13 October 2020
EMA/CHMP/602725/2020
Committee for Medicinal Products for Human Use (CHMP)
EMEA/H/C/005056/0000

Assessment report

Tibsovo

International non-proprietary name: ivosidenib

Procedure No. EMEA/H/C/005056/0000

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
5-HT3	Serotonin
ADME	Absorption, distribution, metabolism and excretion
ADR	Adverse drug reaction
AE	Adverse Event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AME	Absorption, metabolism, and excretion
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
API	Active Pharmaceutical Ingredient
AR	Assessment Report
AST	Aspartate aminotransferase
ASXL1	Additional sex combs-like 1
ATC	Anatomical therapeutic chemical
AUC	Area under the curve
AUC0-10hr	AUC from time 0 to 10 hours
AUC0-12hr	AUC from time 0 to 12 hours
AUC0-24hr	AUC from time 0 to 24 hours
AUC0-72hr	AUC from time 0 to 72 hours
AUC0-∞	AUC from time 0 to infinity
AUC0-t	AUC from time 0 to the end of the dosing interval
AUCss	AUC at steady state
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics classification system
BID	Twice daily
BM	Bone marrow
BMMC	Bone marrow mononuclear cell
BSC	Best supportive care
C2D1	Cycle 2, Day 1
Caco-2	Human colonic adenocarcinoma
CDx	Companion diagnostic
CEBPα	Transcription factor CCAAT/enhancer binding protein α
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL/F	Apparent clearance
CLp	Plasma clearance
CLss/F	Apparent clearance at steady state
Cmax	Maximum plasma concentration
CNS	Central nervous system
CoA	Certificate of Analysis
CPP	Critical process parameter
CQA	Critical Quality Attribute
CR	Complete remission
CRh	Complete remission with partial haematologic recovery
CRi	Complete remission with incomplete blood count recovery
CRp	Complete remission with incomplete platelet recovery
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
CYP	Cytochrome P450
DCM	Dichloromethane
DDI	Drug-drug interaction
DLT	Dose-limiting toxicity
DMAP	N,N-dimethylpyridine-4-amine
DMSO	Dimethyl sulfoxide

DNA	Deoxyribonucleic acid
DNMT3A	DNA (cytosine-5)-methyltransferase 3α
dPCR	Digital polymerase chain reaction
DRF	Dose range finding
DSC	Differential Scanning Calorimetry
DVS	Dynamic vapour sorption
EC	European Commission
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EP	European Pharmacopoeia
ESMO	European Society for Medical Oncology
EU	European Union
FAS	Full Analysis Set
FAS1	Full Analysis Set 1
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridisation
FLAIR	Fluid attenuated inversion recovery
FLT3	Fms-like tyrosine kinase 3
FT-IR	Fourier Transform Infrared Spectroscopy
GC	Gas Chromatography
GD	Gestation Day
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GVS	Gravimetric vapour sorption
H2	Histamine 2
HBG 1/2	Hemoglobin gamma 1/2
HDPE	High Density Polyethylene
hERG	Human ether-à-go-go related gene
HLT	High-level terms
HNSTD	Highest non-severely toxic dose
HPLC	High performance liquid chromatography
HPMCAS	Hydroxypropyl methylcellulose (hypromellose) acetate succinate
HR	Hazard ratio
HSCT	Haematopoietic stem cell transplant
HT1080	Human chondrosarcoma cell line
IC	Ion chromatography
IC	Intensive chemotherapy
IC20	Concentration of drug that achieved 20% inhibition
IC50	Concentration of drug that achieved half maximal inhibition
IC50	Half-maximal inhibitory concentration
ICH	International Council for Harmonization
ICP-MS	Inductively coupled plasma mass spectrometry
ICP-OES	Inductively coupled plasma-optical emission spectroscopy
IDH	Isocitrate dehydrogenase
IDH1	Isocitrate dehydrogenase 1
IDH2	Isocitrate dehydrogenase 2
IDH3	Isocitrate dehydrogenase 3
IKr	Rapidly activating delayed rectifier potassium current
IPC	In-process control
i-PrOAc	Isopropyl acetate
IR	Infrared
ISS	Integrated Summary of Safety
IU	International Units
IUPAC	International Union of Pure and Applied Chemistry
IV	Intravenous
IVDD	In vitro diagnostic directive
IWG	International Working Group
JCV	John Cunningham polyomavirus
KF	Karl Fischer titration
KLF-1	Kruppel-like factor 1

KRBC/PL	Red blood cell/plasma ratio
LAC	Low-dose cytarabine
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LDPE	Low Density Polyethylene
LOAEL	Lowest-observed-adverse-effect-level
LoD	Limit of Detection
LOD	Loss on drying
LOQ	Limit of Quantitation
LoQ	List of Questions
LT	Less than
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation holder
MC	Mutation clearance
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MLFS	Morphologic leukaemia-free state
MRI	Magnetic resonance imaging
MS	Mass Spectrometry
MTBE	Methyl ter-butyl ether
MTD	Maximum tolerated dose
N/A	Not applicable
NA	Not assessed
NADP	Nicotinamide adenine dinucleotide phosphate
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
ND	Not detected
NDA	New Drug Application
NE	Not estimable
NEC	Not elsewhere classified
NLT	Not less than
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NOAEL	No observed adverse effect level
NOR	Normal Operating Range
NPM	Nucleophosmin
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
OCT2	Organic cation transporting polypeptide 2
ODWG	Organ Dysfunction Working Group
OECD	Organization for Economic Co-operation and Development
OOS	Out of Specifications
OPA	Oriented polyamide film
ORR	Objective response rate
OS	Overall survival
Papp	Apparent permeability
PAR	Proven Acceptable Range
PBMC	Peripheral blood mononuclear cells
PBPK	Physiologically based PK
PBPK	Physiologically-based pharmacokinetics
PCR	Polymerase chain reaction
PD	Progressive disease
PDE	Permitted Daily Exposure
PDX	Patient-derived xenograft
PE	Polyethylene
PGI	Potential genotoxic impurity
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PIP	Pediatric investigation plan
PK	Pharmacokinetics
PK/PD	Pharmacokinetic/pharmacodynamic
PML	Progressive multifocal leukoencephalopathy

PP	Polypropylene
PR	Partial remission
PS	Performance status
PSD	Particle Size Distribution
PT	Preferred Term
PVAP	Polyvinyl acetate phthalate
QbD	Quality by design
QC	Quality Control
QD	Once daily
QOS	Quality Overall Summary
QP	Qualified person
QTc	Heart rate-corrected QT interval
QTcB	Heart rate-corrected QT interval corrected for heart rate using Bazett's formula
QTcF	Heart rate-corrected QT interval using Fridericia's equation
QTPP	Quality target product profile
QWP	Quality Working Party
R/R	Relapsed or refractory
R132C	Arginine-132 mutated to cysteine
R132G	Arginine-132 mutated to glycine
R132H	Arginine-132 mutated to histidine
R132L	Arginine-132 mutated to leucine
R132S	Arginine-172 mutated to serine
R140Q	Arginine-140 mutated to glutamine
R172K	Arginine-172 mutated to lysine
RBC	Red blood cell
RH	Relative Humidity
RMP	Risk management plan
RP2D	Recommended phase 2 dose
RRT	Relative retention time
RSD	Relative standard deviation
RTK	Receptor tyrosine kinase
SAE	Serious adverse event
SAS	Safety Analysis Set
SAWP	Scientific Advice Working Party
SCS	Summary of Clinical Safety
SCT	Stem cell transplant
SD	Stable disease
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA query
sNDA	Supplemental New Drug Application
SOC	System organ class
STD10	Severely toxic dose in 10% of animals
t½	Terminal elimination half-life
TAMC	Total aerobic microbial count
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TET2	Tet oncogene family member 2
TF-1	Human erythroid leukaemia cell line
TFE	Trifluoroethanol
TGA	Thermo-Gravimetric Analysis
THF	Tetrahydrofuran
TK	Toxicokinetics
Tmax	Time to maximum plasma concentration
TSE	Transmissible Spongiform Encephalopathy
TTC	Threshold of toxicological concern
TYMC	Total yeasts and molds count
ULN	Upper limit of normal (range)
US	United States
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
VAF	Variant allele frequency
Vss	Volume of distribution at steady state
WBC	White blood cell
WHO	World Health Organization

XR(P)D	X-Ray (Powder) Diffraction

1. CHMP Recommendations

Based on the review of the data on quality, safety, and efficacy, the CHMP considers that the application for Tibsovo, an orphan medicinal product,

- Initially proposed: for the treatment of adult patients (≥18 years old) with relapsed or refractory acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation:
- At D150 adapted to: as monotherapy for the treatment of adult patients with intermediate or poor cytogenetic risk, relapsed or refractory acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are ineligible for intensive treatment including HSCT
- And subsecuently adapted to: as monotherapy for the treatment of relapsed or refractory acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation in adult patients who:
  - have received at least 2 prior regimens, including at least 1 standard intensive chemotherapy regimen, or
  - are not candidates for standard intensive chemotherapy and have received at least 1 prior non-intensive regimen.

is **not approvable** since a "major objection" has been identified, which precludes a recommendation for marketing authorisation at the present time.

Questions to be posed to additional experts

SAG Oncology was consulted with regard to the relevance of the ivosidenib data to support an indication in R/R AML with an IDH1 mutation.

Inspection issues

GLP inspections

Nineteen non-clinical GLP safety studies were completed between December 2013 and June 2017 at American facilities and test sites. Five studies were analysed in detail by the ANSM for GLP compliance. The choice of studies was made in such a way as to cover all the test facilities and the times when the studies were carried out and the pivotal studies in the file.

In conclusion, of the 5 studies reviewed, all 5 are GLP compliant or overall GLP compliant.

GMP inspection(s)

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 European GMP.

GCP inspection(s)

FDA performed the following GCP inspections for study AG120-C-001:

- Sponsor inspection:

- Agios Pharmaceuticals, Inc., Cambridge, MA, USA (01-02, 05-06 & 09 March 2018)

- Site inspections for the following sites:
  - Dana Farber Cancer Institute, Boston, MA, USA (12-16 & 20 February 2018)
  - Memorial Sloan-Kettering Cancer Center, New York, NY, USA (20-23 & 27 February 2018)
  - University of Texas MD Anderson Cancer Center, Houston, TX, USA (12-16 March 2018)
  - Institut Gustave Roussy – Service DITEP, Villejuif, France (23-26 April 2018)

No further GCP inspection was requested based on the current information.

Similarity with authorised orphan medicinal products

It is considered that Tibsovo is not similar to Dacogen, Rydapt, Mylotarg, Vyxeos, Xospata and Daurismo within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

Following discussions with the Committee, the Company revised the proposed indication to include patients in a last line treatment setting as follows: "Tibsovo is indicated as monotherapy for the treatment of relapsed or refractory acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation in adult patients who:

- have received at least 2 prior regimens, including at least 1 standard intensive chemotherapy regimen, or
- are not candidates for standard intensive chemotherapy and have received at least 1 prior non-intensive regimen."

According to NCCN guidelines:

- Relapse following complete response is defined as reappearance of leukemic blasts in the peripheral blood or the finding of more than 5% blasts in the bone marrow, not attributable to another cause (bone marrow regeneration after consolidation therapy) or extramedullary relapse.
- Induction failure or refractory AML is defined as failure to attain CR following exposure to at least 2 courses of intensive induction therapy (2 cycles of 7+3 or one cycle of 7+3 and one cycle of HiDAC).

A number of studies have examined the prognostic impact of isocitrate dehydrogenase 1 (IDH1) mutations 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 could confer 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). IDH1-mutated R/R AML is associated with a worse prognosis compared to wild-type IDH1.

2.1.2. Epidemiology

According to the Surveillance of Rare Cancers in Europe (RARECARE 2016) project on patients diagnosed from 1995 to 2002 and archived in 64 European population-based cancer registries, the overall annual incidence of AML was 3.7 per 100,000 (4.0 per 100,000 for males and 3.4 per 100,000 for females) and the 5-year relative survival rate was 19% (Visser, et al. 2012). Based on these incidence data and the total European Union of 27 member states (EU-27) population, approximately 18,500 cases of AML are diagnosed annually in the EU. According to these data, the incidence of AML gradually increases with age, with an incidence rate per 100,000 of 0.7 for the age group of 0-14 years, 0.8 for the group of 15-24 years, 2.4 for the group of 25-64 years, and 13.7 for the oldest age group (65 years or older) (Visser, et al. 2012).

In the first study of isocitrate dehydrogenase (IDH) mutations in AML, IDH1 mutations were identified in 16 (8.5%) of the 188 cases analysed (Mardis et al, 2009). In subsequent studies, the IDH1 mutation frequency was reported to range from 8% to 14% (Marcucci et al, 2010; Ward et al, 2010). Recently, the overall frequency of IDH1 mutations in AML has been estimated to be between 6% and 10% (Bullinger et al, 2017), making IDH1 mutation-positive AML a rare disease within a recognised orphan condition.

2.1.3. Biologic features

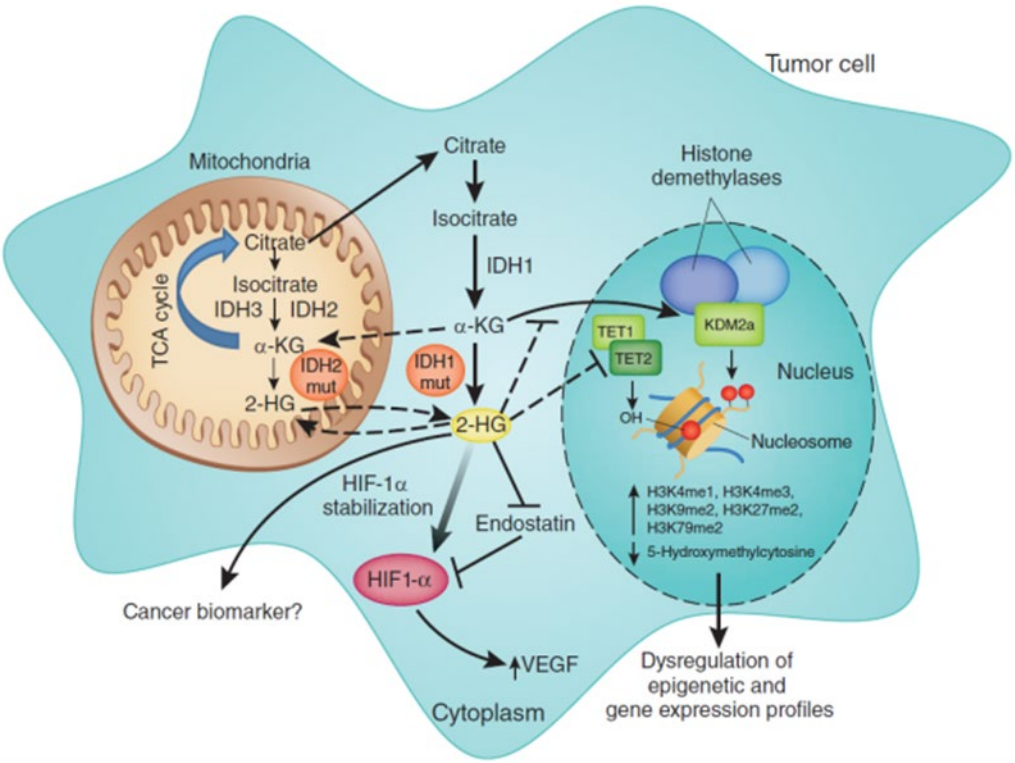
AML is a heterogeneous haematologic malignancy that is characterised by clonal expansion of myeloid blasts in the bone marrow and frequently also in the peripheral blood and/or other tissues. It is characterised by clonal heterogeneity at the time of diagnosis, with the presence of both a founding clone and at least 1 subclone. The clonal heterogeneity has a different pattern at diagnosis compared to relapse. AML relapse is associated with the addition of new mutations and clonal evolution, which is shaped in part by the chemotherapy that the patients receive to establish and maintain remissions (Ding, 2012).

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 catalyse the reduction of alpha-ketoglutarate (α-KG) to R(-)2-hydroxyglutarate (2-HG) (Dang et al, 2009). 2-HG exerts its oncogenic 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 haematopoietic stem cells into mature blood cells, contributing to oncogenesis (Dang et al, 2009; Figueroa et al, 2010).

Figure 1. Mutant IDH1 and IDH2 activity in tumour cells



Source: Prensner and Chinnaiyan 2011 (Nature Medicine 17, 291–293 (2011); doi:10.1038/nm0311-291)

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Acute myeloid leukaemia is characterised by uncontrolled proliferation of clonal neoplastic haematopoietic 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). Clinical manifestations of AML result either from the proliferation of leukaemic cells or from bone marrow failure that leads to a 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 dyspnoea on exertion.

According to 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]. In accordance with the 2016 WHO classification, a diagnosis of AML is based on the presence of 20% or more blasts in the marrow or peripheral blood.

The 2016 WHO classification of AML is presented in Table 1. In cytogenetically normal AML, somatic mutations of the genes FLT3 (a receptor tyrosine kinase), NPM1 (nucleophosmin) or CEBPα (a transcription factor) have been identified as important prognostic factors. Additional gene mutations have been observed in the IDH genes, in the TET oncogene family member 2 (TET2) genes, the genes for DNA (cytosine-5)-methyltransferase 3α (DNMT3A) and additional sex combs-like 1 (ASXL1). [Fey et al, 2013]

Table 1. WHO classification of the major subtypes of AML [Arber et al. Blood 2016;127(20):2391]

Acute myeloid leukemia (AML) and related neoplasms
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);*RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22);*CBFB-MYH11*
APL with *PML-RARA*
AML with t(9;11)(p21.3;q23.3);*MLLT3-KMT2A*
AML with t(6;9)(p23;q34.1);*DEK-NUP214*
AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2, MECOM*
AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);*RBM15-MKL1*
Provisional entity: AML with BCR-ABL1
AML with mutated *NPM1*
AML with biallelic mutations of *CEBPA*
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome

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.

The largest and most recent meta-analysis of outcomes for the IDH1 mutation was conducted by Xu et al and involved 33 publications with 12,747 AML cases reported across Europe, Asia, Australia, and America. The IDH1 mutation conferred worse OS (P=0.0047) and EFS (P=0.011), including in patients with normal cytogenetics (OS P=0.039; EFS P=0.0002). In addition, the IDH1 mutation was associated with an inferior CR rate (P=0.029) (Xu et al, 2017).The German-Austrian AML Study Group assessed 2,825 AML patients with a median age of 55 years (range 18-84 years) treated across eight consecutive frontline intensive studies (Paschka et al, 2016). Of the 2,822 patients with IDH1 mutation information available, 212 had an IDH1 mutation (R132 n=211, other n=1) for a mutational frequency of 7.5%. The median OS for the 111 patients with IDH1-mutated primary refractory disease or disease in first relapse was 7.4 months, with an OS of 6.4 months for 31 IDH1-mutant patients with refractory disease and 7.6 months for 80 patients in first relapse.

In a study by DiNardo et al, in 14 patients with IDH1 mutations in second and greater salvage, 5 achieved a CR or CRi and the median OS was 4.0 months (DiNardo et al, 2015).

Management

Treatment options for patients with IDH1-mutated R/R AML are the same as those for the general R/R AML population, with no approved targeted therapies in the EU and no effective standard of care.

Patients with IDH1-mutated R/R AML represent a rare population with a serious unmet medical need for safe and effective targeted therapies.

There are limited effective therapies for adult patients with R/R AML (Craddock et al, 2005; Estey, 2000; Forman and Rowe, 2013; Kell, 2016; Leopold and Willemze, 2002; Mangan and Luger, 2011; Ramos et al, 2015; Szer, 2012; Thol et al, 2015, Döhner et al, 2015).

Intensive chemotherapy

Intensive chemotherapy is usually reserved for the small number of patients who achieved CR with a relapse free interval of greater than 12 months and who are still fit to receive induction-consolidation therapy. No treatment regimen has demonstrated improved benefit over another (Kell, 2016; Ramos et al, 2015). Several commonly used treatment options include intensive salvage chemotherapy comprising an anthracycline/anthracenedione, cytarabine, and/or a purine analog (eg, fludarabine, cladribine, clofarabine). In a randomised study of 381 patients with advanced R/R AML randomised to treatment with the experimental agent elacytarabine versus investigator's choice of conventional therapies, the median OS in the elacytarabine arm was 3.5 months compared with 3.3 months in the control arm (P=0.96) (Roboz et al, 2014).

These therapies have been associated with significant treatment-related mortality. Thirty-day mortality has been observed to be 2% to 7% with cytarabine alone (Kell, 2016), 10% to 17% for standard combination therapies (Kell, 2016; Ramos et al, 2015; Roboz et al, 2014), and over 20% for more aggressive combination therapies (Ramos et al, 2015).

2.1.4.1. Haematopoietic stem cell transplant (HSCT)

Allogeneic haematopoietic stem cell transplant (HSCT) may be offered either as salvage therapy or as subsequent therapy following CR attained by salvage therapy, though survival outcomes are poor (Duval et al, 2010).

2.1.4.2. Nonintensive regimens

Nonintensive treatments are offered to patients who cannot tolerate more intensive therapies or who do not have a sufficient expectation of response due to disease-related factors, such as their cytogenetic and molecular status.

Nonintensive treatment options include LDAC and hypomethylating agents. These nonintensive therapies are frequently the default therapy for patients who are over 60 years of age, particularly those >75 years of age, or those with unfavourable risk factors. Complete remission rates with these treatments are approximately 10% to 20% and the median OS is between 6 and 9 months depending on the duration of the first CR and cytogenetic risk factors (Itzykson et al, 2015; Kell, 2016; Ritchie et al, 2013).

2.1.4.3. Supportive care

Supportive care measures are used to address the underlying comorbidities associated with AML and include hydroxyurea (World Health Organization [WHO] Drug Dictionary Enhanced [DDE] name: hydroxycarbamide) to control leukocytosis, blood product transfusions, haematopoietic 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 leukaemia and patients ultimately die from their disease.

Clinical trials

Enrolment in clinical trials is strongly recommended, especially for patients who are older or unable to receive standard intensive therapies, given the lack of effective, tolerable treatment options for patients with R/R AML (Döhner et al, 2017; NCCN, 2018).

2.2. 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 IDH1-mutated 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 proposed indication for ivosidenib is the treatment of adult patients with R/R AML with an IDH1 R132 mutation.

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 without food until disease progression or unacceptable toxicity. Patients without disease progression or unacceptable toxicity should be treated for a minimum of 6 months to allow time for clinical response.

2.3. The development programme/compliance with CHMP guidance/scientific advice

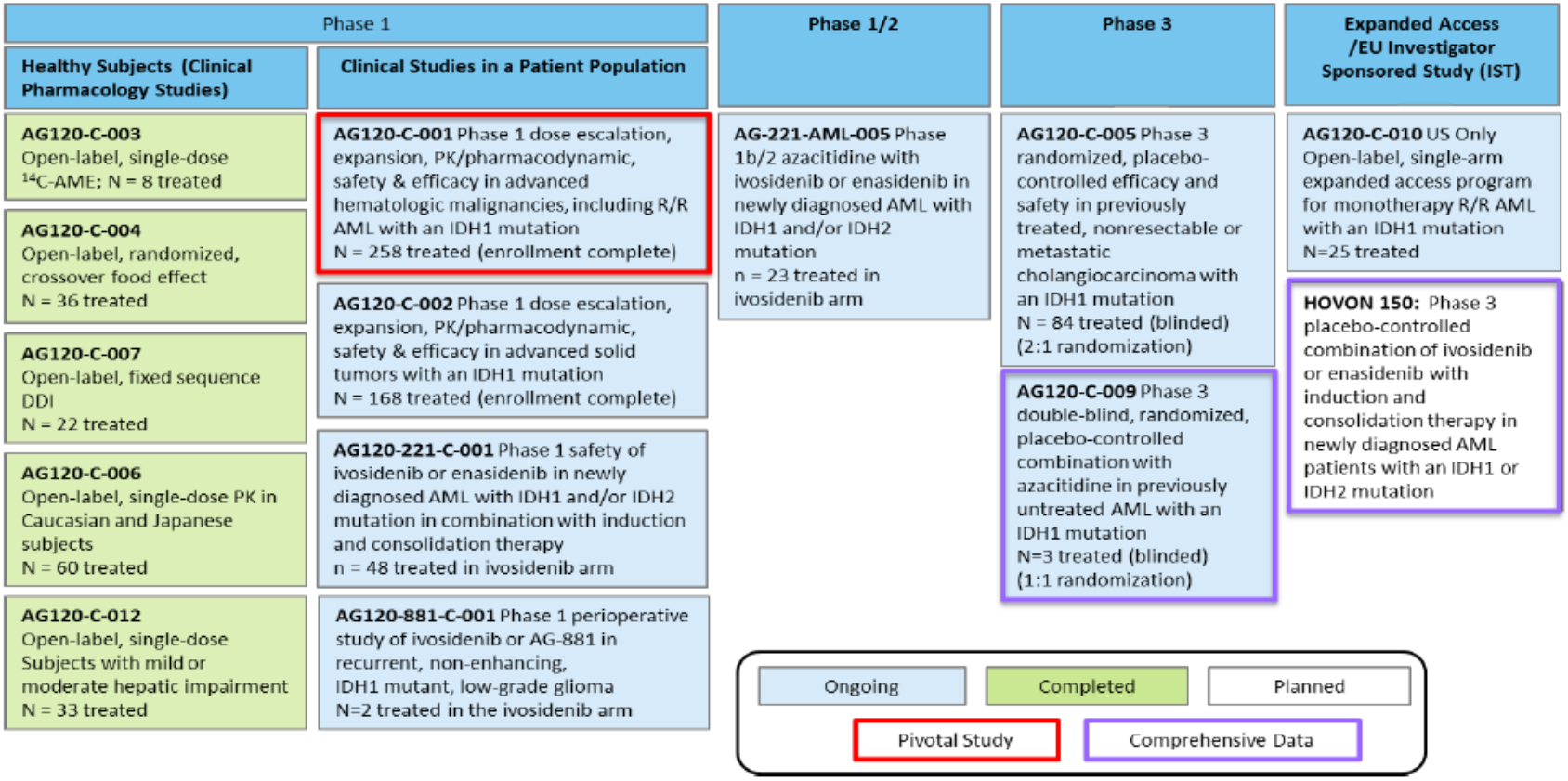
The ivosidenib clinical development programme was initiated in March 2014 in the US and in May 2014 in France. A total of 13 clinical studies are completed or ongoing, including 5 studies in subjects with AML or other haematologic malignancies, 3 studies in subjects with solid tumours, and 5 clinical pharmacology studies in healthy subjects or subjects with hepatic impairment.

The pivotal study to support an indication in IDH1 mutation-positive R/R AML patients is the ongoing Phase 1 clinical study in subjects with advanced haematologic malignancies, including R/R AML (Study AG120-C-001: A Phase 1, Multicenter, Open-Label, Dose Escalation and Expansion, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-120 in Subjects with Advanced Hematologic Malignancies with an IDH1 Mutation). This study includes a dose escalation portion to determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) and an expansion portion to further evaluate the safety, tolerability, and clinical activity of ivosidenib.

The applicant has requested a Conditional marketing authorisation.

The applicant proposes, as a confirmatory study, a prospective clinical study in a last line IDH1-mutated R/R AML patient population, aligned with the claimed indication with provision of the primary clinical study report in Q3 2024. Two efficacy and safety studies (HOVON 150 / AMLSG 29-18 and AG120-C-009) were initially proposed by the applicant to provide further clinical data.

Figure 2. Ivosidenib Clinical Development Programme: Completed and Ongoing Studies as of 11 May 2018



Abbreviations: AME = absorption, metabolism, excretion; AML = acute myeloid leukemia; DDI = drug-drug interaction; IDH = isocitrate dehydrogenase; PD = pharmacodynamic; PK = pharmacokinetic; R/R = relapsed or refractory.
Notes: Study AG-221-AML-005 is sponsored by Celgene Corporation. The enrollment as of 11 May 2018 is provided for ongoing studies.

Scientific Advice / Protocol Assistance was given by the Committee for Medicinal Products for Human Use (CHMP) / Committee for Orphan Medicinal Products (COMP) in November 2016 (EMA/CHMP/SAWP/713016/2016) and May 2018 (EMA/CHMP/SAWP/300933/2018).

- EMA/CHMP/SAWP/713016/2016

  In October 2016, Agios sought scientific advice regarding the design of a phase 3 study (AG120-C-009) investigating the combination of ivosidenib with azacitidine in adult subjects with previously untreated AML with an IDH1 mutation, who are candidates for non-intensive therapy. The proposed study design included the primary endpoint of OS.

- EMA/CHMP/SAWP/234175/2018

  On 16 May 2018, Agios sought scientific advice on the clinical development strategy of ivosidenib, particularly the prospects for a conditional marketing authorisation in R/R AML based on Study AG120–C-001, with subsequent confirmatory data to be provided by Study AG120-C-009. The SAWP indicated that the provision of an historical control for the single-arm AG120–C-001 pivotal study will be important, and that the data should be aligned on a patient level to adjust for heterogeneity. In addition, guidance was sought on proposed revisions to the study design for Study AG120-C-009, including the proposal to evaluate Event Free Survival (EFS) as the primary efficacy endpoint in order to provide a direct measure of clinical benefit.

Ivosidenib has an agreed Paediatric Investigation Plan (PIP) in the condition "treatment of acute myeloid leukaemia" (P/0280/2018, EMEA-002247-PIP03-17). The PIP comprises four studies (quality, clinical, modelling and simulation, and extrapolation). All studies have been deferred and the agreed completion date for all is December 2029. A waiver in infants and toddlers from birth to less than 2 years has been agreed.

Non-clinical studies were performed according to the ICH guideline "Nonclinical Evaluation For Anticancer Pharmaceuticals S9. Current Step 4 version dated 29 October 2009".

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

GMP

No GMP inspections were deemed necessary.

GLP

Nineteen non-clinical GLP safety studies were completed between December 2013 and June 2017 atAmerican facilities and test sites. Five studies were analysed in detail by the ANSM for GLP compliance. The choice of studies was made in such a way as to cover all the test facilities and the times when the studies were carried out and the pivotal studies in the file.

In conclusion, of the 5 studies reviewed, all 5 are GLP compliant or overall GLP compliant.

GCP

In accordance with Article 8 (ib) of Directive 2001/83/EC, the applicant confirmed that all of the clinical trials within this Marketing Authorisation Application (MAA) conducted outside the European Union (EU) meet the ethical requirements of Directive 2001/20/EC.

According to the applicant, 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).

Routine GCP inspections of trial AG120-C-001, a Phase 1, multicentre, open-label, dose-escalation and expansion, safety, pharmacokinetic, pharmacodynamic, and clinical activity study of orally administered AG-120 in subjects with advanced haematologic malignancies with an IDH1 mutation have been performed by the US FDA.

Protocol Number	Date of Inspection	Regulatory Agency (Inspecting Authority)
AG120-C-001	12-16 & 20 February 2018	FDA
	20-23 & 27 February 2018	FDA
	01-02, 05-06 & 09 March 2018	FDA
	12-16 March 2018	FDA
	23-26 April 2018	FDA

2.5. Type of application and other comments on the submitted dossier

Legal basis

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

Accelerated assessment

Not applicable.

Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14(7) of the Regulation (EC) No 726/2004.

During the assessment, a prospective clinical study in a last line IDH1-mutated R/R AML patient population was proposed as a confirmatory study to align with the revised indication. The proposed study was a global, multicentre, single-arm study of ivosidenib in subjects with IDH1-mutated R/R AML who have received at least 2 prior regimens, including at least 1 standard intensive chemotherapy regimen, or are not candidates for standard intensive chemotherapy and have received at least 1 prior nonintensive regimen.

Marketing authorisation under exceptional circumstances

Not applicable.

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.

Orphan designation

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

Similarity with orphan medicinal products

The application contained a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products.

Derogation(s) from orphan market exclusivity

N/A

Information on paediatric requirements

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) and on the granting of a waiver.

The waiver applies to:

- the paediatric population from birth to less than 2 years of age;
- the film-coated tablet, oral use, age-appropriate solid dosage form, oral use, nasogastric use;
- on the grounds that clinical studies with the specific medicinal product cannot be expected to be of significant therapeutic benefit to or fulfil a therapeutic need of the specified paediatric subset(s).

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

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

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

Other ingredients are:

For the tablet core: microcrystalline cellulose (E460), croscarmellose sodium (E468), hypromellose acetate succinate, colloidal silicon dioxide (E551), magnesium stearate (E572), sodium lauryl sulfate (E487)

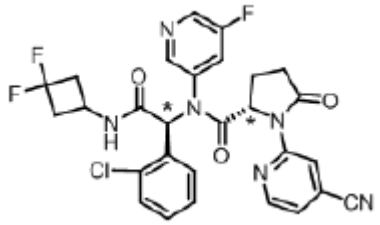
For the film coating: hypromellose (E464), titanium dioxide (E171), lactose (as lactose monohydrate), triacetin (E1518), indigo carmine aluminium lake (E132)

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

3.1.2. Active substance

General Information

The chemical name of ivosidenib is (2*S*)-*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:



* denotes stereocentre

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. 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). Crystalline anhydrous Form L was selected as the final active substance form. Other forms include hydrate Form B and solvates: Form E, Form G, and Form O. Formation conditions of each polymorphic form were described.

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

The applicant has performed a 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.

Manufacture, process controls and characterisation

The active substance intended for the proposed commercial process is obtained from a single manufacturer A QP declaration was provided signed by the QP of the batch-releasing site on behalf of all manufacturers and based on an on-site GMP audit carried out on 27-28 Sept 2018 on the premises of the API manufacturer.

The active substance is synthesised by a four-stage process involving five starting materials.

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

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

The specifications and control methods for starting materials, intermediate products and reagents have been presented and are considered adequate.

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 drug 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 drug substance along with the points of control for each of them was 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 characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new 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 was also addressed; however, due to the indication for advanced cancer, ICH M7 is not applicable and therefore the discussion and related controls proposed are in general considered sufficient taking into account the proposed indication.

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 EC directive EC 10/2011 as amended.

Specification

The active substance specification was provided and included standard tests such as description (visual), identification (FTIR), assay (HPLC), related impurities (HPLC), chiral impurity (HPLC), residual solvents (GC), water content (Ph. Eur.), residue on ignition (Ph. Eur.) and elemental impurities (Ph. Eur.).

The proposed specifications are satisfactory, in particular, related substance specifications are in compliance with the GL ICH Topic Q 3 A (R2) Impurities in new Drug Substances. The limit for specified impurities are below the qualification threshold. 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. Specifications for elemental impurities are in compliance with ICH guideline Q3D (R1) on elemental impurities. The absence of polymorphism control in the active substance specifications is considered justified in compliance with ICH Topic Q 6A 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 adequately described and non-compendial methods appropriately validated in accordance with ICH guidelines.

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

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

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 36 months under long term conditions at 30ºC / 65% RH and for up to 6 months under accelerated conditions at 40ºC / 75% RH according to ICH guidelines were provided.

The parameters tested are the same as for release with the exception of XRPD and microbial limits testing. The analytical methods used were the same as for release except for the assay and impurities determination method used for time points before 24 months.

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

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

All tested parameters during stability studies conducted at long term and accelerated conditions were within the specifications with the exception of an out of specification (OOS) result at 40°C/75% RH at the 3-month time-point, for one batch for the mean assay result. The observed out of specification result does not pose any concern because the assay value for the subsequent 6 -month time-point complies with the current specification.

According to the primary stability results summary, "no change in solid state form (crystalline) ie, form L was observed after storage at 30°C/65% RH for up to 36 months, or at 40°C/75% RH for up to 6 months."

The stability results obtained for long term and accelerated conditions justify the proposed retest period of 48 months when stored at not more than 30°C in the proposed container.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Description of the product

The drug product, film coated tablets is a standard pharmaceutical form. The tablets are oval, blue, film-coated, debossed with 'IVO' on one side and '250' on the other side, whose approximate dimensions are of length 18.4 mm and width 8.7 mm.

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

The composition (excipients) of the drug productare: (Tablet core): Microcrystalline cellulose (E460), Croscarmellose sodium (E468), Hypromellose acetate succinate, Colloidal silicon dioxide (E551), Magnesium stearate (E572), Sodium lauryl sulfate (E487) and (Film-coating): Hypromellose (E464), Titanium dioxide (E171), Lactose (as lactose monohydrate), Triacetin (E1518), Indigo carmine aluminum lake (E132).

The information provided on the composition of the tablets is adequate. No overages are used in the composition of the drug product. Details on the dimensions of the tablets were provided.

Pharmaceutical development

The roles of the excipients have been described and a justification for their use was provided.

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.

No details were provided for the development of the packaging systems for the intermediate and for the drug product, reference was made to the stability studies results.

Manufacture of the product and process controls

Manufacture

The drug product manufacturing process is relatively standard and consists of two main steps: the manufacture of the drug product intermediate and the manufacture of the final drug product.

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

Process controls

The controls applied during the manufacturing process were presented under two categories, ie, 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 normal operating ranges, as well as proven acceptable ranges). Details of the control strategy were provided.

Similarly, in-process controls were provided, with similar types of limits (target, normal operating range and proven acceptable range), as well as a short description of the method used. The proposed ranges are supported by the development studies performed.

Although ranges were provided for the control of the critical parameters, no design space was claimed.

Process validation / verification

The validation of the drug product manufacturing process was conducted. The results are compliant with the acceptance criteria and are similar between the batches, and the validation of the manufacturing process is considered acceptable.

Excipients

The majority of the excipients used in the composition of the drug product are compendial and claimed compliant with their respective Ph. Eur. Monographs.

Specifications used for the control of hypromellose acetate succinate and the film-coating were provided. A discussion on the testing of the functional characteristics of the excipients was provided.

Product specification, analytical procedures, batch analysis

Specifications

The specification proposed for the control of the drug product contains the typical tests for this type of pharmaceutical form: description (visual), identification (HPLC/UV, HPLC/DAD), assay (HPLC), degradation products (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur., HPLC), water content (Ph. Eur.), microbial enumeration (Ph. Eur.) and specified microorganism (Ph. Eur.).

The specification proposed for the control of the drug product covers the majority of the essential parameters for this type of pharmaceutical form.

Only the control of the degradation products that could be formed in the drug product was considered in the control of the related substances. The drug product manufacturer has justified for not controlling the related substances from the synthesis of the active substance by the fact that these related substances do not increase during the storage of the drug product. It was confirmed that the 'total degradation products' value is the sum of the reported unspecified degradation products.

Analytical procedures and reference standards

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 adequately described and validated. The complete validation results for the methods used for the control of the microbiological quality and for the method used for the control of the crystalline form in the drug product were provided.

Batch analysis

Batch results were provided on three drug product production batches of an acceptable batch size (production size), manufactured in October 2017 at the proposed drug product manufacturing site. 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.

Container closure

The tablets are packed in HDPE bottles closed with polypropylene child resistant closures with a polyethylene film bonded to aluminium foil. A silica gel desiccant (in a canister) was included in the bottle. This type of container is often use for this type of product.

The documentation provided for its materials included specifications, example CoA, and confirmation of compliance with the relevant Ph. Eur. monographs and EU amended regulation 10/2011. A confirmation of the child resistant packaging with the Unites States C.P.S.C. and a commitment to test the packaging for child resistance in accordance with the recommended International Standard (EN ISO 8317) before distribution of the product on the EU market were also provided.

Stability of the product

A shelf life of 48 months was proposed for the drug 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. No shelf-life after opening was proposed, a commitment to perform this study was provided following CHMP request.

The main stability study (longest) was performed on three pilot scale batches (batch size 28 kg), and data up to 36 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.

A supportive stability study was performed on three batches of ivosidenib tablets. Results up to 12 months were provided for this study.

The data provided shows that the drug 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 drug 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 drug 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.

No in-use stability studies (after opening of the container) were performed, the applicant proposed to use another study to support a shelf life after opening; however, this data cannot replace a study performed in accordance with the Note for guidance on in-use stability testing of human medicinal products CPMP/QWP/2934/99.

The proposed shelf life of 48 months for the drug product is considered acceptable.

The stability of the product after first opening of the container should be established. A commitment to perform an in-use stability study in line with the Note for guidance on in-use stability testing of human medicinal products CPMP/QWP/2934/99 and to introduce an in-use storage period in the SmPC was provided following CHMP request.

Post approval change management protocol(s)

n/a

Adventitious agents

n/a

GMO

n/a

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Based on the review of the quality data provided, the CHMP considers that the marketing authorisation application for ivosidenib film coated tablets could be approvable from the quality point of view.

3.2. Non clinical aspects

3.2.1. Pharmacology

Primary pharmacodynamics

The proposed indication for ivosidenib is for the treatment of adult patients with R/R AML with an IDH1 R132 mutation. The German-Austrian AML Study Group assessed 2,825 AML patients with a median age of 55 years (range 18-84 years) treated across eight consecutive frontline intensive studies (Paschka et al, 2016). Of the 2,822 patients with IDH1 mutation information available, 212 had an IDH1 mutation (R132 n=211, other n=1) for a mutational frequency of 7.5%. IDH1 mutations are detected in 6.6% of 1414 AML patients and are associated with intermediate risk karyotype and unfavourable prognosis in adults younger than 60 years. The applicant was asked to discuss the effect of the drug on the different variations (R132S, R132G, R132L and R132E) that have not been studied in the *in vivo* non-clinical pharmacodynamic models and to discuss the clinical relevance of the absence of these data. This issue is not totally resolved from a non-clinical point of view where uncertainties remained. The applicant was asked to further study the pharmacological mechanism of action of the drug especially on mutant alleles R132S, R132G and R132L in *in vivo* non-clinical studies. Otherwise, the applicant was asked to strongly justify the non-clinical and clinical pharmacology proof of concept of the drug regarding:

- its effect on all mutations
- the variability of the high inter-individual variability (in vitro and clinical)
- the benefice of lower 2-HG levels and thereby DNA methylation,
- IDH inhibition that could lead to undesired effects

Regarding the fact that a conditional MA as well as a last line of treatment could be decided and from a non-clinical point of view, some further non clinical studies should be considered:

- Pursue the development of an AML IDH1 mutant PDX model in immunodeficient mice for the mutant IDH1 alleles R132S, R132G and R132L.
- Identify a biomarker from available nonclinical AML models, with a possible clinical relevance

If a positive B/R is considered, and if all CMA requirements are met, the applicant should commit to providing additional non-clinical testing to enhance the proof of concept **(OC).**

In vitro, ivosidenib exhibited low nanomolar potency inhibition against IDH1 and is highly selective for IDH1 isoforms, showing no inhibition of an IDH2 isoform at >100 µM concentrations. Ivosidenib was also shown to be a potent inhibitor of 2-HG production in cells expressing IDH1 (R132C), IDH1 (R132H), and IDH1 (R132S) mutations, but does not inhibit 2-HG production in cells expressing IDH2 (R140Q).

According to the results of the binding study, ivosidenib's affinity to mutant IDH1 is around four-fold higher than to wt IDH1. However, after prolonged incubation, the affinity towards wt IDH1 markedly increases. Thus, after repeated administration of ivosidenib in animals or humans, inhibition of wt and mutated IDH1 is most likely similar. If so, the applicant was asked to discuss potential consequences of wt IDH1 inhibition, ie, the IDH1 form occurring in all tissues outside the tumour cells. The applicant was also asked to address the NC findings of non-beneficial effects of IDH1 inhibition resulting in neoplastic cell proliferation in some tumours (eg, glioma) in function of the pre-existing DNA/histone methylation pattern. The aim of this question and also of the toxicology questions was further characterisation of the pharmaco-toxicological properties of ivosidenib and the prediction of possible side effects because the amount of clinical data is limited. Thus, benefit-risk assessment from clinical data could be supported by limited mechanistic considerations based on non-clinical observations. According to the applicant's response, at least some inhibition of wt IDH1 cannot be excluded at therapeutic doses. In respect to the other aspects, no further insight could be provided.

Treatment with ivosidenib reversed TF-1 IDH1 (R132H)-induced GM-CSF-independent growth in a dose-dependent manner. Because blasts from patients with AML express high procaspase protein levels, we asked whether granulocyte-macrophage colony-stimulating factor (GM-CSF) enhances procaspase protein production in AML cells. GM-CSF exerts a dual effect: it stimulates cell division but contemporaneously up-regulates Jak-Stat-dependent proapoptotic proteins. Up-regulation of procaspase levels in AML is thus a beacon for an ongoing growth-stimulatory signal. Expression of the mutant IDH1 enzyme in TF-1 cells induces growth factor-independent proliferation, suggesting that the mutant enzyme confers a biological gain of function.

In the non-clinical primary PD programme, there were several hints that – in line with published literature data – IDH1 inhibition does not necessarily trigger differentiation of the malignant cells; also the opposite may be the case, reflected as decreased expression of differentiation markers and enhanced proliferation. Studies investigating primary AML cells obtained from different patients revealed high inter-individual variability in the type of response of the AML cells to ivosidenib. Furthermore, when patient AML cells were used to induce xenograft leukaemia in mice, ivosidenib treatment of these mice led to decreased survival time and increased leukaemia cell mass. The applicant was asked to discuss these observations and in particular discuss whether patient AML cells routinely should be tested for their response to ivosidenib *in vitro* (increase or decrease in differentiation marker expression and proliferation) before starting ivosidenib therapy. The applicant could not provide new insights. The general problems of assessing the sequels of mutIDH1 inhibition in AML cells remain the following:

- Although it is fully agreed that ivosidenib can lower 2-HG levels and thereby affect DNA methylation, it is not clear whether this is beneficial. The cellular response depends on the actual sites of methylation in the genome.
- Since differentiation of AML cells starts with a proliferative burst, differentiation is difficult to distinguish from an undesired increase in proliferation due to increased malignancy.

There were two hints in the non-clinical development programme which gave rise for concern. First, AML cells from different patients displayed very heterogeneous responses to ivosidenib treatment *in vitro*; in some cases, genes which are regarded as myeloid differentiation markers (eg, CD14 and

CD15) were actually down-regulated. Second, in mice bearing xenograft tumours from human AML cells ivosidenib decreased survival.

For the first aspect, the applicant indicated that AML is characterised by the presence of myeloid cells "locked" in various phases of cell differentiation (myeloblast through segmented neutrophil), in which each population of myeloid cells is variable and highly unique to individual patients. Therefore, for any given patient, the progression in flow cytometric phenotype towards a more differentiated state depends upon the initial distribution of maturation states of these populations. This complex biology manifested in each of the ex vivo samples tested, exemplifying distinct mature myeloid lineage population pools following inhibition of 2HG production.

For the second aspect, the applicant pointed out that (in contrast to other anti-neoplastic agents) the AML cells are not eliminated by ivosidenib but induced to differentiate to less malignant myeloid cells. However, according to the applicant, the mice can also be killed by differentiated human myeloid cells. It is acknowledged that the possibility exists; the effect could be similar to the differentiation syndrome observed in humans. No histology or other information on the cause of death of the animals is available so this assumption cannot be confirmed. Regarding potential pre-testing of patient AML cells for responsiveness, it is agreed that at present no recommendation for such a test can be given. Evaluation of clinical data may reveal whether identification of a suitable target population should include characterisation of patient AML cells.

An assay was used to determine colony-forming properties of the AML cells after ivosidenib treatment. Colony formation was assumed by the applicant to indicate differentiation into more mature leukocytes. In the patient samples shown, an increase in colony-forming units (CFU) was observed; as expected, cells not carrying mutated IDH1 (Pat. #7) did not react on ivosidenib. The applicant explained that the results for Patients #1 and #8 were not shown because their cells did not form colonies so the effects of ivosidenib could not be determined.

Ex vivo, treatment of primary IDH1 Mutant (R132H or R132C) AML Patient Samples with AG-120 for up to 7 days, but not WT, reduced 2-HG and induced a proliferative burst followed by myeloblast differentiation in IDH1 R132C primary human AML bone marrow samples. *Ex vivo*, treatment with AG-120 (0.5, 1 and 5 μM) inhibited the production of 2-HG and induced differentiation of IDH1 mutant (R132H or R132C) patient myeloblast cells.

Different *in vivo* pharmacology studies in a subcutaneous HT1080 xenograft BALB/c nude mouse model (chondrosarcoma with an endogenous IDH1 (R132C) mutation) confirmed the potency of ivosidenib in inhibiting 2-HG production in both plasma and tumour tissue with proof of exposure.

Two additional PK/PD studies were performed in mice bearing disseminated AML PDX tumour cells. In both models, dose-dependent inhibition of tumour 2-HG by ivosidenib in the spleen, with maximal 2-HG inhibition of ≥90%, was observed at both doses. 2-HG production returns to near baseline levels after 24 hours in each dose group, thus justifying the use of a twice-daily dosing protocol of AG-120 in the AML11655 model. AG-120 effectively inhibited 2-HG production (≥94.3% based on AUC0-12hr) in plasma, bone marrow, and spleen tissue in a human IDH1 (R132H) AML xenograft mouse model following BID oral gavage dosing of AG-120 at 50 or 150 mg/kg for 7 days.

In conclusion, ivosidenib is a highly potent suppressor of 2-HG production in human AML cells *in vivo,* and inhibition of 2-HG with ivosidenib in primary human AML cells promotes the induction of differentiation *in vivo*. However, considering the fact that leukaemia cells can spread outside the blood to other parts of the body, including the central nervous system (brain and spinal cord), the applicant was asked to justify the absence of AG-120 concentration in brain and discuss the clinical relevance in normal and pathologic conditions. From a clinical point of view, ivosidenib tumour concentrations of 299 ng/g were observed in mutant IDH1 R132H positive low grade glioma patients. Moreover,

according to the applicant, there is no experience with the use of ivosidenib in patients with active CNS leukaemia and CNS involvement in adult AML is rare with a reported frequency of ~2%. If so, intrathecal administration of cytotoxic agents could be considered to target the disease. The applicant proposed to add in Section 4.4 of the SmPC wording that there is no experience of the use of ivosidenib in patients with active CNS leukaemia).

Secondary pharmacodynamics

Ivosidenib was evaluated at a concentration of 10,000 nM (equivalent to 5,830 ng/mL) for its potential to inhibit binding and enzymatic activity in a panel of 80 receptors, ion channels, and enzymes. At the single concentration of 10,000 nM, ivosidenib did not exhibit significant inhibition (>50%) of any of the 80 targets tested. These data support that ivosidenib is a selective molecule with no significant off-target activity observed.

Safety pharmacology

In the *in vitro* automated patch clamp assay, ivosidenib demonstrated a weak inhibition against the rapid delayed rectifier current, IKr, (hERG). In the *in vitro* manual patch clamp assay, ivosidenib was also demonstrated to weakly inhibit the same IKr. Ivosidenib did not inhibit any other ion channel current at up to 30μM, the highest concentration tested. There is no safety margin with these inhibitions. Therefore, QTc prolongation was expected in humans. The applicant has provided two different study reports to assess the cardiovascular hERG current inhibition with automated patch clamp (AG120-N-009-R1 and AG120-N-005-R1). Results are different in the two studies (two-fold) with the same method. The applicant was asked to discuss the presence of two study reports and the discrepancy in these results and to give its final conclusion. All assays indicated a potential for hERG current inhibition, and hERG current inhibition was confirmed to occur both in *in vivo* non-clinical and clinical studies.

In the non GLP study, single oral gavage doses of ivosidenib at 15 mg/kg to male cynomolgus monkeys did not affect heart rate, blood pressure (systolic, diastolic, or mean arterial), pulse pressure, body temperature, ECG intervals, or ECG waveform morphology. Ivosidenib at 45 and 135 mg/kg were associated with prolonged QTc and QTcB. In the GLP 28-day study in monkeys, ventricular bigeminy (heart rhythm problem in which there are repeated rhythms heart beats, one long and one shorter) occurred in 1 high-dose male and 1 high-dose female (270 mg/kg/day) and reversibility was not assessed. Ventricular bigeminy did not occur in any other study. Possible or probable QTcB prolongation occurred in the 28-day and 3-month studies. No other effects on the heart rate or interval parameters were observed at any dose level.

QT prolongation in patient clinical trial: Adverse events within the SMQ (broad) Torsade de pointes/QT prolongation were reported in 49 subjects (27.4%) with R/R AML whose starting dose was 500 mg QD in Study AG120-C-001. The majority of events were assessed by the Investigator as treatment-related. Grade ≥3 AEs in the SMQ (broad) Torsade de pointes/QT prolongation were reported in 21 subjects (11.7%), which were assessed as treatment-related in 14 (7.8%).

In conclusion, regarding the non-clinical (*in vitro* and *in vivo*) data observed during safety pharmacology and toxicology studies, the risk for QT prolongation cannot be excluded in the clinical setting and adequate measures should be taken. Regarding the *in vivo* safety pharmacology, the assessment of the respiratory and central nervous systems showed according to the applicant no treatment-related clinical observations. However, no detailed clinical observations following dosing were presented in the overview or in the study reports. The applicant provided information on potential toxicity on these systems.

Pharmacodynamic drug interactions

The lack of any PDDI studies is acceptable.

3.2.2. Pharmacokinetics

Methods of analysis

The average correlation coefficient from nine standard curves was >0.9900. The analytical methods were adequately validated for quantitative determination of ivosidenib in the plasma of all animal species. Acceptable linearity, precision, accuracy and specificity of test items were observed over different concentration ranges.

Absorption

***In Vitro* Absorption**

Concerning the absorption, ivosidenib has been shown to be a substrate of P-gp, but not BCRP *in vitro*. Ivosidenib was absorbed following oral single dosing in rats, with Tmax of 4.0 or 12 hours postdose.

***In vivo* Single Dose Pharmacokinetics**

A comparison of the pharmacokinetics of three AG-120 oral dosage forms (Free form ivosidenib, ivosidenib+HPMCAS-M, ivosidenib+PVAP) was made in Male Sprague Dawley Rats: Ivosidenib PVAP formulation showed higher oral exposures compared to its free form or the ivosidenib HPMCAS formulation. The ivosidenib PVAP formulation was primarily used in the rat and, ivosidenib HPMCAS was used in the rabbit and monkey. Ivosidenib HPMCAS formulation provided acceptable ivosidenib oral exposures in monkeys after a single dose (free form, ivosidenib HPMCAS formulation). The ivosidenib HPMCAS formulation was used in Phase 1 clinical trials. The applicant was asked to justify the proportion of ivosidenib in the formulation in some of the animal PK studies as it differed from the commercial formulation.There was only one nonclinical study that used a drug load of ivosidenib that differed from the commercial formulation. All other nonclinical studies utilizing ivosidenib formulations, including all GLP *in vivo* toxicology studies, were conducted with formulations that had the same proportion of ivosidenib as the commercial form. The sponsor considers that the change did not have any non-clinical or pharmacokinetic implications in terms of the non-clinical safety programIn a 28-day repeat-dose toxicity study, exposure was higher with the ivosidenib PVAP formulation as compared to the free form.

Ivosidenib PK is characterised by rapid oral absorption; low total body plasma clearance; low to moderate volume of distribution; and moderate to long apparent terminal elimination half-life in rats, dogs, and monkeys after a single oral administration. Oral bioavailability of the free form was 39.5%, 25.9% and 53.8% in the rat, dog and monkey.

The PK of ivosidenib was also studied in monkeys following oral administration of coated and uncoated tablets. The coating and particle size distribution did not significantly affect ivosidenib oral PK in monkeys. PK from coated and uncoated formulations of ivosidenib tablets in monkeys was similar.

The harder tablet resulted in approximately 19% lower exposure in terms of dose-normalised Cmax and area under the concentration-versus-time curve from time 0 to 72 hours (AUC0-72hr). The oral bioavailability of the prototype tablet formulation (utilised in the first-in-human study [Clinical Study AG120-C-001] and subsequent clinical studies) was approximately 37.0% in monkeys. Plasma exposure to ivosidenib in fasted monkeys was similar to that in fed monkeys.

In vivo Repeat Dose Pharmacokinetics

Ivosidenib PVAP formulation was primarily used in the rat and, ivosidenib HPMCAS was used in the rabbit and monkey. The ivosidenib HPMCAS formulation was used in Phase 1 clinical trials.

Systemic exposure, as estimated by AUC0-12hr, AUC0-24hr and Cmax, increased less than in proportion to the increase in dose in the 7-Day (Twice Daily Dosing) oral gavage toxicity and toxicokinetic study of AG-120 in Sprague Dawley Rats. Systemic exposure in male and female rats given 2,000 mg/kg/day was similar on Day 0 but was lower in males than in females on Day 6 for the free form. In comparison, systemic exposure in male and female rats given 2,000 mg/kg/day was lower in males than in females on Day 0 and Day 6 for the PVAP formulation. The applicant was asked to discuss the lack of an *in vivo* 7-Day (Twice Daily Dosing) oral gavage tolerability study in Sprague Dawley Rats for the comparison of the HPMCAS with the free form and the PVAP formulation and to justify the choice of a 7-day duration study. In both the 28-day and 3-month repeat dose GLP studies, in addition to a vehicle group, an additional group of animals administered vehicle + excipient (PVAP in the rat or HPMCAS in the monkey) was included to further support the safety profile of the ivosidenib formulations. There was no dose proportionality in the non-clinical HPMCAS data and PK values submitted.

After a single dose oral administration in Male Sprague-Dawley Rats, the Free form, HPMCAS-M formulation and PVAP formulation have shown different Cmax (1,600±139; 6,820±2,860 and 30,500±4,330 ng/mL) and AUC (18,900±4,600, 95,100±31,900 and 402,000±69,200 hr•ng/mL). Ivosidenib PVAP formulation showed higher oral exposures compared to its free form or ivosidenib HPMCAS formulation in rats. Concerning the 7-Day (Twice Daily Dosing) Oral Gavage Tolerability Study of AG-120 in Sprague Dawley Rats, systemic exposure to ivosidenib PVAP formulation and ivosidenib free form was not similar on Day 0 (AUC of 171,000hr•ng/mL in Males for the free form in comparison with an AUC of 116,000 hr•ng/mL in Males for the PVAP formulation). The use of the PVAP formulation in toxicology studies in rats was justified by the safety profile established for PVAP based on the literature, and then in repeat-dose toxicity studies of 28-day and 3-month ivosidenib in rats, in which an additional group of animals was administered. The toxicity profile of ivosidenib in rats, independent of the PVAP excipient, was clearly established. The toxicity profile of HPMCAS was well characterised in the repeat-dose and reproductive/developmental toxicity studies (as reported in the literature). HPMCAS is a well-characterised excipient with an acceptable safety profile in humans and has been used as an excipient in several drugs approved through the EMA centralised procedure.

According to the applicant, the safety profile of ivosidenib is based on the animal exposure of ivosidenib rather than the excipient used in the formulation which is acceptable. Ivosidenib has an acceptable nonclinical safety profile to support a Marketing Authorisation Application for the treatment of patients with relapsed or refractory AML.

Similarly, in the rat embryo/foetal studies, exposure to ivosidenib was lower on Gestation Day (GD) 17 when compared to GD 6 at dose levels of 20, 100 and 500 mg/kg/day whereas exposure was similar on GD 6 and GD 17 at 1,000 mg/kg/day. There were no gender-related differences in the exposure on Day 0; however, females had higher exposure than males on Day 27 at all dose levels in a 28-Day (Twice Daily Dosing) Oral Gavage Toxicity and Toxicokinetic Study of AG-120 in Sprague Dawley Rats with a 14-Day Recovery Period. In the rat 28-day and 3-month repeat-dose toxicity studies (PVAP formulation), exposure to ivosidenib was lower on Day 27 and Day 90, respectively, when compared to Day 0 and exposure to ivosidenib was higher in females as compared to males on Day 27 and Day 90.`

In the 10-day rabbit tolerability study, plasma accumulation was noted at 30, 100, and 300 mg/kg on Day 9. In the rabbit embryo/foetal studies, there was an increase in plasma exposure at 30, 90, 100, 180 and 240 mg/kg/day on GD 20 as compared to GD 7.

In the monkey 28-day repeat-dose toxicity study, exposure to ivosidenib was lower on Day 27 at 30 and 90 mg/kg/day when compared to Day 0; in males at 270 mg/kg/day, exposure to ivosidenib was higher on Day 27 compared to Day 0. Exposure, as indicated by the mean AUC0-12 value, was greater in males than in females at each dose level on Days 0 and 27. In the 3-month study, exposure to ivosidenib was lower on Day 90 at 30 and 90 mg/kg/day when compared to Day 0; at 180 mg/kg/day, exposure to ivosidenib was higher on Day 90 compared to Day 0 in both sexes. There were no gender differences in exposure.

Distribution

[14C]Ivosidenib-derived radioactivity widely distributed into rat tissues following a single oral administration (high concentration in liver, white adipose tissue, brown adipose tissue, lacrimal glands, and adrenal gland). AG-120 distributions in brain and CSF were low. Considering the fact that leukaemia cells can spread outside the blood to other parts of the body, including the central nervous system (brain and spinal cord), the applicant was asked to justify the absence of AG-120 concentration in brain and discuss clinical relevance in normal and pathologic conditions. No retention, accumulation, or affinity were observed for any tissue and there was no affinity for tissues containing melanin or for any other tissue. AG-120 showed low RBC/plasma partitioning in human, monkey, dog, and rat blood. The plasma protein binding of ivosidenib was high in all species. Finally, it was shown that placental transfer of ivosidenib occurs in utero in both rats and rabbits. However, the applicant was asked to discuss the different absorption of the different formulations (Free form, HPMCAS, or PVAP) in link with the Cmax and consequently on the placental transfer.

Metabolism

In vitro ivosidenib had a low turnover rate in liver microsomes derived from rat, monkey and human. The metabolite profiles were similar in rat, dog, monkey, and human liver microsomal incubations: M1 through M4 were identified. No unique human metabolites were identified.

In the rat, ivosidenib and metabolites M1, M2 and M30 were detected in plasma whereas in the monkey two additional minor metabolites, M5 and M6, were identified alongside ivosidenib and metabolites M1 and M2. M1 in rats represents 4.8% and 7.1% of the parent compound at D0 and D6, respectively. In monkeys, M1, M2 and M6 represent 14%, 3.2%, 8% and 14%, 3.0%, 2% of the parent compound at D0 and D6, respectively.

Clinically, only [14C]ivosidenib was detected in plasma (92.4% of the total radioactivity) and there were no circulating metabolites. In urine, unchanged ivosidenib represented 8.82% of total dose, M1 2.74% of total dose, and the rest less than 1%. In faeces, unchanged ivosidenib represented 58.5% of total dose, M3 2.17%, M44 1.46%, and M31 1.06%, the rest represented less than 0.5% of total dose. In the reports, no information was provided on the pharmacological activity of metabolites (mostly M1). The applicant was asked to discuss the pharmacological activity of the different metabolites. Since no circulating metabolites were observed in human plasma, the sponsor did not characterise the pharmacological activity of metabolites and considers that this approach is scientifically justified.

Ivosidenib is mainly metabolised by CYP3A4 (minor CYP2B6 and CYP2C8).

Excretion

Faecal excretion was the major elimination route in rats, with 91.1% of the administered dose recovered in faeces and urinary excretion was a minor elimination route, with 7.17% of the administered dose recovered. Urinary excretion of ivosidenib in rats, dogs, and monkeys, and biliary excretion in rats, was negligible. No studies have been conducted on milk excretion or the passage in the sperm. Consequently, it is unknown whether ivosidenib and its metabolites are excreted in human milk. A risk to the breastfeeding child cannot be excluded. Moreover, women of childbearing potential should use effective contraception during treatment with ivosidenib and for at least one month after the last dose.

3.2.3. Toxicology

The applicant was asked to compare the two formulations studied in the study AG120-N-044-R1 with the ivosidenib HPMCAS formulation used in Phase 1 clinical trials, including the primary clinical study supporting the MAA, and is a component of the proposed formulation for registration and commercialisation. The formulations differ in the polymer used to manufacture the formulation.

Single dose toxicity

After single administration of ivosidenib free form in monkeys, gastrointestinal toxicity (soft faeces and emesis) was found at ≥ 100 mg/kg. 250 mg/kg (the highest dose tested) was the maximum tolerated dose.

Repeat-dose toxicity

The non-clinical treatment schedule based on the clinical schedule is acceptable as well as the species and the route of administration in these studies.

Liver cell hypertrophy was a prominent finding in rats and monkeys in the repeat-dose studies. The applicant suggested that this was related to induction of metabolic enzymes by ivosidenib. The applicant had to further substantiate this hypothesis and discuss whether enzyme induction could also explain the liver damage observed in some groups and identified by histopathology and by changes in serum chemistry parameters. The applicant agreed that histological correlates of enzyme induction were observed in addition to degeneration and necrosis.

The reason for the decreased RBC and Hb is not known. Obviously, this was not due to bone marrow suppression because haematopoiesis was increased in rats; no histological signs of bone marrow suppression were reported in monkeys. The fate of the red blood cells also is not known. No signs of haemolysis became obvious. Brown material in the spleen was reported; this might correspond to RBCs sequestered in the spleen after damage caused by ivosidenib. This possibility was discussed by the applicant and other explanations were sought. The applicant attributed the haematological changes mainly to gastrointestinal (GI) bleeding, resulting in anaemia and increased blood regeneration in the bone marrow. According to the applicant, the reason for GI bleeding was gastric erosions together with impaired coagulation. The observed brown pigment in the spleen could not be fully explained. It could indicate haemolysis. Increased bilirubin was observed only with high doses of ivosidenib; other markers for haemolysis such as LDH or haptoglobin were not measured in the toxicology studies.

In monkeys, signs of GI haemorrhage and correlating changes in haematology parameters were observed at higher doses.

The red material in faeces, indicative for GI haemorrhage, may not only come from gastric erosions but also from lower parts of the GI tract due to mucosal damage in the gut as observed at high doses in rats and monkeys.

GI bleeding and perhaps haemolysis obviously contributed to the observed haematological changes. The mechanisms underlying GI bleeding or haemolysis could not be elaborated. Reassuringly, the effects were observed in monkeys mostly at high doses which led to supratherapeutic exposure. Haematological findings are mentioned in the SmPC. This is considered appropriate.

In general, the applicant had to discuss whether inhibition of wild-type IDH1 could be responsible for at least some of the toxicological findings observed in the rat and monkey repeat-dose toxicology studies. The applicant referred to the new *invitro* study AG120-881-N-001 conducted in intact cells to determine the extracellular concentration of ivosidenib required to inhibit wt IDH1. From this study it turned out that plasma concentrations achieved in toxicology studies could well inhibit wt IDH1 so that some toxicological findings could be due to wt IDH1 inhibition.

Human therapeutic ivosidenib plasma levels most likely cannot inhibit wt IDH1 completely. The applicant argued 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 IDH1. This argument of the applicant is not fully agreed since the difference in plasma protein binding between humans and animals was low. Furthermore, 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.

Existing data do not allow a final conclusion whether side effects due to wt IDH1 inhibition can be expected in humans.

Potential inhibition of wt IDH inhibition and potential consequences thereof were discussed by the applicant as requested.

In rats

In the 7-day (twice daily dosing) oral gavage tolerability study in Sprague-Dawley Rats, the main target organs were the liver and the thyroid consistent with the longer-term studies. The objective was to compare the ivosidenib free form & PVAP formulation. There was a decrease in the Body weight gain in the PVAP formulation only. Gastrointestinal and haematologic toxicities were the main toxicities in the two formulations.

Ivosidenib administered as the PVAP formulation provided higher Day 6 exposures in both males and females at both dose levels assessed compared to the ivosidenib free form formulation. Ivosidenib PVAP formulation was chosen as the formulation for the 28-day GLP-compliant study in Sprague-Dawley rats. The applicant was asked to compare the two formulations studied in the study AG120-N-044-R1 with the ivosidenib HPMCAS formulation used in Phase 1 clinical trials, including the primary clinical study supporting the MAA, and is a component of the proposed formulation for registration and commercialisation.

Dose-limiting toxicity in the 28-day GLP rat study observed between 1.2 and 3.5-fold the human AUC0-10hr value was centrilobular hepatocellular degeneration and necrosis, with renal tubular necrosis and vacuolation; gastrointestinal and small intestinal atrophy; bone marrow hypocellularity, haemorrhage, and necrosis; lymphoid depletion and gastric ulcerations and/or erosions. None of these findings were observed in GLP -repeat dose monkey studies. The dosage of 100 mg/kg/day was very well tolerated. The dosage level of 500 mg/kg/day was tolerated and did not result in lethality. 2,000 mg/kg/day was considered the STD10.

Five males (4 toxicology and 1 toxicokinetic) and 9 females (5 toxicology and 4 toxicokinetic) in the 2,000 mg/kg/day group were found dead or euthanised *in extremis*. For 8 animals (tox group), death occurred between Days 2 and 6, and moderate, bridging, centrilobular hepatocellular degeneration/necrosis accompanied by haemorrhage was considered the cause of death. The cause of moribundity for the 2,000 mg/kg/day group male euthanised *in extremis* on Day 20 was determined to be mucosal atrophy of the intestines, erosion/ulceration of the glandular stomach and/or rectum, and lymphoid depletion and lymphoid necrosis of the lymphoid organs. Two early mortalities in the 2,000 mg/kg/day group were considered to be unrelated to test article administration. These deaths were attributed to gavage error (1 male found dead on Day 1) and pelvic inflammation (1 male found dead on Day 28).

In the 3-month GLP toxicology study in rats, target tissues and findings included liver findings consistent with hepatocellular CYP3A4 enzyme induction (ie, increase liver weights, hepatocellular hypertrophy), red blood cell parameter alterations and splenic extramedullary haematopoiesis and bone marrow increased haematopoiesis consistent with a red cell regenerative response. Findings observed in the 3-month rat study were consistent with those noted at tolerable doses in the 28-day study with the exception of the novel finding of a higher urine potassium fractional excretion that occurred at ≥0.3-fold the human AUC0-10hr value. No deaths were considered test article-related because of evidence of dosing trauma, aspiration, or lack of other test article-related mortalities at similar or higher dosage levels. In the toxicology groups, 1 vehicle control group female, 1 male and 1 female in the 20 mg/kg/day group, and 1 male and 1 female in the 500 mg/kg/day group were found dead or were euthanised *in extremis* prior to the primary necropsy at study Week 13. From the toxicokinetic groups, one 100 mg/kg/day group male was euthanised *in extremis* and one 500 mg/kg/day group female was found dead prior to the scheduled study Week 13 necropsy. None of the deaths were considered test article-related because of evidence of dosing trauma, aspiration, or lack of other test article-related mortalities at similar or higher dosage levels.

According to the applicant, ivosidenib was well tolerated at dosage levels of 20, 100, and 500 mg/kg/day and resulted in no test article-related deaths. At the end of the 4 week recovery period, all findings in the 100 and 500 mg/kg/day groups had partially or fully recovered.

In Monkeys

Twice daily oral (nasogastric) administration of ivosidenib free form to male cynomolgus monkeys at doses up to 200 mg/kg/day was well tolerated over a 7-day dosing period.

Ivosidenib PVAP formulation administered orally (nasogastric) BID (approximately 12 hours apart) to cynomolgus monkeys over a 7-day period was not tolerated at doses of ≥500 mg/kg/day. In addition, vehicle + PVAP excipient load equivalent to that administered to the 1,000 mg/kg/day group was not tolerated over a 7-day period (inappetence, soft faeces, thin body condition, reddened facial area, diarrhoea/watery diarrhoea, faeces containing red material, and emesis, all of which were associated with cumulative body weight losses. The control article (vehicle + PVAP load) was considered to be the cause of moribundity and early mortality in this study and complicated the interpretation of the ivosidenib-related effects. The excipient PVAP was excluded from use in subsequent monkey toxicology studies.

Ivosidenib HPMCAS formulation was not tolerated when administered orally (nasogastric) BID (approximately 12 hours apart) for 3 consecutive days to female cynomolgus monkeys at dosage levels of 500 and 1,000 mg/kg/day. Thus, the top dose chosen for the subsequent 28-day GLP study in cynomolgus monkeys was lower than 500 mg/kg/day.

In monkeys, the dosage level of 180 mg/kg/day (highest dosage tested in the 3-month study) was well tolerated over a 3-month dosing period and did not result in any test article-related moribundity or mortality (with significant exposure). At 500 mg/day, intermittent diarrhoea as well as liver findings and a test article-related QTcB prolongation was noted in individual animals. All findings were partially or fully reversible following a 28-day non dosing period. The findings observed in the 3-month study in cynomolgus monkeys were largely consistent with those noted at tolerable doses in the 28-day study (DLT of 270 mg/kg/day in the 28-day study was characterised by a general malaise, poor body condition, gastrointestinal clinical signs leading to emesis, and secondary aspiration). Three animals in the 3-month study were found dead or euthanised *in extremis* during the course of the study. These early deaths occurred in the vehicle control (Day 16), vehicle + HPMCAS (Day 84), and 90 mg/kg/day (Day 2) groups. The cause of death for these animals was attributed to mechanical trauma related to the dosing procedure.

In 28-day and 3-month GLP toxicology studies in monkeys, liver findings consistent with hepatocellular enzyme induction (ie, increase liver weights, hepatocellular hypertrophy) occurred at ≥0.2-fold the human AUC0-10hr value. In toxicology studies (Ref AG120-N-002-R1, AG120-N-058-R1, AG120-N-043-R1, AG120-N-007-R1, AG120-N-001-R1, AG120-N-059-R1), a large number of deaths occurred and was unsatisfactory justified or explained. The cause of death was justified by technical problems (mechanical trauma, gavage error) and not related to test-article according to the applicant. The applicant was requested to provide a summary table including all observed deaths during toxicity studies specifying the treatment date, the day of death, the comparison between animals and human exposures, the microscopic and macroscopic assessment and to strongly discuss the potential cause of death related.

The cause of death for animals was attributed to:

- Mechanical trauma related to the dosing procedure
- Liver degeneration
- Gastrointestinal changes
- Inflammatory disease

All these side effects are adequately monitored during clinical studies.

The excipient PVAP was excluded from use in subsequent monkey toxicology studies.

The ivosidenib HPMCAS formulation was used in Phase 1 clinical trials, including the primary clinical study supporting the MAA (Clinical Study AG120-C-001), and is a component of the proposed formulation for registration and commercialisation.

The pronounced gastrointestinal effects in monkeys (soft faeces, diarrhoea) may be related to cytotoxic effects of ivosidenib on intestinal epithelial cells, particularly because ivosidenib may reach high local concentrations in the gut. The applicant was asked to discuss this possibility as well as alternative explanations. The applicant pointed out that no histologic alterations of the gut mucosa were observed in the 13-wk monkey study so that the applicant considered the GI effects functional and not related to cytotoxicity. However, at higher doses (in the 7-day study AG120-N- 043), damage of the intestinal mucosa was observed. 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. No further insight could be provided whether the GI effects could be related to IDH1 wt inhibition in the gut mucosa; the applicant could not exclude this possibility.

Toxicokinetics

In nonclinical studies, all references to exposure margins compared to humans are based on an AUC0-24 hr value of 117,348 hr.ng/mL and a Cmax value of 6551 ng/mL, which are the mean values observed on Cycle 2 Day 1 in humans at the recommended human daily dose of 500 mg/day in Study AG120-C-001.

With the exception of the single-dose monkey study, all toxicology studies were conducted with a twice daily (BID) dosing regimen. A BID dosing regimen was chosen for the 3-month toxicology studies in rats and monkeys, as well as the embryo/foetal development studies in rats and rabbits, to better mimic the once daily ivosidenib clinical PK profile that exhibits sustained exposure while minimizing the peak/trough ratio. Because of the BID dosing regimen, AUC values for the toxicology studies are reported as AUC0-12hr values. Comparison of toxicology study exposures to the human exposure were done by multiplying the relevant toxicology study AUC0-12hr value by 2 to calculate the associated AUC0-24hr value, and then dividing the product by the human AUC0-24hr value (117,348 hr•ng/mL).

Genotoxicity

Ivosidenib free form was concluded to be negative in the non-GLP bacterial reverse mutation assay, in the GLP bacterial reverse mutation assay, and for the induction of micronuclei in HPBLs in the presence and absence of the exogenous metabolic activation system (GLP). The administration of ivosidenib PVAP formulation at doses up to and including 2,000 mg/kg/day was concluded to be negative in the micronucleus assay. The applicant has provided exposition data on rodent bone marrow in the *in vivo* micronucleus assay in male Sprague-Dawley rats. However, in order to have a comparison with human data, the applicant was asked to prove that the dose formulation used in clinic (HPMCAS) would not have a different impact in comparison with the PVAP dose formulation used in this *In Vivo* Micronucleus Assay in rats. HPMCAS is considered safe from a nonclinical toxicological perspective based on published literature. Moreover, HPMCAS has been used as an excipient in several medicinal products approved via the Centralised Procedure at the European Medicines Agency (EMA).

Carcinogenicity

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

Reproductive and developmental toxicity

Fertility and pre-post-natal toxicity studies were not conducted, in line with recommendations of the ICH S9 guideline. Effects on male and female reproductive organs were observed in the 28-day rat toxicity study. In males, a decrease in prostate weight was noted at ≥500 mg/kg/day. In females, estrous cycle changes with uterine (atrophy) and ovarian (decreased number of corpora lutea) findings were observed at 2000 mg/kg/day as well as a decrease in the weight of uterus at ≥500 mg/kg/day. These changes were reversible. In males euthanised prematurely at 2000 mg/kg/day, testicular degeneration was reported. At the dose of 2000 mg/kg/day, exposure ratios for males and females were 1.2 and 1.7, respectively. Adverse findings on the histology of the reproductive organs were observed neither in the 3-month rat toxicity study at up to 500 mg/kg/day (0.8-fold human exposure), nor in 28-day and 3-month monkey studies at up to 270 mg/kg/day and 180 mg/kg/day, respectively (1.9 to 2.3-fold human exposure). The clinical relevance of uterine atrophy and testicular degeneration observed in rats is not known.

Embryo-foetal development studies were performed in rats and rabbits. In rats, a decrease in foetal weight and subsequent skeletal variations (delayed ossification) were observed at the non-maternotoxic high dose level of 500 mg/kg/day. In rabbits, the high dose level of 180 mg/kg/day

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. This maternal toxicity may have contributed to the decrease in foetal weights, visceral variations (small spleen), and skeletal variations (delayed ossification) at the same dose level. Increased mean litter data for early and late resorptions, viable foetuses, and post-implantation loss were reported at the high dose level and attributed to a single totally resorbed litter (female #1902) in this group. The applicant was requested to submit the mean group litter data for these parameters, including and excluding female #1902, as well as a comparison to historical control data. A justification for excluding female #1902 from calculations of mean litter data should also be provided. Any treatment-related effect on intra-uterine survival should then be discussed.

The applicant provided tables summarising foetal data after exclusion of female #1902. It showed that the %post-implantation loss in the high dose group was almost twice that of the concurrent control group (11.6% vs. 6.0%) and was also outside of the historical control range (11.6% vs. 1.26-10.15%). The number of viable foetuses was also outside of the historical control range (88.4% vs. 89.85-98.74%). The %late resorptions was above that of concurrent controls (4.7% vs. 0.5%); it lied within the historical control range (0.0-5.51%) but at the higher end (75th quartile of historical control data for this parameter is 1.53%). Taking all these data into account, a treatment-related increase in the %postimplantation loss at the high dose level of 180 mg/kg/day cannot be excluded. This effect should be mentioned in the SmPC 5.3**.**

Prenatal and postnatal development, including maternal function

Since ivosidenib is intended for the treatment of patients with R/R AML, studies of pre- and postnatal toxicity and maternal function were not conducted and are not warranted (ICH S9; (FDA, 2010)).

Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

No dedicated toxicology studies in juvenile animals have been conducted, and none are warranted. Ivosidenib is subject to an approved Paediatric Plan and no studies in juvenile animals were considered necessary (EMA/PDCO/302015/2018).

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.

No antigenicity, immunotoxicity, dependence or metabolites studies were conducted.

Studies on impurities

Studies on the mutagenic potential of impurities are out of scope in line with the ICH S9 guideline.

Phototoxicity

The UV/visible spectrum of the drug substance in methanol has two absorption bands with maxima at 245 nm and 305 nm. Moreover, no affinity for tissues containing melanin or for any other tissue was observed in distribution studies. Ivosidenib free form did not demonstrate phototoxic potential in the *in vitro* neutral red uptake phototoxicity assay in BALB/c 3T3 mouse fibroblasts, with PIF < 5, MPE < 0.15, and the UVR% survival > 80%. Some properties of the clinical formulation that could influence the potential phototoxic response cannot be evaluated using the 3T3 NRU-PT alone. Therefore, confirmation of the overall negative result in an evaluation using the clinical formulation and/or

monitoring during clinical trials can still be warranted. The applicant was asked to discuss the phototoxic potential of the HPMCAS formulation. The presence of HPMCAS with ivosidenib in a formulation does not pose a potential for phototoxicity.

Excipient Study

HPMCAS was chosen for GLP-compliant studies in cynomolgus monkey because it was well tolerated and was used in Phase 1 clinical trials. Commercially, the ivosidenib drug substance is the free form and the drug product intermediate is a composition of ivosidenib drug substance and HPMCAS, M grade (HPMCAS-M). HPMCAS-M is an excipient described in a third country pharmacopoeia (EMEA/CHMP/QWP/396951/2006) and is a commonly used polymer with a well-established safety profile. Twice daily (approximately 12 hours apart) oral (nasogastric) administration of HPMC-as or HPMC-p for 7 days to cynomolgus monkeys was well tolerated at a dose level of 1000 mg/kg/day.

3.2.4. Ecotoxicity/environmental risk assessment

The logKow value of ivosidenib is below 4.5 (ie, log10Pow values of 3.2, 3.2 and 3.1 at pH 5, pH 7 and pH 9). Consequently, this substance cannot be identified as a persistent, bioaccumulative and toxic (PBT) substance. The Phase I PECsw of Ivosidenib (0.0055 µg/L) does not exceed the action limit of 0.01µg/L, and no other environmental concerns are apparent. The refined Fpen has been calculated by submitting European disease prevalence data for the sought indication. Using a maximum conservative incidence of 20% for IDH1 mutations in AML gives an overall prevalence/ revised Fpen of 2.2 x 10-5 (=prevalence of 0.22 in 10,000 people). The PECSW value calculated using the refined Fpen value based on prevalence of the IDH1 mutation in AML in the total EU population is below the action limit of 0.01µg/L so a Phase II environmental fate and effects analysis is not required.

Therefore, it is concluded that the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients.

3.2.5. Discussion on non-clinical aspects

The nonclinical pharmacology programme included *in vitro*, *ex vivo* and *in vivo* studies designed to develop a model of isocitrate dehydrogenase (IDH) mutant-induced tumourigenesis and to characterise the potency of ivosidenib and its ability to inhibit the target mutated IDH1 and reduce concentrations of 2-HG.

From the applicant's studies, it also became obvious that ivosidenib not only inhibits the enzymatic action of mutated IDH1, ie, formation of 2-HG from α-ketoglutarate, but also the wild-type (wt) enzyme. IDH1 wt has a different enzymatic action than the mutated form, catalysing the conversion of isocitrate to α-ketoglutarate. IDH1 wt inhibition by ivosidenib was time-dependent, the IC50 value decreased over several hours. Hence, it can be expected that wt IDH1 will also be inhibited by ivosidenib when the latter is administered chronically. In contrast to mutated IDH1, which is restricted to tumour cells, wt IDH1 is found in all cells and tissues so that inhibition of wt IDH1 could give rise to systemic toxicological effects. The aspects were not sufficiently discussed by the applicant.

In conclusion, the translation of some non-clinical findings into the corresponding clinical scenario are not appropriate regarding the Xenograft models. In regards to IDH1 inhibition leading to undesired effects, IDH1 wild-type inhibition in the clinical setting cannot be ruled out at the recommended dose level.

Regarding the fact that a conditional MA as well as a last line of treatment could be decided and from a non-clinical point of view, some further non clinical studies should be considered:

- Pursue the development of an AML IDH 1 mutant PDX model in immunodeficient mice for the mutant IDH1 alleles R132S, R132G and R132L.
- Identify a biomarker from available nonclinical AML models, with a possible clinical relevance

If a positive B/R is considered, and if all CMA requirements are met, the applicant should commit to providing additional non-clinical testing to enhance the proof of concept.

Agios agreed to post authorisation measures, classified as recommendations by the Committee [REC], to enhance the proof of concept through further nonclinical studies. Agios will address and implement the recommendations identified by the CHMP as tabulated in the formal Letter of Recommendations.

Table 2. Post-Authorisation Measures - Recommendations by the Committee

Description	Recommended Within Procedure Number
Pursue the development of an AML IDH1 mutant PDX model in immunodeficient mice for the mutant IDH1 alleles R132S, R132G, and R132L	EMEA/H/C/005056/0000
Use known mutant IDH1 AML PDX nonclinical models to validate and test hypothesis driven biomarker candidates identified from clinical data	EMEA/H/C/005056/0000

Agios remains committed to pursue the development of an AML IDH1 mutant PDX model in immunodeficient mice for the mutant IDH1 alleles R132S, R132G, and R132L, despite the low frequency of the alleles within the patient population and our previous lack of success transforming mutant IDH1 alleles of higher frequency into PDX models.

Agios acknowledges the Committee's recommendation to identify a biomarker from available nonclinical AML models, with a possible clinical relevance. Agios' nonclinical efforts to date have not yielded a clinically relevant biomarker for efficacy. Inhibition of 2-HG production has been demonstrated in both the nonclinical and clinical setting to represent target engagement; however, neither the baseline level of 2-HG, nor the degree of suppression following treatment with ivosidenib, correlated with clinical response (AG120-C-001 – Translational-Biomarker (Version 2.0)).

Agios further recognises that a single nonclinical model may not accurately reflect the clonal heterogeneity of R/R AML, and thereby lowers the possibility of successful translation of a biomarker from the nonclinical to clinical setting. Given the limitations of nonclinical models to appropriately replicate the molecular diversity and heterogeneity of AML, emerging data from the ivosidenib clinical development programme are considered the most relevant to identify specific, sensitive and predictive biomarkers that may correlate with clinical outcomes. Further research in the ongoing Phase 3 studies AG120-C-009 (AGILE) and HOVON 150 / AMLSG 29-18 is intended to identify and characterise correlative biomarkers based on analysis of genetic, epigenetic, and global gene expression profiles in bone marrow and peripheral blood. Agios, therefore, proposes to use known mutant IDH1 AML PDX nonclinical models to validate and test hypothesis driven biomarker candidates identified from clinical data.

Agios considers this approach appropriate to investigate clinically relevant biomarkers in a nonclinical setting as a mechanism to provide meaningful data to further understand the relationship between molecular profiles and clinical outcomes for ivosidenib in R/R AML.

In mice carrying human AML cells as xenograft leukaemia, survival time was markedly shortened with ivosidenib treatment compared to vehicle control. Hence, ivosidenib obviously not always leads to differentiation and decreased proliferation in AML cells. Also the opposite may be true. To date, the actual response of a cell population to ivosidenib cannot be predicted.

The proof of concept has not been entirely demonstrated in non-clinical pharmacology for the treatment of patients with an IDH1 mutation in R/R AML. Some clarifications on the different variations of IDH1 gene (R132S, R132G, R132L and R132E) that have not been studied in *in vivo* non-clinical pharmacodynamic models and the clinical relevance of the absence of these data still should be provided.

Ivosidenib PK is characterised by rapid oral absorption; low total body plasma clearance; low to moderate volume of distribution; and moderate to long apparent terminal elimination half-life in rats, dogs, and monkeys after a single oral administration. Oral bioavailability of the free form was 39.5%, 25.9% and 53.8% in the rat, dog and monkey. According to the applicant, nonclinical studies were conducted using ivosidenib free form drug substance and ivosidenib formulations. As a result of the poor bioavailability of ivosidenib free form, alternative formulations were developed to improve bioavailability. One ivosidenib formulation was primarily administered in the rat, and another was administered in the rabbit and monkey. One ivosidenib formulation was used in Phase 1 clinical trials, including the primary clinical study supporting the MAA, and is a component of the proposed formulation for registration and commercialisation which is acceptable **(resolved issue)**.

The safety profile of ivosidenib has been well characterised in rats and monkeys through the conduct of single- and repeat-dose toxicity studies of up to 3-months in duration, toxicokinetic, genotoxicity, embryo foetal development, impurities, excipient and phototoxicity studies. The justification and the impact of the formulation used is now clear **(resolved issue).**

According to the pre-clinical data and consistent with the pharmacologic activity (potent, selective, orally active small molecule inhibitor of mutated isocitrate dehydrogenase-1), primary target organ findings included haematologic system, spleen, liver, uterus, kidney and gastrointestinal system in one or both species.

These treatment-related findings occurred at levels lower than or comparable to clinical exposures and were reversible or partially reversible during recovery periods of 14-days or 4-weeks. However, a large number of deaths occurred and was unsatisfactory justified or explained. The causes of death were justified by technical problems (mechanical trauma, gavage error) and not related to test-article according to the applicant.

Liver cell hypertrophy, which was consistently observed in the repeat-dose toxicology studies, may be related to induction of metabolic enzymes by ivosidenib as suggested by the applicant. The applicant agreed that histological correlates of enzyme induction were observed in addition to degeneration and necrosis. The issue was resolved with SmPC changes.

The reason for the decreased RBC and Hb is not known. Obviously, this was not due to bone marrow suppression because haematopoiesis was increased in rats; no histological signs of bone marrow suppression were reported in monkeys. The fate of the red blood cells also is not known. No signs of haemolysis became obvious. Brown material in the spleen was reported; this might correspond to RBCs sequestered in the spleen after damage caused by ivosidenib. GI bleeding and perhaps haemolysis obviously contributed to the observed haematological changes. The mechanisms underlying GI bleeding or haemolysis could not be elaborated. Reassuringly, the effects were observed in monkeys mostly at high doses which led to supratherapeutic exposure. Haematological findings are mentioned in the SmPC. This is considered appropriate.

The applicant pointed out that no histologic alterations of the gut mucosa were observed in the 13-wk monkey study so that the applicant considered the GI effects functional and not related to cytotoxicity. However, at higher doses (in the 7-day study AG120-N- 043), damage of the intestinal mucosa was observed. 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. No further

insight could be provided whether the GI effects could be related to IDH1 wt inhibition in the gut mucosa; the applicant could not exclude this possibility.

However, the adverse events of ivosidenib seem to be predictable and manageable.

No fertility studies have been conducted with ivosidenib. Embryo-foetal studies in animals have demonstrated that ivosidenib has the potential to cause embryo-foetal lethality.

Regarding the non-clinical data observed in safety pharmacology and toxicology studies (weak inhibition against hERG in vitro and prolonged QTc and QTcB in monkeys), the risk for QT prolongation cannot be excluded in clinic. However, Electrocardiogram QT prolonged is considered an important identified risk of ivosidenib.

Ivosidenib is considered a non-phototoxic compound.

Ivosidenib is not mutagenic or clastogenic based on non-clinical *in vitro* and *in vivo* studies. Carcinogenicity studies have not been conducted with ivosidenib.

3.2.6. Conclusion on non-clinical aspects

From a non-clinical point of view, there is no major objection. However, in link with the efficacy in the clinical setting, some uncertainties remain on the pharmacological proof of concept of ivosidenib.

Indeed, a positive B/R is not considered, and all CMA requirements are not met. Consequently, the applicant should commit to providing additional non-clinical testing to enhance the proof of concept:

- To pursue the development of an AML IDH1 mutant PDX model in immunodeficient mice for the mutant IDH1 alleles R132S, R132G, and R132L
- To identify and characterise correlative biomarkers based on analysis of genetic, epigenetic, and global gene expression profiles in bone marrow and peripheral blood using known mutant IDH1 AML PDX nonclinical models to validate and test hypothesis driven biomarker candidates identified from clinical data.

3.3. Clinical aspects

3.3.1. Tabular overview of clinical studies

Table 3. Tabular Listing of All Clinical Studies

Type of study	Protocol Number and Study Title	Countries Involved: No of Sites & Subjects
Bioavailability, food effect	AG120-C-004: Phase 1, open-label, randomized, two-period crossover study to evaluate the effect of food on AG-120 PK following single oral dose administration to healthy subjects	United States: 1 site; N=36
PK, absorption, metabolism, excretion (AME)	AG120-C-003: Phase 1, open-label study to investigate the absorption, metabolism and excretion of [^{14}C]-AG-120 following single oral dose administration in healthy male subjects	United States: 1 site; N=8

PK, Japanese vs Caucasian subjects	AG120-C-006: Phase 1, single-dose, open-label trial to evaluate the PK and safety of AG-120 in healthy male Japanese subjects relative to healthy male caucasian subjects	United States: 1 site; N=60
PK, hepatic impairment	AG120-C-012: Phase 1, open-label, single-dose study to evaluate the PK, safety and tolerability of AG-120 in subjects with mild or moderate hepatic impairment or normal hepatic function	United States: 2 sites; N=33
Drug-drug Interaction, itraconazole	AG120-C-007: Open-label, 2-period, fixed-sequence study to determine the effect of multiple oral doses of itraconazole on the single-dose PK of AG-120 in healthy adult subjects	United States: 1 site; N=22
Pivotal Study Efficacy & safety	**AG120-C-001: Phase 1, multicenter, open-label, dose-escalation and expansion, safety, PK, PD, and clinical activity study of orally administered AG-120 in subjects with advanced hematologic malignancies with an IDH1 mutation**	**United States: 20 sites; N=223 France: 2 sites; N=35**
Efficacy & safety	AG120-C-002: Phase 1, multicenter, open-label, dose-escalation and expansion, safety, PK, PD, and clinical activity study of orally administered AG-120 in subjects with advanced solid tumors, including glioma, with an IDH1 mutation	United States: 12 sites; N=159 France: 1 site; N=15
Efficacy & safety	AG120-221-C-001: Phase 1, multicenter, open-label, safety study of AG-120 or AG-221 in combination with induction therapy and consolidation therapy in patients with newly diagnosed AML with an IDH1 and/or IDH2 mutation	United States: 11 sites; N=45 Netherlands: 1 site; N=2
Efficacy & safety	AG-221-AML-005: Phase 1b/2, open-label, randomized study of 2 combinations of IDH mutant targeted therapies plus azacitidine: oral AG-120 plus sc azacitidine and oral AG-221 plus sc azacitidine in subjects with newly diagnosed AML harboring an IDH1 or an IDH2 mutation, respectively, who are not candidates to receive intensive induction chemotherapy	United States: 8 sites; N=15 France: 2 sites; N=2 Australia: 1 site; N=1 Canada: 1 site; N=2 Germany: 1 site; N=0 Italy: 1 site; N=1 South Korea: 1 site; N=1 Spain: 1 site; N=1

3.3.2. Pharmacokinetics

Absorption

Absolute bioavailability for ivosidenib was not assessed. Ivosidenib film-coated tablets demonstrated rapid absorption (median T_{max} of 3 hours). Inferring from the AME study AG120-C-003 and the following PK study AG120-C-004, bioavailability of the coated, non-debossed 250 mg tablet appears to be greater than 58.8%. In any case, bioavailability has not been proven to be equal to or greater than 85%.

The relative bioavailability of the different tablet presentations was not assessed, as the minor change (introduction of film coating) was bridged by *in vitro* comparative dissolution methods. Only study AG120-C-001 and AG120-C-002 used a non-coated tablet, the other studies used the coated tablets. In AG120-C-001, after 500 mg single dose, average AUC_{0-72h} was at 147226 h•ng/mL, and average

C_{max} was at 4481 ng/mL. In AG120-C-004, after 500 mg single dose, average AUC_{0-72h} was at 81898 and average 112490 h•ng/mL, and C_{max} was at 2374 and 3657 ng/mL. Both are in ranges consistent with AG120-C-004.

Study AG120-C-004 showed an effect of food on AG-120 exposure, with an approximate 2-fold increase in Cmax, and an approximately 25% increase in AUC, following 500 mg AG-120 administration in the fed compared to the fasted state.

Distribution

Plasma protein binding of ivosidenib ranged from 91.6% to 95.8% over the concentration range of 0.2 to 10 microM and distribution into red blood cells was low.

Partitioning of ivosidenib between red blood cells (RBCs) and plasma was determined in human blood. Red blood cell distribution of ivosidenib was low (KRBC/PL <1) in human blood.

The population PK (2-compartment) model suggests an apparent volume of the central compartment of 234 L and an apparent volume of the peripheral compartment of 151 L. This is consistent with findings in clinical studies, with average Vds between 216 L and 545 L.

Elimination

Mean terminal half-life for ivosidenib after single doses of 250 to 1,000 mg in healthy subjects (AG120-C-003, AG120-C-004, AG120-C-006 and AG120-C-007) ranged from approximately 41 to 77 hours. In subjects with advanced haematologic malignancies (AG120-C-001), mean t½ was generally higher than observed in healthy subjects and ranged from approximately 72 to 138 hours following single doses of 100 to 1,200 mg ivosidenib. Steady-state appears to be achieved in subjects with advanced haematologic malignancies and solid tumours within 14 days.

CLss/F was assessed in AG120-C-001 and generally increased with increasing dose levels after multiple doses and ranged from 2.68 to 6.09 L/h across the 100 mg BID and 300 to 1,200 mg QD dose range. Based on population PK modelling of data from Study AG120-C-001, the apparent clearance of ivosidenib was estimated to be 1.63 L/h after a single dose of 500 mg, and 5.39 L/h after multiple dosing at 500 mg QD.

Excretion

In the ADME study AG120-C-003, faecal excretion appeared to be the predominant route of elimination of the administered radioactive dose with an observed mean recovery of total radioactivity in urine and faeces of 16.9% and 77.4%, respectively, through the last collection interval (360 hours [15 days] post-dose). Unchanged [14C]-Ivosidenib on average accounted for approximately 8.82% and 58.5%, or an extrapolated 9.92% and 67.4%, of the total recovered dose in urine and faeces, respectively.

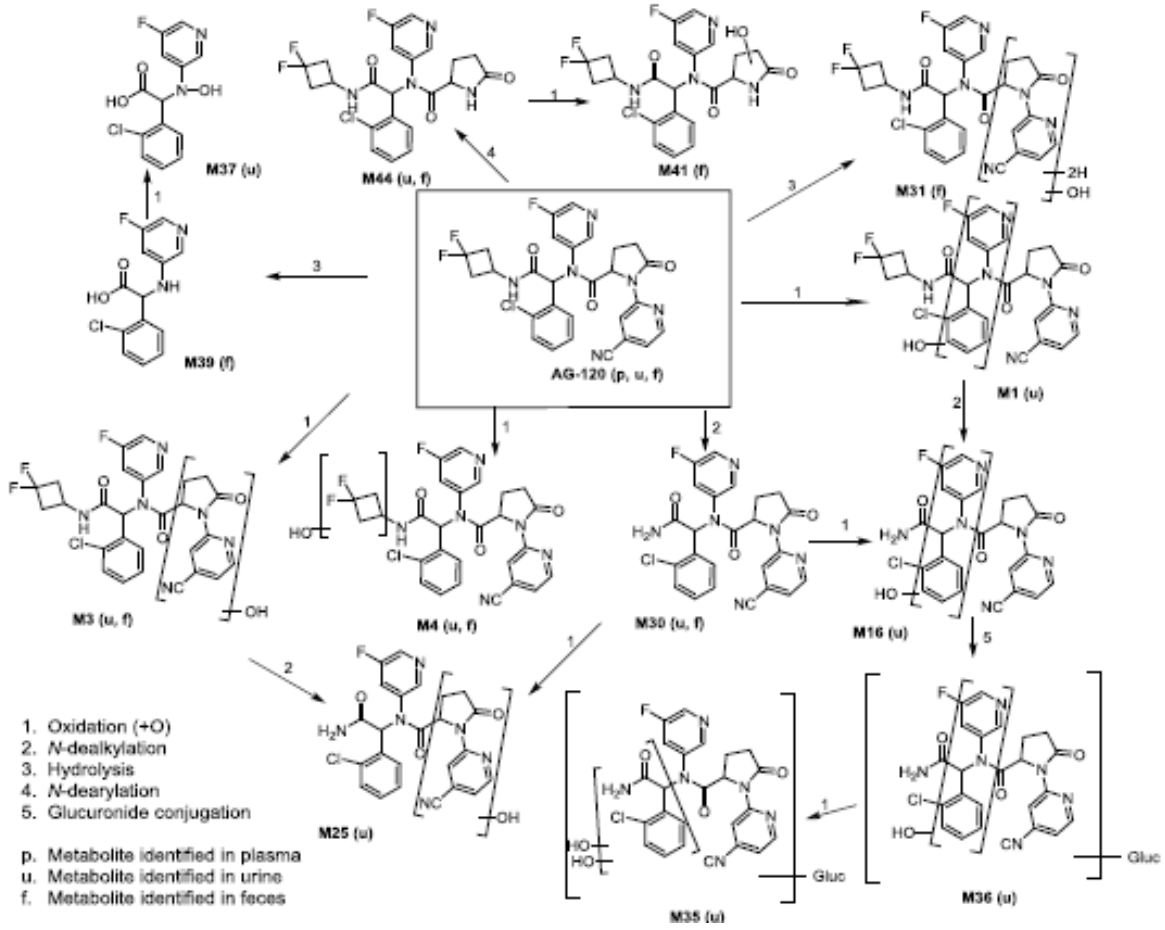
In urine, unchanged ivosidenib represented 8.82% of total dose, M1 2.74% of total dose, and the rest less than 1%. The arithmetic mean renal clearance (CLR) of ivosidenib was 0.537 L/hr in healthy subjects, which is less than the typical glomerular filtration rate of approximately 7.5 L/hr.

In faeces, unchanged ivosidenib represented 58.5% of total dose, M3 2.17%, M44 1.46%, and M31 1.06%, and the rest represented less than 0.5% of total dose.

Metabolism

Ivosidenib was the predominant circulating component (approximately 92.4% of plasma radioactivity). Ivosidenib is slowly metabolised in humans. Elimination of absorbed ivosidenib occurred largely by

oxidative metabolism with minor contributions by N-dealkylation and hydrolytic metabolism. *In vitro* studies with human liver microsomes using CYP selective chemical inhibitors and recombinant human CYP enzymes suggested that ivosidenib is mainly metabolised by CYP3A4, with minor contributions from CYP2B6 and CYP2C8. The primary metabolic processes for [^{14}C]ivosidenib were oxidations at the chlorobenzyl-N-5-fluoropyridinyl (M1), cyanopyridinyl-pyrrolidone (M3), and difluorocyclobutyl (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.



Interconversion

There is no risk of interconversion.

PK of metabolites

As they could not be measured in plasma, PK of metabolites was not discussed by the applicant.

Consequences of possible genetic polymorphism between poor and non-poor CYPD6 metabolisers was provided in study AG102-C-003. The difference between CYP2D6 non-poor and poor metabolisers appeared negligible, which is consistent since other CYPs (CYP3A4, CYP2B6 and CYP2C8) are predominant in the degradation of ivosidenib.

Dose proportionality and time dependency

Dose proportionality

Ivosidenib exposure increases with increasing dose, however the increases were less than dose proportional after both single and multiple dosing. In Study AG120-C-006 following single doses of 250, 500 and 1,000 mg in healthy subjects, AUC0–∞ increased approximately 2-fold, with a 4-fold increase in dose. In Study AG120-C-001, AUC0-tau and Cmax after multiple dosing (C2D1) increased approximately 8-fold and 4-fold, respectively, for a 12-fold increase in dose (100 mg BID to 1,200 mg QD). Population PK modelling of the data from AG120-C-001 confirmed the dose-nonlinearity and noted that a doubling of dose translates approximately to a 40% increase in ivosidenib exposure across the dose range.

Time dependency

In the population PK analysis in subjects with advanced haematologic malignancies, ivosidenib CLss/F was estimated to be 5.39 L/hr at 500 mg QD and an approximately 3-fold increase in CL/F was observed from single dose to steady-state. These results suggest that autoinduction may play a role in the time-dependent increase of CL/F.

The estimated PK parameters for ivosidenib in subjects with haematologic malignancies exhibited time-dependency. In the population PK model of data from Study AG120-C-001, the apparent clearance of ivosidenib was estimated to be 1.63 L/hr on the first day and 5.39 L/hr at steady-state. The change was attributed to a 2-fold decrease in relative bioavailability and a 1.66-fold increase in clearance. The change was modelled as occurring at 96 hours.

Ivosidenib is mainly metabolised by CYP3A4 and is a CYP3A4 inducer. These data suggest that it is plausible that autoinduction of ivosidenib metabolism may play a role in the observed increase in apparent clearance. However, the magnitude of autoinduction appears to be moderate and approximately 1.9-fold accumulation has been achieved at steady-state on Day 14.

Intra and inter individual variability

No biopharmaceutic clinical pharmacology study with a multiple-dose design or replicated crossover design was conducted in healthy subjects and no subject received the same treatment more than once. Therefore, the intra-subject variability in healthy subjects could not be determined. The inter-subject variability of ivosidenib was classified as moderate, with CVs for AUC0-t and Cmax of 31.6% and 21.3%, respectively, in healthy subjects treated with a single 500 mg oral dose under fasting conditions (CSR AG120-C-004). This is consistent with other studies.

PK in target population

Ivosidenib PK profiles are likely comparable among subjects with R/R AML who did not take strong or moderate CYP3A4 inhibitors, and subjects with cholangiocarcinoma/chondrosarcoma.

Special populations

Impaired renal function

In the population PK analysis, no correlations of renal function indicators (CrCl) and renal impairment category to clearance was observed, although conclusions should be interpreted with caution because there were only 2 subjects with severe renal impairment (CrCl below 30 mL/min).

Impaired hepatic function

In clinical Study AG120-C-012, mild hepatic insufficiency resulted in an 0.8 fold decrease in AUC and 0.9 fold in Cmax; moderate hepatic insufficiency resulted in 0.7 fold decrease in AUC and 0.6 fold decrease in Cmax.

In the population PK analysis, no correlation of hepatic function indicators (ALT, AST, bilirubin) and hepatic impairment category (based on NCI-ODWG criteria) to clearance was observed, although conclusions should be interpreted with caution because of the small number of subjects with moderate or severe hepatic impairment.

Please see discussion in the efficacy and safety sections if those changes can be considered clinically significant or not.

There is not enough data for conclusion on effect of severe hepatic insufficiency.

Race: In Study AG120-C-006, the average exposure to AG-120, as measured by Cmax, AUC0-t, and AUC0-inf, was lower overall by 17%, 31%, and 30%, respectively, in the 30 Japanese subjects compared with the 30 Caucasian subjects after a single dose of AG-120 at 250 mg, 500 mg, and 1000 mg. Please see discussion in the efficacy and safety sections if those changes can be considered clinically significant or not. Population PK modelling did not show an effect of race as a covariate.

Population PK study did not detect an effect of gender, weight or age as covariate. No PK data are available on ivosidenib in the paediatric population.

Exposure relevant for safety evaluation

Exposition data for all subjects with R/RAML from study AG120-C-001 after multiple dosing is the most relevant for safety exposure: geometric mean of AUC0-24 was 119104 ng•h/mL (geometric CV 49.3%), geometric mean of Cmax was 6705 ng/mL (geometric CV 42.6%).

Interaction

CYPs interactions as victim and perpetrator

Ivosidenib is substrate and induces CYP3A4. Warning and caution of use has been added to SmPC.

CYPs interaction: induction

Ivosidenib induction potential for CYP3A4, 2B6, and CYP2C8, 2C9 and 2C19 cannot be excluded based on *in vitro* data. Ivosidenib has been contraindicated for concomitant use with strong CYP3A4 inducers or dabigatran and acceptable warning and caution of use has been added to the appropriate SmPC section. The applicant plans a clinical induction study to validate induction results from the submitted PBPK model and to remove the CYP3A4 contraindication from the SmPC using these data.

Transporter mediated interactions

Ivosidenib is substrate of P-gp and not BCRP based *in vitro* data. It inhibits P-gp, OAT3 and OATP1B1. Acceptable warnings and caution of use have been added in the SmPC.

Clinical DDI study

As clinical DDI study was conducted with 22 healthy volunteers in a fixed sequential design determine the effect of multiple oral doses of itraconazole (strong CYP3A4 and P-gp inhibitor) on the single oral dose of 250 mg ivosidenib in healthy adult subjects. The Company has conducted an assessment to

quantify the magnitude of DDIs between ivosidenib and strong/moderate CYP3A4 inhibitors after repeated administration of ivosidenib and CYP3A4 inhibitors using Population PK analysis and PBPK modelling. As a worst-case scenario, a strong inhibitor modelled to not have elimination through inducible enzymes or transporters was predicted to produce a 223% increase in ivosidenib AUC at steady state. No additional data has been provided to support high impact application, such as waiving a clinical study. The predictive performance of the PBPK model is considered insufficient. Therefore, the applicant was asked to remove the PBPK reference from SmPC.

PD interactions

Ivosidenib can lead to prolonged QT interval; therefore, caution should be exercised when co-administered with other drugs inducing bradycardia (beta blockers, class 3 antiarrhythmic agent) or hypokalemia.

3.3.3. Pharmacodynamics

Ivosidenib is a potent, selective, orally active small molecule inhibitor of mutated isocitrate dehydrogenase. No significant off target activity was observed. Direct inhibition of mutated IDH1 suppresses production of 2-hydroxyglutarate (2-HG), inducing differentiation of the cancerous cell and directly impacting clinical outcomes.

Mutations in the enzyme cytosolic isocitrate dehydrogenase 1 (IDH1) may occur at a single amino acid residue of the IDH1 active site, resulting in loss of the enzyme's ability to catalyse conversion of isocitrate to alpha-ketoglutarate. Dang L *et al* (Nature 2009) showed that cancer-associated IDH1 mutations result in a new ability of the enzyme to catalyse the NADPH-dependent reduction of α -ketoglutarate to R (2)-2-hydroxyglutarate (2-HG). Structural studies demonstrate that when arginine 132 is mutated to histidine, residues in the active site are shifted to produce structural changes consistent with reduced oxidative decarboxylation of isocitrate and acquisition of the ability to convert α -ketoglutarate to 2-HG. Excess accumulation of 2-HG was shown to lead to an elevated risk of malignant brain tumours in patients with inborn errors of 2-HG metabolism. Furthermore, based on a mutational and epigenetic profiling of an AML cohort, Figueroa ME et al (Cancer Cell 2010) showed that expression of 2-HG-producing IDH alleles in cells induced global DNA hypermethylation. Expression of mutant IDH impaired haematopoietic differentiation and increased stem/progenitor cell marker expression, suggesting a shared pro-leukaemogenic effect. The 2-HG level was chosen and validated as a primary PD biomarker.

Clinical pharmacodynamic data were derived from patient samples from the Phase I study AG120-C-001 and were analysed for translational biomarkers (2-hydroxyglutarate, variant allele frequency, co mutational burden), exposure-response relationships and cardiac effects. The primary presentation and discussion of PD data is focussed on the population targeted in the proposed indication, ie, R/R AML patients with an IDH1 R132 mutation whose starting dose was 500 mg QD, which includes Arm 1 and Arm 4 patients from the expansion portion and patients with R/R AML in the dose escalation portion.

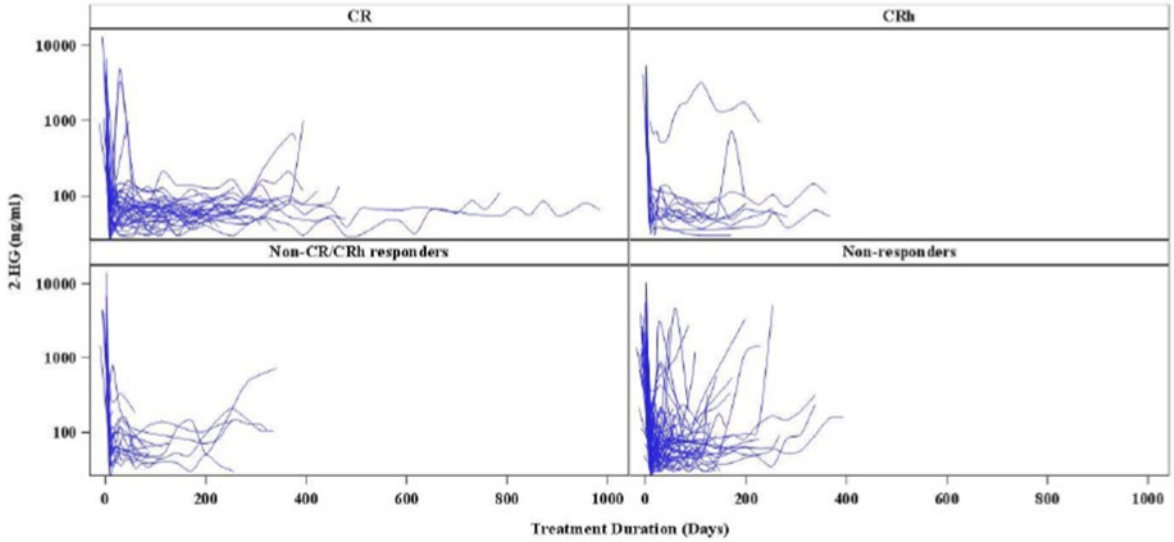
In the dose escalation part, ivosidenib doses from 100mg BID to 1200mg QD reduced total 2-HG levels both in plasma and bone marrow to levels near normal as in HV or wtIDH within less than 2 weeks of treatment.

Plasma 2-HG levels were available at BL for 178 patients. BL plasma 2-HG levels for all patients ranged from 46 to 21800 ng/mL, with over 98% of patients having levels above the mean for normal healthy patients (72.6 ng/mL).

The overall median suppression across all patients at C2D1 was 94.8% in CR/CRh responders and 94.1% for non(CR/CRh)-responders, with no significant difference between BL 2-HG levels between the

groups (p=0.717). Most patients who achieved CR or CRh responses had sustained reduction in 2-HG when treated with ivosidenib.

Figure 3. Plasma 2-HG levels and during treatment by BOR



Source: Figure 14.6.18B. Data Cutoff Date: 11 May 2018

After multiple dosing of 500 mg QD ivosidenib, the plasma 2-HG decreases from baseline reached a plateau within 14 days of dosing, and were maintained from Day 15 onward at a level similar to those observed in healthy subjects.

The suppression of 2-HG concentrations was comparable across expansion arms, by R/R AML subgroup, and between different IDH1 mutation subtypes. 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.

Genomic DNA extracted from bone marrow mononuclear cells (BMMCs), neutrophils, and peripheral blood mononuclear cells (PBMCs) was evaluated to assess the impact of ivosidenib on the IDH1 mutant haematopoietic clone as measured by mIDH1 %VAF. BMMC mIDH1 VAF data were available for 83% (149 of 179) of R/R AML patients.

A weak positive association between baseline 2-HG and bone marrow %myeloblasts and a moderate positive association between 2-HG and mIDH1 %VAF (whole bone marrow samples) was found, suggesting that 2-HG reflected clinical and molecular disease burden. In isoform specific analyses, no correlation of BL 2-HG and %VAF was found for the R132S isoform (n=6). A moderately positive correlation (Spearman's rank correlation, ρ=0.338) was observed between % mIDH1 VAF and % bone marrow myeloblasts, ie, tumour burden, for patients with R/R AML.

There were no significant differences in bone marrow baseline mIDH1 %VAF between CR/CRh responders vs. non-(CR/CRh)-responders (p=0.067 for dose escalation and p=0.273 for expansion).

Figure 4. mIDH1 %VAF at BL by best overall response in expansion

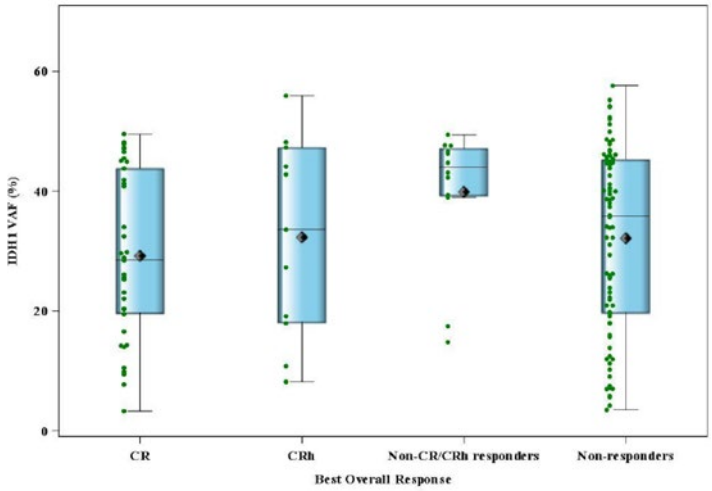
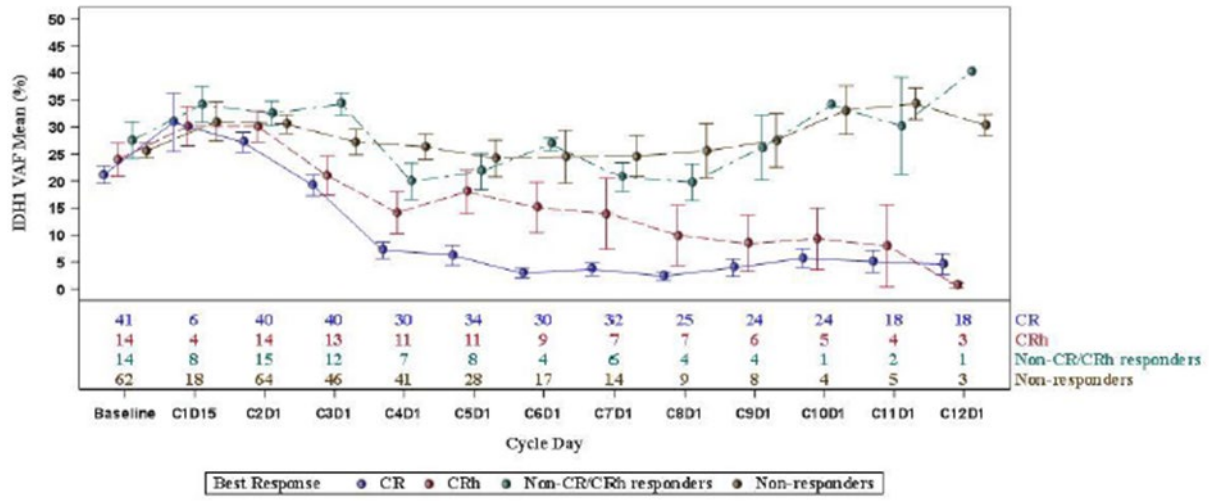


Figure 5 presents the mean mIDH1 %VAF in BMMCs over time according to best overall response. Reductions in the mean mIDH1 VAF were observed for patients with CR/CRh. By contrast, mean mIDH1 VAF levels remained persistently elevated in non-(CR/CRh) responders. The BL mIDH1 %VAF in PBMCs and neutrophils appeared lower than that of BMMCs but also followed a similar pattern of change over time within best response categories.

Figure 5. Longitudinal plot of mean (SE) mIDH1 %VAF by BOR in BMMCs



Source: Figure 14.6.13B. Data Cutoff Date: 11 May 2018

Upon ivosidenib treatment, there was an initial increase in mean mIDH1 VAF for all response categories, which is consistent with the known mechanism of action of ivosidenib, release from differentiation block.

IDH1-mutation clearance (IDH1-MC) was defined as reduction in the mIDH1 %VAF to below the limit of detection (no mutation detectable=NMD; analytical sensitivity for mIDH1 detection of 0.02% for R132C/G/L/S- and 0.04% for R132H-isoenzymes) of the dPCR assay for at least 1 on-treatment time point. Table 4 summarises mutation clearance by best overall response in BMMCs, PBMCs and neutrophils.

The data provided show that the IDH1 mutation clearance by best overall response was observed in bone marrow mononuclear cells (BMMC) in 14 (24%) subjects with R/R AML at 500 mg QD who achieved CR, CRh and CR+CRh response. In contrast, BMMC IDH1-MC was not observed in any of the

subjects (0/88) with R/R AML who did not achieve CR or CRh. These results could be highly associated with favourable clinical outcomes (CR or CRh responses).

Table 4. mIDH1 mutation clearance

a) mIDH1 mutation clearance in BMMCs

Best response	R/R AML at 500 mg QD (N=145)			Untreated AML at 500 mg QD (N=30)		
	N	Mutation clearance n (%)	No mutation clearance n (%)	N	Mutation clearance n (%)	No mutation clearance n (%)
CR+CRh	57	14 (24.6)	43 (75.4)	14	9 (64.3)	5 (35.7)
CR	43	12 (27.9)	31 (72.1)	10	5 (50.0)	5 (50.0)
CRh	14	2 (14.3)	12 (85.7)	4	4 (100.0)	0
Other Responses	88	0	88 (100.0)	16	0	16 (100.0)
Non-CR/Rh responders	17	0	17 (100.0)	5	0	5 (100.0)
Non-responders	71	0	71 (100.0)	11	0	11 (100.0)
p-value[1]		<0.001			<0.001	

Source: Table 14.6.2. Data Cutoff Date: 11 May 2018

b) in PBMCs **c) in neutrophils**

Best response	R/R AML at 500 mg QD (N=128)			R/R AML at 500 mg QD (N=115)		
	N	Mutation clearance n (%)	No mutation clearance n (%)	N	Mutation clearance n (%)	No mutation clearance n (%)
CR+CRh	48	13 (27.1)	35 (72.9)	44	18 (40.9)	26 (59.1)
CR	37	11 (29.7)	26 (70.3)	34	15 (44.1)	19 (55.9)
CRh	11	2 (18.2)	9 (81.8)	10	3 (30.0)	7 (70.0)
Other Responses	80	2 (2.5)	78 (97.5)	71	1 (1.4)	70 (98.6)
Non-CR/CRh responders	12	0	12 (100.0)	12	0	12 (100)
Non-responders	68	2 (2.9)	66 (97.1)	59	1 (1.7)	58 (98.3)
p-value[1]		<0.001			<0.001	

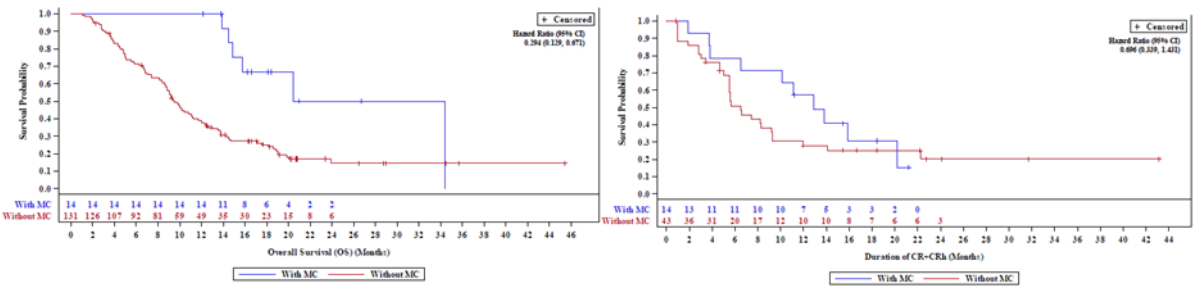
Source: Table 14.6.2B. Data Cutoff Date: 11 May 2018 Date: 11 May 2018

Median time to mIDH1-MC was 5.32 months (range: 2.8 - 11.1 months) for patients with CR/CRh. Median time to CR/CRh was similar between R/R AML patients with IDH1-MC (1.94 [range: 1.0 - 4.6] months) and 2.69 (range: 0.9 - 5.6) months for those without.

Median DoCR/CRh was 12.9 (range: 3.8 - 20.2) months for patients with IDH1-MC compared to 6.5 (range 5. - 9.3) months for those patients without.

Median OS was 27.4 months (95% CI: 14.5, 34.4) for patients with IDH1-MC and 9.5 months (95% CI: 8.6, 11.1) for those without.

Figure 6. KM-plots of OS (left) and DoCR/CRh (right) by mutation clearance in BMMC



Bone marrow samples for analyses of co-mutational burden were available for >96% of patients included in the FAS across all analysis groups, and peripheral blood samples were available for >91%, indicating that the results were representative of the patients enrolled in Study AG120-C-001.

Results indicate that IDH1 mutations are observed in combination with other commonly occurring mutations in AML. Among the 172 patients with R/R AML, 154 patients were determined to have at least one known or likely co-occurring mutation other than IDH1.

For subjects with R/R AML whose starting dose was 500 mg QD, co-mutational burden was not associated with best overall response for subjects in the dose escalation portion; however, a significant association was observed between lower co-mutational burden and achievement of CR or CRh responses compared to other responses for subjects in the expansion portion. In dose escalation (N=30), the mean number of co-occurring mutations was lower in CR/CRh-responders (2.7 mutations) compared to non-(CR/CRh)-responders (3.6 mutations); (p=0.136). In the expansion portion with 142 patients, the mean difference between the groups was also 0.9 (1.7 vs. 2.6) (p<0.001).

Table 5. Number of co-occurring mutations at baseline by best overall response

Number of Co-occurring Mutations	CR or CRh Responders			Other Response Categories		
	CR	CRh	Total	Non-CR/CRh Responders	Non-responders	Total
Expansion (Brigham and Women's Hospital Rapid Heme Panel)						
N[1]	37	11	48	12	82	94
Mean (StdDev)	1.7 (1.43)	1.7 (1.56)	1.7 (1.44)	2.5 (1.17)	2.7 (1.60)	2.6 (1.55)
Median	1.0	1.0	1.0	2.0	2.0	2.0
Min, Max	0, 6	0, 4	0, 6	1, 5	0, 6	0, 6
p-value[2]	<0.001					
Subjects with at least one co-occurring mutation in expansion						
n (%)[3]	30 (81)	8 (73)	38 (79)	12 (100)	75 (91)	87 (93)

Source: Table 14.6.7B Data Cutoff Date: 11 May 2018
Abbreviations: AML = acute myeloid leukemia; CR = complete remission; CRh = complete remission with partial hematologic recovery; FAS = Full Analysis Set; Max = maximum; Min = minimum; QD = once daily; R/R = relapsed or refractory; StdDev = standard deviation.
[1] Number of subjects who have known/likely mutations at baseline based on testing results from available bone marrow samples.
[2] p-value is based on Student's t-test comparing mean number of co-occurring mutations in subjects with CR or CRh and subjects with other responses (non-CR/CRh responders and non-responders).
[3] Percentages are based on the number of subjects who have known/likely mutations at baseline based on testing results from bone marrow samples.

Among the R/R AML patients in the FAS, the most frequent co-occurring mutations were DNMT3A, NPM1, SRSF2, ASXL1, RUNX1, NRAS, and TP53. The occurrence of DNMT3A, NPM1, TP53, NRAS, and RUNX1 mutations is consistent with previously published de novo AML surveys (Ley et al, 2013; Papaemmanuil et al, 2016). SRSF2 and ASXL1 mutations commonly occur in patients with secondary AML with a history of myelodysplastic syndrome (Lindsley et al, 2015). FLT3 mutations were detected in 10% (dose escalation) or 6% (expansion) of R/R AML patients. This rate is lower than the frequency of FLT3 mutations reported in the general AML population of ~20% to 30% (Ley et al, 2013; Papaemmanuil et al, 2016), but similar to the rate of 9% reported by Molenaar in a cohort of 78 patients with IDH1-mutant myeloid malignancies (Molenaar et al, 2015).

Among the 74 subjects who had data available at the time of relapse/progression regardless of best response, mutations in RTK pathway genes (NRAS, KRAS, PTPN11, KIT or FLT3) were identified in 20 (27%) subjects; IDH-related mutations occurred at a similar frequency (17 subjects; 23%) and included second-site mutations in IDH1 (10 subjects; 14%) and canonical mutations in IDH2 (9 subjects; 12%). IDH2 mutations and second-site IDH1 mutations were not mutually exclusive (ie, both were observed in two subjects). A subset of patients with NRAS or FLT3 mutations achieved a response

to ivosidenib and, thus, the specific genetic and cellular context in which IDH1 and RTK pathway mutations co-occur may be important in the biology of response to therapy.

Among the 26 subjects who achieved a best response of CR or CRh, IDH-related mutations emerged at a similar frequency (35%) as RTK pathway genes at the time of relapse/progression.

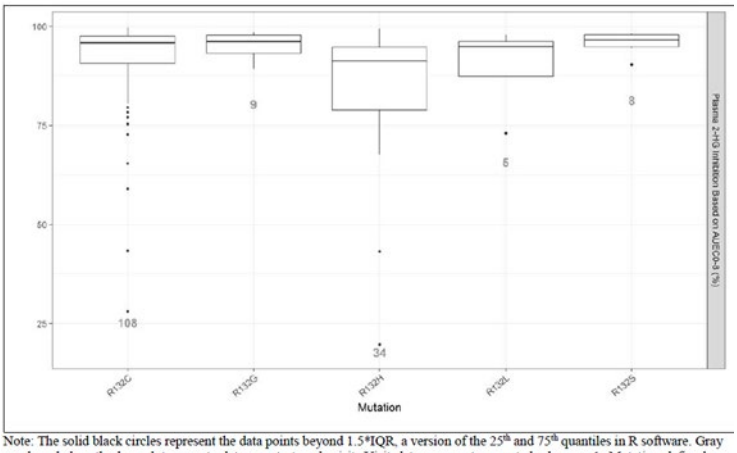
The second-site IDH1 mutations that emerged during treatment with ivosidenib included the previously described mIDH1-S280F (Intlekofer et al., Nature, 2018), in addition to five novel previously unidentified mutations (R119P, G131A, D279N, G289D, and H315D). Although no dominant second-site IDH1 mutation was detected in this dataset, the second-site IDH1 mutations clustered into two subregions of the IDH1 protein. Notably, all IDH2 mutations that emerged during treatment were R140Q in this R/R AML data set. The majority of the newly identified second-site IDH1 and IDH2 mutations (15 of 16 with available 2-HG data at relapse) were associated with a concurrent increase in 2-HG levels and are thus termed "2-HG-restoring mutations".

Other confounding clinical and biological factors were not considered in this analysis due to limited sample size. Additional research will be required to determine the pattern of co-occurring mutations that predict clinical response or resistance to treatment with ivosidenib.

No correlations between Cmax, Cmin or AUC and % 2-HG inhibition were observed. There was no relationship between exposure and the probability of achieving a clinical response of OR, CR and CR+CRh, the E-R profiles appeared flat. Assuming an Emax shaped E-R profile, these findings suggested that at a dose of 500 mg QD the maximum effect has been achieved.

Genetic differences in PD response for the mIDH isoforms are summarised in Figure 7, Table 6, and Figure 8.

Figure 7. Effect of IDH1 mutation type on plasma %2-HG inhibition based on AUEC0-8 – Dose Escalation and Expansion combined

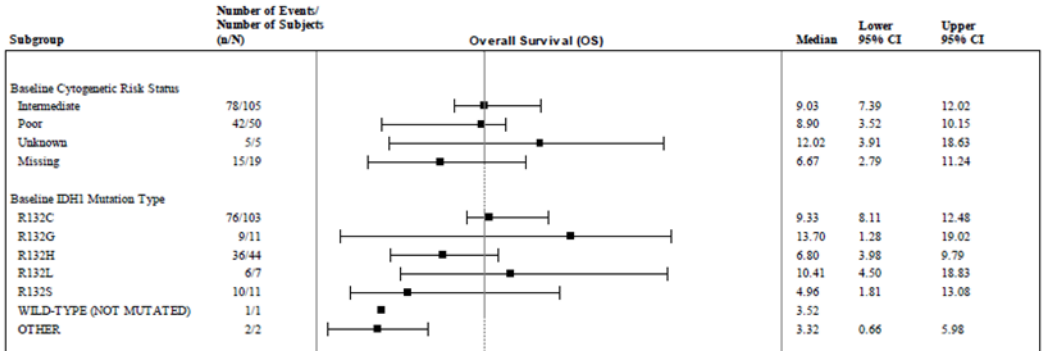


Note: The solid black circles represent the data points beyond 1.5*IQR, a version of the 25th and 75th quantiles in R software. Gray numbers below the box plot presents data count at each visit. Visit data were not presented when n =1. Mutation defined as "OTHER" were not presented.
Source: Figure 14.4.5.1

Table 6. Drug treatment effect by mutation (FAS1/Arm1+); cut-off 12.05.2017

Obs	Mutation	Total No.	No. Respond	Response Rate (%)	Lower 95% Exact CI (%)	Upper 95% Exact CI (%)
1	R132C	75	29	38.67	27.64	50.62
2	R132H	26	3	11.54	2.45	30.15
3	R132G	9	3	33.33	7.49	70.07
4	R132S	7	2	28.57	3.67	70.96
5	R132L	3	1	33.33	0.84	90.57

Figure 8. OS by subgroup (FAS=9.03 months); cut-off 11.05.2018



Secondary pharmacodynamics

QT

Nonclinical studies have been shown to inhibit *in vitro* the rapidly activating, delayed rectified cardiac potassium current, IKr, encoded by hERG, and to prolong QTc in cynomolgus monkeys at free maximum plasma concentrations (Cmax) values ≥0.7-fold the free Cmax value at the recommended human daily dose of 500 mg once daily. QT interval prolongation was documented in clinical trials and is classified as an identified risk associated with AG-120 treatment.

A concentration-ΔQTc analysis to characterise the relationship between AG-120 exposure and QTc prolongation, using data from studies in subjects with advanced malignancies and healthy subjects was performed. It includes a descriptive analysis of the ECG records collected in the clinical studies and a modelling approach.

This analysis was based on data from three Phase 1 studies:

- AG120-C-001, a dose escalation and expansion study in subjects with advanced haematologic malignancies with an IDH1 mutation;
- AG120-C-002, a dose escalation and expansion study in subjects with advanced solid tumours with an IDH1 mutation;
- AG120-C-004, a single-dose, two-period food-effect crossover study in healthy subjects

The assessments of heart-rate corrected QT (QTc) intervals are based on recommendations in the ICH E14 guidelines. Digital capture of 12-lead electrocardiograms (ECGs), partly in triplicate at matched time points to enable evaluation of the relationship between AG-120 exposure and changes in QT/QTc. This approach of a concentration- QT analysis was agreed upon with FDA in 2016 as an alternative approach to a thorough QT (TQT) study.

From initially 4140 ECG records, 2821 and 2377 records could be analysed within the full data set and the triplicate data set, respectively. The triplicate dataset contains mainly records of the 500 mg dose group.

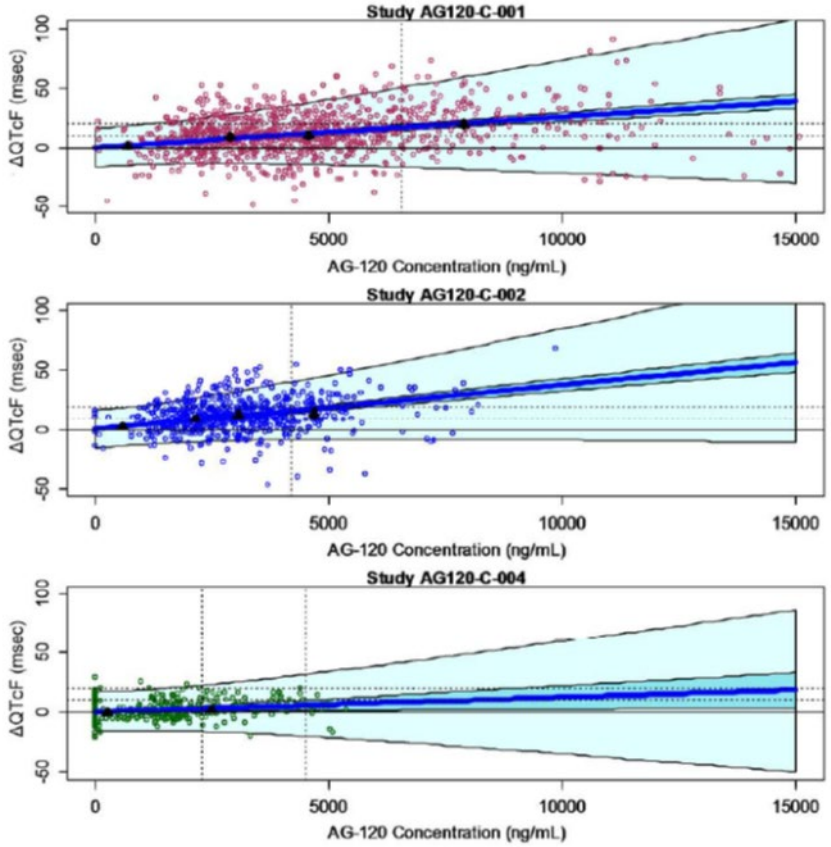
Linear mixed effects models were estimated to quantify the concentration-ΔQTc relationship. A study effect on slope was tested. Tested covariates included baseline demographic variables, baseline QTcF, electrolytes (as continuous variables and also as binary flags indicating values greater than the mean), study effects, effects in healthy subjects vs. subjects with cancer, tumour type, flags for medications with known QT interval prolongation and torsades de pointes (TdP) risk, and a flag for cardiac disorder at baseline.

Applying the final model, the primary analysis of the relationship of ΔQTcF to ivosidenib concentration showed significant positive slopes, resulting in a predicted mean effect on QTcF of 17.2 msec, with a 90% CI upper bound of 19.7 msec, at the geometric mean Cmax of 6551 ng/ml in Study AG120-C-001 for the recommended clinical dose of 500 mg QD. The modelled AG-120 concentration can be increased to determine the hypothetical point at which the 90% CI upper bound of ΔQTcF reaches 20 msec. In the triplicate-data combined model, this point was reached at 6659 ng/mL in Study AG120-C-001 and 4591 ng/mL in Study AG120-C-002. This dose concentration is reached at the recommended dose. According to the results of study AG120-C-001 for the 500 mg dose at steady state, (eg, C1D15) observed dose levels were geometric mean 7108 ng/ml, median 7400 ng/ml, and range 3510-17600 ng/ml. Even for the lower dose of 300 mg at steady state, observed dose levels were geometric mean 5583 ng/ml, median 5660 ng/ml, and range 3950-7700 ng/ml. For the majority of patients treated with the recommended 500 mg dose, Cmax drug levels can be expected to be higher than the calculated hypothetical point at which the 90% CI upper bound of ΔQTcF reaches 20 msec. Thus, there is no safety interval and clinically relevant QT prolongations are expected at the recommended dose. Discussion on expected ΔQTcF for patients whose drug levels reach the upper quartile of the range was provided. The frequency of clinically relevant QT prolongations appeared to be comparable to the observations in the safety data set.

Predictions for ΔQTcF at the supratherapeutic doses of 800 and 1,200 mg exceeded 20 msec. ΔQTcF predictions were lower for subjects with solid tumours (study AG120-C-002) compared to subjects with haematologic malignancies (AG120-C-001).

Figure 9. Predicted relationship between ΔQTcF and AG-120 concentration overlaid with observations (primary model)

b. Mean Predictions with CI and Quantile Mean ± 90% CI Bars, Superimposed with Data and Prediction Intervals



Results are shown by study, but projections come from the combined model ($\Delta QTcF = Intercept + Slope_{001} \times Conc_{001} + Slope_{002} \times Conc_{002} + Slope_{004} \times Conc_{004}$). Study populations: subjects with cancer (Studies AG120-C-001, AG120-C-002), healthy subjects (Study AG120-C-004). Points: data; center blue line: projected mean ΔQTcF (with covariates set to sample means); dark blue shaded area: its 90% CI; heavy black vertical bars: mean ± 90% CI of ΔQTcF at the mean of each concentration quartile (for Study AG120-C-004, just the below-median and above-median means, because of a high proportion of zero concentrations); light blue shaded area: 90% Prediction Interval using between-subject and residual variability; dotted horizontal lines: ΔQTcF = 10 and 20 msec; dotted vertical lines: C_{max} values for each study (see Table 6-7 footnote; separate lines are shown for fasted and fed in AG120-C-004). Not shown: Study AG120-C-001 outlier at (12600 ng/mL, 186.7 msec).

Table 7. Projections of Mean (90% CI) ΔQTcF at Various Doses in Study AG120-C-001 (primary model)

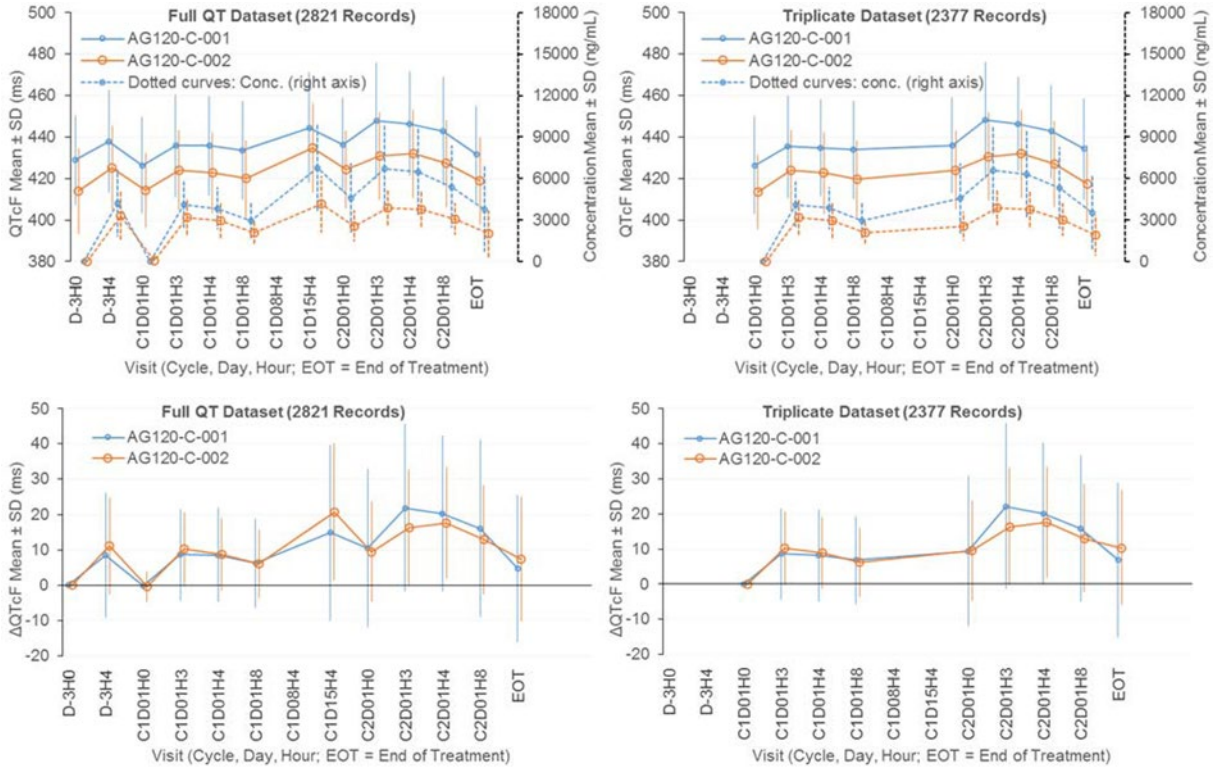
Dose	C_{max} (ng/mL)*	ΔQTcF Mean (90% CI)			
		Model: Primary	Full-Data Combined	Study 001 Alone	R/R AML Alone
250 mg QD	4600	12.1 (10.4, 13.9)	11.5 (9.9, 13.0)	12.0 (10.4, 13.7)	11.5 (9.5, 13.4)
300 mg QD	5048	13.3 (11.4, 15.2)	12.5 (10.9, 14.2)	13.2 (11.4, 15.0)	12.5 (10.4, 14.6)
500 mg QD	**6551**	**17.2 (14.7, 19.7)**	**16.2 (14.0, 18.3)**	**17.0 (14.6, 19.4)**	**16.1 (13.3, 18.9)**
800 mg QD	8325	21.8 (18.6, 25.0)	20.5 (17.7, 23.3)	21.5 (18.4, 24.6)	20.4 (16.8, 24.0)
1200 mg QD	10238	26.7 (22.8, 30.7)	25.1 (21.7, 28.6)	26.4 (22.5, 30.2)	25.0 (20.4, 29.5)

* C_{max} for 500 mg QD is from Table 6-7; for other doses C_{max} was approximated, accounting for decreasing bioavailability with dose from the Study AG120-C-001 population pharmacokinetic model [Report AG120-C-001-PPK], as $6551\ (dose/500)^{1-0.49}$.

The concentration vs QT plots (Figure 10) of the triplicate dataset show similar curves for the drug concentration and mean QTcF and ΔQTcF, respectively. Furthermore, it illustrates the rather wide range of drug concentrations given the fact that the triplicate data set included patients with the 500 mg dose, the separation between studies AG120-C-001 and AG120-C-002 apparently increased from

the first to the second cycle with higher drug concentrations observed in study AG120-C-001. The majority of QT-prolongations were documented for cycle 2.

Figure 10. Concentration, QTcF, and ΔQTcF by Visit/Time, Study, and Dataset



Points show means; bars show standard deviations
From the scattered plots it becomes obvious that the information on higher drug concentrations is rather limited thus the uncertainty is increased.

Categorical analysis of QTcF/ ΔQTcF for the time points measured in cycles 1 and 2 of studies AG120-C-001 and AG120-C-002 are presented for the data sets generated for the concentration-QTc modelling. Categorical analysis for the entire safety dataset of the respective studies were provided. As the triplicate dataset was a subset of the full safety data set deviations may occur, however, it appears that patient records with substantial increases in QTcF are underrepresented in relation to the full safety dataset.

According to categorical analysis of maximum post-baseline QTcF, 8.9% and 1.2% of patients in studies AG120-C-001 and AG120-C-002 experienced QTcF of >500 msec. The relative proportion of patient records included in the triplicate dataset is substantially lower: 4.6% and 0%.

According to categorical analysis of maximum post-baseline QTcF, 14.3% and 5.4% of patients in studies AG120-C-001 and AG120-C-002 experienced increase in QTcF of >60 msec. The relative proportion of patient records included in the triplicate dataset is substantially lower: 3.5% and 0.9%.

3.3.4. Discussion on clinical pharmacology

Pharmacokinetics

Ivosidenib (AG-120) has been studied in healthy subjects and in subjects with advanced haematologic malignancies or solid tumours with oral doses ranging from 100 mg twice daily [BID] to 1200 mg once daily [QD].

A total of 7 clinical studies have contributed to the characterisation of the clinical pharmacology of ivosidenib. Five studies have been conducted in healthy subjects (all single dose studies including 1 study in otherwise healthy subjects with mild or moderate hepatic impairment; Study AG120-C-012), and 2 studies have been conducted in subjects with advanced malignancies (single and multiple doses). Pharmacokinetic endpoints have been assessed in plasma and urine. Pharmacodynamic endpoints (2-HG inhibition) have also been assessed in plasma and bone marrow (studies in subjects with advanced haematologic malignancies only).

Two tablet presentations have been used during clinical development: (1) uncoated tablets (50, 200, and 250 mg); and (2) blue non-debossed film-coated tablets (250 mg). An oral suspension formulation of radiolabelled ivosidenib was used for the single-dose Phase 1 human AME study (AG120-C-003).The intended commercial product is an oval, blue, film-coated tablet, debossed with "IVO" on one side and "250" on the other side of the tablet face. No bioequivalence studies have been submitted and dissolution data have been used to justify bridging the tablet strengths and presentations used in the clinical studies with the planned commercial tablet presentation. According to the applicant, the only difference between the commercial tablet presentation and the 250 mg clinical tablet presentation used in the primary study supporting the MAA, (Study AG120-C-001), is the non-functional film coat and debossing. In response to questions raised at D120, the applicant further justified that additional tablets with different strengths (10, 50 and 200 mg) were used in studies AG120-C-001 and AG120-C-002. In summary, tablet compositions are proportional between each strength and dissolution profiles are similar between a 250 mg tablet and a 200 mg tablet plus a 50 mg tablet. This was regarded acceptable.

The proposed BCS classification (BCS class II) was inadequately justified. The absolute bioavailability has not been clinically determined and clinical data are not regarded adequate to reliably justify complete absorption in line with the requirements of the BE-GL. As stated by the applicant, results of Study AG120-C-003 indicate that "*at least 32.6% of the dose was absorbed from the suspension (assuming that non-absorption was responsible for all of the 67.4% of the total recovered dose excreted in faeces as unchanged drug).*" In Section 3 it is stated that "*The absorption of ivosidenib film-coated tablets is estimated to be at least 58.8%, or 1.8-fold higher than the estimated absorption of the oral suspension ≥32.6%*". As not otherwise investigated in humans, the results from study AG120-C-003 indicating "at least 58.8% absorption of ivosidenib film-coated tablets", only allow a BCS classification of Class IV: Low Solubility – Low Permeability, which was accepted by the applicant.

In healthy subjects, ivosidenib was readily absorbed following oral administration under fasting conditions. For the 500 mg QD dose in Caucasian healthy volunteers, the AUC0-∞ was found to be 185,000 ng*hr/ml, Cmax was 2850 ng/ml and Tmax was approximately 3 hours. Pharmacokinetic data from study AG120-C-003 in healthy volunteers confirmed that AG-120 is readily absorbed after administration as an oral suspension with Tmax values around 4 hours.

In subjects with advanced haematologic malignancies with an IDH1 mutation, the AUC0-24 was found to be 61135 ng*hr/ml, Cmax was 4481 ng/ml and Tmax was approximately 2.4 hours after administration of a single dose of 500 mg dose. The somewhat higher Cmax compared to healthy volunteers might be explained by the high degree of patients with r/r AML taking CYP3A4 inhibitors (see also the interaction section of this AR). The terminal half-life was found to be 93 hours (CV% 67).

In subjects with advanced haematologic malignancies with an IDH1 mutation, after multiple dosing of 500 mg QD, the AUC0-tau and Cmax values were comparable in C1D15 and C2D1, indicating steady state was reached within 14 days of continuous dosing. Results for pre-dose concentrations confirmed that steady state was reached within 14 days.

Mean concentration-time profiles of AG-120 at cycle 2 day 1 showed higher concentrations than those observed after the first dose administration (Day -3). The geometric mean Racc(AUC) and Racc(Cmax)

across 100 mg BID and 300 to 1200 mg QD dose levels ranged from 1.73 to 3.46 and from 1.37 to 3.09, respectively, suggesting moderate accumulation at this time point. Mean Racc(AUC) and Racc(Cmax) at 500 mg QD was found to be comparable between the escalation and expansion portions.

The PK data for subjects with R/R AML from the dose escalation and expansion combined receiving AG-120 500 mg QD are consistent with those observed for the overall study population (all subjects in dose escalation and expansion at AG-120 500 mg QD). As the results are consistent and are based on a broader database, it is acceptable that this analysis is the basis for the following general PK information stated in the SmPC: "*The median time to Cmax (Tmax) is approximately 3 hours. The mean peak plasma concentration (Cmax) is 4,503 ng/ml (% coefficient of variation (%CV: 38) after a single dose and 6,551 ng/ml (%CV: 44) at steady-state. The steady-state area under the concentration time curve (AUC) is 117,348 ng*hr/ml (%CV: 50). Accumulation ratios are approximately 1.9 for AUC and 1.5 for Cmax over one month. Steady-state plasma levels are reached within 14 days.*" The applicant amended the SmPC to consistently highlight in which population the cited results were gained.

Food effects were investigated in study AG-120-C-004. The effect of concomitant food intake (ie, high fat meal) on the rate of absorption (Cmax) was remarkable, an increase by nearly 100% (2-fold). This increase of Cmax represents a potential risk with regard to QTC effects and was not adequately covered by warnings / clear instructions in the posology section. The effects of a standardised "FDA high-fat breakfast" vs. no meal (10 h overnight fast) have been investigated, subjects that had a standardised high fat-breakfast showed markedly elevated Cmax concentrations. The effects of a "normal" meal ("not high-fat") have, however, not been investigated. It is therefore not known to what extent a "normal meal" could influence Cmax concentrations. In response to the questions raised, the applicant amended the SmPC and PL stating that ivosidenib should be taken only without food including definite time frames.

Results of blood/plasma total radioactivity AUC0-72 ratio showed minimal association of radioactivity with red blood cells and indicated very limited drug partitioning into red blood cells. Plasma protein binding of ivosidenib ranged from 91.6% to 95.8 *in vitro*. The currently proposed SmPC states that the mean apparent volume of distribution (Vc/F) of ivosidenib at steady state is 234 L (%CV: 47). The stated Vc/F in the SmPC is the one at steady state after multiple oral dosing in patients with advanced haematologic malignancies with an IDH1 mutation taken from the population PK analysis, which is acceptable. In line with questions raised at D120, the volume of distribution is now stated as "L/kg".

The results of AME study AG120-C-003 indicated that faecal excretion is the major route of elimination, while urinary excretion is the minor elimination pathway. An overall mean recovery of radioactivity in urine and faeces samples above 90% (94.3%) indicates an adequate amount of sampling and is endorsed. The SmPC states "*In healthy subjects, 77% of a single ivosidenib dose is found in the faeces of which 67% is recovered unchanged. Approximately 17% of a single dose is found in the urine of which 10% is recovered unchanged*". AG-120 is metabolised by multiple pathways. The primary metabolic processes for [14C]-AG-120 in human male subjects were oxidations at the chlorobenzyl-N-5-fluoropyridinyl (M1), cyanopyridinyl-pyrrolidone (M3), and difluorocyclobutyl (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 a combination of these primary pathways and glucuronide conjugation. Only [^{14}C]-AG-120 was detected in plasma, representing on average 92.4% of the total radioactivity in pooled plasma samples from the 8 human male subjects. Information provided in the SmPC is in line with the study results and acceptable.

With regard to special populations, subjects with reduced renal function (mild or moderate impairment) at study entry were permitted in study AG120-C-001 and the potential impact of baseline renal

function on ivosidenib exposure and safety was also assessed. Comparisons between normal renal function and mild or moderate renal impairment were conducted after single doses and at steady state. The results of the ANOVA supported that the CLss/F of AG-120 following administration in subjects with varying degrees of renal dysfunction (ie, mild, and moderate renal impairment) were not statistically different relative to subjects with normal renal function. The clinical study programme and hence the safety and PK data are too limited to be able to draw meaningful conclusions in patients with severe renal impairment. The proposed SmPC overall reflects the clinical results related to PK in patients with renal impairment as assessed above, however, the applicant has provided limited safety data in patients with renal impairment. Safety data indicate that a higher percentage of subjects with any Grade ≥3 AE, any treatment-related AE, any SAE, and any AE leading to study drug being permanently discontinued was observed in the moderate renal impairment group compared with those subjects having normal renal function or mild impairment. A detailed warning for ivosidenib in patients with moderate and severe renal impairment (in order to reduce the risk for fatal renal failure) was therefore considered by the applicant at D180, see further details in the Safety section below.

Ivosidenib is eliminated predominantly by hepatic metabolism and hence there is the potential for hepatic impairment to affect ivosidenib exposure. The effect of mild and moderate hepatic impairment (based on Child-Pugh classification) on the PK of ivosidenib was formally assessed in a dedicated Clinical Study (AG120-C-012). Statistical analysis of the total AG-120 plasma Cmax and AUC parameters suggests that mild hepatic impairment has a negligible effect on total AG-120 exposure with point estimates for the geometric mean ratios of 0.819 to 0.933 and 90% confidence intervals that included 1. Moderate HI appears to reduce total AG-120 exposure by approximately 28-44% although the 90% CIs for AUC0-inf also included 1.00.

Marked increases of up to 40% in Cmax_free in patients with hepatic impairment have been seen in study AG120-C-012. Based on the results of AG120-C-012, the applicant was asked to thoroughly discuss safety in patients with hepatic impairment with regard to potential increase in free Cmax (Cmax_free). As highlighted by the applicant, a clear increase in Cmax_free as the severity of hepatic impairment increased from mild to moderate was not observed. As investigated in Study AG120-C-012, geometric mean Cmax_free values were similar between subjects with moderate HI (61.1 ng/mL) and the non-matched subjects with normal hepatic function in Cohort 1b (62.7 ng/mL). The highest geometric mean Cmax_free value of 87.5 ng/mL was, however, found in patients with mild hepatic impairment. Possible underlying reasons for the lower total AUC and Cmax in patients with hepatic impairment have been discussed by the applicant. According to the discussion, there are a number of factors which may contribute to altered ivosidenib PK in subjects with hepatic impairment: reduced gastrointestinal absorption; decreased protein binding which may increase total body clearance and tissue distribution and ascites due to cirrhosis. The apparent increase in Vz/F with increasing hepatic impairment was thought to be likely attributable to a decrease in protein binding (ie, increased fraction unbound (Fu)) observed for subjects with hepatic impairment, particularly at higher concentrations approximating Cmax. A decrease in protein binding and increased fraction unbound (Fu) could maybe partly explain that results found in CSR AG120-C-012 for total plasma AG-120 (decrease) seem not to translate into a similar decrease in Cmax_free values. Results of Cmax_free have to be interpreted with caution, however, as Study AG120-C-012 can only give an approximation of free Cmax as total Cmax occurred between 1 and 12 hours postdose whereas Fu was only available at 3 hours postdose in this time-range.

As discussed in more detail in the Safety section below, in the pivotal study a remarkably higher percentage of subjects with any treatment-related AEs (all grades and grade ≥3 AE), with treatment-related SAEs, and with AEs leading to study drug being permanently discontinued, leading to drug reduced, leading to drug held and leading to on-treatment death was observed in the mild hepatic

impairment group compared with those subjects having normal hepatic function (please be referred to the Safety section below for further assessment).

The potential influence of other covariates (eg, age, gender) on the PK of ivosidenib was tested in a population pharmacokinetic analysis. The Pop-PK analysis indicated no clear influence of gender, age or weight on apparent volume of distribution and apparent clearance. Study AG120-C-006 showed an average exposure that was lower overall in Japanese subjects compared with the Caucasian subjects by approximately 30 to 31% (AUC parameters), and 17% (Cmax). Based on current data, the applicant's conclusion can be concurred that the exposure-efficacy analysis can be interpreted in a way that the lower average exposure seen in Japanese Patients might not be of clinical relevance, however, this could conclusively only be investigated in clinical efficacy studies in Japanese patients. In the population PK analysis, no clear influence of race on Volume of distribution and Clearance was found, however, the numbers of subjects with a race other than Caucasian was low. Thus, currently no conclusions on the potential influence of race on the pharmacokinetics of ivosidenib can be drawn from latter analyses.

The currently proposed SmPC states as follows with regard to PK in this subset of "special populations": "No clinically meaningful effects on the pharmacokinetics of ivosidenib were observed based on gender, race, body weight or ECOG performance status." which seems acceptable based on the results discussed above.

Non-clinical and Clinical studies dedicated to investigating the potential for drug-drug interactions with ivosidenib showed that clinically relevant interactions with CYP enzymes and cellular transporters can be expected. This is true for ivosidenib effects on other drugs (as a perpetrator) and effects of other drugs on ivosidenib (as a victim).

With regard to AG-120 as a perpetrator, AG-120 was shown to induce CYP3A4 and subsequent warnings with regard to CYP3A4 induction can be found in the submitted SmPC. Weak induction of CYP2B6, CYP2C8 and CYP2C9 activity has also been seen in *in vitro* experiments and this information is given in Section 5.2 of the SmPC. However, Section 4.5 of the former SmPC only listed CYP2C9 as enzyme which may be induced at D120. Taking into account the lack of clinical DDI induction studies and the weak induction of CYP2B6, CYP2C8 and CYP2C9 activity that has been seen in *in vitro* experiments, concerned SmPC sections have been amended in line with the CHMP comments.

Section 5.2 of the initial SmPC stated as follows with regard to possible effects of ivosidenib on transporters: "Ivosidenib is an inhibitor of OAT3 and P-gp. However, available data suggest that the potential for clinically relevant interactions with ivosidenib and substrates of OAT3 or P-gp is low. Ivosidenib does not inhibit BCRP, OATP1B1, OATP1B3, OAT1 and OCT2 at clinically relevant concentrations." As discussed above, ivosidenib has the potential to inhibit OAT3 activity and cause DDIs with sensitive OAT3 substrates. As the clinical relevance of the in vitro OAT3 inhibition has not been studied in a clinical drug interaction study, the applicant amended Section 4.5 and respective sections of the PL to inform about possible DDIs with OAT3 substrates in line with the CHMP comment.

Further, Section 4.4 was amended to highlight that co-administration of ivosidenib may decrease the concentrations of combined hormonal contraceptives and that additional contraceptive measures (non-hormonal methods) should be used.

With regard to AG-120 as a victim, in subjects taking moderate and strong CYP3A4 inhibitors, a statistically significant difference in the apparent clearance (CLss/F) of AG-120 was found relative to subjects who did not take CYP3A4 inhibitors. The results of study AG120-C-001 concerning Cmax showing an increase in case of concomitant CYP3A4 inhibitor usage is somewhat different compared to the results of study AG120-C-007, where AUC0-t and AUC0-inf were increased by 156.30% (GMR 256.30%) and 168.69% (GMR 268.69%), respectively, when AG-120 was co-administered with

itraconazole but Cmax was not affected by co-administration. The applicant was therefore asked to justify the design of the single dose DDI study AG120-C-007 in light of the results observed for DDI effects of CYP3A4 inhibitors after multiple dosing at steady state that seem to be more pronounced for Cmax compared to the results after single doses (like administered in AG120-C-007). Overall, it is understood and agreed that concomitant administration of moderate or strong inhibitors of CYP3A4 should be avoided wherever possible. However, with regard to the known QTc prolonging effect of ivosidenib and in the context of the interdisciplinary treatment of AML patients, this issue is more complex than it seems. For further discussion, please be referred to Assessment of QTc Prolongation in the Safety section.

The SmPC states that ivosidenib is a substrate of P-glycoprotein (P-gp) but it is not a substrate of BCRP or the hepatic transporters OATP1B1 and OATP1B3.The applicant was asked to justify the extent of information regarding weak, moderate and strong P-gp inhibitors based on their potential to alter the disposition of ivosidenib. A relatively high permeability was found in *in vitro* studies suggesting that the role of P-gp in the absorption of ivosidenib is minimal. In addition, the strong P-gp inhibitor itraconazole did not increase ivosidenib Cmax in clinical study AG120-C-007 CSR, further indicating that involvement of intestinal P-gp is not significantly limiting the absorption of ivosidenib *in vivo* (eg, due to P-gp inhibition and decreased efflux to intestinal lumen). A SmPC amendment stating the low potential for clinically relevant interactions with inhibitors of P-gp (ivosidenib as a victim) was therefore adequately justified.

Ivosidenib is practically insoluble in aqueous solutions between pH 1.1 and 7.5 (solubility of 38 µg/mL to 66 µg/mL). The argumentation of the applicant, that plasma exposure of ivosidenib should be expected to be unchanged when ivosidenib is co-administered with pH modulators such as antacids, PPI or histamine 2 (H2) antagonists, can be followed. This assessment is supported by the results of the population PK analysis conducted based on Study AG120-C-001 where some patient samples (eg, 7% for pantoprazole) were also evaluable for possible interactions with PPIs and H2 antagonists.

Pharmacodynamics

Ivosidenib (also known as AG-120 and AGI-16678) is a first-in-class, orally selective small molecule, and reversible inhibitor of mutant isocitrate dehydrogenase isoform 1 (IDH1). The IDH1-R132 mutation is associated with the over-production of 2-HG. Expression of mutant IDH impaired haematopoietic differentiation and increased stem/progenitor cell marker expression, suggesting a shared pro-leukaemogenic effect.

The assessed PD data relevant for the proposed indication are derived from R/R AML patients treated with 500 mg ivosidenib in the dose escalation and expansion phases of the sole single-arm phase 1 study AG120-C-001. No comparative data for contextualisation of the information are available.

The proposed MoA of ivosidenib is the inhibition of mutated IDH1, resulting in inhibition of production of the oncometabolite D2-hydroxyglutarate, reversal of growth factor-independent cell growth, and induction of cellular differentiation.

In vitro assays revealed that when the intracellular 2-HG levels were inhibited to near normal physiologic ranges in a TF-erythroleukemia cell line, a colour change of the cell pellets was observed resultant from the partially restored expression of haemoglobin. Further, early clinical *ex vivo* studies proved the proposed MoA to restore the cells' differentiation capability via FACS analyses. However, the underlying cell differentiation dataset is very small (2 and 6 patients) so the results are considered preliminary only and these analyses were not repeated in study AG120-C-001.

Regarding bioanalytical methods, it is stressed that the PD marker for ivosidenib's on-target effect, 2 HG, was only measured with a non-enantioselective bioanalytical method instead of only analysing the

solely produced D-2-HG. However, the applicant points out that these investigations had explorative/supportive purposes only. This could be accepted by the Rapporteurs.

In *in vitro* cell-free assays, the IC50s at the 5 mIDH1 isoforms R132C / R132H / R132S / R132G / R132L were similar between 2-17 nM and also wtIDH1 was inhibited at 24-71 nM. mIDH2 was not inhibited even at micromolar concentrations, neither was any further off-target activity observed. At a mean Cmax of 6551 ng/ml and a PPB of 96%, free Cmax of ivosidenib is about 262.04 ng/ml (~450 nM) which is 20-200-fold above the IC50s at mIDH1.

As such, it is not surprizing that no correlations between Cmax, Cmin or AUC and % 2-HG inhibition were observed and the exposure-efficacy analysis did not reveal any relationships over the investigated dose range in the dose escalation part. Despite this, the applicant continued to develop the 500mg dose once daily in the proposed population.

A broad range of baseline 2-HG concentrations was observed. It was revealed that a few patients were enrolled without a confirmed IDH1-R132 mutation, so their BL 2-HG levels were within the wtIDH1 range. 2- HG levels of <100 ng/ml had been reported for HV and wtIDH patients by Fathi et al. (Blood 2012). 2-HG levels in bone marrow and plasma were correlated. Independent of the BL level, 500mg QD ivosidenib dose reduced 2-HG levels both in plasma and bone marrow to levels near normal as in HV or wtIDH within less than 2 weeks of treatment.

Patients who did not respond (as of BOR) retained variable but mainly high(er) 2-HG levels under treatment. With 2-HG as the proposed biomarker for ivosidenib's highly selective on-target effect to inhibit mIDH1 catalysed 2-HG production, this was questioned. It was clarified that 2-HG production could not be inhibited in patients with eg, a co-occurring mIDH2 mutation, no IDH1-R132 mutation or too low ivosidenib exposure. However, it was revealed that neither the BL 2-HG level, nor the % suppression by ivosidenib correlated with clinical response as of BOR. This could suggest that 2-HG suppression may be necessary but not sufficient to induce clinical response.

On the other hand, only in some cases the initially diminished 2-HG levels increased again at relapse or progression, obviously due to continued inhibition of mIDH1 but progression from other factors, ie, co-occurring clones.

Weak or moderate correlations were found between plasma 2-HG baseline levels with bone marrow blasts or with mIDH1 %variant allele frequency, respectively. 2-HG plasma levels may thus indicate clinical and mIDH1 molecular disease burden in R/R AML patients with this mutation.

It is further noted that the applicant only measured total 2-HG, which might have impacted the results. The D/L ratio was repeatedly discussed to be a more specific test rather than total 2-HG and significant correlations have been found between plasma D/L-ratio and % mutant allele frequency in AML patients (eg, Wiseman et al., 2015, Leukemia, 2421-22); in contrast, the applicant did only find a moderate correlation between mIHD1 VAF and baseline 2-HG levels. Based on the applicant's argumentation, in most AML cases, total 2-HG would be regarded as a mirror of D-2-HG produced by (confirmed) mutant IDH. But it has not yet been justified that mIDH1/2-AML is mutually exclusive with eg, metabolic diseases such as L-2-Hydroxyglutaric aciduria, and with this changing the D:L-ratio and impairing the levels of total 2-HG.

Based on the limited study data obtained to date, an enantioselective BA method would have probably not relevantly improved the PD results of ivosidenib. This and the D:L-ratio may become more relevant in future when ivosidenib pharmacodynamics and prognostic AML factors could be further elucidated and understood to serve as a valuable tool for monitoring mIDH1/2-targeted treatment in AML.

Tumour mutational burden was evaluated by analyses of %VAF from genomic DNA extracted from bone marrow aspirates (BMMCs), peripheral blood (PBMCs) and neutrophils. The main method for

detection in the expansion phase was a deep dPCR method with detection limits of 0.02%VAF for R132C/G/L/S isoforms and 0.04% for the R132H isoform. Regarding dPCR validation, several questions remain on method description as well as on various validation parameters. Validity of the quantitative readout has not been adequately demonstrated, even though the method is used for determination of percent mutant fraction. Also, specificity of the method is questionable due to extensive cross-reactivity for the 5 mutant types determined by dPCR. The applicant confirms that the data generated by this method are considered explorative/supportive and that the method is not used for patient selection.

In most samples, VAF was below 50%, indicating mainly heterodimeric mIDH1 enzymes, as expected, but a VAF >50% in some samples seemed to indicate also the presence of mIDH1 homodimers. At baseline, only a moderately positive correlation was found between mIDH1 VAF and % bone marrow myeloblasts, ie, tumour burden, showing that mIDH1 was not the only blast-forming clone in this R/R AML population.

Comparing the baseline mIDH1 VAF levels in the 3 different sample types, VAF was the highest in BMMCs (BMMC 20-30%, PBMCs 10-20%, neutrophils 5-25%). For all 3, no differences in BL mIDH1 VAF between CR/CRh-responders and non-responders was found. In all 3 sample types an initial increase in VAF of +10 to +30% within the first 2 weeks of treatment was noted, which was highest in neutrophils. The applicant attributes this to the release from cell differentiation block.

mIDH1 VAF was reduced for patients with CR/CRh response and a clear separation of VAF curves for CR/CRh-responders from non-(CRh)-responders was evident under treatment. The decrease in VAF is indicative of a reduction of the mIDH1-containing cells. Still, in some CR/CRh patients the mIDH1 variant allele in peripheral blood cells and BMMCs was retained, consistent with ivosidenib's MoA of ongoing differentiation of immature into mature cells devoid of eradication of mIDH1. This was also confirmed from longitudinal data of 2 CR/CRh study patients having been transferred to HSCT after ivosidenib response. These patients were positively re-tested for the initial R132C mutation at relapse post HSCT and were re-treated with ivosidenib.

Longitudinal data of mIDH VAF showed that in cases of relapse, VAF re-increases were typically detected earliest in bone marrow, as compared to PBMCs and neutrophils. The plots also confirmed that relapse can occur, both, from the same mIDH1 clone (despite previous VAF reduction to below the limit of detection) and independently from a re-detection of the initially detected mIDH1 mutation.

It might hence be likely that a reduction of VAF to below the limit of detection, ascribed as mutational clearance (MC), could be suggestive of a more favourable or more durable clinical response to ivosidenib. However, as the applicant discusses, "while longer duration of CR+CRh and OS were observed in subjects with IDH1-MC in BMMCs, additional data are required to establish whether achieving IDH1-MC status is significantly associated with these measures of clinical benefit in AML".

This is supported – especially in view of the fact that the non-detectability of the mIDH1 clones does not mean having eradicated it, based on ivosidenib's MoA. Although the underlying phase 1 SAT-dataset is too limited for conclusions, it also seems that the sensitivity of the analytical methods of mIDH1 VAF detection applied here might either be too low for an exhaustive predictive relevance for ivosidenib treatment of mIDH1 R/R-AML, or it is, in general, of less importance in a population with several co-mutations to be a potential exclusive tool for MRD monitoring of mIDH1-positive R/R AML patients. Likewise, in Schurhuis et al. (Blood, 2018;131(12):1275-1291) the LeukemiaNet MRD Working Party "recommend against the use of mutations in […] IDH1 […] as single markers of MRD", but these "may have more prognostic significance when used in combination with a second MRD marker."

In addition, it was discussed by Chaturvedi et al. (Leukemia (2016) 30, 1708-1715; studied in cells) that it is not sufficient to inhibit the R-2-HG production to inhibit the mIDH protein. Even though circulating R-2-HG also acts in a paracrine manner on susceptible cells, the mIDH1 protein "has additional oncogenic potency and function beyond R-2-HG".

Investigation of baseline co-mutational burden revealed a broad range of 0-6 co-occurring mutations, mostly of DNMT3A, NPM1, SRSF2, ASXL1, RUNX1, NRAS, and TP53, and with co-mutational burden of <25% up to >75%VAF. Overall, results were in agreement with published data of co-occurring mutations with mIDH1.

CR/CRh responders had significantly less (mean 1.7 mutations) co-mutations compared to the other responder categories (mean 2.6 mutations). Mutations in different RTK pathway genes (NRAS, PTPN11) were found significantly associated with non-CR/CRh responders and non-responders to ivosidenib.

Unfortunately, co-occurring mutations were only fully analysed at BL. Upon request, the applicant provided new genetic data from a limited patient dataset from time of relapse/progression showing that new mutations identified then were either "AML-related" (ie, non-IDH-related) or "IDH-related":

Mutations in RTK pathway genes and IDH-related mutations occurred at similar frequencies, of which second-site mutations in IDH1 and mutations in IDH2 also occurred at similar frequencies and were not mutually exclusive. Mostly, they led to concurrent rebound of 2-HG levels; secondary IDH1 mutations mostly occurred in positions at/near to the binding pocket of ivosidenib or the co-factor NADPH, impairing their binding sterically or by different charge. This was most obvious for the new S280F mutation which decreased the IC50 of ivosidenib more than 1000-fold at mIDH1-R132C (cf., Intlekofer et al., 2018); within the R/R AML patients, secondary IDH2 mutations occurred exclusively at position R140Q.

Overall, these new mutational data show that resistance mechanisms to ivosidenib treatment are complex and that cellular and genetic contexts that influence mIDH1-R/R AML evolution are to date neither fully elucidated nor completely understood. The data also strongly underline that the treatment of mIDH1 alone, ie, as a monotherapy, is insufficient in R/R AML, but combinations or sequential administrations with different targeted treatments or chemotherapy are crucial for durable clinically relevant responses and increase of overall survival.

With regard to the 5 studied isoforms of R132-mIDH1, the PD and efficacy responses of ivosidenib were found to differ dependent on the amino acid when arginine 132 was replaced through mutation. Although the pre-clinical *in vitro* tests had revealed comparable IC50s, differences were observed for % 2-HG inhibition, the CR/CRh rate, DoCR and OS between the R/R AML patients on 500mg QD in this study. The variances seen are, in part, considered clinically relevant, as for OS: 13.7 vs. 4.96 months, for R132G vs. R132S, respectively (FAS 9.03 months).

Acknowledging that the number of study patients with R132L/S/G replacements was quite low compared to R132C, from the requested mIDH1 isoform specific subgroup evaluation the trend for an R132S mutant isoform specific difference seemed further supported, as also no correlation between % variant allele frequency at baseline and 2-HG level was found. The small sample size is, of course, hampering any definite conclusions.

A drug concentration-QTc investigation was undertaken. Single and triplicate 12-lead ECGs were collected predose and at specific time points postdose in Study AG120-C-001 and AG120-C-002, and in Study AG120-C-004. Concurrent samples for assessment of ivosidenib plasma concentrations were obtained at the same nominal time points.

The approach to analyse QT changes in ECG further and to correlate them with drug concentration is acknowledged. However, triplicate ECG documentation as the most reliable technique was preplanned for the expansion cohort and a subset of time points, ie, for Day 1 of cycles 1 and 2 and end of treatment. Singlet ECG, but no triplicate ECG monitoring were planned for the escalation cohort and for certain time points in the expansion cohort. Moreover, it is unfortunate that more than 40% of the available initial data set could not contribute to this approach, as information was incomplete. Thus, the retrieved data set appears rather selected. The mode of ECG assessments in line with the requirements of ICH E14 was provided.

Applying the final model, the primary analysis of the relationship of ΔQTcF to ivosidenib concentration showed significant positive slopes, resulting in a predicted mean effect on QTcF of 17.2 msec, with a 90% CI upper bound of 19.7 msec, at the geometric mean Cmax of 6551 ng/ml for the recommended clinical dose of 500 mg QD. The modelled AG-120 concentration can be increased to determine the hypothetical point at which the 90% CI upper bound of ΔQTcF reaches 20 msec. In the triplicate-data combined model, this point was reached at 6659 ng/mL in Study AG120-C-001 and 4591 ng/mL in Study AG120-C-002. This dose concentration is reached at the recommended dose.According to the results of study AG120-C-001 for the 500 mg dose at steady state, (eg, C1D15), observed dose levels were geometric mean 7108 ng/ml, median 7400 ng/ml, and range 3510-17600 ng/ml. Even for the lower dose of 300 mg at steady state, observed dose levels were geometric mean 5583 ng/ml, median 5660 ng/ml, and range 3950-7700 ng/ml (Study report AG120-C-001, Table 14.5.2.2). These data indicate that for the majority of patients treated with the recommended 500 mg dose, Cmax drug levels can be expected higher than the calculated hypothetical point at which the 90% CI upper bound of ΔQTcF reaches 20 msec. Discussion on expected ΔQTcF for patients whose drug levels reach the upper quartile of the range was provided. The frequency of clinically relevant QT prolongations appeared to be comparable to the observations in the safety data set.

The degree of representability of the drug concentration-QT model was discussed as it affects the value of the generated estimations. As the triplicate dataset is a subset of the full safety data set deviations may occur, however, it appears that patient records with substantial increase in QTcF were underrepresented in relation to the full safety dataset. For the categorical analysis of QTcF/ ΔQTcF, there were substantial differences between the triplicate dataset used in the drug concentration-QT model and the full safety dataset. The drug-concentration-QT model appears not sufficiently representative for the clinical situation in AML to generate drug concentration thresholds. Accordingly, the clinical observations from the full safety dataset were prioritised for the assessment and patient data listings were requested and discussed.

ICH E14 indicates the importance of the analysis of outliers rather than central tendency in late stage clinical trials. While the categorical analysis of maximum post-baseline QTcF was presented, a presentation of the extremes in absolute numbers and increase of QTcF was not identified. In the Concentration-QTc modelling report, a maximum ΔQTcF of 186.7 msec is mentioned. The applicant was requested to provide a listing of all occurrences of QTcF of >500 msec and/or QTcF of >60 msec with absolute QTcF duration, ΔQTcF, concomitant QT-relevant co-medication and drug concentration if available and to discuss these data. With the responses, a listing was provided including 104 observations from 47 patients in whom QTcF of >500 msec and/or ΔQTcF of >60 msec were recorded. The extreme values observed were QTcF 558 msec (subject 504-022) and change in QTcF from baseline 151.7 msec (subject 511-037). QT prolongations were recorded repeatedly for 17/47 patients, ie, up to 18 visits (subject 504-022). The first occurrence ranged from cycle 1 day 1 to cycle 11 day 1.

Only in a minority of observations (9/104) did the patients receive a relevant co-medication. Drug levels were reported for 25/104 observations and ranged from <LLOQ – 22500 ng/ml, median 6430 ng/ml. These values are in line with the dose levels found in study AG120-C-001 for 500 mg dose at

steady state (geometric mean 7180 ng/ml, median 7400 ng/ml, range 3510-17600 ng/ml) and close to the hypothetical point at which the 90% CI upper bound of ΔQTcF reaches 20 msec.

As patients with baseline QTc of ≥450 msec (unless the QTc ≥450 msec was due to a pre-existing bundle branch block) or with a history of long QT syndrome or uncontrolled or significant cardiovascular disease were excluded, these changes occurred in patients without previously known cardiac risks. In the majority of cases with measured drug levels these were found to be in the range expected for the 500 mg QD dose level and only in a small minority of cases concomitant medication may have contributed to the QT-prolongation.

Furthermore, it appeared that the frequency for QT prolongation given in the SmPC was rather low. The applicant was invited to comment and to discuss the frequency of QT-prolongation based on the full information – AESI, AE reporting and ECG documentation - and to adapt the product information appropriately.

In conclusion, although the submitted PD data largely seem to corroborate the proposed mechanism of action of ivosidenib as being an inhibitor of R132-mIDH1 and secondary a releasing agent for the cells' differentiation block, there are several points that still need further in depth investigation – truly in a comparative study with a sufficiently comprehensive patient number. These relate, at least, to:

- Definition of a "threshold of clinically and treatment relevant molecular mIDH1-positivity" in the proposed R/R AML population: ie, to diagnose R132-mIDH1-positivity based on 2-HG levels, and R132-mIDH1 VAF (isoform specific?), which are necessary and sufficient and, above all, clinically relevant for treatment initiation with and (potentially also predictive of) response to ivosidenib in the targeted R/R AML population? For VAF, Medeiros et al. (Leukemia, 2017) had discussed that "a too-low VAF positivity threshold (for example, <2%) may have ambiguous clinical relevance…" – in the study population minimal baseline VAF was measured with 0.86% in a non-responder.
- There may be clinical differences seen in response to ivosidenib treatment between the five R132 mutant isoforms with (at least) R132H/S showing less benefit than the others. This needs to be further evaluated.
- Nature and number of co-existing and secondary mutations do play a role in the R/R AML patient population and are relevant with regard to extent and duration of pharmacodynamic and clinical response to ivosidenib, and for relapses. Individual patient data have shown that relapse from CR is often observed even with continued mutation clearance of mIDH1. Thus, treatment as a monotherapy, as applied for, is considered unsatisfactory in this heterogeneous AML population for durable disease control.
- According to the concentration-ΔQTcF model, relevant QT prolongation can be expected at drug levels that correspond to mean and median values for the recommended 500 mg dose at steady state in AG120-C-001. This represents an important risk for the majority of patients even without co-medication. The observed QT prolongations included extremes of QTcF prolongation up to 558 msec (subject 504-022) and change in QTcF from baseline of 151.7 msec.

3.3.5. Conclusions on clinical pharmacology

All pharmacokinetic and pharmacodynamic concerns have been adequately addressed by the applicant. However, the data generated from this single-arm study AG120-C-001 reflect an insufficiently sized cohort for training and validation of the proposed and investigated pharmacodynamic markers. Even

for a new medicinal product in a R/R AML patient population with limited treatment options, it is considered insufficient (see also non-clinical section).

As a result, it is necessary to perform the discussed analyses similarly in a confirmatory phase 3 study in R/R AML (and further upcoming studies) for corroboration of the PD data, validation of the biomarkers and investigation of missing information. The applicant confirmed implementation of corresponding objectives in 2 ongoing phase 3 studies

Approval can be recommended from a pharmacological point of view.

3.3.6. Clinical efficacy

Introduction

Following discussions with the Committee, the Company has revised the proposed indication to include patients in a last line treatment setting as follows: "Tibsovo is indicated as monotherapy for the treatment of relapsed or refractory acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation in adult patients whohave received at least 2 prior regimens, including at least 1 standard intensive chemotherapy regimen, or are not candidates for standard intensive chemotherapy and have received at least 1 prior non-intensive regimen."

The applicant has mainly provided clinical efficacy results taken from one single phase 1 study AG120-C-001 in subjects with advanced haematologic malignancies with an IDH1 Mutation. This study includes a dose escalation portion to determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) and an expansion portion to further evaluate the safety, tolerability, and clinical activity of ivosidenib. The revised indication proposal is supported by data from the Last line Arm 1+ population (N=109) with a data cutoff date of 02 November 2018. Only patients who have received at least 2 prior regimens including at least 1 standard intensive chemotherapy regimen or patients who are not candidates for standard intensive chemotherapy and have received at least 1 prior non-intensive regimen were included in the Last line Arm1+ population.

Last line Arm 1+data have been retrospectively compared to a subset of patients with confirmed mutated IDH1 status from combination of two databases: AML Study Group (AMLSG) Bioregistry and European Real World Data (RWD) by propensity score matching.

The applicant proposes, as a confirmatory study, an uncontrolled prospective clinical study in a last line IDH1-mutated R/R AML patient population.

Frequency and clinical outcomes of IDH1 mutations in AML

In AML, the IDH1 mutation frequency seems to range between 4.4% and 13.7% (Mardis et al. 2009, Marcucci et al, 2010; Ward et al, 2010; Bullinger et al, 2017, Medeiros et al, 2017). Table 8 shows details regarding the frequency and clinical outcomes of IHD1/2 mutations in AML.

Table 8. IDH mutations in AML: frequency and clinical outcome

	All mIDH		mIDH1-R132		mIDH2 (All)	
Study[a]	**Frequency**	**Prognostic impact of mutation**	**Frequency**	**Prognostic impact of mutation**	**Frequency**	**Prognostic impact of mutation**
Abbas, 2010 (N=893)	17%	↔ OS	6%	↔ OS	11%	OS ↔
Aref, 2015 (N=211)	19%	↓ OS↔CR	8.5%	NR	10.4%	NR
Boissel, 2010 (N=520)	NR	NR	9.6%	↑ RR[a]↓OS[a]	NR	NR
Chotirat, 2012 (N=230)	19.1%	↔ OS	8.7%	↔ OS	10.4%	OS ↔
Chou, 2011 (N=446)	18.2%	↑ OS (trend)	6.1%	↓ OS (trend)	12.1%	OS ↑ DFS ↔ RFS ↔
DiNardo, 2015 (N=826)	20%	↔ OS ↔ CR	7.1%	↔ OS ↔ CR	12.8%	OS ↔ CR ↔
Feng et al 2012 (N=8121)	NR	NR	4.4-9.3%	↓ OS↔CR↓CR[a]		
Green, 2011 (N=1473)	17%	NR	7%	↔ OS	10%	NR
Marcucci, 2010 (N=358)	33.0%	NR	13.7	↔ OS↓DFS	19.3%	OS ↔ CR ↓
Paschka, 2010 (N=805)	16%	↓ OS in NPM1mut/no FLT3-ITDwta mut wta	7.6%	↔ OS	8.7%	OS ↔
Patel, 2011 (N=398)	14.1%	↑ OS in NPM1mut/FLT3-ITDwta	5.8%	↑ OS	8.3%	OS ↑
Ravandi, 2012 (N=358)	30%	↔ OS ↔ CR ↔ EFS	7%	↔ OS ↔ CR ↔ EFS	14%	OS ↔ CR ↔ EFS ↔
Schnittger et al (N=1414)	NR	NR	6.6%	↓ OS (trend)↓EFS↑RR		
Thol, 2010 (MDS=153, AML=53)	NR	NR	NR	NR	12.1%	OS ↔ CR ↔
Wagner, 2010 (N=275)	NR	NR	10.9%	↔OS[c]↔CR↔RFS	NR	NR
Willander, 2014 (N=189)	21.7%	NR	7.9%	↔ OS[c]	13.7%	NR
Yamaguchi, 2014 (N=233)	16.7%	↓ OS↓CR ↔ RFS	8.6%	NR	8.2%	NR

↔ = no effect; ↑ = improved; ↓ = worsened; ALL = acute lymphocytic leukaemia; AML = acute myeloid leukaemia; CR = complete remission; DFS = disease-free survival; EFS = event-free survival; MDS = myelodysplastic syndromes; mIDH2 = mutant isocitrate dehydrogenase isoform 2; NR = not reported; OS = overall survival; RFS = relapse-free survival.
[a] Citations for these publications can be found in Medeiros, 2017.
[b] limited to cytogenetically normal AML
Source: 'clinical overview', table 2, page 14 (adapted from Medeiros 2017)

According data from the literature, the frequency of reported IDH1 R132 gene-mutated AML is between 6% and 13.7%. Insofar, the frequency seems to be slightly lower than that of IDH2 mutations in AML. In subjects with IDH1 mutated AML, the R132 mutation is nearly exclusively described with 5 subtypes (R132C, R132H, R132G, R132S and R132L).

The prognostic impact of mutated IDH1/2 in AML still remains controversial. As to Medeiros 2017, several studies have suggested an association with adverse outcomes whereas others have failed to identify any clear influence on clinical response or survival and still others report improved survival. Differences in prognostic findings may reflect variations in study methodologies; also, the mutational context may influence AML prognosis. Although the meta-analyses presented above may allow reasoning that the presence of an IDH1 mutation may be associated with a worse prognosis compared to wild-type IDH1, this view is not fully shared in the scientific literature. Therefore, in the current 2017 ELN Risk Stratification by Genetics, neither IDH 1 nor IDH2 mutations could be categorised.

Currently, it can only be stated that there seems to be no clear or overwhelming prognostic impact for mutated IDH1 in AML and further confirmation in prospective studies is needed to more clearly elucidate the effect.

Dose-response studies and main clinical studies

As of 11 May 2018, a total of 78 subjects with advanced haematologic malignancies with an IDH1 mutation, primarily R/R AML, had been treated with ivosidenib doses of 100 mg BID, 300 mg QD, 500 mg QD, 800 mg QD, and 1,200 mg QD in dose escalation (Table 9), and 180 subjects were treated with 500 mg QD in expansion.

Table 9. Number of Treated Subjects in Study AG120-C-001 Dose Escalation

100 mg BID n	300 mg QD n	500 mg QD n	800 mg QD n	1,200 mg QD n	Overall n
4	4	48	15	7	78

Pharmacokinetic evaluations included the assessment of dose-proportionality of single- and multiple-dose plasma exposure of ivosidenib (maximum concentration [Cmax], area under the curve from 0 to 24 hours [AUC0-24hr], and area under the curve from 0 to 72 hours [AUC0-72hr]), steady-state PK, and accumulation ratio.

In dose escalation, following a single dose, the mean terminal t½ ranged from 71.8 to 138 hours at doses from 100 to 1,200 mg, supporting a QD dosing regimen.

Following both single and multiple doses, ivosidenib exposures increased less than dose proportionally from 100 mg BID to 1,200 mg QD. Following multiple doses of 500 mg QD, steady-state conditions were achieved by Cycle 1, Day 15, with a range of 1.77- to 2.89-fold accumulation based on area under the curve (AUC) and a range of 1.43- to 1.79-fold accumulation based on Cmax at Cycle 1, Day 15.

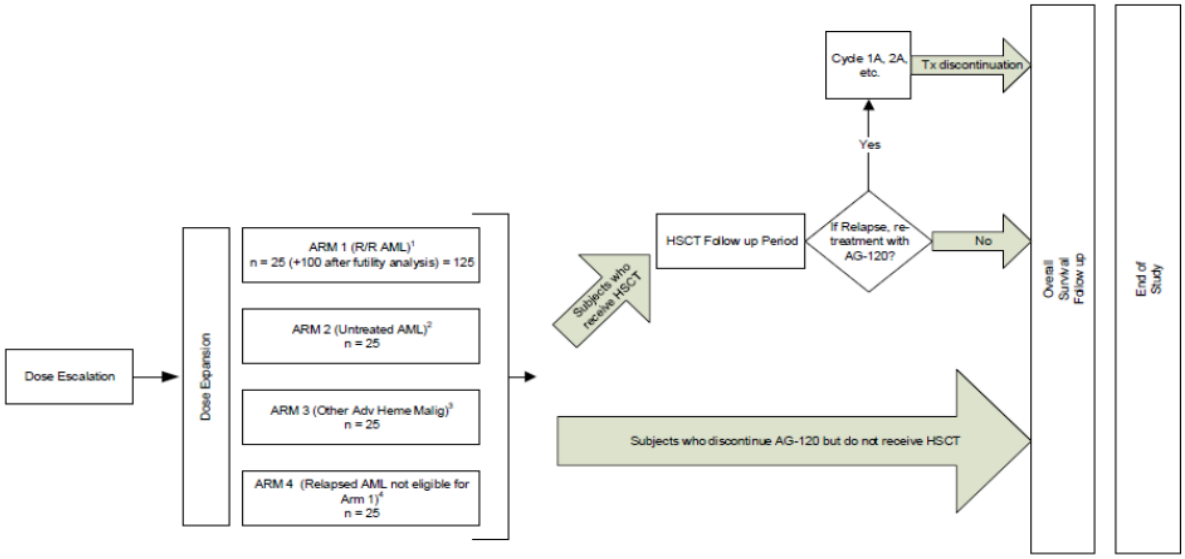
The inter-subject variability in ivosidenib exposure at 500 mg QD in dose escalation was low to moderate, with geometric CV% for the area under the curve over the entire dosing interval (AUC0-tau) and Cmax ranging from 23.1% to 53.1% on Cycle 1, Day 15, and 14.3% to 39.2% on Cycle 2, Day 1.

The PK in expansion (500 mg QD), including Arm 1, was comparable to the PK observed at 500 mg QD in dose escalation.

In summary, determination of the clinical dose of ivosidenib for the expansion portion of Study AG120-C-001 was based on pharmacodynamics (2-HG inhibition), PK, safety, and efficacy data from the dose escalation portion of the study. The applicant concludes that data from the combined dose escalation and expansion portions confirmed that the dose regimen of 500 mg QD ivosidenib is appropriate for the treatment of R/R AML with an IDH1 mutation. This conclusion is not fully assessable.

Main study

Study AG120-C-001 is a phase 1, multicentre, open-label, dose escalation and expansion, safety, PK/pharmacodynamics, and clinical study designed to assess the activity of orally administered ivosidenib in subjects with advanced haematologic malignancies with an IDH1 mutation.



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.

The primary objectives of the study were mainly to assess the safety and tolerability of ivosidenib, to determine the MTD and/or the RP2D of ivosidenib in subjects with advanced haematologic malignancies, and finally to assess the clinical activity of ivosidenib in subjects with R/R AML with an IDH1 mutation who are enrolled in Arm 1 of the expansion portion.

Secondary objectives of the study were to describe the dose-limiting toxicities of ivosidenib in subjects with advanced haematologic malignancies, to characterise the PK of AG-120 in subjects with advanced haematologic malignancies, and to evaluate the PK/pharmacodynamic relationship of AG-120 and 2-HG.

The trial population included R/R AML (according to WHO criteria), untreated AML (in subjects ≥60 years of age who were not candidates for standard therapy due to age, performance status, and/or

adverse risk factors), or myelodysplastic syndrome (MDS) according to WHO classification with refractory anaemia with excess blasts (refractory anaemia with excess blasts subtype-1 or 2), or considered high-risk by the Revised International Prognostic Scoring System (Greenberg et al, 2012), that was recurrent or refractory, or the subject was intolerant to established therapy known to provide clinical benefit for their condition. Patients with impaired renal and hepatic function were not to be enrolled in the trial. Subjects with clinical symptoms suggesting active central nervous system leukaemia or known CNS leukaemia were excluded from the trial. Overall, inclusion and exclusion criteria are consistent with the population of the claimed indication.

Subjects with IDH1-mutated R/R AML in Study AG120-C-001 included Arm 1+ and Arm 4+ (ie, subjects enrolled in Arm 1 and Arm 4 of the expansion portion of the study, plus subjects with R/R AML in dose escalation whose starting dose was 500 mg QD and who were eligible for Arm 1 and Arm 4 as determined by Investigators).

The Arm 1+ subjects in Study AG120-C-001 represent an R/R AML population with a serious unmet medical need who have no effective therapies available, defined as: subjects who relapsed after transplantation; subjects in second or later relapse; subjects who were refractory to initial induction or reinduction treatment; and/or subjects who relapsed within 1 year of initial treatment, excluding subjects with favorable-risk status (according to National Comprehensive Cancer Network [NCCN] Guidelines, version 1.2015).

Arm 4+ enrolled subjects with R/R AML who did not strictly meet eligibility criteria for Arm 1, but who had failed available standard of care or were unable to receive standard of care due to age, comorbid condition, performance status, and/or adverse risk factors. These subjects can similarly be viewed as a population with an unmet medical need for whom no effective treatments are available, based on the fact that they were enrolled in a clinical trial and had failed or were unable to receive standard of care therapy.

Evaluation of both QD and twice daily (BID) dosing regimens (100 mg BID, 300 mg QD, 500 mg QD, 800 mg QD, and 1,200 mg QD) in the dose escalation portion of the study allowed for the optimal dosing schedule to be selected for the expansion portion of the study. Based on available data, a dose of 500 mg QD was selected for the expansion portion (see Section 4.1 for details).

Methods

Study Participants

Inclusion Criteria

Subjects must have met all of the following criteria to be enrolled in the study:

1. Subjects must be ≥18 years of age.
2. Subjects must have had an advanced haematologic malignancy including:

   Dose Escalation Portion:

   - Relapsed and/or primary refractory AML as defined by WHO criteria; or
   - Untreated AML, ≥60 years of age and not candidates for standard therapy due to age, performance status, and/or adverse risk factors, according to the treating physician and with approval of the Medical Monitor.
   - Myelodysplastic syndrome with refractory anaemia with excess blasts (subtype RAEB-1 or RAEB-2), or considered high-risk by the IPSS-R (Greenberg, et al. 2012), that was

recurrent or refractory, or the subject was intolerant to established therapy known to provide clinical benefit for their condition (ie, subjects must not have been candidates for regimens known to provide clinical benefit), according to the treating physician and with approval of the Medical Monitor. (Subjects with other relapsed and/or primary refractory haematologic cancers, for example CMML, who fulfilled the inclusion/excluding criteria may have been considered on a case-by case basis, with approval of the Medical Monitor.)

Expansion Portion:

- **Arm 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).**
- Arm 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.
- Arm 3: Other non-AML IDH1-mutated R/R advanced haematologic malignancies, where no standard of care treatment option was available. Such as:
  - Myelodysplastic syndrome 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 haematologic 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.
- **Arm 4: Relapsed AML subjects not eligible for Arm 1 who had failed available standard of care or were 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.**

3. Subjects must have had documented IDH1 R132 gene-mutated disease:
   - For subjects in the dose escalation portion, IDH1 mutation could be based on local evaluation. (Centralised testing was performed retrospectively.)
   - For subjects in the expansion portion, central testing of IDH1 gene-mutated disease was required during screening to confirm eligibility.
4. Subjects must have been amenable to serial bone marrow sampling, peripheral blood sampling, and urine sampling during the study.

   The diagnosis and evaluation of AML or MDS was made by bone marrow aspiration and biopsy. If an aspirate was unobtainable (ie, a "dry tap"), the diagnosis could be made from the core biopsy.

5. Subject must have been able to understand and willing to sign an informed consent. A legally authorised representative could consent on behalf of a subject who was otherwise unable to provide informed consent, if acceptable to and approved by the site and/or site's IRB.

In **addition**, subjects must have had Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, platelet count ≥20,000/µL and adequate renal and hepatic function (and fulfil some other commonly used criteria, contraception etc).

Exclusion Criteria

Subjects who met any of the following criteria were not to be enrolled in the study:

1. Subjects who previously received prior treatment with a mutant-specific IDH1 inhibitor and progressed on therapy.
2. Subjects who had undergone HSCT within 60 days of the first dose of AG-120, or subjects on immunosuppressive therapy post-HSCT at the time of screening, or with clinically significant graft-versus-host disease (GVHD). (The use of a stable dose of oral steroids post-HSCT and/or topical steroids for ongoing skin GVHD was permitted with Medical Monitor approval.)
3. Subjects who received systemic anticancer therapy or radiotherapy <14 days prior to their first day of study drug administration. Hydroxyurea was allowed prior to enrolment and after the start of AG-120 for the control of peripheral leukemic blasts in subjects with leukocytosis (eg, white blood cell [WBC] counts >30,000/µL).

5+6. Subjects taking sensitive CYP3A4 or P-gp transporter-sensitive substrate medications were excluded from the study unless they could be transferred to other medications within ≥5 half-lives prior to dosing, or unless the medications can be properly monitored during the study.

7. Subjects for whom potentially curative anticancer therapy was available.
9. Subjects with an active severe infection that required anti-infective therapy.
11. **Subjects with New York Heart Association (NYHA) Class III or IV congestive heart failure or left ventricle ejection fraction (LVEF) <40% or a history of myocardial infarction within the last 6 months of screening/ known unstable or uncontrolled angina pectoris, Subjects with a known history of severe and/or uncontrolled ventricular arrhythmias. Subjects with heart rate corrected QT interval (QTc) ≥450 msec or with other factors that increased the risk of QT prolongation or arrhythmic events (eg, heart failure, hypokalemia, family history of long QT interval syndrome) at screening. Subjects with bundle branch block and a prolonged QTc interval were to be reviewed by the Medical Monitor for potential inclusion or subjects taking medications that were known to prolong the QT interval.**
20. Subjects with clinical symptoms suggesting active central nervous system (CNS) leukaemia or known CNS leukaemia or with other immediately life-threatening, severe complications of leukaemia

Recruiting sites/Regions: In the study report it is summarised that a total of 25 study sites participated in this study, with 23 sites in the United States (US) and 2 sites in France. Most of the patients were recruited in hospitals/centres well-known for high level cancer research and treatment in the US (including MD Anderson n=49, Dana Farber Cancer Institute n=21, Sloan Kettering CC n=30 and others). In addition, 35 European patients from France were also included (Institut Gustave Roussy n=29 / Hopital Haut-Leveque n=6).

Treatments

AG-120 was initially administered orally BID (approximately every 12 hours) on Days 1 to 28 in 28-day cycles. Twice daily dosing was discontinued after the first cohort and a QD dosing regimen was implemented, based on the favorable PK profile. Subjects were given a dosing diary for each treatment cycle.

Objectives

The initial objectives defined are typical and acceptable for a phase 1 trial aiming to characterise safety and tolerability of treatment of a new product or determinethe maximum tolerated dose (MTD) for a phase 2 trial, respectively. Obviously, the intention to assess the clinical efficacy of ivosidenib in subjects with relapsed and/or refractory (R/R) acute myelogenous leukaemia (AML) with an IDH-1 mutation was added later (17.02.2017) to the study protocol. Since the trial was planned as an **exploratory trial no hypothesis was defined**.

According last amendment No.5 (Protocol Version 6.0), dated 17.02.2017

The **primary objectives** of the study were defined:

- To assess the safety and tolerability of treatment with AG-120 administered continuously as a single agent dosed orally on Days 1 to 28 of a 28-day cycle in subjects with advanced haematologic malignancies. The initial dosing regimen was twice daily (approximately every 12 hours). Based on the emerging data, a once daily (approximately every 24 hours) dosing schedule has been implemented. Alternative dosing schedules, including administration of the same total daily dose using different dosing schedules in concurrent cohorts, may be explored as agreed upon by the Clinical Study Team.
- To determine the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D) of AG-120 in subjects with advanced haematologic malignancies.
- **To assess the clinical activity of AG-120 in subjects with relapsed and/or refractory (R/R) acute myelogenous leukaemia (AML) with an IDH1 mutation who are enrolled in Arm 1 of the expansion phase.**

The **secondary objectives** of the study were, to describe the dose-limiting toxicities (DLTs), to characterise the pharmacokinetics and pharmacodynamic (PK/PD) of ivosidenib in subjects with advanced haematologic malignancies including R/R-AML, as well as characterising the clinical activity in subjects with advanced haematologic malignancies.

Outcomes/endpoints

Primary endpoint:

The primary efficacy endpoint was **CR+CRh rate** (rate of complete remission (CR) plus CR with partial haematologic recovery (CRh))

CR was based on Investigator assessment of response per modified IWG response criteria.

CRh was derived by the Sponsor and is defined as having all CR criteria except absolute neutrophil count (ANC) >0.5 × 109/L (500/µL) and platelet count >50 × 109/L (50,000/µL) (Kantarjian et al, 2017). CRh requires a reduction in disease burden of BM blasts to <5% and an improvement in ANC to Grade 3 or better and platelet count to Grade 2 or better.

Secondary efficacy endpoints were the following:

Table 10. Secondary efficacy endpoints, Study AG120-C-001

Secondary Endpoint	Definition
Complete remission rate	Rate of CR
Objective response rate	Rate of CR, CRi, CRp, PR, and MLFS for AML subjects. The best overall response for each subject was determined by the following hierarchical orders: • CR, CRi/CRp, PR, MLFS, SD, PD, and not evaluable. Subjects whose best overall response was either CRi or CRp were presented as 1 response category
Duration of CR+CRh	Among subjects who had a best response of CR or CRh, duration of CR+CRh was calculated as the date of the first documented CR or CRh to the date of the first documented confirmed relapse or death, whichever occurred first. Responders without confirmed relapse or death were censored at the date of last adequate response assessment prior to the date of alternative anticancer therapy. Duration of CR+CRh was applicable to subjects with AML only.
Duration of complete remission	Among subjects who had a best response of CR, DOCR was calculated as the date of the first documented CR to the date of the first documented confirmed relapse or death, whichever occurred first. Responders without confirmed relapse or death were censored at the date of last adequate response assessment prior to the date of alternative anticancer therapy.
Duration of response	Among subjects who had a best response of CR, CRi, CRp, PR, or MLFS/mCR, DOR was calculated as the date of the first occurrence of any response to the date of first documented confirmed relapse/progression or death, whichever occurred first. Responders without confirmed relapse/progression or death were censored at the date of last adequate response assessment that was SD or better prior to the date of alternative anticancer therapy.
Time to CR+CRh	Among subjects who had a response of CR or CRh, time to CR+CRh was assessed from the date of the first dose to the date of the first CR or CRh. Time to CR+CRh was applicable to subjects with AML only.
Time to response	Among responders, time to response was assessed from the date of the first dose to the date of the first occurrence of any response, which includes CR, CRi/CRp, PR, and mCR/MLFS.
Time to complete remission	Among subjects who had a response of CR, time to CR was assessed from the date of the first dose to the date of the first CR.
Event-free survival	Event-free survival was calculated from the date of first dose to the date of documented confirmed relapse/progression or death, whichever occurred first. Subjects without a confirmed relapse/progression or death were censored at the last adequate response assessment that was SD or better prior to the date of alternative anticancer therapy.
Overall survival	Overall survival was defined as the time from first dose to the date of death due to any cause. Subjects who were alive at the analysis cutoff date were censored at the last known alive date. The assessment of survival was added in Protocol Amendment 3 (Version 4.0), so these data may not be available for all subjects.

Abbreviations: AML = acute myeloid leukaemia; CR = complete remission; CRh = CR with partial haematologic recovery; CRi = CR with incomplete blood count recovery; CRp = CR with incomplete platelet recovery; DOCR =

duration of complete remission; DOR = duration of response; mCR = marrow CR; MLFS = morphologic leukaemia-free state; PD = progressive disease; PR = partial remission; SD = stable disease.

Randomisation and blinding (masking)

Randomisation

This is an ongoing, open-label, single arm study. All subjects received AG-120. Treatment assignment did not require randomisation, blinding, or stratification.

Blinding (masking)

N/A

Statistical methods

Details regarding the final planned statistical analyses are documented in the SAP, which was finalised and signed prior to lock of the clinical database.

Data from subjects in the expansion portion were pooled with data from eligible subjects in the dose escalation portion whose starting dose was 500 mg QD. These were designated as Arm 1+, Arm 2+, Arm 3+, and Arm 4+.

- Arm 1+: combined 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.
- Arm 2+: combined untreated AML subjects in Arm 2 of the expansion and untreated AML subjects in the dose escalation whose starting dose was 500 mg QD.
- Arm 3+: combined MDS subjects in Arm 3 of the expansion, and MDS subjects in the dose escalation whose starting dose was 500 mg QD.
- Arm 4+: combines all other R/R AML subjects in the dose escalation and expansion who are not eligible for Arm 1 and whose starting dose was 500 mg QD.

The following subject populations (ie, analysis sets) were planned, as outlined in the protocol and study SAP, and were used for presentation of the data:

- Full Analysis Set (FAS): 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 FAS was used for analyses of efficacy and was the default analysis set for all other analyses, unless otherwise specified.
- Full Analysis Set 1 (FAS1): A subset of subjects in the FAS who received the first dose of AG-120 at least 6 months prior to 12 May 2017. The FAS1 was the primary efficacy analysis set for Expansion Arm 1, including Arm 1 eligible subjects from dose escalation whose starting dose was 500 mg QD.
- Safety Analysis Set (SAS): All subjects who were enrolled and received at least 1 dose of study treatment. Subjects were classified according to the actual treatment received, where treatment received was defined as the assigned dose level/schedule if it was received at least once, or the first dose level/schedule received if assigned treatment was never received. The SAS was used for the analysis of safety data.
- Dose Determining Set (DDS): All subjects who either had a DLT during Cycle 1, or who completed at least 75% of their planned Cycle 1 doses (21 out of 28 days), and were

considered by the Clinical Study Team to have had sufficient safety data available to conclude that a DLT did not occur during Cycle 1. The DDS was used as the analysis set during dose escalation to make dose decisions in determining the MTD/RP2D.

The primary clinical study report (CSR) presented results from the study as of a data cutoff date of 12 May 2017. In the primary CSR, the primary efficacy analysis of the study was based on all treated Arm 1+ subjects from FAS1, ie, whose first dose was at least 6 months prior to the data cut-off date 12 May 2017. An addendum to the CSR was provided to summarise updated efficacy and safety results based on a data cutoff date of 11 May 2018. As of 11 May 2018, the primary efficacy analysis set FAS1 was identical to the FAS since all subjects in the study received their first dose of ivosidenib at least 12 months prior to 11 May 2018; therefore, the efficacy analyses in this MAA are based on the FAS.

According to the clinical overview, the efficacy analysis in this application is primarily based on all subjects with R/R AML whose starting dose was 500 mg QD in the FAS, defined as all subjects who were enrolled and received at least 1 dose of study treatment, ie, Arm 1+ and Arm 4+ subjects.

CR+CRh rate was summarised by the number and percentage of subjects with best overall response of CR or CRh, together with 2-sided exact binomial 95% confidence interval (CI).

Secondary efficacy endpoints included CRR, ORR, duration of CR+CRh, DOCR, DOR, OS, time to CR+CRh, TTCR, TTR, and EFS. Exact binomial 95% CIs were also provided for secondary response endpoints. For time to event endpoints, the 25th percentile, median, and 75th percentile of the response duration with 2-sided 95% CI, as well as Kaplan-Meier (KM) estimates at 3, 6, 9, and 12 months were provided. Kaplan-Meier curves were also presented.

Duration of CR+CRh was calculated as the date of the first documented CR or CRh to the date of the first documented confirmed relapse or death, whichever was earlier. Detailed censoring rules are provided in Table 11. Sensitivity analysis of duration of CR+CRh were also performed with censoring rule variations. Duration of CR and duration of response were analysed analogously. Overall survival was defined as the time from first dose to the date of death due to any cause. Subjects who were alive at the analysis data cutoff date were censored at the last date known to be alive. Time to response analyses included time to CR+CRh, TTR, TTCR, time to first response among CR/CRh subjects, and time to first response among CR subjects. The time to the respective event was calculated from first dose. Event-free survival (EFS) was defined as the interval from the date of the first dose to the date of documented confirmed relapse/progression or death, whichever occurred first; censoring rules are provided in Table 11.

Table 11. Censoring Rules for Time-to-Event Analyses Using Response Assessments

Situation	Date of Censoring
No post-baseline assessment, no death	Date of first dose
No death or documented confirmed PD/relapse**	Date of last adequate* response assessment
Alternate anti-cancer therapy (excluding transplant and conditioning regimen) started prior to documented confirmed PD/relapse or death**	Date of last adequate response assessment prior to the alternate anti-cancer therapy
2 or more consecutive missing scheduled response assessments from last response assessment prior to documented confirmed PD/relapse or death	Date of last adequate response assessment prior to missed scheduled assessments: > 61 days (2 cycles + 5-day window) from last adequate response assessment if within 12 months of first dose, and > 117 days (4 cycles + 5-day window) from last adequate response assessment if after 12 months of first dose***

Abbreviations: PD = progressive disease
* Adequate disease assessment is defined as a response assessment other than "not done" or "not evaluable"
** For subjects who discontinue AG-120 treatment to receive HSCT and remain on study to be followed until documented disease relapse, confirmation of relapse is not required in this situation, and a single occurrence of relapse will be considered as documented "confirmed" relapse in analyses of response.
*** For post-transplant response assessments, the window for missed scheduled assessments will not be applied, all response assessments post-transplant will be included in the calculation.

Formal hypothesis testing was neither planned nor performed but only 95% CIs were provided, although criteria CR and CR+CRh rate to be considered as evidence of clinically significant activity of AG-120 were mentioned in sample size justification. In the original clinical study report, the primary analysis was based on all treated Arm 1+ subjects whose first dose was at least 6 months prior to the data cut-off date 12 May 2017. However, according to the clinical overview, the efficacy analysis in this application is primarily based on all subjects with R/R AML whose starting dose was 500 mg QD in the FAS (ie, all subjects in Arm 1+ and Arm 4+) with data cut-off 12 May 2018. The now proposed restricted indication is supported by data from the Last Line Arm 1+ population (N=109) of Study AG120-C-001, which have been updated through a data cutoff date of 02 November 2018. Performing only descriptive analyses and changing the analysis population post-hoc is acceptable for an exploratory phase 1 study, but is obviously not according to usual standards for a study that shall serve as the single pivotal study supporting an application.

The FAS is defined as all subjects who were enrolled and received at least 1 dose of study treatment. An analysis including patients from Arm 1+ who were enrolled but not treated was provided as sensitivity analysis (considering them as non-responders).

As in the time to event analyses, censoring reasons other than data cut-off are potentially informative. Censoring reasons were provided to allow assessment of the influence of potential informative censoring.

Supportive efficacy analyses to assess the consistency of the primary analysis included:

- Arm 1+ subjects using the FAS
  - This includes all treated Arm 1+ subjects as of the data cutoff date.
- Arm 1 subjects using the FAS
  - This subset does not include eligible dose escalation subjects.
- Per-protocol subset of Arm 1+ subjects using the FAS

- This excludes subjects whose baseline BM blasts are <5%, who do not have IDH1 R132 gene-mutated disease, or who have previously received prior treatment with an IDH1 mutant-specific inhibitor and progressed on therapy.

- Arm 4+ subjects using the FAS
  - This includes all Arm 4+ subjects as of the data cutoff date. Arm 4+ combines all other R/R AML subjects in dose escalation and expansion who are not eligible for Arm 1 and whose starting dose was 500 mg QD.

Subgroup analyses were performed for the CR rate and the CR+CRh rate in all R/R AML subjects whose starting dose was 500 mg QD in FAS and Arm 1+ subjects in FAS.

Results

The primary evidence of efficacy for the initial indication was based on data from all R/R AML subjects across dose escalation and expansion whose starting dose was 500 mg QD using the FAS (i.e., Arm 1+ and Arm 4+ subjects). The data cutoff date for the original MAA efficacy analysis was 11 May 2018.

A total of 258 subjects were enrolled in the pivotal study, including 159 and 20 subjects in Arms 1+ and 4+ (R/R AML patients), respectively. In the R/R AML population, the majority of the subjects enrolled in the study AG120-C-001 had discontinued treatment (94.4%) at the time of the data cut-off date, mainly due to disease progression (54.7%). The median age of the 179 treated subjects with R/R AML was 67 years, and ranged from 18 to 87 years.

All but 3 subjects had IDH1 mutations at the R132 position. Of note, the claimed indication concerns AML with IDH1 R132 mutation. Most subjects (58.7%) had intermediate cytogenetic risk status at baseline.

The median number of prior therapies (prior regimens + investigational therapies) and prior regimens (cytotoxic agents administered to induce a remission) was 2 (range 1 to 6). Overall, the majority of subjects (74 subjects, 41.3%) had received 1 prior therapy, mainly driven by lower number of prior therapies in Arm 4+ (80% with 1 prior therapy) compared with Arm 1+ subjects (respectively 36,5%, 28.9% and 34.6% with 1, 2 or ≥3 prior therapies). Whether all patients were pretreated adequately cannot be inferred according to the data presented. (OC) This is consistent with the characteristics of the 20 subjects from Arm 4+ who did not strictly meet eligibility criteria for Arm 1 but who had failed available standard of care or were unable to receive standard of care due to age, comorbid condition, performance status, and/or adverse risk factors.

A total of 43 (24.0%) R/R AML subjects had undergone prior transplants and 6 (3.4%) had undergone ≥2 prior transplants. No patients had prior transplant in Arm 4+.

Table 12. Key demographic and baseline characteristics for subjects with R/R AML whose starting dose was 500 mg QD (Full Analysis Set)

Parameter	Arm 1+ (N=159)	Arm 4+ (N=20)	All R/R AML at 500 mg QD (N=179)
Sex, n (%)			
Female	77 (48.4)	12 (60.0)	89 (49.7)
Male	82 (51.6)	8 (40.0)	90 (50.3)
Age (years)[1]			
Median (Min, Max)	67.0 (18, 87)	71.5 (59, 80)	67.0 (18, 87)

Age Categories (years)			
<65	62 (39.0)	5 (25.0)	67 (37.4)
≥65	97 (61.0)	15 (75.0)	112 (62.6)
Race, n (%)			
White	99 (62.3)	13 (65.0)	112 (62.6)
Black	8 (5.0)	2 (10.0)	10 (5.6)
Not reported	37 (23.3)	5 (25.0)	42 (23.5)
Other[2]	15 (9.4)	0	15 (8.4)
Baseline ECOG PS, n (%)			
0	31 (19.5)	5 (25.0)	36 (20.1)
1	84 (52.8)	15 (75.0)	99 (55.3)
2	42 (26.4)	0	42 (23.5)
3	2 (1.3)	0	2 (1.1)
Nature of AML, n (%)			
De novo	110 (69.2)	10 (50.0)	120 (67.0)
Secondary	49 (30.8)	10 (50.0)	59 (33.0)
Subjects Who: (≥1 Criteria May Apply), n(%)			
Relapsed After Transplantation	43 (27.0)	0	43 (24.0)
Are in Second or Later Relapse	26 (16.4)	0	26 (14.5)
Are Refractory to Initial Induction or Reinduction Treatment	106 (66.7)	0	106 (59.2)
Relapsed Within 1 Year of Initial Treatment[3]	17 (10.7)	0	17 (9.5)
Were in first relapse	0	15 (75.0)	15 (8.4)
Other[4]	0	5 (25.0)	5 (2.8)
Cytogenetic Risk Status by Investigator, n (%)			
Favorable	0	0	0
Intermediate	89 (56.0)	16 (80.0)	105 (58.7)
Poor	48 (30.2)	2 (10.0)	50 (27.9)
Unknown	5 (3.1)	0	5 (2.8)
Missing	17 (10.7)	2 (10.0)	19 (10.6)
Subjects with Baseline Transfusions[5], n (%)	108 (67.9)	8 (40.0)	116 (64.8)
Subjects with Prior HSCT for AML, n (%)	43 (27.0)	0	43 (24.0)
Number of Prior Anticancer Therapies, n (%)[6]			
0	0	0	0
1	58 (36.5)	16 (80.0)	74 (41.3)
2	46 (28.9)	4 (20.0)	50 (27.9)
≥3	55 (34.6)	0	55 (30.7)
Median (Min, Max)	2.0 (1, 6)	1.0 (1, 2)	2.0 (1, 6)

Number of Prior Anticancer Regimens[6], n (%)			
0	0	2 (10.0)	2 (1.1)
1	60 (37.7)	15 (75.0)	75 (41.9)
2	49 (30.8)	3 (15.0)	52 (29.1)
≥3	50 (31.4)	0	50 (27.9)
Median (Min, Max)	2.0 (1, 6)	1.0 (1, 2)	2.0 (1, 6)

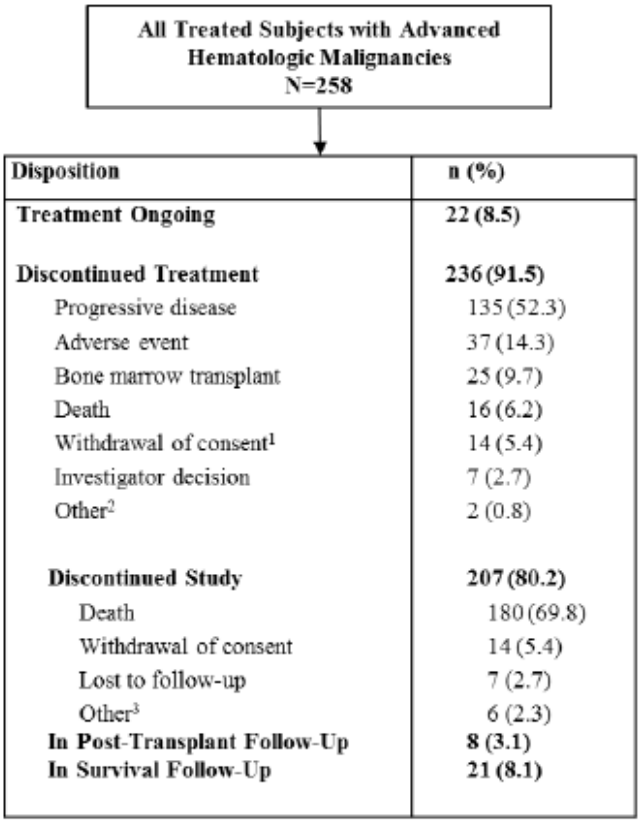
Abbreviations: AML = acute myeloid leukaemia; CR = complete remission; ECOG = Eastern Cooperative Oncology Group; FAS = Full Analysis Set; HSCT = haematopoietic stem cell transplant; NCCN = National Comprehensive Cancer Network; PS = performance status; QD = once daily; R/R = relapsed or refractory.
Note: In accordance with local regulations, race and ethnicity were not reported by study sites in France.
FAS: all subjects who were enrolled and received at least 1 dose of study treatment, analysed according to the dose assigned.
[1] Age (years) = Integer portion of [(ICF date − Date of Birth + 1) / 365.25].
[2] Included race categories of Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, and Other.
[3] Excluding subjects with favorable-risk status according to NCCN Guidelines, Version 1.2015.
[4] Three subjects received initial therapy with other investigational or non-cytotoxic agents and did not achieve CR, 1 subject did not achieve CR to initial therapy with only 1 cycle of first line nonintensive therapy (lack of CR following at least 2 cycles of nonintensive therapy or 1 cycle of intensive therapy was required to fulfil eligibility for Arm 1), and 1 did not achieve CR to initial therapy with 3 cycles of first line nonintensive therapy, though therapy was interrupted and ultimately discontinued due to infectious complications rather than lack of response.
[5] The baseline transfusion period was defined as any transfusion occurring within 56 days prior to the first dose of ivosidenib.
[6] Number of prior therapies and prior regimens was determined by medical review. **Prior regimens** included only cytotoxic agents administered to induce a remission. Non-cytotoxic investigational therapies given alone were not considered a regimen. **Prior therapies** included both prior regimens and investigational therapies; investigational treatments were only counted as a therapy if not already counted as a regimen. Not included in either prior therapies nor prior regimens were supportive care therapies, transplant conditioning chemotherapy, transplant administered to subjects in remission, and consolidation chemotherapy administered to subjects in remission.

Numbers analysed

A total of 268 subjects were enrolled and 258 had received at least 1 dose of AG-120 during the dose escalation (n=78) and expansion (n=180) portions of Study AG120-C-001 across 5 dosing cohorts as of the data cutoff date for the primary CSR (12 May 2017). As of 11 May 2018, a total of 22 subjects remained on treatment and 29 subjects had discontinued treatment and were in either post-transplant follow-up or survival follow-up. Among those 258 subjects, 223 subjects were treated at study sites in the US, and 35 subjects were treated at study sites in France. Median treatment duration for these 258 subjects was 3.9 months (range, 0.07, 45.4 months).

Of the 258 treated subjects, 179 subjects in the FAS had R/R AML whose starting dose was 500 mg QD AG-120; of these, 159 were included in the Arm 1+ subset. Arm 2+ comprised 34 subjects with untreated AML, and Arm 3+ comprised 12 subjects with myelodysplastic syndrome (MDS).

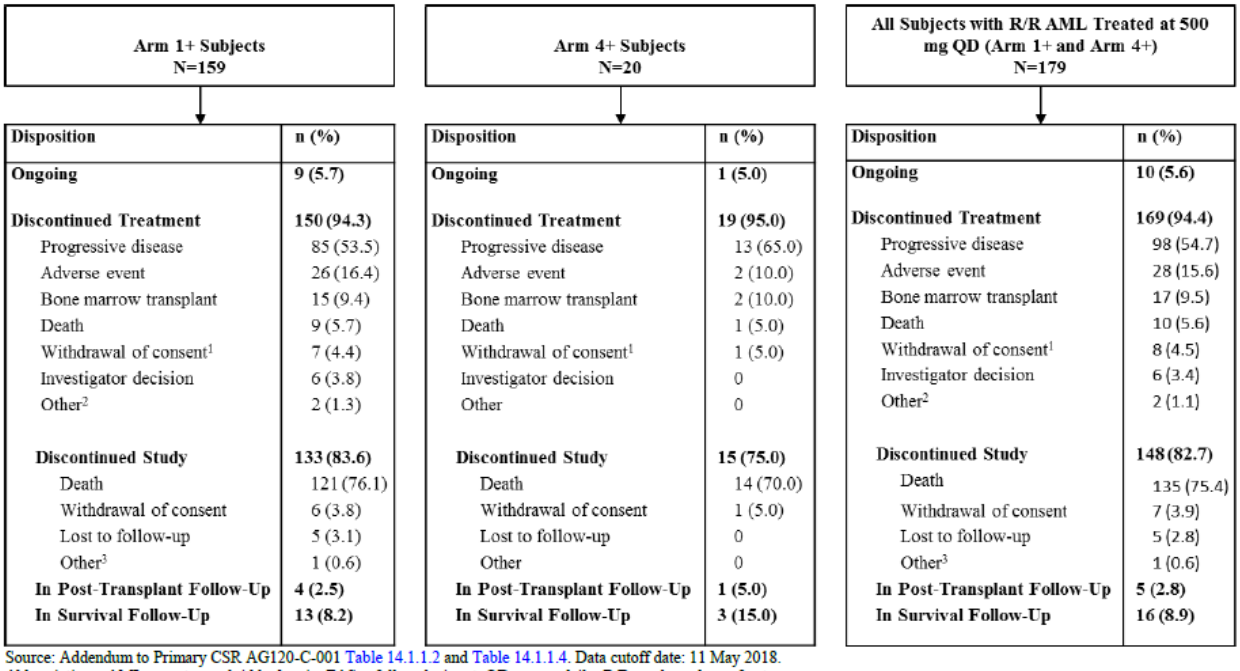
Figure 11. Overall subjects flow diagram (Full analysis set)



Disposition	n (%)
Treatment Ongoing	**22 (8.5)**
Discontinued Treatment	**236 (91.5)**
Progressive disease	135 (52.3)
Adverse event	37 (14.3)
Bone marrow transplant	25 (9.7)
Death	16 (6.2)
Withdrawal of consent[1]	14 (5.4)
Investigator decision	7 (2.7)
Other[2]	2 (0.8)
Discontinued Study	**207 (80.2)**
Death	180 (69.8)
Withdrawal of consent	14 (5.4)
Lost to follow-up	7 (2.7)
Other[3]	6 (2.3)
In Post-Transplant Follow-Up	**8 (3.1)**
In Survival Follow-Up	**21 (8.1)**

Source: Addendum to Primary CSR AG120-C-001 Table 14.1.1.3 and Listing 16.2.1.1. Data cutoff date: 11 May 2018.
[1] Withdrawal of consent includes withdrew consent and subject decision.
[2] Included reasons of: subject sought alternative therapy (n=1) and intercurrent medical condition (n=1).
[3] Included reasons of: disease progression (n=3), subject completed follow-up period (n=1), end of treatment of subject was before the Protocol v4.0 in which all subjects entered the survival follow-up phase (n=1), and study was completed (n=1).

Figure 12. Flow diagram for all subjects with R/R AML whose starting dose was 500 mg QD (FAS)



Disposition	n (%)	Disposition	n (%)	Disposition	n (%)
Ongoing	**9 (5.7)**	**Ongoing**	**1 (5.0)**	**Ongoing**	**10 (5.6)**
Discontinued Treatment	**150 (94.3)**	**Discontinued Treatment**	**19 (95.0)**	**Discontinued Treatment**	**169 (94.4)**
Progressive disease	85 (53.5)	Progressive disease	13 (65.0)	Progressive disease	98 (54.7)
Adverse event	26 (16.4)	Adverse event	2 (10.0)	Adverse event	28 (15.6)
Bone marrow transplant	15 (9.4)	Bone marrow transplant	2 (10.0)	Bone marrow transplant	17 (9.5)
Death	9 (5.7)	Death	1 (5.0)	Death	10 (5.6)
Withdrawal of consent[1]	7 (4.4)	Withdrawal of consent[1]	1 (5.0)	Withdrawal of consent[1]	8 (4.5)
Investigator decision	6 (3.8)	Investigator decision	0	Investigator decision	6 (3.4)
Other[2]	2 (1.3)	Other	0	Other[2]	2 (1.1)
Discontinued Study	**133 (83.6)**	**Discontinued Study**	**15 (75.0)**	**Discontinued Study**	**148 (82.7)**
Death	121 (76.1)	Death	14 (70.0)	Death	135 (75.4)
Withdrawal of consent	6 (3.8)	Withdrawal of consent	1 (5.0)	Withdrawal of consent	7 (3.9)
Lost to follow-up	5 (3.1)	Lost to follow-up	0	Lost to follow-up	5 (2.8)
Other[3]	1 (0.6)	Other	0	Other[3]	1 (0.6)
In Post-Transplant Follow-Up	**4 (2.5)**	**In Post-Transplant Follow-Up**	**1 (5.0)**	**In Post-Transplant Follow-Up**	**5 (2.8)**
In Survival Follow-Up	**13 (8.2)**	**In Survival Follow-Up**	**3 (15.0)**	**In Survival Follow-Up**	**16 (8.9)**

Source: Addendum to Primary CSR AG120-C-001 Table 14.1.1.2 and Table 14.1.1.4. Data cutoff date: 11 May 2018.
Abbreviations: AML = acute myeloid leukemia; FAS = full analysis set; QD = once daily; R/R = relapsed or refractory.
FAS: all subjects who were enrolled and received at least 1 dose of study treatment, analyzed according to the dose assigned.
Arm 1+: R/R AML subjects in expansion Arm 1 and R/R AML subjects in escalation whose starting dose was 500 mg QD and who were eligible for Arm 1 as determined by Investigators.
Arm 4+: all other R/R AML subjects in dose escalation and expansion who are not eligible for Arm 1 and whose starting dose was 500 mg QD.
[1] Withdrawal of consent includes withdrew consent and subject decision.
[2] Included: subject sought alternative therapy (n=1) and intercurrent medical condition (n=1).
[3] Disease progression.

Changes in the conduct of the study or planned analysis

Because study AG120-C-001 is an uncontrolled open-label first-in-human phase 1 study being used as pivotal evidence for a CMA, 6 amendments with partially extensive modifications made to the study design are not surprising. Amendments included modifications of the primary and secondary objectives and endpoints, study population, posology of the study drug, schedule of assessments, statistical methodology, study endpoints, sample size (list incomplete). A comprehensible overview about the relevant changes performed, was submitted (OC). Therefore, data provided from study AG120-C-001 remain highly exploratory at the end; analyses performed are descriptive (which is also acknowledged in the protocol and amendments).

Outcomes and estimation

Primary efficacy endpoint

As of the 11 May 2018 data cutoff date, a total of 258 subjects have been administered AG-120 during the dose escalation and expansion portions of Study AG120-C-001 across 5 dosing cohorts. A total of 179 subjects in the FAS had R/R AML and were treated with 500 mg QD AG-120; of these, 159 were included in the Arm 1+ subset and the remaining 20 subjects met the criteria for Arm 4+.

Overall, the CR+CRh rate in subjects with R/R AML was 31.8% (95% CI: 25.1, 39.2), including 29.6% (95% CI: 22.6, 37.3) in the Arm 1+ subset and 50% (95% CI 27.2, 72.8) in the Arm 4+ subset. Results were consistent in other Arm 1 subsets.

Table 13. CR+CRh rate (Full analysis set)

Best Response	Arm 1+	Arm 1	Per-protocol Subset of Arm 1+	Arm 4+	All R/R AML at 500 mg QD
	(N=159)	(N=126)	(N=154)	(N=20)	(N=179)
CR, n (%)	35 (22.0)	30 (23.8)	35 (22.7)	8 (40.0)	43 (24.0)
95% 2-Sided Exact Binomial CI	15.8, 29.3	16.7, 32.2	16.4, 30.2	19.1, 63.9	18.0, 31.0
CRh[1], n (%)	12 (7.5)	9 (7.1)	12 (7.8)	2 (10.0)	14 (7.8)
95% 2-Sided Exact Binomial CI	4.0, 12.8	3.3, 13.1	4.1, 13.2	1.2, 31.7	4.3, 12.8
CR+CRh, n (%)	47 (29.6)	39 (31.0)	47 (30.5)	10 (50.0)	57 (31.8)
95% 2-Sided Exact Binomial CI	22.6, 37.3	23.0, 39.8	23.4, 38.4	27.2, 72.8	25.1, 39.2

Abbreviations: AML = acute myeloid leukaemia; ANC = absolute neutrophil count; BM = bone marrow; CI = confidence interval; CR = complete remission; CRh = CR with partial haematologic recovery; FAS = Full Analysis Set; QD = once daily; R/R = relapsed or refractory.
FAS: all subjects who were enrolled and received at least 1 dose of study treatment, analysed according to the dose assigned.
Arm 1+: R/R AML subjects in expansion Arm 1 and R/R AML subjects in escalation whose starting dose was 500 mg QD and who were eligible for Arm 1 as determined by Investigators.
Arm 4+: all other R/R AML subjects in dose escalation and expansion who are not eligible for Arm 1 and whose starting dose was 500 mg QD.
Per-protocol subset of Arm 1+: Arm 1+ subjects excluding those whose baseline BM blast was <5%, did not have IDH1 R132 gene-mutated disease (as determined based on local testing for dose escalation subjects and central testing for expansion subjects), and/or had previously received prior treatment with a mutant-specific IDH1 inhibitor and progressed on therapy.
[1] Derived by Sponsor and defined as having all CR criteria except ANC (>0.5 × 109/L [500/µL]) and platelet count (>50 × 109/L [50,000/µL]). When blood counts were not available on the same day as BM blast count, the closest value within ±8 days was used.

Secondary efficacy endpoints

Response assessment

The median duration of CR for subjects with R/R AML was 8.8 months (95% CI: 6.5, 12.9) and the median duration of CR+CRh of 8.2 months (95% CI: 5.5, 12.0). The median duration of CR+CRh for Arm 1+ and Arm 4+ subjects was respectively 8.2 months (95% CI: 5.5, 12.0) and 6.5 months (95% CI: 1.9, NE). Duration of response is a key result but the lack of comparator hampers the ability to demonstrate that the benefit is better than available treatment options.

Table 14. Response to treatment with Ivosidenib in subjects with R/R AML whose starting dose was 500 mg QD (Full Analysis Set)

Efficacy Parameter	Arm 1+ (N=159)	Arm 4+ (N=20)	All R/R AML at 500 mg QD (N=179)
CR rate, n (%)	35 (22.0)	8 (40.0)	43 (24.0)
95% 2-Sided Exact Binomial CI	15.8, 29.3	19.1, 63.9	18.0, 31.0
Median Duration of CR, months (95% CI)	8.8 (5.7, 18.3)	8.8 (1.9, NE)	8.8 (6.5, 12.9)
Median Time to CR, months (Min, Max)	2.8 (0.9, 8.3)	3.22 (1.0, 4.6)	2.8 (0.9, 8.3)
Median Time to First Response Among Subjects Whose Best Response was CR, months (Min, Max)	1.9 (0.9, 4.6)	1.9 (1.0, 4.6)	1.9 (0.9, 4.6)
CR+CRh rate, n (%)	47 (29.6)	10 (50.0)	57 (31.8)
95% 2-Sided Exact Binomial CI	22.6, 37.3	27.2, 72.8	25.1, 39.2
Median Duration of CR+CRh, months (95%	8.2	6.5	8.2
CI)	(5.5, 12.0)	(1.9, NE)	(5.5, 12.0)
Median Time to CR+CRh, months (Min,	2.7	1.9	2.0
Max)	(0.9, 5.6)	(1.0, 4.6)	(0.9, 5.6)
Median Time to First Response Among Subjects Whose Best Response was CR or CRh, months (Min, Max)	1.9 (0.9, 4.7)	1.9 (1.0, 4.6)	1.9 (0.9, 4.7)

Abbreviations: AML = acute myeloid leukaemia; ANC = absolute neutrophil count; BM = bone marrow; CI = confidence interval; CR = complete remission; CRh = complete remission with partial haematologic recovery; CRi = CR with incomplete blood count recovery; CRp = CR with incomplete platelet recovery; FAS = Full Analysis Set; MLFS = morphologic leukaemia-free state; PR = partial remission; QD = once daily; R/R = relapsed or refractory.
FAS: all subjects who were enrolled and received at least 1 dose of study treatment, analysed according to the dose assigned.
Arm 1+: Subjects with R/R AML in expansion Arm 1 and subjects with R/R AML in escalation whose starting dose was 500 mg QD and who were eligible for Arm 1 as determined by Investigators.
Arm 4+: all other R/R AML subjects in dose escalation and expansion who are not eligible for Arm 1 and whose starting dose was 500 mg QD.
Note: CRh was derived by Sponsor and defined as having all CR criteria except ANC (>0.5 × 109/L [500/μL]) and platelet count (>50 × 109/L [50,000/μL]). When blood counts were not available on the same day as BM blast count, the closest value within ±8 days was used. Time to first response (CR, CRi, CRp, PR, MLFS) among subjects whose best response was CR or CRh = time from date of first dose to date of first occurrence of response.

Overall survival

Median OS for subjects with R/R AML was 9.0 months (95% CI: 7.1, 10.2) as of 11 May 2018; and respectively 8.8 months (6.8, 10.2) and 10.6 months (4.8, 12.6) in Arm 1+ and Arm 4+. OS in such a single arm trial is hardly interpretable.

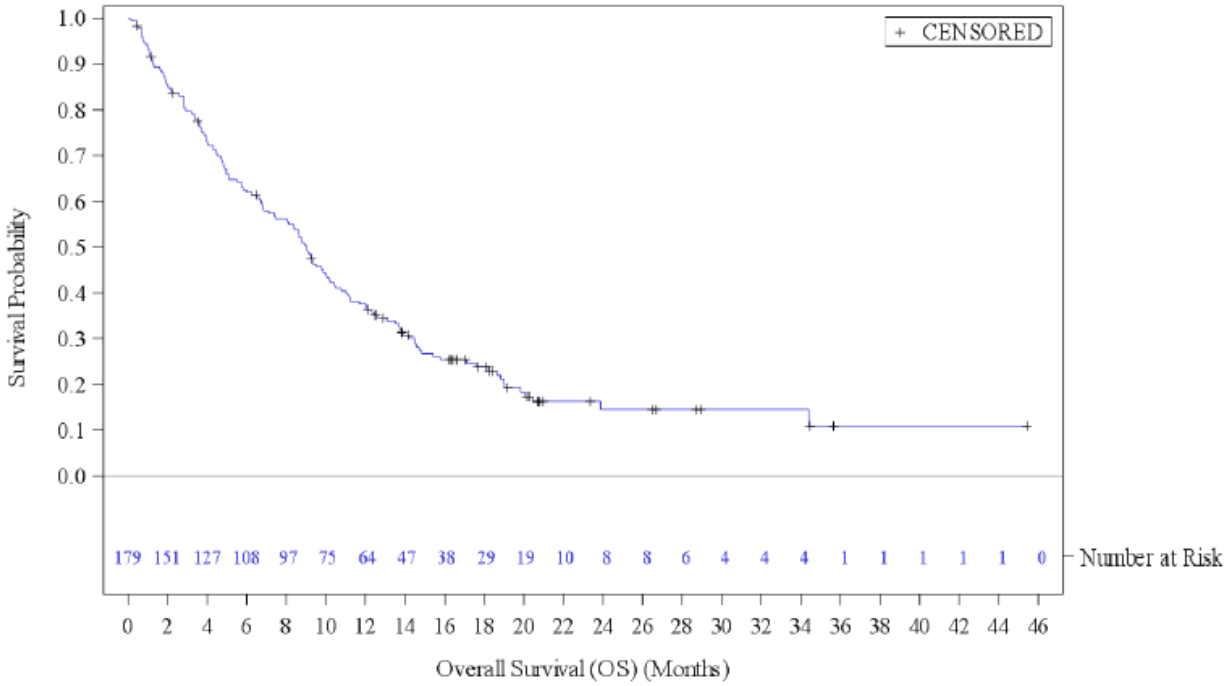
Table 15. Overall survival (Full Analysis Set)

Overall Survival (months)	Arm 1+ (N=159)	Arm 4+ (N=20)	All R/R AML at 500 mg QD (N=179)
Events, n (%)	125 (78.6)	15 (75.0)	140 (78.2)
Censored, n (%)	34 (21.4)	5 (25.0)	39 (21.8)
Median (95% CI)	8.8 (6.8, 10.2)	10.6 (4.8, 12.6)	9.0 (7.1, 10.2)
Min, Max	0.2, 35.6*	0.7, 45.4*	0.2, 45.4*
Kaplan-Meier estimate, %			
3 months	78.4	90.0	79.7
6 months	60.9	70.0	61.9
9 months	49.1	60.0	50.4
12 months	36.5	45.0	37.5

Abbreviations: AML = acute myeloid leukaemia; CI = confidence interval; FAS = Full Analysis Set; QD = once daily; R/R = relapsed/refractory.
Note: Overall Survival = time from first dose to the date of death due to any cause. Subjects who were alive at the analysis data cutoff date were censored at the last date known to be alive.
FAS: all subjects who were enrolled and received at least 1 dose of study treatment, analysed according to the dose assigned.
Arm 1+: R/R AML subjects in expansion Arm 1 and R/R AML subjects in escalation whose starting dose was 500 mg QD and who were eligible for Arm 1 as determined by Investigators.
Arm 4+: all other R/R AML subjects in dose escalation and expansion who are not eligible for Arm 1 and whose starting dose was 500 mg QD.
* indicates censored observation

The Kaplan-Meier curve of OS for all subjects with R/R AML whose starting dose was 500 mg QD is provided in Figure 13. The median duration of follow-up for these 179 subjects was 20.7 months (range: 0.2, 45.4).

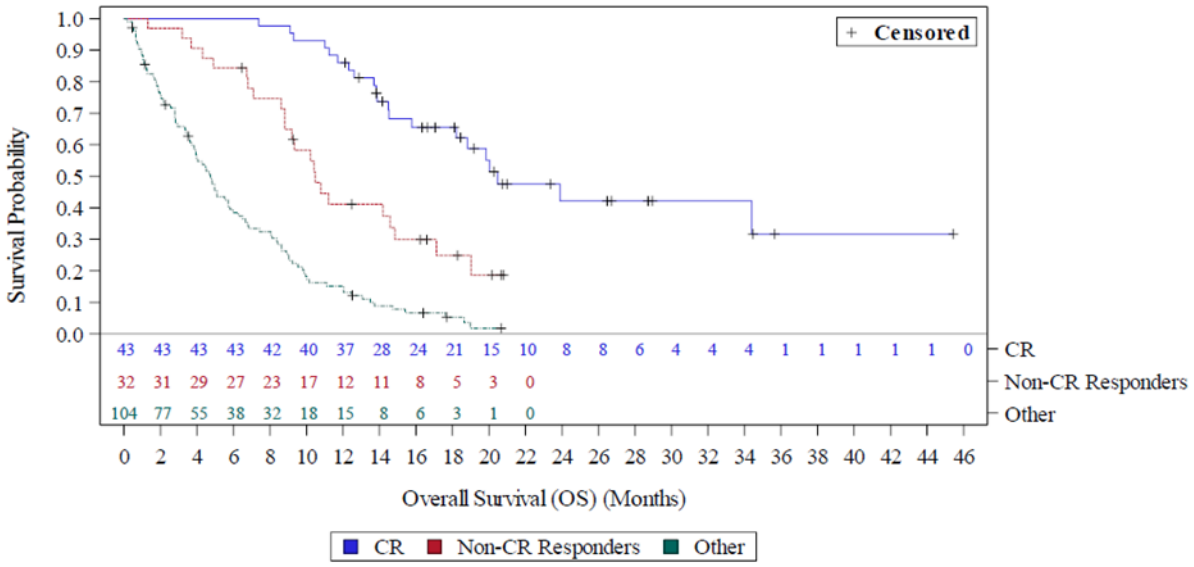
Figure 13. Kaplan-Meier curve of OS for all subjects with R/R AML whose starting dose was 500 mg QD (Full Analysis Set)



Source: Addendum to Primary CSR AG120-C-001 Figure 14.2.6.1D. Data cutoff date: 11 May 2018.
Abbreviations: AML = acute myeloid leukemia; CSR = clinical study report; QD = once daily; R/R = relapsed or refractory.
Full Analysis Set: All subjects who were enrolled and received at least 1 dose of study treatment, analyzed according to the dose assigned.

Median OS estimates for non-CR responders and non-responders were 10.5 months (95% CI: 8.8, 14.9) and 4.7 months (95% CI: 3.7, 5.7), respectively.

Figure 14. Kaplan-Meier Curve of Overall Survival by Best Response: CR vs Non-CR Responders vs Other for R/R AML Subjects Whose Starting Dose was 500 mg QD (Full Analysis Set)



Source: Addendum to Primary CSR AG120-C-001 Figure 14.2.10.2D. Data cutoff date: 11 May 2018.
Abbreviations: AML = acute myeloid leukemia; CR = complete remission; CRi = complete remission with incomplete blood count recovery; CRp = complete remission with incomplete platelet recovery; FAS = Full Analysis Set; MLFS = morphologic leukemia-free state; NA = not assessed; PD = progressive disease; PR = partial remission; R/R = relapsed or refractory; QD = once daily; SD = stable disease.
Non-CR responders included responders whose best overall response was CRi, CRp, PR, or MLFS. Other includes subjects with best responses of SD, PD, or NA.
FAS: all subjects who were enrolled and received at least 1 dose of study treatment, analyzed according to the dose assigned

OS was longest for subjects who achieved CR with a median duration of OS of 20.5 months (95% CI: 15.8, NE). The duration of OS was shorter for non-responders (best response of SD, PD or NE) with a median duration of OS of 4.7 months (95% CI: 3.7, 5.7).

However, the analysis of OS according to response status is influenced by immortal time bias (ie, patients need to have survived for some time in order to achieve response) such that a clear conclusion on the causal relationship between response and longer survival time is not possible based on these data.

This effect is certainly of interest and supports the CR results discussed above. However, contribution of treatment to time related endpoints such as OS cannot be directly ascertained in a single arm study and therefore needs contextualisation, especially given the very heterogeneous study and target population.

About 21% of patients were censored in the OS analysis. However, censoring reasons were missing and should be given and the completeness of follow-up should be evaluable. If a relevant number of censorings was non-administrative (ie, not due to patient known to be alive at analysis cut-off), the potential influence of informative censoring on the results should be discussed.

Event-Free Survival

The median EFS for Arm 1+ subjects was 3.8 months (95% CI: 3.6, 5.5 months) and was consistent for all R/R AML subjects in FAS. The estimated EFS at 3, 6, 9, and 12 months was 59.4%, 38.0%, 27.2%, and 18.2% for Arm 1+ subjects in FAS, respectively; and was similar for all R/R AML subjects whose starting dose was 500 mg QD in FAS.

Table 16. Event Free Survival

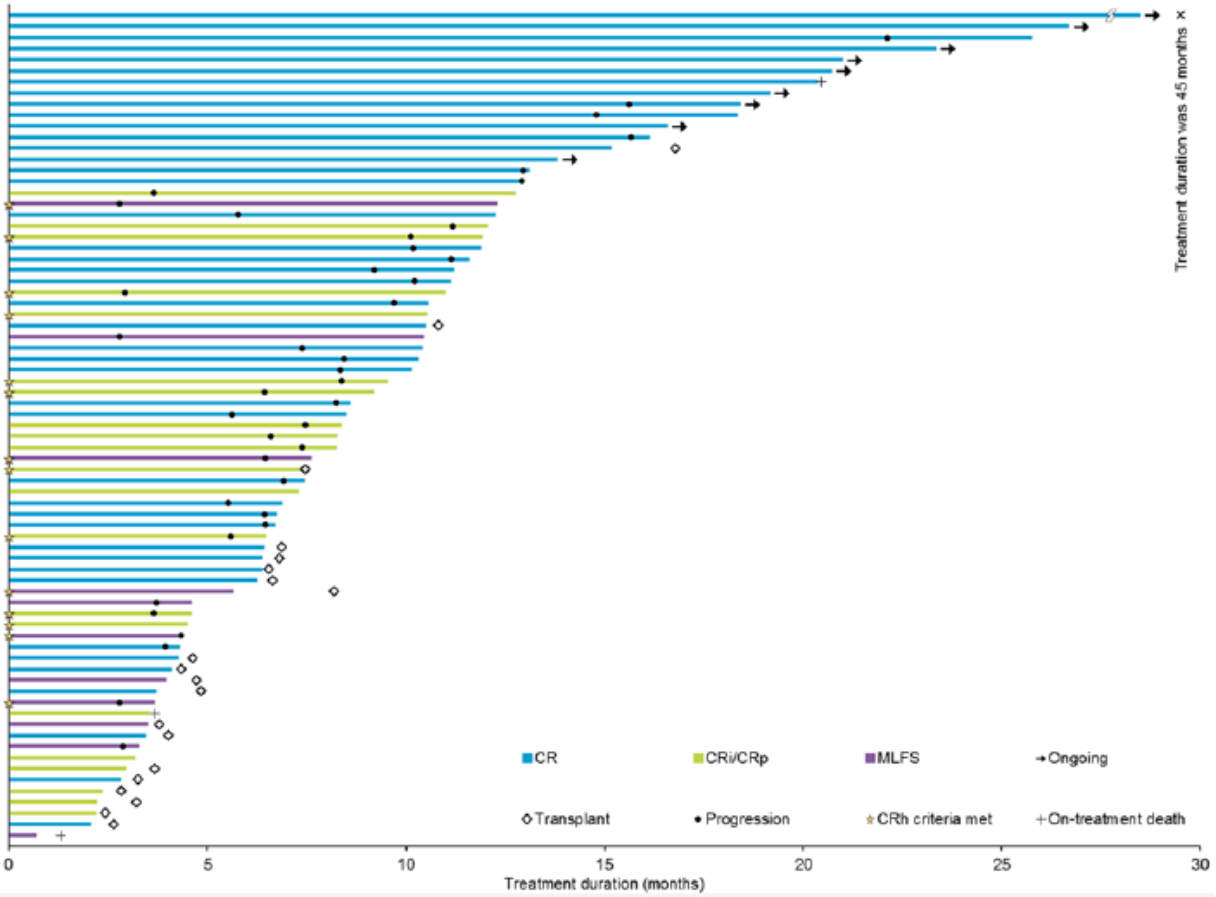
Event-free Survival (months)	Arm 1+ (N=159)	All R/R AML at 500 mg QD (N=179)
Events, n (%)	126 (79.2)	142 (79.3)
Censored, n (%)	33 (20.8)	37 (20.7)
Median (95% CI)	3.8 (3.6, 5.5)	3.8 (3.7, 5.6)
Min, Max	0.0*, 34.5*	0.0*, 44.3*
Kaplan-Meier estimate, %		
3 months	59.4	61.0
6 months	38.0.9	39.7
9 months	27.2	26.7
12 months	18.2	18.9

Data cutoff date: 11 May 2018.
Abbreviations: AML = acute myeloid leukaemia; CI = confidence interval; Max = maximum; Min = minimum; QD = once daily; R/R = relapsed and/or refractory.
Note: Event-free survival = interval from first dose date to date of documented confirmed progressive disease/relapse or death, whichever occurred first.
[1] Subjects without documentation of confirmed relapse/progression or death were censored at the date of last adequate response assessment that was stable disease or better before the start of alternative anticancer therapy.
* indicates censored observation.

Duration of treatment

As of 11 May 2018, the maximum treatment duration was 45.4 months for all subjects with R/R AML and 26.7 months for Arm 1+ subjects, which included patients with extensive prior treatments.

Figure 15. Duration of treatment and best response for responders with R/R AML whose starting dose was 500 mg QD (Full Analysis Set)



Source: Addendum to Primary AG120-C-001 CSR Figure 14.2.2.4B. Data cutoff date: 11 May 2018.
Abbreviations: CR = complete remission; CRh = complete remission with partial hematologic recovery; CRi = complete remission with incomplete blood count recovery; CRp = complete remission with incomplete platelet recovery; MLFS = morphologic leukemia-free state; PD = progressive disease.
Note: This figure excludes non-responders (subjects with stable disease, with PD, not assessed, or not evaluated). Star symbol on left margins indicates only that CRh was achieved in a given subject; this does not indicate time that CRh criteria were met.
FAS: all subjects who were enrolled and received at least 1 dose of study treatment, analyzed according to the dose assigned.

In response to D180 LoOI, the applicant revised the proposed indication to include patients in a last line treatment setting.

A subset of subjects treated with ivosidenib in Arm 1+ who meet the criteria for a last line treatment setting described in the revised indication were identified according to the following criteria:

- Subjects who were candidates for standard IC had to have received a minimum of 2 lines of prior therapy; a standard IC regimen as initial treatment followed by either an additional standard IC regimen and/or a non-intensive HMA regimen.
  - Reinduction for refractory disease was considered an independent regimen if the chemotherapy agents changed in dose or duration compared to the initial induction.
  - Induction regimens administered to treat relapsed disease were considered an independent regimen, even if identical in composition to a prior regimen administered to achieve remission.

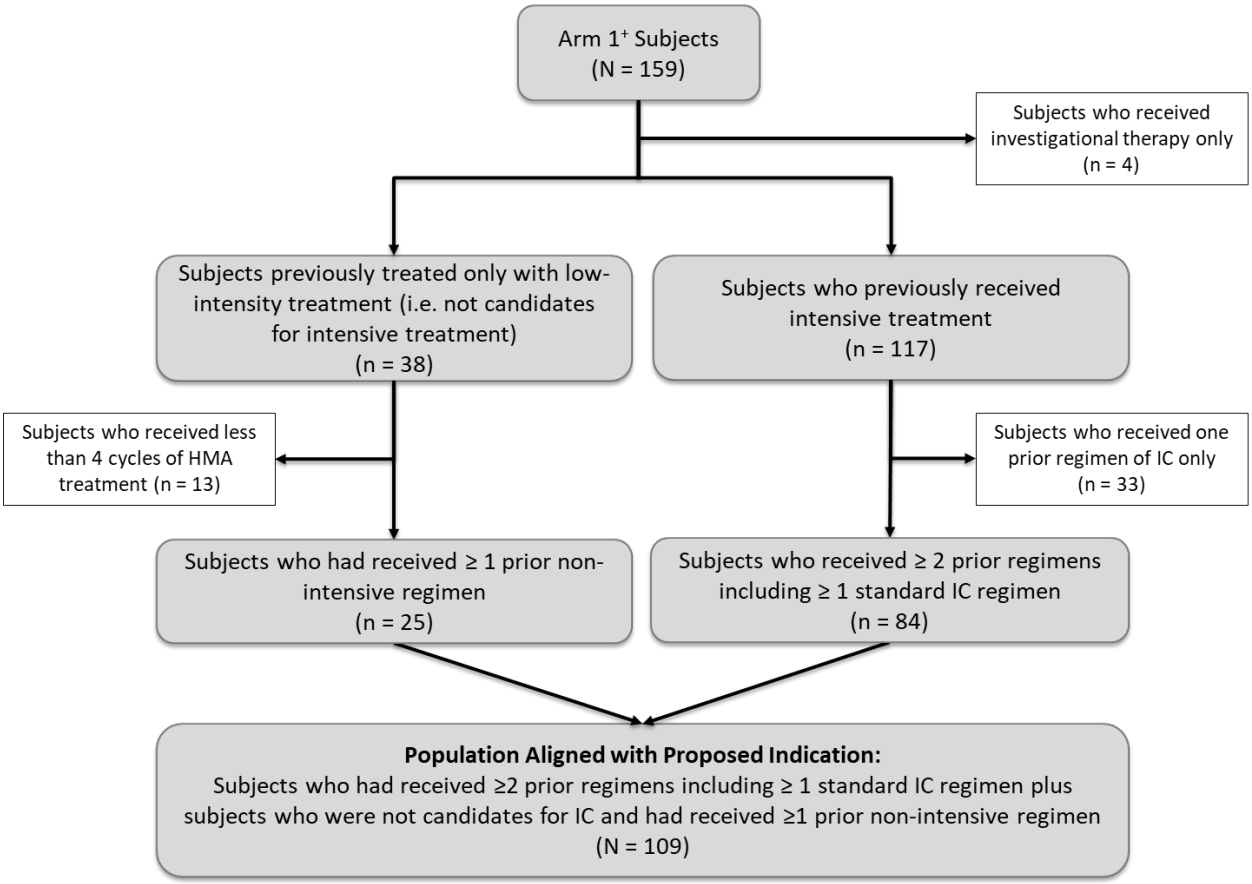
- Consolidation and HSCT administered in remission were considered a single regimen; HSCT was only considered a separate regimen if it was administered as salvage treatment to a subject with active disease (ie, not in remission).
- A minimum of 2 cycles of HMA treatment was required to be considered a regimen.
- Therapies administered to treat disease symptoms or comorbidities were not considered a regimen.

- Subjects who were not candidates for standard IC had to have received a minimum of 4 cycles of an HMA to be considered as having received a non-intensive regimen.
- Investigational therapy was only considered as part of a line of therapy if given in conjunction with a standard IC regimen or a non-intensive regimen. If investigational therapy was given alone, it was not considered a prior regimen.

Based on this review, 109 subjects treated with ivosidenib in Arm 1+ met the last line indication criteria (Figure 16):

- 84 subjects who received at least 2 prior regimens including at least 1 standard IC regimen; and
- 25 subjects who were not candidates for standard IC and had received at least 1 prior non-intensive regimen.

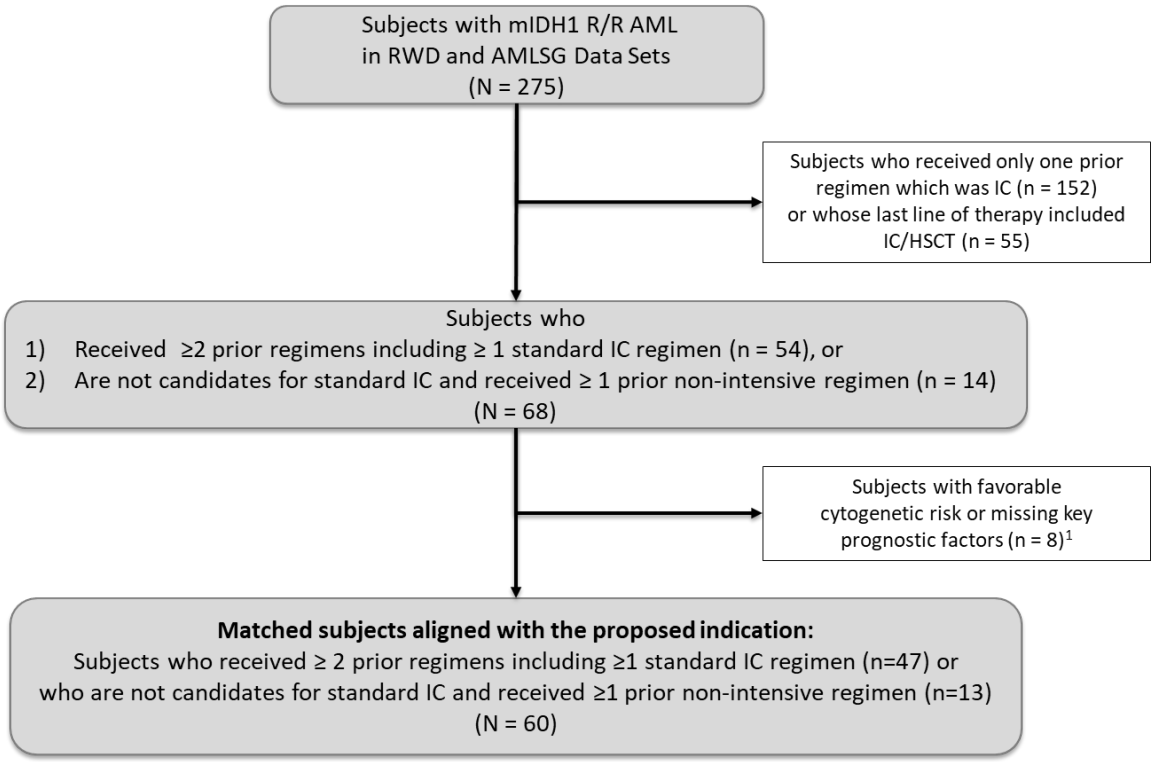
Figure 16. Identification of Subjects Treated with Ivosidenib in Arm 1+ in a Last Line Setting



Historical Control Data for Patients Treated in a Last Line Setting

In order to provide further supportive evidence of benefit of treatment with ivosidenib in a last line R/R AML setting, the applicant summarised outcomes in patients with similar baseline and disease characteristics from an external historical control cohort of patients (comprising the AMLSG database and a set of European RWD collected by Agios). Figure 17 shows how patients in the historical control data set (AMLSG + RWD data sets) were selected to match the patient population treated with ivosidenib in Arm 1^+ in a last line setting.

Figure 17. Historical Control Data Set – Patients with mIDH1 Relapsed or Refractory AML Treated in a Last Line Setting



Source: AG120-C-001 Table 14.1.1.1A.

Table 17 shows the distribution of prognostic factors for the subjects treated with ivosidenib in Arm 1^+ in a last line setting and for patients in the historical control data set prior to matching and after matching.

Table 17. Summary of Prognostic Factors – Subjects Treated with Ivosidenib in Arm 1+ in a Last Line Setting and Historical Control Data Set for a Last Line Setting

Parameter	Last Line Arm 1+ (N=109)	AMLSG + RWD (N=60)	Standardised Difference	Weighted Standardised Difference[1]	
				Optimal Full[2]	IPTW[3]
Prior HSCT, n (%)	31 (28.4)	16 (26.7)	0.040	0.038	0.016
Age, years					
Mean (StDev)	64.1 (14.00)	61.8 (13.05)	0.167	-0.121	-0.012
Median (Min, Max)	67 (18, 85)	64 (30, 83)			
Number of Prior Regimens, n (%)					
<2	23 (21.1)	12 (20.0)	0.027	-0.249	-0.028
≥2	86 (78.9)	48 (80.0)	-0.027	0.249	0.028
Nature of AML, n (%)					
De novo	77 (70.6)	45 (75.0)	-0.098	0.057	0.012
Secondary	32 (29.4)	15 (25.0)	0.098	-0.057	-0.012
Cytogenetic Risk Status, n (%)					
Intermediate	68 (62.4)	44 (73.3)	-0.236	-0.003	0.021
Poor	41 (37.6)	16 (26.7)	0.236	0.003	-0.021
Primary refractory, n (%)	36 (33.0)	14 (23.3)	0.217	-0.010	-0.018

[1] Propensity scores are estimated using prognostic factors: history of HSCT, age, number of prior regimens for AML (<2, ≥2), nature of AML (de novo, secondary), cytogenetic risk, primary refractory status.
[2] Based on the weights estimated by optimal full matching method.
[3] Based on the weights estimated by inverse probability of treatment weighting method.

The same restrictions (patients have received at least 2 prior regimens including at least 1 standard intensive chemotherapy regimen, or are not candidates for standard intensive chemotherapy and have received at least 1 prior non-intensive regimen) as the Last line Arm1+ population were applied for the external historical control cohort of patients (comprising the AMLSG database and a set of European RWD collected by the applicant) in order to define a subset of patients who met the criteria for a last line treatment setting. 60 patients were selected from the historical cohort.

After propensity score matching, demographic baseline criteria and history of the disease criteria, such as history of HSCT, number of prior regimens for AML, and nature of AML were well-balanced between Last line Arm1+ and the AMLSG + RWD database. Poor cytogenetic risk and primary refractory status were in a higher proportion of patients in Last line Arm1+ which could not favour efficacy and safety results in this arm. The data cutoff date for the Last Line Arm 1+ results is 02 November 2018. Table 18 presents the CR rates for subjects treated with ivosidenib in Arm 1^+ in a last line setting and for the patients in the matched historical control data set. For the historical control, only data from the RWD dataset (collected by Agios; N=43) are included as the CR rate could not be estimated in the AMLSG dataset since only "response to therapy" was available without a distinction on the type of response (CR, CRi, CRp or MLFS); thus leading to a 2.5 size ratio between Last line Arm 1+ and RWD cohorts. A higher CR rate (18.3%) was observed in Last line Arm1+ than in historical arm (7%). This result should be taken with caution as the CIs overlapped.

Table 18. Summary of Complete Remission – Subjects Treated with Ivosidenib in Arm 1^+ in a Last Line Setting and Historical Control Data Set for a Last Line Setting

Complete Remission (CR)	Last Line Arm 1^+ (N=109)	RWD[1] (N=43)
n (%)	20 (18.3)	3 (7.0)
95% CI[1]	11.6, 26.9	1.5, 19.1

Source: AG120-C-001 Table 14.2.1.14.9. Data cutoff date for AG120-C-001: 02 November 2018.

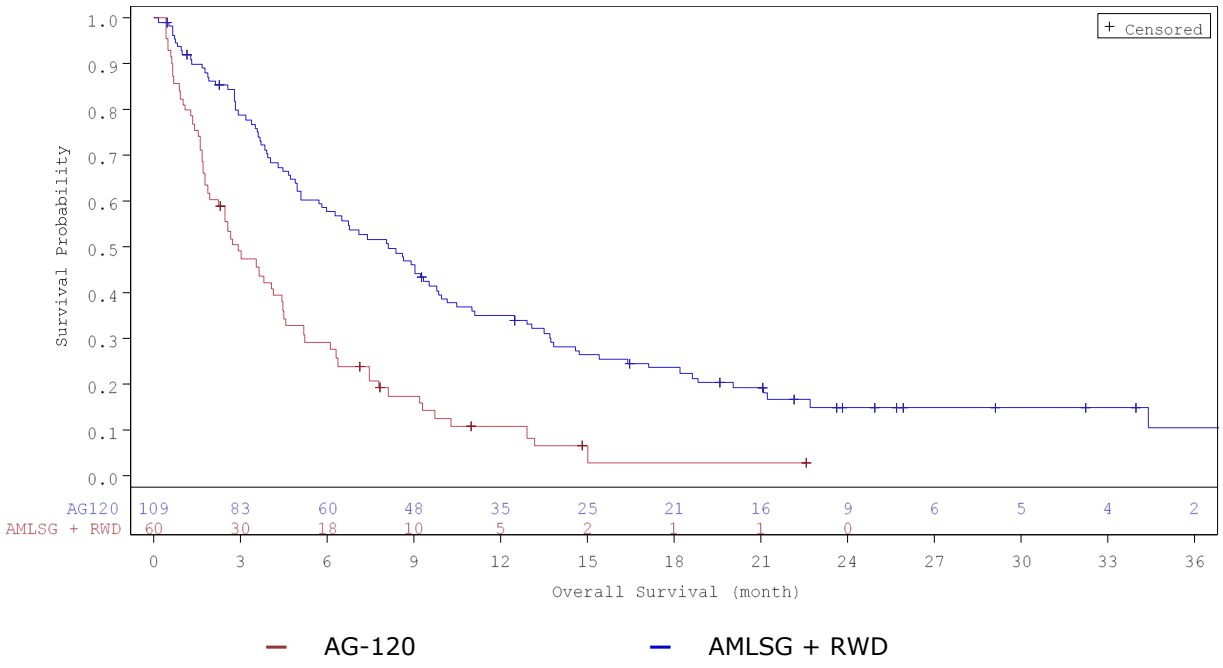
Overall survival data for subjects treated with ivosidenib in Arm 1^+ in a last line setting and for the patients in the matched historical control (AMLSG + RWD) data set are presented in Table 19 and Figure 18. The median OS was 8.1 months (95% CI: 5.7, 9.8) with ivosidenib compared with 2.9 months (95% CI: 1.9, 4.5) in the historical control matched data. The hazard ratio for OS was 0.396 (95% CI: 0.279, 0.562) (P <0.0001).

Table 19. Summary of Overall Survival After Propensity Score Matching Using IPTW Method – Subjects Treated with Ivosidenib in Arm 1+ in a Last Line Setting and Historical Control Data Set for a Last Line Setting

Overall Survival (months)	Last Line Arm 1+ (N=109)	AMLSG + RWD (N=60)
Events, n (%)	90 (82.6)	54 (90.0)
Censored, n (%)	19 (17.4)	6 (10.0)
Median (95% CI)[1]	8.1 (5.7, 9.8)	2.9 (1.9, 4.5)
Minimum, Maximum	0.2, 41.9+	0.4, 22.6+
Kaplan-Meier estimate, % (95% CI)[2]		
1 month	91.9 (86.7, 97.1)	82.2 (72.3, 92.2)
2 months	86.2 (79.6, 92.8)	60.3 (47.6, 73.0)
3 months	78.7 (70.9, 86.6)	49.1 (36.2, 62.1)
6 months	57.7 (48.2, 67.2)	29.1 (17.4, 40.8)
9 months	46.0 (36.4, 55.7)	17.4 (7.6, 27.1)
12 months	35.0 (25.7, 44.3)	10.8 (2.7, 18.9)
Hazard Ratio (95% CI)[3]	0.396 (0.279, 0.562)	
P-value[4]	<.0001	

Source: AG120-C-001 Table 14.2.10.12h. Data cutoff date for AG120-C-001: 02 November 2018.
Note: Propensity scores are estimated using prognostic factors: history of HSCT, age, number of prior regimens for AML (<2, ≥2), nature of AML (de novo, secondary), cytogenetic risk, primary refractory status.
[1] Median estimates from product-limit (Kaplan-Meier) method. Confidence intervals obtained from linear transformation.
[2] Based on Survival Distribution Function estimates from product-limit method.
[3] Hazard ratio is derived from a Cox's proportional hazard regression model with cohort indicator, history of HSCT, age, number of prior regimens for AML (<2, ≥2), nature of AML, cytogenetic risk, and primary refractory status as covariates. A hazard ratio less than 1 indicates a benefit of AG120 therapy compared to AMLSG+RWD cohort.
[4] P-value is based on 2-sided log-rank test.
+ indicates censored observation for maximum statistic.

Figure 18. Kaplan-Meier Plot for Overall Survival After Propensity Score[1] Matching Using IPTW Method - Subjects Treated with Ivosidenib in Arm 1+ in a Last Line Setting and Historical Control Data Set for a Last Line Setting



Source: AG120-C-001 Figure 14.2.10.12h. Data cutoff date for AG120-C-001: 02 November 2018.

In spite of matching and adjustment, a conclusion that the observed differences in OS are causally explained by treatment is questionable because relevant residual unobserved confounding factors cannot be excluded and are even highly likely. The early separation of the survival curves raises uncertainties to define first response to ivosidenib treatment in a historical database.

The Rapporteur acknowledges that ivosidenib provides benefit in R/R AML patients in a last line treatment setting. However, considering the methodology weakness in this single arm pivotal study, controlled data are needed to substantiate this benefit.

Ancillary analyses

Post-treatment Haematopoietic Stem Cell Transplant (HSCT)

Patients reaching HSCT and showing a successful course of treatment is of significant benefit in this claimed indication. Eighteen (10.1%) of the 179 subjects with R/R AML had an HSCT immediately following ivosidenib treatment. Twelve of these 18 subjects (66.7%) achieved CR with ivosidenib prior to undergoing transplant. There were 5 subjects who achieved CRi/CRp (including CRh in 1 subject) and 1 subject with MLFS. The median OS among the 18 R/R AML subjects who underwent HSCT immediately following ivosidenib treatment was 14.5 months (95% CI: 9.2, NE) from the first dose of ivosidenib, with estimated survival rates of 94.4% and 61.1% at 6 and 12 months, respectively. Median relapse-free survival post-transplant in these patients was 6.9 months (95% CI: 2.6, NE) and median OS posttransplant was 11.5 months (95% CI: 6.0, NE).

The potential for a bridge to transplant achieved for 10% of subjects could be considered as relevant.

Subjects who underwent HSCT immediately following ivosidenib treatment tended to be younger (median age 61.5 years) than the overall group of R/R AML subjects whose starting dose was 500 mg QD, and a higher proportion had de novo AML (83.3%), normal cytogenetics (55.6%), and were refractory to initial induction or reinduction treatment (72.2%) (Table 20).

Table 20. Key Demographic and Baseline Disease Characteristics for Subjects with R/R AML Whose Starting Dose Was 500 mg QD Who Underwent Transplant Following Ivosidenib Treatment (Full Analysis Set)

Parameter	**Subjects With Transplant Following Study Treatment (N=18)[1]**	**All R/R AML at 500 mg QD (N=179)**
Sex, n (%)		
Female	8 (44.4)	89 (49.7)
Male	10 (55.6)	90 (50.3)
Age (years)[2]		
Median (Min, Max)	61.5 (36, 68)	67.0 (18, 87)
Subjects Who: (≥1 Criteria May Apply), n (%)		
Relapsed After Transplantation	2 (11.1)	43 (24.0)
Second or Later Relapse	2 (11.1)	26 (14.5)
Refractory to Initial Induction/Reinduction Treatment	13 (72.2)	106 (59.2)
Relapsed Within 1 Year of Initial Treatment[3]	1 (5.6)	17 (9.5)
Other	2 (11.1)[4]	20 (11.2)

Parameter	Subjects With Transplant Following Study Treatment (N=18)[1]	All R/R AML at 500 mg QD (N=179)
Nature of AML, n (%)		
De novo	15 (83.3)	120 (67.0)
Secondary	3 (16.7)	59 (33.0)
Prior History of MDS, n (%)	1 (5.6)	29 (16.2)
Cytogenetics Results, n (%)		
Normal	10 (55.6)	60 (33.5)
Abnormal	5 (27.8)	100 (55.9)
Missing	3 (16.7)	19 (10.6)
Cytogenetic Risk Status by Investigator, n (%)		
Favorable	0	0
Intermediate	12 (66.7)	105 (58.7)
Poor	3 (16.7)	50 (27.9)
Unknown	0	5 (2.8)
Missing	3 (16.7)	19 (10.6)
Subjects with Prior HSCT for AML, n (%)	2 (11.1)	43 (24.0)
Number of Prior Anticancer Regimens[5], n (%)		
0	0	2 (1.1)
1	7 (38.9)	75 (41.9)
2	6 (33.3)	52 (29.1)
≥3	5 (27.8)	50 (27.9)
Number of Relapses, n (%)		
0	6 (33.3)	64 (35.8)
1	10 (55.6)	87 (48.6)
≥2	2 (11.1)	28 (15.6)
Number of Salvage Therapies, n (%)		
1	8 (44.4)	74 (41.3)
2	5 (27.8)	51 (28.5)
≥3	5 (27.8)	54 (30.2)

Source: Addendum to Primary CSR AG120-C-001 Table 14.1.3.4.1. Data cutoff date: 11 May 2018. Abbreviations: AML = acute myeloid leukaemia; FAS = Full Analysis Set; HSCT = haematopoietic stem cell transplant; MDS = myelodysplastic syndrome; QD =once daily; R/R = relapsed or refractory FAS: all subjects who were enrolled and received at least 1 dose of study treatment, analyzed according to the dose assigned.

[1] One subject (Subject 511-039) with R/R AML with a starting dose of 500 mg QD who underwent transplant received intensive induction chemotherapy prior to receiving transplant, and is not included in this Table.

[2] Age (years) = Integer portion of [(ICF date − Date of Birth + 1) / 365.25].

[3] Excluding subjects with favorable-risk status according to NCCN Guidelines, Version 1.2015.

[4]Both subjects had first relapse >12 months after response to initial therapy and received ivosidenib as first salvage therapy.

[5]Number of prior regimens was determined by medical review. Prior regimens included only cytotoxic agents administered to induce a remission. Non-cytotoxic investigational therapies given alone were not considered a

regimen. Not included in prior regimens were supportive care therapies, transplant conditioning chemotherapy, transplant administered to subjects in remission, and consolidation chemotherapy administered to subjects in remission.

The applicant provided at D180 overall survival data of patients reaching HSCT. Eight (7.3%) of the 109 subjects treated with ivosidenib in Arm 1+ in a last line setting underwent HSCT immediately following response to ivosidenib.

All had received prior intensive chemotherapy (Table 21). Six of these 8 subjects achieved a best response to ivosidenib of CR and 2 achieved CRi/CRp. Among these 8 subjects, post-transplant relapse-free survival ranged from 0.8 months to 35.7+ months and OS ranged from 3.2 months to 41.9+ months (Table 21). In the Kaplan-Meier analysis, estimated survival rates for these subjects were 87.5% and 50.0% at 6 and 12 months, respectively (AG120-C-001, Table 14.2.6.9.9A, data cutoff date 02 November 2018).

Half of the patients who received HSCT have survived beyond 12 months after HSCT despite two prior lines of therapy. The Rapporteur acknowledges that a benefit is observed in these patients. However, these results should be taken with caution considering the small number of patients who received HSCT (n=8).

Table 21. Prior Therapy and Post-Transplant Outcomes in Subjects Treated with Ivosidenib in Arm 1+ in a Last Line Setting Who Received Transplant Following Response to Ivosidenib

Subject	Number of Prior Regimens	Received Prior Intensive Therapy?	Prior Regimens Received[1]	Best Response to Prior Regimen(s)[2]	Best Response to Ivosidenib	Last Response to Ivosidenib Prior to Post-Ivosidenib HSCT	Relapse-Free Survival Post-HSCT (months)	Overall Survival Post-HSCT (months)	Overall Survival
508-007	3	Yes	IC/IC/IC	CR/RD/RD	CR	CR	2.6	2.6	7.4
510-003	2	Yes	IC/IC	CR/RD	CR	CR	29.0+	29.4+	34.0+
511-023	3	Yes	IC/IC/HMA	SD/SD/SD	CRi/CRp	CRp	2.3	3.4	7.1
514-004	3	Yes	IC/IC/IC	RD/CR/PD	CRi/CRp	MLFS	0.8	0.8	3.2
701-006	2	Yes	IC/HMA	CR/CR	CR	CRp	12.4	31.1+	41.9+
701-007	2	Yes	IC/IC	CR/RD	CR	CR	35.7+	35.7+	40.0+
701-015	2	Yes	IC/HMA	CR/RD	CR	CR	4.5	4.5	11.0
701-030	2	Yes	IC/IC	CR/CR	CR	NE	14.2+	14.2+	21.1+

Source: AG120-C-001 Listing 16.2.4.4.1C and Listing 16.2.6.1.3. Data cutoff date: 02 November 2018.

Transfusion independence

The majority of subjects with R/R AML had received at least 1 transfusion within 56 days prior to their first dose of ivosidenib (116 subjects, 64.8%); 50.8% received platelet transfusions and 54.2% received RBC transfusions.

Overall, among all 115 subjects with R/R AML whose starting dose was 500 mg QD who were dependent on RBC and/or platelet transfusions at baseline, 41 (35.7%) became independent of RBC and platelet transfusions for a period of ≥56 days during treatment. Of the 64 subjects who were independent of both RBC and platelet transfusions at baseline, 38 (59.4%) remained transfusion independent during a ≥56-day post-baseline period.

Table 22. Transfusions by Best Overall Response Adjusted by Person Exposure Time for R/R AML Subjects at 500 mg QD (Full Analysis Set)

Post-Baseline Transfusion	Best Overall Response				
	CR (N=43)	CRh (N=14)	Non-CR/CRh Responders[1] (N=18)	Non-Responders[2] (N=104)	Overall (N=179)
RBC Transfusions per 100 Person-Months (95% CI)	54.86 (48.91, 61.53)	126.82 (107.33, 149.85)	177.93 (153.62, 206.08)	185.86 (171.71, 201.17)	114.01 (107.79, 120.59)
Platelet Transfusions per 100 Person-Months (95% CI)	42.65 (37.45, 48.57)	175.53 (152.32, 202.28)	254.90 (225.45, 288.18)	306.53 (288.20, 326.02)	157.24 (149.91, 164.94)
Any RBC and/or Platelet Transfusions per 100 Person-Months (95% CI)	97.51 (89.47, 106.27)	302.35 (271.39, 336.85)	432.82 (393.92, 475.57)	492.38 (469.01, 516.92)	271.25 (261.57, 281.30)

Source: Addendum to Primary CSR AG120-C-001 Table 14.2.13.2B. Data cutoff date: 11 May 2018.

The applicant provided transfusion requirements data for the 109 subjects treated with ivosidenib in Arm 1+ in a last line setting. Assessments were planned prospectively in 89 (83.5%) of the 109 subjects since Study Protocol Amendment 3 (Version 4.0, dated 12 February 2015).

All subjects who achieved CR who were platelet transfusion dependent at baseline (n=4) became transfusion independent for a period of 56 days or longer, and 6 of 8 CR responders who were RBC transfusion dependent at baseline became transfusion independent for a period of 56 days or longer. In some cases, subjects who did not achieve CR achieved transfusion independence for a period of 56 days or longer (14 of 53 subjects who were platelet transfusion dependent and 16 of 50 subjects who were RBC transfusion dependent at baseline). Transfusion-independence observed in a subset of patients treated with ivosidenib is considered clinically relevant. However, these exploratory results should be taken with caution because of the lack of a control making it impossible to establish the size of the effect.

Infection, Bleeding, and Febrile Neutropenia by Best Overall Response

As shown in Table 23, data presented show a signal that subjects who achieved a response had reduced incidence of grade 3/4 infection, bleeding, and febrile neutropenia during the periods of response compared with non-responders. However, it remains difficult to evaluate the clinical benefit and relevance of this trend since the event rates are not reported and only exposure-adjusted

incidence calculations in terms of AEs per 100 person-months are provided. Overall, these findings are not surprising as haematologic improvements in platelets, haemoglobin and ANC, such as those associated with response to ivosidenib or other AML therapeutics, are generally accompanied by a numerical reduction in adverse events associated with these laboratory parameters; ie, bleeding events, infections and febrile neutropenia.

Table 23. Grade ≥3 Infection and Infestations, Grade ≥3 Bleeding Events, and any Grade Febrile Neutropenia by Best Overall Response Adjusted by Person- Time for Subjects with R/R AML Whose Starting Dose was 500 mg QD (Full Analysis Set)

Adverse Event	CR (N=43)	CRh (N=14)	Non-CR/CRh Responders (N=18)	Non-Responders (N=104)	Overall (N=179)
Grade ≥3 Infection and Infestations[1]					
AEs per 100 Person-Months (95% CI)	2.44 (1.42, 4.21)	6.43 (3.07,13.49)	12.99 (7.55, 22.38)	20.92 (16.52, 26.49)	9.52 (7.84, 11.56)
Grade ≥3 Bleeding Events[2]					
AEs per 100 Person-Months (95% CI)	0.38 (0.09, 1.50)	0	0	2.12 (1.01, 4.45)	0.84 (0.44, 1.62)
Any Grade Febrile Neutropenia[3]					
AEs per 100 Person-Months (95% CI)	1.69 (0.88, 3.25)	3.68 (1.38, 9.79)	6.00 (2.69, 13.35)	11.82 (8.64, 16.18)	5.42 (4.19, 7.01)

Source: Addendum to Primary CSR AG120-C-001 Table 14.2.12.2B and Table 14.2.12.4B. Data cutoff date: 11 May 2018.
Abbreviations: AE = adverse event; AML = acute myeloid leukaemia; CI = confidence interval; CR = complete remission; CRh = complete remission with partial haematologic recovery; FAS = full analysis set; QD = once daily; remission; PT = preferred term; R/R = relapsed or refractory; SOC = system organ class; SMQ = Standardised MedDRA Query.

1 Includes best responses of CRi, CRp, PR, and MLFS, for subjects who did not meet CRh criteria.

2 Includes best responses of SD, PD, NA, or not evaluable.

3 System Organ Class (SOC).

4 Haemorrhage terms (excluding laboratory terms) Standardised MedDRA Query (SMQ).

5 Preferred Term (PT), including febrile bone marrow aplasia PT.

Comparison of results of subpopulations

The efficacy of ivosidenib was evaluated for the subgroups of age, sex, region, race, baseline ECOG PS, prior history of myelodysplastic syndrome (MDS), prior number of regimens, prior HSCT for AML, baseline cytogenetic risk status, and baseline IDH1 mutation subtype among all subjects with R/R AML.

Unfavourable baseline characteristics (ECOG performance status of 2, had poor cytogenetic risk, had relapsed after transplantation or were in second relapse or later, with prior history of MDS) were associated with lower response CR rates, which can be expected from the diseases characteristics.

Interestingly, favourable CR outcome was observed for subjects older than 70 years compared with younger subjects. The reason might be that older subjects were less likely to have received intensive chemotherapy and had overall fewer therapies prior to study entry. Because younger patients are

generally more fit, they would likely have received more therapies and more intensive regimens by the time of enrolment.

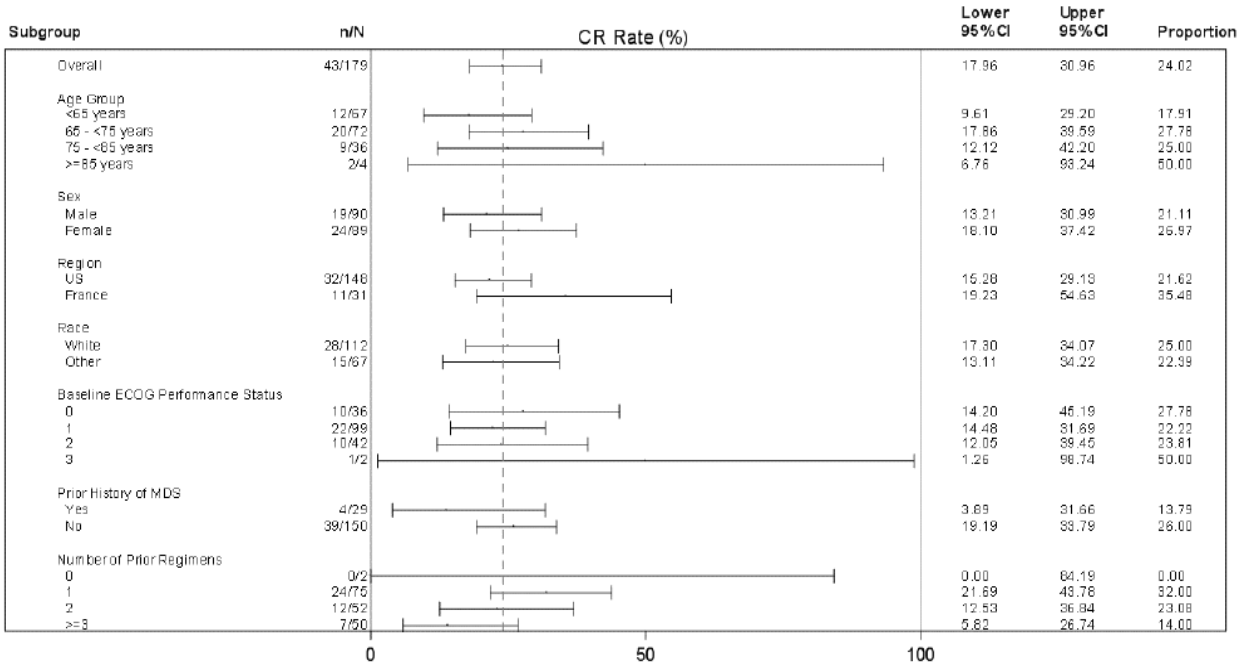
However, it is notable that in a biomarker selected study population and a study drug targeted against this specific biomarker, treatment response varies significantly between subgroups differing by the line of therapy (1st vs 2nd vs 3rd line), although all patients were IDH1 mutation inhibitor naïve. The applicant was invited to discuss the specificity of the mode of action. (OC)

In general, it should be noted that analysis of subgroups is confounded by the inherent heterogeneity of AML as a disease, the fact that subjects are included in more than one subgroup, and the small number of subjects in some of the subgroups, as is evident by the wide range of the confidence intervals. Therefore, results of such analyses should be interpreted with caution.

Moreover, subgroup analysis illustrating the OS in the FAS according baseline characteristics in the R/R-AML population was missing. Therefore, the applicant was requested to provide a table illustrating the OS in the FAS according baseline characteristics in the R/R-AML population. (OC)

However, no conclusion can be drawn considering the limited sample size and the non-comparative design.

Figure 19. Forest Plot of CR Rate by Subgroup for R/R AML Subjects Whose Starting Dose was 500 mg QD (Full Analysis Set)



Clinical studies in special populations

The effect of intrinsic factors on the PK of ivosidenib was assessed in Studies AG120-C-001 and AG120-C-002. These data support that no dose adjustment is required for patients with mild or moderate renal or hepatic impairment. No data in patients with severe renal or hepatic impairment was available. No dose adjustments are required on the basis of the other intrinsic factors.

Summary of main efficacy results

Table 24 summarises the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 24. Summary of efficacy for trial AG120-C-001

Title: Phase 1, multicenter, open-label, dose escalation and expansion, safety, PK/pharmacodynamics, and clinical activity evaluation of orally administered AG-120 in subjects with advanced haematologic malignancies with an IDH1 mutation.		
Study identifier	AG120-C-001	
Design	Phase I, multicentre, open-label study of IVOSIDENIB in in patients with R/R AML with IDH1 mutation. • Dose escalation portion with 3+3 design • Expansion portion with 4 non-randomised arms	
	Duration of main phase:	56 months
Hypothesis	Exploratory: PK/PD, safety, efficacy	
Treatment groups	*Dose escalation*	Ivosidenib 100 mg BID (N=4) Ivosidenib 300 mg QD (N=4) Ivosidenib 500 mg QD (N=48) Ivosidenib 800 mg QD (N=15) Ivosidenib 1200 mg QD (N=7)
	Expansion	Ivosidenib 500 mg QD (N=180)
	Arm1	R/R AML: • 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
	Arm 2	Untreated AML who were not candidates for standard therapy due to comorbid condition, performance status, and/or adverse risk factors
	Arm 3	Other non-AML IDH1-mutated R/R advanced haematologic malignancies, where no standard of care treatment option was available: Myelodysplastic syndrome, Relapsed and/or primary refractory CMML, Other non-AML IDH1-mutated R/R advanced haematologic malignancy
	Arm 4	Relapsed AML subjects not eligible for Arm 1 who 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

Endpoints and definitions	*Primary efficacy endpoint*	CR+CRh rate	CR: complete remission based on Investigator assessment CRh: complete remission with partial haematologic recovery is defined as having all CR criteria except absolute neutrophil count (ANC) >0.5 × 109/L (500/µL) and platelet count >50 × 109/L (50,000/µL)
	Secondary efficacy endpoint	CR rate	Complete remission based on Investigator assessment
		Duration of CR	Duration of complete remission: the date of the first documented CR to the date of the first documented confirmed relapse or death among subjects who had a best response of CR, whichever occurred first.
		Duration of CR+CRh	Duration of CR+CRh: the date of the first documented CR or CRh to the date of the first documented confirmed relapse or death among subjects who had a best response of CR or CRh, whichever occurred first.
		ORR	Objective response rate: Rate of CR, CRi, CRp, PR, and MLFS for AML subjects. The best overall response for each subject was determined by the following hierarchical orders: CR, CRi/CRp, PR, MLFS, SD, PD, and not evaluable. Subjects whose best overall response was either CRi or CRp were presented as 1 response category
		OS	Overall survival: time from first dose to the date of death due to any cause
		EFS	Event-free survival: was calculated from the date of first dose to the date of documented confirmed relapse/progression or death, whichever occurred first.
	Exploratory	• Blood and bone marrow samples to explore early clinical activity and the prognostic relationship of pharmacodynamic markers. • Plasma samples for cholesterol and 4β-OH-cholesterol levels as a potential CYP3A4 induction marker for subjects enrolled in the dose escalation portion. • Plasma, urine (dose escalation only), and leukemic blast cells for metabolic profiling.	
Database lock	11 May 2018		

Results and Analysis				
Analysis description	Primary Analysis			
Analysis population and time point description	Full analysis set (subjects who received at least 1 dose of AG-120)			
Descriptive statistics and estimate variability	**Treatment group**	**Arm 1+**	**Arm 4+**	**All R/R AML at 500 mg QD**
	Number of subject	**N=159**	**N=20**	**N=179**
	CR+CRh rate (%)	**29.6**	**50.0**	**31.8**
	95% CI	22.6, 37.3	27.2, 72.8	25.1, 39.2
	Duration of CR+CRh (months)	**8.2**	**6.5**	**8.2**
	95% CI	5.5, 12.0	1.9, NE	5.5, 12.0
	CR rate (%)	**22.0**	**40.0**	**24.0**
	95% CI	15.8, 29.3	19.1, 63.9	18.0, 31.0
	Duration of CR (months)	**8.8**	**8.8**	**8.8**
	95% CI	5.7, 18.3	1.9, NE	6.5, 12.9
	ORR (CR, CRi/CRp, PR, MLFS)	**40.9**	**50.0**	**41.9**
	95% 2-Sided Exact Binomial CI	33.2, 48.9	27.2, 72.8	34.6, 49.5
	OS (months)	**8.8**	**10.6**	**9.0**
	95% CI	6.8, 10.2	4.8, 12.6	7.1, 10.2
	Censored events (n, %)	34 (21.4)		39 (21.8)
	Kaplan-Meier Estimate OS, %			
	3 months	78.4	NR	79.7
	6 months	60.9	NR	61.9
	9 months	49.1	NR	50.4
	12 months	36.5	NR	37.5
	EFS (months)	**3.8**		**3.8**
	95% 2-Sided Exact Binomial CI	3.6, 5.5		3.7, 5.6
	Post Baseline Transfusion	**CR (N=35)**	**Non Resp. (N=94)**	**Overall**
	RBC Transfusions per 100 Person-Months (95% CI)	57.54 (50.79, 65.18)	195.54 (180.26, 212.12)	123.56 (116.58, 130.95)

	Platelet Transfusions per 100 Person-Months (95% CI)	42.63 (36.88, 49.28)	323.66 (303.82, 344.80)	171.98 (163.72, 180.66)
	Any RBC and/or Platelet Transfusions per 100 Person- Months (95% CI)	100.17 (91.14, 110.10)	519.20 (493.91, 545.79)	295.54 (284.64, 306.85)
Notes	Study AG120-C-001 is an uncontrolled open-label first-in-human phase 1 study being used as single pivotal evidence in an MAA for CMA. The study was amended 5 times. Amendments included modifications of the study population, posology of the study drug, schedule of assessments, statistical methodology, study endpoints, sample size (list incomplete). In conclusion, data provided from study AG120-C-001 are exploratory, analyses performed are descriptive. **In response to D180, the applicant provided results for Last line Arm 1+ subjects (N=109) with a data cutoff date of 02 November 2018:** • **median CR rate was** 18.3% (95% CI: 11.6, 26.9) • **median duration of CR was** 18.3 (5.6, NE) • **median OS was** 8.1 months; CI: 5.7, 9.8)			

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

Since data provided for this application for ivosidenib are derived exclusively from an uncontrolled, Phase 1 study, the applicant has submitted external historical control data in order to facilitate a comparison regarding response and survival outcomes from patients with IDH1-mutation positive R/R AML. Three approaches were undertaken for the provision of this external historical control data:

- A review of literature
- A matched subject comparison from AML Study Group (AMLSG) registry data
- A matched subject comparison from combination of two databases (AMLSG + European RWD)

Literature review (R/R AML irrespective of IDH mutational status)

The populations studied by DiNardo et al, Paschka et al and Bertoli et al are all comparable to the population treated with ivosidenib in Study AG120-C-001 with respect to the fact that they include a R/R AML population with an IDH1 mutation. However, focusing on the number of previous therapies differences became easily obvious. Moreover, the Paschka and Bertoli publications are not suitable benchmarks in that they both report outcomes in patients with R/R AML solely treated with intensive chemotherapy and when feasible, subsequent allo-HSCT in the salvage 1 setting.

Furthermore, patients eligible to receive intensive therapy typically seemed to have better outcomes due to more favorable subject-, disease- and treatment-related factors. This is not further assessable from published literature data. Furthermore, they are additionally limited by the fact that the Bertoli series is quite small and the Paschka series reported OS from initial AML diagnosis as opposed to from relapse or refractory diagnosis or treatment initiation, further complicating any comparison. Last not least: all these trials were retrospectively analysed.

In the applicant's view, the population in the study published by Roboz et al is seen to most closely match the subject population in Study AG120-C-001 and was the only one that assessed OS in the same timeframe as performed in Study AG120-C-001, ie, from the date of first dose of study treatment to death. However, from a regulator's perspective this view is not fully shared, because the target population investigated by Roboz et al is not really comparable with patients included in trial AG120-C-001. The population in this trial was significantly more intensively pre-treated as shown in the number of prior treatments: in Study AG120-C-001 41.9% had one prior treatment, but only 9% of the patients included in the Roboz analysis were treated with a similar comparable low intensity treatment.

This means that the Roboz population seems to be clearly a later line population than that included in Study AG120-C-001, which is also illustrated by the fact that nearly three-fold more patients in the Roboz trial (Roboz: 67% versus AG120: 29.1%) received 2 prior regimens before the trial. In conclusion, it is highly questionable that the OS reported of 3.3 months in the Roboz population can be seriously taken as valid for a comparison. This is confirmed also by the recent analysis of Hill et al, 2018 in which OS differences between the arms were significantly smaller and the CIs were overlapping.

Wattad et al (2017) retrospectively refers to the impact of salvage regimens and allogeneic haematopoietic cell transplantation (allo-HCT) in AML with induction failure and reports a median duration of survival and 24-month survival rate of patients receiving intensive therapy of 12.5 months and 29% (95% CI, 26–33%), respectively; median survival of patients receiving palliative care was 3.1 months. This wide range indicates the inherent difficulties in retrospective data evaluations for historical controls and again illustrates at the end the low validity of retrospective comparisons of OS in the R/R AML setting.

In summary, the submitted published data may allow discussion that ivosidenib has a favorable outcome in patients with R/R AML and IDH1 mutation. However, the reliability of such a retrospective literature comparison remains critical. Limitations of cross-study comparisons are well known and are open to many sources of hidden bias. They are of particular importance in AML.

This is also illustrated by the findings provided from Hill et al, 2018. They analysed outcomes from the United Kingdom NCRI trials of AML for R/R-AML patients with IDH1/IDH2 mutations and reported that although median survival was slightly extended, the one-year survival was not greatly improved (ivosidenib 1-year survival approximately 35% vs 32%).

Matched subject comparison from AML Study Group (AMLSG) registry data

In order to understand the overall survival (OS) benefit of ivosidenib in the context of conventional therapies available for patients in the R/R AML setting, the AG120-C-001 efficacy data for the 179 subjects with R/R AML whose starting dose was ivosidenib 500 mg QD were compared retrospectively with data from subjects from the AML Study Group (AMLSG) registry who had IDH1 mutant R/R AML and received treatment for R/R AML with conventional therapies. This approach aimed to create a surrogate comparative arm for the purpose of comparing the clinical efficacy of subjects with IDH1m R/R AML treated with ivosidenib on Study AG120-C-001 to those with IDH1m R/R AML who received conventional therapies.

Subjects must have met all of the following criteria to be included in the AMSLG analyses: Documented IDH1m status; Age ≥18 years at baseline; diagnosis of AML according to World Health Organization (WHO) classification, and received at least one treatment for relapsed and/or refractory disease. Preliminary analyses of OS were conducted among matched subjects from AMLSG and AG120-C-001 datasets using a propensity score matching method. AML prognostic factors used for estimating the

propensity score included age, number of prior regimens, history of MDS, and post treatment haematopoietic stem cell transplantation (HSCT) in subjects with R/R AML who achieved a response (CR, CRi/CRp, MLFS) to therapy for R/R AML. A nearest neighbour 1:1 matching method (random order) without replacement was applied to identify matched subjects based on the logit of the propensity scores that were within a calliper width of 0.2 standard deviation of propensity score on logit scale and implemented using R Package MatchIt. Different starting points have been used to determine OS; the AMLSG cohort has calculated OS from the time of the most recent determination of R/R AML status, while the AG120- C-001 cohort results present OS measured from the time of ivosidenib study treatment initiation.

A Cox proportional hazard model was applied using Sandwich estimator for variance to compare the matched subjects from AMLSG and AG120-C-001 datasets. A sensitivity analysis for the Cox proportional hazard model was also applied to include the 4 prognostic factors specified above as covariates. The distributions of the prognostic factors were evaluated prior to and post matching. The comparison of OS data between AMLSG and AG120-C-001 was to be further evaluated and included in a subsequent report.

The impact of treatment on OS cannot be disentangled from prognostic factors in a single arm trial (SAT). Therefore, a treatment effect on OS can be established only in comparison to an adequate control, which has to be an external control group for single arm trials. However, it is in general almost impossible to establish the comparability of a treatment group and an external control group, and in particular in this case where the underlying disease is very heterogeneous with many known prognostic factors influencing OS (age at relapse, relapsed or refractory disease, nature of AML (de novo vs secondary), cytogenetics, relapse-free interval from first CR, number of prior therapies, prior HSCT, the performance status of the patients, therapy after failure of ivosidenib (list incomplete)). Additionally, the existence of additional yet unknown prognostic factors influencing survival is very likely. Therefore, the inability to control bias is the major and well-recognised limitation of comparisons to external controls. Thus, OS results from this SAT must remain descriptive and non-inferential.

Beside these general considerations, the following specific remarks can be made regarding the applicant's approach for indirect comparison to the AMLSG data.

Although reducing differences between the treatment group and respective external control group with regard to the 4 matching covariates, the propensity score matching cannot establish comparability of the treatment group and the external control group. These four covariates represent only a small subset from the known prognostic factors potentially influencing OS in R/R AML. In addition, imbalances may exist with regard to yet unknown important covariates. Therefore, a conclusion that the observed differences in OS are causally explained by treatment is not valid because relevant confounding cannot be excluded and is even highly likely.

Although the response to ivosidenib takes time (median time to CR 2.7 months (min: 0.9 months), median time to OR: 1.9 months, min 0.8 months), differentiation between the survival curves for the matched cohorts starts from the beginning of follow-up. This early differentiation may not be explained by treatment and supports the concern of a selection bias

There are several possible choices with regard to matching methods. It is not clear why the specific approach was chosen, whether there was an element of pre-specification (also with regard to the matching factors), and whether the conclusions are robust with regard to the choice of the method. Furthermore, for the chosen nearest neighbour matching method, the (random) order in which patients in the treated group are chosen determines how the matched pairs are formed, and thus can lead to several different post-matched populations. It is not clear whether a seed was pre-specified and whether results are robust to changes of the order.

Although it is acknowledged that post treatment haematopoietic stem cell transplantation (HSCT) in subjects with R/R AML who achieved a response is an important prognostic factor, using factors whose values are determined after beginning treatment for matching is generally problematic because these may be influenced by treatment. For example, by matching for post-treatment HSCT, possible differences between treatments in the proportion of patients being eligible for HSCT, which may contribute to OS differences between treatments, are lost.

Matched analysis using the combined AMLSG and European real world data (RWD) datasets

The applicant proposed extensive exploratory approaches for the overall survival analysis. Various propensity score matching procedures to compare patients treated with ivosidenib to AMLSG historical controls were included. The eleven analysis proposals were unstratified and stratified analyses, involving 6 to 9 co-variates to compute the propensity score and increased constraints for matching control and ivosidenib patients.

However, after matching, some imbalances in baseline data could still be observed and responsible variables were used as additional co-variates in the cox regression models.

These analyses show consistent HR point estimates <1, derived from adjusted cox models associated to these various approaches. However, most of the KM overall survival curves provided seem to indicate that HR are non-proportional (curves are crossing-over at some point), making the reliability of cox model analyses questionable, the assumption of HR constant in time needed for that model not being met.

In addition, similar concerns apply for the comparisons to the compared external controls as for the matched comparison to the AMLSG data alone. In spite of matching and adjustment, a conclusion that the observed differences in OS are causally explained by treatment is not valid because relevant residual confounding cannot be excluded and is even highly likely. The concern for a relevant selection bias is supported by the very early separation of the survival curves that is still observed after propensity score matching, which is unlikely to be explained by treatment.

Of note, for non-randomised comparisons, confidence intervals do not only represent the true effect of the experimental treatment, but also the associated chance-related variations. Indeed, inter-arm differences do not depend on these factors only but on uncontrolled, possibly unknown confounders. In other terms, significant confidence interval upper limits must not only remain below the value of 1 to support the evidence of benefit, but must go well below this limit.

Although it is acknowledged that the historical data selected mainly for OS comparisons by the applicant may allow discussion that ivosidenib may demonstrate favorable outcomes in patients with R/R AML with an IDH1 mutation, this discussion remains exploratory and not pivotal at the end. From a methodological point of view, the reliability of retrospective literature and data comparisons for pivotal purposes is not acceptable. Limitations of cross-study comparisons are well known and are open to many sources of hidden bias. They are of particular importance in AML.

Matched analysis using the combined AMLSG and European real world data (RWD) datasets in the setting of last line treatment

In response to the D180 LoOI, the applicant revised the proposed indication to include patients in a last line treatment setting. Based on this review, 109 subjects treated with ivosidenib in Arm 1+ met the last line indication criteria: 84 subjects who received at least 2 prior regimens, including at least 1 standard IC regimen; and 25 subjects who were not candidates for standard IC and had received at least 1 prior non-intensive regimen. Regarding the historical cohort, 60 patients have been selected.

Only RWD data (n=43) were considered for the comparison of CR rate (as CR rate could not be estimated in the AMLSG dataset) leading to a 2.5 size ratio between the Last line Arm 1+ and RWD cohorts. A higher CR rate was observed in Last line Arm1+ (18.3%; 95%CI: 11.26, 26.9) than in the historical arm (3%; 1.5, 19.1%). This result should be taken with caution as the CIs overlapped.

The median OS was 8.1 months (95% CI: 5.7, 9.8) with ivosidenib compared with 2.9 months (95% CI: 1.9, 4.5) in the historical control matched data. The hazard ratio for OS was 0.396 (95% CI: 0.279, 0.562) (*P* <0.0001). In spite of matching and adjustment, a conclusion that the observed differences in OS are causally explained by treatment is questionable because relevant residual unobserved confounding factors cannot be excluded and are even highly likely. The early separation of the survival curves raises uncertainties to define first response to ivosidenib treatment in a historical database.

The Rapporteur acknowledges that ivosidenib could provide benefit in R/R AML patients in a last line treatment setting. However, considering the methodology weakness in this single arm pivotal study, controlled studies are needed to provide comprehensive data.

Supportive study

Not applicable.

3.3.7. Discussion on clinical efficacy

Basics

The efficacy claims of ivosidenib in IDH1-R132 mutant R/R AML patients are based on a single pivotal uncontrolled phase 1 study, namely study AG120-C-001.

To assess the benefit and value of ivosidenib in the context of existing therapies used in the R/R AML population, the applicant performed:

- a systematic review of published literature
- a comparison of the AG120-C-001 data versus AML registry data collected in R/R AML patients with an IDH1-R132 mutation treated with conventional treatments in a real-world setting (the mentioned registry being the AMLSG (Germany)
- a comparison of the AG120-C-001 data versus combination of two databases (AMLSG + European realworld data RWD)

AML is agreed to be a life-threatening disease.

Ivosidenib was designated an orphan medicinal product in the EU for the treatment of AML on 12 Dec 2016 (EU/3/16/1802). The application for orphan drug designation was based on the criterion of significant benefit over existing methods of treatment for the condition.

Frequency and clinical outcomes of IDH1-R132 mutations in AML

According to data from the literature, the frequency of reported IDH1 R132 gene-mutated AML is between 6% and 13.7%. Insofar, the frequency seems to be slightly lower than that of IDH2 mutations in AML. In subjects with IDH1 mutated AML, the R132 mutation is nearly exclusively described with 5 subtypes (R132C, R132H, R132G, R132S and R132L).

The prognostic impact of mutated IDH1/2 in AML remains controversial. As to Medeiros 2017, several studies have suggested an association with adverse outcomes whereas others have failed to identify any clear influence on clinical response or survival, and still others report improved survival. Differences in prognostic findings may reflect variations in study methodologies; also the mutational context may influence AML prognosis. Although the meta-analyses presented above may allow to reason that the presence of an IDH1 mutation may be associated with a worse prognosis compared to wild-type IDH1, this view is not fully shared in the scientific literature. Therefore, in the current 2017 ELN Risk Stratification by Genetics, neither IDH1 nor IDH2 mutations could be categorised.

Currently it can only be stated that there seems to be no clear or overwhelming prognostic impact for mutated IDH1 in AML and further confirmation in prospective studies is needed to more clearly elucidate the effect.

Moreover, in the R/R setting the data presented showed that at least more than 90% of the patients have additional AML mutations detectable. It is likely that without additional targeted therapy these mutations significantly contribute to relapses in the target population, even if ivosidenib is fully efficacious. This issue additionally questions significantly the concept behind the here applied monotherapy for the R/R-AML population. The company seems to acknowledge this concern also as indicated by the design for the additional trials currently ongoing and originally claimed for CMA purposes.

Design and conduct of clinical study

Study AG120-C-001

Study AG120-C-001 is an uncontrolled, open-label, multicentre first-in-human phase 1 study.

Study AG120-C-001 is divided into a dose escalation and a dose expansion portion in patients with advanced haematologic malignancies with an IDH1 mutation, ie, the R/R AML population was a subpopulation of the larger study.

Since initiation, the study was amended 5 times, finally with the aim to use it as pivotal evidence in an MAA. Amendments of this study performed in an open-label design include modifications of the study population, posology of the study drug, schedule of assessments, statistical methodology, study endpoints, and sample size (list incomplete). In conclusion, data provided from study AG120-C-001 are exploratory, and analyses performed are descriptive.

The study population included in study AG120-C-001 is considered representative of a very high-risk R/R AML population with few effective alternatives [ie, patients with curative options (ie, intensive chemotherapy and/or HSCT were excluded). Therefore, it is notable that the initial claimed indication (ie, all R/R AML patients with an IDH1-R132 mutation) includes a relevantly broader and lower-risk population than the studied population. On average, these lower-risk patients show a better treatment response to available treatment options than patients from the study population.

Furthermore, it is notable that the study population is very heterogeneous, which makes the comparison with external/historical controls complicated. Factors such as age at relapse, relapsed or refractory disease, nature of AML (de novo vs secondary), cytogenetics, relapse-free interval from first CR, number of prior therapies, prior HSCT, the performance status of the patients (list incomplete) all affect to different degrees response to treatment and survival.

Efficacy endpoints as defined in the study protocol are adequate for a phase 1 trial, and in this early trial setting, they sufficiently reflect the study objectives. However, regarding the registrational claim of the study fundamental limitations are noted:

- EFS, CR rate and CR/CRi/CRp rate are not considered established or validated surrogate markers for OS in AML.
- No hierarchy of the efficacy endpoints is pre-defined in the study protocol. In Protocol Amendment 3 introducing the expansion part, CRR and ORR were considered as the basis to provide evidence of clinically significant activity, which was changed in Amendment 5 to CR+CRh. This is further weakened by the fact that no hypothesis tests were pre-specified, AG120-C-001 being an uncontrolled phase 1 trial without a confirmatory claim.
- ORR in study AG120-C-001 is defined as the rate of responses (CR, CRi, CRp, PR, MLFS). This definition of ORR is broader than the one typically used in AML, which would only include CR+CRi/CRp. This is understood due to the fact that the original intent of the phase 1 study was to identify an efficacy signal with ivosidenib. However, the clinical relevance of ORR is unclear in the AML setting. In conclusion, ORR is not acceptable as the main efficacy endpoint for registrational purposes.
- Analyses to support the clinical benefit, such as, eg, transfusion independence, rates of infection, bleeding, and neutropenia during response periods are certainly clinically relevant, but results are considered difficult to interpret because of the potential for bias and the lack of a control making it impossible to establish the size of effect attributable to treatment in the frame of an uncontrolled trial.

Contribution of treatment to time related endpoints such as OS and EFS cannot be directly ascertained in a single arm study.

In conclusion, efficacy assessment of the uncontrolled phase 1 study AG120-C-001 presented as a single pivotal evidence will primarily focus on CR rate and Duration of CR. OS is seen as the relevant supportive endpoint for contextualisation of the results of study AG120-C-001 (ie, the comparison with external/ historical controls).

Sample size calculation was primarily based on safety considerations for the dose escalation part and the first part of the expansion cohort, which is acceptable.

The additional expansion with enrolment of an additional 100 patients in Arm 1 aimed at assessment of clinical activity. While 'clinical significance' was originally considered as excluding a CR rate of ≤15% from the two-sided 95% CI or excluding an ORR rate of ≤25%, this was changed to excluding a CR+CRh rate of ≤10% from the 2-sided 95% CI with Amendment 5. However, independently from the question of what could be considered as an adequate threshold for a conclusion of clinically significant activity, a minimal requirement for a conclusion of clinically significant benefit from an exploratory single arm trial is overwhelming clinical activity in terms of CR, whereby the threshold what could be considered as overwhelming activity is by far larger than the thresholds proposed for clinical activity by the applicant.

Formal hypothesis testing was neither planned nor performed but only 95% CIs were provided, which is acceptable for a phase 1 study. According to the clinical overview, this application was primarily based on all subjects with R/R AML whose starting dose was 500 mg QD in the FAS (ie, all subjects in Arm 1+ and Arm 4+) with data cut-off 11 May 2018, while the primary analysis population in the original clinical study report was based on all treated Arm 1+ subjects whose first dose was at least 6 months prior to the data cut-off date 12 May 2017. Performing only descriptive analyses and changing the analysis population post-hoc is acceptable for an exploratory phase 1study but is obviously not according to usual standards for a study that shall serve as the single pivotal study supporting an application.

In response to feedback from the CHMP, the Company revised the proposed indication to include patients in a last line treatment setting as follows: "Tibsovo is indicated as monotherapy for the treatment of relapsed or refractory acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation in adult patients whohave received at least 2 prior regimens, including at least 1 standard intensive chemotherapy regimen, or are not candidates for standard intensive chemotherapy and have received at least 1 prior non-intensive regimen."

The same restrictions (patients have received at least 2 prior regimens, including at least 1 standard intensive chemotherapy regimen or are not candidates for standard intensive chemotherapy and have received at least 1 prior non-intensive regimen) as the Last line Arm1+ population were applied for the external historical control cohort of patients (comprising the AMLSG database and a set of European RWD collected by the applicant) in order to define a subset of patients who meet the criteria for a last line treatment setting.

Efficacy data and additional analyses

Study AG120-C-001

Study AG120-C-001 started recruitment on 12March 2014 and the study is still ongoing. At the time of the 11 May 2018 data cutoff date, 22 subjects remained on treatment; 29 subjects had discontinued treatment and remained in either post-transplant follow-up or survival follow-up. A total of 258 subjects have been administered AG-120 during the dose escalation and expansion portions of Study AG120-C-001 across 5 dosing cohorts. A total of 179 subjects in the FAS had R/R AML and were treated with 500 mg QD AG-120; of these, 159 were included in the Arm 1+ subset and the remaining 20 subjects met the criteria for Arm 4+. A total of 34 subjects in the FAS had previously untreated AML and were treated with 500 mg QD AG-120; these subjects were included in the Arm 2+ subset. In addition, 12 subjects in the FAS with MDS were treated with 500 mg QD AG-120 and were included in the Arm 3+ subset.

The efficacy data presented for study AG120-C-001 in this current MAA are focussing only on the data from the subpopulation of 179 R/R AML subjects treated with ivosidenib monotherapy 500 mg daily based on a data cut-off date of 11 May 2018.

As to the key baseline demographics and disease characteristics, the R/R AML study (sub)population receiving ivosidenib monotherapy 500 mg daily represents an advanced IDH1-R132 mutated R/R AML population (median age: 67 years; relapsed disease: 27.0%; refractory disease: 66.7%, intermediate risk cytogenetics: 58.7%; prior MDS: 14.5%; AML not otherwise specified according to WHO classification: 64.8%; median number of prior anticancer therapies: 2.0; IDH1-R132 mutation: 98.3%). However, some issues remain to be clarified.

A total of 43/179 (24.0%; 95% CI 18.0, 31.0) subjects in the R/R AML population treated with 500 mg ivosidenib daily achieved a best response of CR (investigator assessment). Median Duration of CR was 8.8 months (95% CI 6.5, 12.9). CR+CRh rate and ORR and their respective duration of response and the presented sensitivity analyses are regarded as supportive of the discussed CR data. In conclusion, these data clearly indicate clinical activity of ivosidenib monotherapy in the studied population. However, the shown effect size is certainly not sufficiently outstanding to justify conditional approval.

Best response in patients is regularly achieved not before 5 months indicating that treatment with ivosidenib should be continued for at least 6 months unless experiencing disease progression or unacceptable toxicities.

Median OS in the R/R AML population treated with ivosidenib 500 mg daily was 9.0 months (95% CI 7.1, 10.2). Median OS was longer for patients achieving CR compared to patients achieving only ORR

or non-responders. However, the analysis of OS according to response status is influenced by immortal time bias (ie, patients need to have survived for some time in order to achieve response) such that a clear conclusion on the causal relationship between response and longer survival time is not possible based on these data. The OS effect is certainly of interest and supports the CR results discussed above. However, contribution of treatment to time related endpoints such as OS cannot be directly ascertained in an uncontrolled study.

With respect to the submitted historical data for OS comparison, it can currently only be stated that OS in the applied target population may range between 3.3 in an advanced population and 13.1 months in an early disease population. Insofar any clear advantage of the 9.0 months observed in AG120-C-001 for ivosidenib is difficult to confirm due to the significant impact of heterogeneity in the populations; in particular, as the prognostic impact of mutated IDH1-R132 in AML itself remains controversial. The presented data from published literature and the AMLSG registry is deemed not sufficient to allow a valid comparison regarding efficacy with the OS outcome of AG120-C-001. The ongoing approach to provide data from a retrospective, observational, multi-centre, chart-review study aiming to identify at least 260 patients, who are 18 years and older with R/R IDH1-R132 mutated AML (confirmed by local testing), but have not been treated with ivosidenib, will not be able to overcome the fundamental concerns on the lack of reliability of indirect comparisons such that these data will be at best supportive only.

A total of 18/179 (10.1%) R/R AML patients were able to electively discontinue ivosidenib and to directly proceed to allogeneic HSCT. Twelve of these 18 subjects (66.7%) achieved CR with ivosidenib prior to undergoing transplant. There were 5 subjects who achieved CRi/CRp (including CRh in 1 subject) and 1 subject with MLFS. The median OS among the 18 R/R AML subjects treated at 500 mg QD who underwent HSCT immediately following ivosidenib treatment was 14.5 months (95% CI: 9.2, NE) from the first dose of ivosidenib. Median relapse-free survival post-transplant in these subjects was 6.9 months (95% CI: 2.6, NE) and median OS post-transplant was 11.5 months (95% CI: 6.0, NE). This supports the feasibility of allo-HSCT after treatment with ivosidenib in the R/R AML setting in selected subjects. However, as numbers are very low in an uncontrolled setting, further randomised controlled studies will be necessary, to clarify, whether R/R AML patients show a clinically relevant benefit from allo-HSCT after adequate response under ivosidenib monotherapy.

In response to feedback from the CHMP, the Company revised the proposed indication to include patients in a last line treatment setting as follows: "Tibsovo is indicated as monotherapy for the treatment of relapsed or refractory acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation in adult patients whohave received at least 2 prior regimens, including at least 1 standard intensive chemotherapy regimen, orare not candidates for standard intensive chemotherapy and have received at least 1 prior non-intensive regimen."

After propensity score matching, demographic baseline criteria and history of the disease criteria, such as history of HSCT, number of prior regimens for AML, and nature of AML were well-balanced between the Last line Arm1+ subjects and the AMLSG + RWD database. Poor cytogenetic risk and primary refractory status were in a higher proportion of patients in Last line Arm1+ which could not favour efficacy and safety results in this arm. Only RWD data were considered for the comparison of CR rate (as CR rate could not be estimated in the AMLSG dataset) leading to a 2.5 size ratio between the Last line Arm 1+ and RWD cohorts. A higher CR rate was observed in Last line Arm1+ (18.3%; CI: 11.6, 26.9) than in the historical arm (7.0%; CI: 1.5, 19.1). This result should be taken with caution as the CIs overlapped.

An improvement in the median OS was observed in subjects treated with ivosidenib (8.1 months; CI: 5.7, 9.8) compared to the historical control matched data (2.9 months; CI: 1.9, 4.5), which could demonstrate a clinical benefit for patients with R/R AML treated with ivosidenib in a last line setting.

This is supported by a Hazard Ratio of 0.396 (0.279, 0.562) with a p value <.0001. In spite of matching and adjustment, a conclusion that the observed differences in OS are causally explained by treatment is questionable because relevant residual unobserved confounding factors cannot be excluded and are even highly likely. The early separation of the survival curves raises uncertainties to define first response to ivosidenib treatment in a historical database.

Median OS was not estimable (95% CI: 7.4, NE) in subjects with CR and HSCT, 34.4 months (95% CI: 16.4, 34.4) in subjects with CR and no HSCT, and 5.7 months (95% CI: 4.0, 8.0) in subjects without CR. The median OS for non-responders is consistent with the poor prognosis of patients in this treatment setting. Half of the patients who received HSCT have survived beyond 12 months after HSCT despite two prior lines of therapy. The Rapporteur acknowledges that a benefit is observed in these patients. However, these results should be taken with caution considering the small number of patients who received HSCT (n=8).

The Rapporteur acknowledges that ivosidenib could be of benefit in R/R AML patients in a last line treatment setting. However, considering the methodology weakness in this single arm pivotal study, controlled data are needed to substantiate this benefit.

The applicant provided transfusion requirements data for the 109 subjects treated with ivosidenib in Arm 1+ in a last line setting. Assessments were planned prospectively in 89 (83.5%) of the 109 subjects since Study Protocol Amendment 3 (Version 4.0, dated 12 February 2015). Transfusion-independence observed in a subset of patients treated with ivosidenib is considered clinically relevant. All subjects who achieved CR who were platelet transfusion dependent at baseline (n=4) became transfusion independent for a period of 56 days or longer and 6 of 8 CR responders who were RBC transfusion dependent at baseline became transfusion independent for a period of 56 days or longer. In some cases, subjects who did not achieve CR achieved transfusion independence for a period of 56 days or longer (14 of 53 subjects who were platelet transfusion dependent and 16 of 50 subjects who were RBC transfusion dependent at baseline). However, these exploratory results should be taken with caution because of the lack of a control making it impossible to establish the size of the effect.

Subjects who achieved a response had reduced incidence of grade 3/4 infection, bleeding, and febrile neutropenia during the periods of response compared with non-responders. However, this finding is not surprising as haematologic improvements in platelets, haemoglobin and ANC, such as those associated with response to ivosidenib or other AML therapeutics, are generally accompanied by a reduction in adverse events associated with these laboratory parameters; ie, bleeding events, infections and febrile neutropenia. Furthermore, the magnitude of the effect cannot be contextualised due to the uncontrolled study design and the effect size is not outstanding. The comparison to historical control is not deemed acceptable also for this endpoint, as too many confounding factors impact infections and bleeding. In consequence, no relevant efficacy claims regarding the benefit/risk assessment in an MAA can be derived from this descriptive data.

In the second D180 responses, the applicant did not present new data or additional analyses but only additional justification why the previously presented results can be considered sufficient for resolving the CHMP's concerns. Overall, this justification does not provide relevant new aspects which could change the previous CHMP conclusion that the application is not approvable.

(i) Further justification of the benefit in the intended target population

The provided justification is not considered sufficient for the same reasons as in the previous assessment rounds

- Even for the now proposed "last line" setting, the observed CR of 18.3% (95%CI (11.6%,26.9%) needs to be considered as far below what could be unequivocally considered as "outstanding" compared to available therapies. A reliable estimation of the duration of

remission is not possible, given that only 20 remissions were observed in the analysis set restricted to "last line" patients.

- The difference in OS observed in the comparison vs historical data cannot be accepted as evidence of efficacy but only as supporting information, due to the inability to control bias for comparisons to external controls. Methods such as inverse probability treatment weighting aiming to adjust for imbalances for comparisons to external controls need to rely on strong and verifiable assumptions.
- Half of the patients who received HSCT have survived beyond 12 months after HSCT despite two prior lines of therapy. It is acknowledged that a benefit is observed in these patients. However, these results should be taken with caution considering the small number of patients who received HSCT (n=8).
- Data on the effect of treatment on transfusion independence are fraught with methodological problems and cannot establish pivotal evidence of efficacy

(ii) Restriction of the indication to a subpopulation

It is acknowledged that the applicant's definition of the last line population aimed to reflect the definition from therapeutic guidelines. However, the question still remains whether the applicant's definition was the only possible 'last line' definition based on the guidelines or whether there were alternative choices. If there were alternative choices, the outcomes for these alternative populations would be of interest. It is also acknowledged that, as it is expected for a last line population, the outcomes were worse in the analysis set restricted to "last line" patients than in the overall Arm 1+ population. However, the number of non-last line patients (according to applicant's definition) in this study was small anyway.

(iii) Therapeutic advantage of ivosidenib in the proposed indication

The benefit in the intended target population is not considered to be established (see (i)). The applicant proposes, as a confirmatory study, a prospective clinical study in a last line IDH1-mutated R/R AML patient population, aligned with the claimed indication. Another uncontrolled study just replicating the currently provided unconvincing results is not considered sufficient for providing comprehensive data.

Additional expert consultation

SAG Oncology has been consulted on 22 July 2019.

Assessment of paediatric data on clinical efficacy

N/A

Additional efficacy data needed in the context of a conditional MA

Two efficacy studies (HOVON 150 / AMLSG 29-18 and AG120-C-009) were initially proposed by the applicant to provide further clinical data. In the second D180 responses, the applicant proposed, as a confirmatory study, a prospective clinical study in a last line IDH1-mutated R/R AML patient population, aligned with the claimed indication.

3.3.8. Conclusions on clinical efficacy

The efficacy claim of ivosidenib in IDH1 mutant R/R AML patients is based on a single pivotal uncontrolled phase 1 study including a dose escalation portion to determine the maximum tolerated

dose (MTD) and/or recommended Phase 2 dose (RP2D) and an expansion portion to further evaluate the safety, tolerability, and clinical activity of ivosidenib.

Justification of the clinical benefit of ivosidenib is based on Last line Arm 1+ data which have been retrospectively compared to a subset of patients with confirmed mutated IDH1 status from a combination of two databases: AML Study Group (AMLSG) Bioregistry and European real world data by propensity score matching. Based on the results of this study, a benefit could be observed in these patients. However, taking into account the methodology weakness in this single arm pivotal study as AG120-C-001 was amended 6 times impacting multiple fundamental aspects of the study design (eg, study population, posology of the study drug, schedule of assessments, statistical methodology, study endpoints, sample size), controlled data are needed to substantiate this benefit.

3.3.9. Clinical safety

The primary focus of the safety analyses for this submission is on *Study AG120-C-001* in subjects with advanced haematologic malignancies with an IDH1 mutation. It should be noted that most of the studies, including the pivotal one, remained ongoing at the time of submission of this application.

The AG120-C-001 Phase 1 study included 258 treated subjects, of whom 179 were subjects with R/R AML with an IDH1 mutation assigned to ivosidenib 500 mg daily dose treatment. 22 subjects remained on treatment as of the cut-off date. The safety data is presented as combined analyses of patients in the dose escalation and expansion portions. The median duration of exposure to ivosidenib was 3.9 months.

Additional safety data came from sponsored ongoing studies in subjects with haematologic malignancies (AG120-221-C-001, AG-221-AML-005, AG120-C-009), an expanded access programme (AG120-C-010), four completed studies in healthy subjects (AG120-C-003, AG120-C-004, AG120-C-006 and AG120-C-007), one study in healthy subjects with hepatic impairment (AG120-C-012) and two studies in subjects with solid tumours (AG120-C-002 and AG120-C-005). As of 11 May 2018, 770 subjects (611 subjects with haematologic malignancies or solid tumours and 159 healthy/hepatically impaired subjects) had received at least one dose of ivosidenib as a single agent or in combination with other antineoplastic treatments.

Safety assessments included standard baseline and safety evaluations: disposition, extent of exposure, dose modifications, demographics and baseline characteristics, AE summaries, and clinical laboratory, vital signs, and ECG assessments.

Additional analyses were conducted to further evaluate identified risks, potential risks, and other AEs of clinical importance in the ivosidenib clinical development programme based on nonclinical and clinical safety findings; analyses of AEs related to potential drug interactions with concomitantly administered medications were also presented.

Demographics and baseline characteristics

Across the Safety Analysis Set of 179 patients from study AG120-C-001 (R/R AML, starting dose 500 mg QD), the majority were male (50.3%) and white (62.6%). The median age was of 67 years and the majority of patients (62.5%) were aged 65 years or older. ECOG Performance status (PS) was of ≥1 in 265 patients (79.9%). Overall, 131 patients (82.4%) had a normal value of creatinine clearance, and 27 (17.0%) had values between 30 and 60 mL/min. Similar demographic features were observed in the other ongoing studies.

Patient exposure

The dosage of ivosidenib was established based on phase 1 dose-escalationand expansion data, and fixed to 500mg QD on days 1 to 28 in 28-days cycles. The drug was administered until progression and/or unacceptable toxicity. In the AG120-C-001 study (Safety Analysis Set), the median duration of ivosidenib administration was 3.9 months (0.01-45.44). 9.3% (19 of 258) of patients were treated with ivosidenib for 12 to <24 months and 1.5% (3 of 258) of patients were treated with ivosidenib for ≥24 months. The median relative dose intensity was 98.7%.

As presented in Table 25, at the data cut off of 11 May 2018, 91.5% of all patients discontinued treatment, mainly due to disease progression. 80.2% of patients discontinued the study.

Table 25. Overall Subject Disposition in Study AG120-C-001

Disposition	Arm 1+ (N=159)	R/R AML at 500 mg QD (N=179)	Overall (N=258)
Ongoing, n (%)	**9 (5.7)**	**10 (5.6)**	**22 (8.5)**
Discontinued Treatment	**150 (94.3)**	**169 (94.4)**	**236 (91.5)**
Disease progression	85 (53.5)	98 (54.7)	135 (52.3)
Adverse event	26 (16.4)	28 (15.6)	37 (14.3)
Bone marrow transplant	15 (9.4)	17 (9.5)	25 (9.7)
Death	9 (5.7)	10 (5.6)	16 (6.2)
Withdrawal of consent	7 (4.4)	8 (4.5)	14 (5.4)
Investigator decision	6 (3.8)	6 (3.4)	7 (2.7)
Other	2 (1.3)	2 (1.1)[1]	2 (0.8)[1]
Discontinued Study	**133 (83.6)**	**148 (82.7)**	**207 (80.2)**
Death	121 (76.1)	135 (75.4)	180 (69.8)
Lost to follow-up	5 (3.1)	5 (2.8)	7 (2.7)
Withdrawal of consent	6 (3.8)	7 (3.9)	14 (5.4)
Other	1 (0.6)	1 (0.6)[2]	6 (2.3)[3]
In Post-Transplant Follow-Up	**4 (2.5)**	**5 (2.8)**	**8 (3.1)**
In Survival Follow-Up	**13 (8.2)**	**16 (8.9)**	**21 (8.1)**

Source: Addendum to Primary CSR AG120-C-001, Table 14.1.1.2, Table 14.1.1.3, Table 14.1.1.4, and Listing 16.2.1.1. Data cutoff date: 11 May 2018.
Abbreviations: AML = acute myeloid leukemia; CSR = Clinical Study Report; QD = once daily; R/R = relapsed or refractory.
Note: Full Analysis Set is defined as all subjects who were enrolled and received at least 1 dose of study treatment, analyzed according to the dose assigned.
[1] Other includes reasons of: subject sought alternative therapy (n=1) and inter-current medical condition (n=1).
[2] Subject discontinued study due to disease progression.
[3] Other includes reasons of: disease progression (n=3), subject completed follow-up period (n=1), end of treatment for subject was before AG120-C-001 Protocol (Version 4.0) was implemented in which all subjects entered the survival follow-up phase (n=1), and study was completed (n=1).

At the data cutoff 02 Nov 2018, the median duration of follow-up for all subjects with R/R AML whose starting dose was 500 mg QD (N=179) and for subjects in Arm 1+ (N=159) was 25.7 and 25.9 months, respectively.

Adverse events

All AEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0. The severity of all AEs were graded based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03.

In general, the overall summary of AE table included numbers and percentages of subjects with any AE, any grade ≥3 AE, any treatment-related AE, any treatment-related grade ≥3 AE, any serious AE, any treatment-related serious AE, any AE leading to study drug permanently discontinued, any AE leading to study drug reduced, any AE leading to study drug held, and any AE leading to on-treatment

death (on-treatment death was defined as any subject with death occurring within 28 days of the last dose of study drug). Time-to-first-event tables displayed time to first occurrence of an AE (in days) using summary statistics, and by ≤15, 16-30, 31-45, 46-60, and >60 days from start of the treatment, for any grade AEs.

Table 26 presents a summary of all adverse events for all patients with R/R AML by total daily dose of 500 mg and overall.

Table 26. Overall Summary of Adverse Events in Study AG120-C-001

Adverse Event, n (%)	Arm 1+ (N=159)	R/R AML at 500 mg QD (N=179)	Overall (N=258)
Any AE	159 (100.0)	179 (100.0)	258 (100.0)
Any Grade ≥3 AE	133 (83.6)	151 (84.4)	213 (82.6)
Any treatment-related AE	96 (60.4)	110 (61.5)	167 (64.7)
Any treatment-related Grade ≥3 AE	31 (19.5)	38 (21.2)	68 (26.4)
Any SAE	121 (76.1)	137 (76.5)	187 (72.5)
Any treatment-related SAE	30 (18.9)	36 (20.1)	56 (21.7)
Any AE leading to study drug permanently discontinued	23 (14.5)	25 (14.0)	31 (12.0)
Any AE leading to study drug reduced	4 (2.5)	6 (3.4)	12 (4.7)
Any AE leading to study drug held	60 (37.7)	68 (38.0)	102 (39.5)
Any AE leading to on-treatment death	27 (17.0)	28 (15.6)	41 (15.9)

Source: Addendum to Primary CSR AG120-C-001, Table 14.3.1.1.1, Table 14.3.1.1.2, Table 14.3.1.1.3. Data cutoff date: 11 May 2018.
Abbreviations: AE = adverse event; AML = acute myeloid leukemia; CSR = clinical study report; QD = once daily; R/R = relapsed or refractory; SAE = serious adverse event.

Treatment-related treatment emergent adverse events

Table 27 summarises the number of subjects with TEAEs suspected by the investigator of being treatment-related and that occurred in ≥2% of subjects overall.

Table 28 summarises the number of subjects with suspected treatment-related TEAEs by maximum grade 3-4 that occurred in ≥2% of subjects overall.

Table 27. Treatment-Related Adverse Events (≥2%) by MedDRA Preferred Term (Investigator Assessment) in Study AG120-C-001 (Safety Analysis Set)

Preferred Term, n (%)	Arm 1+ (N=159)	R/R AML at 500 mg QD (N=179)	Overall (N=258)
At Least 1 Treatment-Related AE	**96 (60.4)**	**110 (61.5)**	**167 (64.7)**
Electrocardiogram QT prolonged	21 (13.2)	26 (14.5)	34 (13.2)
Nausea	22 (13.8)	26 (14.5)	38 (14.7)
Fatigue	18 (11.3)	22 (12.3)	34 (13.2)
Diarrhoea	18 (11.3)	19 (10.6)	34 (13.2)
Decreased appetite	13 (8.2)	17 (9.5)	25 (9.7)
IDH differentiation syndrome	13 (8.2)	17 (9.5)	27 (10.5)
Vomiting	13 (8.2)	14 (7.8)	19 (7.4)
Leukocytosis	11 (6.9)	13 (7.3)	19 (7.4)
Pleural effusion	5 (3.1)	5 (2.8)	5 (1.9)
Rash maculo-papular	4 (2.5)	5 (2.8)	8 (3.1)
White blood cell count increased	4 (2.5)	5 (2.8)	5 (1.9)
Anaemia	3 (1.9)	4 (2.2)	10 (3.9)
Asthenia	4 (2.5)	4 (2.2)	6 (2.3)
Constipation	4 (2.5)	4 (2.2)	6 (2.3)
Dyspnoea	4 (2.5)	4 (2.2)	10 (3.9)
Headache	4 (2.5)	4 (2.2)	5 (1.9)
Oedema peripheral	4 (2.5)	4 (2.2)	5 (1.9)
Dysgeusia	2 (1.3)	3 (1.7)	6 (2.3)
Thrombocytopenia	1 (0.6)	3 (1.7)	6 (2.3)
Rash	2 (1.3)	2 (1.1)	8 (3.1)

Source: Addendum to Primary CSR AG120-C-001 Table 14.3.1.5.1, Table 14.3.1.5.2, and Table 14.3.1.5.3. Data cutoff date: 11 May 2018.
Abbreviations: AE = adverse event; AML = acute myeloid leukemia; CSR = clinical study report; IDH = isocitrate dehydrogenase; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily; R/R = relapsed or refractory.
Note: If a subject experienced multiple AEs under the same preferred term within a System Organ Class, then the subject was counted only once for the preferred term by the worst grade within that System Organ Class. Preferred terms were sorted by descending frequency in subjects with R/R AML whose starting dose was 500 mg QD.

Table 28. Grade ≥3 Treatment-Related Adverse Events (≥2%) by MedDRA Preferred Term (Investigator Assessment) in Study AG120-C-001 (Safety Analysis Set)

Preferred Term, n (%)	Arm 1+ (N=159)	R/R AML at 500 mg QD (N=179)	Overall (N=258)
At Least 1 Grade ≥3 Treatment-related AE	**31 (19.5)**	**38 (21.2)**	**68 (26.4)**
Electrocardiogram QT prolonged	12 (7.5)	14 (7.8)	19 (7.4)
IDH differentiation syndrome	5 (3.1)	7 (3.9)	12 (4.7)
Anaemia	3 (1.9)	4 (2.2)	6 (2.3)

Source: Addendum to Primary CSR AG120-C-001 Table 14.3.1.6.1, Table 14.3.1.6.2, and Table 14.3.1.6.3. Data cutoff date: 11 May 2018.
Abbreviations: AE = adverse event; AML = acute myeloid leukemia; CSR = clinical study report; IDH = isocitrate dehydrogenase; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily; R/R = relapsed or refractory.
Note: If a subject experienced multiple AEs under the same preferred term within a System Organ Class, then the subject was counted only once for the preferred term by the worst grade within that System Organ Class. Preferred terms were sorted by descending frequency in subjects with R/R AML whose starting dose was 500 mg QD.

Adverse events of special interest (AESIs)

Adverse events of special interest (AESIs) are identified risks based on nonclinical and clinical safety findings and are defined in the study protocols, including clinical guidelines for management. The AESIs in Study AG120-C-001 were ivosidenib related (IDH) differentiation syndrome, leukocytosis and QT interval prolongation.

IDH Differentiation syndrome

IDH Differentiation syndrome is a life-threatening drug related adverse event comparable with the "retinoid acid syndrome" described for retinoid acid (eg, for Vesanoid) in the treatment of acute promyelocytic leukaemia (APL). It is characterised by rapid weight gain, pleural and pericardial effusions, peripheral oedema, respiratory distress, and fever. Additionally, it can be accompanied by leukocytosis and TLS. The incidences of the TEAE of IDH differentiation syndrome are presented in Table 29.

Table 29. Overall Summary of IDH Differentiation Syndrome Adverse Events and Time to Onset in Study AG120-C-001 (Safety Analysis Set)

Adverse Event, n (%)	Arm 1+ (N=159)	All R/R AML at 500 mg QD (N=179)	Overall (N=258)
Any IDH differentiation syndrome AE	16 (10.1)	20 (11.2)	30 (11.6)
Any Grade ≥3 AE	8 (5.0)	10 (5.6)	15 (5.8)
Any treatment-related AE	13 (8.2)	17 (9.5)	27 (10.5)
Any treatment-related Grade ≥3 AE	5 (3.1)	7 (3.9)	12 (4.7)
Any SAE	15 (9.4)	19 (10.6)	28 (10.9)
Any treatment-related SAE	12 (7.5)	16 (8.9)	25 (9.7)
Any AE leading to study drug permanently discontinued	0	0	0
Any AE leading to study drug reduced	0	0	0
Any AE leading to study drug held	4 (2.5)	6 (3.4)	11 (4.3)
Any AE leading to on-treatment death	0	0	0

Source: Addendum to Primary CSR AG120-C-001, Table 14.3.1.1.4. Data cutoff date: 11 May 2018.
Abbreviations: AE = adverse event; AML = acute myeloid leukemia; CSR = clinical study report; IDH = isocitrate dehydrogenase; QD = once daily; R/R = relapsed or refractory; SAE = serious adverse event.

Treatment with ivosidenib can induce myeloid proliferation, which can manifest as an increase in WBC count without evidence of infection or clinical signs of IDH differentiation syndrome. Incidence of TEAEs of *leukocytosis* in Study AG120-C-001 is presented in Table 30.

Table 30. Overall Summary of Leukocytosis Adverse Events in Study AG120-C-001 (Safety Analysis Set)

Adverse Event, n (%)	Arm 1+ (N=159)	R/R AML at 500 mg (N=179)	Overall (N=258)
Any leukocytosis AE	61 (38.4)	69 (38.5)	98 (38.0)
Any Grade ≥3 AE	16 (10.1)	16 (8.9)	21 (8.1)
Any treatment-related AE	14 (8.8)	18 (10.1)	25 (9.7)
Any treatment-related Grade ≥3 AE	3 (1.9)	3 (1.7)	4 (1.6)
Any SAE	17 (10.7)	18 (10.1)	24 (9.3)
Any treatment-related SAE	4 (2.5)	5 (2.8)	6 (2.3)
Any AE leading to study drug permanently discontinued	0	0	1 (0.4)
Any AE leading to study drug reduced	0	0	0
Any AE leading to study drug held	5 (3.1)	5 (2.8)	7 (2.7)
Any AE leading to on-treatment death	0	0	0

Source: SCS, Table 18.3.1.1. Data cutoff date: 11 May 2018.
Abbreviations: AE = adverse event; AML = acute myeloid leukemia; SCS = Summary of Clinical Safety; MedDRA = Medical Dictionary for Regulatory Activities; R/R = relapsed or refractory; SAE = serious adverse event.
Note: Leukocytosis was identified by searching with the MedDRA preferred terms white blood cell count increased, leukocytosis, and hyperleukocytosis.

QTc prolongation

Heart rate-corrected QT interval prolongation occurs in subjects treated with ivosidenib. A concentration-QT analysis suggested a concentration-dependent QTc interval prolongation of approximately 16.1 msec (90% CI: 13.3, 18.9) at the geometric mean observed steady state Cmax at the 500 mg daily dose. A summary of Adverse Events in the SMQ (broad) Torsade de Pointes/QT Prolongation is presented in Table 31.

Table 31. Overall Summary of Adverse Events in the SMQ (broad) Torsade de Pointes/QT Prolongation in Study AG120-C-001 (Safety Analysis Set)

Adverse Event, n (%)	Arm 1+ (N=159)	R/R AML at 500 mg QD (N=179)	Overall (N=258)
Any AEs within the SMQ (broad) Torsade de pointes/QT prolongation	42 (26.4)	49 (27.4)	68 (26.4)
Any Grade ≥3 AE	18 (11.3)	21 (11.7)	29 (11.2)
Any treatment-related AE	21 (13.2)	26 (14.5)	34 (13.2)
Any treatment-related Grade ≥3 AE	12 (7.5)	14 (7.8)	19 (7.4)
Any SAE	14 (8.8)	17 (9.5)	22 (8.5)
Any treatment-related SAE	8 (5.0)	10 (5.6)	14 (5.4)
Any AE leading to study drug permanently discontinued	0	0	0
Any AE leading to study drug reduced	2 (1.3)	2 (1.1)	5 (1.9)
Any AE leading to study drug held	12 (7.5)	15 (8.4)	20 (7.8)
Any AE leading to on-treatment death	1 (0.6)	1 (0.6)	2 (0.8)

Source: SCS, Table 18.3.27.1. Data cutoff date: 11 May 2018.
Abbreviations: AE = adverse event; AML = acute myeloid leukemia; CSR = clinical study report; QD = once daily; R/R = relapsed or refractory; SAE = serious adverse events; SCS = Summary of Clinical Safety; SMQ = Standardized Medical Dictionary for Regulatory Activities query

Among the 179 subjects with R/R AML whose starting dose was 500 mg QD, results from the categorical analysis of maximum post-baseline absolute QTcF showed that the majority of subjects had a maximum post-baseline absolute QTcF of ≤500 msec. However, approximatively 19% of patients in the pivotal study AG120-C-001 experienced either QTcF of >500 msec and/or change of QTcF of >60 msec from baseline, partly with extreme QT-prolongation up to 151.7 msec. This is most likely due to ivosidenib exposure. Thus, Section 4.8 indicates that 19% of patients in the pivotal study experienced either QTcF of >500 msec and/or change of QTcF of >60 msec from baseline**.**

Across the ivosidenib clinical development programme, there were no AEs of Torsade de pointes. The most common PT in this SMQ was electrocardiogram QT prolonged. Among the 179 subjects with R/R AML whose starting dose was 500 mg QD, 18 subjects (10.1%) had Grade 3 AEs of electrocardiogram QT prolonged (none of the events were Grade 4 or Grade 5). Additionally, within this SMQ, there were 2 subjects (1.1%) with Grade ≥3 AEs of syncope and 2 subjects (1.1%) with Grade ≥3 AEs of cardiac arrest, and the following Grade ≥3 AEs were reported in 1 subject (0.6%) each: ventricular tachycardia and ventricular arrhythmia.

For subjects with R/R AML whose starting dose was 500 mg QD, the incidence of AEs in the SMQ (broad) Torsade de pointes/QT prolongation was higher among subjects who were receiving concomitant medications known to prolong the QT interval compared with those who were not (≥29.1% [48/165] vs 7.1% [1/14], respectively). Further, there is a trend of a higher incidence of QTc prolonging AEs in patients taking moderate/strong CYP3A4 inhibitors.

Adverse events of clinical importance

The majority of the AEs of clinical importance were selected because they are potential risks across the ivosidenib clinical development programme. These events include tumour lysis syndrome, sensorimotor neuropathy/polyneuropathy and Guillain-Barre syndrome, rash, gastrointestinal symptoms, leukoencephalopathy, liver dysfunction, renal dysfunction and blood and lymphatic disorders / infections.

Development of *tumour lysis syndrome* is a known risk associated with AML. Clinical risk factors include leukocytosis (with or without disease progression) and concurrent use of cytoreductive agents such as hydroxyurea.

Ivosidenib can induce myeloid proliferation resulting in a rapid reduction in tumour cells, which may pose a risk for tumour lysis syndrome. In some instances, tumour lysis syndrome events occurred in subjects who also had rising WBC counts, suggesting the possibility that these events were related to the underlying malignancy, concurrent infections or in a few cases were co-occurring with differentiation syndrome.

The incidence of leukocytosis was higher among subjects with tumour lysis syndrome (52.6% in the overall study population and 58.3% in Arm 1+) than the incidence among all subjects (38.8% in the overall study population and 38.4% in Arm 1+). Whereas the incidence of differentiation syndrome was similar or lower in subjects with tumour lysis syndrome (15.8% in the overall study population and 8.3% in Arm 1+) compared with the incidence among all subjects (19.4% in the overall study population and 18.2% in Arm 1+), suggesting the occurrence of tumour lysis syndrome did not increase the risk of differentiation syndrome.

The incidence of TEAEs of tumour lysis syndrome in Study AG120-C-001 is presented in Table 32.

Table 32. Overall Summary of Adverse Events of Tumour Lysis Syndrome in Study AG120-C-001 (Safety Analysis Set)

Adverse Event, n (%)	Arm 1+ (N=159)	All R/R AML at 500 mg QD (N=179)	Overall (N=258)
Any TLS AE	12 (7.5)	15 (8.4)	19 (7.4)
Any Grade ≥3 AE	10 (6.3)	12 (6.7)	16 (6.2)
Any treatment-related AE	0	0	2 (0.8)
Any treatment-related Grade ≥3 AE	0	0	2 (0.8)
Any SAE	5 (3.1)	6 (3.4)	7 (2.7)
Any treatment-related SAE	0	0	0
Any AE leading to study drug permanently Discontinued	0	0	0
Any AE leading to study drug reduced	0	0	0
Any AE leading to study drug held	1 (0.6)	1 (0.6)	1 (0.4)
Any AE leading to on-treatment death	0	0	0

Source: SCS, Table 18.3.3.1. Data cutoff date: 11 May 2018.
Abbreviations: AE = adverse event; AML = acute myeloid leukemia; SCS = Summary of Clinical Safety; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; QD = once daily; R/R = relapsed or refractory; SAE = serious adverse event; TLS = tumour lysis syndrome.
Note: Tumour lysis syndrome AEs were identified by searching with the MedDRA PT of tumour lysis syndrome.

Sensorimotor neuropathy/polyneuropathy and Guillain-Barre syndrome: The incidence of these TEAEs in study AG120-C-001 is presented in Table 33.

Table 33. Overall Summary of Polyneuropathy Adverse Events in Study AG120-C-001 (Safety Analysis Set)

Adverse Event, n (%)	Arm 1+ (N=159)	R/R AML at 500 mg QD (N=179)	Overall (N=258)
Any polyneuropathy AE	15 (9.4)	15 (8.4)	19 (7.4)
Any Grade ≥3 AE	1 (0.6)	1 (0.6)	1 (0.4)
Any treatment-related AE	5 (3.1)	5 (2.8)	7 (2.7)
Any treatment-related Grade ≥3 AE	1 (0.6)	1 (0.6)	1 (0.4)
Any SAE	2 (1.3)	2 (1.1)	3 (1.2)
Any treatment-related SAE	2 (1.3)	2 (1.1)	3 (1.2)
Any AE leading to study drug permanently discontinued	2 (1.3)	2 (1.1)	2 (0.8)
Any AE leading to study drug reduced	0	0	0
Any AE leading to study drug held	2 (1.3)	2 (1.1)	3 (1.2)
Any AE Leading to on-treatment death	0	0	0

Source: SCS, Table 18.3.5.1. Data cutoff date: 11 May 2018.
Abbreviations: AE = adverse event; AML = acute myeloid leukemia; SCS = Summary of Clinical Safety; MedDRA = Medical Dictionary for Regulatory Activities; NEC = not elsewhere classified; QD = once daily; R/R = relapsed or refractory; SAE = serious adverse event.
Note: Polyneuropathy was identified by searching with the MedDRA high-level terms of acute polyneuropathies, chronic polyneuropathies, mononeuropathies, and peripheral neuropathies NEC.

Polyneuropathy, including Guillain-Barre syndrome, was included in Section 4.8 of the product label. The SmPC also states that patients should be monitored for the onset of new signs/symptoms of motor and/or sensory neuropathy (Section 4.4 of the SmPC), and that treatment should be discontinued in any patients diagnosed with Guillain-Barre syndrome (Section 4.2 of the SmPC). Additionally, Guillain-Barre syndrome has been included as an important identified risk of ivosidenib in the RMP.

Rash is a further potential risk associated with ivosidenib treatment based on clinical safety findings. The incidence of rash TEAEs in study AG120-C-001 is presented in Table 34.

Table 34. Overall Summary of Rash Adverse Events in Study AG120-C-001 (Safety Analysis Set)

Adverse Event, n (%)	Arm 1+ (N=159)	R/R AML at 500 mg QD (N=179)	Overall (N=258)
Any rash AE	42 (26.4)	47 (26.3)	66 (25.6)
Any Grade ≥3 AE	4 (2.5)	4 (2.2)	7 (2.7)
Any treatment-related AE	10 (6.3)	11 (6.1)	20 (7.8)
Any treatment-related Grade ≥3 AE	2 (1.3)	2 (1.1)	4 (1.6)
Any SAE	2 (1.3)	4 (2.2)	9 (3.5)
Any treatment-related SAE	1 (0.6)	1 (0.6)	4 (1.6)
Any AE leading to study drug permanently discontinued	1 (0.6)	1 (0.6)	1 (0.4)
Any AE leading to study drug reduced	0	0	2 (0.8)
Any AE leading to study drug held	1 (0.6)	1 (0.6)	5 (1.9)
Any AE Leading to on-treatment death	0	0	0

Source: SCS, Table 18.3.6.1. Data cutoff date: 11 May 2018.
Abbreviations: AE = adverse event; AML = acute myeloid leukemia; SCS = Summary of Clinical Safety; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily; R/R = relapsed or refractory; SAE = serious adverse event.
Note: Rash was identified by searching with the MedDRA preferred terms acute febrile neutrophilic dermatosis, drug eruption, skin erosion, skin exfoliation, exfoliative rash, rash macular, dermatitis allergic, dermatitis bullous, rash erythematous, rash generalized, urticaria, rash maculo-papular, rash, rash papular, rash pruritic, rash pustular, rash vesicular, skin ulcer, butterfly rash, dermatitis acneiform, and dermatitis.

While causality of *gastrointestinal disorders* (overall common in this patient population) is hard to ascertain in an uncontrolled study, the nonclinical toxicology data, short time to onset of gastrointestinal TEAEs, as well as common attribution of TEAE causality to ivosidenib by the investigators, suggest a potential gastrointestinal tract irritation associated with ivosidenib administration. The incidence of TEAEs of gastrointestinal disorders in Study AG120-C-001 is presented in Table 35.

Table 35. Overall Summary of Gastrointestinal Symptoms Adverse Events in Study AG120-C-001 (Safety Analysis Set)

Adverse Event, n (%)	Arm 1+ (N=159)	All R/R AML at 500 mg QD (N=179)	Overall (N=258)
Any gastrointestinal symptom AE	102 (64.2)	113 (63.1)	173 (67.1)
Any Grade ≥3 AE	8 (5.0)	9 (5.0)	15 (5.8)
Any treatment-related AE	40 (25.2)	45 (25.1)	70 (27.1)
Any treatment-related Grade ≥3 AE	1 (0.6)	1 (0.6)	5 (1.9)
Any SAE	9 (5.7)	9 (5.0)	14 (5.4)
Any treatment-related SAE	1 (0.6)	1 (0.6)	2 (0.8)
Any AE leading to study drug permanently discontinued	0	0	1 (0.4)
Any AE leading to study drug reduced	1 (0.6)	1 (0.6)	1 (0.4)
Any AE leading to study drug held	4 (2.5)	4 (2.2)	7 (2.7)
Any AE Leading to On-treatment Death	0	0	0

Source: SCS, Table 18.3.9.1. Data cutoff date: 11 May 2018.
Abbreviations: AE = adverse event; AML = acute myeloid leukemia; SCS = Summary of Clinical Safety; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily; R/R = relapsed or refractory; SAE = serious adverse event.
Note: Gastrointestinal symptoms were identified by searching the SMQ (narrow) AEs of gastrointestinal nonspecific symptoms and therapeutic procedures.

The MedDRA HLTs of encephalopathies NEC and demyelinating disorders NEC create a search strategy that encompassed medically equivalent terminology to define the AE of *leukoencephalopathy*. In the overall study population from AG120-C-001, 3 (1.2%) of the 258 subjects experienced at least 1 AE under the search strategy for leukoencephalopathy. One subject (503-022) experienced a non-serious AE of encephalopathy, one subject (511-037) experienced 2 SAEs of progressive multifocal leukoencephalopathy (PML) and 1 subject (510 001) experienced an SAE of posterior reversible encephalopathy syndrome (PRES). Leukoencephalopathy is not considered an important risk of ivosidenib due to the multiple confounding factors observed in the cases reported. However, it is proposed by the applicant to add progressive multifocal leukoencephalopathy (PML) as an important potential risk in the RMP to monitor any additional occurrences of these events, which is acceptable. PML is classified as an important potential risk as it is often a fatal viral disease and was observed in 1 patient treated with ivosidenib (511-037), although both the Investigator and Sponsor assessed the 2 SAEs of PML as not related to ivosidenib based on the subject's history of cladribine exposure and underlying AML. In the context of SAT, it could not entirely be excluded that PML in the AG120-C-001 study could be relative to treatment. PML should be included as a warning in Section 4.4 of the SmPC (whatever the AE grade). As a single case of PRES occurred in a patient with untreated AML, the applicant considers that there is currently insufficient evidence, based on the available data, to include PRES as an important potential risk in the RMP. This is acceptable.

Liver dysfunction is a potential risk associated with ivosidenib treatment based on nonclinical safety findings. The incidence of liver dysfunction TEAEs in Study AG120-C-001 is presented in Table 36.

Table 36. Overall Summary of Liver Dysfunction Adverse Events in Study AG120-C-001 (Safety Analysis Set)

Adverse Event, n (%)	Arm 1+ (N=159)	R/R AML at 500 mg QD (N=179)	Overall (N=258)
Any liver dysfunction AE	6 (3.8)	6 (3.4)	13 (5.0)
Any Grade ≥3 AE	2 (1.3)	2 (1.1)	8 (3.1)
Any treatment-related AE	1 (0.6)	1 (0.6)	2 (0.8)
Any treatment-related Grade ≥3 AE	1 (0.6)	1 (0.6)	2 (0.8)
Any SAE	1 (0.6)	1 (0.6)	4 (1.6)
Any treatment-related SAE	0	0	0
Any AE leading to study drug permanently discontinued	0	0	0
Any AE leading to study drug reduced	0	0	0
Any AE leading to study drug held	1 (0.6)	1 (0.6)	2 (0.8)
Any AE Leading to On-treatment Death	0	0	0

Source: SCS, Table 18.3.12.1. Data cutoff date: 11 May 2018.
Abbreviations: AE = adverse event; AML = acute myeloid leukemia; SCS = Summary of Clinical Safety; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily; R/R = relapsed or refractory; SAE = serious adverse event; SOC = System Organ Class.
Note: Liver dysfunction were defined as the MedDRA SOC hepatobiliary disorders.

As ivosidenib is metabolised predominantly by CYP3A4 there is a potential for hepatic impairment to affect ivosidenib exposure.

The incidences of treatment-related AEs and treatment-related SAEs were slightly higher in subjects with mild hepatic impairment compared with those with normal hepatic function (Arm 1+ treatment-related AEs: 72.7% vs 58.7%, respectively, and treatment-related SAEs: 24.2% vs 18.2%, respectively).

The following preferred terms were reported more frequently (difference in incidence >5.0%) in subjects with mild hepatic impairment vs those with normal hepatic function in Arm 1+: electrocardiogram QT prolonged, diarrhoea, dyspnoea, fatigue, leukocytosis, rash, alanine aminotransferase increased, aspartate aminotransferase increased, and dizziness.

Concerning treatment-related SAEs, the following preferred terms were reported more frequently (difference in incidence >2.0%) in subjects with mild hepatic impairment vs those with normal hepatic function in Arm 1+: electrocardiogram QT prolonged, leukocytosis, and ventricular tachycardia.

In summary, there is a clear trend to a higher incidence of AEs in patients with mild hepatic impairment. Of note, the incidence of QTc interval prolongation events (which have a dose dependent trend) was higher in patients with impaired hepatic function. The applicant agreed to adapt according wording in Section 4.4 and 4.8 of the SmPC.

Renal dysfunction is a potential risk associated with ivosidenib treatment based on nonclinical safety findings. Causal relationship between exposure to ivosidenib and renal injury was hardly assessable in pivotal study AG120-C-001, mainly due to the confounding effect of leukaemia- and treatment-related complications as differentiation syndrome, leukocytosis, tumour lysis syndrome or GI disorders. The incidence of renal dysfunction TEAEs in Study AG120-C-001 is presented in Table 37.

Table 37. Overall Summary of Renal Dysfunction Adverse Events in Study AG120-C-001 (Safety Analysis Set)

Adverse Event, n (%)	Arm 1+ (N=159)	R/R AML at 500 mg QD (N=179)	Overall (N=258)
Any Renal AE	17 (10.7)	19 (10.6)	26 (10.1)
Any Grade ≥3 AE	5 (3.1)	6 (3.4)	8 (3.1)
Any treatment-related AE	1 (0.6)	1 (0.6)	1 (0.4)
Any treatment-related Grade ≥3 AE	0	0	0
Any SAE	6 (3.8)	7 (3.9)	9 (3.5)
Any treatment-related SAE	0	0	0
Any AE leading to study drug permanently discontinued	1 (0.6)	2 (1.1)	2 (0.8)
Any AE leading to study drug reduced	0	0	0
Any AE leading to study drug held	2 (1.3)	3 (1.7)	4 (1.6)
Any AE Leading to On-treatment Death	0	0	1 (0.4)

Source: SCS, Table 18.3.13.1. Data cutoff date: 11 May 2018.
Abbreviations: AE = adverse event; AML = acute myeloid leukemia; SCS = Summary of Clinical Safety; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily; R/R = relapsed or refractory; SAE = serious adverse event; SMQ = standardized Medical Dictionary for Regulatory Activities query.
Note: Renal AEs were identified by searching with the MedDRA SMQ of acute renal failure (narrow).

Based on the data in Arm 1+, worsening renal impairment in patients treated with ivosidenib could not be excluded. Tumour lysis syndrome was more frequent in subjects with moderate renal impairment (N=4, 16%) than in those with normal renal function (N=1, 1.4%), and acute kidney injury was more frequent in subjects with moderate renal impairment (N=3, 12%) than in those with normal renal function (N=2, 2.8%). Thus, a special warning in patients with pre-existing renal disorders in order to reduce the risk for fatal renal failure has been implemented in the SmPC**.** Use in patients with severe renal impairment has been considered as an area of missing information in the RMP**.**

AEs in the SOC *blood and lymphatic system disorders* and in the SOC *infections and infestation*s were frequently observed during treatment with ivosidenib (Table 38). In the context of SAT, based on the data provided, it could not be excluded that thrombocytopenia, anaemia, febrile neutropenia and infectious risk observed in the AG120-C-001 study could be relative to treatment; these AEs have been included in Section 4.8 of the SmPC**.**

In addition, treatment with ivosidenib seemed to reduce TEAEs in the SOC of *blood and lymphatic system disorders* and the SOC of *infections* over time. As presented in efficacy sections, patients who achieved a response had reduced incidence of grade 3/4 infection, bleeding, and febrile neutropenia during the periods of response compared with non-responders.

Table 38. Adverse Events by MedDRA System Organ Class (Investigator Assessment) in Study AG120-C-001 (Safety Analysis Set)

System Organ Class, n (%)	Arm 1+ (N=159)	R/R AML at 500 mg QD (N=179)	Overall (N=258)
Blood and lymphatic system disorders	110 (69.2)	125 (69.8)	179 (69.4)
Infections and infestations	112 (70.4)	124 (69.3)	168 (65.1)

Serious adverse events and deaths

In 36 subjects (20.1%), at least one treatment-related SAE was observed. The treatment-related SAEs reported by ≥2 subjects were IDH differentiation syndrome (16 subjects, 8.9%); electrocardiogram QT prolonged (10 subjects, 5.6%); leukocytosis (5 subjects, 2.8%); Guillain-Barre syndrome and pyrexia (2 subjects each, 1.1%).

Adverse events leading to on-treatment death were reported in 28 subjects (15.6%) with R/R AML whose starting dose was 500 mg QD. Many were associated with comorbidities of advanced haematologic malignancies. Those reported in >1 subject included sepsis (4 subjects, 2.2%); pneumonia (3 subjects, 1.7%); pneumonia aspiration and respiratory failure (2 subjects each, 1.1%). None of the on-treatment deaths were due to AEs assessed by the Investigator as treatment-related.

Laboratory findings

Platelets, ANC, and haemoglobin over time for all subjects are presented in Figure 20, Figure 21, and Figure 22, respectively.

Figure 20. Mean Platelet Count Over Time for Subjects with R/R AML Whose Starting Dose was 500 mg QD in Study AG120-C-001 (Safety Analysis Set)

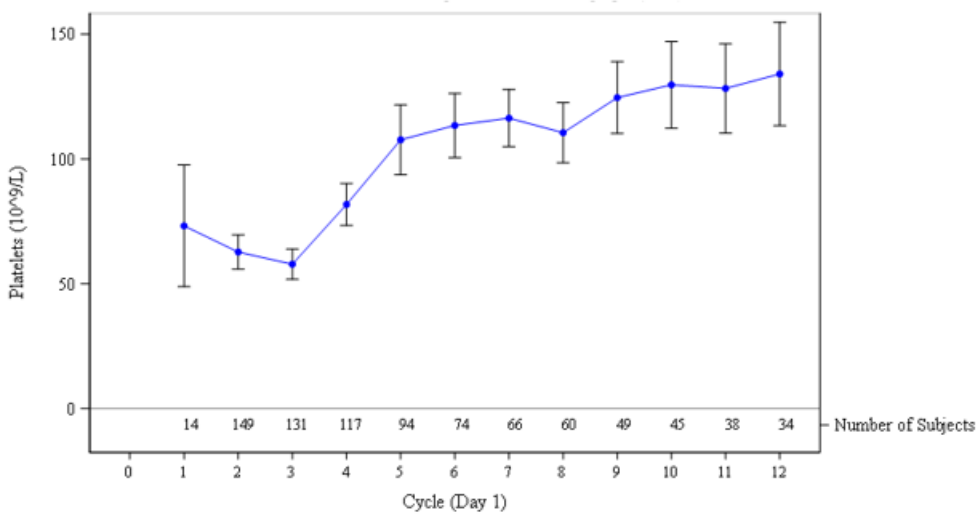


Figure 21. Mean Absolute Neutrophil Count Over Time for Subjects with R/R AML Whose Starting Dose was 500 mg QD in Study AG120-C-001 (Safety Analysis Set)

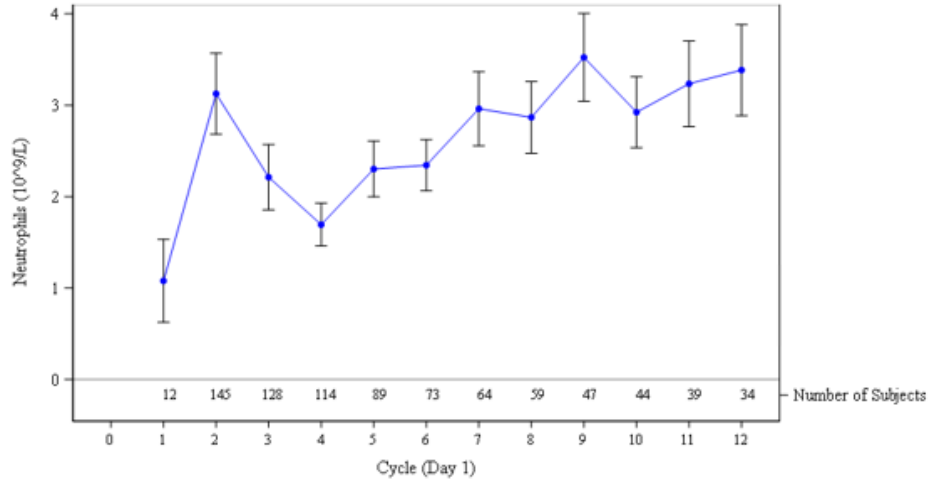
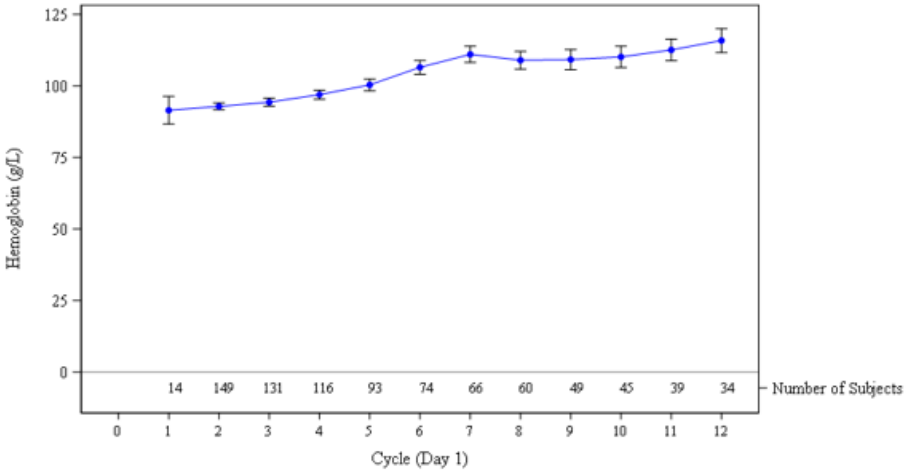


Figure 22. Mean Hemoglobin Concentration Over Time for Subjects with R/R AML Whose Starting Dose was 500 mg QD in Study AG120-C-001 (Safety Analysis Set)



Adverse events associated with clinical chemistry laboratory abnormalities reported in ≥2% of subjects are summarised in Table 39.

Table 39. Common Adverse Events (≥2%) Associated with Clinical Chemistry Laboratory Abnormalities by MedDRA Preferred Term in Study AG120-C-001 (Safety Analysis Set)

Preferred Term, n (%)	Arm 1+ (N=159)	R/R AML at 500 mg QD (N=179)	Overall (N=258)
Hypokalaemia	29 (18.2)	34 (19.0)	50 (19.4)
Hypomagnesaemia	17 (10.7)	22 (12.3)	35 (13.6)
Hyperuricaemia	18 (11.3)	20 (11.2)	28 (10.9)
Hypophosphataemia	13 (8.2)	15 (8.4)	23 (8.9)
Hyponatraemia	10 (6.3)	14 (7.8)	21 (8.1)
Hypocalcaemia	10 (6.3)	11 (6.1)	18 (7.0)
Hyperphosphataemia	9 (5.7)	10 (5.6)	13 (5.0)
Hyperkalaemia	9 (5.7)	10 (5.6)	12 (4.7)
Blood creatinine increased	8 (5.0)	9 (5.0)	15 (5.8)
Aspartate aminotransferase increased	6 (3.8)	7 (3.9)	12 (4.7)
Hyperglycaemia	5 (3.1)	7 (3.9)	15 (5.8)
Hypoalbuminaemia	5 (3.1)	7 (3.9)	12 (4.7)
Alanine aminotransferase increased	4 (2.5)	6 (3.4)	10 (3.9)
Blood creatine increased	4 (2.5)	4 (2.2)	4 (1.6)
Blood alkaline phosphatase increased	3 (1.9)	3 (1.7)	10 (3.9)
Blood bilirubin increased	3 (1.9)	3 (1.7)	8 (3.1)
Blood cholesterol increased	1 (0.6)	2 (1.1)	6 (2.3)

Source: Addendum to Primary CSR AG120-C-001, Table 14.3.1.2.1, Table 14.3.1.2.2, and Table 14.3.1.2.3. Data cutoff date: 11 May 2018.
Abbreviations: AML = acute myeloid leukemia; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily; R/R = relapsed or refractory.
Note: If a subject experienced multiple adverse events under the same preferred term within a System Organ Class, then the subject was counted only once for the preferred term by the worst grade within that System Organ Class. Preferred terms were sorted by descending frequency of the R/R AML at 500 mg dose group.

The following AEs were reported for subjects with R/R AML whose starting dose was 500 mg QD: coagulopathy (6 subjects, 3.4%); activated partial thromboplastin time prolonged and disseminated intravascular coagulation (3 subjects each, 1.7%); blood fibrinogen decreased, international normalised ratio increased, and prothrombin time prolonged (1 subject each, 0.6%). These events were generally mild or moderate. Three subjects (1.7%) experienced SAEs of disseminated intravascular coagulation.

Safety in special populations

Evaluation of *demographic characteristics* is primarily based on the combined dose escalation and expansion population of Study AG120-C-001. Adverse events Grade ≥3 by Age, Sex, Race and Baseline ECOG Performance Status are presented in Table 40.

Table 40. Adverse Events Grade ≥3 by Age, Sex, Race and Baseline ECOG Performance Status for Arm 1⁺ Subjects and Subjects with R/R AML Whose Starting Dose was 500 mg QD (Safety Analysis Set)

Subgroup Category	Grade ≥3 Adverse Events	
	Arm 1⁺ (N=159)	All R/R AML at 500 mg QD (N=179)
Age, n/N (%)		
<65 years	56/62 (90.3)	60/67 (89.6)
65 to <75 years	48/65 (73.8)	55/72 (76.4)
≥75 to <85 years	25/28 (89.3)	32/36 (88.9)
≥85 years	4/4 (100.0)	4/4 (100.0)
Sex, n/N (%)		
Male	69/82 (84.1)	75/90 (83.3)
Female	64/77 (83.1)	76/89 (85.4)
Race, n/N (%)		
White	80/99 (80.8)	92/112 (82.1)
Other[1]	53/60 (88.3)	59/67 (88.1)
Baseline ECOG Performance Status, n/N (%)		
0	27/31 (87.1)	31/36 (86.1)
1	69/84 (82.1)	83/99 (83.8)
2	35/42 (83.3)	35/42 (83.3)
3	2/2 (100)	2/2 (100)

Source: Addendum to Primary CSR AG120-C-001, Table 14.3.1.14.1A, Table 14.3.1.14.1B, Table 14.3.1.14.2A, Table 14.3.1.14.2B, Table 14.3.1.14.4A, Table 14.3.1.14.4B, Table 14.3.1.14.5A, and Table 14.3.1.14.5B. Data cutoff date: 11 May 2018.
Abbreviations: AML = acute myeloid leukemia; CSR = clinical study report; ECOG = Eastern Cooperative Oncology Group; QD = once daily; R/R = relapsed or refractory
Note: n/N=number of subjects with event/number of subjects within the subgroup in that treatment arm.
[1] "Other" includes Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, not reported, and other. In accordance with local regulations, race and ethnicity were not reported by study sites in France.

Hepatic impairment

Ivosidenib is metabolised 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. A summary of the AE incidence by baseline hepatic function for subjects with R/R AML whose starting dose was 500 mg QD is presented in Table 41. As discussed

above, there is a clear trend to a higher incidence of AEs in patients with mild hepatic impairment. A warning in Section 4.4 has been included in the SmPC**.**

Table 41. Summary of Adverse Events by Baseline Hepatic Function in Subjects with R/R AML Whose Starting Dose was 500 mg QD (Safety Analysis Set)

Adverse Event Category, n (%)	Baseline Hepatic Function				
	Normal (N=139)	Mild (N=35)	Moderate (N=1)	Severe (N=1)	Missing (N=3)
Any AE	139 (100.0)	35 (100.0)	1 (100.0)	1 (100.0)	3 (100.0)
Any Grade ≥3 AE	117 (84.2)	30 (85.7)	1 (100.0)	1 (100.0)	2 (66.7)
Any treatment-related AE	83 (59.7)	26 (74.3)	0	0	1 (33.3)
Any treatment-related Grade ≥3 AE	28 (20.1)	10 (28.6)	0	0	0
Any SAE	107 (77.0)	26 (74.3)	1 (100.0)	1 (100.0)	2 (66.7)
Any treatment-related SAE	26 (18.7)	10 (28.6)	0	0	0
Any AE leading to study drug permanently discontinued	19 (13.7)	6 (17.1)	0	0	0
Any AE leading to study drug reduced	4 (2.9)	2 (5.7)	0	0	0
Any AE leading to study drug held	52 (37.4)	14 (40.0)	0	1 (100.0)	1 (33.3)
Any AE leading to on-treatment death	20 (14.4)	7 (20.0)	0	1 (100.0)	0

Source: SCS, Table 18.3.17.1.2. Data cutoff date: 11 May 2018.
Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AML = acute myeloid leukemia; AST = aspartate aminotransferase; SCS = Summary of Clinical Safety; QD = once daily; R/R = relapsed or refractory; SAE = serious adverse event; ULN = upper limit of normal.
Note: Events with missing relationship were considered related to study drug.
Liver function is categorized as follows: normal (total bilirubin ≤ULN and AST ≤ULN); mild (total bilirubin ≤ULN), and AST >ULN, or ULN <total bilirubin ≤1.5×ULN and AST = any; moderate (1.5×ULN <total bilirubin ≤3 ×ULN and AST = any), severe (total bilirubin >3×ULN and AST=any)

Renal impairment

The potential impact of baseline renal function on ivosidenib safety was assessed as well. Baseline renal function categories (normal, mild, moderate, or severe) were determined using estimated glomerular filtration rate (eGFR). A summary of AEs by baseline eGFR in subjects with R/R AML whose starting dose was 500 mg QD is presented in Table 42.

The safety and efficacy of ivosidenib have not been established in patients with severe renal impairment (eGFR < 30ml/min/1.73 m2). Use in patients with severe renal impairment has been included as an area of missing information in the RMP**.** As discussed above, in patients with a history of renal disease, a trend to a higher incidence of AEs was observed. Warnings in Section 4.4 of the SmPC include this patient population.

Table 42. Summary of Adverse Events by Baseline eGFR in Subjects With R/R AML Whose Starting Dose was 500 mg QD (Safety Analysis Set)

Adverse Event Category, n (%)	Baseline Estimated Glomerular Filtration Rate			
	Normal (N=76)	Mild (N=73)	Moderate (N=30)	Severe (N=0)
Any AE	76 (100.0)	73 (100.0)	30 (100.0)	0
Any Grade ≥3 AE	64 (84.2)	60 (82.2)	27 (90.0)	0
Any treatment-related AE	45 (59.2)	45 (61.6)	20 (66.7)	0
Any treatment-related Grade ≥3 AE	17 (22.4)	15 (20.5)	6 (20.0)	0
Any SAE	57 (75.0)	54 (74.0)	26 (86.7)	0
Any treatment-related SAE	17 (22.4)	15 (20.5)	4 (13.3)	0
Any AE leading to study drug permanently discontinued	11 (14.5)	8 (11.0)	6 (20.0)	0
Any AE leading to study drug reduced	1 (1.3)	5 (6.8)	0	0
Any AE leading to study drug held	27 (35.5)	30 (41.1)	11 (36.7)	0
Any AE leading to on-treatment death	14 (18.4)	10 (13.7)	4 (13.3)	0

Source: SCS, Table 18.3.15.1.2. Data cutoff date: 11 May 2018.
Abbreviations: AE = adverse event; AML = acute myeloid leukemia; eGRF = estimated glomerular filtration rate; SCS = Summary of Clinical Safety; QD = once daily; R/R = relapsed or refractory; SAE = serious adverse event.
Renal function as defined by eGFR is categorized as follows: normal (≥90 mL/min/1.73m^2), mild (≥60 and <90 mL/min/1.73 m^2), moderate (≥30 and <60 mL/min/1.73 m^2), and severe (≥15 and <30 mL/min/1.73 m^2). Baseline eGFR is calculated as: eGFR (mL/min/1.73 m^2) = 175 × (Scr/88.4)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female) × (1.212 if African American) (SI units) where Scr is SI units of serum creatinine.

Pregnancy and lactation

There are limited human data available regarding the potential effect of ivosidenib on pregnancy or development of the embryo or foetus; 1 pregnancy has been reported in the safety database for a subject in Study AG120-221-C-001, with unknown outcome.

Animal reproduction studies with ivosidenib have been performed in 2 species to evaluate embryo-foetal developmental toxicity. Ivosidenib administered to pregnant rats at a dose of 500 mg/kg/day during organogenesis (gestation days 6-17) was associated with adverse embryo-foetal effects including lower foetal weights, and skeletal variations. These effects occurred in rats at approximately 2.0 times the clinical exposure at the recommended human daily dose of 500 mg daily. In pregnant rabbits treated during organogenesis (gestation days 7-20), ivosidenib was maternally toxic at doses of 180 mg/kg/day (exposure approximately 3.9 times the clinical exposure at the recommended human daily dose of 500 mg/day) and caused spontaneous abortions as well as decreased foetal weights, skeletal variations, and visceral variations.

Based on animal embryo-foetal toxicity studies, ivosidenib can cause foetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if a woman becomes pregnant while taking this drug, she should be advised of the potential risk to a foetus. Female patients of childbearing potential should be instructed to use effective contraceptive measures (barrier method) during and for at least 1 month after the last dose of ivosidenib treatment. Embryo-foetal toxicity is listed as an important potential risk in the risk management plan (RMP). There are no well controlled studies to assess the presence or absence of ivosidenib in human milk, the effects on the breastfed infant, or the effects on milk production. There are no nonclinical data on excretion in milk, effects on the breastfed infant, or effects on milk production. Woman must be advised to discontinue breastfeeding during treatment with ivosidenib and for at least 1 month after the last dose of ivosidenib treatment.

Safety related to drug-drug interactions and other interactions

The main elimination route of ivosidenib is hepatic metabolism via CYP3A4; therefore, co-administration with inhibitors or inducers of CYP3A4 has the potential to affect ivosidenib exposure. Drug-drug interactions with moderate or strong CYP3A4 inhibitors is considered as an important potential risk.

Ivosidenib induces CYP3A4 and may induce CYP2C9. Therefore, it decreases systemic exposure to substrates of CYP3A4 (eg, cyclosporine, everolimus, fentanyl, itraconazole, ketoconazole, sirolimus, tacrolimus and hormonal contraceptives) and may decrease systemic exposure to substrates of CYP2C9 (eg, phenytoin, warfarin).

Due to the complexity of the interactions, the resulting potential risk of QTc prolongation and the new proposal for a dose reduction, drug-drug interactions has been kept as an important potential risk in the RMP**.**

Discontinuation due to AEs

Adverse events leading to study drug discontinuation

Of the subjects with R/R AML whose starting dose was 500 mg QD, 25 (14.0%) had at least 1 AE leading to study treatment discontinuation. The AEs leading to study treatment discontinuation experienced by 2 subjects (1.1%) included acute kidney injury, Guillain Barre syndrome, pneumonia, pneumonia fungal, and sepsis. Out of the 25 subjects with R/R AML whose starting dose was 500 mg QD group, 4 experienced treatment-related AEs as assessed by the investigator leading to study treatment discontinuation; 2 subjects had events of Guillain Barre syndrome (1 event was Grade 2 and 1 event was Grade 3), 1 subject had an event of febrile neutropenia (Grade 3), and 1 subject had an event of rash (Grade 3).

Adverse Events Requiring Dose Adjustment or Study-drug Interruption

Dose reductions were uncommon during the study. In subjects with R/R AML whose starting dose was 500 mg QD, 6 subjects (3.4%) had AEs leading to dose reductions; dose reductions were from 500 mg QD to 250 mg QD. In subjects with R/R AML whose starting dose was 500 mg QD, the only AE leading to a dose reduction in >1 subject was electrocardiogram QT prolonged (2 subjects, 1.1%; considered serious in 1 subject). Additional AEs leading to dose reductions in 1 subject each (0.6%) were the AEs of anaemia, platelet count decreased, alanine aminotransferase increased, aspartate aminotransferase increased, neutropenia, and thrombocytopenia, as well as the SAEs of diarrhoea and nausea. Of the subjects with R/R AML whose starting dose was 500 mg QD, 68 (38.0%) had study treatment held due to AEs during the study. The most common AEs (≥2% subjects) leading to dose holds were electrocardiogram QT prolonged (13 subjects, 7.3%); sepsis (9 subjects, 5.0%); febrile neutropenia and pneumonia (7 subjects each, 3.9%); IDH differentiation syndrome (6 subjects, 3.4%); and leukocytosis (4 subjects, 2.2%). The median number of days that doses were held was 7.0 (range: 1-57 days).

Expanded access programme (EAP) and post marketing experience

The first approval for ivosidenib was obtained in the US on 20 Jul 2018. Five cases had serious AEs reported in the period from initial approval to 20 Sept 2018 (60 days) that were reported in Module 5.3.6. At the cut-off of 19 July 2019, approximately 705 patients have been exposed to ivosidenib in the post-approval setting. An update of the post-marketing safety data from 21 Sep 2018 to 19 Jul 2019 was provided. During post-marketing exposure, a total of 139 cases were reported.

To 19 Jul 2019, ivosidenib had been shipped to patients in the US and the EU for compassionate use, including but not limited to France. The tolerance of ivosidenib in post-market use could not be optimally assessed.

However, all AEs related-to-treatment effect reported in the frame of compassionate use have been reflected in the SmPC in a dedicated paragraph Section 4.8.

3.3.10. Discussion on clinical safety

The assessment of the safety profile of oral ivosidenib as a single agent in the claimed indication (eg, for the treatment of adult patients with r/r AML with an IDH1 mutation) is mainly based on data from *pivotal study AG120-C-001* (Phase 1, multicentre, open-label, dose escalation and expansion, safety, PK/pharmacodynamics, and clinical activity evaluation of orally administered AG-120 in subjects with advanced haematologic malignancies with an IDH1 mutation). Enrolment in study AG120-C-001 has been completed as of 08 May 2017, the study remains ongoing at the data cut-off date of 11 May 2018. 258 subjects were enrolled and have received at least 1 dose of study treatment. 78 subjects participated in the dose escalation phase.

Additional safety data came from ongoing studies in subjects with haematologic malignancies (AG120-221-C-001, AG-221-AML-005, AG120-C-009), an expanded access programme (AG120-C-010), four completed studies in healthy subjects (AG120-C-003, AG120-C-004, AG120-C-006 and AG120-C-007), one study in healthy subjects with hepatic impairment (AG120-C-012) and two study in subjects with solid tumours (AG120-C-002 and AG120-C-005). As of 11 May 2018, 770 subjects (611 subjects with haematologic malignancies or solid tumours and 159 healthy/hepatically impaired subjects) had received at least one dose of ivosidenib as a single agent or in combination with other antineoplastic treatments.

Clinical safety data included standard reporting of AEs, SAEs, vital signs, ECGs and other laboratory data. Additional safety assessments were done by organ system or syndrome and included evaluation of ivosidenib-related (IDH) differentiation syndrome, leucocytosis, QT interval prolongation, tumour lysis syndrome, sensorimotor neuropathy/polyneuropathy, rash, gastrointestinal disorders, leukoencephalopathy, hepatic dysfunction, renal dysfunction, blood and lymphatic system disorders, and infections.

Across the *Safety Analysis Set* (SAS) of 258 patients from study AG120-C-001, 137 (53.1%) were male (58.3%) and 121 (46.9%) female. Median age was of 68 years with the majority of patients aged 65 years or older and with an ECOG score ≥1 (80.5%). Overall, in light of the rare claimed indication, the size of the *safety database* is considered adequate, and the observed demographic and disease-related features in the SAS are overall representative of the target population. In particular, the majority of subjects in the SAS (179/258) had R/R AML as per the claimed indication.

As a general concern, it should be noted, however, that the uncontrolled design of pivotal study AG120-C-001 limits robust evaluation of the ivosidenib safety profile, in particular when the known heterogeneity of AML in terms of disease symptoms, organ involvement and toxicity from prior regimens is taken into account. Only data from proper randomisation in the context of well-controlled trials are therefore considered adequate to inform B/R evaluations in a regulatory context.

These safety results remain descriptive, in the absence of a comparative arm and considering the heterogeneity of the treated population.

The chosen dose regimen for ivosidenib was 500mg QD on days 1 to 28 in 28-day cycles. The median time of *exposure* to ivosidenib in the SAS was 3.9 months for the overall population as well as for patients with R/R AML treated with 500 mg. Although short, the reported median exposure can be

considered acceptable in light of the high-risk population evaluated in the pivotal study, yet further characterisation of the long-term toxicity profile of ivosidenib is still considered of interest.

Most of subjects with R/R AML who received ivosidenib at the target dose for MA discontinued treatment (169/179; 94.4%) mainly due to disease progression (54.7%), while AEs were the second main reason for discontinuation (15.6%).

All subjects experienced at least one AE and 110 (61.5%) subjects experienced at least one AE that was suspected by the investigator to be related to ivosidenib. Overall, 151 (84.4%) subjects had an AE that was Grade 3 or 4 in severity, 38 (21.2%) subjects had a treatment-related AE that was Grade 3 or 4 in severity. 137 (76.5%) subjects had a SAE, 36 (20.1%) subjects had a treatment related SAE. 25 (18.8%) subjects had an AE leading to ivosidenib discontinuation, four (2.2%) had a treatment related TEAE leading to discontinuation.

In the pivotal study, AEs reported in ≥20% of overall patients were diarrhoea (36.4%), leucocytosis (32.2%), nausea (33.3%), fatigue (32.9%), febrile neutropenia (26.4%), electrocardiogram QT prolonged (23.6%); oedema peripheral (24.0%); dyspnoea (24.4%); pyrexia (22.5%); anaemia (24.0%); and cough (20.9%). Related AEs were consistent with these observations. Of note, almost all reported IDH differentiation syndrome AEs were related (11.6% globally, and incidence of 10.5% related AE).

Among these most common AEs, the following were mainly grade ≥3: febrile neutropenia, anaemia, thrombocytopenia, pneumonia and sepsis. Moreover, 9.3% of patients overall presented with grade ≥3 elctrocardiogram QT prolonged, 8.9% with grade ≥3 neutropenia and 6.2% with grade ≥3 tumour lysis syndrome (TLS). Similarly, related grade 3 AEs included Electrocardiogram QT prolonged (7.4%), IDH differentiation syndrome (4.7%) and anaemia (2.3%).

In summary, the safety profile raised from the pivotal study is non-negligible, particularly considering the incidence of severe QT prolongationand IDH differentiation syndrome.

The proportion of subjects who experienced an AE, treatment-related AE, Grade 3 or 4 AE, or SAE was similar in subjects with R/R AML versus the entire population of subjects with haematologic malignancies enrolled in this study. However, it is notable that the study population is very heterogeneous. Factors such as age at relapse, relapsed or refractory disease, nature of AML (de novo vs secondary), cytogenetics, relapse-free interval from first CR, number of prior therapies, prior HSCT, and the performance status of the patients (list incomplete) all may affect to different degrees the presented safety data.

Besides QTc interval prolongation, no dose-dependent trends across the dose groups were noted for any of the subcategories of TEAEs and incidences and type of TEAEs were similar.

The potential ADRs were adequately presented by the applicant.

The *adverse events of special interest* (AESIs, identified risks based on nonclinical and clinical safety findings) in Study AG120-C-001 were ivosidenib-related (IDH) differentiation syndrome, leucocytosis and QTc interval prolongation.

Differentiation syndrome (DS) is a life-threatening drug related adverse event comparable with the "retinoid acid syndrome" (differentiation syndrome) described for retinoid acid (eg, for Vesanoid) in the treatment of acute promyelocytic leukaemia (APL). It is characterised by rapid weight gain, pleural and pericardial effusions, peripheral oedema, respiratory distress, and fever. The actual incidence of ivosidenib related DS is hard to establish, due to frequent overlapping with other clinical manifestations, such as eg, respiratory failure consequent to infections. In the Phase 1 study, treatment-emergent AEs of ivosidenib related differentiation syndrome were reported in 50 (19.4%) subjects with R/R AML and, and with the exception of 3 cases, all were attributed to the study drug

treatment. Treatment emergent events Grade 3 were reported in 34 (13.2%) patients. In addition, IDH differentiation syndrome was considered a SAE for 19 (10.6%) subjects. As agreed at the clarification meeting with CHMP, the incidence of differentiation syndrome has been identified in Study AG120-C-001 using a slightly modified algorithmic approach than reported by Montesinos et al, 2009. In addition to the cases identified by the algorithm and medical review, Investigator-reported AEs of IDH differentiation syndrome (PT) were added as a single criterion since investigators who reported this AE may not have reported the individual components of the syndrome. This is consistent with the approach used by Norsworthy et al, 2018. The first episode occurred mostly within the first month on treatment and it can be accompanied by leucocytosis and Tumour lysis syndrome (TLS). The available clinical information regarding diagnosis, incidence, severity, treatment and outcomes of differentiation syndrome are included in Section 4.2, 4.4 and 4.8 of the SmPC.

While WBC elevation is commonly caused by infectious processes and is frequent in patients with haematologic malignancies, *leucocytosis* not associated with infectious processes or disease progression has been observed with ivosidenib. The cause of ivosidenib-associated leucocytosis is likely to be similarto that of differentiation syndrome, but it does not involve WBC migration from the intra-vascular space. In the Phase 1study, treatment-emergent AEs of leucocytosis (all grades) were reported in 69 (38.5%) subjects with R/R AML. 10.1% of AEs were considered to be treatment related. Treatment-emergent AEs Grade 3-4 were reported in 16 (8.9%) subjects. 1.7% of TEAEs were considered to be treatment-related. Leucocytosis was considered a SAE for 18 (10.1%) subjects; for 5 (2.8%) subjects, the SAE of leucocytosis was considered related to study treatment. In the absence of a proper control, however, reliable estimates of the actual incidence of ivosidenib-related vs. leukaemia-related leucocytosis are difficult. Leucocytosis does not appear to be life-threatening, and seems to be manageable with the start of hydroxyurea. All available clinical information regarding diagnosis, incidence, severity, treatment (including recommendations on the dose of hydroxyurea) and outcomes of leukocytosis with ivosidenib were adequately included in Section 4.2, 4.4 and 4.8 of the SmPC.

Heart rate-corrected QT interval prolongation occurs in subjects treated with ivosidenib. A concentration-QT analysis suggested a concentration-dependent QTc interval prolongation of approximately 16.1 msec (90% CI: 13.3, 18.9) at the geometric mean observed steady-state Cmax at the 500 mg daily dose. In summary, 18% of patients in the pivotal study AG120-C-001 experienced either QTcF of >500 msec and/or change of QTcF of >60 msec from baseline, partly with extreme QT-prolongation up to 151.7 msec. This is most likely due to ivosidenib exposure.

Although it is agreed that there is individual variability in the drug concentration - ΔQTcF relationship, the concentration-QT analysis showed that ivosidenib causes concentration-dependent increases in the maximum QTc interval at the proposed therapeutic dose. In addition, the dose-exposure relationship is 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 considered that a large proportion of patients will be exposed to potentially critical concentrations with respect to QT-interval prolongation. In the evaluation of the concentration - ΔQTcF relationship, the applicant considers a QT prolongation of 20 ms as critical. With respect to the ICH E14 guideline, data in the range of 5 to less than 20 ms prolongation of the mean QT/QTc interval are considered as inconclusive, because of QT prolongation in this range, some compounds have been associated with proarrhythmic risk. This means that the threshold defined by the model (6659ng/ml) cannot be defined as a threshold below which there will be no risk of QT prolongation. The drug-concentration-QT model appears not to be sufficiently representative for the clinical situation in AML to generate drug concentration thresholds. Close clinical ECG monitoring is considered necessary (for further discussion / information regarding QTc prolongation please be referred to the discussion of clinical pharmacology).

The impact of co-factors, eg, pre-existing QT-prolongation, congenital long QTc syndrome, a history of uncontrolled or significant cardiovascular disease, electrolyte abnormalities as well as concomitant medication cannot be estimated and should definitely be avoided.

It is understood and agreed that products known to prolong the QTc interval, as well as moderate or strong CYP3A4 inhibitors, should be avoided whenever possible. However, with regard to the supportive / prophylactic therapy required for most R/R AML patients, these approaches seem to be hardly feasible in clinical practice. Thus, the applicant proposes, additionally to the recommendations regarding monitoring and management of QT interval prolongations, a dose reduction to 250 mg if moderate and strong CYP3A4 inhibitors cannot be avoided. This approach is supported.

The available clinical information regarding diagnosis, incidence, severity, treatment and outcomes of Heart rate-corrected QT interval prolongation are included in Section 4.2, 4.4 and 4.8 of the SmPC.

The *adverse events of clinical importance* described by the applicant include tumour lysis syndrome, sensorimotor neuropathy/polyneuropathy and Guillain-Barre syndrome, rash, gastrointestinal symptoms, leukoencephalopathy, myalgia, liver dysfunction, and renal dysfunction

Development of *tumour lysis syndrome* (TLS) is a known risk associated with AML. Clinical risk factors include leucocytosis (with or without disease progression) and concurrent use of cytoreductive agents, such as hydroxyurea. Ivosidenib can induce myeloid proliferation resulting in a rapid reduction in tumour cells which may pose a risk for tumour lysis syndrome. 8% of patients with R/R AML whose starting dose was 500 mg QD had at least one AE of tumour lysis syndrome. In several cases, TLS followed the onset of differentiation syndrome and/or leucocytosis and could have been caused by the breakdown of WBC infiltrates in the peripheral tissue. All available clinical information regarding diagnosis, incidence, severity, treatment and outcomes of TLS with ivosidenib were adequately included in Section 4.2, 4.4 and 4.8 of the SmPC.

15 (9.4%) subjects had at least one *AE of polyneuropathy*, five of these events were considered treatment-related by investigators. Of note, the majority of subjects with R/R AML whose starting dose was 500 mg QD who experienced an event within the polyneuropathy search strategy had received prior chemotherapy or had a prior medical history of peripheral neuropathy. Additionally, two patients experienced Guillain-Barré syndrome and both discontinued treatment due to this adverse reaction. Details on all AEs of polyneuropathy (including Guillain-Barré syndrome) observed in the pivotal study, including severity, time to onset and (eventually) time to resolution were discussed adequately and were included in the SmPC. Additionally, Guillain-Barre syndrome has been included as an important identified risk of ivosidenib in the RMP.

42 (26.3%) subjects with R/R AML had at least *one AE of rash*, 10 of these events were considered treatment-related by investigators. Of note, the incidence may be related to concomitant administration of medications known to be associated with rash events (eg, cephalosporins, penicillins, fluoroquinolones, and allopurinol). Details on all AEs of rash, including severity, time to onset and (eventually) time to resolution were discussed and included in Section 4.8.

Treatment-emergent AEs in the SOC *gastrointestinal disorders* were reported for 67.1% of subjects overall, and approximately one third of the events (27.1%) were considered by the investigator to be treatment related. Gastrointestinal disorder SAEs were reported for 5.4% of subjects. The AEs of diarrhoea, nausea and vomiting were among the most commonly reported gastrointestinal symptoms. The majority of gastrointestinal symptom AEs occurred during the first cycle of treatment with ivosidenib and were Grade 1 or 2 in severity. Most AEs were adequately managed through standard of care measures and did not represent a severe or life-threatening condition. Reassuringly, treatment interruptions and dose modifications due to GI AEs were uncommon. As these AEs indicate a relevant burden for the patients, these points have been included in the SmPC in Section 4.8.

The incidence of adverse events *of leukoencephalopathy* (including PML and PRES) was extremely rare. It is acknowledged that in subjects with R/R AML, confounding factors may include tumour and disease burden, co-occurring infections (such as babesiosis), persistent immunosuppression, such as from lymphodepleting purine analogues, and the immunosuppressed clinical state secondary to the underlying disease at the time of event onset. However, the applicant added progressive multifocal leukoencephalopathy (PML) as an important potential risk in the RMP to monitor any additional occurrences of these events. This approach is acceptable. In addition, as in the context of SATit could not entirely be excluded that PML in AG120-C-001 study could be related to treatment, PML is also included as a warning in Section 4.4 of the SmPC (whatever the AE grade).

Liver dysfunction is a potential risk associated with ivosidenib treatment based on nonclinical safety findings. However, as the applicant stated, the incidence of liver dysfunction AEs observed in the R/R AML population was low (3.4%) and no ivosidenib-treated subjects met Hy's Law criteria for drug-induced liver injury. Overall, no new safety signal was identified. However, based on clinical and non-clinical data, close monitoring of liver function will be recommended in the SmPC.

Despite the observed rate of renal AEs being not negligible, causal relationship between exposure to ivosidenib and *renal injury* is hardly assessable in pivotal study AG120-C-001, mainly due to the confounding effect of leukaemia- and treatment-related complications and the limits of the uncontrolled design. As the applicant stated, the incidence of renal dysfunction AEs in the absence of IDH differentiation syndrome (PT), tumour lysis syndrome, or leukocytosis within +/- 7 days was 53.8% in the overall study population and 58.8% in Arm 1+ of Study AG120-C-001. Overall, no new safety signal was identified. However, based on clinical and non-clinical data, close monitoring of renal function will be recommended in the SmPC**.**

Treatment with ivosidenib seems to reduce AEs in the *SOC of blood and lymphatic system and in the SOC infections and infestations* in patients that respond to treatment. These findings are not surprising as haematologic improvements in platelets, haemoglobin and ANC, such as those associated with response to ivosidenib or other AML therapeutics, are generally accompanied by a reduction in adverse events associated with these laboratory parameters; ie, bleeding events, infections and febrile neutropenia. However, the magnitude of these effects cannot be contextualised, as study AG120-C-001 is uncontrolled. In addition, the incidence of grade 3-4 infections in pivotal trial AG120-C-001 (Table 14.3.1.4.3) is not considered significantly different from that reported for subjects with R/R AML exposed to common chemotherapy salvage regimens (eg, FLA-Ida, MEC, HiDAC, HAM), and this is rather unexpected due to the pro-differentiating mechanism of action of ivosidenib. However, in summary, in the context of SAT, it could not be excluded that febrile neutropenia and infectious risk observed in AG120-C-001 study could be related to treatment; thus, they are included in Table 2 of the SmPC (whatever the AE grade).

The available data on *haematologic values* over time can be considered supportive of the pro-differentiating mechanism of action of Ivosidenib. In particular, the observed median increase in blood parameter levels and the concomitant decrease in transfusion need (see efficacy data) are encouraging. On the other hand, the significant level of confounding due to the significant impact of the underlying disease on haematologic values and the absence of proper control do not allow robust conclusions on a possible myelosuppressive effect with ivosidenib. In addition, laboratory values of platelet counts indicate a moderate drop in the first three therapy cycles, indicating potential for increased risk of thrombocytopenia. While these platelet values seem to normalise over the course of therapy, there seems to be an earlier effect on platelets in the first 3 cycles. In summary, the absence of a myelosuppressive effect of ivosidenib cannot be definitively demonstrated, especially with respect to the first treatment cycles, when the positive effects of re-established cell differentiation seem not be evident yet. In summary, this issue cannot be resolved by data from study AG120 C-001 and should be further pursued. Thrombocytopenia and Anaemia are added to Section 4.8 of the SmPC.

As the applicant stated, the majority of the common AEs associated with clinical chemistry laboratory abnormalities were not considered treatment-related, and the incidence of Grade ≥3, treatment-related AEs associated with clinical chemistry laboratory abnormalities was low. Chemistry parameter shifts and associated AEs may occur in the setting of conditions commonly associated with advanced haematologic malignancies. With regard to the presented data this statement can be accepted.

Regarding age, gender, ethnicity and ECOG performance status, subgroup analyses were provided and information was adequately included in the SmPC.

The incidences of treatment-related AEs and treatment-related SAEs were slightly higher in subjects with mild hepatic impairment compared with those with normal hepatic function (Arm 1+ treatment-related AEs: 72.7% vs 58.7%, respectively, and treatment-related SAEs: 24.2% vs 18.2%, respectively). The following preferred terms were reported more frequently (difference in incidence >5.0%) in subjects with mild hepatic impairment vs those with normal hepatic function in Arm 1+: electrocardiogram QT prolonged, diarrhoea, dyspnoea, fatigue, leukocytosis, rash, alanine aminotransferase increased, aspartate aminotransferase increased, and dizziness. In summary, with regard to the data presented so far, the applicant's conclusion, that there was no clinically relevant increase in treatment-related AEs or SAEs in subjects with mild hepatic impairment compared to those with normal hepatic function, is still not shared. There is a clear trend to a higher incidence of AEs in patients with mild hepatic impairment. Of note, the incidence of QTc interval prolongation events (which have a dose dependent trend) was higher in patients with impaired hepatic function. An appropriate warning is implemented in Section 4.4.

The safety data presented regarding patients with renal impairment was limited. However, a higher percentage of subjects with any Grade ≥3 AE, any treatment-related AE, any SAE, and any AE leading to study drug being permanently discontinued was observed in the moderate renal impairment group compared with those subjects having normal renal function or mild impairment. Albeit this should be interpreted with caution due to the smaller sample size in the moderate renal impairment group (N=30), it should be kept in mind that pre-existing renal impairment might become clinically relevant when renal function deteriorates secondary to TLS, leucocytosis or differentiation syndrome. A detailed warning for ivosidenib in patients with moderate and severe renal impairment (in order to reduce the risk for fatal renal failure) is implemented in Section 4.4.

Pregnancy exposure: One case of pregnancy was reported in a 25-year-old subject treated with ivosidenib in Study AG120-221-C-001. Treatment was stopped and pregnancy outcome remains unknown. The subject was treated with ivosidenib + cytarabine + daunorubicin in Study AG120-221-C-001 received ivosidenib from 13 May 2016 to 07 Apr 2018 (695 days on treatment). The subject was on monthly Lupron (leuprolide) until 16 Feb 2017, and since that date, her only method of contraception was condoms.

This subject was in complete remission and was receiving ivosidenib for maintenance therapy. On 07 Apr 2018, the subject took a home pregnancy urine test which was positive, and she self-discontinued treatment with ivosidenib. The subject experienced her last menstrual period on 13 Mar 2018 and had received ivosidenib for approximately 26 days between her last menstrual cycle and confirmation of pregnancy. There were no AEs immediately prior to the pregnancy (confirmed). Non-serious complications during pregnancy included genitourinary tract infection and vaginitis. The subject also experienced a Grade 1 foetal breech presentation that was detected via ultrasound.

Further clarification was expected regarding the effective contraception to be used in male patients and the post treatment contraception duration. "Recommendations related to contraception and pregnancy testing in clinical trials" (Final version 2014-09-15) from CTFG specifies in Section 2.3 that male contraception (condom) is recommended in order to avoid exposure of an existing embryo/foetus for non-genotoxic IMPs with demonstrated or suspected human teratogenicity/fetotoxicity. There are

limited human data available regarding the potential effect of ivosidenib on pregnancy or development of the embryo or foetus. Therefore, ivosidenib cannot be considered to be a suspected human teratogen/fetotoxic.

Moreover, regarding "Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling" (EMEA/CHMP/203927/2005), given that studies in animals have shown reproductive toxicity and there is a limited amount of data from the use of ivosidenib in pregnant women, only contraception in women of childbearing potential treated by ivosidenib is required.

Otherwise, the applicant proposed a period of two months of contraception after stopping treatment. Given that ivosidenib is not genotoxic and half-life is 96 hours, a period of one month seems more appropriate. The applicant was required to update SmPC.

With the limits of indirect comparisons, the *all-cause mortality* rates within 30 days and 60 days of first dose seem to be lower than in the historical controls. The incidence of AEs with an outcome of death (15.6%) observed in study AG120-C-001 was overall in line with that expected for a population of patients with R/R AML. The most frequent causes of on-treatment death were infections as frequently reported in this patient population. However, the information that cardiac disorder adverse reactions (electrocardiogram QT prolonged, ventricular tachycardia, ventricular arrhythmia) could not be ruled out as a possible contributing factor to the death of 3 patients (2%) as well as the information that differentiation syndrome could not be ruled out as a possible contributing factor to the death of at least 2 patients (1.3%) is included in 4.4.

The supportive study AG120-C-002 included subjects with advanced solid tumours that harbour an IDH1 mutation. The ADRs of ivosidenib were mainly consistent with those in the haematologic malignancy study, except that, as could be expected in non-blood tumours, no events of differentiation syndrome, leucocytosis or tumour lysis syndrome were observed in this study.

Due to the small numbers of enrolled subjects, safety data of the supportive studies (AG120-C-009, AG120-221-C-001, AG-221-AML-005, and AG120-C-005) have not been analysed. In addition – due to the singular application of ivosidenib in the studies with healthy subjects (AG120-C-003, AG120-C-004, AG120-C-006 and AG120-C-007, AG120-C-012), no clinically significant adverse events attributable to ivosidenib were observed.

The tolerance of ivosidenib from post-marketing and compassionate use settings could not be optimally assessed. However, all AEs related-to-treatment effect reported in these databases are reflected in the SmPC in a dedicated paragraph Section 4.8**.**

In summary, the applicant studied and discussed the safety profile of ivosidenib monotherapy mainly with regard to the safety data analysed for Study AG120-C-001. Overall, the described toxicities appear to be manageable. However, as Study AG120-C-001 was a single-arm study without an active comparator arm not all issues could be completely elaborated.

3.3.11. Conclusions on clinical safety

Overall, the available data suggest that the safety profile of ivosidenib is not negligible (potential life-threatening AEs like differentiation syndrome and QTc prolongation were identified). Most uncertainties are related to the lack of proper controls, that hampers robust safety evaluations in a heterogeneous condition like AML and/or the use of concomitant medicinal products (eg, antifungal/antibiotics).

Key safety concerns (a*dverse events of special interest)* identified were ivosidenib-related (IDH) differentiation syndrome, leucocytosis and QTc prolongation.

Adverse events of clinical importance described and discussed by the applicant include tumour lysis syndrome, sensorimotor neuropathy/polyneuropathy and Guillain-Barre syndrome, rash, gastrointestinal symptoms, leukoencephalopathy, myalgia, liver and renal dysfunction and blood and Lymphatic disorders.

In summary, the safety profile appears to be manageable.

However, as the risk of the observed AE of *differentiation syndrome* is new and seems to be quite specific to IDH-inhibitors there is still a need to further characterise this risk (eg, identify subgroups at particular risk, better characterise frequency in a larger population, specify time to onset and effectiveness of precautionary and protective measures).

In addition, it should be kept in mind, that the concentration-QT analysis suggested a *concentration-dependent QTc interval prolongation* of approximately 16.1 msec (90% CI: 13.3, 18.9) at the geometric mean observed steady-state C_{max} at the 500 mg daily dose. In summary, 18% of patients in the pivotal study AG120-C-001 experienced either QTcF of >500 msec and/or change of QTcF of >60 msec from baseline, partly with extreme QT-prolongation up to 151.7 msec. This is most likely due to ivosidenib exposure and represents an important risk for the majority of patients even without co-medication. Close clinical ECG monitoring as well as adequate RMMs are considered necessary.

Safety data regarding hepatic and renal impairment as well as drug-drug interactions and long-term safety data is currently incomplete or missing, and thus cannot be assessed entirely.

3.4. Risk management plan

3.4.1. Safety Specification

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP version 0.4:

Table 43. Summary of safety concerns

Summary of safety concerns	
Important identified risks	Differentiation syndrome Electrocardiogram QT prolonged Guillain-Barré syndrome
Important potential risks	Progressive multifocal leukoencephalopathy Embryo-foetal toxicity Drug-drug interactions with moderate or strong CYP3A4 inhibitors and/or concomitant use of drugs with QT prolongation potential
Missing information	Use in patients with severe hepatic impairment Use in patients with severe renal impairment Use in paediatric population Long term safety in patients with haematologic malignancies

3.4.2. Discussion on safety specification

Differentiation syndrome and Electrocardiogram QT prolonged were categorised as important identified risks. PML has been categorised as an important potential risk, based on dedicated discussion in the previous section. Use in paediatric patients and long-term safety have been added as missing information.

3.4.3. Conclusions on the safety specification

Overall, the applicant's proposal for the safety specification is adequate based on the assessment of human clinical safety data and acceptable.

3.4.4. Pharmacovigilance plan

As part of Routine pharmacovigilance activities, the applicant proposes specific adverse reaction follow-up questionnaires for the risks of differentiation syndrome, PML, Guillain-Barré syndrome and embryo-foetal toxicity.

3.4.5. Summary of planned additional PhV activities from RMP

Table 44. On-going and planned additional pharmacovigilance activities

Title and Study Status	Summary of objectives	Safety concerns addressed	Milestones	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				
AG120-C-001 Phase 1, multicentre, open-label, dose-escalation and expansion, safety, pharmacokinetic, pharmacodynamic, and clinical activity study of orally administered ivosidenib in subjects with advanced haematologic malignancies with an IDH1 mutation Ongoing	To evaluate the safety, pharmacokinetics, pharmacodynamic, and clinical activity of ivosidenib in patients with advanced haematologic malignancies with an IDH1 mutation	• Long term safety in patients with haematologic malignancies	Final study report	Q3 2022

Title and Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
AG120-221-C-001 Phase 1, multicentre, open-label, safety study of ivosidenib or enasidenib in combination with induction therapy and consolidation therapy in patients with newly diagnosed acute myeloid leukaemia with an IDH1 and/or IDH2 mutation Ongoing	To evaluate the safety of ivosidenib in patients with an IDH1 mutation and the safety of enasidenib in patients with an IDH2 mutation in combination with AML induction and consolidation therapy	• Long term safety in patients with haematologic malignancies	Final study report	Q4 2023
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 Planned	To evaluate the PK, safety and tolerability, PD, and clinical activity 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 severe hepatic impairment • Use in patients with severe renal impairment	Final substudy report	Q4 2025

Title and Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Physicians survey to assess the effectiveness of the risk minimisation measures Planned	To assess physicians' awareness and understanding of differentiation syndrome and QT interval prolongation as described within the Guide for Healthcare Professionals and of the requirement for their patients to carry and follow the guidance in the Patient Alert Card.	• Differentiation syndrome • Electrocardiogram QT prolonged	Final study report	6 months after the end of data collection

Regarding the survey study to assess the effectiveness of the educational material, **when submitting the study protocol, the applicant should ensure that additional countries are added to the survey** to represent all countries in the EU. The applicant **should also include a question in the survey regarding the receipt of the educational material**.

Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that the proposed pharmacovigilance activities are accepted.

3.4.6. Plans for post-authorisation efficacy studies

There are no planned or ongoing post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

3.4.7. Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Differentiation syndrome	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, 4.8 PIL Section 4 and 2 Restricted medical prescription Additional risk minimisation measures: • Guide for Healthcare Professionals • Patient Alert Card	Routine pharmacovigilance activities beyond AR reporting and signal detection: Differentiation syndrome follow-up Form Additional pharmacovigilance activities: *Physicians survey to assess the effectiveness of the risk minimisation measures*

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Electrocardiogram QT prolonged	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, 4.5, 4.8 PIL Section 4 and 2 Restricted medical prescription Additional risk minimisation measures: *Guide for Healthcare Professionals*	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: none proposed Additional pharmacovigilance activities: *Physicians survey to assess the effectiveness of the risk minimisation measures*
Guillain-Barré syndrome	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, 4.8 PIL Section 4 and 2 Restricted medical prescription Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Guillain-Barré syndrome follow-up Form Additional pharmacovigilance activities: None proposed
Progressive multifocal leukoencephalopathy (PML)	Routine risk minimisation measures: SmPC Section 4.4 PIL Section 2 Restricted medical prescription Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: PML follow-up Form Additional pharmacovigilance activities: None proposed
Embryo-foetal toxicity	Routine risk minimisation measures: SmPC Sections 4.4, 4.5, 4.6 and 5.3 PIL Section 2 Restricted medical prescription Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: Tibsovo exposure during pregnancy follow-up form Additional pharmacovigilance activities: None proposed
Drug-drug interactions with moderate or strong CYP3A4 inhibitors and/or concomitant use of drugs with QT prolongation potential	Routine risk minimisation measures: SmPC Sections 4.2, 4.4, 4.5 and 5.2 PIL Section 2 Restricted medical prescription Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None proposed Additional pharmacovigilance activities: None proposed
Use in patients with severe hepatic impairment	Routine risk minimisation measures: SmPC Sections 4.2, 4.4 and 5.2 PIL Section 2 Restricted medical prescription Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None proposed Additional pharmacovigilance activities: • Organ impairment substudy of AG120-C-001

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in patients with severe renal impairment	Routine risk minimisation measures: SmPC Sections 4.2, 4.4 and 5.2 PIL Section 2 Restricted medical prescription Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None proposed Additional pharmacovigilance activities: • Organ impairment substudy of AG120-C-001
Use in paediatric population	Routine risk minimisation measures: SmPC Sections 4.2 PIL Section 2 Restricted medical prescription Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None proposed Additional pharmacovigilance activities: None proposed
Long term safety in patients with haematologic malignancies	Routine risk minimisation measures: Restricted medical prescription Additional risk minimisation measures: None proposed	Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection: None proposed Additional pharmacovigilance activities: • Study AG120-C-001 • Study AG120-221-C-001

Additional risk minimisation measures

The proposed additional risk minimisation activities in the form of a Guide for Healthcare Professionals and a Patient Alert Card for the risk of differentiation syndrome, and Guide for Healthcare Professionals for the risk of QT interval prolongation are accepted.

Overall conclusions on risk minimisation measures

The PRAC Rapporteur, having considered the data submitted, is of the opinion that the proposed risk minimisation activities are accepted.

3.5. PRAC overall conclusion and recommendations

Pending a positive benefit-risk balance, the RMP Part III-VI is acceptable.

3.6. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

4. Benefit risk assessment

4.1. Therapeutic Context

The claimed therapeutic indication in this MAA for Tibsovo (ivosidenib) is:

- Initially proposed for the treatment of adult patients (≥18 years old) with relapsed or refractory acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation.
- Adapted to: "Tibsovo is indicated as monotherapy for the treatment of relapsed or refractory acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation in adult patients whohave received at least 2 prior regimens, including at least 1 standard intensive chemotherapy regimen, or are not candidates for standard intensive chemotherapy and have received at least 1 prior non-intensive regimen."

The proposed restricted indication is supported by data from the Last line Arm 1+ population (N=109).

4.1.1. Disease or condition

Acute myeloid leukaemia is characterised by uncontrolled proliferation of clonal neoplastic haematopoietic 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). Relapsed or refractory AML carries an adverse prognosis and there is no standard of care therapy. Survival is limited, except for a minority of patients who achieve response after relapse and can proceed to allogeneic SCT. The overall annual incidence of AML is 3.7 per 100,000 (4.0 per 100,000 for males and 3.4 per 100,000 for females) and the 5-year relative survival rate is 19% (Visser, *et al*. 2012).

The frequency of reported IDH1 mutations in AML is between 4.4% and 13.7%. In subjects with IDH1 mutated AML, the R132 mutation is nearly exclusively described with 5 subtypes (R132C, R132H, R132G, R132S and R132L).

Survival for R/R AML differs significantly due to the large heterogeneity of this target population. The prognostic impact of mutated IDH1 in AML remains controversial. Currently it can only be stated that there seems to be no clear or overwhelming prognostic impact for mutated IDH1 in AML.

While in the curative treatment setting of AML, OS and EFS are the most relevant efficacy endpoints, in the non-curative setting OS alone is considered the most relevant efficacy endpoint as the clinical relevance of CR (as one important aspect of the composite endpoint EFS) in patients not being able to receive HSCT is not evident. These considerations apply to both 'newly diagnosed' and 'relapsed/refractory' AML.

4.1.2. Available therapies and unmet medical need

There are limited effective therapies for adult patients with R/R AML. While options include intensive chemotherapy, this is usually reserved for the small number of patients who achieved CR with a relapse free interval of greater than 12 months and who are still fit to receive induction-consolidation therapy. Given the epidemiology of the disease and the outcomes with current treatment, the most common treatment option for patients with R/R AML consists of non-intensive therapies and supportive care. Several commonly used treatment options include intensive salvage chemotherapy comprising an anthracycline/anthracenedione, cytarabine, and/or a purine analog (eg, fludarabine, cladribine, clofarabine). Allogeneic haematopoietic stem cell transplant (HSCT) may be offered either as salvage

therapy or as subsequent therapy following CR attained by salvage therapy, though survival outcomes are poor (Duval et al, 2010).

Non-intensive treatments are offered to patients who cannot tolerate more intensive therapies or who do not have a sufficient expectation of response due to disease-related factors, such as their cytogenetic and molecular status. These options include LDAC and hypomethylating agents. These non-intensive therapies are frequently the default therapy for patients who are over 60 years of age, particularly those >75 years of age, or those with unfavourable risk factors. Complete remission rates with these treatments are approximately 10% to 20% and the median OS is between 6 and 9 months depending on the duration of the first CR and cytogenetic risk factors (Itzykson et al, 2015; Kell, 2016; Ritchie et al, 2013).

Treatment options for patients with IDH1-mutated R/R AML are the same as those for the general R/R AML population, with no approved targeted therapies in the EU and no effective standard of care.

In European LeukemiaNet ELN 2017 (Döhner et al.) recommendations, the following statements are mentioned:

- No specific salvage regimen has emerged as the standard for treating primary R/R AML
- Enrolment in a clinical trial should therefore be the priority for such patients whenever possible
- Patients considered not candidates for IC have the choice to be treated with hypomethylating agents (azacitidine or decitabine) or low-dose cytarabine or best supportive care (including hydroxyurea). LDAC is generally well-tolerated and produces CR rates in the order of 15% to 25%; however, OS (median, 5-6 months) is unsatisfactory. An increase in median OS with decitabine vs mostly LDAC (7.7 vs 5.0 months) was observed.
- Outcome for patients relapsing after allogeneic HCT during first or second CR is particularly poor. The Center for International Blood and Marrow Transplant Research (CIBMTR) recently found 3-year OS was 4%, 12%, 26%, and 38% for relapses within 1 to 6 months, 6 months to 2 years, 2 to 3 years, and ≥3 years after allogeneic HCT, respectively. Use of HMA has modest efficacy in AML relapsing post-HCT, producing CR rates of ~15%; responses may be higher when combining donor lymphocyte infusion and azacitidine.

Thus, patients not fit for intensive salvage chemotherapy are left without effective approved treatment options. Azacitidine and decitabine induce CR rates of 16% to 21% and median survival times were less than 1 year; median post-relapse survival after therapy with LDAC is 5 to 6 months. For patients in second or third relapse, various therapeutic options are associated with CR rates of ~20% and median OS outcomes of ~3 months, stressing the need for enrolment into clinical trials. This suggests the need to consider alternative treatments.

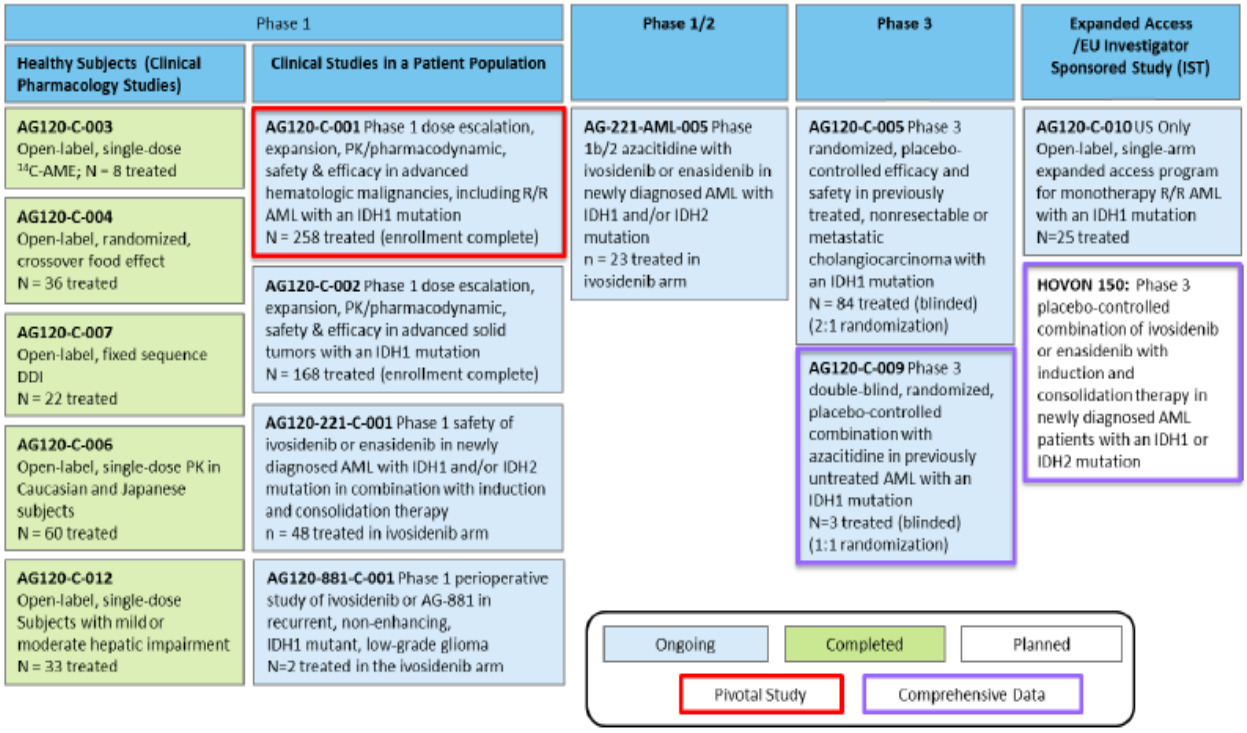
4.1.3. Main clinical studies

The applicant has provided clinical efficacy results mainly taken from one single phase 1 study AG120-C-001 in subjects with advanced haematologic malignancies with an IDH1 Mutation. This study includes a dose escalation portion to determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) and an expansion portion to further evaluate the safety, tolerability, and clinical activity of ivosidenib.

Historical data to try to put the clinical effectiveness of ivosidenib into context using 3 different approaches were also provided:

1. a systematic review of the literature to identify large published studies in r/r AML, regardless of IDH1 mutation, that included conventional treatment options which may be used to compare against the AG120-C-001 data; and
2. data from the pivotal study were retrospectively compared with a matched-patient analysis from AML Study Group (AMLSG) registry data
3. data from the pivotal study were retrospectively compared with a matched-patient analysis using the combination of two databases: AMLSG and European real world data (RWD).

Initially, comprehensive data to convert the requested CMA to a full MA was intended to be provided by safety and efficacy data from the study HOVON 150 / AMLSG-29-18, a phase 3, multicentre, double-blind, randomised, placebo-controlled study of ivosidenib or enasidenib in combination with induction therapy (ara-C and daunorubicin) and consolidation therapy (mitoxantrone and etoposide or ara-C) followed by maintenance therapy in patients with newly diagnosed acute myeloid leukaemia or myelodysplastic syndrome with excess blasts-2, with an IDH1 or IDH2 mutation, respectively, eligible for intensive chemotherapy. Additional data from a Phase 3 placebo-controlled study of ivosidenib in combination with azacitidine in subjects with previously untreated AML who are considered appropriate candidates for non-intensive therapy (Study AG120-C-009) was also intended to convert the requested CMA to a full MA. Both studies are currently ongoing.

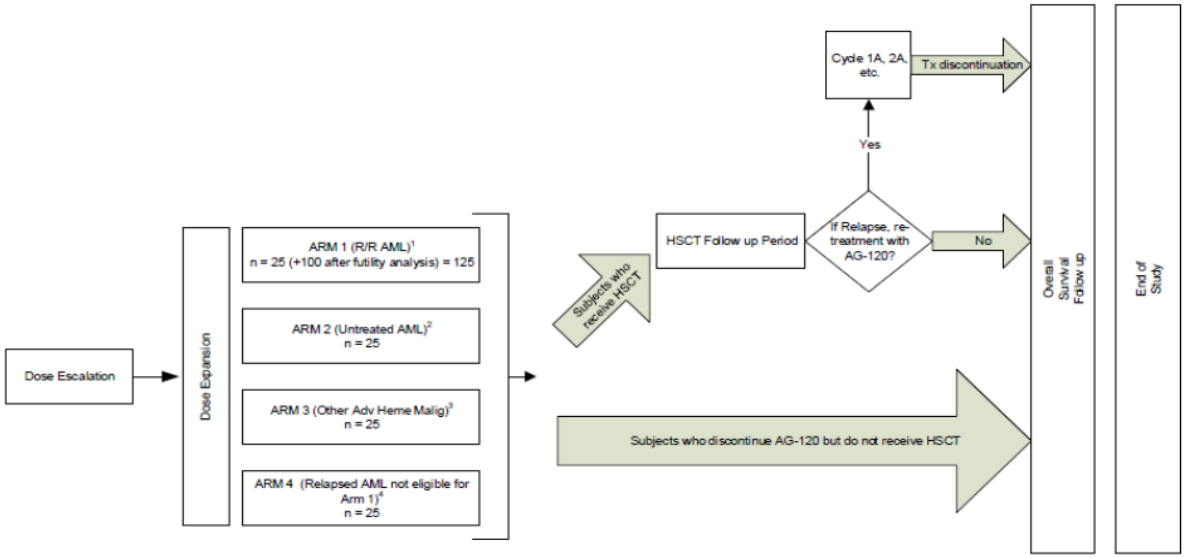


Abbreviations: AME = absorption, metabolism, excretion; AML = acute myeloid leukemia; DDI = drug-drug interaction; IDH = isocitrate dehydrogenase; PD = pharmacodynamic; PK = pharmacokinetic; R/R = relapsed or refractory.
Notes: Study AG-221-AML-005 is sponsored by Celgene Corporation. The enrollment as of 11 May 2018 is provided for ongoing studies.

In the response to the second D180 List of Outstanding Issues, the applicant proposed, as a confirmatory study, an uncontrolled prospective clinical study in a last line IDH1-mutated R/R AML patient population to convert the requested CMA to a full MA.

Main study

Study AG120-C-001 is a phase 1, multicentre, open-label, dose escalation and expansion, safety, PK/pharmacodynamics, and clinical activity study designed to assess the activity of orally administered ivosidenib in subjects with advanced haematologic malignancies with an IDH1 mutation.



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 must have had documented IDH1 R132 gene-mutated disease, as confirmed by centralised testing. Subjects with IDH1-mutated R/R AML in Study AG120-C-001 were included in Arm 1+ and Arm 4+. Overall, inclusion and exclusion criteria are consistent with the population of the claimed indication. Patients with impaired renal and hepatic function were not to be included in the trial. Subjects with clinical symptoms suggesting active central nervous system leukaemia or known CNS leukaemia were excluded from the trial.

The determination of the clinical dose of ivosidenib for the expansion portion was based on pharmacodynamics (2-HG inhibition), PK, safety, and efficacy data from dose escalation. The dose escalation portion utilised a standard "3+3" design. Data from the combined dose escalation and expansionconfirmed that the dose regimen of 500 mg QD ivosidenib could be appropriate for the treatment of advanced haematologic malignancies with an IDH1 mutation.

The primary objectives of the study were mainly to assess the safety and tolerability of ivosidenib, to determine the MTD and/or the RP2D of ivosidenib in subjects with advanced haematologic malignancies, and finally to assess the clinical activity of ivosidenib in subjects with R/R AML with an IDH1 mutation who are enrolled in Arm 1 of the expansion portion.

Secondary objectives of the study were to describe the dose-limiting toxicities of ivosidenib in subjects with advanced haematologic malignancies, to characterise the PK of AG-120 in subjects with advanced haematologic malignancies, and to evaluate the PK/pharmacodynamic relationship of AG-120 and 2-HG.

The primary efficacy endpoint was CR+CRh rate (rate of complete remission (CR) plus CR with partial haematologic recovery (CRh)). Secondary endpoints were notably CR rate, ORR, duration of CR+CRh, duration of complete remission, duration of response, time to response, EFS and OS.

4.2. Favourable effects

In response to feedback from the CHMP, the Company revised the proposed indication to include patients in a last line treatment setting as follows: "Tibsovo is indicated as monotherapy for the treatment of relapsed or refractory acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation in adult patients whohave received at least 2 prior regimens, including at least 1 standard intensive chemotherapy regimen, or are not candidates for standard intensive chemotherapy and have received at least 1 prior non-intensive regimen."

The same restrictions (patients have received at least 2 prior regimens including at least 1 standard intensive chemotherapy regimen or are not candidates for standard intensive chemotherapy and have received at least 1 prior non-intensive regimen) as the Last line Arm1+ population were applied to the external historical control cohort of patients (comprising the AMLSG database and a set of European RWD collected by the applicant) in order to define a subset of patients who met the criteria for a last line treatment setting. 60 patients were selected from the historical cohort.

After propensity score matching, demographic baseline criteria and history of the disease criteria, such as history of HSCT, number of prior regimens for AML, and nature of AML were well-balanced between Last line Arm1+ and the AMLSG + RWD database. Poor cytogenetic risk and primary refractory status were in a higher proportion of patients in Last line Arm1+ which could not favour efficacy and safety results in this arm.

The median OS was 8.1 months (95% CI: 5.7, 9.8) with ivosidenib compared with 2.9 months (95% CI: 1.9, 4.5) in the historical control matched data. The hazard ratio for OS was 0.396 (95% CI: 0.279, 0.562) (P <0.0001). In spite of matching and adjustment, a conclusion that the observed differences in OS are causally explained by treatment is questionable because relevant residual unobserved confounding factors cannot be excluded and are even highly likely. The early separation of the survival curves raises uncertainties to define first response to ivosidenib treatment in a historical database.

For the comparison of CR rate, only historical control data from the RWD dataset (collected by Agios; N=43) are included as the CR rate could not be estimated in the AMLSG dataset since only "response to therapy" was available without a distinction on the type of response (CR, CRi, CRp or MLFS); thus leading to a 2.5 size ratio between Last line Arm 1+ and RWD cohorts. A higher CR rate was observed in Last line Arm1+ (18.3%; 95%CI: 11.6, 26.9) than in the historical arm (7.0; 95%CI: 1.5, 11.9). This result should be taken with caution as CIs overlapped.

Ivosidenib is an orally administered monopharmacotherapy, rendering outpatient pharmacotherapy of the underlying disease in a population with short life expectancy possible.

4.3. Uncertainties and limitations about favourable effects

From the **non-clinical** primary PD studies, it became obvious that ivosidenib markedly reduced 2-HG production in malignant cells carrying a R132 mutation of IDH1. However, in contrast to the expectation, this did not always lead to a less malignant, more mature phenotype of the AML cells. The effect of ivosidenib on leukocyte differentiation markers was heterogeneous when testing AML cells from several different patients. This is in line with literature reports on glioma cells in which mutated IDH1 may lead to a less malignant phenotype so that IDH1 inhibition would be unfavourable. Hence, due to the heterogeneity of the response of AML cells to ivosidenib, more extensive testing (beyond

confirmation of a R132 mutation in IDH1) could be necessary before initiation of ivosidenib treatment, at least when ivosidenib is not only used for last-line therapy.

Since the **PD** marker for ivosidenib's on-target effect, 2-HG, was only measured with a non-enantioselective bioanalytical method instead of only analysing the solely produced D-2-HG, it can currently not be finally concluded whether the results of the total 2-HG analyses provide valuable information.

A "threshold of molecular mIDH1-positivity" in the target population is yet undefined, ie, to diagnose mIDH1-positivity based on D-2-HG levels, or better the D/L-ratio, and mIDH1 %VAF which are necessary and sufficient and, above all, clinically relevant for ivosidenib treatment initiation.

There may be clinical differences seen in response to ivosidenib treatment between the five R132 isoforms with (at least) R132H showing less benefit than the others.

The inhibition of mIDH1 leads to differentiation of immature leukemic blasts into functional and mature cells while even in CR/CRh responders the IDH1 mutation is retained at levels below the detection limit and not eradicated.

Nature and number of co-existing mutations play an important role in this R/R AML patient population with regard to extent and duration of pharmacodynamic and clinical response to ivosidenib, as relapse is often observed despite continued non-detectability of mIDH1. Since about 90% of screened patients in the R/R-AML setting had evidence for additional mutated AML clones, the impact of inhibition of IDH1 in the applied target population seems low. Thus, ivosidenib treatment as a monotherapy is insufficient for durable disease control.

The applicant commits to providing additional non-clinical testing to enhance the proof of concept:

- Agios remains committed to pursue the development of an AML IDH1 mutant PDX model in immunodeficient mice for the mutant IDH1 alleles R132S, R132G, and R132L, despite the low frequency of the alleles within the patient population and our previous lack of success transforming mutant IDH1 alleles of higher frequency into PDX models.
- Further research in the ongoing Phase 3 studies AG120-C-009 (AGILE) and HOVON 150 / AMLSG 29-18 is intended to identify and characterise correlative biomarkers based on analysis of genetic, epigenetic, and global gene expression profiles in bone marrow and peripheral blood. Agios, therefore, proposes to use known mutant IDH1 AML PDX nonclinical models to validate and test hypothesis driven biomarker candidates identified from clinical data.

Study AG120-C-001

The efficacy claims of ivosidenib in IDH1 mutant R/R AML patients are based on a single phase I pivotal study.

The efficacy claims of ivosidenib in IDH1 mutant R/R AML patients are based on an uncontrolled study.

The lack of proper controls in study AG120-C-001 hampers any robust evaluation of clinical benefit in the context of a heterogeneous condition such as AML. In particular, time-to-event endpoints strongly associated with clinical benefit in AML, such as OS, are difficult to interpretat in single-arm studies, mainly because of the numerous factors involved in survival times that can hardly be controlled in the absence of proper randomisation. Further, the uncontrolled design of study AG120-C-001 also prevented the collection of relevant HR-QoL measures that are of significant importance in life-threatening conditions like AML with a strong impact on patient well-being and life-expectancy.

Since initiation, the first-in-human study AG120-C-001 was amended 6 times, finally with the aim to use it as pivotal evidence in an MAA. Amendments of this study include modifications of the study population, posology of the study drug, schedule of assessments, statistical methodology, study endpoints, sample size (list incomplete).

It remains uncertain whether all patients defined as patients having R/R AML had really an adequate AML first-line treatment.

Younger subjects (ie, patients aged <70 years) benefit less from ivosidenib compared to older subjects in terms of ORR and CR rates as well as median OS. Response to ivosidenib in this subgroup might be confounded by the increased number of previous chemotherapy lines received.

The clinical relevance of response rates (CR, CR+CRh,/CRi/CRp and ORR respectively) in the non-curative setting of R/R AML is unclear.

Contribution of treatment to time related endpoints such as OS and EFS cannot be directly ascertained in a single arm study.

Analyses to support the clinical benefit, such as, eg, transfusion independence, rates of infection, bleeding, and neutropenia during response periods are regarded as clinically relevant, but results are of limited value because of the potential for bias and the lack of a control making it impossible to fully establish the size of effect attributable to treatment in the frame of an uncontrolled trial.

Ivosidenib might still represent a valuable option as bridging therapy to HSCT, due to its limited myelotoxicity. Median OS was not estimable (95% CI: 7.4, NE) in subjects with CR and HSCT, 34.4 months (95% CI: 16.4, 34.4) in subjects with CR and no HSCT, and 5.7 months (95% CI: 4.0, 8.0) in subjects without CR. The median OS for non-responders is consistent with the poor prognosis of patients in this treatment setting. Half of the patients who received HSCT have survived beyond 12 months after HSCT despite two prior lines of therapy. The Rapporteur acknowledges that a benefit is observed in these patients. However, these results should be taken with caution considering the small number of patients who received HSCT (n=8).

Subjects with ECOG ≥2, CNS involvement and recent HSCT were excluded from trial participation, and no information on the efficacy of ivosidenib in these clinically relevant populations is available.

Severe chemotherapy-resistance is not unusual in heavily pre-treated patients, and these limited data suggest that mutated IDH1-R132 inhibition alone might not be sufficient to overcome the negative impact of prior treatments.

4.4. Unfavourable effects

The TEAEs of ivosidenib-related (IDH) differentiation syndrome, leucocytosis and QTc prolongation were determined as *adverse events of special interest (AESIs)*.

Treatment-emergent AEs of ivosidenib-related (IDH) differentiation syndrome (ie, rapid weight gain, pleural and pericardial effusions, peripheral oedema, respiratory distress, and fever) were reported in 50 (19.4%) subjects. The majority of events were attributed to the study drug treatment. Treatment emergent AEs Grade 3-4 were reported in 34 (13.2%) patients. In addition, IDH differentiation syndrome was considered a SAE for 19 (10.6%) subjects. The first episode occurred mostly within the first 3 months on treatment and it can be accompanied by leucocytosis and TLS.

Treatment-emergent AEs of leucocytosis (all grades) were reported in 69 (38.5%) subjects. 10.1% of AEs were considered to be treatment-related. Treatment-emergent AEs Grade 3-4 were reported in 16 (8.9%) subjects. 1.7% of TEAEs were considered to be treatment-related. In addition, leucocytosis

was considered a SAE for 18 (10.1%) subjects; for 5 (2.8%) subjects, the SAE of leukocytosis was considered related to study treatment.

19% of patients in the pivotal study AG120-C-001 experienced either QTcF of >500 msec and/or change of QTcF of >60 msec from baseline, partly with extreme QT-prolongation up to 151.7 msec. This is most likely due to ivosidenib exposure. The TEAEs of tumour lysis syndrome, sensorimotor neuropathy/polyneuropathy and Guillain-Barre syndrome, rash, gastrointestinal symptoms, leukoencephalopathy, liver dysfunction, renal dysfunction and blood and lymphatic disorders / infections were determined as *adverse events of clinical importance.*

15 (8.4%) subjects had an AE (all grades) of tumour lysis syndrome. None were considered by the investigator to be treatment related. Treatment-emergent AEs Grade 3-4 were reported in 12 (6.7%) subjects. Tumour lysis syndrome was considered a SAE for 6 (3.4%) subjects.

15 (8.4%) subjects had an AE (all grades) of polyneuropathy, 5 (2.8%) of these events were considered by the investigator to be treatment related.

47 (26.3%) subjects had an AE (all grades) of rash, 11 (6.1%) of these events were considered by the investigator to be treatment related.

Treatment-emergent AEs in the SOC gastrointestinal disorder were reported for 67.1% of subjects overall, and approximately half of the events (27.1%) were considered by the investigator to be treatment related. Gastrointestinal disorder SAEs were reported for 14.5% of subjects.

In the overall study population from AG120-C-001, 3 (1.2%) of the 258 subjects experienced at least one AE under the search strategy for leukoencephalopathy. However, all cases were graded as unrelated. One subject (503-022) experienced a non-serious AE of encephalopathy, one subject (511-037) experienced 2 SAEs of progressive multifocal leukoencephalopathy (PML) and one subject (510 001) experienced an SAE of posterior reversible encephalopathy syndrome (PRES).

19 subjects (10.6%) had at least one renal dysfunction AE. However, most AEs were assessed as unrelated to study treatment per Investigator assessment.

Adverse events leading to on-treatment death were reported in 28 subjects (15.6%) with R/R AML whose starting dose was 500 mg QD.

4.5. Uncertainties and limitations about unfavourable effects

The uncontrolled design of pivotal study AG120-C-001 limits robust evaluation of the ivosidenib safety profile.

The actual incidence of ivosidenib related AESIs and adverse events of clinical interest is hard to establish without proper controls, due to frequent overlapping with other clinical manifestations of AML, or with persisting toxicity from previous treatments.

Although it is agreed that there is individual variability in the drug concentration - ΔQTcF relationship, the concentration-QT analysis showed that ivosidenib causes concentration-dependent increases in the maximum QTc interval with the proposed therapeutic dose. In addition, the dose-exposure relationship is 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 considered that a large proportion of patients will be exposed to potentially critical concentrations with respect to QT-interval prolongation. In the evaluation of concentration - ΔQTcF relationship, the applicant considers a QT prolongation of 20 ms as critical. With respect to the ICH E14 guideline, data in the range of 5 to less than 20 ms prolongation of the mean QT/QTc interval data is considered inconclusive, because of QT prolongation in this range, some compounds have been associated with

proarrhythmic risk. This means that the threshold defined by the model (6659ng/ml) cannot be defined as a threshold below which there will be no risk of QT prolongation. The drug-concentration-QT model appears not be sufficiently representative for the clinical situation in AML to generate drug concentration thresholds. Close clinical ECG monitoring is considered necessary.

Information and data regarding severe hepatic impairment and severe renal impairment are incomplete.

Long-term safety data is limited. Only 22/179 (12.3%) patients in the R/R AML ivosidenib 500 mg population and 39/258 (15.1%) patients in the total population have been exposed to ivosidenib for >12 months. No separate analysis on the safety in these patients has been provided until now.

4.6. Effects Table

Table 45. Effect table for ivosidenib

	Effect				
Full analysis set (subjects who received at least 1 dose of AG-120) **Favourable effects**					
Treatment group	**Arm 1[+]**	**Arm 4[+]**	**All R/R AML at 500 mg QD**	**Last Line Arm1[+]**	**AMLSG + RWD**
Number of subjects	**N=159**	**N=20**	**N=179**	**N=109**	**N=60**
CR+CRh rate (%)	**29.6**	**50.0**	**31.8**	**22**	
95% CI	22.6, 37.3	27.2, 72.8	25.1, 39.2	14.5, 31.0	
Duration of CR+CRh (months)	**8.2**	**6.5**	**8.2**	**12.9**	
95% CI	5.5, 12.0	1.9, NE	5.5, 12.0	5.6, NE	
CR rate (%)	**22.0**	**40.0**	**24.0**	**18.3**	**7.0[*]**
95% CI	15.8, 29.3	19.1, 63.9	18.0, 31.0	11.6, 26.9	1.5, 19.1
Duration of CR (months)	**8.8**	**8.8**	**8.8**	**18.3**	
95% CI	5.7, 18.3	1.9, NE	6.5, 12.9	5.6, NE	
ORR (CR, CRi/CRp, PR, MLFS)	**40.9**	**50.0**	**41.9**	**33.0**	
95% 2-Sided Exact Binomial CI	33.2, 48.9	27.2, 72.8	34.6, 49.5	24.3, 42.7	
OS (months)	**8.8**	**10.6**	**9.0**	**8.1**	**2.9**
95% CI	6.8, 10.2	4.8, 12.6	7.1, 10.2	5.7, 9.8	1.9, 4.5
EFS (months)	**3.8**		**3.8**		
95% 2-Sided Exact Binomial CI	3.6, 5.5		3.7, 5.6		
Clinical safety					
Serious AEs			**20.1%**		
Main related SAEs: IDH differentiation syndrome (8.9%), electrocardiogram QT prolonged (5.6%) and leukocytosis (2.8%); Guillain-Barre syndrome and pyrexia were also reported in 2 patients each (1.1%).					

Death/fatal AEs (incidence)			**15.6%** mainly infectious, including sepsis (4/28) and pneumonia (3/28)		
IDH differentiation syndrome (incidence)			**11.2%** 17/20: treatment-related 7/20: grade 3		
QTc interval prolongation (incidence)			**25.7% (46 cases)** 14/46: related grade ≥3 events		
No AE of Torsade de pointes, sudden cardiac death, or sudden death; 2 grade ≥3 syncope and cardiac arrest, and 1 ventricular tachycardia and ventricular arrhythmia.					
leukocytosis (incidence)			**38.5%** 3/69: related grade ≥3 AEs		
Tumour lysis syndrome (incidence)			**8.4%** 0/15: treatment-related grade ≥3		
Rash (incidence)			**26.3%** 11/47: treatment-related 2/47: grade 3		
Gastrointestinal disorders (incidence) Diarrhoea Nausea Vomiting Abdominal pain			 **33.5%** 19/60: treatment-related 1/60: grade ≥3 **31.8%** 26/57: treatment-related **17.9%** 14/32: treatment-related **12.3%** 1/22: treatment-related		
Myalgia (incidence)			**29.1%** 3/52: treatment-related 1/52: grade ≥3		
Chest pain (incidence)			**12.3%** (all grade 3.4%)		

* Only data from the RWD dataset (collected by Agios; N=43) are included as the CR rate could not be estimated in the AMLSG dataset since only "response to therapy" was available without a distinction on the type of response (CR, CRi, CRp or MLFS)

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

Favourable effects

Study AG120-C-001, which is a single pivotal study supporting the application, is an uncontrolled, open-label phase 1 study. The analysis population discussed in this MAA – being a subpopulation of the study population – was a high-risk R/R AML population in a non-curative setting.

Due to limited life expectancy, overall survival (OS) represents the best endpoint to inform benefit/risk evaluation in the target population. The impact of treatment on OS, however, cannot be disentangled from prognostic factors. Therefore, a treatment effect on OS can be established only in comparison to an adequate control, which has to be an external control group for single arm trials. However, it is in general almost impossible to establish the comparability of a treatment group and an external control group. This applies in particular in this case where the underlying disease is very heterogeneous with many known prognostic factors influencing OS [eg, age at relapse, relapsed or refractory disease, nature of AML (de novo vs secondary), cytogenetics, relapse-free interval from first CR, number of prior therapies, prior HSCT, the performance status of the patients, therapy after failure of ivosidenib (list incomplete)]. Furthermore, the existence of additional yet unknown prognostic factors influencing survival cannot be excluded. Therefore, the inability to control bias is the major and well-recognised limitation of comparisons to external controls, making these approaches unsuitable as the main source of evidence to draw B/R conclusions. Thus, OS results from the proposed pivotal single arm trial SAT AG120-C-001 must remain descriptive and non-inferential.

In contrast, complete remission (CR) only occurs rarely in the absence of active treatment. Therefore, all CR seen in a SAT can be ascribed to the test agent (whereby CR needs to be evaluated in conjunction with DoR). Relevant activity in terms of response and duration of response (DoR) is a necessary condition for clinically relevant benefit, ie, an effect on hard clinical endpoints such as OS can be expected only if a relevant activity is observed. Consequently, CR (+ DoR) must be the basis for the inference of a potential clinical benefit from the presented pivotal SAT. However, in the context of indirect comparisons, the results in terms of CR and DoR must be outstanding in relation to what can be achieved with existing therapeutic options in order to be sufficiently confident that the activity of the new compound is clearly superior to the existing therapeutic options. Furthermore, it is noted, that CR is not an established surrogate endpoint for OS in AML, therefore, even if an outstanding effect on CR is observed, the assumption that this translates into an effect on OS should still be supported by a comparison of OS to external controls (acknowledging the limitations of such a comparison discussed above).

In a last line treatment setting, improvement in the median OS was observed in subjects treated with ivosidenib (8.1 months; CI: 5.7, 9.8) compared to the historical control matched data (2.9 months; CI: 1.9, 4.5) which could demonstrate a clinical benefit for patients with R/R AML treated with ivosidenib. This is supported by a Hazard Ratio of 0.396 (0.279, 0.562) with a p value <.0001. In spite of matching and adjustment, a conclusion that the observed differences in OS are causally explained by treatment is questionable because relevant residual unobserved confounding factors cannot be excluded and are even highly likely. The early separation of the survival curves raises uncertainties to define first response to ivosidenib treatment in a historical database.

Median OS was not estimable (95% CI: 7.4, NE) in subjects with CR and HSCT, 34.4 months (95% CI: 16.4, 34.4) in subjects with CR and no HSCT, and 5.7 months (95% CI: 4.0, 8.0) in subjects without CR. The median OS for non-responders is consistent with the poor prognosis of patients in this treatment setting. Half of the patients who received HSCT have survived beyond 12 months after HSCT despite two prior lines of therapy. The Rapporteurs acknowledge that a benefit could be observed in these patients. However, these results should be taken with caution considering the small number of patients who received HSCT (n=8).

The Rapporteurs acknowledge that ivosidenib could be of benefit in R/R AML patients in a last line treatment setting. However, considering the methodology weakness in this single arm pivotal study, controlled data are needed to substantiate this benefit.

Further uncertainties

The pivotal open-label study AG120-C-001 was amended 6 times impacting multiple fundamental aspects of the study design (eg, study population, posology of the study drug, schedule of assessments, statistical methodology, study endpoints, sample size). In addition, the population of R/R AML patients being analysed in this MAA is a subpopulation of the overall study population from study AG120-C-001. Summarising these aspects, data provided from study AG120-C-001 are exploratory, and analyses performed are descriptive.

The early, not treatment related separation of the curves in the Kaplan Meyer diagrams is indicative of unidentified bias in the included target population.

The prognostic impact of mutated IDH1 in AML remains controversial. Currently it can only be stated that there seems to be no clear or overwhelming prognostic impact for mutated IDH1 in AML according to the current 2017 ELN Risk Stratification by Genetics.

Unfavourable effects

Importance / clinical relevance, strength of the evidence and impact of the uncertainties

The available data suggest that the safety profile of ivosidenib is not negligible, as potential life-threatening AEs like ivosidenib related differentiation syndrome were identified, yet still manageable in the context of a severe condition like r/r AML. However, the uncontrolled design of the pivotal study limits also a robust evaluation of the ivosidenib safety profile, in particular when the known heterogeneity of AML in terms of disease symptoms, organ involvement and toxicity from prior regimens is taken into account.

The AEs of ivosidenib-related (IDH) differentiation syndrome, leucocytosis and QTc prolongation as well as tumour lysis syndrome, polyneuropathy, rash and gastrointestinal disorders were determined as ADRs associated with the mechanism of action of ivosidenib. Overall, these toxicities appear to be manageable.

As the risk of the observed AE of differentiation syndrome is new and seems to be quite specific to IDH-inhibitors there is still a need to further characterise this risk (eg, identify subgroups at particular risk, better characterise frequency in a larger population, specify time to onsetand effectiveness of precautionary and protective measures).

Heart rate-corrected QT interval prolongation occurs in subjects treated with ivosidenib. A concentration-QT analysis suggested a concentration-dependent QTc interval prolongation of approximately 16.1 msec (90% CI: 13.3, 18.9) at the geometric mean observed steady-state C_{max} at the 500 mg daily dose. In summary, 18% of patients in the pivotal study AG120-C-001 experienced either QTcF of >500 msec and/or change of QTcF of >60 msec from baseline, partly with extreme QT-

prolongation up to 151.7 msec. This is most likely due to ivosidenib exposure and represents an important risk for the majority of patients even without co-medication. Close clinical ECG monitoring as well as adequate RMMs are considered necessary.

With regard to the data provided, it is understood and agreed that products known to prolong the QTc interval, as well as moderate or strong CYP3A4 inhibitors, should be avoided whenever possible. However, with regard to the supportive / prophylactic therapy required for most R/R AML patients, these approaches seem to be hardly feasible in clinical practice. Finally, dose reductions if use of moderate or strong inhibitors of CYP3A4 cannot be avoided and close monitoring, and several RMMs were implemented in the SmPC and educational materials for healthcare professionals were planned

Further information is needed regarding tumour lysis syndrome, renal safety, myelosuppression and infections as well as regarding severe hepatic and severe renal impairment and drug-drug interactions.

4.7.2. Balance of benefits and risks

The Rapporteurs acknowledge that ivosidenib could be of benefit to R/R AML patients in a last line treatment setting. However, considering the methodology weakness in this single arm pivotal study, controlled data are needed to further substantiate this benefit. The applicant therefore proposed, as a confirmatory study, a prospective clinical study in a last line IDH1-mutated R/R AML patient population, aligned with the claimed indication. However, another uncontrolled study just replicating the currently provided unconvincing results is not considered sufficient for providing comprehensive data.

4.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

The applicant proposed, as a confirmatory study, an uncontrolled prospective clinical study in a last line IDH1-mutated R/R AML patient population. However, considering that the benefit risk balance is not considered positive at the time being, the product cannot fall within the scope of Regulation (EC) No 507/2006 concerning conditional marketing authorisations.

Otherwise, the applicant commits to providing additional non-clinical testing to enhance the proof of concept:

- development of an AML IDH1 mutant PDX model in immunodeficient mice for the mutant IDH1 alleles R132S, R132G, and R132L
- use known mutant IDH1 AML PDX nonclinical models to validate and test hypothesis driven biomarker candidates identified from clinical data.

4.8. Conclusions

The applicant did not present new data or additional analyses but only additional justification why the previously presented results can be considered sufficient for resolving CHMP's concerns. Overall, this justification does not provide relevant new aspects which could change the previous CHMP conclusion that the application is not approvable.

(i) Further justification of the benefit in the intended target population

The provided justification is not considered sufficient for the same reasons as in the previous assessment rounds

- Even for the now proposed "last line" setting, the observed CR of 18.3% (95%CI (11.6%,26.9%)) needs to be considered as far below what could be unequivocally considered as "outstanding" compared to available therapies. A reliable estimation of the duration of remission is not possible, given that only 20 remissions were observed in the analysis set restricted to "last line" patients.
- The difference in OS observed in the comparison vs historical data cannot be accepted as evidence of efficacy but only as supporting information, due to the inability to control bias for comparisons to external controls. Methods such as inverse probability treatment weighting aiming to adjust for imbalances for comparisons to external controls need to rely on strong and unverifiable assumptions.
- Half of the patients who received HSCT have survived beyond 12 months after HSCT despite two prior lines of therapy. It is acknowledged that a benefit is observed in these patients. However, these results should be taken with caution considering the small number of patients who received HSCT (n=8).
- Data on the effect of treatment on transfusion independence are fraught with methodological problems and cannot establish pivotal evidence of efficacy.

(ii) Restriction of the indication to a subpopulation

It is acknowledged that the applicant's definition of the last line population aimed to reflect the definition from therapeutic guidelines. However, the question still remains whether the applicant's definition was the only possible 'last line' definition based on the guidelines or whether there were alternative choices. If there were alternative choices, the outcomes for these alternative populations would be of interest. It is also acknowledged that, as it is expected for a last line population, the outcomes were worse in the analysis set restricted to "last line" patients than in the overall Arm 1+ population. However, the number of non-last line patients (according to applicant's definition) in this study was small anyway.

(iii) Therapeutic advantage of ivosidenib in the proposed indication

The benefit in the intended target population is not considered to be established (see (i)). Another uncontrolled study just replicating the currently provided unconvincing results is not considered sufficient for providing comprehensive data.

From the non-clinical primary PD studies, it became obvious that ivosidenib markedly reduced 2-HG production in malignant cells carrying a R132 mutation of IDH1. However, in contrast to the expectation, this did not always lead to a less malignant, more mature phenotype of the AML cells. The effect of ivosidenib on leukocyte differentiation markers was heterogeneous when testing AML cells from several different patients. This is in line with literature reports on glioma cells in which mutated IDH1 may lead to a less malignant phenotype so that IDH1 inhibition would be unfavourable. Hence, due to the heterogeneity of the response of AML cells to ivosidenib, more extensive testing (beyond confirmation of a R132 mutation in IDH1) could be necessary before initiation of ivosidenib treatment, at least when ivosidenib is not only used for last-line therapy. Some additional non-clinical testing to enhance the proof of concept are also expected:

- Agios remains committed to pursue the development of an AML IDH1 mutant PDX model in immunodeficient mice for the mutant IDH1 alleles R132S, R132G, and R132L, despite the low frequency of the alleles within the patient population and our previous lack of success transforming mutant IDH1 alleles of higher frequency into PDX models.
- Further research in the ongoing Phase 3 studies AG120-C-009 (AGILE) and HOVON 150 / AMLSG 29-18 is intended to identify and characterise correlative biomarkers based on analysis

of genetic, epigenetic, and global gene expression profiles in bone marrow and peripheral blood. Agios, therefore, proposes to use known mutant IDH1 AML PDX nonclinical models to validate and test hypothesis driven biomarker candidates identified from clinical data.

In conclusion, the major objection was not resolved. Results from a controlled clinical trial are needed to establish the clinical benefit in the proposed target population.