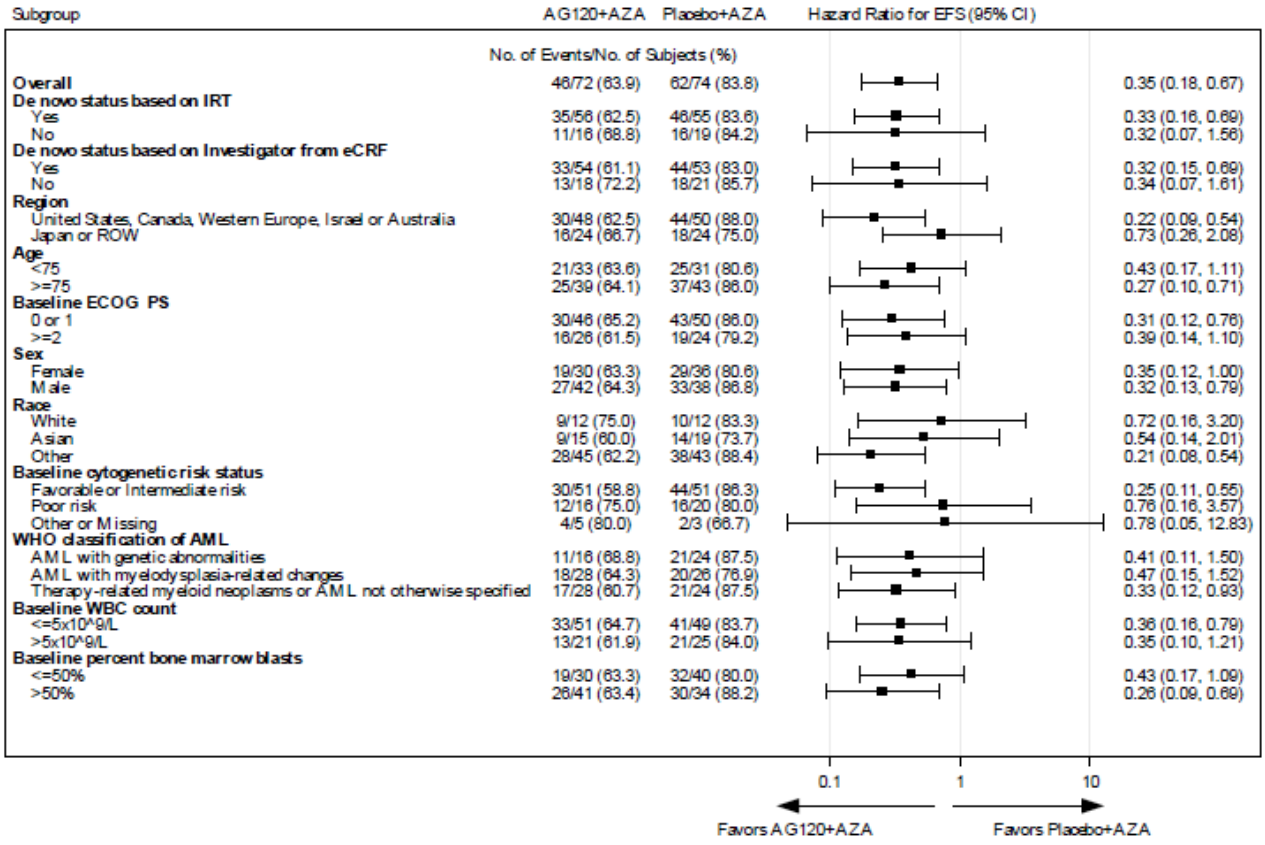
Overall Survival

As of the effective date for Protocol Amendment 5 (09 January 2020), an OS benefit was observed favouring the ivosidenib + azacitidine arm relative to the placebo + azacitidine arm (HR=0.54; 95% CI, 0.27 to 1.06, 1-sided P=0.0336). Median OS was not estimable (95% CI, 7.5 months, NE) in the ivosidenib + azacitidine arm and 5.2 months (95% CI, 1.9 to 15.1 months) in the placebo + azacitidine arm.

Analyses of EFS by Subgroup (DCO 18 March 2021)

Subgroup analyses of EFS were conducted with an unstratified log-rank test and an unstratified Cox regression model. The HR (ivosidenib + azacitidine / placebo + azacitidine) with its 95% CI was displayed for all subgroups graphically in the Forest plot.

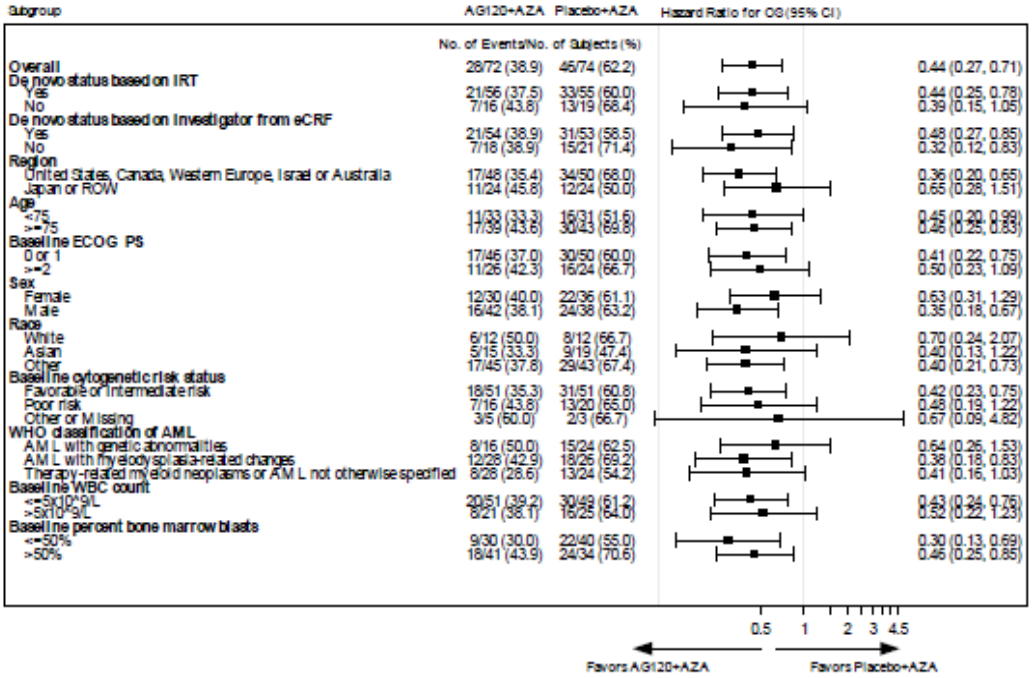
Figure 48. Forest Plot of EFS By Subgroup in study AG120-C-009, Full analysis set



Analyses of OS by subgroup (DCO 18 March 2021)

The ivosidenib + azacitidine arm showed a numerically improved OS result compared with placebo + azacitidine arm in the same subgroups evaluated for. A Forest plot of OS by subgroups of the FAS is provided below.

Figure 49. Forest Plot of Overall Survival (OS) By Subgroup in study AG120-C-009, Full analysis set



Source: Figure 14.2.1-2.2, Listing 16.1-3.5, Listing 16.1-6.1, 16.2.1-2.1. Data cutoff date: 18 March 2021.

Abbreviations: AZA = azacitidine; ECOG PS = Eastern Cooperative Oncology Group - Performance Status; WBC = White Blood Cells; IRT = Interactive Response Technology; ROW = Rest of the World.

Hazard ratio is calculated from the unstratified Cox regression model with placebo + azacitidine as the denominator, with two-sided 95% CI.

'> 20%' of baseline blasts was reported for one subject within the AG120+azacitidine group. This subject is not included in the subgroup analyses for baseline percent bone marrow blasts.

Other under Race includes Black or African American, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and not reported.

2.10.11.3. Summary of main efficacy results

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 90. Summary of Efficacy for trial AG120-C-009

Title: A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of AG-120 in Combination with Azacitidine in Subjects ⩾18 Years of Age with Previously Untreated Acute Myeloid Leukemia with an IDH1 Mutation		
Study identifier	Protocol code: AG120-C-009 ; Protocol name: AGILE ; EudraCT number : 2016-004907-30 ; US NCT number : NCT03173248	
Design	Phase 3, multicenter, double-blind, randomized, placebo-controlled	
Hypothesis	Superiority	
Treatments groups	Ivosidenib (AG-120) + azaciditine	Ivosidenib 500 mg PO QD. Azacitidine 75 mg/m² SC or IV days 1-7 or 1-5 and 8-9 Q28 days ≥6 cycles. 72 subjects randomized
	Placebo + azacitidine	Placebo PO QD Azacitidine 75 mg/m² SC or IV days 1-7 or 1-5 and 8-9 Q28 days ⩾6 cycles. 74 subjects randomized

Title: A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of AG-120 in Combination with Azacitidine in Subjects ⩾18 Years of Age with Previously Untreated Acute Myeloid Leukemia with an IDH1 Mutation			
Study identifier	Protocol code: AG120-C-009 ; Protocol name: AGILE ; EudraCT number : 2016-004907-30 ; US NCT number : NCT03173248		
Endpoints and definitions	Primary endpoint	EFS	The time from randomization until treatment failure, relapse from remission, or death from any cause, whichever occurred first. Treatment failure was defined as failure to achieve CR by Week 24.
	Key secondary endpoint	OS	The time from date of randomization to the date of death due to any cause.
	Key secondary endpoint	CR rate	The proportion of subjects who achieved a CR CR: bone marrow blasts <5% and no Auer rods; absence of extramedullary disease; ANC ⩾1.0 × 10^9/L (1000/μL); platelet count ⩾100 ×10^9/L (100,000/μL); and independence of RBC transfusions
	Key secondary endpoint	CR + CRh rate	The proportion of subjects who achieved a CR or CRh. CRh: a CR with partial recovery of peripheral blood counts (<5% bone marrow blasts, platelets >50,000/μL, and ANC >500/μL).
	Key secondary endpoint	ORR	The rate of CR, CRi (including CRp), partial remission (PR), and morphologic leukemia-free state (MLFS).
Data cutoff	DCO 18 March 2021		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analysis set (FAS): all randomized subjects		
Descriptive statistics and estimate variability	Treatment group	Ivosidenib + azacitidine	Placebo + azacitidine
	Number of subjects	72	74
	EFS, number of subjects with event (%)	46 (63.9%)	62 (83.8%)
	CR rate, n (%)	34 (47.2%)	11 (14.9%)
	OS, number of deaths (%)	28 (38.9%)	46 (62.2%)
	CR+CRh rate, n (%)	38 (52.8%)	13 (17.6%)
	ORR, n (%)	45 (62.5%)	14 (18.9%)
Effect estimate per comparison	EFS	Comparison groups	Ivosidenib + azacitidine versus placebo + azacitidine
		HR (95% CI)	0.33 (0.16, 0.69)
	CR	Comparison groups	Ivosidenib + azacitidine versus placebo + azacitidine
		Odds ratio	4.76
		95% CI	2.15, 10.50
	OS	Comparison groups	Ivosidenib + azacitidine versus placebo + azacitidine
		HR	0.44
		95% CI	0.27, 0.73
	CR + CRh	Comparison groups	Ivosidenib + azacitidine versus placebo + azacitidine

Title: A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of AG-120 in Combination with Azacitidine in Subjects ⩾18 Years of Age with Previously Untreated Acute Myeloid Leukemia with an IDH1 Mutation			
Study identifier	Protocol code: AG120-C-009 ; Protocol name: AGILE ; EudraCT number : 2016-004907-30 ; US NCT number : NCT03173248		
		Odds ratio	5.01
		95% CI	2.32, 10.81
	ORR	Comparison groups	Ivosidenib + azacitidine versus placebo + azacitidine
		Odds ratio	7.15
		%95 CI	3.31, 15.44
Notes	On 12 May 2021, the IDMC review of safety data reported a greater number of deaths in the placebo arm versus the ivosidenib arm. The subsequent unblinded analysis for efficacy led to the recommendation to halt recruitment. On 27 May 2021, recruitment was discontinued. Because formal stopping rules were not documented until after this decision had been made, presented results cannot be described as being statistically significant. Therefore p-values have been removed from the above table.		

2.10.11.4. Clinical studies in special populations

Table 91. Elderly patients (≥65 years) included in study AG120-C-009, Full analysis set

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trial - AG120-C-009 Study*			
Ivosidenib+azacitidine (N=72) n (%)/N	29 (40.3)/72	39 (54.2)/72	0 (0)/72
Placebo+azacitidine (N=74) n (%)/N	27 (36.5)/74	35 (47.3)/74	8 (10.8)/74
Total (N=146) n (%)/N	56 (38.4)/146	74 (50.7)/146	8 (5.5)/146
Non Controlled Trial – AG-221-AML-005 Study (ivosidenib + azacitidine arm N=23)*			
Ivosidenib +azacitidine Dose-finding (N=7) n (%)/N	2 (28.6)/7	4 (57.1)/7	1 (14.3)/7
Ivosidenib +azacitidine Expansion (N=16) n (%)/N	6 (37.5)/16	7 (43.8)/16	0 (0)/16
Total (N=23) n (%)/N	8 (34.8)/23	11 (47.8)/23	1 (4.3)/23

Source: Table 14.6-1.1. (AG120-C-009; Data Cutoff Date: 18 March 2021), Table T0102 (AG-221-AML-005; Data Cutoff Date: 08 August 2022)
* 8 patients in AG120-C-009 (4 in each arm) and 3 patients in AG221-AML-005 were <= 64 year-old.

2.10.11.5. In vitro biomarker test for patient selection for efficacy

Enrolment in study AG120-C-009 was restricted to subjects with documented IDH1 gene-mutated disease based on central laboratory testing (R132C/L/G/H/S mutation variants tested) using IDH1 *in vitro* PCR assay. The analyses performed, including subgroup analyses by R132 variant, were based on the FAS.

Considering that ivosidenib potently inhibited the 5 most common IDH1m proteins with a biochemical IC50 in the range of 8 to 17 nM (AG-120 investigator's brochure) when used as monotherapy in Study AG120-C-001, primary resistance based on mutant allele subtype was not anticipated.

For Study AG120-C-009, all subjects were centrally tested for IDH1m. Of the variants analysed, R132-C was the most frequent in the treatment and control arms (62.5% versus 68.9%, respectively). An examination of IDH1m allele sub-type sensitivity to the combination (defined as CR+CRh rates and EFS and OS outcomes) was performed. Based on these exploratory analyses, the R132-C variant had a favourable association with CR+CRh, EFS, and OS in the treatment arm when compared to the control arm. Other R132 variants were detected at a lower frequency. No significant difference in clinical outcome between both arms was identified.

Of the subjects enrolled on Study AG120-C-009, 120 subjects (57 subjects in the treatment arm, 63 in the placebo arm) had a baseline sample available for co-mutation analysis. All harboured at least 1 known or likely baseline co-occurring mutation, DNMT3A, SRSF2, and RUNX1 being the most frequently co-occurring mutations detected among both treatment groups.

An evaluation was conducted to determine whether known or likely mutations in single genes or pathways were associated with the best overall response of CR+CRh.

In the treatment group JAK2 mutations were associated with a lack of CR or CRh response ($p = 0.014$), with 1 out of 7 subjects harboring a JAK2 mutation achieving a CR or CRh, while 33 out of 50 JAK2 wild-type subjects achieved a CR or CRh. Except for JAK2, no single gene mutation from either arm had a significant difference in achieving an outcome of CR or CRh. Upon examination of genes associated with specific pathways, no difference was observed in achieving a CR or CRh when the pathway category was composed of more than one gene.

Of note, receptor tyrosine kinase (RTK) pathway mutations (FLT3, KIT, KRAS, NRAS, and PTPN11), which were associated with the primary resistance to IVO, showed no such association in the IVO+AZA setting, with 7 out of 9(78%) IVO+AZA-treated subjects with RTK pathway mutations achieving CR+CRh.

2.10.11.6. Supportive study

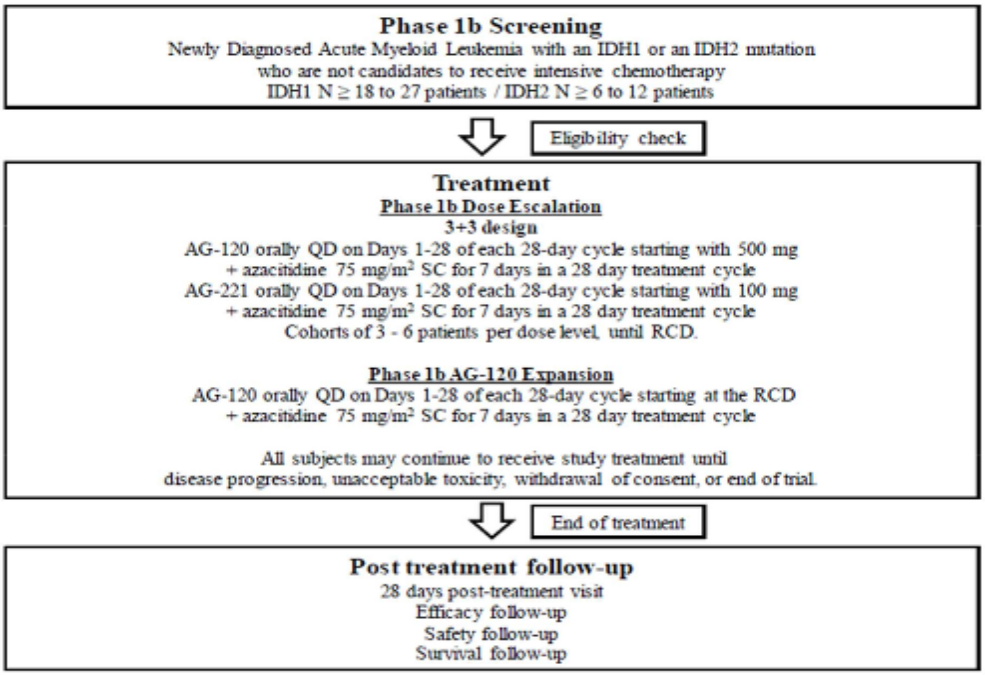
Study AG-221-AML-005 (hereafter mentioned as Study AML-005) is an ongoing Phase 1b/2, multicenter, open-label, randomized study of 2 combinations of IDH mutant targeted therapies plus azacitidine: oral ivosidenib (AG-120) or oral enasidenib (AG-221) plus subcutaneous azacitidine (AZA) in subjects with newly diagnosed AML harboring an IDH1 or an IDH2 mutation, respectively, who are not candidates to receive intensive induction chemotherapy.

The Phase 1b of the study (depicted in Figure 50) included:

- a single-arm assessment of subjects treated with AG-120 in combination with SC AZA (on which the following evaluation will focus) and
- a single-arm assessment of subjects treated with AG-221 100 mg or 200 mg in combination with SC AZA.

The Phase 2 comprised a randomized comparison of subjects treated with AG-221 100 mg in combination with SC AZA 75mg/m² versus subjects treated with SC AZA 75 mg/m² alone.

Figure 50. Overall study design Phase 1b dose-finding and AG-120 expansion stages



IDH1 = isocitrate dehydrogenase 1; IDH2 = isocitrate dehydrogenase 2; QD = once a day; RCD = recommended combination dose; SC = subcutaneous.

Determination of the RCD

The DRT reviewed all Phase 1b safety data to determine the starting doses of AG-120 or AG-221 administered with AZA that were to be used in the treatment arms of the Phase 1b Expansion and randomized Phase 2 stages of the study.

AG-120 expansion stage

Subjects enrolled in the AG-120 expansion were to receive AG-120 + AZA at the RCD.

Objectives

The primary objectives of the study, focusing on ivosidenib treatment, were:

Phase 1b Dose-finding Stage

- To assess the safety and tolerability of oral AG-120 when administered with SC AZA and oral AG-221 when administered with SC AZA in subjects with newly diagnosed AML with an IDH1 or an IDH2 mutation, respectively, who were not candidates to receive intensive IC.
- To establish the RCD of oral AG- 120 and oral AG-221 when administered with SC AZA.

Phase 1b AG-120 Expansion Stage

- To assess the safety and tolerability of oral AG-120 when administered with SC AZA in subjects with newly diagnosed AML with an IDH1 mutation, who were not candidates to receive intensive IC.

Results

Participant flow

Seven subjects were enrolled in the AG-120 + AZA group during the Phase 1b Dose-finding Stage and 17 subjects were enrolled in the AG-120 + AZA group during the Phase 1b Expansion Stage.

All 7 subjects enrolled in the Phase 1b Dose-finding Stage initiated treatment with AG-120 +AZA and 16 of 17 subjects who enrolled in the Phase 1b Expansion Stage initiated treatment with AG-120+ AZA.

Of the 23 subjects overall receiving treatment with AG-120 +AZA, 16 (69.6%) subjects discontinued from treatment and 7 (30.4%) subjects were still receiving treatment at the time of the data cutoff. The most common reasons for treatment discontinuation were AE (4 subjects), withdrawal by subject (4 subjects), and disease relapse (3 subjects).

Analysis sets

The Full Analysis Population (FAP) included all subjects who were enrolled and received at least 1 dose of study treatment. Subjects were classified according to the assigned dose level and schedule. The FAP was the primary analysis population and was the default analysis set for all analyses except the safety analyses, unless otherwise specified. This population was defined for Phase 1b only.

For Phase 1b, the Evaluable Analysis Population (EAP) included all subjects in the FAP for whom the baseline response assessment and at least 1 post-baseline response assessment at Day 28 or later were available and evaluable. The clinical activity of AG-221/AG-120 combined with AZA was primarily assessed in the FAP.

Baseline data

Table 92. Demographics, Study AML-005 Phase 1b FAP

Parameter	AG-120 + AZA 75 mg/m^2		
	AG-120 500 mg + AZA in Dose-finding (N = 7)	AG-120 500 mg + AZA in Expansion (N = 16)	AG-120 500 mg + AZA Total (N = 23)
Age (years)			
Median	81.0	74.0	76.0
Min, Max	72, 88	61, 79	61, 88
Age Categories (years), n (%)			
< 65	0	3 (18.8)	3 (13.0)
≥ 65 to < 75	2 (28.6)	6 (37.5)	8 (34.8)
≥ 75	5 (71.4)	7 (43.8)	12 (52.2)
Sex, n (%)			
Male	4 (57.1)	7 (43.8)	11 (47.8)
Female	3 (42.9)	9 (56.3)	12 (52.2)
Race, n (%)			
Asian	0	1 (6.3)	1 (4.3)
White	7 (100.0)	13 (81.3)	20 (87.0)
Not collected or reported	0	2 (12.5)	2 (8.7)
Ethnicity, n (%)			
Hispanic or Latino	1 (14.3)	0	1 (4.3)
Not Hispanic or Latino	6 (85.7)	14 (87.5)	20 (87.0)
Not reported	0	2 (12.5)	2 (8.7)

AZA = azacitidine; FAP = Full Analysis Population; Max = maximum; Min = minimum.
Percentages were based on the number of subjects enrolled in each dose cohort group.

Table 93. Baseline disease characteristics - Study AML-005 Phase 1b FAP

Parameter	AG-120 + AZA 75 mg/m^2		
	AG-120 500 mg + AZA in Dose-finding (N = 7)	AG-120 500 mg + AZA in Expansion (N = 16)	AG-120 500 mg + AZA Total (N = 23)
IDH Mutation Type, n (%)			
IDH1 Positive	7 (100.0)	16 (100.0)	23 (100.0)
Not Eligible for Intensive Chemotherapy[a], n (%)			
Age	7 (100.0)	11 (68.8)	18 (78.3)
Comorbidities	2 (28.6)	5 (31.3)	7 (30.4)
Performance status	0	2 (12.5)	2 (8.7)
Unfavorable cytogenetics	0	1 (6.3)	1 (4.3)
Subject decision	0	3 (18.8)	3 (13.0)
Other	0	1 (6.3)	1 (4.3)
ECOG Performance Status, n (%)			
Grade 0	0	5 (31.3)	5 (21.7)
Grade 1	7 (100.0)	7 (43.8)	14 (60.9)
Grade 2	0	4 (25.0)	4 (17.4)

Parameter	AG-120 + AZA 75 mg/m^2		
	AG-120 500 mg + AZA in Dose-finding (N = 7)	AG-120 500 mg + AZA in Expansion (N = 16)	AG-120 500 mg + AZA Total (N = 23)
Bone Marrow Blasts Aspirate, Local			
Median (Min, Max)	62.0 (27, 86)	54.0 (13, 92)	60.0 (13, 92)
Bone Marrow Blasts Aspirate Category I, Local, n (%)			
< 20%	0	2 (12.5)	2 (8.7)
≥ 20% to < 30%	1 (14.3)	3 (18.8)	4 (17.4)
≥ 30% to < 50%	0	2 (12.5)	2 (8.7)
≥ 50%	6 (85.7)	9 (56.3)	15 (65.2)
Peripheral Blood Blasts, Local (%)			
Median (Min, Max)	20.0 (0, 39)	11.0 (0, 96)	15.5 (0, 96)
Cytogenetic Risk Status, Local, n (%)			
Intermediate risk	7 (100.0)	9 (56.3)	16 (69.6)
Normal	4 (57.1)	3 (18.8)	7 (30.4)
Poor risk	0	5 (31.3)	5 (21.7)
Failure	0	1 (6.3)	1 (4.3)
Missing	0	1 (6.3)	1 (4.3)
Hemoglobin (g/L)			
Median (Min, Max)	93.5 (78, 141)	89.5 (65, 111)	89.5 (65, 141)
Platelets (x 10^9/L)			
Median (Min, Max)	92.5 (21, 179)	33.0 (11, 200)	42.0 (11, 200)
ANC (x 10^9/L)			
Median (Min, Max)	0.2 (0, 0)	0.3 (0, 3)	0.3 (0, 3)
WBC (x 10^9/L)			
Median (Min, Max)	2.7 (1, 15)	1.6 (1, 25)	1.8 (1, 25)
WBC, n (%)			
< 15 x 10^9/L	5 (71.4)	15 (93.8)	20 (87.0)
≥ 15 to < 30 x 10^9/L	1 (14.3)	1 (6.3)	2 (8.7)
Missing	1 (14.3)	0	1 (4.3)

Parameter	AG-120 + AZA 75 mg/m^2		
	AG-120 500 mg + AZA in Dose-finding (N = 7)	AG-120 500 mg + AZA in Expansion (N = 16)	AG-120 500 mg + AZA Total (N = 23)
GFR, Estimated (mL/min/1.73 m^2)			
Median (Min, Max)	76.0 (65, 91)	81.5 (53, 132)	81.0 (53, 132)
GFR, Estimated (mL/min/1.73 m^2); n (%)			
≥ 45 to < 60	0	3 (18.8)	3 (13.0)
≥ 60	5 (71.4)	13 (81.3)	18 (78.3)
Missing	2 (28.6)	0	2 (8.7)
Number of RBC Transfusions[b]			
Median (Min, Max)	0.0 (0, 3)	1.0 (0, 4)	1.0 (0, 4)
Number of Platelet Transfusions[b]			
Median (Min, Max)	0.0 (0, 5)	0.0 (0, 10)	0.0 (0, 10)
LVEF %			
Median (Min, Max)	60.0 (56, 70)	63.0 (45, 73)	61.5 (45, 73)

ANC = absolute neutrophil count; AZA = azacitidine; ECOG = Eastern Cooperative Oncology Group; FAP = Full Analysis Population; GFR = glomerular filtration rate; IC = intensive chemotherapy; IDH = isocitrate dehydrogenase; IDH1 = isocitrate dehydrogenase 1; LVEF = left ventricular ejection fraction; Max = maximum; Min = minimum; RBC = red blood cell; WBC = white blood cell.

[a] Subjects may have had more than 1 reason for ineligibility for IC.

[b] Number of transfusions within 8 weeks prior to the start of study treatment.

Percentages were based on the number of subjects in each dose cohort group. Baseline was the last nonmissing value on or prior to first dose of study drug.

Outcomes and estimation

ORR and DOR

The summaries of investigator-assessed ORR and duration of response for the Phase 1b FAP in subjects treated with AG-120 +AZA are presented in Table 98 and Table 99 respectively.

Table 94. Summary of Overall Response Rate – Study AML-005 Phase 1b FAP

Parameter	AG-120 + AZA 75 mg/m^2		
	AG-120 500 mg + AZA in Dose-finding (N = 7)	AG-120 500 mg + AZA in Expansion (N = 16)	AG-120 500 mg + AZA Total (N = 23)
Best Response Rate, n (%)			
CR[a]	5 (71.4)	8 (50.0)	13 (56.5)
CRi/CRp	0	2 (12.5)	2 (8.7)
PR	1 (14.3)	0	1 (4.3)
MLFS	1 (14.3)	1 (6.3)	2 (8.7)
SD	0	3 (18.8)	3 (13.0)
PD	0	1 (6.3)	1 (4.3)
Missing	0	1 (6.3)	1 (4.3)
Overall Response Rate, n (%)[b]	7 (100.0)	11 (68.8)	18 (78.3)
95% CI for Overall Response[c]	(59.0, 100)	(41.3, 89.0)	(56.3, 92.5)
CR Rate, n (%)[a]	5 (71.4)	8 (50.0)	13 (56.5)
95% CI for CR[c]	(29.0, 96.3)	(24.7, 75.3)	(34.5, 76.8)

AZA = azacitidine; CI = confidence interval; CR = morphologic complete remission; CRc = cytogenetic complete remission; CRi = morphologic complete remission with incomplete neutrophil recovery; CRp = morphologic complete remission with incomplete platelet recovery; FAP = Full Analysis Population; MLFS = morphologic leukemia-free state; PD = progressive disease; PR = partial remission; SD = stable disease.

[a] CRc is counted as CR.

[b] CR + CRi + CRp + PR + MLFS.

[c] Clopper-Pearson CIs.

The ORR results for the Phase 1b EAP were generally similar to those for the Phase 1b.

Table 95. Summary of Duration of Response – Study AML-005 Phase 1b FAP

Parameter	AG-120 + AZA 75 mg/m^2		
	AG-120 500 mg + AZA in Dose-finding (N = 7)	AG-120 500 mg + AZA in Expansion (N = 16)	AG-120 500 mg + AZA Total (N = 23)
Total Number of Subjects Who Achieved CR/CRi/CRp/PR/MLFS, n (%)	7 (100.0)	11 (68.8)	18 (78.3)
Relapsed/Progressed[b]	0	4 (36.4)	4 (22.2)
Died without Relapse/Progression[b]	1 (14.3)	0	1 (5.6)
Censored[b]	6 (85.7)	7 (63.6)	13 (72.2)
Duration of Response[c] (months)			
Median (95% CI)	NA (0.5, NA)	NA (7.6, NA)	NA (10.3, NA)
Kaplan-Meier DOR (%)			
3 Months	83.3	100	94.1
6 Months	83.3	90.9	88.2
9 Months	83.3	80.8	81.9
12 Months	83.3	70.7	75.6

AZA = azacitidine; CI = confidence interval; CR = morphologic complete remission; CRi = morphologic complete remission with incomplete neutrophil recovery; CRp = morphologic complete remission with incomplete platelet recovery; DOR = duration of response; FAP = Full Analysis Population; MLFS = morphologic leukemia-free state; NA = not available; PR = partial remission.

[a] Percentages were based on the number of subjects in each dose cohort.

[b] Percentages were based on the number of subjects in each dose cohort who achieved CR/CRi/CRp/PR/MLFS.

[c] Duration of response was calculated as the date of the first documented response to the date of the first documented disease relapse, progression, or death due to any cause, whichever occurred first. Median estimate of DOR was from an unstratified Kaplan-Meier analysis.

Response was evaluated by the Investigator according to the 2003 revised IWG criteria for AML or the 2006 modified IWG criteria for MDS.

The median duration of response was NE because 13 (72.2%) of 18 subjects had not relapsed or progressed as of the cutoff date.

Time to response

The time to response for the Phase 1b FAP for subjects treated with AG-120 + AZA is summarised in Table 100.

Table 96. Summary of Time to Response – Study AML-005 Phase 1b FAP

Parameter	AG-120 + AZA 75 mg/m^2		
	AG-120 500 mg + AZA in Dose-finding (N = 7)	AG-120 500 mg + AZA in Expansion (N = 16)	AG-120 500 mg + AZA Total (N = 23)
Total Number of Subjects Who Achieved CR/CRi/CRp/PR/MLFS, n (%)	7 (100.0)	11 (68.8)	18 (78.3)
Time to Response[a] (months)			
n	7	11	18
Median (Min, Max)	1.78 (0.9, 3.5)	1.88 (0.7, 3.8)	1.83 (0.7, 3.8)
Time to Response by Cycle, n (%)			
Cycle 1	0	0	0
Cycle 2	1 (14.3)	4 (25.0)	5 (21.7)
Cycle 3	4 (57.1)	6 (37.5)	10 (43.5)
Cycle 4	0	0	0
Cycle 5	1 (14.3)	1 (6.3)	2 (8.7)
Follow-up	1 (14.3)	0	1 (4.3)

AML = acute myeloid leukemia; AZA = azacitidine; CR = morphologic complete remission; CRi = morphologic complete remission with incomplete neutrophil recovery; CRp = morphologic complete remission with incomplete platelet recovery; FAP = Full Analysis Population; IWG = International Working Group; Max = maximum; Min = minimum; MLFS = morphologic leukemia-free state; PR = partial remission.

[a] Time to response was defined as time from first dose date of study drug to first documented CR/CRi/CRp/PR/MLFS according to modified IWG AML response criteria.

Source: Table 14.2.6.1.

Time to remission

The median time to remission for combined subjects in the Dose-finding and Expansion stages was 3.49 months. Of the 13 (56.5%) subjects who achieved CR, 6 of 13 subjects achieved remission by Cycle 3, 5 of 13 subjects achieved remission during Cycle 5, and 2 of 13 subjects achieved remission during Cycle 7 or later.

Duration of remission

The median duration of remission was NE for subjects treated with AG-120 + AZA in the Dose-finding and Expansion stages because 10 (76.9%) of 13 subjects had not relapsed or progressed as of the cut-off date.

Overall survival

The summary of OS for the Phase 1b FAP for subjects treated with AG-120 + AZA is presented in Table 101**.**

Table 97. Summary of Overall Survival– Study AML-005 Phase 1b FAP

Parameter	AG-120 + AZA 75 mg/m^2		
	AG-120 500 mg + AZA in Dose-finding (N = 7)	AG-120 500 mg + AZA in Expansion (N = 16)	AG-120 500 mg + AZA Total (N = 23)
Number of Subjects with Events, n (%)	1 (14.3)	6 (37.5)	7 (30.4)
Number of Subjects Censored[a], n (%)	6 (85.7)	10 (62.5)	16 (69.6)
Duration of OS[b] (months)			
Median (95% CI)	NA (2.3, NA)	24.2 (14.5, NA)	NA (17.0, NA)
Kaplan-Meier OS (%)			
1 Month	100	100	100
3 Months	85.7	93.8	91.1
6 Months	85.7	87.1	86.3
9 Months	85.7	80.4	81.5
12 Months	85.7	80.4	81.5

AZA = azacitidine; CI = confidence interval; FAP = Full Analysis Population; NA = not evaluable; OS = overall survival.

[a] Subjects alive were censored at the last date known to be alive or a prespecified data cutoff date. Subjects who only had a baseline record were censored at the first dose date.

[b] Overall survival was calculated as the time from the first dose to the date of death due to any cause. Median percentile estimate of OS was from an unstratified Kaplan-Meier analysis.

If a value is unable to be computed, it is presented as "NA."

The median duration of OS was NE for subjects treated with AG-120 +AZA in the Dose-finding Stage because 6 (85.7%) of the 7 subjects were still participating in the study as of the cutoff date. The median duration of OS was 24.2 months for subjects treated with AG-120 +AZA in the Expansion Stage.

Event-free survival

The summary of EFS for the Phase 1b FAP for subjects treated with AG-120 + AZA is presented in Table 102.

The definition of EFS was different from the pivotal study. EFS was here the time to documented morphologic relapse, progression according to modified IWG AML response criteria, or death from any cause, whichever occurs first.

Table 98. Summary of EFS- Study AML-005 Phase 1b FAP

Parameter	AG-120 + AZA 75 mg/m^2		
	AG-120 500 mg + AZA in Dose-finding (N = 7)	AG-120 500 mg + AZA in Expansion (N = 16)	AG-120 500 mg + AZA Total (N = 23)
Number of Events, n (%)	1 (14.3)	6 (37.5)	7 (30.4)
Relapsed/Progressed	0	5 (31.3)	5 (21.7)
Died without Relapse/Progression	1 (14.3)	1 (6.3)	2 (8.7)
Censored[a], n (%)	6 (85.7)	10 (62.5)	16 (69.6)
Duration of EFS[b] (months)			
Median (95% CI)	NA (2.3, NA)	NA (5.7, NA)	NA (9.9, NA)
Kaplan-Meier EFS (%)			
3 Months	83.3	85.7	85.4
6 Months	83.3	77.9	80.1
9 Months	83.3	77.9	80.1
12 Months	83.3	60.6	68.7

AML = acute myeloid leukemia; AZA = azacitidine; CI = confidence interval; EFS = event-free survival; FAP = Full Analysis Population; IWG = International Working Group; MDS = myelodysplastic syndrome; NA = not evaluable.

[a] Subjects who had no postbaseline response were censored at date of the first dose.

[b] Event-free survival was calculated as the interval from the date of the first dose to the date of documented relapse, progression, or death due to any cause, whichever occurred first. Median percentile estimate of EFS was from an unstratified Kaplan-Meier analysis.

Response was evaluated by the investigator according to the 2003 revised IWG criteria for AML or the 2006 modified IWG criteria for MDS.

Follow-up medications and procedures

Subsequent stem cell transplants

For subjects treated with AG-120 + AZA during Phase 1b, 1 (4.3%) subject with a disease status of CR at the time of HSCT had a subsequent allogeneic stem cell transplant for AML.

2.10.12. Discussion on clinical efficacy

Design and conduct of clinical studies

This application is mainly based on efficacy and safety results from:

- the pivotal study AG120-C-009 in subjects with previously untreated IDH1+ AML and ineligible for intensive induction chemotherapy (IC)
- the supportive study AG-221-AML-005, a phase 1b/2 study in newly diagnosed AML subjects with an IDH1 or an IDH2 mutation not candidates for intensive IC.

According to the applicant, both studies were GCP-compliant. At time of submission, no GCP inspection had been requested nor taken place and no inspection was planned.

Based on these studies, the indication sought for Tibsovo was in combination with azacitidine 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 intensive induction chemotherapy. The CHMP requested a small amendment to this by replacing "intensive" with "standard" in line with recent approvals in the same disease setting which was accepted by the applicant.

Pivotal study, AG120-C-009 (AGILE)

Subjects eligible for study treatment were randomized 1:1 to receive oral ivosidenib or matched placebo on each day of the 4-week cycle, both administered in combination with subcutaneous (SC) or intravenous (IV) azacitidine for the first week (7 days) (or on a 5-2-2 schedule) of each 4-week (28-day) cycle.

The final study design limited enrolment to patients with previously untreated AML, excluding patients which were candidates to intensive induction chemotherapy (also considering stem cell transplantation). Overall, eligibility criteria were globally in line with AML guidelines and scientific advice given to the applicant.

The initial objectives and endpoints chosen for this superiority trial were consistent with recommendations from scientific advice and AML guidelines. However, since its initiation (original protocol dated 06 January 2017) the study was amended 9 times. A critical revision was amendment 5 (09 January 2020); at that time 117 patients were already recruited. With protocol amendment 5, the primary endpoint was changed from OS to EFS, OS was added as a key secondary endpoint and the corresponding statistical analyses were updated. This modification was not supported by the CHMP (EMEA/H/SA/3403/3/2018/PA/II) since EFS is not considered a validated surrogate for OS in AML.

In addition, the number of subjects to be enrolled in the study were reduced from 392 to 200 based on updated sample size estimations. The number of study-centres and countries was increased. The planned interim analyses for efficacy were removed. Despite the double-blind design of the study, which is partially reassuring, all these changes were considered by the CHMP as potentially compromising the integrity of the trial. Demographics and disease characteristics were presented at baseline for subjects randomised before and after protocol amendment 5 and were found to be generally similar, with observed differences not thought to have a meaningful impact on efficacy outcomes. The applicant also provided EFS and OS analyses at the effective date of protocol amendment 5. While the treatment effect estimates for EFS and OS were respectively slightly larger and smaller than at the final analysis, results can be considered relatively consistent overall, especially considering the increased variability and the less mature database at the time of protocol amendment 5.

After observing an imbalance in the number of deaths, a request was made by the IDMC to obtain additional data, including unblinded efficacy results. Based on these data, a recommendation was made to halt the recruitment. The applicant followed the IDMC recommendation and then discontinued the recruitment, which led to the early reporting of study results. It is noted that the IDMC considered this recommendation to be based on a safety concern, for ethical reasons. Given that the imbalance in deaths was in favour of the ivosidenib arm (i.e., not a safety concern for the experimental arm), the discontinuation of the study can be interpreted as an unplanned early stopping based on efficacy which raised further concerns about the trial integrity.

The applicant highlighted the precautions that were taken to protect the study integrity. Only a small team was unblinded to handle interactions with IDMC and FDA, while the rest of the study team remained blinded. In addition, a blinded statistician derived the updated significance boundaries prior to database lock. The applicant concluded that, because of these steps taken prior to database lock, the internal validity of the study remains intact.

The precautions that were taken by the applicant are acknowledged and appear to have limited the damage to the study integrity. However, they do not resolve the main issue of the prior decision to halt the recruitment and perform an analysis that could lead to study discontinuation. Indeed, this decision was made by an unblinded team who had access to efficacy analyses performed by the IDMC. This opportunity to stop the trial early for efficacy was not planned by the amended protocol, i.e., there was

no planned type I error control for it. Consequently, the applicant removed the p-values from all endpoints which are presented in the SmPC.

The ad hoc set of statistical boundaries used the O'Brien-Fleming alpha spending function (Lan-DeMets method), and was defined in a document separate from the SAP and dated 10-Jul-2021, by the blinded study statistician however this was done after the review of unblinded efficacy data by the unblinded team and after the decision to halt recruitment and perform the analysis. The proposed O'Brien-Fleming boundaries would only be acceptable if the unblinded look at efficacy (which led to trial discontinuation) had been prospectively planned in the study protocol. It is acknowledged that Lan-DeMets O'Brien-Fleming boundaries are commonly used for group sequential testing strategies, and that the method was initially planned in the original protocol, when the primary endpoint was OS, and before interim analyses were removed (with amendment 5). Nevertheless, other types of adjustment of sequential testing would have been possible. As requested, the applicant has provided updated Lan-DeMets O'Brien-Fleming boundaries when accounting for all past IDMC meetings as additional interim analyses. Even though this does still not provide formal control of the study type I error (due to lack of prospective planning), it is noted that p-values remain below the updated significance thresholds, thereby providing some reassurance regarding the robustness of the statistical results.

It was also acknowledged that the reported results suggest a large treatment effect and are further supported by a number of additional sensitivity analyses. Together with the information provided about the measures to preserve the integrity of the trial offers the CHMP was reassured that it could rely on the results of the study to determine the benefit/risk balance of ivosidenib in the claimed indication.

The censoring rules of the primary EFS strategy are not in line with the general recommendations in Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man (CHMP/27994/2008 Rev. 1), as they do not closely follow the ITT principle. Nevertheless, it is noted that several sensitivity analyses were planned for EFS, including an analysis considering events regardless of subsequent therapy or more missing disease assessments. This should allow the assessment of the primary analysis under different assumptions.

Statistical methods for primary and secondary endpoints (stratified log-rank tests for EFS and OS, stratified CMH tests for response endpoints) are generally deemed appropriate.

Supportive study AG-221-AML-005

Approximately 24 subjects were planned for enrolment in Study AML-005 (start date: 03 June 2016) for the Phase 1b AG-120 + AZA combination. As of the study DCO of 19 August 2019, 23 subjects have been enrolled, 7 in the dose-finding stage and 16 in the expansion stage of the Phase 1b.

The eligibility criteria established for the supportive trial adequately frame the inclusion of treatment-nave subjects with IDH1 or IDH2 AML.

The phase 1b dose finding stage was based on the standard 3+3 design. The primary aim of this supportive study was to determine the RCD for the treatment of IDH-mutated AML subjects based on the tolerability data of the tested doses. ORR, CR and sponsor-derived CRh were secondary endpoints of the study, while PD was an exploratory endpoint. These endpoints were appropriate to assess the suitability of AG-120 + AZA for both efficacy and safety.

Efficacy data and additional analyses

AG120-C-009 (AGILE)

A total of 146 patients was randomized, including 72 in ivosidenib + azacitidine arm (71 received the treatment), and 74 in placebo + azacitidine arm (73 received the treatment).

Clinically relevant improvement in the primary endpoint of EFS was observed following treatment with ivosidenib + azacitidine with a 67% reduction in the risk of progression/relapse or death compared to the placebo + azacitidine arm (HR = 0.33; 95% CI: 0.16-0.69). Results of the sensitivity analysis were consistent with these primary analysis results.

The third quartile of EFS shows that EFS was highly superior in ivosidenib + azacitidine arm (23.98 months; 95% CI: 14.78-NE months) compared to placebo + azacitidine arm (0.03 months; 95% CI: 0.03, 11.30 months).

As part of secondary endpoints, the CR rate in the FAS was higher in ivosidenib + azacitidine arm compared to placebo + azacitidine arm: 47.2% (95% CI: 35.3-59.3) versus 14.9% (95% CI: 7.7-25.0) with an odds ratio of 4.76 (95% CI: 2.15-10.50).

Medians OS of 24.0 months (95% CI: 11.3-34.1 months) in ivosidenib + azacitidine arm and 7.9 months (95% CI: 4.1-11.3 months) in placebo + azacitidine arm were observed. Median follow-up time was approximately 15 months for both treatment arms. Although OS is immature, clinically relevant improvement in OS was shown for subjects in ivosidenib + azacitidine arm compared to placebo + azacitidine arm (HR = 0.44; 95% CI: 0.27-0.73 which is highly superior to the HR of 0.71 assumed in the initial sample size assumptions).

Subgroup analysis on EFS and OS did not retrieve discrepancies between subgroups.

A Restricted Mean Survival Time (RMST) analysis has been provided regarding the primary endpoint EFS. The reported results supported the primary analysis. A RMST has been provided for OS, supporting the main OS analysis and the relevance of the effect in this endpoint.

The CR+CRh rate was higher in ivosidenib + azacitidine arm than in placebo + azacitidine arm (52.8% [95% CI: 40.7-64.7] versus 17.6% [95% CI: 9.7-28.2]; odds ratio of 5.01 [95% CI: 2.32-10.81]).

ORR was achieved in 62.5% (95% CI: 50.3-73.6) of the subjects in ivosidenib + azacitidine arm and 18.9% (95% CI: 10.7-29.7) of the subjects in placebo + azacitidine arm. ORR was higher in the ivosidenib + azacitidine arm than in the placebo + azacitidine arm (odds ratio of 7.15 [95% CI: 3.31-15.44]).

Median DOCR were non evaluable in both arms at the data cutoff date. However, durability of the treatment effect was observed in the ivosidenib + azacitidine arm in 93.3, 88.4, 88.4, 78.6 and 58.9% of patients at 6, 9, 12, 18 and 24 months, respectively.

Quality of life data was collected as part of the study. Even if HRQoL analyses are rather exploratory, it should be noted that more than 90% of subjects in each treatment arm completed baseline EORTC QLQ-C30 and EQ-5D-5L questionnaires. Compliance decreased over the course of treatment cycles (80% at cycle 5 versus 70% at cycle 19 with no data for the placebo + azaciditine group). For similar baseline scores, a clinically meaningful improvement was observed in the experimental arm characterized by less fatigue and better general condition.

Regardless of baseline transfusion status, a greater proportion of subjects in the ivosidenib + azacitidine arm experienced post-baseline RBC and platelet transfusion independence compared with the placebo + azacitidine arm (56.9% versus 37.8%).

Five subjects underwent an allogeneic HSCT (alloHSCT), including four from the experimental arm (5.6%) – two of them had progressive disease. Based on the narratives provided for each subject, alloHSCT was performed based on investigator's judgement and mean overall survival was 24.05 months at data cut-off.

In vitro biomarker analyses suggested that neither baseline co-mutation nor IDH1 R132 variant presence are anticipated to lead to primary treatment resistance, including primary resistance pathways identified from the ivosidenib monotherapy clinical studies.

AG-221-AML-005

A total of 23 subjects were included and treated with ivosidenib + azacitidine.

Three of the seven subjects enrolled in the dose-finding stage discontinued treatment either due to an adverse event, withdrawal of consent or transition to a marketed treatment (1 subject each, 14.3%).

Thirteen of the 17 subjects of the Expansion Phase discontinued treatment, most frequently following an AE, withdraw of consent or disease relapse. At data cut-off, only 7 subjects remained on treatment.

Due to the small sample sizes, it was not possible to make meaningful comparisons between the dose finding and expansion stages. The assessment of efficacy results was therefore be based on the pooled results of these two steps of the Phase 1b.

The investigator-assessed ORR for the combined subjects was 78.3% (95% CI: 56.3, 92.5) for 18 subjects. The overall CR rate was 56.5% (95% CI: 34.5, 76.8) for subjects who received treatment with AG-120 + AZA with a median time to remission (CR) of 3.49 months (range: 0.5-15.7).

The sponsor-derived CR/CRh response was 65.2% (95% CI: 42.7, 83.6) for 15 of 23 subjects who achieved a response of CR/CRh and the median time to response was 1.83 months (range: 0.7-3.8).

These results support what was observed in AGILE study: a clinically meaningful improvement of ORR, CRR, CR/CRh, time to remission and time to response in subjects from the ivosidenib + azacitidine arm compared to the control arm.

2.10.13. Conclusions on the clinical efficacy

The clinical efficacy data submitted in this MAA support the benefit of ivosidenib + azacitidine in the final agreed indication.

2.10.14. Clinical safety

2.10.14.1. Patient exposure

The characterisation of the safety profile of ivosidenib in combination with azacitidine in AML is primarily based on the ongoing pivotal phase 3 study AG120-C-009 (AGILE). The applicant during the procedure submitted updated safety data with a new cut-off date of 1st of October 2021 and which are presented in this section along the initial cut-off date of 18th of March 2021 unless otherwise stated.

Patients included had newly diagnosed AML with an IDH1 mutation and were considered ineligible to intensive induction therapy. Patients were treated with ivosidenib 500mg QD or matching placebo + azacitidine 75 mg/m²/day SC or IV for 7 days of each 4-weeks cycle, which is the intended posology. A summary of study treatment duration is presented in Table 103.

Table 99. Summary of study treatment duration in study AG120-C-009, Safety Analysis Set

	sNDA (Data cutoff date: 18 March 2021)		Safety Update (Data cutoff date: 01 October 2021)	
	IVO + AZA (N=71)	PBO + AZA (N=73)	IVO + AZA (N=72)	PBO + AZA (Before crossover) (N=74)
Treatment Duration (months)				
n	71	73	72	74
Mean (SD)	8.80 (8.086)	4.73 (4.971)	11.07 (9.832)	5.37 (5.528)
Median (Q1, Q3)	5.98 (1.74, 15.08)	2.76 (1.38, 5.59)	7.84 (2.17, 18.66)	3.19 (1.41, 8.61)
Min, Max	0.1, 33.5	0.1, 19.8	0.1, 40.0	0.1, 26.3
Treatment Duration Category (months) n (%)				
>0 - ≤4	25 (35.2)	44 (60.3)	23 (31.9)	41 (55.4)
>4 - ≤8	17 (23.9)	14 (19.2)	13 (18.1)	12 (16.2)
>8 - ≤12	6 (8.5)	8 (11.0)	7 (9.7)	13 (17.6)
>12 - ≤16	7 (9.9)	3 (4.1)	6 (8.3)	3 (4.1)
>16 - ≤20	9 (12.7)	4 (5.5)	8 (11.1)	4 (5.4)
>20 - ≤24	5 (7.0)	0	8 (11.1)	0
>24 - ≤28	0	0	3 (4.2)	1 (1.4)
>28 - ≤32	1 (1.4)	0	2 (2.8)	0
>32	1 (1.4)	0	2 (2.8)	0

Abbreviations: Q1 = first quartile; Q3 = third quartile; SD = standard deviation.
Notes: Treatment duration (months) = (end date of the study treatment - start date of the study treatment + 1)/30.4375.

The median duration of treatment was >2 times longer in the IVO + AZA arm than in the PBO+ AZA arm, and the median relative dose intensity of IVO experienced by subjects randomized to the IVO + AZA arm was similar to the PBO + AZA arm for both cut-off dates (Table 104).

Table 100. Summary of exposure to ivosidenib in study AG120-C-009, Safety Analysis Set

	sNDA (Data cutoff date: 18 March 2021)		Safety Update (Data cutoff date: 01 October 2021)	
	IVO + AZA (N=71)	PBO + AZA (N=73)	IVO + AZA (N=72)	PBO + AZA (Before crossover) (N=74)
Duration of Exposure (days)				
n	71	73	72	74
Mean (SD)	264.7 (245.93)	143.6 (150.40)	330.8 (297.98)	162.3 (167.30)
Median (Q1, Q3)	180.0 (53.0, 459.0)	84.0 (42.0, 170.0)	227.5 (66.0, 549.5)	95.5 (43.0, 261.0)
Min, Max	4, 1019	3, 588	4, 1216	3, 796
Duration of Exposure Category (weeks) n (%)				
>0 - ≤4	12 (16.9)	15 (20.5)	11 (15.3)	14 (18.9)
>4 - ≤8	6 (8.5)	13 (17.8)	6 (8.3)	12 (16.2)
>8 - ≤12	5 (7.0)	9 (12.3)	4 (5.6)	8 (10.8)
>12 - ≤16	1 (1.4)	7 (9.6)	1 (1.4)	7 (9.5)
>16 - ≤20	4 (5.6)	4 (5.5)	3 (4.2)	5 (6.8)
>20 - ≤24	6 (8.5)	6 (8.2)	5 (6.9)	5 (6.8)
>24	37 (52.1)	19 (26.0)	42 (58.3)	23 (31.1)
Cumulative Dose (mg)				
n	71	73	72	74
Mean (SD)	112394.4 (107966.45)	66054.8 (71715.64)	139493.1 (129797.23)	72787.2 (77488.64)
Median (Q1, Q3)	78250.0 (25500.0, 175750.0)	36500.0 (17500.0, 83500.0)	90875.0 (31000.0, 232750.0)	43500.0 (19500.0, 112500.0)
Min, Max	2000, 509500	1500, 284500	2000, 608000	1500, 324250

	sNDA (Data cutoff date: 18 March 2021)		Safety Update (Data cutoff date: 01 October 2021)	
	IVO + AZA (N=71)	PBO + AZA (N=73)	IVO + AZA (N=72)	PBO + AZA (Before crossover) (N=74)
Actual Dose Intensity (mg/day)				
n	71	73	72	74
Mean (SD)	446.05 (81.411)	457.18 (68.862)	443.43 (84.294)	450.67 (77.440)
Median (Q1, Q3)	491.80 (427.54, 500.00)	488.31 (446.43, 500.00)	484.30 (431.65, 500.00)	487.51 (443.61, 500.00)
Min, Max	230.3, 501.2	137.3, 500.0	230.3, 500.8	137.3, 500.0
Relative Dose Intensity (%)				
n	71	73	72	74
Mean (SD)	89.21 (16.282)	91.44 (13.772)	88.69 (16.859)	90.13 (15.488)
Median (Q1, Q3)	98.36 (85.51, 100.00)	97.66 (89.29, 100.00)	96.86 (86.33, 100.00)	97.50 (88.72, 100.00)
Min, Max	46.1, 100.2	27.5, 100.0	46.1, 100.2	27.5, 100.0

Abbreviations: Q1 = first quartile; Q3 = third quartile; SD = standard deviation.
Notes: Duration of Exposure (days) = (date of last dose - date of first dose + 1); Cumulative dose (mg) = sum of the actual doses; Planned Dose Intensity (mg/day) = 500; Actual Dose Intensity (mg/day) = Cumulative dose (mg)/ Duration of Exposure(day);Relative Dose Intensity (%) = 100×Actual Dose Intensity (mg/day)/Planned Dose Intensity (mg/day).

Supportive safety data relevant for the combination are provided by the ongoing phase 1b/2 study AG-221-AML-005 in which 23 patients with newly diagnosed AML harbouring IDH1 mutation and not eligible to induction therapy received the combination at the intended dose.

Additional safety data are provided by the ongoing phase I study AG120-C-001 in patients with advanced hematologic malignancies with an IDH1 mutation. This was the pivotal study for the previous Application of ivosidenib in monotherapy for patients with R/R AML with IDH1 mutation. 34 patients with newly diagnosed AML received ivosidenib in monotherapy at the intended dose (500mg QD).

Finally, 2 other studies provide more limited information on ivosidenib safety: study AG120-221-C-001 in patients with newly diagnosed AML with IDH1/2 mutation who received ivosidenib 500mg QD in combination with induction and consolidation therapy, and study CS3010 in Chinese patients with advanced haematologic malignancies who received ivosidenib 500 mg QD as monotherapy.

2.10.14.2. Adverse events

Almost all subjects included in the safety analysis set experienced a Treatment-Emergent Adverse Event (TEAE) as seen in Table 105.

Table 101. Overall Summary of Treatment-Emergent Adverse Events in study AG120-C-009 (Safety Analysis Set)

Number of Subjects with	sNDA (Data cutoff date: 18 March 2021)		Safety Update (Data cutoff date: 01 October 2021)	
	IVO + AZA (N=71) n (%)	PBO + AZA (N=73) n (%)	IVO + AZA (N=72) n (%)	PBO + AZA (Before crossover) (N=74) n (%)
Any TEAE	70 (98.6)	73 (100.0)	71 (98.6)	74 (100)
Treatment-related TEAE				
Related to IVO or PBO only	27 (38.0)	18 (24.7)	28 (38.9)	22 (29.7)
Related to AZA only	40 (56.3)	37 (50.7)	42 (58.3)	38 (51.4)
Related to both IVO or PBO and AZA	42 (59.2)	36 (49.3)	43 (59.7)	37 (50.0)
Grade ≥3 TEAE	66 (93.0)	69 (94.5)	66 (91.7)	71 (95.9)
Grade ≥3 treatment-related TEAE				
Related to IVO or PBO only	11 (15.5)	8 (11.0)	11 (15.3)	9 (12.2)
Related to AZA only	22 (31.0)	22 (30.1)	23 (31.9)	24 (32.4)
Related to both IVO or PBO and AZA	32 (45.1)	22 (30.1)	33 (45.8)	23 (31.1)

Number of Subjects with	sNDA (Data cutoff date: 18 March 2021)		Safety Update (Data cutoff date: 01 October 2021)	
	IVO + AZA (N=71) n (%)	PBO + AZA (N=73) n (%)	IVO + AZA (N=72) n (%)	PBO + AZA (Before crossover) (N=74) n (%)
Serious TEAE	49 (69.0)	60 (82.2)	49 (68.1)	62 (83.8)
Serious treatment-related TEAE				
Related to IVO OR PBO only	5 (7.0)	3 (4.1)	5 (6.9)	3 (4.1)
Related to AZA only	5 (7.0)	5 (6.8)	5 (6.9)	5 (6.8)
Related to both IVO or PBO and AZA	16 (22.5)	9 (12.3)	16 (22.2)	10 (13.5)
TEAE leading to discontinuation of study drug				
Discontinuation of IVO or PBO only	3 (4.2)	2 (2.7)	3 (4.2)	3 (4.1)
Discontinuation of AZA only	2 (2.8)	1 (1.4)	2 (2.8)	1 (1.4)
Discontinuation of both IVO or PBO and AZA	19 (26.8)	19 (26.0)	19 (26.4)	19 (25.7)
TEAE leading to dose reduction of study drug				
Dose reduction of IVO or PBO only	10 (14.1)	6 (8.2)	12 (16.7)	6 (8.1)
Dose reduction of AZA only	9 (12.7)	4 (5.5)	10 (13.9)	4 (5.4)
Dose reduction of both IVO or PBO and AZA	4 (5.6)	0	4 (5.6)	1 (1.4)
TEAEs leading to interruption of study drug				
Interruption of IVO or PBO only	20 (28.2)	28 (38.4)	21 (29.2)	29 (39.2)
Interruption of AZA only	19 (26.8)	17 (23.3)	20 (27.8)	18 (24.3)
Interruption of both IVO or PBO and AZA	37 (52.1)	28 (38.4)	38 (52.8)	30 (40.5)
TEAE leading to death	10 (14.1)	21 (28.8)	11 (15.3)	23 (31.1)
Treatment-related TEAE leading to death				
Related to IVO or PBO only	0	0	0	0
Related to AZA only	0	0	0	0
Related to both IVO or PBO and AZA	0	0	0	0

Abbreviations: TEAE = treatmentemergent- adverse events.
Notes: For Brazilian subjects, the relatedness to Azacitidine was not assessed; MedDRA Version 23.1 and Version 24.0 and CTCAE Version 4.03 are used

Common adverse events

A summary of the most common TEAEs in study AG120-C-009 is displayed in Table 106.

Table 102. Summary of Most Common (≥10% of Subjects in Either Treatment Arm) Treatment-Emergent Adverse Events by Preferred Term in study AG120-C-009 (Safety Analysis Set)

Preferred Term	sNDA (Data cutoff date: 18 March 2021)		Safety Update (Data cutoff date: 01 October 2021)	
	IVO + AZA (N=71) n (%)	PBO + AZA (N=73) n (%)	IVO + AZA (N=72) n (%)	PBO + AZA (Before crossover) (N=74) n (%)
Any event	70 (98.6)	73 (100.0)	71 (98.6)	74 (100)
Nausea	30 (42.3)	28 (38.4)	32 (44.4)	29 (39.2)
Vomiting	29 (40.8)	19 (26.0)	29 (40.3)	20 (27.0)
Diarrhoea	25 (35.2)	26 (35.6)	25 (34.7)	29 (39.2)
Pyrexia	24 (33.8)	29 (39.7)	25 (34.7)	32 (43.2)
Anaemia	22 (31.0)	21 (28.8)	23 (31.9)	23 (31.1)
Febrile neutropenia	20 (28.2)	25 (34.2)	20 (27.8)	25 (33.8)
Neutropenia	20 (28.2)	12 (16.4)	22 (30.6)	16 (21.6)
Thrombocytopenia	20 (28.2)	15 (20.5)	20 (27.8)	15 (20.3)
Constipation	19 (26.8)	38 (52.1)	22 (30.6)	39 (52.7)
Pneumonia	17 (23.9)	23 (31.5)	17 (23.6)	24 (32.4)
Electrocardiogram QT prolonged	14 (19.7)	5 (6.8)	15 (20.8)	5 (6.8)
Insomnia	13 (18.3)	9 (12.3)	13 (18.1)	9 (12.2)
Asthenia	11 (15.5)	24 (32.9)	11 (15.3)	25 (33.8)
Decreased appetite	11 (15.5)	19 (26.0)	12 (16.7)	21 (28.4)
Dyspnoea	11 (15.5)	9 (12.3)	11 (15.3)	10 (13.5)
Hypokalaemia	11 (15.5)	21 (28.8)	11 (15.3)	21 (28.4)
Differentiation syndrome	10 (14.1)	6 (8.2)	10 (13.9)	6 (8.1)
Pain in extremity	10 (14.1)	3 (4.1)	10 (13.9)	4 (5.4)
Fatigue	9 (12.7)	10 (13.7)	9 (12.5)	10 (13.5)
Haematoma	9 (12.7)	1 (1.4)	10 (13.9)	1 (1.4)
Arthralgia	8 (11.3)	3 (4.1)	12 (16.7)	4 (5.4)
Headache	8 (11.3)	2 (2.7)	8 (11.1)	2 (2.7)
Leukocytosis	8 (11.3)	1 (1.4)	8 (11.1)	2 (2.7)
Oedema peripheral	8 (11.3)	16 (21.9)	9 (12.5)	17 (23.0)
Platelet count decreased	8 (11.3)	6 (8.2)	9 (12.5)	6 (8.1)
Rash	7 (9.9)	9 (12.3)	7 (9.7)	10 (13.5)
Cough	6 (8.5)	11 (15.1)	6 (8.3)	12 (16.2)
Haemorrhoids	5 (7.0)	8 (11.0)	5 (6.9)	8 (10.8)
Weight decreased	4 (5.6)	12 (16.4)	4 (5.6)	12 (16.2)
Pruritis	7 (9.9)	4 (5.5)	8 (11.1)	4 (5.4)
Hyponatraemia	3 (4.2)	1 (1.4)	5 (6.9)	8 (10.8)

Abbreviations: TEAE = treatment-related adverse events.
Notes: Adverse events leading to interruption of study treatment are those leading to interruption of both study drugs that are part of the combination treatment; Summarized in order of decreasing frequency of subjects with events based on the frequencies observed for ivosidenib + azacitidine; Subjects with multiple adverse events within a preferred term are counted only once in that preferred term.

Grade ≥ 3 Adverse events

The most common severe TEAEs (Grade 3 and above according to the Common Terminology Criteria for Adverse Event (CTCAE) in study AG120-C-009 are summarised in Table 107.

Table 103. Summary of Most Common (≥5% of Subjects in Either Treatment Arm) Grade 3 or Higher Treatment-Emergent Adverse Events by Preferred Term in study AG120-C-009 (Safety Analysis Set)

	sNDA (Data cutoff date: 18 March 2021)		Safety Update (Data cutoff date: 01 October 2021)	
Preferred Term	IVO + AZA (N=71) n (%)	PBO + AZA (N=73) n (%)	IVO + AZA (N=72) n (%)	PBO + AZA (Before crossover) (N=74) n (%)
Any event	66 (93.0)	69 (94.5)	66 (91.7)	71 (95.9)
Diarrhoea	1 (1.4)	5 (6.8)	1 (1.4)	6 (8.1)
Anaemia	18 (25.4)	19 (26.0)	19 (26.4)	20 (27.0)
Febrile neutropenia	20 (28.2)	25 (34.2)	20 (27.8)	25 (33.8)
Neutropenia	19 (26.8)	12 (16.4)	22 (30.6)	16 (21.6)
Thrombocytopenia	17 (23.9)	15 (20.5)	17 (23.6)	15 (20.3)
Pneumonia	16 (22.5)	21 (28.8)	16 (22.2)	22 (29.7)
Electrocardiogram QT prolonged	7 (9.9)	2 (2.7)	7 (9.7)	2 (2.7)
Asthenia	0	5 (6.8)	0	6 (8.1)
Decreased appetite	1 (1.4)	6 (8.2)	1 (1.4)	6 (8.1)
Hypokalemia	2 (2.8)	6 (8.2)	2 (2.8)	7 (9.5)
Platelet count decreased	6 (8.5)	6 (8.2)	8 (11.1)	6 (8.1)
Leukopenia	5 (7.0)	2 (2.7)	5 (6.9)	2 (2.7)
Neutrophil count decreased	6 (8.5)	5 (6.8)	6 (8.3)	5 (6.8)
Hyponatraemia	3 (4.2)	5 (6.8)	3 (4.2)	6 (8.1)
Hypotension	0	4 (5.5)	0	4 (5.4)
Pulmonary embolism	4 (5.6)	1 (1.4)	4 (5.6)	1 (1.4)
Sepsis	2 (2.8)	6 (8.2)	2 (2.8)	6 (8.1)

Notes: The table includes TEAEs that occurred in ≥5% of subjects in any column at the PT level; "Subjects with Any Grade ≥3 TEAE" are summarized for all TEAEs. Summarized in order of decreasing frequency of subjects with events in any grade based on the frequencies observed for ivosidenib + azacitidine; Subjects with multiple adverse events within a PT are counted only once in that PT; For subjects with multiple occurrences of an adverse event, the adverse event with the worst CTCAE grade is included in the summary; MedDRA Version 23.1 and CTCAE Version 4.03 are used.

In supportive study AG-221-AML-005, drug related TEAE with grade ≥ 3 severity were overall consistent with pivotal study. However, one patient in that study experienced a grade ≥ 3 tumour lysis syndrome.

Following a review and a discussion of all TLS cases observed in patients treated with ivosidenib, a significant incidence of TLS (7.4% of treated patients) in the monotherapy study AG120-C-001 compared to the pivotal AG120-C-009 (one case of TLS in control arm, none in ivosidenib arm) and the supportive studies was highlighted.

2.10.14.3. Serious adverse event/deaths/other significant events

Serious adverse events

A summary of the most frequently reported serious TEAEs reported in study AG120-C-009 is provided in Table 108.

Table 104. Summary of Serious Treatment-Emergent Adverse Events Related to both ivosidenib or Placebo and Azacitidine by System Organ Class and Preferred Term - Newly Diagnosed AML in study AG120-C-009 (Safety Analysis Set)

System Organ Class Preferred Term	sNDA (Data cutoff date: 18 March 2021)		Safety Update (Data cutoff date: 01 October 2021)	
	IVO + AZA (N=71) n (%)	PBO + AZA (N=73) n (%)	IVO + AZA (N=72) n (%)	PBO + AZA (Before crossover) (N=74) n (%)
Any events	16 (22.5)	9 (12.3)	16 (22.2)	10 (13.5)
Blood and lymphatic system disorders	7 (9.9)	5 (6.8)	7 (9.7)	5 (6.8)
Febrile neutropenia	5 (7.0)	5 (6.8)	5 (6.9)	5 (6.8)
Neutropenia	1 (1.4)	0	1 (1.4)	0
Thrombocytopenia	1 (1.4)	0	1 (1.4)	0

System Organ Class Preferred Term	sNDA (Data cutoff date: 18 March 2021)		Safety Update (Data cutoff date: 01 October 2021)	
	IVO + AZA (N=71) n (%)	PBO + AZA (N=73) n (%)	IVO + AZA (N=72) n (%)	PBO + AZA (Before crossover) (N=74) n (%)
Infections and infestations	5 (7.0)	4 (5.5)	6 (8.3)	5 (6.8)
Bronchopulmonary aspergillosis	1 (1.4)	0	1 (1.4)	1 (1.4)
Enterococcal infection	1 (1.4)	0	1 (1.4)	0
Pneumonia	1 (1.4)	0	1 (1.4)	0
Pneumonia pseudomonal	1 (1.4)	0	1 (1.4)	0
Pneumonia respiratory syncytial viral	1 (1.4)	0	1 (1.4)	0
Sepsis	1 (1.4)	0	1 (1.4)	0
Urinary tract infection	0	0	1 (1.4)	0
Enterococcal sepsis	0	1 (1.4)	0	1 (1.4)
Escherichia sepsis	0	1 (1.4)	0	1 (1.4)
Influenza	0	1 (1.4)	0	1 (1.4)
Lower respiratory tract infection	0	1 (1.4)	0	1 (1.4)
Pneumonia staphylococcal	0	1 (1.4)	0	1 (1.4)
General disorders and administration site conditions	2 (2.8)	0	2 (2.8)	0
Fatigue	1 (1.4)	0	1 (1.4)	0
Pyrexia	1 (1.4)	0	1 (1.4)	0
Gastrointestinal disorders	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)
Lower gastrointestinal haemorrhage	1 (1.4)	0	1 (1.4)	0
Diverticular perforation	0	1 (1.4)	0	1 (1.4)
Investigations	1 (1.4)	0	1 (1.4)	0
Blast cell count increased	1 (1.4)	0	1 (1.4)	0

System Organ Class Preferred Term	sNDA (Data cutoff date: 18 March 2021)		Safety Update (Data cutoff date: 01 October 2021)	
	IVO + AZA (N=71) n (%)	PBO + AZA (N=73) n (%)	IVO + AZA (N=72) n (%)	PBO + AZA (Before crossover) (N=74) n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)
Differentiation syndrome	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)
Nervous system disorders	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)
Cerebral infarction	1 (1.4)	0	1 (1.4)	0
Dementia	0	1 (1.4)	0	1 (1.4)
Respiratory, thoracic and mediastinal disorders	1 (1.4)	0	1 (1.4)	0
Pneumonitis	1 (1.4)	0	1 (1.4)	0
Renal and urinary disorders	0	1 (1.4)	1 (1.4)	1 (1.4)
Renal failure	0	1 (1.4)	0	1 (1.4)
Renal disorder	0	0	1 (1.4)	0

Abbreviations: SAE = serious adverse events.
Notes: Summarized in order of decreasing frequency of subjects with events based on the frequencies observed for ivosidenib + azacitidine.

Data of supportive study AG-221-AML-005 were overall consistent with pivotal study data.

Deaths

On-treatment death was defined as death that occurred after the start of study treatment and within 28 days after the last dose of study treatment. A summary of the TEAEs leading to death is presented Table 109.

Table 105. Summary of Treatment-Emergent Adverse Events Leading to Deaths by System Organ Class and Preferred Term in study AG120-C-009 (Safety Analysis Set)

System Organ Class Preferred Term	sNDA (Data cutoff date: 18 March 2021)		Safety Update (Data cutoff date: 01 October 2021)	
	IVO + AZA (N=71) n (%)	PBO + AZA (N=73) n (%)	IVO + AZA (N=72) n (%)	PBO + AZA (Before crossover) (N=74) n (%)
Subjects with Any TEAE Leading to On-Treatment Death[1]	10 (14.1)	21 (28.8)	11 (15.3)	23 (31.1)
Nervous system disorders	4 (5.6)	0	4 (5.6)	0
Haemorrhage intracranial	2 (2.8)	0	2 (2.8)	0
Ischaemic stroke	1 (1.4)	0	1 (1.4)	0
Seizure	1 (1.4)	0	1 (1.4)	0

System Organ Class Preferred Term	sNDA (Data cutoff date: 18 March 2021)		Safety Update (Data cutoff date: 01 October 2021)	
	IVO + AZA (N=71) n (%)	PBO + AZA (N=73) n (%)	IVO + AZA (N=72) n (%)	PBO + AZA (Before crossover) (N=74) n (%)
Infections and infestations	3 (4.2)	14 (19.2)	4 (5.6)	15 (20.3)
COVID-19	1 (1.4)	0	1 (1.4)	0
Pneumonia	1 (1.4)	5 (6.8)	2 (2.8)	6 (8.1)
Septic shock	1 (1.4)	2 (2.7)	1 (1.4)	2 (2.7)
Abdominal infection	0	1 (1.4)	0	1 (1.4)
Bronchopulmonary aspergillosis	0	1 (1.4)	0	1 (1.4)
COVID-19 pneumonia	0	1 (1.4)	0	1 (1.4)
Corynebacterium sepsis	0	1 (1.4)	0	1 (1.4)
Pneumonia bacterial	0	1 (1.4)	0	1 (1.4)
Sepsis	0	2 (2.7)	0	2 (2.7)
General disorders and administration site conditions	1 (1.4)	3 (4.1)	1 (1.4)	3 (4.1)
Multiple organ dysfunction syndrome	1 (1.4)	1 (1.4)	1 (1.4)	1 (1.4)
General physical health deterioration	0	2 (2.7)	0	2 (2.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (1.4)	0	1 (1.4)	0
Adenocarcinoma	1 (1.4)	0	1 (1.4)	0
Respiratory, thoracic and mediastinal disorders	1 (1.4)	2 (2.7)	1 (1.4)	3 (4.1)
Pulmonary embolism	1 (1.4)	0	1 (1.4)	0
Haemoptysis	0	0	0	1 (1.4)
Lung disorder	0	1 (1.4)	0	1 (1.4)
Respiratory failure	0	1 (1.4)	0	1 (1.4)

System Organ Class Preferred Term	sNDA (Data cutoff date: 18 March 2021)		Safety Update (Data cutoff date: 01 October 2021)	
	IVO + AZA (N=71) n (%)	PBO + AZA (N=73) n (%)	IVO + AZA (N=72) n (%)	PBO + AZA (Before crossover) (N=74) n (%)
Blood and lymphatic system disorders	0	1 (1.4)	0	1 (1.4)
Febrile neutropenia	0	1 (1.4)	0	1 (1.4)
Psychiatric disorders	0	1 (1.4)	0	1 (1.4)
Delirium	0	1 (1.4)	0	1 (1.4)

In supportive study AG120-AML-005, 3 other deaths from infectious origin were also reported (Enterobacter bacteraemia, Enterococcal infection, and Sepsis). None was assessed as related to study treatment.

In additional study AG120-C-001 within patients with *newly diagnosed AML* who received ivosidenib monotherapy, 5 subjects (14.7%) had a TEAE leading to on-treatment death, including 3 subjects related to infectious events (Pneumonia, Febrile neutropenia and Infection), and 1 to haemorrhage (Retroperitoneal haemorrhage).

Adverse events of special Interest

- QT prolongation

Incidence of electrocardiogram QT prolonged was higher in ivosidenib + azacitidine arm (19.7%) than in placebo + azacitidine arm (6.8%). Among these, 9.9% (7 patients) in ivosidenib + azacitidine arm and 2.7% (2 patients) in placebo + azacitidine arm met the definition of AESI. In addition, one patient experienced a grade 3 syncope in placebo + azacitidine arm. There were no Grade 4 or Grade 5 TEAEs of Electrocardiogram QT prolonged, Torsades de Pointes, or fatal arrhythmias in either treatment arm. With an additional 6.5 months of follow-up since the first data cut-off, there was only 1 newly reported AESI of serious Grade 3 Syncope reported in the ivosidenib + azacitidine arm (and none on the placebo+ azacitidine arm) which was assessed by the Investigator as not related to both study drugs.

Median (min, max) time to first TEAE of electrocardiogram prolonged, assessed in study AG-120-C-009, was 29.0 days (1-561 days) with 26.7 % of first events that occurred > 60 days showing that event of QT prolonged can occur weeks after reaching the concentration at steady state (Css). Median time to first event was consistent in supportive study and other additional studies.

ECG QT prolonged led to interruption of treatment in 5 patients (6.9%), to dose reduction in 7 patients (9.7%) and to treatment discontinuation in one patient (1.4%).

Supportive study AG-221-AML-005 confirmed the high frequency of events of QT prolongation (30%, 7 patients) with 17% (4 subjects) who had a grade 3 event and no grade ≥ 4 observed.

Moreover in monotherapy study AG120-C-001, 9% of patients had a grade 3 event of ECG QT prolongation and one patient developed a ventricular fibrillation considered related to ivosidenib.

- Leukocytosis

In study AG120-C-009 (AGILE), any event of leukocytosis assessed as Grade ≥3, irrespective of seriousness, was to be reported as an AESI. No leucocytosis event was ≥ grade 3 therefore no AE met the definition of AESI. Up to the first cut-off date, leucocytosis of any grade occurred in 11.3% (8 patients) vs 1.4% (1 patient) in ivosidenib + azacitidine and placebo + azacitidine arm respectively. With

an additional 6.5 months of follow-up to the second cut-off date, there was only one new nonserious event of Grade 3 leukocytosis reported in the placebo + azacitidine arm.

Grade 3 events remained rare in supportive and additional studies.

In Study AG120-C-009, Median (range) time to first onset of leucocytosis was 20 days (9-33 days) for patients in ivosidenib + azacitidine arm and 22 days (22 to 22 days) in placebo + azacitidine arm.

- Differentiation syndrome

The overall incidence of Differentiation syndrome in the ivosidenib + azacitidine and placebo + azacitidine arms was 10 (14.1%) vs. 6 (8.2%) subjects, respectively. Incidence of serious TEAEs of differentiation syndrome was also higher in experimental arm (8.5%) than in control arm (1.4%). No patients died from Differentiation syndrome in either study arm.

In 8 subjects in the experimental arm and 5 subjects in the control arm, differentiation syndrome was assessed by the Investigator as related to ivosidenib. The incidence was higher in AG-221-AML-005 (17.4%), including some SAEs. Incidences were similar in the rest of studies.

The median number of days to first onset of the PT of Differentiation syndrome was for the subjects who received treatment with ivosidenib + azacitidine, 19.5 days (range: 3 to 33 days) and for the subjects who received treatment with azacitidine + placebo, 44 days (range: 4 to 86 days). Here again, differentiation syndrome due to azacitidine may explain the difference in number of days to first onset between both arms. Nevertheless, the incidence in experimental arm was double than in control arm.

Additional adverse events of clinical importance

- Guillain-Barré syndrome

While no events of Guillain Barré syndrome were observed in pivotal study AG120-C-009 (AGILE) and supportive study AG-221-AML-005, 2 cases of Guillain-Barré syndrome occurred in study AMG-C-001 (ivosidenib monotherapy at 500mg QD) and were considered as related to the study treatment by the investigator. In addition, 3 cases of Guillain-Barré syndrome were retrieved in Eudravigilance database including 2 post marketing cases in US and one case in an indication of leukaemia relapse prophylaxis at an unspecified dose from a compassionate use in France.

Searches using the MedDRA HLTs of acute polyneuropathies, chronic polyneuropathies, led to the identification of several cases of peripheral neuropathy in supportive study AG-221-AML-005 (2 patients), in the post-marketing setting (4 patients) and in the pivotal study (2 patients whose event were considered related to ivosidenib).

- Leukoencephalopathy

Regarding Progressive multifocal leukoencephalopathy (PML), while no event was reported in the pivotal and supportive studies, two events were reported in one subject with R/R AML in the monotherapy study AG120-C-001, 225 and 302 days after treatment initiation. The first event resolved within 2 days with sequelae without interruption of study treatment. The treatment was interrupted on study day 305 during the second event due to the neurological symptoms. JC virus was detected in the CSF on D309 and treated with BK virus cytotoxic T lymphocyte cells, then study treatment was resumed on D331. Both events were considered as not related to study treatment by the investigator. At the data cut off, the subject remained on study treatment and the PML was ongoing. The patient had previously received cladribine which is a confounding factor.

Concerning Posterior reversible encephalopathy syndrome (PRES), one case was retrieved in a patient who did not receive any previous therapy 94 days after treatment initiation in the same study AG120-C-001. The treatment was permanently discontinued on day 94 patient and the event of PRES was

considered resolved with sequalae on study day 106. The SAE was considered as possibly related to study treatment by the investigator.

No such cases were retrieved in the pivotal and in the supportive study AG-221-AML-005 in which the search strategy for leukoencephalopathies events was more restrictive (only PT Progressive multifocal leukoencephalopathy and Posterior reversible encephalopathy syndrome). A thorough analysis of data from the pivotal study AG120-C-009, the supportive study AG-221-AML-005 and post-marketing data with the search strategy applied for study AG120-C-001 was provided by the applicant which did not identify additional cases of PML and PRES.

Other adverse events of Interest

- Infections

The incidence of events within SOC infection and infestation was high in both treatment arms but was lower in experimental arm (72.2%) than in control arm (79.7%). The overall incidence of Infections of any grade was lower in ivosidenib + azacitidine arm (30.6%) than in placebo + azacitidine (51.4%) as well as Grade ≥3 TEAEIs of infection (21.1% vs 30.1%), serious TEAEIs of infection (16.9% vs 23.3%), fatal TEAEIs of infection (2.8% vs 9.6%), and discontinuations of both ivosidenib or placebo and azacitidine due to infection (4.2% vs 9.6%).

The applicant provided an analysis on the number of fungal infections in each arm which do not suggest an increase of fungal infection in patient receiving ivosidenib with regards to the high incidence of neutropenia and neutropenia grade ≥ 3 events.

- Bleeding

TEAE of bleedings of any grade occurred more frequently in ivosidenib + azacitidine arm (41.7%) than in placebo + azacitidine arm (31.1%). The applicant noted that grade ≥ 3 events and serious bleeding events were comparable in both treatment arms. However, among the 3 SAE related to bleeding events which occurred in experimental arm, 2 events were grade 5 haemorrhage intracranial while no fatal event occurred in control arm. The 3rd SAE was a grade 3 lower gastrointestinal haemorrhage. This latter patient had platelets at 15x10^9g/L 6 days before the report of the event of lower gastrointestinal haemorrhage.

In one of the fatal cases reported, the patient died of an intracranial haemorrhage 17 days after the last dose of ivosidenib (study day 139). There was no supporting evidence which confirmed this diagnosis as an autopsy was not performed. The Investigator considered the event of Haemorrhage intracranial related to concomitant medication or disease and clarified that epilepsy and acute cerebrovascular disease were not excluded. However, mean terminal half-life of ivosidenib is 98 hours, meaning elimination occurs about 20 days after the last administration. It is therefore difficult to definitely rule out ivosidenib as a cause of the haemorrhage intracranial that occurred 17 days after the last dose.

Another patient was diagnosed with an SAE of haemorrhage intracranial on study day 110, 26 days after the last dose of ivosidenib. This patient had thrombocytopenia grade 4 at D111 (1.10^9/L). The investigator considered the event of haemorrhage intracranial as not related to ivosidenib but notably associated with thrombocytopenia, which is recognized as an ADR of ivosidenib.

In addition, listing of adverse events leading to on treatment death of study AG120-C-001 describes that in patients with *R/R AML* receiving ivosidenib monotherapy at 500mg QD (Arm 1 expansion phase) one patient died of a cerebral haemorrhage, one patient died of a subarachnoid haemorrhage, one patient died of a CNS haemorrhage. Additionally, one patient died of haemorrhage intracranial in escalation phase at 100 mg BID.

Furthermore, a higher incidence of haematoma in experimental arm (12.7%) compared to control arm (1.4%) was observed in the pivotal study.

- Covid-19

Overall, less patients experienced a TEAE of COVID-19 in experimental arm (2.8%, 2 patients) than in control arm (6.8%, 5 patients). SAE were observed in both patients in experimental arm and in 1 patient in control arm. Number of events that led to discontinuation or interruption was comparable in both treatment arms. 1 event in each arm led to death. The low number of cases of COVID-19 does not allow to draw any conclusions.

2.10.14.4. Laboratory findings

- Haematology parameters

Overall laboratory abnormalities were consistent with that expected within newly diagnosed AML population and safety profile of both ivosidenib and azacytidine.

- Clinical chemistry parameters

In the pivotal study, AST elevations of any grade were higher in the experimental arm (36.6%) than in control arm (23.3%). Conversely, ALT elevations of any grade were higher in the control arm (31.5%) than in the experimental arm (18.3%). No transaminases grade 3-4 elevation were observed. In addition, although any grade bilirubin elevation was similar between groups (22.5% and 21.9% for the experimental and control treatment arms respectively), grade 3/4 bilirubin elevation was observed only in the experimental arm (4.2%). Considering the low number of cases, no firm conclusion on causal association could be drawn.

- Coagulation analysis

The combination of ivosidenib + azacitidine did not seem to have a major impact on Activated Partial Thromboplastin Clotting Time (aPTT) with similar newly occurring or worsening event of any grade in both treatment arms in the pivotal study (18.2%, 12/66 patients in the experimental arm and 14.3%, 9/63 patients in control arm) and 1 case of newly occurring or worsening to grade 3 aPTT in each treatment arm and no grade 4 events.

2.10.14.5. Vital signs, physical findings and other observations related to safety

Vital signs abnormalities were comparable between both arms although a numerical higher incidence of hypertension (9.9%) in the experimental arm compared to the control arm (6.8%) was noted (see Clinical Safety discussion for the cholangiocarcinoma indication).

In addition, for all the QTcF parameters prolongation assessed, incidence was higher in ivosidenib + azacitidine arm than in placebo + azacitidine, confirming the high incidence of QT prolongation. Supportive studies confirm this observation.

2.10.14.6. In vitro biomarker test for patient selection for safety

Not applicable.

2.10.14.7. Safety in special populations

Table 106. Summary of selected Treatment Emergent Adverse Events by Age-Before Crossover on Study AG120-C-009, Safety Analysis Set

MedDRA Terms	<65 years		65 – 74 years		75 – 84 years		≥ 85 years	
	Placebo + Azacitidine N=4 n (%)	Ivosidenib + Azacitidine N=4 n (%)	Placebo + Azacitidine N=27 n (%)	Ivosidenib + Azacitidine N=30 n (%)	Placebo + Azacitidine N=34 n (%)	Ivosidenib + Azacitidine N=38 n (%)	Placebo + Azacitidine N=9 n (%)	Ivosidenib + Azacitidine N=0 n (%)
Number of Total TEAEs	4 (100)	4 (100)	27 (100)	29 (96.7)	34 (100)	38 (100)	9 (100)	0
Serious TEAEs – Total	3 (75.0)	3 (75.0)	22 (81.5)	18 (60.0)	29 (85.3)	28 (73.7)	8 (88.9)	0
Fatal	1 (25.0)	1 (25.0)	7 (25.9)	6 (20.0)	13 (38.2)	4 (10.5)	3 (33.3)	0
Hospitalisation/prolong existing hospitalisation	3 (75.0)	3 (75.0)	19 (70.4)	17 (56.7)	28 (82.4)	28 (73.7)	8 (88.9)	0
Life-threatening	0	0	3 (11.1)	5 (16.7)	8 (23.5)	5 (13.2)	1 (11.1)	0
Disability/incapacity	0	0	2 (7.4)	1 (3.3)	0	0	0	0
Other medically significant	0	0	5 (18.5)	1 (3.3)	5 (14.7)	6 (15.8)	0	0
TEAEs leading to drop-out [1]	0	1 (25.0)	6 (22.2)	4 (13.3)	5 (14.7)	7 (18.4)	2 (22.2)	0
Psychiatric disorders	2 (50.0)	1 (25.0)	5 (18.5)	10 (33.3)	10 (29.4)	11 (28.9)	3 (33.3)	0
Nervous system disorders	0	3 (75.0)	8 (29.6)	9 (30.0)	10 (29.4)	13 (34.2)	3 (33.3)	0
Accidents and injuries	0	0	3 (11.1)	3 (10.0)	4 (11.8)	8 (21.1)	2 (22.2)	0
Cardiac disorders	2 (50.0)	1 (25.0)	7 (25.9)	4 (13.3)	8 (23.5)	7 (18.4)	1 (11.1)	0
Vascular disorders	2 (50.0)	1 (25.0)	6 (22.2)	8 (26.7)	9 (26.5)	15 (39.5)	2 (22.2)	0
Cerebrovascular disorders	0	1 (25.0)	1 (3.7)	3 (10.0)	0	4 (10.5)	0	0
Infections and infestations	2 (50.0)	4 (100)	22 (81.5)	19 (63.3)	28 (82.4)	29 (76.3)	7 (77.8)	0
Anticholinergic syndrome	2 (50.0)	3 (75.0)	16 (59.3)	13 (43.3)	21 (61.8)	22 (57.9)	5 (55.6)	0
Quality of life decreased	0	0	0	0	3 (8.8)	1 (2.6)	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	2 (50.0)	0	6 (22.2)	5 (16.7)	9 (26.5)	11 (28.9)	0	0

The denominator used to calculate percentages is N, the number of subjects in the safety analysis set within each column.
1] TEAE leading to drop-out is defined as AE leading to discontinuation of AG-120/Placebo regardless of azacitidine.
Source: AG120-C-009 MAA D120 Listing 16.6.1-1.1[f, Table 14-6-3.1c (Data cutoff date 01OCT2021)

2.10.14.8. Immunological events

Not applicable.

2.10.14.9. Safety related to drug-drug interactions and other interactions

2.10.14.10. Discontinuation due to adverse events

Discontinuation

The number of patients who discontinued ivosidenib or placebo only due to a TEAE were low in both treatment arms (4.2%, i.e. 3 patients and 4.1%, i.e. 3 patients in the experimental and control arm respectively). The reported PTs (one each) for these discontinuations were anaemia, ECG QT prolonged and insomnia in the experimental arm and thrombocytopenia, pneumonia, sepsis and myalgia for the control arm.

The number of patients who discontinued azacitidine only were also low in both treatment arms (2.8%, i.e. 2 patients and 1.4%, i.e. 1 patient in experimental and control arm respectively). The TEAE leading to discontinuation of azacitidine were all within the SOC Blood and lymphatic system disorders: febrile neutropenia (one in each treatment arm) and thrombocytopenia.

Dose interruption

Occurrences of dose interruption were higher in the ivosidenib + azacitidine arm (38 patients or 52.8%) than in placebo + azacitidine arm (30 patients or 40.5%) as well as mean (SD) (12.2 days (11.9) vs 7.4 days (10.1) and median (Q1, Q3) number of days with dose interruptions 7.0 days (3.0, 14.0) vs 3.0 (1.0, 10.0). These differences should be considered in the context of a longer treatment duration in experimental arm.

Overall, events leading to treatment interruption related to haematological toxicity (neutropenia and thrombocytopenia) and infections.

Dose reduction

In the pivotal study AGILE, the number of subjects with any cause reduction of ivosidenib or placebo was higher in experimental arm (12 patients or 16.7%) than in control arm (6 patients or 8.1%). This was expected in the context of a more than doubled median exposure duration in the active group (5.98 vs 2.76 months). Overall in the ivosidenib + azacitidine arm, events that led to dose reduction were related to haematological toxicity.

2.10.14.11. Post marketing experience

Cumulatively, as of 31 December 2021, approximately 3084 patients have been exposed to ivosidenib in the post-approval setting.

No new safety findings from marketing experience have arisen through 16 January 2022.

2.10.15. Discussion on clinical safety

The pivotal safety data for ivosidenib in combination with azacitidine are from the ongoing pivotal phase 3 study AG120-C-009 (AGILE) in patients who received the combination at the intended dose.

Even though this safety data base is limited, the intended target population is also quite small and limited to a small subset of AML patients who are ineligible to receive intensive chemotherapy and are harbouring IDH1 mutation. Thus, the size of the safety database is considered acceptable.

Baseline characteristics in the pivotal study were overall consistent with expected AML patient characteristics and balanced between both treatment arms except for platelets count which makes difficult any analysis of bleeding events.

The median duration of exposure to ivosidenib/placebo was twice longer in the ivosidenib + azacitidine arm than in the placebo + azacitidine arm, and more than twice patients received ivosidenib for more than 24 weeks in ivosidenib + azacitidine arm than in placebo + azacitidine arm.

The incidence of TEAEs, as well as grade 3 TEAEs, was similar between the experimental and the control arm in the pivotal trial.

As could be expected, more patients experienced a treatment-related TEAE to ivosidenib/placebo alone in ivosidenib + azacitidine arm than in placebo + azacitidine arm or to both ivosidenib/placebo and azacitidine. Nevertheless, Grade ≥ 3 TEAE related to ivosidenib/placebo alone or to azacitidine alone were comparable in experimental and control arm respectively.

Although serious TEAE were less frequent in ivosidenib + azacitidine arm than in placebo + azacitidine arm, more patients experienced serious treatment related TEAE to both ivosidenib and azacitidine than to both placebo and azacitidine.

TEAE leading to death were lower in ivosidenib + azacitidine arm than in placebo + azacitidine arm (15.3 % and 31.1% respectively) and none of them were considered related to any of the study treatments.

Treatment Emergent Adverse Events

In the pivotal study AGILE, common TEAE in experimental arm were mainly related to haematological and gastrointestinal toxicities. Indeed, the most frequently reported AE in experimental arm were PT of nausea (42.3%), vomiting (40.8%), diarrhoea (35.2%), pyrexia (33.8%), anaemia (31.0%), febrile neutropenia (28.2%), neutropenia (28.2%), thrombocytopenia (28.2%), constipation (26.8%) and

pneumonia (23.9%). In addition, electrocardiogram QT prolongation (19.7%) and differentiation syndrome (14.1%) were also frequently observed.

The most frequently reported treatment related TEAE to ivosidenib and azacitidine pertained to SOC Gastrointestinal disorders (36.6%) and Blood and lymphatic system disorders (28.2%).

Regarding haematological toxicities, the PTs of neutropenia (28.2% vs 16.4%), thrombocytopenia (28.2% vs 20.5%) and leucocytosis (11.3% vs 1.4%) were more frequently reported in ivosidenib + azacitidine arm than in placebo + azacitidine arm respectively. Although azacitidine is known to be associated with haematological toxicity, differences between both treatment arms suggest that ivosidenib is also associated with neutropenia and thrombocytopenia. Furthermore, within experimental arm, the more frequent grade ≥ 3 TEAEs included febrile neutropenia (28.2%), neutropenia (26.8%), anaemia (25.4%), thrombocytopenia (23.9%) and pneumonia (22.5%), thus relating to haematological and infectious events.

The leucocytosis events that were reported did not appear to be life-threatening, and seemed to be manageable with hydroxyurea. The SmPC of ivosidenib recommends a periodic blood count as well as dose modifications and management in section 4.2 if leucocytosis occurs which are deemed adequate considering data from pivotal study. Neutropenia and thrombocytopenia are also described as ADRs in the SmPC for the AML indication.

A higher incidence of bleeding events was observed in the experimental arm (40.8%) compared to control arm (28.8%) including 2 events of fatal intracranial haemorrhage. Incidence of haematoma was also higher in experimental arm (12.7%) than in control arm (1.4%). Additional analysis meant to highlight confounding factors for events of haemorrhage are hampered as mentioned by the imbalance in platelet count at baseline between the treatment groups. Nevertheless, haemorrhage will be closely monitored in PSURs.

With regards to the risk of infection, although neutropenia any grade and grade 3 neutropenia were more frequent in experimental arm than in control arm, incidence of febrile neutropenia was lower in experimental arm compared to control arm. The incidence of events within the SOC Infections and infestations was high in both treatment arms but was lower in experimental arm (70.4%) than in control arm (79.5%). The incidence of Infections of any grade was lower in ivosidenib + azacitidine arm (28.3%) than in placebo + azacitidine (49.3%) as well as Grade ≥3 TEAEIs of infection, serious TEAEIs of infection, fatal TEAEIs of infection, and discontinuation of both ivosidenib or placebo and azacitidine due to infection. Therefore, the risk of infection does not seem to be increased by the combination.

Regarding PT related to gastrointestinal toxicities, incidences were similar between both treatment arms except for the PT of vomiting which was higher in experimental arm (40.8%) than in control arm (26.0%). Although azacitidine is also associated with gastrointestinal toxicities (diarrhoea, vomiting, constipation, nausea, abdominal pain), here again the difference between both treatment arms suggests than ivosidenib is associated with vomiting. Vomiting is described as an ADR without further warning or recommendation which is endorsed as gastrointestinal toxicities were of low grade in general.

Other commonly reported TEAE were observed more frequently in the experimental arm compared to the control arm: insomnia, pain in extremities, arthralgia, headache, dizziness, oropharyngeal pain and back pain. These events are described as ADRs in the SmPC.

Adverse Event of Special Interest

Incidence of Electrocardiogram QT prolongation was higher in ivosidenib + azacitidine arm (19.7% with 9.9% of grade≥ 3) than in placebo + azacitidine arm (6.8% with 2.7% of grade≥ 3). Thus, QT prolongation was frequent and with high grade in half of the cases. ECG QT prolonged led to interruption

of treatment in 4 cases (5.6%), to dose reduction in 6 cases (8.5%) and to treatment discontinuation in one case (1.4%).

Median (min, max) time to first AESI of electrocardiogram prolonged, assessed in study pivotal study AGILE (AG-120-C-009), was 29.0 days (1-141 days) with 21.4 % of first events that occurred > 60 days showing that event of QT prolonged can occur several weeks after reaching the concentration at steady state (Css).

Based on these observations, ivosidenib is contraindicated in patients with congenital long QT syndrome, familial history of sudden death or polymorphic ventricular arrythmia or a QT/QTc interval > 500 msec, regardless of the correction method.

In addition, ECG QT prolonged has been listed in section 4.8 of the SmPC, and currently, to mitigate the risk, it is recommended to monitor ECG prior initiation of the treatment, at least weekly for the first 3 weeks and then monthly. Recommendation to avoid concomitant treatment known to prolong the QTc interval or moderate or strong CYP3A4 inhibitors is also provided. Dose modifications are further recommended in case of grade 2, 3 and 4 ECG QT prolongation and in case administration of a strong CYP3A4 inhibitor is unavoidable (section 4.2 of the SmPC). In addition, a warning regarding QT prolongation is provided in section 4.4 with the recommendation to closely monitor patients with congenital long QTc syndrome, congestive heart failure or electrolyte abnormalities.

Considering that patients were carefully selected (QT <450 ms, no cardiac disease) in clinical studies which will not be the case in post-marketing setting and that dose-exposure relationship is highly variable, with a large proportion of patients exposed to potentially critical concentration with respect to QT interval prolongation, the recommendations were further strengthened to ensure better prevention and management of the risk. In addition, as QT prolongation is considered as an important identified safety concern in the RMP, events will be closely monitored in PSURs.

Incidence of differentiation syndrome was higher in experimental arm (14.1% with 9.9% Grade 2, 4.2% Grade 3) than in control arm (8.2% with 4.1% Grade 2, 2.7% Grade 3, and 1.4% Grade 4). The median number of days to first onset of Differentiation syndrome was 19.5 days (range: 3 to 33 days) in the experimental arm and 44 days (range: 4 to 86 days) in control arm.

Differentiation syndrome has been listed in section 4.8 of the SmPC. In addition, a warning describing the symptoms of differentiation syndrome and a recommendation to administer corticosteroids and initiate hemodynamic monitoring until resolution is provided. Treatment with Hydroxycarbamide is recommended in case of leucocytosis, by leukapheresis if clinically indicated and interruption of ivosidenib is required in case of grade 3 events (sections 4.2 and 4.4).

Although AML patients will be closely monitored at the beginning of the treatment, differentiation syndrome occurred at a high frequency, is a potential-life threatening event and can induce non-specific symptoms. In addition, given the oral administration of ivosidenib, patients will be mostly without HCP supervision whilst on treatment. Therefore, a patient alert card was considered necessary for patients with AML, in order to alert patients on the symptoms of differentiation syndrome and the importance of seeking medical advice.

Additional events of clinical importance

Guillain Barré Syndrome: Although no event of Guillain Barré syndrome were observed in the pivotal study AGILE (AG120-C-009) or the supportive study AG-221-AML-005, 2 cases were reported in study AMG-C-001 (ivosidenib monotherapy at 500mg QD) and were assessed as related to the study treatment by the investigator. Moreover, 3 additional cases (2 post-market in US and 1 in France from compassionate use in another indication) were retrieved from EudraVigilance albeit with limited information. The applicant agreed to closely monitor cases of Guillain Barré in PSURs. In addition, given

the cases of peripheral neuropathy identified in association with ivosidenib in cholangiocarcinoma indication, the applicant agreed to the CHMP request to list peripheral neuropathy as an ADR.

Leukoencephalopathy: 1 patient developed PRES in the monotherapy study AMG-C-001. This patient had previously been treated with cladribine which is a confounding factor, however the event was considered as possibly related to ivosidenib by the investigator. The applicant comfirmed that these events will be closely monitored in post-marketing setting through PSURs.

Tumour Lysis Syndrome: 7.4% of treated patients in the monotherapy study AG120-C-001 experienced TLS but only one case of TLS was reported in the control arm of the pivotal study (and none in the ivosidenib. This apparent discrepancy could be explained by the investigators were aware about the risk of TLS in the pivotal study and had taken precautionary measures to mitigate its occurence. TLS is described in the SmPC as a potential symptom of differentiation syndrome and cases of TLS will be closely monitored throughout PSURs.

Safety in special populations

The Analysis in special populations did not identify any trend but the limited number of patients in each sub-group does not allow any conclusion.

As the safety and efficacy of ivosidenib has not been established in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) or in patients with moderate and severe hepatic impairment (Child Pugh class B and C). Ivosidenib should be used with caution in these patients who should be closely monitored.

Given the limited information available in patients with organ impairment the applicant will conduct a study to evaluate the pharmacokinetics, safety and tolerability of ivosidenib in patients with haematologic malignancies with an IDH1 mutation with moderate hepatic impairment, severe hepatic impairment or severe renal impairment as described in the RMP.

2.10.16. Conclusions on the clinical safety

The size of the safety database used to characterise the safety profile of ivosidenib in combination with azacitidine in AML is acceptable due to the limited intended target population. Importantly the pivotal study for this application was a phase 3 study randomised and controlled versus azacitidine + placebo which allows to differentiate the toxicity due to ivosidenib.

The safety profile of ivosidenib in combination with azacitidine in patients with newly diagnosed AML is mainly related to QT prolongation, differentiation syndrome, haematological and gastrointestinal toxicity.

All these risks are managed through appropriate wording in the product information, most notably for QT prolongation which is contraindicated in patients with relevant medial history and detailed warnings on precautions to be taken prior to administration, monitoring and management of this risk.

Patients will be given a patient alert card to recognise the symptoms and highlight the importance of seeking medical advice if experiencing differentiation syndrome. A patient survey cross-sectional study will assess the effectiveness of the patients' alert card for ivosidenib in AML patients (see RMP).

2.11. Risk Management Plan

2.11.1. Safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

Table 107. 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

2.11.2. Pharmacovigilance plan

Table 108. 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 substudy of AG120-C-001 Substudy to evaluate the PK, safety and tolerability, PD, and clinical activity of ivosidenib in subjects with moderate hepatic impairment, severe hepatic impairment, or severe renal impairment with haematologic malignancies with an IDH1 mutation **Status:** Ongoing	To evaluate the pharmacokinetics, safety and tolerability of ivosidenib in patients with haematologic 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 Q4 2025.

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 for ivosidenib in AML patients. **Status:** Planned	To evaluate the effectiveness of the PAC for awareness of differentiation syndrome in AML patients, using process indicators for awareness, receipt of the material, utility and knowledge.	• Differentiation Syndrome in the AML indication.	Protocol submission	Within 3 months following EC decision
			Final report available	Planned for Q4 2025

2.11.3. Risk minimisation measures

Table 109. 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 for ivosidenib in AML patients. • Final report due date: Planned for Q4 2025.
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.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	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	
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.*	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
	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	
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.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: • Organ impairment substudy of AG120-C-001.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Legal status: Prescription only medicine. Treatment to be initiated by experienced oncologist Additional risk minimisation measures: None	• Final report due date: Planned for Q4 2025.
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. 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 substudy of AG120-C-001. • Final report due date: Planned for Q4 2025.

2.11.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

2.12. Pharmacovigilance

2.12.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.12.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.13. Product information

2.13.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.13.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Tibsovo (ivosidenib) is included in the additional monitoring list as it contains a new active substance.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Cholangiocarcinoma

3.1. Therapeutic Context

The initially sought indication for Tibsovo was: "Tibsovo monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 mutation who were previously treated by at least one prior line of systemic therapy."

The new wording for the sought indication is "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."

The recommended dose of ivosidenib is 500 mg (2 x 250 mg tablets) taken orally once daily.

3.1.1. Disease or condition

Cholangiocarcinomas are rare cancers that arise from intrahepatic or extrahepatic biliary epithelium.

IDH1 mutations occur globally in approximately 16%, up to 29% in some reports, of intrahepatic cholangiocarcinomas and approximately 0-7% of extrahepatic cholangiocarcinomas. Using a maximum incidence of 14% (13% for intrahepatic + 1% for extrahepatic) for IDH1 mutations in cholangiocarcinoma indicates an overall prevalence of 0.182 in 10,000 people. The 5-year survival rates associated with intrahepatic and extrahepatic cholangiocarcinoma are 9% and 10%, respectively, and only 2% for patients with distant metastases (ACS 2021).

3.1.2. Available therapies and unmet medical need

Cholangiocarcinoma is a lethal disease for which there is significant unmet need. The first-line, standard-of-care treatment for patients with unresectable and metastatic disease is gemcitabine and platinum based chemotherapy (ESMO 2016).

Beyond the first-line setting, 5-FU regimens, including modified folinic acid, fluorouracil and oxaliplatin (mFOLFOX) regimen, are typically considered after progression on a gemcitabine-containing regimen.

Approved targeted treatments for cholangiocarcinoma are limited to pemigatinib (Pemazyre approved in the EU in March 2021) 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.

There is therefore an unmet medical need for an effective agent for the treatment of adult patients with locally advanced cholangiocarcinoma with an IDH1 mutation who were previously treated by at least one prior line of systemic therapy.

3.1.3. Main clinical studies

Study AG120-C-005 was a phase 3, multicenter, randomized, double-blind, placebo-controlled study of orally administered ivosidenib in previously treated subjects with non-resectable or metastatic cholangiocarcinoma with an IDH1 R132 mutation. Subjects were randomized in a 2:1 ratio to receive ivosidenib 500 mg QD or placebo QD. The primary efficacy endpoint was PFS as assessed by IRC. Secondary endpoints were OS, ORR, DOR, TTR and HRQoL outcomes.

3.2. Favourable effects

At the time of DCO of 31 January 2019, 61.3% (76/124) of the patients in the ivosidenib arm had progressed compared to 82.0% (50/61) of the patients in the placebo arm. The PFS gain by IRC was of 1.3 months favouring ivosidenib arm (2.7 months (95% CI: 1.6, 4.2) with ivosidenib vs 1.4 months (95% CI: 1.4, 1.6) with placebo). The HR was of 0.37 (95% CI: 0.25, 0.54; 1-sided p-value <0.0001). Sensitivity analysis of PFS by investigator assessment showed similar results with a HR of 0.47 (95% CI: 0.33-0.68; 1-sided P<0.001)). The concordance rate was of 77.3%.

PFS results for the predefined sensitivity analyses were in line with PFS by IRC assessment. The results of the subgroup analysis demonstrated a consistent treatment effect across the predefined subgroups.

Among subjects who were randomized to placebo and who crossed over to receive ivosidenib following initial progression (N= 43), the median PFS after crossover by inv was 1.6 months (95% CI: 1.4-3.8).

The ORR based on IRC was of 2.4%, 95%CI (0.5, 6.9) in the ivosidenib arm (3 subjects with PR), compared with 0% (95%CI (0.0, 5.9)) in the placebo arm (p-value= 0.299). Approximately half (50.8%) of subjects in the ivosidenib arm had a BOR of SD, while 17 (27.9%) subjects in the placebo arm had a BOR of SD before crossover. The median duration of SD was 6.5 months in subjects randomized to ivosidenib, 6.4 months in subjects after crossover to ivosidenib, and 3.0 months in the placebo arm before crossover.

As of the 21 June 2021 DCO date, the mOS was 10.3 months (95% CI: 7.8-12.4) in the ivosidenib arm versus 7.5 months (95% CI: 4.8-11.1) in the placebo arm (HR=0.79; 95% CI: 0.56-1.12; 1-sided p=0.093).

As of the DCO date of 31 May 2020, the decline on the EORTC QLQ-C30 PF and Emotional Functioning subscales in the placebo arm was clinically meaningful at Cycle 2, Day 1, while the ivosidenib arm showed no clinically meaningful worsening.

3.3. Uncertainties and limitations about favourable effects

The choice of placebo instead of active comparator hamper the interpretation/contextualisation of the reported efficacy data particularly in the second line setting. Overall survival would have been a more persuasive and the preferred primary endpoint in this setting given the lack of effective treatment options, the poor prognosis of the condition, and uncertainties on the actual toxicity of ivosidenib, as it is a first in class medicinal product.

The reported tumour responses (PR) with ivosidenib are very modest (2.4%) and did not reach statistical significance compared to placebo.

The treatment effect on OS did not reach statistical significance (1-sided p-value = 0.093). OS data are confounded by the allowed cross-over from placebo to ivosidenib arm. An OS supplemental analysis using the RPFST model to adjust for cross-over was provided (see Discussion on Clinical Efficacy).

3.4. Unfavourable effects

The safety profile of ivosidenib 500 mg QD as monotherapy in previously treated IDH1 mutation-positive locally advanced or metastatic cholangiocarcinoma is based on data from the pivotal study AG120-C-005 which includes a comparative analysis by treatment group of safety from ivosidenib arm (N=123) versus placebo arm (N=59) completed by safety data from a pooled cholangiocarcinoma population treated with ivosidenib at the same dosing regimen (N=228). As per study design, patients initially assigned to placebo could cross-over to active treatment once they progressed. Safety data pre/post cross-over have been provided separately.

Overall, the safety profile of ivosidenib could be considered acceptably characterised although.

In the pivotal study, the incidences of subjects with TEAEs were almost similar in both arms (97.6% vs 96.0%) however the incidence of Grade ≥3 TEAEs, was higher in the ivosidenib arm (51.2% vs 37.3%). A similar trend is observed in the polled cholangiocarcinoma population treated 97.8% of subjects experienced a TEAE (any grade) and half (50.0%) of the subjects with Grade ≥3 TEAEs

In the pivotal study, the most frequent TEAEs (≥20%) that occurred in subjects randomized and exposed to ivosidenib were: Fatigue (30.9%), Decreased appetite (24.4%), Cough (25.2%), and gastrointestinal events (Nausea [42.3%], Vomiting [22.8%], Diarrhoea [35.0%], Abdominal Pain [24.4%], and Ascites [22.8%]).

As compared with placebo, among the commonly reported TEAE, ivosidenib treatment in subjects in ivosidenib arm resulted in a higher incidence (≥5%) of gastrointestinal TEAEs (78% vs 64.4% including: Ascites, Nausea, Diarrhoea , Abdominal pain), Anaemia (18.7% vs 5.1%), Fatigue (30.9% vs 16.9%), Cough (25.2% vs 8.5%), Hypertension (8.9% vs 3.4%), Decreased appetite, Headache, Electrocardiogram QT prolongation (9.8% vs 3.4%), Hyperbilirubinaemia, Neuropathy peripheral (6.5% vs 0%), Rash (8.1% vs 0%), Hyperglycaemia (7.3% vs 1.7%), and laboratory abnormalities (Aspartate aminotransferase increased, Alanine aminotransferase increased, White blood cell count decreased).

In the pivotal study, the most frequent Grade ≥3 TEAEs (≥5% of subjects) in the ivosidenib arm were Ascites (8.9%), Anaemia (7.3%), Blood bilirubin increased (5.7%), and Hyponatremia (5.7%). In the pooled cholangiocarcinoma population the most frequent Grade ≥3 TEAEs (≥5% of subjects) were Ascites (7.9%) and Anaemia (6.6%).

In the pivotal study, few (6) subjects (4.9%) experienced a TEAE leading to on-treatment death in the ivosidenib arm. The most frequent TEAE leading to on-treatment death was sepsis (2 patients). None of the TEAEs leading to on-treatment deaths among the pooled cholangiocarcinoma population was assessed by the Investigator as treatment-related.

In the pivotal study, the incidence of SAEs was higher in the ivosidenib arm when compared to placebo (35.0% and 23.7%, respectively). SAEs assessed by the Investigator as treatment-related occurred in 2.4% of subjects in the ivosidenib arm and included Hyperbilirubinaemia, Jaundice cholestatic, Electrocardiogram QT prolonged, and Pleural effusion (each event in 1 subject).

For the cholangiocarcinoma indication, Electrocardiogram QT prolonged was identified as an AESI:

Electrocardiogram QT prolonged is an important risk associated with ivosidenib treatment which can lead to life-threatening ventricular arrhythmias, and result in sudden cardiac death. This risk emerged from non-clinical data and has been confirmed through the clinical development program. Drug-drug interactions with moderate or strong CYP3A4 inhibitors and/or concomitant use of drugs known to prolong the QT interval is part of the risk associated with QT prolongation.

Indeed, in the pivotal study, the incidence of QT prolongation (any Grade) was higher in the ivosidenib arm compared with the placebo arm (9.8% vs 3.4%) with 2 (1.6%) grade $\geq$3 TEAE in ivosidenib arm. In the ivosidenib arm some subjects required dose reduction (3.3%) and one subject presented an AE Electrocardiogram QT prolonged in the ivosidenib arm assessed by the investigator as related to the study drug.

Among overall cholangiocarcinoma population the incidence of QT prolongation (any Grade) was 9.2% of subjects) with 2.2% of subject with grade $\geq$3 grade TEAE.

No case of fatal arrhythmia or Torsades de Pointes in pivotal study and overall cholangiocarcinoma population.

In the pivotal study, the median time to onset of QT prolongation (any Grade) in the ivosidenib arm was 28 days, (range: 1 to 698 days) and in at least 75% of subjects with events in the ivosidenib arms, time to first event onset was within the first 30 days. The median time to the first event of any grade was similar among overall cholangiocarcinoma population (29 days). The occurrence of events after 3 weeks reinforces the need to prolong close monitoring after the first 3 weeks of treatment.

For cholangiocarcinoma, concentration-QTc interval analyses were conducted with data from studies AG120-C-002 and AG120-C-005 and demonstrated that the risk of QT interval prolongation increases with increased Cmax in plasma.

ECG QT prolonged is listed in section 4.8 of the SmPC, and to mitigate the risk, contraindications have been added in section 4.3 of the SmPC (congenital long QT syndrome, Familial history of sudden death or polymorphic ventricular arrhythmia and QT/QTc interval > 500 msec, regardless of the correction method) it is recommended to monitor ECG prior initiation of the treatment, at least weekly for the first 3 weeks and monthly thereafter. Recommendation to avoid concomitant treatment known to prolong the QTc interval or moderate or strong CYP3A4 inhibitors is also provided. Dose modifications are further recommended in case of grade 2, 3 and 4 ECG QT prolongation and in case administration of a strong CYP3A4 inhibitor is unavoidable (section 4.2 of the SmPC). In addition, a warning regarding QT prolongation is provided in section 4.4 with the recommendation to closely monitor patients with congestive heart failure or electrolyte abnormalities, and it is added in section 4.4 that in case of vomiting and/or diarrhoea an assessment of serum electrolyte disturbances, especially hypokalemia and magnesium, must be performed.

Long term safety is insufficiently characterised since in the pivotal study AG120-C-005 reported a median exposure in ivosidenib arm of 2.8 months with only 15.4% of subjects exposed for more than 12 months and in the pooled cholangiocarcinoma population, a slightly longer exposure to ivosidenib was reported with median duration of 3.6 months and exposure ≥12 months in 17.1% of subjects. Nevertheless, this lack of long-term data appears acceptable given the poor prognosis of the disease.

3.5. Uncertainties and limitations about unfavourable effects

The most important uncertainties about the unfavourable effect are related to the **risk of QT prolongation.**

Indeed, even though the measures provided in the SmPC seems restrictive, ECG QT prolonged was a frequent TEAE including frequent grade 3 events which are a risk factor associated with polymorphic ventricular arrhythmias. Considering that patients were carefully selected (QT <450 msec, no cardiac disease) in clinical trials, considering furthermore that dose-exposure relationship is highly variable, with a large proportion of patients exposed to potentially critical concentration with respect to QT interval prolongation, the risk may be more frequent and more severe in real-life conditions. Thus, restrictive recommendations were implemented in the PI and events of "QT prolongation", as "important identified risk" events, and will be closely monitored through PSURs provided a favourable outcome of the marketing authorization by the CHMP.

Despite absence of reporting if cases of Progressive Multifocal Leukoencephalopathy (PML) and Posterior Reversible Encephalopathy Syndrome (PRES) in any subject with solid tumors, including cholangiocarcinoma to date, cases were reported in other indications. Events of PML and PRES will be closely monitored in post-marketing setting in each PSUR by reviewing and discussing each reported case in the PSUR.

No cases of Guillain-Barré syndrome were reported in clinical trials in subjects with solid tumors, including cholangiocarcinoma to date. However, considering 2 cases of Guillain–Barré syndrome reported in clinical trials in hematologic malignancies indications and in addition 3 more cases (2 post-market in US and 1 in France from compassionate use in another indication) retrieved from EudraVigilance and considering that neuropathy peripheral is listed as ADR of ivosidenib in patients treated for cholangiocarcinome based on studies AG120-C-005 and AG120-C-002, this risk of Guillain–Barré syndrome cannot be excluded in cholangiocarcinoma indication. Guillain-Barré syndrome cases will be closely monitored in PSURs.

Considering that patients with CGC often present hepatic-related abnormalities, the potential for ivosidenib-related hepatotoxicity was identified as a matter of concern.

Hepatic disorders with a ≥5% greater incidence in the ivosidenib compared with placebo included: ascites, aspartate aminotransferase increased, alanine aminotransferase, and hyperbilirubinaemia. No subjects met Hy's Law criteria.

Several of the treatment-emergent adverse events for drug related hepatic disorder were still ongoing (had not resolved) at the time of the data cut-off date (June 2021). The reasons for end of study of the subjects whose AEs had not yet resolved by the time of the study data cut-off (45 and 12 in the ivosidenib and placebo groups, respectively) were clarified: the most common reason across treatment groups appears to be death due to disease progression. The remaining reasons leading to death were AEs and "other". This risk is included as an important potential risk.

In the CGC population, which often presents/develops liver function abnormalities during the course of the disease, any potential to induce hepatotoxicity is considered as a matter of concern. Drug-related hepatic disorders will be monitored in PSURs.

In addition, considering that serious adverse event of haemorrhage has been reported concomitantly with thrombocytopenia, causal role of ivosidenib cannot be excluded. "Haemorrhage" cases will be closely monitored in PSURs.

3.6. Effects Table

Table 110. Effects Table for Tibsovo for the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 mutation (data cut-off: 31 Jun 2019/ 31 May 2020)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS by IRC	median	months	2.7	1.4	HR = 0.37 95% CI: 0.25, 0.54 1 sided p-value: <0.0001	Study AG120-C-005 DCO: 31 January 2019
OS	median	months	10.3	7.5	-HR = 0.82 95% CI: (0.58, 1.14) 1 sided p-value: 0.093	Study AG120-C-005 DCO: 21 June 2021.
ORR		%	2.4 95%CI (0.5, 6.9)	0	OR: NE (0.29, NE) 1 sided p-value= 0.299	Study AG120-C-005 DCO: 31 January 2019

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Unfavourable Effects Cholangiocarcinoma (pivotal study (AG120-C-005)- data lock date: 21 June 2021)						
TEAEs	Regarless causality	%	97.6	96.6		
TAE Grade ≥3	Regarless causality (drug related)	%	51.2 (6.5)	37.3 (0)		
Serious TEAEs	Regardless causality	%	35	23.7		
TEAE leading to death	Regardless causality (drug related)	%	4.9 (0)	0 (0)		
TEAE leading to discontinuation	Regardless causality (drug related)	%	7.3 (1.6)	8.5 (0)		
SOC Gastrointestinal disorder (Diarrhoea)	Regardless causality	%	78 (35)	64.4 (16.9)		
Fatigue		%	30.9	16.9		
Electrocardiogram T prolonged (AESI) (Grade ≥ 3	All grade	%	9.8 (1.6)	3.4 (0)	(No Grade 4 or Grade 5 AE)	
Myalgia	All grade	%	4.9	0		
Cough	All grade	%	25.2	8.5		
Anemia		%	18.7	5.1		
Neuropathy peripheral		%	6.5	0		
Hyperglycaemia		%	7.3	1.7		
Hypertension		%	8.9	3.4		

Abbreviations:

Notes:

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

To support the intended indication of ivosidenib in previously treated patients with cholangiocarcinoma, clinical data from one single study AG120-C-005, were submitted. Ivosidenib was associated with a 63% reduction in risk of disease progression or death and some improvement in OS with a median OS of 10.3 months for ivosidenib and 7.5 months for placebo though non-statistically significant.

Taking into account the dismal prognosis of this disease, the placebo controlled design of the study with PFS as a primary endpoint is not fully supported. An actively controlled design (investigator's choice as a control arm) without cross-over and with OS as the primary endpoint should have been considered to provide a valid and reliable measure of the clinical benefit of ivosidenib. Indirect comparisons of available results (KM estimates of PFS and OS) with ivosidenib against those reported with mFolfox (ABC-06 study) and regorafenib (REACHIN study) for all comer advanced biliary tract cancers seem reassuring keeping in mind the limitations inherent to this comparison. The median PFS outcome for patients with IDH1m CCA receiving ivosidenib is similar to the PFS outcomes reported with other available and recommended treatments for patients with 2L advance biliary tract cancers (per NCCN 2022). The mOS of 10.7 months is however numerically longer than the median OS (5-6 months) reported with both chemotherapy (e.g. mFOLFOX) and targeted therapy (e.g. regorafenib). Disease control rate was superior with ivosidenib 2L (58%) compared to mFolfox (24-33%).

Based on clinical safety data available, the safety profile of ivosidenib as monotherapy in patients with previously treated locally advanced or metastatic cholangiocarcinoma with an IDH1 mutation showed that in general ivosidenib is well characterized.

However, Electrocardiogram QT prolongation is an important risk of ivosidenib and has been observed in subjects with cholangiocarcinoma. Despite absence of ventricular arrhythmias, torsade de pointe and sudden deaths cases reported in clinical trials, since Ivosidenib significantly prolongs the QTc interval duration, it is more than likely that this drug will cause polymorphic ventricular arrhythmias in real-life conditions in a non-selected population. Restrictive recommendations were implemented in the SmPC and the Package Leaflet and events of "QT prolongation", as "important identified risk" events, will be closely monitored through PSURs.

Overall, it appears that taking into account the recommendations implemented to minimize the risk of QT prolongation, the safety profile is considered acceptable and manageable.

3.7.2. Balance of benefits and risks

Despite some uncertainties mainly related to study design and endpoints, the results provided from study AG120-C-005 have shown efficacy in term of reduction in risk of disease progression or death and durability of stable disease. Taking into account the recommendations implemented to minimize the risk of QT prolongation, the safety profile is considered manageable.

Given the poor prognosis of the disease, the limited treatment options to chemotherapy and the high medical need in this patient population, the benefit of ivosidenib is considered established.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall benefit/risk balance of Tibsovo is positive, subject to the conditions stated in section 'Recommendations'.

Acute myeloid leukaemia

3.9. Therapeutic Context

3.9.1. Disease or condition

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.

Acute myeloid leukaemia is characterised by uncontrolled proliferation of clonal neoplastic hematopoietic precursor cells and impaired haematopoiesis, leading to neutropenia, anaemia, and thrombocytopenia. If untreated, patients die of infection or bleeding usually in a matter of weeks (Tallman et al, 2005; Fey et al, 2013).

3.9.2. Available therapies and unmet medical need

The standard treatment strategy for newly diagnosed AML includes the option of standard Induction Chemotherapy (IC) and consolidation chemotherapy, or non-intensive treatment. Consolidation therapy for patients in complete response after IC consists of either chemotherapy, autologous hematopoietic stem cell transplantation (HSCT) or allogeneic HSCT.

Hypomethylating agents (HMA) such as azacitidine and decitabine are still considered options for patients who are not candidates for intensive chemotherapy.

Recently, venetoclax in combination with HMA and glasdegib in combination with low-dose cytarabine have been approved in the EU (on 19 May 2021 and 26 June 2020, respectively) as first line treatment for adult patients with newly diagnosed AML who were not eligible for intensive chemotherapy. Despite the newly approved therapies, there are no targeted combination therapies approved for patients with newly diagnosed IDH1-mutated AML who are not eligible for intensive IC.

3.9.3. Main clinical studies

The main evidence of efficacy is based on the AGILE study (n=146), a Phase 3, multicenter, double-blind, randomized, placebo-controlled clinical trial to evaluate the efficacy and safety of ivosidenib + azacitidine vs placebo + azacitidine in adult subjects with previously untreated IDH1-mutated AML and who are considered appropriate candidates for non-intensive therapy. A total of 146 patients were randomized, including 72 in the ivosidenib + azacitidine arm, and 74 in the placebo + azacitidine arm. The treatment arms were balanced in terms of demographics and baseline characteristics.

3.10. Favourable effects

An improvement in the primary endpoint of EFS was observed following treatment with ivosidenib + azacitidine with a 67% reduction in the risk of progression/relapse or death compared to the placebo + azacitidine arm (HR = 0.33; 95% CI: 0.16-0.69). Results of the sensitivity analysis were consistent with these results.

The CR+CRh rate was higher in ivosidenib + azacitidine arm than in placebo + azacitidine arm (52.8% [95% CI: 40.7-64.7] versus 17.6% [95% CI: 9.7-28.2]; odds ratio of 5.01 [95% CI: 2.32-10.81]).

The CR rate in the FAS was higher in ivosidenib + azacitidine arm compared to placebo + azacitidine arm: 47.2% (95% CI: 35.3-59.3) versus 14.9% (95% CI: 7.7-25.0) with an odds ratio of 4.76 (95% CI: 2.15-10.50).

Medians OS of 24.0 months (95% CI: 11.3-34.1 months) in ivosidenib + azacitidine arm and 7.9 months (95% CI: 4.1-11.3 months) in placebo + azacitidine arm were observed. Median follow-up time was approximately 15 months for both treatment arms. Clinically relevant improvement in OS was shown for subjects in ivosidenib + azacitidine arm compared to placebo + azacitidine arm (HR = 0.44; 95% CI: 0.27-0.73 which is highly superior to the HR of 0.71 assumed in the initial sample size assumptions). This was confirmed by an updated median OS was 29.3 months in the treatment arm (HR = 0.42; 95% CI: 0.27-0.65) as of 30 June 2022.

ORR was achieved in 62.5% (95% CI: 50.3-73.6) of the subjects in ivosidenib + azacitidine arm and 18.9% (95% CI: 10.7-29.7) of the subjects in placebo + azacitidine arm. ORR was higher in the ivosidenib + azacitidine arm than in the placebo + azacitidine arm (odds ratio of 7.15 [95% CI: 3.31-15.44]).

Duration of complete remission was observed in the ivosidenib + azacitidine arm in 93.3, 88.4, 88.4, 78.6 and 58.9% of patients at 6, 9, 12, 18 and 24 months, respectively.

Quality of life data was collected as part of the study. More than 90% of subjects in each treatment arm completed baseline EORTC QLQ-C30 and EQ-5D-5L questionnaires. For similar baseline scores, a clinically meaningful improvement was observed in the experimental arm characterized by less fatigue and better general condition. Although these data are not statistically significant, they can be considered supportive of the observed clinical benefit.

No significant difference in transfusion requirement was observed between the two treatment arms during the study, regardless of the baseline transfusion status. The fact that the combination does not increase the need for transfusion is reassuring from both an efficacy and safety point of view.

3.11. Uncertainties and limitations about favourable effects

The main uncertainty regarding the combination of ivosidenib and azacitidine efficacy is related to the magnitude of the treatment effect due to the critical changes to the protocol made during the conduct of the study, including the change of the primary endpoint from OS to EFS. Together with the change in primary endpoint, the planned sample size was reduced (from 392 to 200) and the initially planned interim analysis was removed from the protocol The discontinuation of the study based on an unplanned analysis of unblinded efficacy data raised further concerns about the trial integrity, and specifically about the inflation of the type I error. In the absence of any pre-specified interim analysis rules, and despite the implementation of post-hoc boundaries, the type I error cannot be considered to be formally controlled.

At the request of the CHMP the applicant provided a detailed discussion of the major changes introduced by protocol amendments, as well as supplementary analyses. Based on this information there seems to be a limited impact on the reported results from these major changes to study design and analysis plan. Nevertheless, the lack of type I error resulting from the unplanned early stop of the trial remains an issue, regardless of initial or updated post-hoc adjustments, and cannot be resolved retrospectively. Consequently, the applicant removed the p-values from all endpoints which are presented in the SmPC. On the other hand, it is acknowledged that the results are strong and further supported by a number of additional sensitivity analyses. This together with the evidence provided that the most concerning

amendments in the study were implemented when the applicant was still blinded, offers reassurance about the reported results.

HRQoL analyses remain exploratory and should be interpreted with caution especially as compliance decreased over the course of treatment cycles (80% at cycle 5 versus 70% at cycle 19 with no data for the placebo + azacitidine group).

3.12. Unfavourable effects

In the pivotal AGILE study, the incidence of TEAE as well as grade 3 TEAE were similar between experimental and control arm.

TEAE in experimental arm were mainly related to haematological and gastrointestinal toxicities. In addition QT prolongation and differentiation syndrome were also frequently observed.

Regarding haematological toxicities, neutropenia (28.3% vs 16.4%), thrombocytopenia (28.2% vs 20.5%) and leucocytosis (11.3% vs 1.4%) were more frequently reported in ivosidenib + azacitidine arm than in placebo + azacitidine arm respectively and include frequent grade ≥ 3 toxicities. Although azacitidine is known to be associated with haematological toxicity, differences between both treatment arms suggest that ivosidenib is also associated with neutropenia and thrombocytopenia. Overall, haematological toxicities were managed with treatment interruption or dose reductions which are described extensively in the product information

On the other hand, gastrointestinal toxicities were similar between both arms except for vomiting (40.8% in experimental arm vs 26.0% in control arm). Azacitidine is also known to be associated with gastrointestinal toxicity but ivosidenib appears to be associated mostly with vomiting. Unlike haematological event, gastrointestinal events were mainly low grade.

The major risk of ivosidenib is the risk of QT prolongation, occurring in 19.7% of patients with 9.9% of grade≥ 3. Thus, QT prolongation was frequent and occurred at high grade in half of the cases, with the potential risk of ventricular arrhythmias.

Furthermore, incidence of differentiation syndrome was higher in experimental arm (14.1% with 9.9% Grade 2, 4.2% Grade 3) than in control arm (8.2% of subjects with 4.1% Grade 2, 2.7% Grade 3, and 1.4% Grade 4). The median number of days to first onset of the PT of Differentiation syndrome was longer in experimental arm with 19.5 days (range: 3 to 33 days) than in experimental arm and 44 days (range: 4 to 86 days) in control arm.

3.13. Uncertainties and limitations about unfavourable effects

The main limitation in the characterisation of the safety profile of ivosidenib is the size of the safety database which is very small (71 patients in the pivotal study + 23 patients in the supportive study), although acceptable considering the very specific target population which is a subpopulation of patients with AML and the larger safety database in monotherapy provided by post-marketing data in the US; moreover, a direct comparison with the control group allows to discriminate AE due to ivosidenib.

Concerns are raised about the risk of haemorrhage considering that a higher incidence of bleeding events was observed in the experimental arm (41.7%) compared to control arm (31.1%) although grade 3 haemorrhage were similar (6.9% and 8.1% in the experimental and control arm respectively). A higher incidence of haematoma was also observed in the experimental arm compared to the control arm (12.7% and 1.4% respectively). The evaluation of the risk of haemorrhage related to the treatment is difficult as baseline characteristics showed that median platelets count was lower in experimental arm compared to control arm. As thrombocytopenia is already listed in the SmPC no further measures for this risk were considered necessary but will remain under close monitoring in the post-marketing setting.

Moreover, although no events of Guillain-Barré syndrome or leukoencephalopathy were observed in the pivotal study or the supportive study AG-221-AML-005, a small number of these events were reported in the monotherapy study in patients with R/R AML and from the post-marketing setting. Information on these events is limited but the applicant agreed to set up a close monitoring of these in the PSURs.

Finally, no conclusion can be drawn from description in safety in special groups and populations related to limited number of patients in each subgroup and this is reflected in the product information.

3.14. Effects Table

Table 111. Effects Table for Tibsovo in newly diagnosed IDH1-mutated AML (data cut-off: 18 March 2021)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
EFS	Events (%)	n (%)	46 (63.9)	62 (83.8)	HR = 0.33 95% CI: 0.16, 0.69	Study AG120-C-009
OS	Median	months	24.0	7.9	HR = 0.44 95% CI: 0.27, 0.73	
CR+CRh	Rate of complete remission	n (%)	38 (52.8)	13 (17.6)	HR = 5.01 95% CI: 2.32, 10.81	
Unfavourable Effects						
Leukocytosis	Incidence	%	11.3	1.4		Study AG120-C-009
ECG QT prolonged		%	19.7	6.8		
Thrombocytopenia		%	28.2	220.5		
Neutropenia		%	28.2	16.4		
Differentiation syndrome		%	14.1	8.2		

Abbreviations: EFS: event free survival; HR: hazard ratio; CI: confidence interval; OS: overall survival, CR: complete remission; CRh: complete remission with partial haematologic recovery; ECG: electrocardiogram

3.15. Benefit-risk assessment and discussion

3.15.1. Importance of favourable and unfavourable effects

The most important efficacy effects were the clinically relevant improvements in EFS, OS and CR/CRh in the treatment group compared to the control group. Overall survival is considerably prolonged in patients who received the combination: this 16-month improvement indicates a meaningful clinical benefit in these fragile and poor-prognosis subjects.

These survival data, along with the EFS and remission results are considered encouraging despite statistical considerations on the reporting of the results.

The major risk of ivosidenib is the risk of QT prolongation, which was frequently observed and and occurred at high grade in half of the cases, with the potential risk of ventricular arrhythmias. This risk is managed by restricting the use of the product in patients at high risk for these events and extensive warnings in the product information. In addition, events of QT prolongation will be closely monitored through PSURs.

Furthermore, a high incidence of differentiation syndrome was observed in association with ivosidenib use. A warning describing the symptoms of differentiation syndrome and a recommendation to

administer corticosteroids and initiate hemodynamic monitoring until resolution is included in the product information. To further mitigate this risk, a patient alert card describing the symptoms and the need to seek medical advice will be given to patients.

3.15.2. Balance of benefits and risks

The benefit/risk balance of ivosidenib use is positive for the treatment in combination with azacitidine 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.

3.16. Conclusions

The overall benefit/risk balance of Tibsovo is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Tibsovo is not similar to Pemazyre, Dacogen, Rydapt, Mylotarg, Vyxeos liposomal, Xospata and Daurismo within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Tibsovo is favourable in the following indications:

- Tibsovo in combination with azacitidine is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy.
- 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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.
- **Additional risk minimisation measures**

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:

o Information for patients with AML that Tibsovo treatment may cause differentiation syndrome.

o Description of signs or symptoms of the safety concern and when to seek medical care if differentiation syndrome is suspected.

o A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using Tibsovo.

o Contact details of the treating physician who has prescribed Tibsovo.

o Need 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).

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that ivosidenib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.