23 February 2023
EMA/173663/2023
Committee for Medicinal Products for Human Use (CHMP)

# Withdrawal assessment report

## Tidhesco

International non-proprietary name: ivosidenib

Procedure No. EMEA/H/C/006174/0000

## Note

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

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# List of abbreviations

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

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

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

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

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

The applicant Les Laboratoires Servier submitted on 24 June 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Tidhesco, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 May 2021.

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

The applicant applied for the following indication:

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

## *1.2. Legal basis, dossier content and multiples*

**The legal basis for this application refers to:**

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

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

This application is submitted as a multiple of Tibsovo simultaneously being under initial assessment in accordance with Article 82.1 of Regulation (EC) No 726/2004.

## *1.3. 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).

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

## *1.4. Information relating to orphan market exclusivity*

### 1.4.1. Similarity

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

### 1.4.2. New active substance status

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

## *1.5. Protocol assistance*

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

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

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

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

## *1.6. Steps taken for the assessment of the product*

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

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

| | |
|---|---|
| The application was received by the EMA on | 24 June 2022 |
| The procedure started on | 19 July 2022 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on | 27 June 2022 |
| The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on | 1 July 2022 |
| The CHMP agreed on the consolidated List of Questions to be sent to the | 21 July 2022 |

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|---|---|
| applicant during the meeting on | |
| The applicant submitted the responses to the CHMP consolidated List of Questions on | 17 October 2022 |
| The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on | 24 November 2022 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 1 December 2022 |
| The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on | 15 December 2022 |
| The applicant submitted the responses to the CHMP List of Outstanding Issues on | 23 January 2023 |
| The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on | 8 February 2023 |
| The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on | N/A |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tidhesco on | 23 February 2023 |
| The CHMP adopted a report on similarity of Tidhesco with Dacogen, Rydapt, Mylotarg, Vyxeos liposomal, Xospata and Daurismo on | 23 February 2023 |
| Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product on | 23 February 2023 |

# 2. Scientific discussion

## *2.1. Problem statement*

### 2.1.1. Disease or condition

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

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

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

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

## 2.1.2. Epidemiology and risk factors, screening tools/prevention

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

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

The risk factors for AML are well characterised and include advancing age, male gender, family history, exposure to benzene, formaldehyde and cigarette smoke, exposure to ionizing radiation, exposure to cytotoxic and/or immunosuppressive agents, alkylating agents, topoisomerase II inhibitors, blood disorders including myelodysplasia, polycythaemia vera, thrombocythaemia and idiopathic myelofibrosis, genetic disorders such as Fanconi anaemia, Bloom syndrome, ataxia-telangiectasia, Diamond-Blackfan anaemia, Shwachman-Diamond syndrome, Li-Fraumeni syndrome, neurofibromatosis type 1, severe congenital neutropenia (Kostmann syndrome), and Down's syndrome and Trisomy 8 (ACS, 2021; Godley and Larson, 2008).

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

## 2.1.3. Biologic features, aetiology and pathogenesis

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

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

transcription of many genes important in cell differentiation (Chowdhury et al, 2011; Koivunen et al, 2012; Xu et al, 2011).

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

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

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

## 2.1.5. Management

The standard treatment strategy for newly diagnosed AML includes the option of standard IC and consolidation chemotherapy, or non-intensive treatment. Consolidation therapy for patients in complete response after IC consists of either chemotherapy, autologous haematopoietic stem cell transplantation (HSCT) or allogeneic HSCT. Patients are encouraged to participate in clinical trials whenever possible. The initial treatment decisions for newly diagnosed AML are based on patient age, history of prior myelodysplastic syndrome, prior genotoxic therapy, genetic classification of AML, Eastern Cooperative Oncology Group performance status (ECOG PS), and presence of serious comorbidities (Heuser et al, 2020).

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

including hypomethylating agents (HMAs), low-dose cytarabine (LDAC) and best supportive care with either 6-mercaptopurine or low-dose melphalan or hydroxycarbamide (Heuser et al, 2020).

Supportive care measures are used to address the underlying comorbidities associated with AML and include hydroxyurea (also called hydroxycarbamide) to control leukocytosis, blood product transfusions, 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.

While the treatment options in the first line setting have recently expanded, the HMAs azacitidine and decitabine are still considered options for patients who are not candidates for intensive chemotherapy. Complete remission rates associated with these therapies are low (approximately 10%-20%), and median OS ranges from 2 to 10 months (Dombret et al, 2015; Kantarjian et al, 2012).

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

In the pivotal Phase 3, double-blind, randomised trial in subjects with newly diagnosed AML ineligible for IC, median OS was 14.7 months (95% CI 11.9, 18.7) in the venetoclax + azacitidine arm compared with 9.6 months (95% CI 7.4, 12.7) in the placebo + azacitidine arm (HR = 0.662; P<0.001) (DiNardo et al, 2020). In the pivotal Phase 2, open-label, randomised trial in subjects with newly diagnosed AML ineligible for IC, median OS was 8.3 months (80% CI 6.6, 9.5) in the glasdegib + LDAC arm compared with 4.3 months (80% CI 2.9, 4.9) with LDAC alone (HR=0.46; P=0.0002) (Cortes et al, 2019). As per the ESMO guidelines, patients should be treated for at least 4 cycles and, in case of clinical benefit, should continue until progression or intolerance. Patients responding to initial treatment should be re-evaluated regarding their ability to undergo allogeneic HSCT using reduced-intensity conditioning, which may cure a portion of these patients (Heuser et al, 2020).

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

## *2.2. 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 IDH1mutated AML. In blood samples from patients with AML with mutated IDH1, ivosidenib decreased 2-HG levels, reduced blast counts and increased percentages of mature myeloid cells.

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

The CHMP adopted a positive opinion for the following indication:

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

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

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

## 2.3. Type of application and aspects on development

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

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

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

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

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

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

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

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

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

**GMP**

- Batch release site:

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

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

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

**GLP**

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

**GCP**

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

## *2.5. Quality aspects*

## 2.5.1. Introduction

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

Other ingredients are:

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

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

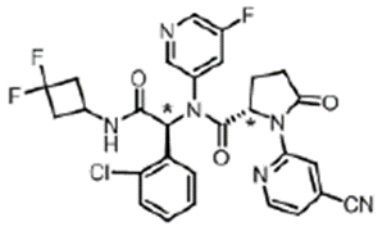
The product is available in white, high density polyethylene (HDPE) bottle with polypropylene (PP) child-resistant closure and polyethylene (PE)-faced induction heat seal liner as described in section 6.5 of the SmPC.

## 2.5.1. Active substance

### *2.5.1.1. General information*

The chemical name of Ivosidenib is (2S)-N-{(1S)-1-(2-chlorophenyl)-2-[(3,3-difluorocyclobutyl)amino]-2-oxoethyl}-1-(4-cyanopyridin-2-yl)-N-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide corresponding to the molecular formula $C_{28}H_{22}ClF_3N_6O_3$. It has a relative molecular mass 583.0 g/mol and the following structure:

**Figure 1.** Active substance structure



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

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

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

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

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

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

### *2.5.1.1. Manufacture, characterisation and process controls*

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

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

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

The selection and control of starting materials is discussed.

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

The manufacturing process development has been well documented. While a traditional drug development approach was used to define the commercial manufacturing process for ivosidenib, some elements of an enhanced approach under Quality by Design were employed to define the process

criticality and process parameters. Over the course of development, the synthetic route, starting materials, and intermediates have remained the same. However, changes to reagents, catalysts, solvents, specifications (for starting materials, intermediates and active substance), and process parameters have been made. In general changes introduced have been presented in sufficient detail and have been well justified.

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

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

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

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

#### *2.5.1.2. Specification*

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

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

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

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

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

#### *2.5.1.3. Stability*

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

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

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

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

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

### 2.5.2. Finished medicinal product

#### *2.5.2.1. Description of the product and pharmaceutical development*

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

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

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

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

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

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

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

The overall manufacturing process for finished product has remained the same since the beginning of ivosidenib clinical development. The primary packaging is HDPE bottles closed with polypropylene child resistant closures with a polyethylene film bonded to aluminium foil. A silica gel desiccant (in a

canister) is included in the bottle. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

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

### *2.5.2.2. Manufacture of the product and process controls*

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

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

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

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

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

### *2.5.2.3. Product specification*

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

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

A risk-based assessment of potential sources of elemental impurities based on ICH Guideline for Elemental Impurities Q3D has been performed. This risk assessment involved an evaluation of the individual components of the finished product, manufacturing equipment, packaging materials, and an evaluation of the materials used during manufacture of the finished product. Based on the risk assessment, no testing of elemental impurities of the finished product is warranted, and elemental impurities are suitably controlled in the finished substance specification.

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

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

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

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

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

### *2.5.2.4. Stability of the product*

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

It was proposed to calculate the shelf life of the finished product using as the starting time the moment when the intermediate is mixed with the excipients. Data to support a separate holding time of for the intermediate were presented. The main stability study (longest) was performed on three pilot scale batches), and data up to 60 months from the storage under long term conditions (30±2°C/65±5%RH) and 6 months under accelerated conditions (40±2°C/75±5%RH) was provided. The analytical procedures used are stability indicating.

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

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

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

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

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

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

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

#### *2.5.2.5. Adventitious agents*

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

## 2.5.3. Discussion on chemical, pharmaceutical and biological aspects

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

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

## 2.5.4. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical

performance of the product have been investigated and are controlled in a satisfactory way.

## 2.5.5. Recommendation for future quality development

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

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

# *2.6. Non-clinical aspects*

## 2.6.1. Introduction

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

## 2.6.2. Pharmacology

### *2.6.2.1. Primary pharmacodynamic studies*

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

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

Cell differentiation induced by ivosidenib *in vitro* was studied using the permanent human erythroleukaemia cell line TF-1 transfected with mutant IDH1 or control. Expression of haemoglobin (HBG) and Krueppel-like factor 1 (KLF-1) served as differentiation markers. Ivosidenib (200 nM and 1 µM) dose-dependently increased expression of the differentiation markers HBG and KLF1. TF-1 cells transfected with mutant (R132H) IDH1 produced 2-HG, and this production was strongly inhibited with ascending concentrations of ivosidenib. Proliferation was reduced with 1 µM ivosidenib but not with 200 nM. 2-HG inhibition was studied in several additional cell lines in addition to TF-1 cells. Part of these cell lines express mutated IDH1 spontaneously, and the other were transfected with the respective expression vector. For comparison, cell lines expressing IDH2 were also included. The IC50 range of ivosidenib for 2-HG inhibition in cells expressing endogenous or overexpressed R132C, R132H

or R132S was 2 to 20 nM and no inhibition of 2-HG production in cells expressing IDH2 mutations was confirmed.

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

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

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

#### *2.6.2.2. Secondary pharmacodynamic studies*

Secondary pharmacodynamics were conducted to evaluate the potential inhibition on several receptors, enzymes or ion channels. Ivosidenib showed no cross reactivity against a panel of 80

receptors, ion channels, transporters and enzymes at a concentration of 10 µM (equivalent to 5 830 ng/mL). The concentration tested (10 µM) is close to the Cmax value expected in the clinical exposure.

#### *2.6.2.3. Safety pharmacology programme*

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

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

#### *2.6.2.4. Pharmacodynamic drug interactions*

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

### 2.6.3. Pharmacokinetics

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

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

Plasma protein binding of ivosidenib was high, ivosidenib showed low RBC/plasma partitioning. Ivosidenib was mainly distributed to liver and adipose tissue; this is in line with the lipophilic property of the ivosidenib molecule. No retention, accumulation, or affinity observed for any tissue and there was no affinity for tissues containing melanin or for any other tissue. Ivosidenib distribution in brain were low (4%). No dedicated studies for placental transfer and milk excretion studies in animals were performed for ivosidenib. However, placental transfer of ivosidenib was shown in the pivotal studies on embryo-fetal development in rats and rabbits (as reflected in section 5.3 of the SmPC).

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

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

## 2.6.4. Toxicology

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

### *2.6.4.1. Single dose toxicity*

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

### *2.6.4.2. Repeat dose toxicity*

In repeated dose toxicity studies in rats, the main findings were liver hypertrophy, accompanied by increase of liver enzymes in serum, and increased and extramedullar haematopoiesis combined with decreased red cell count and related parameters as well as increased reticulocyte count. The results were fairly consistent across the studies. Soft or otherwise abnormal faeces were only observed at very high doses (2000 mg/kg). Two pivotal studies were performed in rats (28 day and 3-month duration). Rats (15 animals/sex/group) were dosed for 28 days at 0, 100, 500 and 2000 mg/kg/day (0, 50, 250 and 1000 mg/kg/dose BID) and 14 days recovery was added. There was early mortality in the high-

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

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

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

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

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

#### *2.6.4.3. Genotoxicity*

Ivosidenib did not show any evidence for a relevant genotoxic potential.

#### *2.6.4.4. Carcinogenicity*

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

#### *2.6.4.5. Reproductive and developmental toxicity*

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

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

#### *2.6.4.6. Toxicokinetic data*

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

#### *2.6.4.7. Local Tolerance*

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

#### *2.6.4.8. Other toxicity studies*

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

## 2.6.5. Ecotoxicity/environmental risk assessment

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

**Table 1.** Summary of main study results

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

## 2.6.6. Discussion on non-clinical aspects

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

tested. Uncertainties of the ivosidenib mechanism of action raised during the previous procedure are superseded as clinical efficacy is satisfactorily demonstrated (see discussion on clinical efficacy).

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

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

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

In animal studies at clinically relevant exposures, ivosidenib induced haematologic abnormalities (bone marrow hypocellularity, lymphoid depletion, decreased red cell mass together with extramedullary haematopoiesis in the spleen), gastrointestinal toxicity, thyroid findings (follicular cell hypertrophy/hyperplasia in rats), liver toxicity (elevated transaminases, increased weights, hepatocellular hypertrophy and necrosis in rats and hepatocellular hypertrophy associated with increased liver weights in monkeys) and kidney findings (tubular vacuolation and necrosis in rats). Toxic effects observed on haematologic system, GI system and kidney were reversible whereas the toxic effects observed on liver, spleen and thyroid were still observed at the end of the recovery period.

With regard to gastro intestinal effects, it is difficult to distinguish between functional and cytotoxic effects because cytotoxicity not leading to overt cell death would indeed lead to disturbance of the normal cellular function. The possibility that the GI effects could be related to IDH1 wt inhibition in the gut mucosa could not be excluded. Moreover, plasma concentrations achieved in toxicology studies could inhibit wt IDH1 so that some toxicological findings could be due to wt IDH1 inhibition. With regard to IDH1 inhibition leading to undesired effects in patients, IDH1 wild-type inhibition in the clinical setting cannot be ruled out at the recommended dose level. Indeed, the difference in plasma protein binding between humans and animals was low and it is not known whether plasma protein binding plays a major role at all when the affinity of the target structure of a drug substance (IDH1 in this case) has a markedly higher affinity to the drug than albumin. Therefore, the argument that that plasma protein binding of ivosidenib is higher in humans than in animals so that even higher plasma levels of total ivosidenib would be required to achieve wt IDH1is not considered agreed. Potential inhibition of wt IDH inhibition and potential consequences are discussed in clinical part.
Hepatic dysfunction, renal dysfunction and gastrointestinal symptoms, in the repeat-dose toxicity studies in the rat and monkey were observed in humans.
Finally, QT prolongation observed in vitro (hERG inhibition) and in vivo in animals and in humans at clinically relevant plasma levels. ECG QT prolonged is classified as an important identified risks in the RMP.

NOAEL levels could not be determined since toxicological findings were observed already at the lowest dose and some of them with were not recovered. Exposure margins relative to human therapeutic exposure were rather low or absent. The reason for this observation could be induction of CYP enzymes by ivosidenib which are responsible for ivosidenib metabolism. It could not be clearly established in the PK studies whether ivosidenib indeed induces its own metabolism, but the TK data are a clear hint for it. For calculation of the exposure margins a human exposure value taken from population PK analysis was used which represents the situation after repeated administration (Day 1 of Cycle 2). Thus, the (lower) exposure margin calculated from the animal exposure at study end appears more relevant.

The mechanism of liver cell hyperplasia is not clearly identified. It is not possible to conclude that hepatocellular damage is only due to enzyme induction. Haematological changes results mainly to gastrointestinal (GI) bleeding, resulting in anaemia and increased blood regeneration in the bone marrow. GI bleeding and perhaps haemolysis obviously contributed to the observed haematological changes. The mechanisms underlying GI bleeding or haemolysis has not been demonstrated. The effects were observed in monkeys mostly at high doses which led to a limited margin of exposure (about 2-fold human exposure). Haematological findings were observed in patients and are mentioned in the SmPC.

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

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

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

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

## 2.6.7. Conclusion on the non-clinical aspects

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

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

## *2.7. Clinical aspects*

### 2.7.1. Introduction

***GCP aspects***

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

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

- **Tabular overview of clinical studies**

**Table 2**. Clinical studies contributing to clinical pharmacology with ivosidenib in healthy subjects, special populations and patients

| Study Number | Study Design | N | Report date/ analysis cute-off date |
|---|---|---|---|
| **Healthy Subjects** | | | |
| AG120-C-004<br>Bioavailability-availability, food effect<br>Complete | A Phase 1, open-label, 2 part study:<br>Part 1: randomized 2 period crossover (fed & fasted) to determine food effect on PK of a single 500 mg dose of ivosidenib<br>Part 2: single period safety & PK of a single 1,000 mg dose of ivosidenib | 36 | Report date: 17 June 2016 |
| AG120-C-003<br>PK, absorption, metabolism, excretion (AME)<br>Complete | A Phase 1, open-label, non-randomized, single-dose (500 mg [$^{14}$C]-ivosidenib), mass balance AME study in healthy male subjects | 8 | Report date:<br>23 March 2016 |

| Study Number | Study Design | N | Report date/ analysis cute-off date |
|---|---|---|---|
| AG120-C-006<br>PK, Japanese vs Caucasian subjects<br>Complete | A Phase 1, open-label, single-dose, PK study in healthy male Japanese & Caucasian subjects after single oral ivosidenib doses (250, 500 or 1,000 mg) | 60 | Report date:<br>06 September 2017 |
| AG120-C-007<br>Drug-drug Interaction, itraconazole<br>Complete | A Phase 1, open-label, 2 period, fixed sequence, drug-drug interaction study to evaluate the effect of multiple doses of itraconazole on the PK of a single 250 mg dose of ivosidenib in healthy subjects | 21 | Report Date:<br>04 April 2017 |
| **Special Populations** | | | |
| AG120-C-012<br>PK, hepatic impairment<br>Complete | A Phase 1, open-label, single-dose (500 mg ivosidenib) study to compare the PK in subjects with mild or moderate hepatic impairment to that in matched subjects with normal hepatic function | 32 | Report Date:<br>23 August 2018 |
| **Patients with Cholangiocarcinoma** | | | |
| AG120-C-005<br>Pivotal for cholangiocarcinoma<br>Complete | (see Table 3 for main Phase 3 study design)<br>Pharmacology objectives:<br>To characterize the PK of ivosidenib in subjects with advanced cholangiocarcinoma.<br>To evaluate the PK/pharmacodynamic relationship of ivosidenib and 2-HG. | 156<br><br>Population PK analysis:<br>N=166 | Cut-off date:<br>31 January 2019<br><br>Population PK and E-R analyses cut-off:<br>31 May 2020 |
| **Patients with Cholangiocarcinoma and Other solid Tumors** | | | |
| AG120-C-002[2]<br>Supportive for cholangiocarcinoma<br>Ongoing | (see Table 3 for main Phase 1 study design)<br>Pharmacology objectives:<br>To characterize the PK of ivosidenib in subjects with advanced solid tumors.<br>To evaluate the PK/pharmacodynamic relationship of ivosidenib and 2-HG.<br>To monitor plasma cholesterol and 4β-OH-cholesterol as a potential CYP3A4 induction marker (dose escalation). | 168[1]<br><br>Population PK analysis:<br>N=73[3] | Cut-off date:<br>16 January 2019<br>(relevant for PK and pharmacodynamic data)<br><br>Population PK and E-R analyses cut-off:<br>31 May 2020 |
| **Patients with Hematologic Malignancies** | | | |
| AG120-C-009<br>Pivotal for newly diagnosed AML<br>Ongoing | (see Table 5 for main Phase 3 study design)<br>Pharmacology objectives:<br>To characterize the PK of ivosidenib in combination with azacitidine in subjects with newly diagnosed AML.<br>To evaluate the PK/pharmacodynamic relationship of ivosidenib and 2-HG. | 71[1]<br><br>Population PK analysis:<br>N=64 | Cut-off date:<br>18 March 2021 |

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

## 2.7.2. Clinical pharmacology

### *2.7.2.1. Pharmacokinetics*

***Methods***

Pharmacokinetic analyses

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

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

Statistical analysis

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

***Absorption***

Biopharmaceutical Classification System (BCS) Classification

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

Healthy volunteers

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

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

Patients

*Advanced Haematologic malignancies*

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

*AML*

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

Absolute bioavailability

The absolute bioavailability of ivosidenib has not been investigated.

Relative bioavailability/ Bioequivalence

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

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

The commercial tablet formulation is the same as the 250 mg clinical tablet formulation used in the Phase 3 studies, differing only in the debossing, wherein mentions as "IVO" on one side and "250" on the other, serves as a product identifier and does not impact the performance, exposure, or stability of the drug product.

Influence of food

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

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

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

Influence of gastric modifier

Ivosidenib does not contain ionisable groups under physiological condition and its aqueous solubility is

pH independent. Therefore, plasma exposure of ivosidenib should be expected to be unchanged when co-administered with pH modulators such as antiacids, PPI or H2 receptor antagonists.

***Distribution***

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

***Elimination***

Healthy volunteers

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

Patients

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

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

*Newly diagnosed AML*

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

- Mass balance

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

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

The arithmetic mean renal clearance was 0.537 L/h.

- Metabolism

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

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

- Interconversion

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

- Pharmacokinetic of metabolites

No major metabolites were detected in plasma.

- Consequences of possible genetic polymorphism

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

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

***Dose proportionality and time dependencies***

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

Based on the results from study **AG120-C-001** (patients with haematological malignancies) and studies **AG221-AML-005 AG120-C-009** (newly diagnosed AML) after the recommended 500 mg QD regimen in patients, steady state is claimed to be reached by Day 15 and low to moderate accumulation (Racc ≤ 2 for both AUCtau and Cmax) was observed in C2D1.

**Intra-and inter-individual variability**

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

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

***Pharmacokinetics in target population***

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

Pivotal Phase 3 study

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

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

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

PK parameter estimates of patients receiving ivosidenib 500 mg QD from Study **AG120-C-009** are presented in Table 7 and compared to other subjects with AML observed in studies **AG221-AML-005** and **AG120-C-001**.

**Table 3.** Summary of ivosidenib plasma PK parameters after SD or MD administration dose of ivosidenib 500 mg for studies AG120-C-001, AG221-AML-005 and AG120-C-009.

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

Population PK modelling and simulation

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

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

Report AG120-C-001-PPK

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

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

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

Relative bioavailability (Frel) of ivosidenib was found to increase in a less than dose-proportional manner. The dose-nonlinearity exponent on Frel is -0.49, thus a doubling of dose translates approximately only to a 40% increase in exposure. Moderate to high IIV was observed with %CVs of

35% (CLss/F), 47% (Vc/F) to 108% (Ka) respectively, with the highest variability estimated on the absorption parameter. The magnitude of the residual log-additive errors was moderate (CV= 26%).

Final model PK parameter estimates are presented in Table 4, GOF on Figure 2 and sensitivity effects of covariates on steady-state ivosidenib AUC in Figure 33.

**Table 4.** Final population PK parameter estimates

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

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

**Figure 2.** GOF plots for the final population PK model

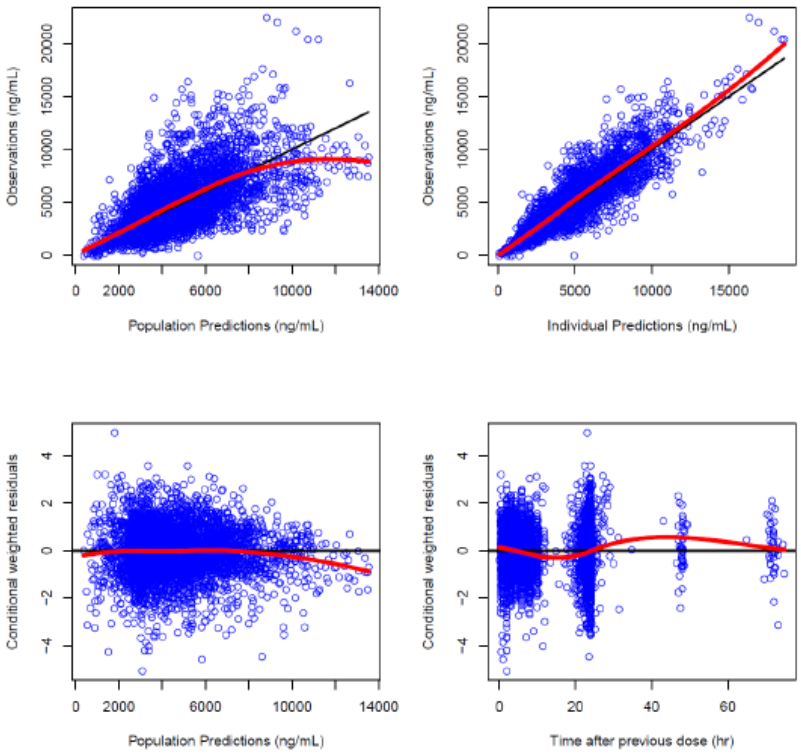
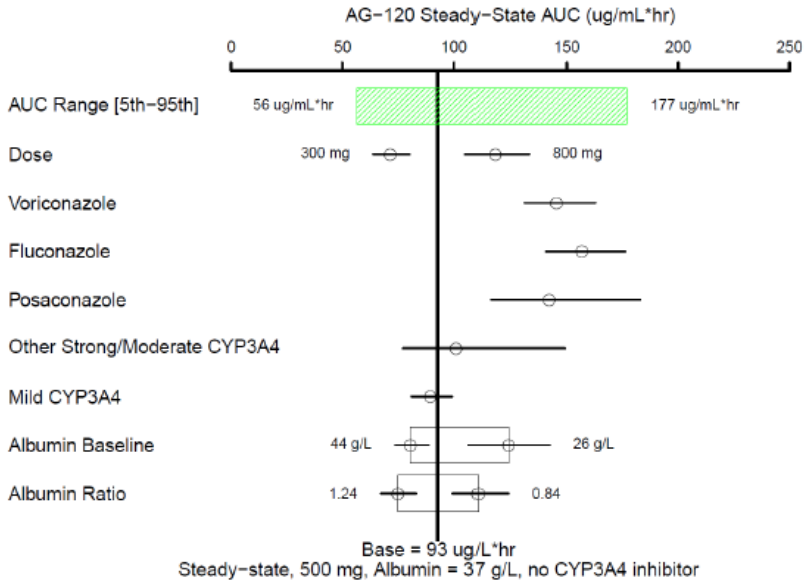



**Figure 3.** Sensitivity of steady-state AUC to covariates and dose




Report AG120-C-001-untreated AML-PPK

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

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

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

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

Report AG120-C-009-PPK

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

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

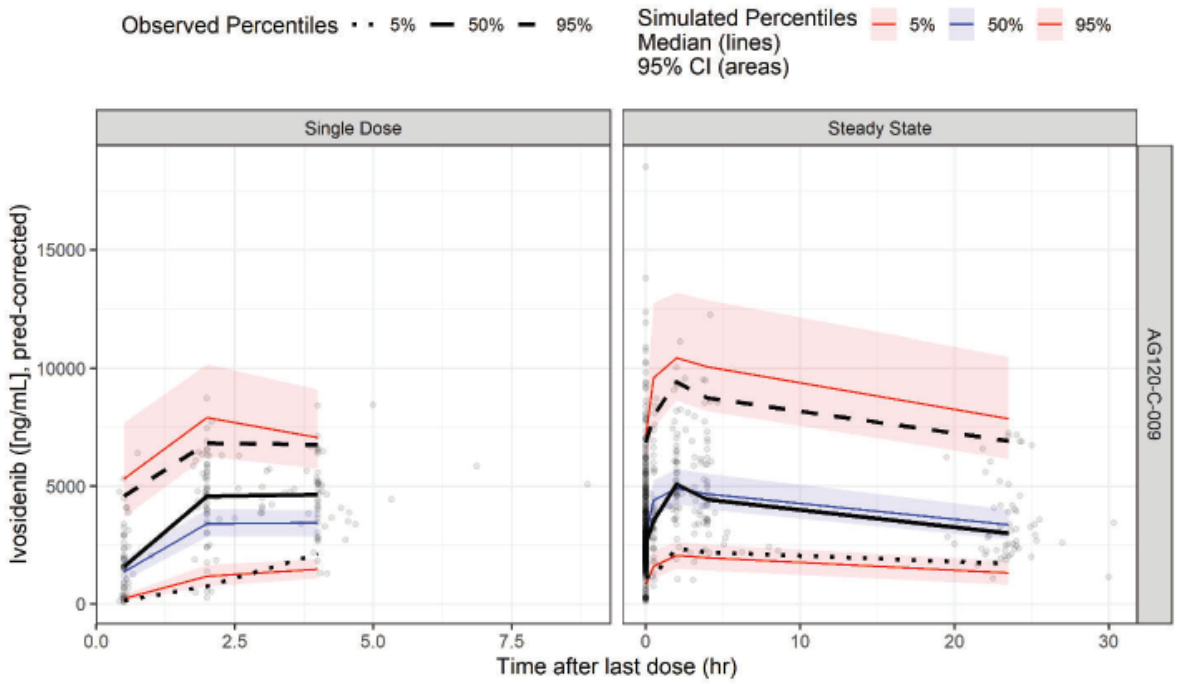
Post-hoc parameter estimates are presented in Table 5.

**Table 5**. Summary statistics of post hoc parameter estimates from studies AG120-C-009 and AG120-C-001

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

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

**Figure 4**. pcVPC of ivosidenib concentrations vs time since last dose




The derived exposures metrics (Table 6) indicated that the systemic ivosidenib exposures at steady state using the recommended oral 500 mg QD regimen were comparable between the two studies AG120-C-009 and AG120-C-001. In fact, geometric means of $AUC_{tau}$, $Cmax_{ss}$, or $Cmin_{ss}$ were calculated to be 117000 ng.h/mL, 5960 ng/mL, 4040 ng/mL, respectively for Study AG120-C-009 (n=64 patients untreated AML) versus 120000 ng.h/mL, 5990 ng/mL and 4250 ng/mL, respectively for AG120-C-001 (n= 254); with GMRs ratio not significantly different from 1.

**Table 6.** Summary exposure metrics calculated with a dose of 500 mg for subjects from studies AG120-C-001 and AG120-C-009

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

***Special populations***

- Renal impairment

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

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

From Study **AG120-C-001**, following multiple dose of ivosidenib 500 mg, a comparison between normal renal function vs mild or moderate renal impairment at baseline (eGFR) was conducted and showed no significant difference between both populations (Table 7).

**Table 7**: Geometric LS means ratios and 95% CIs of AG120 CLss/F following administration of AG-120 at steady-state (C2D1), effect of baseline eGFR

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

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

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

- Hepatic impairment

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

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

Statistical summary of the effect of hepatic impairment on ivosidenib PK and free concentration presented in Table 8 and Table 9, respectively.

**Table 8**. Statistical summary of the effect of hepatic impairment on ivosidenib PK

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

**Table 9**: ANOVA for unbound plasma ivosidenib PK parameters by Child-Pugh classification

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

An evaluation of hepatic impairment status using NCI-ODWG criteria was performed for patients with advanced haematologic malignancies (AG120-C-001 and AG120-C-009). The observed steady-state PK parameters at Cycle 2 Day 1 (C2D1) for ivosidenib following 500 mg QD regimen by study is provided in Table 10.

**Table 10.** Summary of plasma pharmacokinetic parameters at steady-state (C2D1) of ivosidenib after oral administration of ivosidenib 500 mg QD stratified by baseline hepatic impairment NCI classification - by study.

| Study | PK parameter | Normal | Mild | Moderate |
|---|---|---|---|---|
| AG120-C-001 (R/R AML) | AUC0-24 (ng*h/mL) | 119000 (48.6); 146 | 94000 (62.8); 27 | 93200 (44.1); 2 |
| | AUC0-t (ng*h/mL) | 45300 (47); 148 | 39200 (60.4); 28 | 40000 (60.7); 2 |
| | Cmax (ng/mL) | 6590 (42.7); 148 | 5840 (54.1); 28 | 5700 (43.8); 2 |
| | Ctrough (ng/mL) | 4200 (71); 149 | 2750 (149); 29 | 2430 (3.2); 2 |
| AG120-C-009 (ND AML) | AUC0-24 (ng*h/mL) | 102000 (42.7); 25 | 111000 (40.3); 7 | |
| | AUC0-t (ng*h/mL) | 104000 (43.3); 25 | 113000 (40.7); 7 | |
| | Cmax (ng/mL) | 5920 (35.4); 25 | 6260 (30.5); 7 | |
| | Ctrough (ng/mL) | 3510 (49.1); 27 | 3960 (39.4); 7 | |

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

- Race

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

Concentration-time profiles for ivosidenib are presented in Figure 5 and associated PK parameters in Table 11, statistical analysis in Table6.

**Table 11.** Summary of PK parameters in Japanese vs Caucasians subjects

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

**Figure 2.** Mean (SD) plasma ivosidenib concentration-time profiles in Japanese and Caucasian subjects

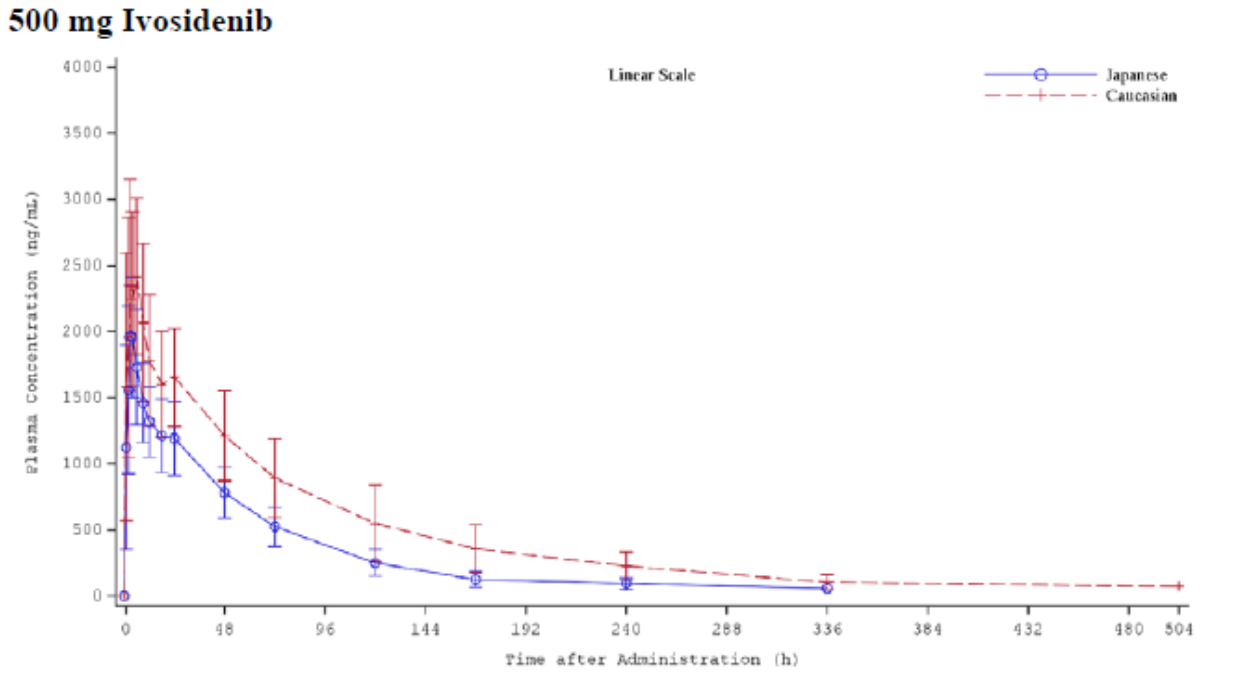


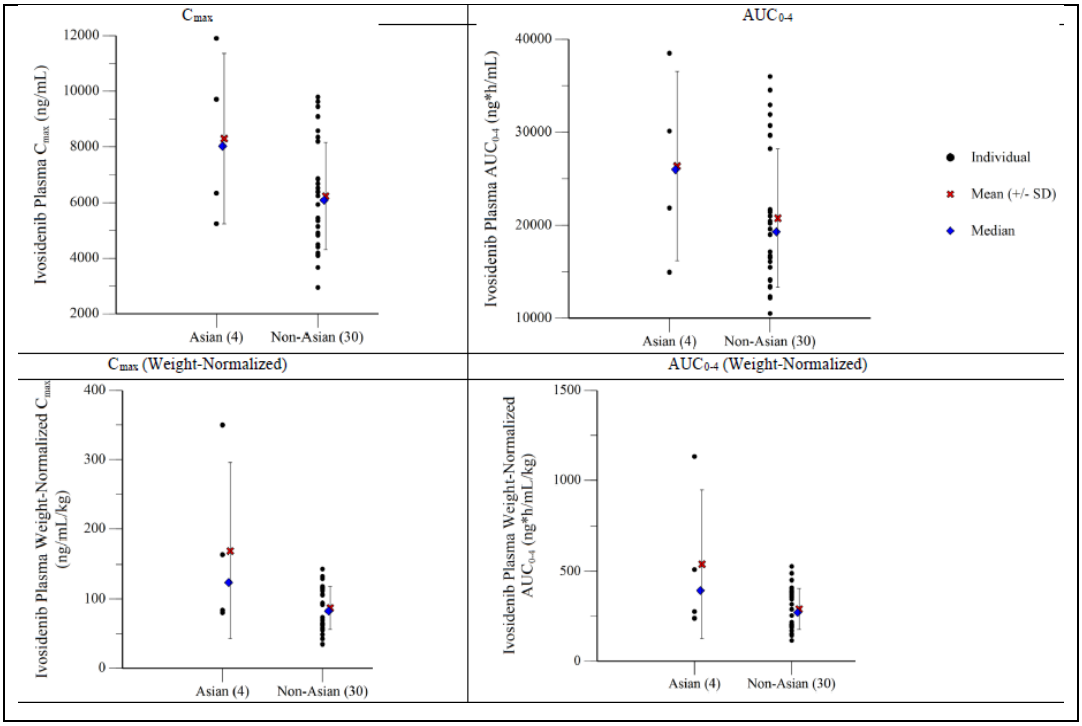
**Table 12.** Statistical summary of the effect of race (Japanese vs Caucasian) on ivosidenib PK

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

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

Besides Study AG120-C-006, an exploratory assessment of ivosidenib PK in Asian (Japanese, Taiwanese and Korean) vs non-Asian (Caucasian) subjects was performed in the pivotal phase 3 Study AG120-C-009 in adult subjects with newly diagnosed AML with an IDH1 mutation. Strip charts with and without weight-normalised ivosidenib PK parameters for Asians vs non-Asians after oral administration of ivosidenib 500 mg QD on C2D1 (repeat dose) are presented in Figure 6.

**Figure 3.** Strip charts of plasma ivosidenib AUC0-4, and Cmax – Asians vs. Non-Asians – C2D1 (PK analysis set)




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

- Gender

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

- Weight

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

- Elderly

A summary of ivosidenib PK parameters ($AUC_{0-8}$, $AUC_{0-24}$, $AUC_{0-T}$, $C_{max}$, $C_{trough}$) estimated on Cycle 2 Day 1 following 500 mg OD ivosidenib dosing is presented by study (AG120-C-001, AG120-C-002, AG120-C-005, AG120-C-009, and AG-221-AML-005) and age group (< 65, 65 to 74, 75 to 84, 85 years of age or older) in Table 17.

**Table 13.** Summary PK parameters of ivosidenib following multiple once-daily oral administrations of 500 mg ivosidenib (C2D1) by study

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

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

- Children

Ivosidenib PK has not been investigated in children.

***Pharmacokinetic interaction studies***

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

**Ivosidenib as victim drug**

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

The DDI study conducted with itraconazole –AG120-C-007 following ivosidenib 250 mg administration which is half therapeutic dose, showed a 2.69 fold exposure increase (GMR AUC 0-inf = 268.69 % with 90% CI [244.90 – 294.78]) without affecting Cmax (GMR Cmax = 102.41 % with 90% CI [52.71 – 113.13]). These results could not be extrapolated to the therapeutic dose of 500 mg due to ivosidenib auto-induction. PBPK modelling approach was thus used to support the expected magnitude of interactions between ivosidenib and strong CYP3A4 inhibitors. The PBPK framework is considered valid for DDI prediction of CYP3A4 substrates in AML patients. Collectively, the performed in vivo study, although not conducted at the therapeutic dose, and the PBPK model results provide some weight of evidence that interaction of ivosidenib at 500 mg with strong CYP3A4 inhibition is expected to increase ivosidenib exposure by two to three-fold.

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

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

**Ivosidenib as perpetrator**

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

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

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

### *2.7.2.2. Pharmacodynamics*

#### *Mechanism of action*

Ivosidenib is a potent, selective inhibitor of mutated IDH1.

The IDH family of proteins comprises 3 isoforms: IDH1, IDH2, and IDH3. Cancer-associated mutations have been identified in IDH1 and IDH2. Isocitrate dehydrogenase converts isocitrate to alpha-ketoglutarate (α-KG) through oxidative carboxylation and results in the production of nicotinamide adenine dinucleotide phosphate (NADPH). IDH mutations confer neomorphic enzymatic activity resulting in the reduction of α-KG to form 2-HG, which consumes NADPH and renders the cell

vulnerable to oxidative stress. High levels of 2-HG inhibit α-KG-dependent enzymes involved in DNA and histone methylation. These impairments have been linked to a block in cellular differentiation promoting tumorigenesis in both haematologic and non-haematologic malignancies.

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

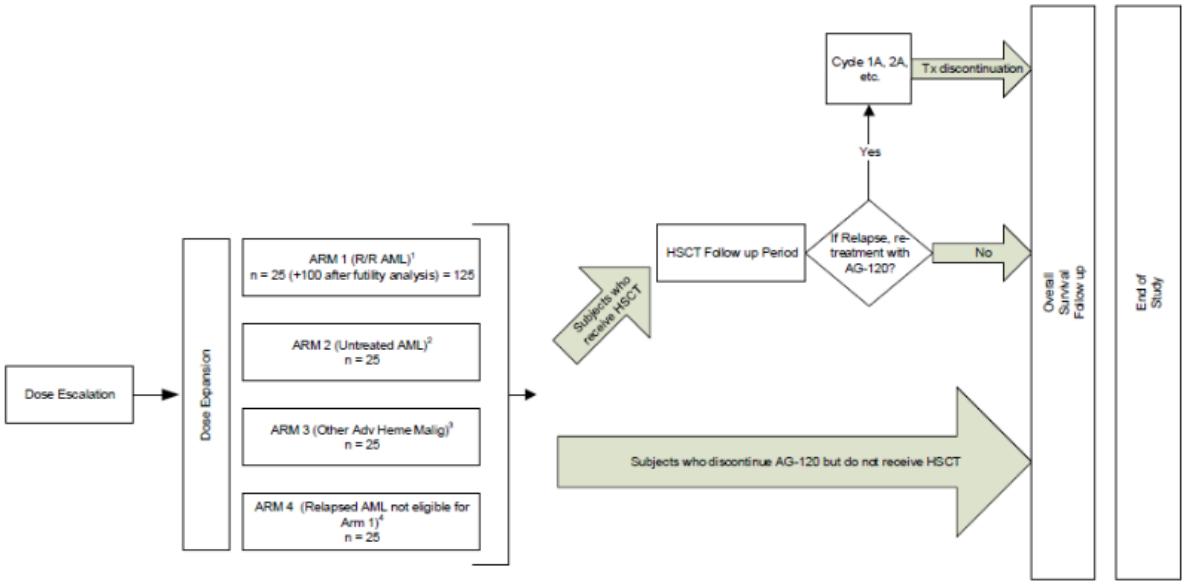
***Primary and Secondary pharmacology***

**Primary Pharmacology**

**AG120-C-001: advanced haematologic malignancies**

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

**Figure 7.** Overall study schema of Study AG120-C-001




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

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

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

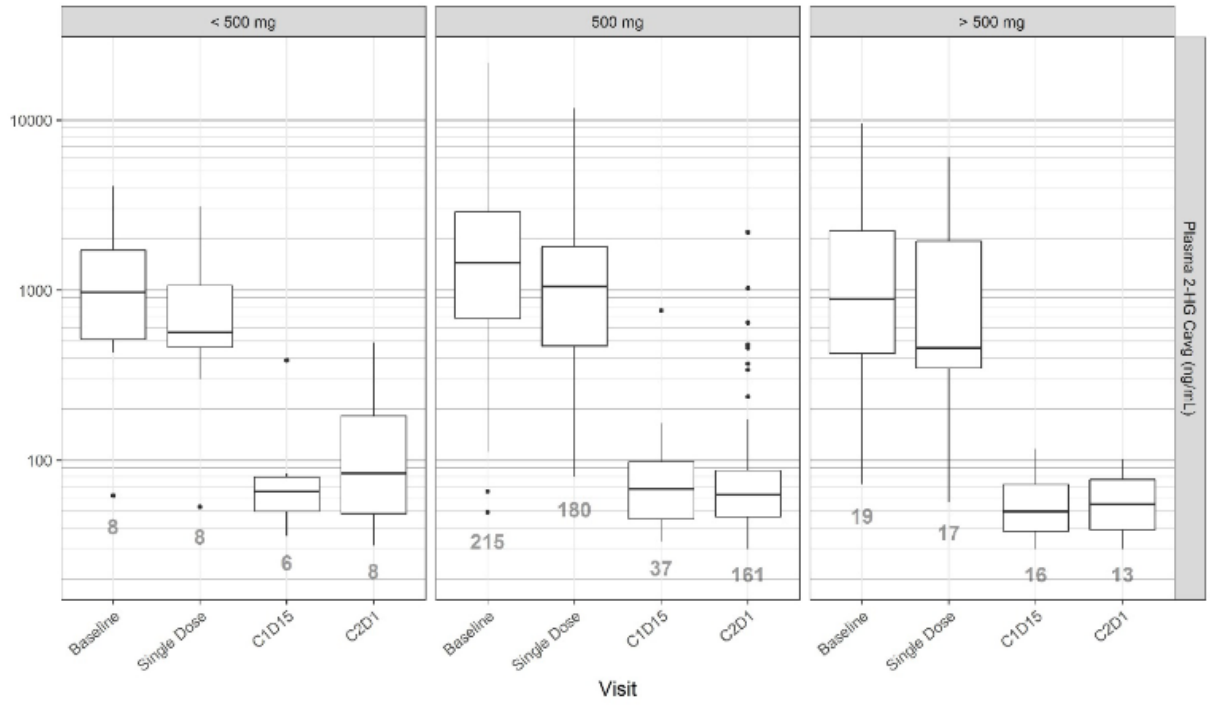
[3] Other non-AML IDH1-mutated R/R advanced hematologic malignancies, where no standard of care treatment option was available; such as: MDS that was recurrent or refractory after having failed hypomethylating agent(s) and with the approval of Medical Monitor; relapsed and/or primary refractory CMML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

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

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

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

**Figure 8**. Box plots of plasma 2-HG Cavg vs. visit after oral administration of ivosidenib, by dose category – all haematologic malignancy types (dose escalation and expansion combined)




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

**Table 14.** Summary of plasma 2-HG Pharmacodynamic Parameters of Ivosidenib After Multiple Oral Administration of 500 mg QD Ivosidenib at C2D1 in subjects with relapsed or refractory AML (AG120-C-001)

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

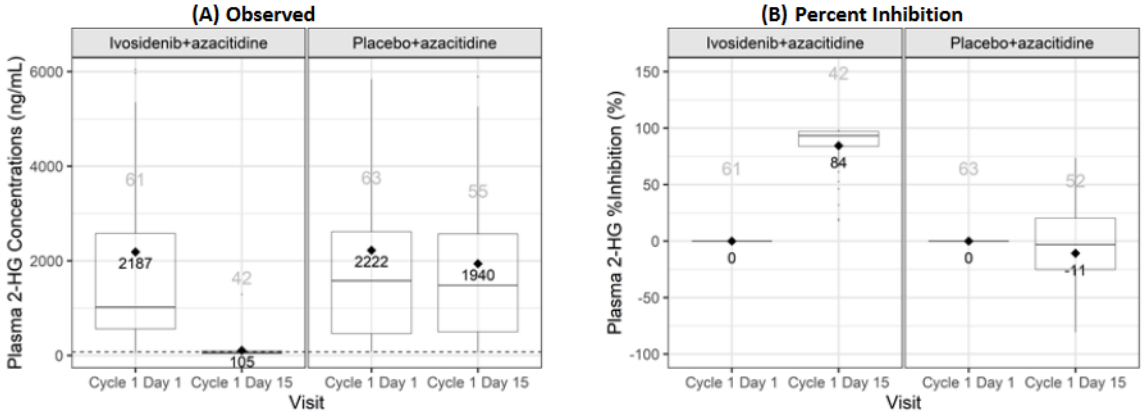
Source: Report AG120-C-001-PKPD Table 33, Table 34, and Table 35. Data cutoff date: 12 May 2017.
Abbreviations: $AUEC_{0\text{-}8hr}$ = area under the effect concentration-time curve from time 0 (predose) through 8 hours; $\%BAUEC_{0\text{-}10hr}$ = percent inhibition for $AUEC_{0\text{-}8hr}$; $\%BC_{avg}$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

**AG120-C-009: Subjects with Newly Diagnosed AML**

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

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

**Figure 9.** Box plots of plasma predose (trough) of 2-HG concentrations (observed and percent inhibition) versus visit after oral administration of ivosidenib or placebo with azacitidine (AG120-C-009)




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

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

**Secondary pharmacology**

*Ivosidenib has the potential to prolong the QTc interval.*

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

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

In clinical studies provided in newly diagnosed AML indication, events of QT prolongation were also reported as frequent (19.7% in AML indication with r 9.9 % of grade ≥ 3).

***Ivosidenib has the potential to inhibit wt IDH1.***

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

**Relationship between plasma concentration and response**

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

## 2.7.3. Discussion on clinical pharmacology

**Pharmacokinetics**

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

*Absorption*

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

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

*Food effect*

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

*Population PK modelling*

The clinical pharmacology properties of ivosidenib in patients with advanced haematological malignancies have been characterised through a population PK model including experimental evidence gathered from Study AG120-C-0001 (Phase 1) in 253 subjects and 4656 samples.

The final population PK model (addendum report) developed in patients with advanced haematological malignancies includes different structural PK parameters (CL/F, Vc/F, Q/F, and Vp/F) between first dose and steady-state conditions, which is unexpected because time-dependent factors should be explained using structural functions able to address and explain the behaviour observed. A time-varying function to describe the change over time of CL/F was statistically significant (a reduction of the OFV value of 65 units). A rate of change to steady-state conditions was estimated with a half-life of 18 hours, which is in line with the step-change set at 96-h. Therefore, the continuous function of time-

varying and the step-change model at 96h provide similar conclusions. The selection of the step-change model over the time-varying CL was justified by the lack of sufficient experimental evidence during the induction phase, which is accepted. Even though further clinical evidence during the induction phase would be needed to be incorporated to the model to finally update the time-varying function of CL, based on the current limitations and the lack of appropriate experimental evidence to mechanistically describe the observed effects, the current population PK model is considered purely descriptive and no extrapolation analysis should be conducted.

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

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

**Special Populations**

*Hepatic impairment*

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

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

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

PK results in patients with hepatic impairment

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

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

Very few data (n=2) were available in the moderate HI group in patients with R/R AML (AG120-C-001). No reliable conclusion could be drawn from such limited data. Moreover, patients with R/R AML are not in the scope of the claimed / target populations. The lack of PK data in these patients has been reflected in the SmpC. As the two hepatic function classifications (NCI versus CP) are discordant and as PK data are only available with the NCI classification, the text in the SmpC indicates clearly the classification used together with the information on the lack of PK data using the recommended Child Pugh classification. No PK data are available in patients with severe HI and this is reflected in the

SmpC (see SmPC section 4.2). An organ impairment substudy of AG120-C-001 will evaluate the pharmacokinetics, safety and tolerability of ivosidenib in patients with haematologic malignancies with an IDH1 mutation with moderate hepatic impairment, severe hepatic impairment or severe renal impairment as a category 3 post authorisation study (see RMP).

*Race*

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

Ivosidenib systemic exposure ($C_{max}$ and $AUC_{0-24}$) in Asians largely overlapped those observed in non-Asians. Overall, taken all data together, the tendency of lower systemic exposure in Asian (PK data in patients with AML are very immature), the flat exposure- efficacy relationships, this do not suggest a clinically significant impact on ivosidenib PK between Asian and Caucasian patients. Thus, no dose adjustment for ivosidenib based on race is needed.

*Weight*

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

Based on the results from the C-QTc analysis and the mean Cmax of 5440 ng/mL or median Cmax (min max) of 4830 (3390-8690) ng/mL, a QTc prolongation of 19.8 msec (for mean Cmax) and 31.3 msec (max Cmax) was predicted.

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

*Elderly*

Sufficient and representative sample size of patients in age groups [65-74 y] and [75-84 y] are available. However, no PK data in patients > 85 years old are available for the claimed patient. Limited data exist for this subgroup in R/R AML patients.

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

**Exposure-Response (ER)**

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

The exposure-efficacy evaluation did not identify any relevant relationship between AUCss and the efficacy endpoints selected in patients with advanced haematological malignancies and acute myeloid leukaemia. Model-predicted AUCss were simulated based on the final population PK model considering

nominal dose (scenario 1). This simplification (nominal dose) attenuates changes in AUCss due to dose modifications or time-varying covariates, which could increase the AUCss range in order to identify any likely exposure-efficacy relationship. Additional logistic regressions were conducted using observed and model predicted probability of response versus AUC at cycle 1, suggesting no significant and positive trend of higher probability of response with higher AUC. A minor deviation (14.1% in cycle 1) from the actual dose was observed for newly diagnosed AML, suggesting no relevant differences between the actual and predicted AUC at cycle 1, which reinforces the conclusions gathered from the current analysis. Based on the results available, no clinically relevant exposure-efficacy relationship was established in patients with advanced haematological malignancies and acute myeloid leukaemia, which may impact the identification of an optimal dose selection.

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

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

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

*PK interactions*

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

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

evidence provided, the PBPK framework is considered valid for DDI prediction of CYP3A4 substrates in AML patients, but further improvement in terms of bioavailability and oral absorption of ivosidenib are required before conducting any extrapolation in special sub-groups of patients for dose selection.

**Pharmacodynamics**

AML

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

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

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

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

Secondary PD

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

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

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

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

## 2.7.4. Conclusions on clinical pharmacology

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

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

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

## 2.7.5. Clinical efficacy

### *2.7.5.1. Dose response study*

There was no dedicated dose-response study. Exposure-response analyses for safety and efficacy were conducted using data from 64 subjects with newly diagnosed AML receiving ivosidenib (500 mg QD) + azacitidine from the pivotal Study AG120-C-009 (hereafter AGILE Study or Study 009).

Four efficacy endpoints were selected for evaluation of potential exposure-efficacy relationships for ivosidenib + azacitidine response: complete remission (CR), CR with partial haematologic recovery (CR + CRh), objective response (OR), and event-free survival (EFS).

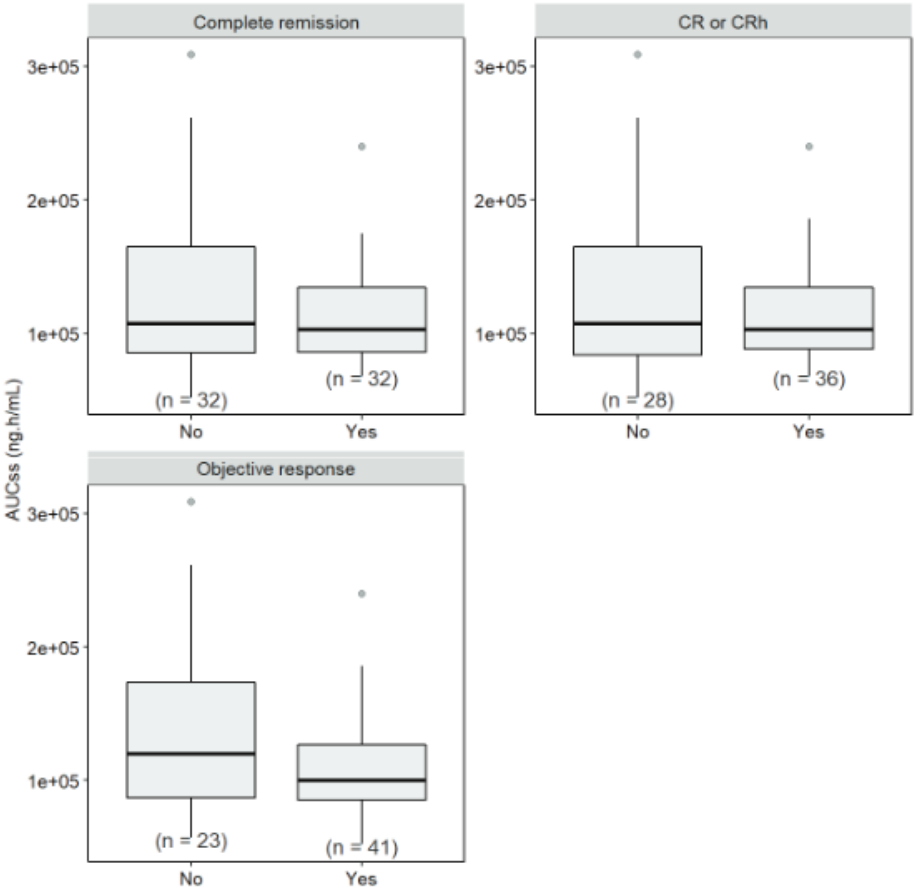
The E-R analyses of these endpoints were impacted by the fact that subjects who achieved an efficacy response (responders based on CR, CR + CRh and OR) stayed longer on treatment than subjects who did not achieve efficacy response (non-responders) and dropped out early from the study. Because the likelihood of dose modifications was correlated with treatment duration, responders received a lower average daily dose than non-responders due to dose reductions and dose interruptions during the course of treatment. As a result, exposure was confounded with treatment duration and as such with clinical response, and results from the analysis should be interpreted with care.

The difference in average daily dose between responders and non-responders was less pronounced when the average daily dose in Cycle 1 was considered.

These observations advocate the use of exposure metrics based on the average daily dose in Cycle 1 to reduce the effect of dose reductions associated with efficacy response.

Exposure distributions were explored with boxplots for responders and non-responders for CR, CR + CRh, and OR, as depicted in the figure below.

**Figure 10.** Exposure distributions in responders and non-responders for the binary efficacy endpoints CR, CR + CRh, and OR




Source: exploratory-er-analysis.docx
Notes: The solid line represents the median, the box represents the IQR, the whiskers represent the 1.5× IQR, and the dots represent the data points ("outliers") beyond the end of the whiskers.
Abbreviations: AUCss=area under the concentration-time curve at steady state for the average daily dose in first treatment cycle; CR=complete remission; CRh=complete remission with partial hematologic recovery; n=number of subjects; IQR=interquartile range

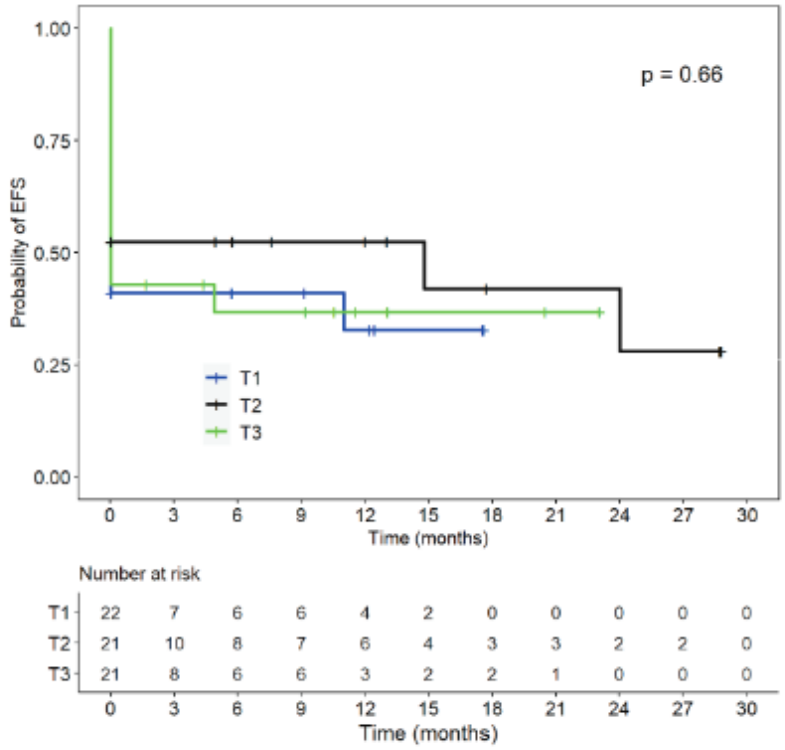
In general, the distributions for both subject groups were overlapping. The AUCs distribution for responders were narrower than for nonresponders for the 3 endpoints. The median AUCs and the distributions were overlapping for CR and CR + CRh. The median AUCs appeared to be lower for responders compared to nonresponders for OR.

Logistic regression was applied to further quantify exposure effects. For all 3 endpoints, an inverse relationship with lower efficacy with increasing exposure was observed. This effect reached statistical significance for OR (p = 0.03): increase in exposure was associated with a decrease in probability of achieving OR. The inverse E-R relationship for OR was still observed when adjusted for baseline covariates (age, body weight, sex, AML nature, ECOG PS score, cytogenetic risk, and geographical region, respectively). No statistically significant relationship between exposure and the probability of response was observed for the other 2 endpoints (CR and CR + CRh).

Similar but somewhat more pronounced trends were observed using the exposure estimates based on the average daily dose in the whole treatment.

Kaplan-Meier Estimation and Cox PH Regression of Event-Free Survival

**Figure 11.** Kaplan-Meier curves for event-free survival as a function of tertiles of AUCss




Source: exploratory-er-analysis.docx
Notes: The p-value in the upper right corner in the plot represents the p-value of no difference between the exposure tertiles based on the log-rank test.
Abbreviations: AUCss=area under the concentration-time curve at steady state for the average daily dose in first treatment cycle; EFS=event-free survival. T1-T3=first (T1), second (T2), and third (T3) tertiles of the AUCss distribution

The figure above shows KM estimates of the proportion of subjects with EFS for tertiles of AUCss distribution. The KM curves for the 3 exposure tertiles were overlapping and showed no apparent E-R relationship (log-rank test: p = 0.66). A Cox PH model was applied to quantify the exposure effect on EFS. The estimated AUCss effect on EFS from the Cox PH model was not statistically significant (p = 0.44). Similar results were found using the exposure estimates based on the average daily dose in the whole treatment period.

### *2.7.5.2. Main study*

**Study AG120-C-009 (AGILE):** a Phase 3, multicentre, double-blind, randomised, placebo-controlled clinical trial to evaluate the efficacy and safety of ivosidenib + azacitidine vs placebo + azacitidine in adult subjects with previously untreated IDH1-mutated AML and who are considered appropriate candidates for non-intensive therapy.

***Methods***

- **Study Participants**

Main inclusion criteria

1. Were ≥ 18 years of age and met at least 1 of the following criteria defining ineligibility for intensive IC:

a. ≥ 75 years old
b. ECOG PS = 2
c. Severe cardiac disorder (e.g., congestive heart failure requiring treatment, LVEF IC: , or chronic stable angina)
d. Severe pulmonary disorder (e.g., diffusing capacity of the lungs for carbon monoxide 65% or forced expiratory volume in 1 second apacitCreatinine clearance <45 mL/minute
e. Bilirubin >1.5 times the upper limit of normal (× ULN)
f. Any other comorbidity that the Investigator judged to be incompatible with intensive IC
g. Had previously untreated AML, defined according to WHO criteria. Subjects with extramedullary disease alone (i.e., no detectable bone marrow and no detectable peripheral blood AML) were not eligible for the study.

2. Had an IDH1 mutation resulting in an R132C, R132G, R132H, R132L, or R132S substitution, as determined by central laboratory testing (using an investigational polymerase chain reaction [PCR] assay) in their bone marrow aspirate (or peripheral blood sample if bone marrow aspirate was not available).
3. Local testing for eligibility and randomisation was permitted; however, results had to state an IDH1 mutation resulting in an R132C, R132G, R132H, R132L, or R132S substitution.
4. Had an ECOG PS score of 0 to 2
5. Had adequate hepatic function, as evidenced by:
    a. Serum total bilirubin ≤2 × upper limit of normal (ULN), unless considered to be due to Gilbert's disease or underlying leukaemia, where it had to be <3 x ULN.
    b. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) ≤3×ULN, unless considered to be due to underlying leukaemia.
6. Had adequate renal function, as evidenced by serum creatinine ≤2.0 x ULN or creatinine clearance >30 mL/min based on the Cockcroft-Gault glomerular filtration rate.
7. Agreed to undergo serial blood and bone marrow sampling.
8. If female with reproductive potential, must have had a negative serum pregnancy test prior to the start of study therapy. Females of reproductive potential, as well as fertile men with female partners of reproductive potential, were required to use 2 effective forms of contraception (including at least 1 barrier form) as per study protocol, from the time of giving informed consent throughout the study and for 90 days following the last dose of study drug(s).

Main exclusion criteria

1. Were candidates for intensive IC for their AML.
2. Had received any prior treatment for AML with the exception of non-oncolytic treatments to stabilise disease such as hydroxyurea or leukapheresis.
3. Had received a hypomethylating agent for MDS.
4. Subjects who had previously received treatment for an antecedent haematologic disorder, including investigational agents, were not to be randomised until a washout period of at least 5 half-lives of the investigational agent had elapsed since the last dose of that agent.
5. Had received prior treatment with an IDH1 inhibitor.

6. Had a known hypersensitivity to any of the components of ivosidenib, matched placebo, or azacitidine.
7. Were female and pregnant or breastfeeding.
8. Were taking known strong cytochrome P450 (CYP)3A4 inducers or sensitive CYP3A4 substrate medications with a narrow therapeutic window, unless they could be transferred to other medications within ≥5 half-lives prior to dosing.
9. Had an active, uncontrolled, systemic fungal, bacterial, or viral infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other treatment.
10. Had a prior history of malignancy other than MDS or myeloproliferative disorder, unless the subject had been free of the disease for ≥1 year prior to the start of study treatment. However, subjects with the following history/concurrent conditions or similar indolent cancer were allowed to participate in the study:
    a. Basal or squamous cell carcinoma of the skin
    b. Carcinoma in situ of the cervix
    c. Carcinoma in situ of the breast
    d. Incidental histologic finding of prostate cancer
11. Had significant active cardiac disease within 6 months prior to the start of study treatment, including New York Heart Association (NYHA) Class III or IV congestive heart failure, myocardial infarction, unstable angina, and/or stroke.
12. Had a heart-rate corrected QT interval using Fridericia's method (QTcF) ≥470 msec or any other factor that increases the risk of QT prolongation or arrhythmic events. Subjects with prolonged QTcF interval in the setting of bundle branch block could participate in the study.
13. Had a known infection caused by human immunodeficiency virus (HIV) or active hepatitis B virus or hepatitis C virus that cannot be controlled by treatment.
14. Had uncontrolled hypertension (systolic blood pressure [BP] >180mmHg or diastolic BP >100mmHg).
15. Had clinical symptoms suggestive of active central nervous system (CNS) leukaemia or known CNS leukaemia. Evaluation of cerebrospinal fluid during Screening was only required if there was a clinical suspicion of CNS involvement by leukaemia during Screening.
16. Had immediate, life-threatening, severe complications of leukaemia, such as uncontrolled bleeding, pneumonia with hypoxia or sepsis, and/or disseminated intravascular coagulation.
17. Had any other medical or psychological condition deemed by the Investigator to be likely to interfere with the subject's ability to give informed consent or participate in the study.
18. Were taking medications that are known to prolong the QT interval unless they could be transferred to other medications within ≥5 half-lives prior to dosing, or unless the medications could be properly monitored during the study.
19. Subjects with a known medical history of progressive multifocal leukoencephalopathy (PML).

- **Treatments**

Treatment was administered as follows:

**AG-120 Arm:** azacitidine 75 mg/m²/day SC or IV for the first week (7 days) (or on a 5-2-2 schedule) of each 4-week (28-day) cycle in combination with 500 mg ivosidenib PO QD on each day of the 4-week cycle.

**Placebo Arm**: azacitidine 75 mg/m²/day SC or IV for the first week (7 days) (or on a 5-2-2 schedule) of each 4-week (28-day) cycle in combination with placebo PO QD on each day of the 4-week cycle.

The same schedule was to be used for each subject throughout the duration of treatment, when possible.

Subjects were instructed to take their ivosidenib QD dose at approximately the same time each day. Subjects were to continue to receive therapy with ivosidenib or placebo + azacitidine until death, disease relapse, disease progression, development of unacceptable toxicity (adverse event), confirmed pregnancy, withdrawal by subject, protocol violation, or end of study.

On days when both ivosidenib or placebo and azacitidine were given, ivosidenib or placebo were to be given prior to azacitidine.

- **Objectives**

The primary objective of the study was to compare EFS between ivosidenib + azacitidine and placebo + azacitidine.

The key secondary objectives of the study were:

- To compare the complete remission (CR) rate between ivosidenib + azacitidine and placebo + azacitidine.
- To compare OS between ivosidenib + azacitidine and placebo + azacitidine.
- To compare the CR + complete remission with partial haematologic recovery (CRh) rate between ivosidenib + azacitidine and placebo + azacitidine; CRh will be derived by the Sponsor.
- To compare the objective response rate (ORR) between ivosidenib + azacitidine and placebo + azacitidine.

- **Outcomes/endpoints**

The primary endpoint of the study was EFS, which was defined as the time from randomisation until treatment failure (TF), relapse from remission, or death from any cause, whichever occurred first. TF was defined as failure to achieve CR by Week 24.

The key secondary endpoints were:

- CR rate, defined as the proportion of subjects who achieved a CR; CR was defined as bone marrow blasts <5% and no Auer rods; absence of extramedullary disease; ANC ≥1.0 × 109/L (1000/µL); platelet count ≥100×109/L (100,000/µL); and independence of RBC transfusions.
- OS, defined as the time from date of randomisation to the date of death due to any cause.
- CR + CRh rate, defined as the proportion of subjects who achieved a CR or CRh. CRh was defined as a CR with partial recovery of peripheral blood counts (<5% bone marrow blasts, platelets >50,000/µL, and ANC >500/µL). CRh was derived by the Sponsor since it was not part of International Working Group criteria.

- ORR, defined as the rate of CR, CRi (including CRp), partial remission (PR), and morphologic leukaemia-free state (MLFS). The best response was calculated using the following order: 1) CR; 2) CRi (including CRp); 3) PR, and 4) MLFS.
- CR + CRi rate, defined as the proportion of subjects who achieved a CR or CRi (including CRp).

Additional secondary endpoints focused on HRQoL assessments and assessment of disease response to treatment through the evaluation of bone marrow biopsies and/or aspirates, along with complete blood counts and examination of peripheral blood films.

- **Sample size**

In the original protocol (6 January 2017)

A total of approximately 392 subjects with previously untreated IDH1m AML were planned to be randomised in this study, with OS as the primary endpoint.

In a previous randomised Phase 3 study of azacitidine in older subjects with newly diagnosed AML with > 30% blasts, median OS of 10.4 months was observed for the azacitidine arm (Dombret, et al. 2015). This was used as the modelling assumption for the control arm in the current study. Assuming an HR of 0.71 for OS (equivalent to a median OS of 10.4 months in the placebo arm vs 14.6 months in the AG-120 arm, assuming an exponential distribution), a total of 278 OS events were required to provide 80% power at a 1-sided alpha of 0.025 level of significance to reject the null hypothesis using a stratified log-rank test.

Assuming a recruitment period of approximately 44 months, with an accrual rate of 5 subjects/month during the first 5 months and 9.6 subjects/month afterwards, along with an assumed 10% dropout rate, approximately 392 subjects were to be randomised to the 2 treatment arms in a 1:1 ratio. Given the above assumptions, it was estimated that the primary analysis of OS would occur approximately 54 months after the first subject was randomised.

From protocol amendment 5 (9 January 2020)

A total of approximately 200 subjects with previously untreated IDH1m AML were planned to participate in this study.

Assumptions for the placebo + azacitidine arm in this study were based on results from Study AZA-AML-001 in newly diagnosed AML patients who are ineligible for intensive IC receiving ivosidenib in combination with azacitidine. Based on results from a retrospective analysis of these data, the CR rate at 24 weeks was assumed to be 20% for the placebo + azacitidine arm. For subjects who achieve CR by 24 weeks, the median EFS is assumed to be 14.6 months.

Assumptions for the ivosidenib + azacitidine arm in this study were based on results from Study AG-221-AML-005 in newly diagnosed AML patients who are ineligible for intensive IC receiving ivosidenib in combination with azacitidine. The CR rate by 24 weeks was assumed to be 40%. For subjects who achieve CR by 24 weeks, a target HR of 0.76 for EFS (equivalent to a median EFS among responders of 14.6 months in the placebo + azacitidine arm vs 19.2 months in the ivosidenib + azacitidine arm, assuming an exponential distribution) was assumed. Based on simulation results, the average overall HR over 10,000 simulations for the entire population was 0.641. Given that the assumption of proportional hazards was not met based on the EFS definition, the overall HR is less meaningful in this context. Therefore, the overall HR for the entire population was not part of the study design assumptions. Under these assumptions, a total of 173 EFS events were required to provide 80% power at a 1-sided alpha of 0.025 level of significance to reject the null hypothesis using a stratified log-rank test. Assuming a recruitment period of approximately 44 months, with an accrual rate of 3 subjects per

month during the first 10 months and 5 subjects per month thereafter, along with an assumed 5% overall dropout rate, approximately 200 subjects were planned to be randomised to the 2 treatment arms in a 1:1 ratio. Given the above assumptions, it was estimated that the analysis of the primary endpoint for EFS will occur approximately 52 months after the first subject was randomised.

- **Randomisation and Blinding (masking)**

This was double-blind randomised trial. Randomisation was stratified by de novo status (de novo AML and secondary AML) and geographic region (United States and Canada; Western Europe, Israel, and Australia; Japan; and rest of world).

- **Statistical methods**

Primary endpoint

EFS was defined as the time from randomisation until TF, relapse from remission, or death from any cause, whichever occurred first. Subjects who did not achieve CR by Week 24 were considered to have had an EFS event at Day 1 of randomisation. For subjects who achieved CR by Week 24 (responders), the EFS time was the time from randomisation to relapse or death, whichever occurred first.

EFS was tested using the log-rank test stratified by the randomisation stratification factors.

Kaplan-Meier estimates (product-limit estimates) were presented by treatment arm together with a summary of associated statistics.

The HR was estimated using a Cox's proportional hazards (PH) model stratified by the randomisation strata. The treatment effect between the treatment arm and the control arm was also assessed based on the difference in Restricted Mean Survival Time (RMST).

*Determination of relapse date*

Only disease assessments performed on or before the start date of subsequent anticancer therapies were considered in the determination of relapse.

Confirmation was required for relapse. Assessments which were not done or were not evaluable were ignored in the derivation of relapse confirmation. A subject was considered to have relapsed if either of the following criteria were met:

- Relapse in 2 consecutive assessments that were at least 4 weeks apart
- Relapse with no further evaluable disease assessments before discontinuation from study or initiation of subsequent anticancer therapy

The date of relapse considered in the analyses was the date when the first relapse, that was subsequently confirmed, was observed.

*Determination of CR by 24 weeks*

CR was assessed until the date of relapse (that was subsequently confirmed). Only assessments performed on or before the start date of subsequent anticancer therapies were considered in the determination of CR.

The protocol allowed a 1-week window for disease assessments. Therefore, a subject was considered to have achieved "CR by 24 weeks" if the date of first CR was within 25 weeks (24 weeks target+1-week window) after the date of randomisation.

Secondary endpoints

The key secondary efficacy endpoints were CR, OS, CR+CRh, and OR rate. CR, CR+CRh and OR were assessed until the date of relapse (that was subsequently confirmed). Only assessments performed on or before the start date of subsequent anticancer therapies were considered in the determination of these response endpoints.

Multiplicity adjustment

To control the overall Type 1 error rate, the fixed sequence testing procedure was to be used to adjust for multiple statistical testing of the primary and key secondary efficacy endpoints.

These endpoints were tested in the following order:

- EFS
- CR rate
- OS
- CR + complete remission with partial haematologic recovery (CRh) rate
- ORR

No control of the alpha level was made for the other analyses.

*Interim analysis*

In the original protocol (6 January 2017) there were 2 planned interim analyses for OS:

The first interim analysis was a futility analysis that was to be performed when approximately 33% of the required deaths (93 deaths) had occurred (projected to occur approximately 26 months after the first subject was randomised). Consideration to terminate the study was to be based on the evaluation of the overall safety and efficacy data available at that time by the IDMC, including an observed HR of OS is > 1.05 (in favour of the placebo + azacitidine arm), based on the gamma (-2) error spending function as implemented in East 6.4 (Hwang, et al. 1990). Besides OS, other efficacy data may also have been evaluated by the IDMC.

The second efficacy interim analysis for superiority was to be performed when approximately 67% of the required deaths (185 deaths) had occurred (approximately 39 months after first subject was randomised). At this interim analysis, the study could have stopped for efficacy reasons if the observed HR of OS was ≤ 0.691 (one-sided p-value ≤ 0.006) in favour of the AG-120 + azacitidine arm based on the O' Brien-Fleming alpha spending function, the Lan-DeMets method (Lan and DeMets 1983). These 2 interim analyses were to be conducted by the IDMC with the assistance of an independent biostatistician. Based on the rules above, the IDMC was to make recommendation to the Sponsor regarding continuation of the study.

There were no planned interim analyses for efficacy in this study following protocol amendment 5 (9 January 2020.

The protocol was amended 9 times (See also Conduct of the study). Some key changes were made to the statistical methods as part of the protocol amendments, as summarised in Table 15.

**Table 15.** Key changes to statistical methods

| Protocol version | Changes to statistical methods |
|---|---|
| Amendment 5, Version 6.0 (09 January 2020) | **Changed the primary endpoint from OS to EFS**, and added OS to the key secondary endpoints |

| | |
|---|---|
| | Updated the corresponding statistical analyses and multiplicity adjustment procedure<br><br>Removed the interim analyses for efficacy<br><br>**Reduced the number of subjects** who will participate in this study from 392 to 200 based on updated sample size estimations, and increased the number of study centres and countries. |
| Amendment 7, Version 8.0 (16 December 2020) | Continued efficacy follow-up of subjects in the study for EFS after initiation of subsequent anticancer therapy for subjects who did not have an EFS event.<br><br>Incorporated a sensitivity analysis for the primary endpoint supporting the continued efficacy follow-up for EFS after initiation of subsequent anticancer therapy for subjects who did not have an EFS event. |

Changes from the protocol-specified analysis to the SAP included the following: a) the Intent-to-treat Analysis Set in the protocol was referred to as the FAS in the SAP and b) the estimation of the treatment effect in terms of odds ratio utilised the Mantel-Haenszel estimate of odds ratio (the 95% CI provided directly from the CMH option in SAS PROC FREQ) instead of using the logistic regression model.

Changes introduced after the final SAP

- *IDMC unplanned analysis and recommendation to discontinue treatment*

On 04 November 2020, the IDMC met to review the safety data as part of their semi-annual monitoring of the study. During the closed meeting session, when unblinded data was reviewed, the IDMC observed that more deaths were occurring in the placebo + azacitidine arm vs. the ivosidenib + azacitidine arm. The IDMC recommended the sponsor continue the study as planned and in closed session requested additional unblinded efficacy analyses (EFS and OS). These analyses were reviewed at an ad-hoc IDMC meeting on 08 December 2020; no significant difference between the treatment arms could be concluded. At the subsequent IDMC meeting held on 12 May 2021, the IDMC reviewed the safety data based on the 146 subjects enrolled in the study at the 18 March 2021 data cut date. A greater number of deaths in the placebo + azacitidine arm vs. the ivosidenib + azacitidine arm continued to be observed. This prompted another unblinded analysis for efficacy, which included OS, EFS, and clinical response, and led to the IDMC recommendation to halt recruitment to the study on 12 May 2021. The applicant maintained the blind for the critical study team members directly involved with study conduct, while segregating a small unblinded group to address the IDMC recommendation. On 24 May 2021, unblinded the applicant team members, in consultation with the sponsor, obtained FDA input regarding the IDMC recommendation to halt recruitment; on 27 May 2021 the applicant instructed investigators to discontinue recruitment to the study. At that time, 148 subjects had been randomised (2 additional from the18 March 2021 data cut date). The database for the study was locked on 15 July 2021. On 30 July 2021, investigators were informed that the study met its primary endpoint and all key secondary endpoints and they were given instructions on how to unblind the subjects' treatment assignments. Subjects on the placebo + azacitidine arm were given the opportunity to cross over to the ivosidenib + azacitidine arm if additional safety inclusion and exclusion criteria were met.

This change in study conduct (i.e. allowance of cross over) was detailed in AG120-C-009 protocol, Version 9.0 dated 01 July 2021. The p-value boundaries for the primary and key secondary efficacy endpoints were adjusted to account for the IDMC's unplanned analysis as described below.

Due to the changes of the study, in addition to the fixed sequence testing procedure pre-specified in the SAP, an individual set of group-sequential boundaries were applied separately to each of the primary and key secondary efficacy endpoints to account for this unplanned analysis and subsequent recommendation to stop enrolment in the study. Specifically, the O'Brien-Fleming alpha spending function (the Lan-DeMets method) was used for each of the primary and key secondary efficacy endpoints. At the time of the analysis, for each of the primary and key secondary endpoints, the p-value calculated based on methodologies pre-specified in the SAP were compared to the p-value boundary calculated from the alpha spending function, respectively. EAST Version 6.5 and R Version 4.0.5 were used for the calculation. For EFS, CR, OS, CR+CRh, and ORR, the 1-sided p-value boundaries are 0.0046, 0.0087, 0.0017, 0.0087, and 0.0087, respectively.

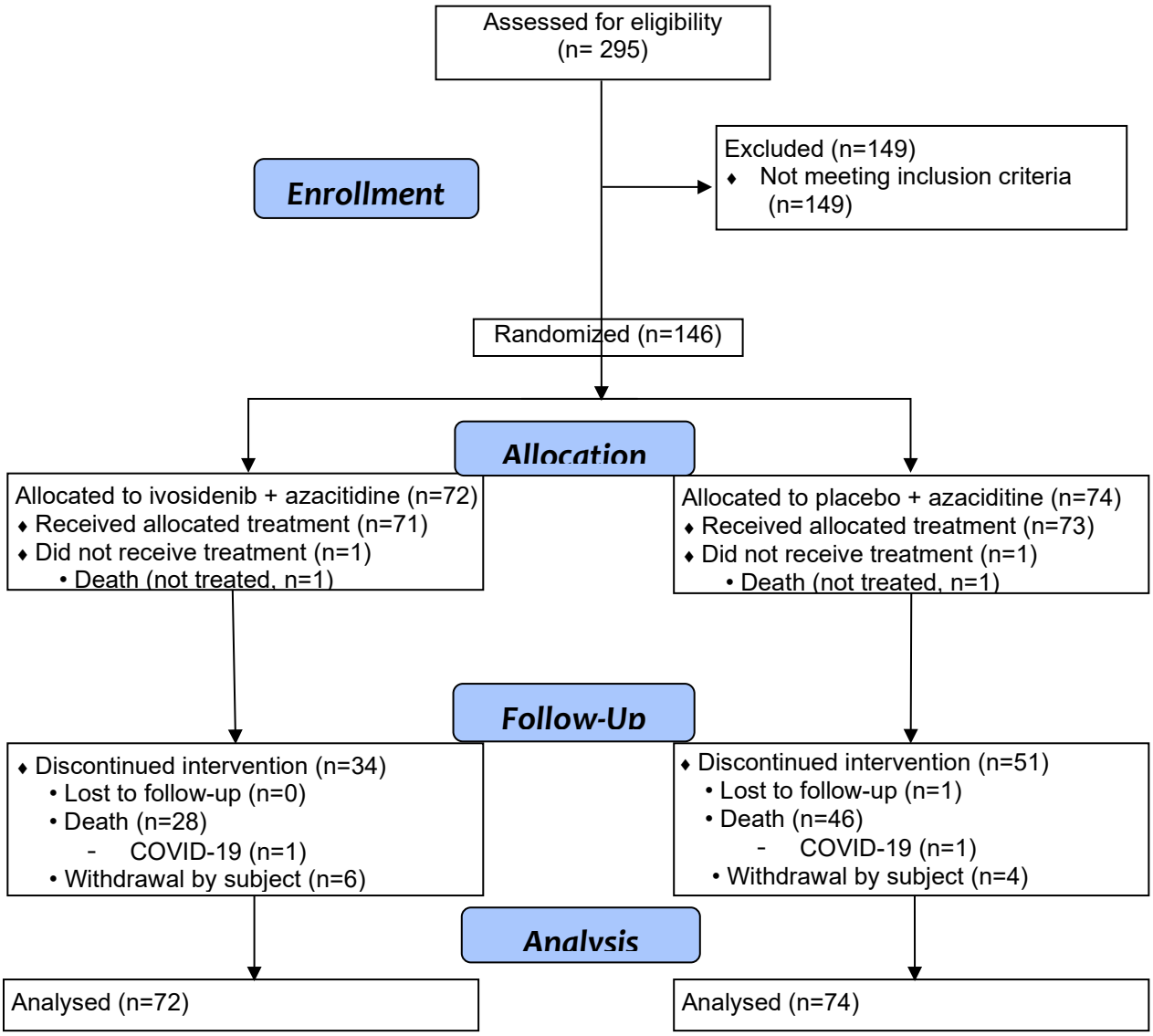
The SAP specified that the CSR would include all data up to the data cut-off date that would be determined on the number of events required for the final analysis of the primary endpoint and a minimum follow-up of 24 weeks for all subjects randomised, but this changed due to the IDMC recommendation.

As of the data cutoff date, 10 subjects remained on treatment with less than or equal to 24 weeks who had not yet achieved CR. These subjects could not be evaluated for TF and were censored at the date of randomisation. These scenarios were not outlined in the SAP.

***Results***

- **Participant flow**

**Figure 12.** Participant flow in study AG120-C-009




- **Recruitment**
  - First subject enrolled: 19 March 2018
  - Last subject completed: N/A - study ongoing
  - Data cut off-date: 18 March 2021

- **Conduct of the study**

Protocol amendments

The original global protocol dated 06 January 2017 was amended nine times. No subjects were enrolled under the original protocol, or Amendments 1, 2, 8 and 9. Ten subjects were enrolled under Amendment 3, 107 subjects were enrolled under Amendment 4, 3 subjects were enrolled under

Amendment 5, 25 subjects were enrolled under Amendment 6, 3 subjects were enrolled under Amendment 7.

The key changes to protocol are outlined in the table below. Country-specific amendments are not listed.

**Table 16.** Main protocol amendments # for study AG120-C-009

| | |
|---|---|
| Amendment 3, Version 4.0 (14 April 2017) | Removed the optional safety run-in portion of the study based on preliminary safety results for the combination of ivosidenib and azacitidine in Study AG221-AML-005.<br><br>Revised the section on unblinding to clarify that the responsibility for breaking the treatment code in emergency situations resides solely with the Investigator and that rapid unblinding is possible when necessary.<br><br>Replaced "treatment failure" with "failure to achieve CR or CR with CRi (including CRp) at 24 weeks" for clarity.<br><br>Added secondary objectives of rate, duration, and time to CR + CRi (including CRp) to align with the revised definition of EFS, with corresponding endpoints and analyses.<br><br>Adjusted the timing of response assessments Week 9 and every eighth week thereafter (Weeks 17, 25, etc) to ensure response assessment after 24 weeks (6 months) of treatment. Quality of life assessments were aligned with response assessments from Week 9 onward.<br><br>Clarified the conditions under which subjects may continue to receive AG-120/placebo after discontinuing azacitidine to mitigate the potential for subjects without CR or CRi (including CRp) to continue on single-agent placebo. Subjects may continue to receive AG-120/placebo following discontinuation of azacitidine, provided they are in CR or CRi (including CRp) and need to discontinue azacitidine due to protocol-specified azacitidine-related toxicity (eg, delayed bone marrow recovery).<br><br>In response to FDA feedback, removed the attainment of a > 30% reduction in bone marrow blast count percentage as a potential indicator for continued treatment in subjects with a response less than CR or CRi (including CRp) at 24 weeks or beyond.<br><br>For consistency with the ivosidenib IB, Version 5.0, added that systemic administration of a moderate or strong CYP3A4 inhibitor requires careful QTcF monitoring and that subjects should be routinely monitored for rash.<br><br>Removed abstinence as an acceptable form of contraception. |
| Amendment 4, Version 5.0 (31 October 2017) Global | Allowed randomisation based on local IDH1 mutation testing (central testing is still required however, and blood and bone marrow samples must be received centrally prior to randomisation).<br><br>Clarified permitted pre-randomisation therapies for disease stabilisation.<br><br>Added an exclusion criterion for subjects taking medications that prolong the QT interval, with certain exceptions.<br><br>Allowed baseline exploratory biomarker samples to be collected as part of Pre-screening. |

| | |
|---|---|
| | Changed disease assessment schedule including: frequency of bone marrow aspirate collection, submission of bone marrow aspirate, and peripheral blood samples for exploratory biomarker analyses.<br><br>Added an ECG on Day 1 of each treatment cycle.<br><br>Added pregnancy testing for females of reproductive age on Day 1 of each cycle and at the end of treatment |
| Amendment 5, Version 6.0 (09 January 2020) | Changed the primary endpoint from OS to EFS and added OS to the key secondary endpoints, and updated the corresponding statistical analyses.<br><br>Updated the additional secondary endpoint evaluating IDH1 mutation clearance (MC) and the corresponding statistical analyses.<br><br>Updated the inclusion criterion to more narrowly define a population of patients who are ineligible for intensive IC, and aligned the associated liver and renal function criteria.<br><br>For consistency with the current edition of the ivosidenib IB, removed the criterion excluding subjects taking P-gp transporter sensitive substrate medications; added a criterion excluding subjects with a medical history of PML as PML is a potential risk of treatment with AG-120; and revised information on drug-drug interactions.<br><br>Removed the interim analyses for efficacy.<br><br>Reduced the number of subjects who will participate in this study from 392 to 200 based on updated sample size estimations, and increased the number of study centres and countries |
| Amendment 7, Version 8.0 (16 December 2020) | Added a section describing temporary protocol modifications to ensure subject safety, maintain compliance with GCP, and minimise risks to study integrity during a COVID-19 public health emergency.<br><br>Continued efficacy follow-up of subjects in the study for EFS after initiation of subsequent anticancer therapy for subjects who did not have an EFS event.<br><br>Incorporated a sensitivity analysis for the primary endpoint supporting the continued efficacy follow-up for EFS after initiation of subsequent anticancer therapy for subjects who did not have an EFS event |

Protocol deviations

A total of 74 (50.7%) subjects had a major deviation, with similar rates of subjects with major deviations reported in the ivosidenib + azacitidine (37 [51.4%] subjects) and placebo + azacitidine (37 [50.0%] subjects) arms.

Fifty (34.2%) subjects had an ICH/GCP deviation. Rates of subjects with ICH/GCP deviations were similar between the ivosidenib + azacitidine (27 [37.5%] subjects) and placebo + azacitidine (23 [31.1%] subjects) arms; most of these subjects (39 [26.7%]) had deviations related to informed consent.

Overall rates of subjects with other protocol deviations were also similar between the treatment arms (24 [33.3%] in the experimental arm and 25 [33.8%] in the control arm); the most common deviations were SAE reporting deviations and missed visits or assessments.

No protocol deviation was judged to have impacted the overall conduct of the study, data analyses, or study conclusions.

- **Baseline data**

Baseline demographic and disease characteristics are summarised in Table 17 and Table 18 respectively.

**Table 17.** Demographics of subjects in study AG120-C-009, Full analysis set

| | AG-120 + azacitidine (N=72) | Placebo + azacitidine (N=74) | Total (N=146) |
|---|---|---|---|
| **Age (years)** | | | |
| n | 72 | 74 | 146 |
| Mean (SD) | 74.5 (6.18) | 75.2 (7.39) | 74.8 (6.81) |
| Median (Q1, Q3) | 76.0 (70.5, 79.5) | 75.5 (70.0, 80.0) | 76.0 (70.0, 80.0) |
| Min, Max | 58, 84 | 45, 94 | 45, 94 |
| **Age Category I (years), n (%)** | | | |
| <65 | 4 (5.6) | 4 (5.4) | 8 (5.5) |
| ≥ 65 | 68 (94.4) | 70 (94.6) | 138 (94.5) |
| **Age Category II (years), n (%)** | | | |
| <75 | 33 (45.8) | 31 (41.9) | 64 (43.8) |
| ≥ 75 | 39 (54.2) | 43 (58.1) | 82 (56.2) |
| **Sex, n (%)** | | | |
| Male | 42 (58.3) | 38 (51.4) | 80 (54.8) |
| Female | 30 (41.7) | 36 (48.6) | 66 (45.2) |
| **Ethnicity, n (%)** | | | |
| Hispanic or Latino | 6 (8.3) | 1 (1.4) | 7 (4.8) |
| Not Hispanic or Latino | 21 (29.2) | 32 (43.2) | 53 (36.3) |
| Not Reported | 45 (62.5) | 41 (55.4) | 86 (58.9) |
| **Race, n (%)** | | | |
| Asian | 15 (20.8) | 19 (25.7) | 34 (23.3) |
| White | 12 (16.7) | 12 (16.2) | 24 (16.4) |
| Black or African American | 0 | 2 (2.7) | 2 (1.4) |
| Other | 1 (1.4) | 1 (1.4) | 2 (1.4) |
| Not Reported | 44 (61.1) | 40 (54.1) | 84 (57.5) |
| **Height (cm)** | | | |
| n | 71 | 74 | 145 |
| Mean (SD) | 166.84 (10.103) | 163.50 (9.422) | 165.14 (9.870) |
| Median (Q1, Q3) | 167.00 (158.00, 176.00) | 162.40 (156.00, 170.00) | 163.00 (158.00, 173.00) |
| Min, Max | 143.0, 188.0 | 145.0, 184.0 | 143.0, 188.0 |
| **Weight (kg)** | | | |
| n | 71 | 74 | 145 |
| Mean (SD) | 73.22 (12.005) | 69.20 (16.170) | 71.17 (14.376) |
| Median (Q1, Q3) | 73.00 (65.00, 78.90) | 65.35 (56.00, 81.40) | 69.00 (61.00, 80.00) |
| Min, Max | 34.0, 105.0 | 38.0, 116.0 | 34.0, 116.0 |
| **BMI ($kg/m^2$)** | | | |
| n | 71 | 74 | 145 |
| Mean (SD) | 26.36 (4.418) | 25.77 (5.034) | 26.06 (4.735) |
| Median (Q1, Q3) | 25.39 (23.41, 28.99) | 25.28 (22.44, 28.40) | 25.32 (23.07, 28.40) |
| Min, Max | 16.6, 42.0 | 16.4, 41.1 | 16.4, 42.0 |
| **BSA ($m^2$)** | | | |
| n | 71 | 73 | 144 |
| Mean (SD) | 1.824 (0.1738) | 1.745 (0.2210) | 1.784 (0.2023) |
| Median (Q1, Q3) | 1.830 (1.720, 1.940) | 1.710 (1.580, 1.880) | 1.770 (1.635, 1.930) |
| Min, Max | 1.17, 2.20 | 1.27, 2.36 | 1.17, 2.36 |

**Table 18.** Baseline disease characteristics of subjects in study AG120-C-009, Full analysis set

| | AG-120 + azacitidine (N=72) | Placebo + azacitidine (N=74) | Total (N=146) |
|---|---|---|---|
| Missing | 14 (19.4) | 13 (17.6) | 27 (18.5) |
| Cytogenetic risk status by Investigator, n(%) | | | |
| Favorable | 3 (4.2) | 7 (9.5) | 10 (6.8) |
| Intermediate | 48 (66.7) | 44 (59.5) | 92 (63.0) |
| Poor | 16 (22.2) | 20 (27.0) | 36 (24.7) |
| Other | 3 (4.2) | 1 (1.4) | 4 (2.7) |
| Missing | 2 (2.8) | 2 (2.7) | 4 (2.7) |
| **Bone marrow blasts (%) [1]** | | | |
| n | 71 | 73 | 144 |
| Mean (SD) | 55.2 (23.30) | 53.3 (23.45) | 54.2 (23.31) |
| Median (Q1, Q3) | 54.0 (32.0, 75.0) | 48.0 (33.0, 70.0) | 52.5 (32.5, 74.5) |
| Min, Max | 20, 95 | 17, 100 | 17, 100 |
| **Bone marrow aspirate blasts (%)** | | | |
| n | 71 | 72 | 143 |
| Mean (SD) | 55.2 (23.30) | 53.7 (23.37) | 54.4 (23.27) |
| Median (Q1, Q3) | 54.0 (32.0, 75.0) | 48.5 (33.5, 71.0) | 53.0 (33.0, 75.0) |
| Min, Max | 20, 95 | 17, 100 | 17, 100 |
| **Bone marrow biopsy blasts (%)** | | | |
| n | 7 | 13 | 20 |
| Mean (SD) | 56.9 (22.97) | 50.8 (24.14) | 53.0 (23.31) |
| Median (Q1, Q3) | 60.0 (40.0, 80.0) | 50.0 (30.0, 59.0) | 50.0 (32.5, 72.5) |
| Min, Max | 25, 88 | 20, 90 | 20, 90 |
| **Peripheral blood blasts (%)** | | | |
| n | 57 | 59 | 116 |
| Mean (SD) | 33.49 (31.344) | 28.14 (30.970) | 30.77 (31.135) |
| Median (Q1, Q3) | 23.00 (4.00, 61.40) | 15.00 (0.50, 50.00) | 20.00 (2.00, 54.85) |
| Min, Max | 0.0, 94.0 | 0.0, 98.0 | 0.0, 98.0 |
| **WBC ($10^9$/L) [2]** | | | |
| n | 72 | 74 | 146 |
| Mean (SD) | 6.971 (15.1384) | 9.421 (15.9593) | 8.213 (15.5548) |
| Median (Q1, Q3) | 2.055 (1.300, 7.165) | 2.315 (1.340, 7.260) | 2.245 (1.300, 7.260) |
| Min, Max | 0.42, 118.40 | 0.50, 83.58 | 0.42, 118.40 |
| **WBC category ($10^9$/L), n(%)** | | | |
| < 15 | 65 (90.3) | 60 (81.1) | 125 (85.6) |
| 15 - < 30 | 4 (5.6) | 5 (6.8) | 9 (6.2) |
| ≥ 30 | 3 (4.2) | 9 (12.2) | 12 (8.2) |

| | AG-120 + azacitidine (N=72) | Placebo + azacitidine (N=74) | Total (N=146) |
|---|---|---|---|
| **ANC ($10^9$/L) [3]** | | | |
| n | 70 | 71 | 141 |
| Mean (SD) | 0.983 (2.2419) | 1.491 (3.6897) | 1.239 (3.0576) |
| Median (Q1, Q3) | 0.210 (0.060, 0.630) | 0.224 (0.090, 0.970) | 0.210 (0.090, 0.780) |
| Min, Max | 0.00, 12.90 | 0.00, 23.73 | 0.00, 23.73 |
| **ANC category ($10^9$/L), n(%)** | | | |
| < 0.5 | 49 (68.1) | 44 (59.5) | 93 (63.7) |
| 0.5 - < 1 | 8 (11.1) | 10 (13.5) | 18 (12.3) |
| ≥ 1 | 13 (18.1) | 17 (23.0) | 30 (20.5) |
| Missing | 2 (2.8) | 3 (4.1) | 5 (3.4) |
| **Hemoglobin (g/L)** | | | |
| n | 72 | 74 | 146 |
| Mean (SD) | 88.63 (14.924) | 91.96 (15.419) | 90.32 (15.216) |
| Median (Q1, Q3) | 87.00 (79.10, 99.50) | 90.00 (82.00, 101.00) | 89.00 (80.00, 100.00) |
| Min, Max | 59.0, 131.0 | 63.0, 143.0 | 59.0, 143.0 |
| **Hemoglobin category (g/L), n(%)** | | | |
| < 80 | 19 (26.4) | 14 (18.9) | 33 (22.6) |
| ≥ 80 | 53 (73.6) | 60 (81.1) | 113 (77.4) |
| **Platelet count ($10^9$/L)** | | | |
| n | 72 | 74 | 146 |
| Mean (SD) | 71.511 (86.4417) | 92.656 (100.7111) | 82.228 (94.2213) |
| Median (Q1, Q3) | 39.000 (21.000, 95.500) | 68.000 (32.000, 129.000) | 56.800 (22.000, 108.000) |
| Min, Max | 2.00, 583.00 | 9.00, 646.00 | 2.00, 646.00 |
| **Platelet count category ($10^9$/L), n(%)** | | | |
| < 50 | 42 (58.3) | 27 (36.5) | 69 (47.3) |
| 50 - < 100 | 14 (19.4) | 20 (27.0) | 34 (23.3) |
| ≥ 100 | 16 (22.2) | 27 (36.5) | 43 (29.5) |
| **Lactate dehydrogenase (LDH) (U/L)** | | | |
| n | 72 | 73 | 145 |
| Mean (SD) | 328.67 (214.486) | 356.15 (239.976) | 342.50 (227.303) |
| Median (Q1, Q3) | 264.50 (203.00, 405.50) | 301.00 (188.00, 421.00) | 272.00 (189.00, 416.00) |
| Min, Max | 116.0, 1320.0 | 65.0, 1397.0 | 65.0, 1397.0 |

| | AG-120 + azacitidine (N=72) | Placebo + azacitidine (N=74) | Total (N=146) |
|---|---|---|---|
| **Creatinine clearance (mL/min) [4]** | | | |
| n | 71 | 74 | 145 |
| Mean (SD) | 75.91 (27.424) | 69.45 (23.807) | 72.61 (25.757) |
| Median (Q1, Q3) | 71.84 (58.39, 91.11) | 67.17 (54.05, 80.81) | 69.92 (55.57, 85.09) |
| Min, Max | 26.9, 174.1 | 24.8, 140.4 | 24.8, 174.1 |
| **Creatinine clearance category I (mL/min), n(%)** | | | |
| 15 - < 40 | 4 (5.6) | 7 (9.5) | 11 (7.5) |
| 40 - < 60 | 18 (25.0) | 20 (27.0) | 38 (26.0) |
| 60 - < 90 | 30 (41.7) | 34 (45.9) | 64 (43.8) |
| ≥ 90 | 19 (26.4) | 13 (17.6) | 32 (21.9) |
| Missing | 1 (1.4) | 0 | 1 (0.7) |
| **Creatinine clearance category II (mL/min), n(%)** | | | |
| <30 | 2 (2.8) | 3 (4.1) | 5 (3.4) |
| 30 - < 45 | 3 (4.2) | 7 (9.5) | 10 (6.8) |
| ≥ 45 | 66 (91.7) | 64 (86.5) | 130 (89.0) |
| Missing | 1 (1.4) | 0 | 1 (0.7) |
| **Extramedullary disease, n(%)** | | | |
| Yes | 4 (5.6) | 2 (2.7) | 6 (4.1) |
| No | 59 (81.9) | 65 (87.8) | 124 (84.9) |
| Unknown | 5 (6.9) | 6 (8.1) | 11 (7.5) |
| Not Assessed | 4 (5.6) | 1 (1.4) | 5 (3.4) |

Source: Table 14.1-6.1; Listing 16.1-6.1. Data cutoff date: 18 March 2021
Abbreviations: AML = acute myeloid leukemia; ECOG = Eastern Cooperative Oncology Group; FAS = full analysis set; IDH1 =Isocitrate dehydrogenase 1; IWRS = Interactive Web Response System; MDS = Myelodysplastic syndrome; MPD = myeloproliferative disease; SD = standard deviation
The denominator used to calculate percentages is N, the number of subjects in the full analysis set within each column.
[1] For bone marrow blasts, bone marrow aspirate will be used as the primary source. If a bone marrow aspirate assessment is not available, a bone marrow biopsy assessment will be used.
[2] WBC: White blood cell.
[3] ANC: Absolute neutrophil count.
[4] Creatinine Clearance (mL/min) = (140 - age)x baseline weight (kg)x (0.85 if female)/ (72xbaseline serum creatinine [mg/dL]).
[5] IDH1 mutation for these subjects was confirmed with local testing.
[6] IDH1 mutation for these subjects was confirmed with central testing.

Baseline demographics were generally similar for subjects enrolled before and after Protocol Amendment 5 (data not shown). In the overall subject population, the proportion of male subjects (56.0% and 52.7%, respectively) and the proportion of subjects over the age of 75 years (53.8% and 60.0%) were similar among subjects enrolled before and after Protocol Amendment 5, respectively. The proportion of subjects enrolled in Western Europe, Israel, and Australia was somewhat higher before versus after Protocol Amendment 5 (70.3% and 52.7%, respectively); this was due to the change of the number of active sites globally during the evolution of the study.

Baseline disease characteristics were also generally similar for subjects enrolled before and after Protocol Amendment 5 (data not shown). The majority of subjects had de novo AML at initial diagnosis both before Protocol Amendment 5 (70.3% per Investigator and 74.7% per IWRS) and after Protocol

Amendment 5 (78.2% per Investigator and 78.2% per IWRS). Per the WHO classification of AML, among subjects enrolled before and after Protocol Amendment 5, respectively, 22.0% and 36.4% of subjects had AML with genetic abnormalities, 38.5% and 34.5% had AML with myelodysplasia-related changes, and 38.5% and 27.3% had AML not otherwise specified. Approximately one third of subjects had an ECOG PS of 2 (33.0% and 36.4% of subjects, respectively). Cytogenetic risk status as assessed by the Investigators based on the 2017 NCCN guidelines was intermediate (63.7% and 61.8% of subjects enrolled before and after Protocol Amendment 5, respectively) or poor (26.4% and 21.8%, respectively) for most subjects at baseline. Most subjects did not have extramedullary disease (84.6% and 85.5% of subjects enrolled before and after Protocol Amendment 5, respectively).

- **Numbers analysed**

As of the 18 March 2021 data cut-off, 146 subjects have been randomised. The study is ongoing. The following data sets were analysed:

- 146 subjects were included in the FAS (all randomised subjects)
    - 141 (96.6%) subjects were included in the per-protocol set (PPS), a subset of the FAS Subjects who meet any of the following criteria will be excluded from the PPS:
        - Do not receive at least 1 dose of the randomised treatment
        - Eligible for intensive chemotherapy (IC)
        - Do not have an IDH1 mutation as determined by central laboratory testing
        - Have an ECOG PS score >2
        - Have received any prior treatment for AML with the exception of non-oncolytic treatments to stabilise disease such as hydroxyurea or leukapheresis
        - Have received any prior hypomethylating agent
        - Have received any prior IDH1 inhibitor
    - 77 (52.7%) subjects were included in the Biomarker Analysis Set, a subset of the safety analysis set that includes all subjects who have at least 1 on-treatment biomarker sample providing valid IDH1m variant allele frequency (VAF) data.
- 144 subjects were included in the Safety Analysis Set (SAS): all subjects who received at least 1 dose of study treatment (71 in the ivosidenib/azacytidine arm and 73 in the placebo/azacitidine arm).

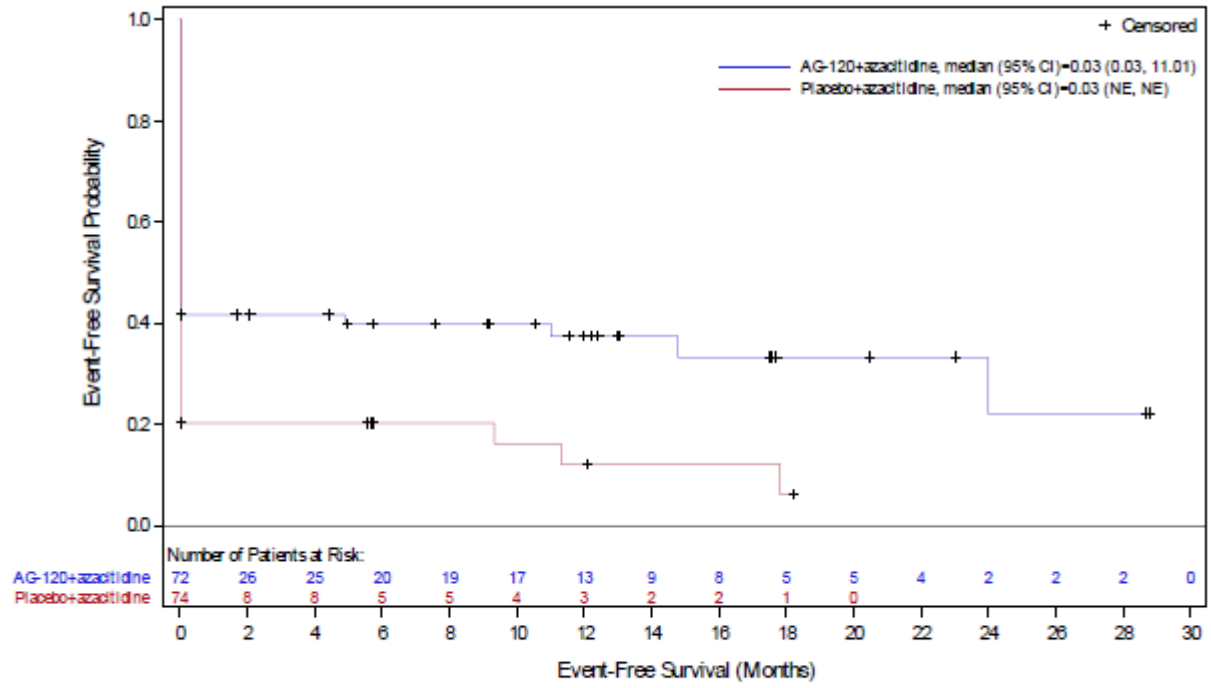
- **Outcomes and estimation**

Event-free Survival (EFS)

**Table 19.** Summary of event-free survival in study AG120-C-009, Full analysis set

| | AG-120 + azacitidine (N=72) | Placebo + azacitidine (N=74) |
|---|---|---|
| **Event-free survival(months) [1]** | | |
| Number (%) of Events | 46 (63.9) | 62 (83.8) |
| Treatment failure | 42 (58.3) | 59 (79.7) |
| TF, on treatment >24 weeks without CR | 16 (22.2) | 11 (14.9) |
| TF, treatment discontinuation ≤ 24 weeks without CR | 26 (36.1) | 48 (64.9) |
| Relapse | 3 (4.2) | 2 (2.7) |
| Death | 1 (1.4) | 1 (1.4) |
| Number (%) Censored [2] | 26 (36.1) | 12 (16.2) |
| CR by 24 weeks, start subsequent anticancer therapy | 1 (1.4) | 0 |
| CR by 24 weeks, relapse/death documented after 2 or more missing disease assessments | 0 | 0 |
| CR by 24 weeks, lost to follow-up | 0 | 0 |
| CR by 24 weeks, withdrawal by subject | 2 (2.8) | 0 |
| CR by 24 weeks, ongoing without relapse or death | 20 (27.8) | 5 (6.8) |
| On treatment ≤ 24 weeks, ongoing, have not achieved CR yet | 3 (4.2) | 7 (9.5) |
| Percentiles (95% CI) [3] | | |
| 25th | 0.03 (NE, NE) | 0.03 (NE, NE) |
| 50th (median) | 0.03 (0.03, 11.01) | 0.03 (NE, NE) |
| 75th | 23.98 (14.78, NE) | 0.03 (0.03, 11.30) |
| Hazard Ratio (95% CI) [4] | | 0.33 (0.16, 0.69) |
| 1-sided p-value [5] | | 0.0011 |
| **Event-free survival rate (%) (95% CI) [6]** | | |
| 1 Day | 41.7 (30.2, 52.7) | 20.3 (12.0, 30.0) |
| 3 Months | 41.7 (30.2, 52.7) | 20.3 (12.0, 30.0) |
| 6 Months | 39.9 (28.6, 51.0) | 20.3 (12.0, 30.0) |
| 9 Months | 39.9 (28.6, 51.0) | 20.3 (12.0, 30.0) |
| 12 Months | 37.4 (25.9, 48.9) | 12.2 (4.3, 24.4) |
| 18 Months | 33.3 (20.9, 46.2) | 6.1 (0.7, 20.9) |
| 24 Months | 22.2 (6.6, 43.4) | NE |
| 36 Months | NE | NE |

**Figure 13.** Kaplan-Meier plot of event-free survival in study AG120-C-009, full analysis set




Source: Figure 14.2.1-1.1; Listing 16.2.1-1.1; Data cutoff date: 18 March 2021
Abbreviations: CI = confidence interval; NE = not estimable

Complete Remission

**Table 20.** Summary of complete remission rate in the FAS

| | AG-120 + azacitidine (N=72) | Placebo+azacitidine (N=74) |
|---|---|---|
| **CR Rate, n (%)** | 34 ( 47.2) | 11 ( 14.9) |
| 95% CI [1] | (35.3, 59.3) | (7.7, 25.0) |
| Odds Ratio (95% CI) [2] | | 4.76 (2.15, 10.50) |
| 1-sided p-value [3] | | <0.0001 |

Source: Table 14.2.1-2.3a, Listing 16.2.1-2.3. Data cutoff date: 18 March 2021
Abbreviations: CR = complete remission
[1] CI: confidence interval. CI of percentage is calculated with the Clopper and Pearson (exact Binomial) method.
[2] Cochran-Mantel-Haenszel (CMH) estimate for odds ratio is calculated with placebo + azacitidine as the control (denominator). CI: confidence interval.
[3] If the primary analysis of EFS is significant, a stratified Cochran-Mantel-Haenszel (CMH) test will be used to compare CR between the 2 treatment arms. 1-sided p-value is calculated from CMH test stratified by the randomization stratification factors (AML status and geographic region).

Overall Survival

The tables below present the summary of OS and OS follow-up time in the FAS, along with the OS KM plot.

**Table 21.** Summary of overall survival in study AG120-C-009, Full analysis set

| | AG-120 + azacitidine (N=72) | Placebo + azacitidine (N=74) |
|---|---|---|
| **Overall Survival (months)** | | |
| Number (%) of Events | 28 (38.9) | 46 (62.2) |
| Number (%) Censored | 44 (61.1) | 28 (37.8) |
| Alive | 38 (52.8) | 23 (31.1) |
| Lost to Follow-up | 0 | 1 (1.4) |
| Withdrawal of consent | 6 (8.3) | 4 (5.4) |
| Percentiles (95% CI) [1] | | |
| 25th | 5.7 (2.1, 11.3) | 2.0 (1.1, 3.1) |
| 50th (median) | 24.0 (11.3, 34.1) | 7.9 (4.1, 11.3) |
| 75th | 34.1 (NE, NE) | 18.1 (11.3, NE) |
| Hazard Ratio (95% CI) [2] | | 0.44 (0.27, 0.73) |
| 1-sided p-value [3] | | 0.0005 |
| **Overall Survival Rate (%) (95% CI) [4]** | | |
| 3 Months | 84.2 (73.3, 91.0) | 66.6 (54.4, 76.2) |
| 6 Months | 72.9 (60.4, 82.0) | 56.3 (43.6, 67.3) |
| 9 Months | 67.5 (54.4, 77.6) | 43.9 (30.9, 56.1) |
| 12 Months | 63.4 (49.8, 74.2) | 36.9 (24.3, 49.7) |
| 18 Months | 60.9 (47.1, 72.2) | 26.4 (14.7, 39.6) |
| 24 Months | 45.4 (26.8, 62.2) | 20.5 (10.0, 33.7) |
| 36 Months | 0 | NE |

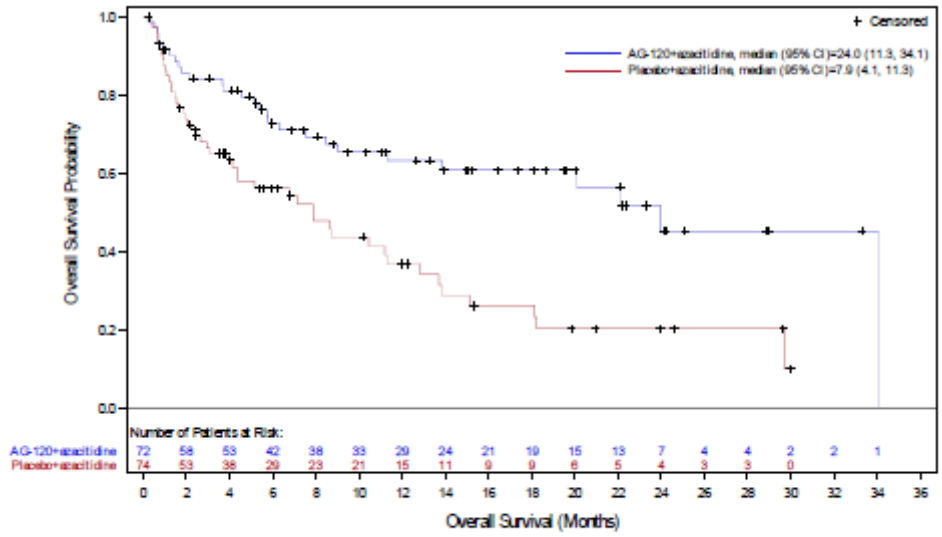
Source: Table 14.2.1-2.1; Listing 16.2.1-2.1. Data cutoff date: 18 March 2021
Abbreviations: CI = confidence interval; NE = not estimable
Percentages are calculated with the number of subjects in each column as the denominator.
[1] Percentiles are estimated from product-limit (Kaplan-Meier) method. Confidence intervals are calculated from Brookmeyer and Crowley method with log-log transformation.
[2] Hazard ratio is estimated using a Cox's proportional hazards model stratified by the randomization stratification factors (AML status and geographic region) with placebo + azacitidine as the denominator.
[3] P-value is calculated from the one-sided log-rank test stratified by the randomization stratification factors (AML status and geographic region).
[4] Overall survival rate is the estimated probability that a subject will remain alive to the specified time point. Overall survival rates are obtained from the Kaplan-Meier survival estimates. Confidence intervals are calculated using Greenwood's formula and log-log transformation.

**Table 22.** Summary of overall survival follow-up time in the FAS

| | AG-120 + azacitidine (N=72) | Placebo + azacitidine (N=74) |
|---|---|---|
| **Overall Survival Follow-up Time (months) [1]** | | |
| 25th Percentile (95% CI) [2] | 8.1 (4.9, 11.2) | 5.4 (3.5, 10.2) |
| Median (95% CI) | 15.2 (11.2, 19.6) | 15.3 (6.8, 24.0) |
| 75th Percentile (95% CI) | 22.3 (19.5, 25.1) | 24.6 (19.8, 30.0) |
| Min, Max | 0.2, 34.1 | 0.3, 30.0 |

Source: Table 14.2.1-2.2; Listing 16.2.1-2.1. Data cutoff date: 18 March 2021
Abbreviation: CI = confidence interval
[1] Overall Survival Follow-up Time is estimated based on reverse Kaplan-Meier method.
[2] Percentiles are estimated from product-limit (Kaplan-Meier) method. Confidence intervals are calculated from Brookmeyer and Crowley method with log-log transformation.

**Figure 14.** Kaplan-Meier plot of overall survival in study AG120-C-009, Full analysis set




Source: Figure 14.2.1-2.1, Listing 16.2.1-2.1. Data cutoff date: 18 March 2021

CR+CRh

**Table 23.** Summary of CR+CRh rates (FAS)

| | AG-120 + azacitidine (N=72) | Placebo + azacitidine (N=74) |
|---|---|---|
| **CR+CRh Rate, n (%) [1]** | 38 (52.8) | 13 (17.6) |
| 95% CI [2] | (40.7, 64.7) | (9.7, 28.2) |
| Odds Ratio (95% CI) [3] | | 5.01 (2.32, 10.81) |
| 1-sided p-value [4] | | <0.0001 |

Source: Table 14.2.1-2.3a; Listing 16.2.1-2.3. Data cutoff date: 18 March 2021

Abbreviations: CI = confidence interval; CR = complete remission; CRh = complete remission with partial hematologic recovery

[1] CRh is defined as a CR with partial hematologic recovery and is derived.

[2] CI: confidence interval. CI of percentage is calculated with the Clopper and Pearson (exact Binomial) method.

[3] Cochran-Mantel-Haenszel (CMH) estimate for odds ratio is calculated with placebo + azacitidine as the control (denominator). CI: confidence interval.

[4] If the primary analyses of EFS, CR and OS are significant, a stratified Cochran-Mantel-Haenszel (CMH) test will be used to compare CR+CRh between the 2 treatment arms. 1-sided p-value is calculated from CMH test stratified by the randomization stratification factors (AML status and geographic region).

ORR

**Table 24.** Summary of ORR in study AG120-C-009, Full analysis set

| | AG-120 + azacitidine (N=72) | Placebo + azacitidine (N=74) |
|---|---|---|
| **OR Rate, n (%)** | 45 (62.5) | 14 (18.9) |
| 95% CI [1] | (50.3, 73.6) | (10.7, 29.7) |
| Odds Ratio (95% CI) [2] | | 7.15 (3.31, 15.44) |
| 1-sided p-value [3] | | <0.0001 |

Source: Table 14.2.1-2.3a; Listing 16.2.1-2.3. Data cutoff date: 18 March 2021
[1] CI: confidence interval. CI of percentage is calculated with the Clopper and Pearson (exact Binomial) method.
[2] Cochran-Mantel-Haenszel (CMH) estimate for odds ratio is calculated with placebo + azacitidine as the control (denominator). CI: confidence interval.
[3] If the primary analyses of EFS, CR, OS and CR+CRh are significant, a stratified Cochran-Mantel-Haenszel (CMH) test will be used to compare ORR between the 2 treatment arms. 1-sided p-value is calculated from CMH test stratified by the randomization stratification factors (AML status and geographic region).

CR + CRi

The CR + CRi parameters are presented in the table below.

**Table 25.** Summary of CR+CRi rate in study AG120-C-009, Full analysis set

| | AG-120 + azacitidine (N=72) | Placebo + azacitidine (N=74) |
|---|---|---|
| **CR+CRi Rate, n (%)** | 39 (54.2) | 12 (16.2) |
| 95% CI [1] | (42.0, 66.0) | (8.7, 26.6) |
| Odds Ratio (95% CI) [2] | | 5.90 (2.69, 12.97) |
| 1-sided p-value [3] | | <0.0001 |

Source: Table 14.2.1-2.3a; Listing 16.2.1-2.3. Data cutoff date: 18 March 2021
Abbreviations: CI = confidence interval; NE = not estimable
[1] CI: confidence interval. CI of percentage is calculated with the Clopper and Pearson (exact Binomial) method.
[2] Cochran-Mantel-Haenszel (CMH) estimate for odds ratio is calculated with placebo + azacitidine as the control (denominator). CI: confidence interval.
[3] 1-sided p-value is calculated from CMH test stratified by the randomization stratification factors (AML status and geographic region).

Duration of Response

*DOCR*

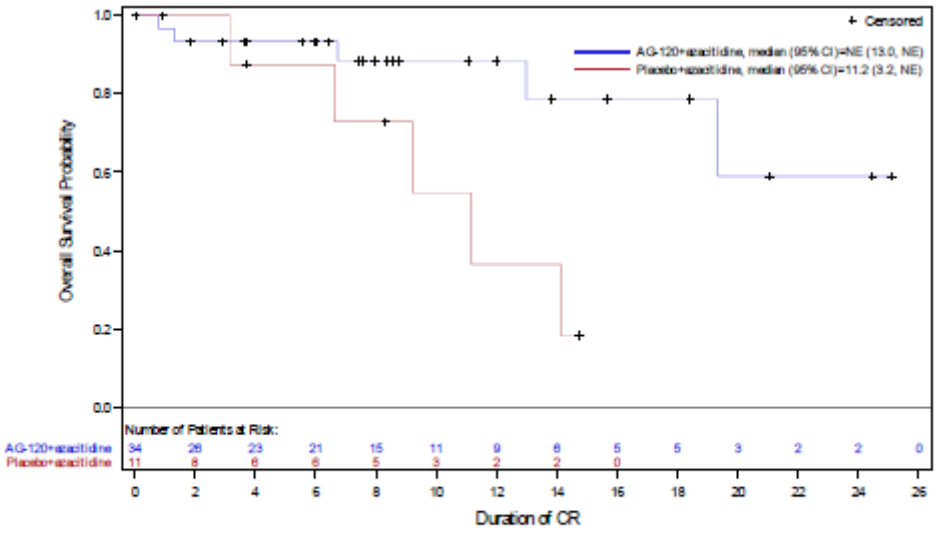
Duration of complete remission (DOCR) is summarised in the table below. The corresponding KM plot of DOCR is also provided.

**Table 26.** Summary of Duration of Complete Remission (DOCR) in study AG120-C-009, Full analysis set

| | AG-120 + azacitidine (N=72) | Placebo + azacitidine (N=74) |
|---|---|---|
| **Number of Subjects who achieved CR** | 34 | 11 |
| **Duration of CR (months) [1]** | | |
| Number (%) of Events | 5 (14.7) | 5 (45.5) |
| Number (%) Censored | 29 (85.3) | 6 (54.5) |
| Start subsequent anticancer therapy | 2 (5.9) | 0 |
| Relapse/death documented after 2 or more missing disease assessments | 0 | 0 |
| Lost to Follow-up | 0 | 0 |
| Withdrawal by subject | 2 (5.9) | 0 |
| Ongoing without relapse or death | 25 (73.5) | 6 (54.5) |
| Percentiles (95% CI) [2] | | |
| 25th | 19.4 (6.7, NE) | 6.6 (3.2, 11.2) |
| 50th (median) | NE (13.0, NE) | 11.2 (3.2, NE) |
| 75th | NE (19.4, NE) | 14.1 (9.2, NE) |
| **Duration of CR Rate (%) (95% CI) [3]** | | |
| 3 Months | 93.3 (75.9, 98.3) | 100 |
| 6 Months | 93.3 (75.9, 98.3) | 87.5 (38.7, 98.1) |
| 9 Months | 88.4 (67.5, 96.2) | 72.9 (27.6, 92.5) |
| 12 Months | 88.4 (67.5, 96.2) | 36.5 (5.3, 70.6) |
| 18 Months | 78.6 (47.5, 92.5) | NE |
| 24 Months | 58.9 (17.7, 85.1) | NE |
| 36 Months | NE | NE |

Source: Table 14.2.1-3.1a; Listing 16.2.1-3.1. Data cutoff date: 18 March 2021
Abbreviations: CI = confidence interval; CR = complete remission; NE = not estimable
Percentages are calculated with the number of subjects who achieved CR in each column as the denominator.
[1] Duration of CR is defined, for subjects who achieved CR, as the time from the first occurrence of CR to confirmed relapse or death due to any cause. DOCR (months)=(Date of event or censoring – first date of CR + 1)/30.4375.
[2] Percentiles are estimated from product-limit (Kaplan-Meier) method. Confidence intervals are calculated from Brookmeyer and Crowley method with log-log transformation.
[3] Duration of CR rate is the estimated probability that a subject will remain CR up to the specified time point. Duration of CR rates are obtained from the Kaplan-Meier survival estimates. Confidence intervals are calculated using Greenwood's formula and log-log transformation.

**Figure 15.** Kaplan-Meier plot of duration of complete remission (DOCR) in study AG120-C-009, Full analysis set




Source: Figure 14.2.1-3.1; Listing 16.2.1-3.1. Data cutoff date: 18 March 2021
Abbreviations: CR = Complete remission; DOCR = duration of complete remission
DOCR was defined, for subjects who achieved CR, as the time from the first occurrence of CR to confirmed relapse or death due to any cause.

Time to Response

Time to response, defined as TTCR, TTCRh and TTCRi, is reported in the table below.

**Table 27.** Summary of Time to CR, CR + CRh, First Response and CR + CRi (TTCR, TTCRh, TTR, TTCRi) in study AG120-C-009, Full analysis set

| | AG-120 + azacitidine (N=72) | Placebo + azacitidine (N=74) |
|---|---|---|
| **Time to CR (months) [1]** | | |
| n | 34 | 11 |
| Mean (SD) | 4.53 (1.934) | 4.76 (2.294) |
| Median | 4.25 | 3.81 |
| Min, Max | 1.7, 9.2 | 1.9, 8.5 |
| **Time to CR + CRh (months) [2]** | | |
| n | 38 | 13 |
| Mean (SD) | 4.11 (1.889) | 4.22 (1.548) |
| Median | 4.02 | 3.91 |
| Min, Max | 1.7, 8.6 | 1.9, 7.2 |
| **Time to first response (months) [3]** | | |
| n | 45 | 14 |
| Mean (SD) | 2.77 (1.320) | 3.86 (1.985) |
| Median | 2.07 | 3.68 |
| Min, Max | 1.7, 7.5 | 1.9, 9.4 |
| **Time to CR + CRi (months) [4]** | | |
| n | 39 | 12 |
| Mean (SD) | 3.36 (1.569) | 3.95 (1.483) |
| Median | 2.79 | 3.76 |
| Min, Max | 1.7, 7.2 | 1.9, 7.2 |

Source: Table 14.2.1-3.5a; Listing 16.2.1-3.1; Listing 16.2.1-3.2;Listing 16.2.1-3.3;Listing 16.2.1-3.4. Data cutoff date: 18 March 2021

Abbreviations: CI = confidence interval; CR = complete remission; CRh = complete remission with partial hematologic recovery; CRi = complete remission with incomplete recovery; NE = not estimable

[1] Time to CR is defined, for subjects who achieved CR, as the time from randomization to first occurrence of CR. TTCR (months)=(first date of CR - date of randomization + 1)/30.4375.

[2] Time to CR+CRh is defined, for subjects who achieved CR or CRh, as the time from randomization to first occurrence of CR or CRh. TTCRh (months)=(first date of CR or CRh - date of randomization + 1)/30.4375.

[3] Time to first response is defined, for subjects who achieved CR, CRi(including CRp), PR or MLFS, as the time from randomization to first occurrence of CR, CRi(including CRp), PR or MLFS. TTR (months)=(first date of CR, CRi(including CRp), PR or MLFS - date of randomization + 1)/30.4375.

[4] Time to CR+CRi is defined, for subjects who achieved CR or CRi(including CRp), as the time from randomization to first occurrence of CR or CRi(including CRp). TTCR (months)=(first date of CR or CRi(including CRp) - date of randomization + 1)/30.4375.

Health-related Quality of Life Assessments

**Table 28.** Summary of EORTC QLQ-C30 Global Health Status/QoL and Fatigue Score Change from Baseline in study AG120-C-009, Full analysis set

| Visit | Ivosidenib + Azacitidine Arm Least Square Mean (95% CI) | Placebo + Azacitidine Arm Least Square Mean (95% CI) | Difference of Least Square Mean (95% CI) | p-value [1] |
|---|---|---|---|---|
| **Global Health Status/QoL (Higher score indicates better status/HRQoL)** | | | | |
| C1D15 | -8.0 (-16.41, 0.37) | -10.4 (-18.78, -1.93) | 2.3 (-5.50, 10.18) | 0.5580 |
| C2D1 | 1.3 (-7.24, 9.90) | -8.9 (-17.37, -0.46) | 10.2 (2.21, 18.27) | 0.0126 |
| C2D15 | -4.8 (-13.50, 3.97) | -14.8 (-23.75, -5.89) | 10.1 (1.43, 18.69) | 0.0225 |
| C3D1 | 4.1 (-4.55, 12.80) | -3.5 (-12.72, 5.66) | 7.7 (-1.14, 16.45) | 0.0879 |
| C5D1 | 11.4 (2.43, 20.36) | 4.5 (-5.38, 14.41) | 6.9 (-2.88, 16.64) | 0.1664 |
| C7D1 | 10.6 (1.23, 19.97) | -2.0 (-12.80, 8.84) | 12.6 (1.51, 23.65) | 0.0261 |
| C9D1 | 15.5 (5.71, 25.32) | -7.1 (-18.48, 4.36) | 22.6 (10.59, 34.57) | 0.0002 |
| C11D1 | 12.3 (2.29, 22.22) | 4.5 (-8.14, 17.08) | 7.8 (-5.51, 21.09) | 0.2505 |
| C13D1 | 19.1 (8.51, 29.72) | 4.2 (-11.94, 20.28) | 14.9 (-2.09, 31.97) | 0.0854 |
| C15D1 | 15.0 (4.53, 25.48) | -0.4 (-16.53, 15.72) | 15.4 (-1.52, 32.34) | 0.0744 |
| C17D1 | 4.1 (-7.24, 15.45) | 2.5 (-17.34, 22.26) | 1.6 (-19.27, 22.57) | 0.8772 |
| C19D1 | 18.5 (6.29, 30.64) | -0.7 (-24.31, 22.89) | 19.2 (-5.77, 44.12) | 0.1316 |

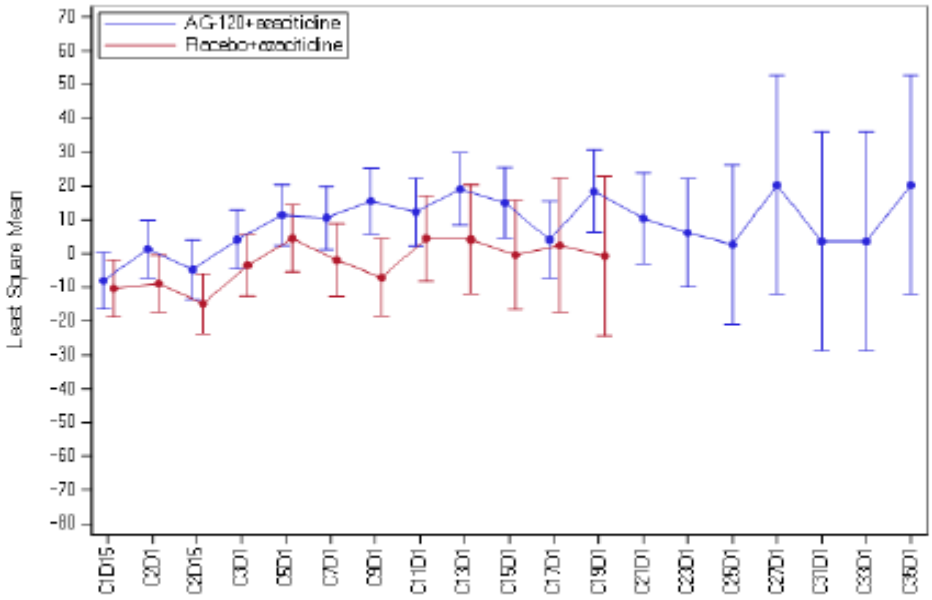
| Visit | Ivosidenib + Azacitidine Arm Least Square Mean (95% CI) | Placebo + Azacitidine Arm Least Square Mean (95% CI) | Difference of Least Square Mean (95% CI) | p-value [1] |
|---|---|---|---|---|
| **Fatigue (Higher score indicates worse symptoms/HRQoL)** | | | | |
| C1D15 | 7.8 (-1.66, 17.26) | 10.6 (1.21, 20.03) | -2.8 (-11.68, 6.04) | 0.5319 |
| C2D1 | 5.4 (-4.21, 15.11) | 9.5 (0.06, 18.92) | -4.0 (-13.11, 5.04) | 0.3824 |
| C2D15 | 8.6 (-1.20, 18.49) | 16.1 (6.13, 26.10) | -7.5 (-17.23, 2.29) | 0.1332 |
| C3D1 | 0.5 (-9.31, 10.26) | 2.9 (-7.36, 13.19) | -2.4 (-12.40, 7.52) | 0.6301 |
| C5D1 | -9.9 (-19.97, 0.27) | -1.8 (-12.92, 9.28) | -8.0 (-19.09, 3.03) | 0.1543 |
| C7D1 | -13.9 (-24.45, -3.28) | -1.2 (-13.38, 11.00) | -12.7 (-25.24, -0.10) | 0.0482 |
| C9D1 | -12.8 (-23.91, -1.75) | 2.2 (-10.69, 15.04) | -15.0 (-28.63, -1.38) | 0.0309 |
| C11D1 | -11.8 (-23.04, -0.50) | -0.7 (-14.94, 13.55) | -11.1 (-26.19, 4.04) | 0.1506 |
| C13D1 | -18.3 (-30.29, -6.28) | 5.9 (-12.40, 24.13) | -24.1 (-43.54, -4.76) | 0.0147 |
| C15D1 | -13.2 (-25.03, -1.32) | -0.1 (-18.41, 18.17) | -13.1 (-32.33, 6.23) | 0.1842 |
| C17D1 | -11.1 (-23.98, 1.73) | -3.4 (-25.93, 19.08) | -7.7 (-31.54, 16.15) | 0.5264 |
| C19D1 | -12.4 (-26.22, 1.40) | 0.7 (-26.13, 27.58) | -13.1 (-41.57, 15.29) | 0.3646 |

Source: Table 14.2.1-4.2; Listing 16.2.1-4.1. Data cutoff date: 18 March 2021

Abbreviations: C1D# = Cycle 1, Day #; FAS = full analysis set [1] Two-sided nominal p-value is reported. P-values were not adjusted for multiplicity.

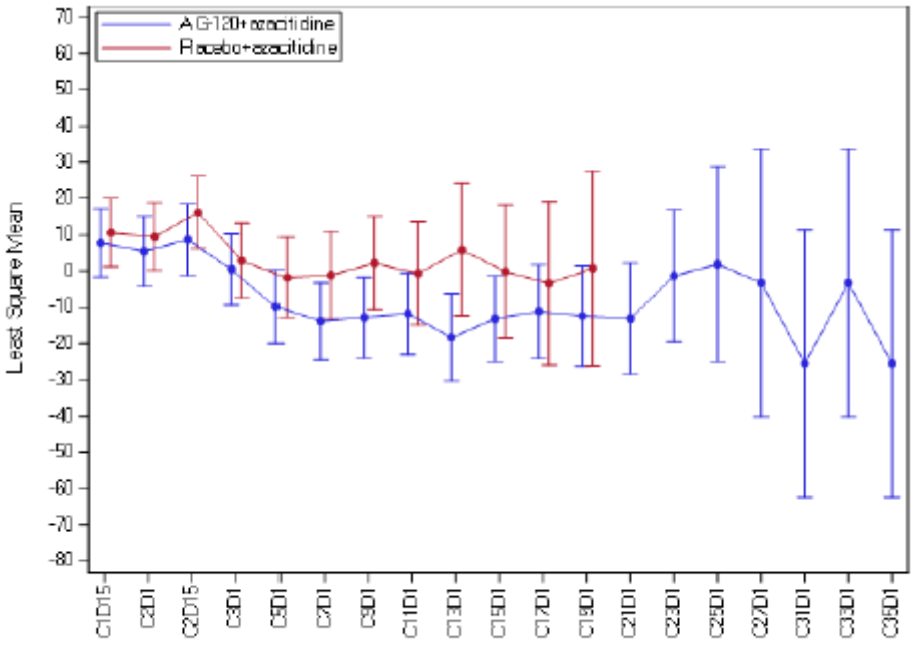
The least square mean and 95% CI are estimated from the mixed effect model on the change from baseline across visits for all scales with baseline score, treatment arm, time, randomization stratification factors (AML status and geographic region) and an interaction between treatment arm and time as fixed effect, and subject as random effects. The unstructured covariance structure is used to define covariance between random effects. Unscheduled visits are excluded from the analysis.

**Figure 16.** Least square means for global health status/QoL over time in study AG120-C-009, Full analysis set




Source: Figure 14.2.1-4.1; Table 14.2.1-4.2. Data cutoff date: 18 March 2021

**Figure 17.** Least square means for fatigue over time, in study AG120-C-009, full analysis set




Source: Figure 14.2.1-4.1; Table 14.2.1-4.2. Data cutoff date: 18 March 2021

Follow-up medications and procedures

*Subsequent stem cell transplants for AML*

Four (5.6%) subjects in the ivosidenib + azacitidine arm (N=71) and 1 (1.4%) subject in the placebo + azacitidine arm (N=73) had an allogeneic HSCT.

- **Ancillary analyses**

Lan-DeMets O'Brien-Fleming boundaries considering all past IDMC meetings as additional interim analyses

At the time of the final analysis and to account for the IDMC's unplanned analysis and subsequent recommendation to stop enrolment in the study, the p-value boundaries for the primary and key secondary efficacy endpoints were adjusted. Specifically, the O'Brien-Fleming alpha spending function (the Lan and DeMets method) was used for each of the primary and key secondary efficacy endpoints (O'Brien and Fleming, 1979; Lan and DeMets, 1983). For the final analyses, for each of the primary and key secondary endpoints, the p-values were calculated based on the methodologies specified in the SAP (version 1.0 dated 22 June 2020) and they were compared to these adjusted p-value boundaries.

At the request of the CHMP, the Lan-DeMets O'Brien-Fleming boundaries were updated to account for all past IDMC meetings as additional interim analyses in the sequence of tests. The 1-sided p-value boundaries calculated as a result of this update are provided in Table 33.

**Table 29.** Original and updated Lan-DeMets O'Brien-Fleming boundaries and calculated P-values for primary and key secondary endpoints

| Endpoint | 1-sided P-value Boundary Used in Final Analysis in AG120-C-009 CSR | Updated 1-sided P-value Boundary, per Assessor Request | Calculated 1-sided P-value |
|---|---|---|---|
| EFS | 0.0046 | 0.0039 | 0.0011 |
| CR rate | 0.0087 | 0.0073 | <0.0001 |
| OS | 0.0017 | 0.0016 | 0.0005 |
| CR + CRh rate | 0.0087 | 0.0073 | <0.0001 |
| ORR | 0.0087 | 0.0073 | <0.0001 |

Abbreviations: CR = complete remission; CRh = CR with incomplete hematologic recovery; EFS = event-free survival; ORR = overall response rate; OS = overall survival.

**Analyses of EFS and OS**

Event-Free Survival

As of the effective date for Protocol Amendment 5 (09 January 2020), an EFS benefit was observed favouring the ivosidenib + azacitidine arm relative to the placebo + azacitidine arm (HR=0.23; 95% CI, 0.08, 0.66; 1-sided P=0.0022). A total of 25 subjects (55.6%) in the ivosidenib + azacitidine arm and 38 subjects (82.6%) in the placebo + azacitidine arm had experienced treatment failure (TF), defined as not achieving a CR by 24 weeks, and therefore were considered to have had an EFS event at Day 1 of randomisation. Data were censored for 19 (42.2%) subjects in the ivosidenib + azacitidine arm and 8 (17.4%) subjects in the placebo + azacitidine arm. The EFS rate at 12 months was 33.3% in the ivosidenib + azacitidine arm versus 17.4% in the placebo + azacitidine arm.

Restricted Mean Survival Time Analysis for Event-Free Survival

The Restricted Mean Survival Time (RMST) is a robust and clinically interpretable summary measure of the survival time distribution (Royston and Parmar, 2011; Zhang, 2013; Uno et al, 2014) and was prespecified to explore the robustness of the EFS analyses and to provide a supplementary efficacy measure to the median survival time and HR.

As of the effective date for Protocol Amendment 5 (09 January 2020), the RMST calculated up to 12.0 months was 5.2 months in the ivosidenib + azacitidine arm and 2.1 months in the placebo + azacitidine arm (AG120-C-009). Difference in RMST, calculated by RMST (ivosidenib + azacitidine) – RMST (placebo + azacitidine), was 3.1 months (95% CI, 1.0 to 5.3 months; 1-sided P=0.0022) (AG120-C-009).

The RMST analysis was consistent with the result of the primary EFS analysis.

Sensitivity Analyses for Event-Free Survival

As of the effective date for Protocol Amendment 5 (09 January 2020), the results of all sensitivity analyses as specified in SAP Version 1 (dated 22 Jun 2020) are summarised below:

- Sensitivity Analysis #1 (EFS tested using the log-rank test stratified by the interactive response technology [IRT] randomisation stratification factors and based on the FAS, with time of relapse or death determined using the actual date of relapse or death, even in situations where relapse or death was observed after 2 or more missing disease assessments or start of subsequent anticancer therapy): HR=0.23; 95% CI, 0.08, 0.66; 1-sided P=0.0022 (AG120-C-009)
- Sensitivity Analysis #2 (EFS tested using the unstratified log-rank test and based on the FAS): HR=0.30; 95% CI, 0.12, 0.75; 1-sided P=0.0041 (AG120-C-009)

- Sensitivity Analysis #3 (EFS tested using the log-rank test stratified by the IRT randomisation stratification factors and based on the PPS): HR=0.21; 95% CI, 0.07, 0.64; 1-sided P=0.0020 (AG120-C-009)
- Sensitivity Analysis #4 (EFS tested using the log-rank test stratified by the randomisation stratification factors derived based on data provided by the Investigator in the eCRF and based on the FAS): HR=0.25; 95% CI, 0.09, 0.70; 1-sided P=0.0030 (AG120-C-009)
- Sensitivity Analysis #5 (EFS tested using the log-rank test stratified by the IRT randomisation stratification factors and based on the FAS; for subjects who did not achieve CR by week 24, instead of being considered to have had an EFS event at Day 1 of randomisation, the event time was either 24 weeks or EOT, whichever was earlier): HR=0.54; 95% CI, 0.30, 0.98; 1-sided P=0.0197 (AG120-C-009)

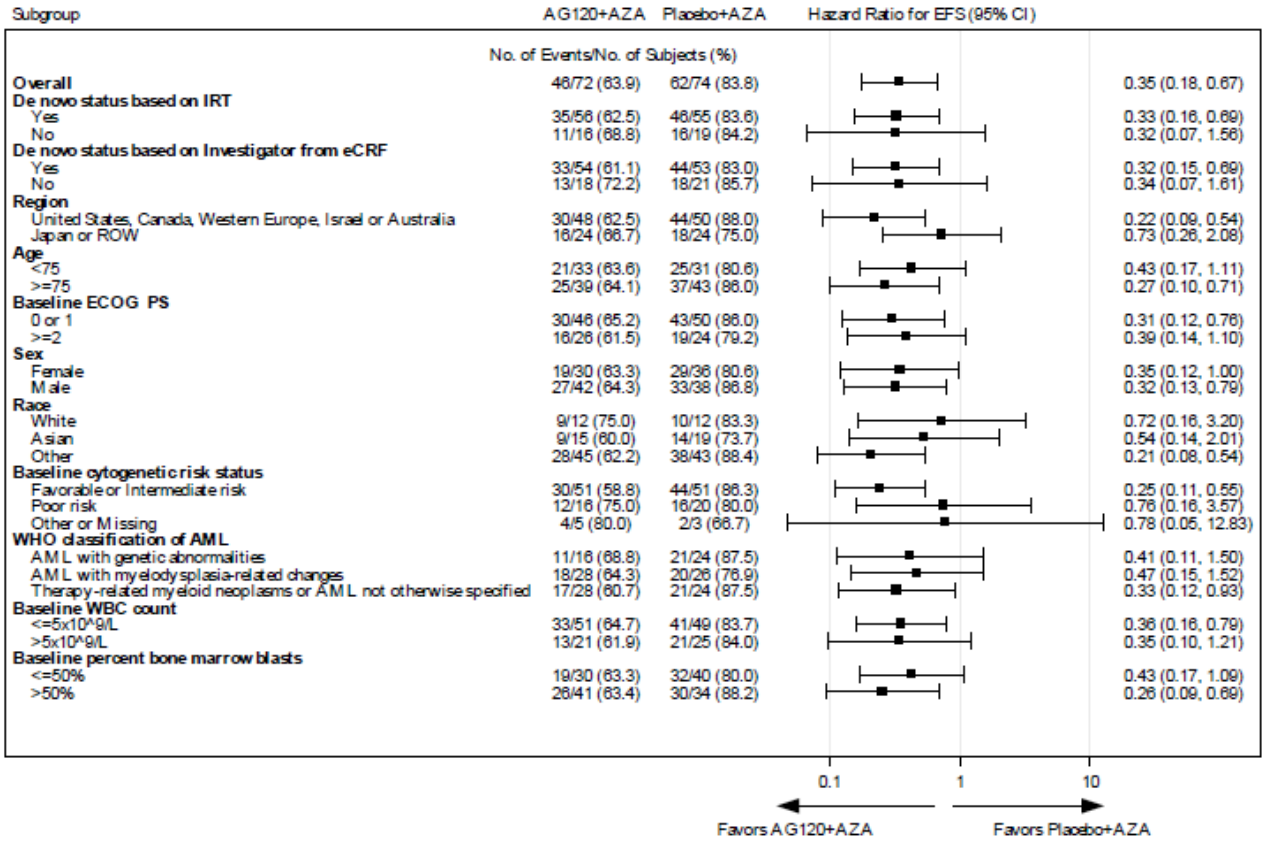
Overall Survival

As of the effective date for Protocol Amendment 5 (09 January 2020), an OS benefit was observed favouring the ivosidenib + azacitidine arm relative to the placebo + azacitidine arm (HR=0.54; 95% CI, 0.27 to 1.06, 1-sided P=0.0336). Median OS was not estimable (95% CI, 7.5 months, NE) in the ivosidenib + azacitidine arm and 5.2 months (95% CI, 1.9 to 15.1 months) in the placebo + azacitidine arm.

Analyses of EFS by Subgroup (DCO 18 March 2021)

Subgroup analyses of EFS were conducted with an unstratified log-rank test and an unstratified Cox regression model. The HR (ivosidenib + azacitidine / placebo + azacitidine) with its 95% CI was displayed for all subgroups graphically in the Forest plot.

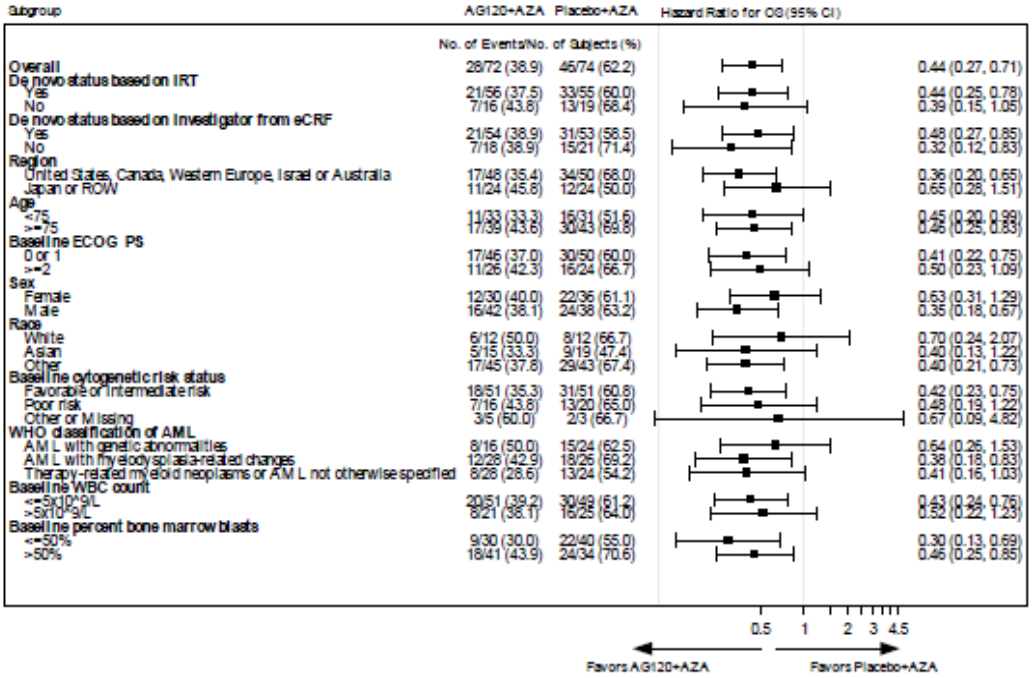
**Figure 18.** Forest plot of EFS by subgroup in study AG120-C-009, full analysis set




Analyses of OS by subgroup (DCO 18 March 2021)

The ivosidenib + azacitidine arm showed a numerically improved OS result compared with placebo + azacitidine arm in the same subgroups evaluated for. A Forest plot of OS by subgroups of the FAS is provided below.

**Figure 19.** Forest plot of overall survival (OS) by subgroup in study AG120-C-009, full analysis set




Source: Figure 14.2.1-2.2, Listing 16.1-3.5, Listing 16.1-6.1, 16.2.1-2.1. Data cutoff date: 18 March 2021.

Abbreviations: AZA = azacitidine; ECOG PS = Eastern Cooperative Oncology Group - Performance Status; WBC = White Blood Cells; IRT = Interactive Response Technology; ROW = Rest of the World.

Hazard ratio is calculated from the unstratified Cox regression model with placebo + azacitidine as the denominator, with two-sided 95% CI.

'> 20%' of baseline blasts was reported for one subject within the AG120+azacitidine group. This subject is not included in the subgroup analyses for baseline percent bone marrow blasts.

Other under Race includes Black or African American, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and not reported.

### *2.7.5.3. Summary of main efficacy results*

- **Summary of main efficacy results**

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

**Table 30.** Summary of Efficacy for trial AG120-C-009

| **Title:** A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of AG-120 in Combination with Azacitidine in Subjects ⩾18 Years of Age with Previously Untreated Acute Myeloid Leukemia with an IDH1 Mutation | | |
|---|---|---|
| Study identifier | Protocol code: AG120-C-009 ; Protocol name: AGILE ; EudraCT number : 2016-004907-30 ; US NCT number : NCT03173248 | |
| Design | Phase 3, multicentre, double-blind, randomized, placebo-controlled | |
| Hypothesis | Superiority | |
| Treatments groups | Ivosidenib (AG-120) + azaciditine | Ivosidenib 500 mg PO QD.<br>Azacitidine 75 mg/m² SC or IV days 1-7 or 1-5 and 8-9 Q28 days ≥6 cycles.<br>72 subjects randomised |
| | Placebo + azacitidine | Placebo PO QD<br>Azacitidine 75 mg/m² SC or IV days 1-7 or 1-5 and 8-9 Q28 days ⩾6 cycles.<br>74 subjects randomised |

| | | | |
|---|---|---|---|
| **Title:** A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of AG-120 in Combination with Azacitidine in Subjects ⩾18 Years of Age with Previously Untreated Acute Myeloid Leukemia with an IDH1 Mutation | | | |
| Study identifier | Protocol code: AG120-C-009 ; Protocol name: AGILE ; EudraCT number : 2016-004907-30 ; US NCT number : NCT03173248 | | |
| Endpoints and definitions | Primary endpoint | EFS | The time from randomisation until treatment failure, relapse from remission, or death from any cause, whichever occurred first. Treatment failure was defined as failure to achieve CR by Week 24. |
| | Key secondary endpoint | OS | The time from date of randomisation to the date of death due to any cause. |
| | Key secondary endpoint | CR rate | The proportion of subjects who achieved a CR<br>CR: bone marrow blasts <5% and no Auer rods; absence of extramedullary disease; ANC ⩾1.0 × $10^9$/L (1000/μL); platelet count ⩾100×$10^9$/L (100,000/μL); and independence of RBC transfusions |
| | Key secondary endpoint | CR + CRh rate | The proportion of subjects who achieved a CR or CRh.<br>CRh: a CR with partial recovery of peripheral blood counts (<5% bone marrow blasts, platelets >50,000/μL, and ANC >500/μL). |
| | Key secondary endpoint | ORR | The rate of CR, CRi (including CRp), partial remission (PR), and morphologic leukaemia-free state (MLFS). |
| Database lock | DCO 18 March 2021 | | |

**Results and Analysis**

| **Analysis description** | **Primary Analysis** | | |
|---|---|---|---|
| Analysis population and time point description | Full analysis set (FAS): all randomised subjects | | |
| Descriptive statistics and estimate variability | Treatment group | Ivosidenib + azacitidine | Placebo + azacitidine |
| | Number of subjects | 72 | 74 |
| | EFS, number of subjects with event (%) | 46 (63.9%) | 62 (83.8%) |
| | CR rate, n (%) | 34 (47.2%) | 11 (14.9%) |
| | OS, number of deaths (%) | 28 (38.9%) | 46 (62.2%) |
| | CR+CRh rate, n (%) | 38 (52.8%) | 13 (17.6%) |
| | ORR, n (%) | 45 (62.5%) | 14 (18.9%) |

| | | | |
|---|---|---|---|
| Effect estimate per comparison | EFS | Comparison groups | Ivosidenib + azacitidine versus placebo + azacitidine |
| | | HR (95% CI) | 0.33 (0.16, 0.69) |
| | CR | Comparison groups | Ivosidenib + azacitidine versus placebo + azacitidine |
| | | Odds ratio | 4.76 |
| | | 95% CI | 2.15, 10.50 |
| | OS | Comparison groups | Ivosidenib + azacitidine versus placebo + azacitidine |
| | | HR | 0.44 |
| | | 95% CI | 0.27, 0.73 |
| | CR + CRh | Comparison groups | Ivosidenib + azacitidine versus placebo + azacitidine |

| | | | |
|---|---|---|---|
| **Title:** A Phase 3, Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of AG-120 in Combination with Azacitidine in Subjects ⩾18 Years of Age with Previously Untreated Acute Myeloid Leukemia with an IDH1 Mutation | | | |
| Study identifier | Protocol code: AG120-C-009 ; Protocol name: AGILE ; EudraCT number : 2016-004907-30 ; US NCT number : NCT03173248 | | |
| | | Odds ratio | 5.01 |
| | | 95% CI | 2.32, 10.81 |
| | ORR | Comparison groups | Ivosidenib + azacitidine versus placebo + azacitidine |
| | | Odds ratio | 7.15 |
| | | %95 CI | 3.31, 15.44 |
| Notes | On 12 May 2021, the IDMC review of safety data reported a greater number of deaths in the placebo arm versus the ivosidenib arm. The subsequent unblinded analysis for efficacy led to the recommendation to halt recruitment. On 27 May 2021, recruitment was discontinued. Because formal stopping rules were not documented until after this decision had been made, presented results cannot be described as being statistically significant. Therefore p-values have been removed from the above table. | | |

### *2.7.5.4. Clinical studies in special populations*

**Table 11.** Elderly patients (⩾65 years) included in study AG120-C-009, Full analysis set

| | **Age 65-74 (Older subjects number /total number)** | **Age 75-84 (Older subjects number /total number)** | **Age 85+ (Older subjects number /total number)** |
|---|---|---|---|
| **Controlled Trial - AG120-C-009 Study*** | | | |
| Ivosidenib+azacitidine (N=72) n (%)/N | 29 (40.3)/72 | 39 (54.2)/72 | 0 (0)/72 |
| Placebo+azacitidine (N=74) n (%)/N | 27 (36.5)/74 | 35 (47.3)/74 | 8 (10.8)/74 |
| Total (N=146) n (%)/N | 56 (38.4)/146 | 74 (50.7)/146 | 8 (5.5)/146 |
| **Non Controlled Trial – AG-221-AML-005 Study (ivosidenib + azacitidine arm N=23)*** | | | |
| Ivosidenib +azacitidine Dose-finding (N=7) n (%)/N | 2 (28.6)/7 | 4 (57.1)/7 | 1 (14.3)/7 |
| Ivosidenib +azacitidine Expansion (N=16) n (%)/N | 6 (37.5)/16 | 7 (43.8)/16 | 0 (0)/16 |
| Total (N=23) n (%)/N | 8 (34.8)/23 | 11 (47.8)/23 | 1 (4.3)/23 |

Source: Table 14.6-1.1. (AG120-C-009; Data Cutoff Date: 18 March 2021), Table T0102 (AG-221-AML-005; Data Cutoff Date: 08 August 2022)
* 8 patients in AG120-C-009 (4 in each arm) and 3 patients in AG221-AML-005 were <= 64 year-old.

### *2.7.5.5. In vitro biomarker test for patient selection for efficacy*

Enrolment in study AG120-C-009 was restricted to subjects with documented IDH1 gene-mutated disease based on central laboratory testing (R132C/L/G/H/S mutation variants tested) using IDH1 *in*

*vitro* PCR assay. The analyses performed, including subgroup analyses by R132 variant, were based on the FAS.

Considering that ivosidenib potently inhibited the 5 most common IDH1m proteins with a biochemical IC50 in the range of 8 to 17 nM (AG-120 investigator's brochure) when used as monotherapy in Study AG120-C-001, primary resistance based on mutant allele subtype was not anticipated.

For Study AG120-C-009, all subjects were centrally tested for IDH1m. Of the variants analysed, R132-C was the most frequent in the treatment and control arms (62.5% versus 68.9%, respectively). An examination of IDH1m allele sub-type sensitivity to the combination (defined as CR+CRh rates and EFS and OS outcomes) was performed. Based on these exploratory analyses, the R132-C variant had a favourable association with CR+CRh, EFS, and OS in the treatment arm when compared to the control arm. Other R132 variants were detected at a lower frequency. No significant difference in clinical outcome between both arms was identified.

Of the subjects enrolled on Study AG120-C-009, 120 subjects (57 subjects in the treatment arm, 63 in the placebo arm) had a baseline sample available for co-mutation analysis. All harboured at least 1 known or likely baseline co-occurring mutation, DNMT3A, SRSF2, and RUNX1 being the most frequently co-occurring mutations detected among both treatment groups.

An evaluation was conducted to determine whether known or likely mutations in single genes or pathways were associated with the best overall response of CR+CRh.

In the treatment group JAK2 mutations were associated with a lack of CR or CRh response ($p = 0.014$), with 1 out of 7 subjects harbouring a JAK2 mutation achieving a CR or CRh, while 33 out of 50 JAK2 wild-type subjects achieved a CR or CRh. Except for JAK2, no single gene mutation from either arm had a significant difference in achieving an outcome of CR or CRh. Upon examination of genes associated with specific pathways, no difference was observed in achieving a CR or CRh when the pathway category was composed of more than one gene.

Of note, receptor tyrosine kinase (RTK) pathway mutations (FLT3, KIT, KRAS, NRAS, and PTPN11), which were associated with the primary resistance to IVO, showed no such association in the IVO+AZA setting, with 7 out of 9(78%) IVO+AZA-treated subjects with RTK pathway mutations achieving CR+CRh.

#### *2.7.5.6. Supportive study*

Study AG-221-AML-005 (hereafter mentioned as Study AML-005) is an ongoing Phase 1b/2, multicentre, open-label, randomised study of 2 combinations of IDH mutant targeted therapies plus azacitidine: oral ivosidenib (AG-120) or oral enasidenib (AG-221) plus subcutaneous azacitidine (AZA) in subjects with newly diagnosed AML harboring an IDH1 or an IDH2 mutation, respectively, who are not candidates to receive intensive induction chemotherapy.

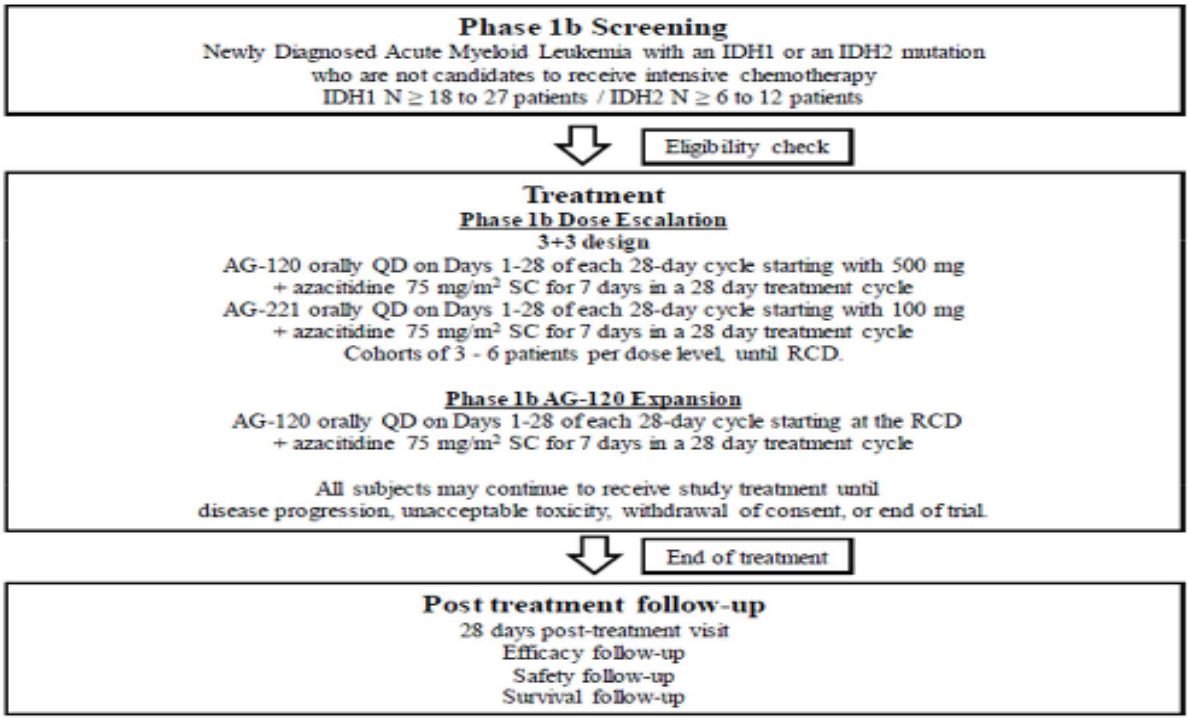
The Phase 1b of the study (depicted in

Figure 20) included:

- a single-arm assessment of subjects treated with AG-120 in combination with SC AZA (on which the following evaluation will focus) and
- a single-arm assessment of subjects treated with AG-221 100 mg or 200 mg in combination with SC AZA.

The Phase 2 comprised a randomised comparison of subjects treated with AG-221 100 mg in combination with SC AZA 75mg/m² versus subjects treated with SC AZA 75 mg/m² alone.

**Figure 20.** Overall study design phase 1b dose-finding and AG-120 expansion stages




IDH1 = isocitrate dehydrogenase 1; IDH2 = isocitrate dehydrogenase 2; QD = once a day; RCD = recommended combination dose; SC = subcutaneous.

Determination of the RCD

The DRT reviewed all Phase 1b safety data to determine the starting doses of AG-120 or AG-221 administered with AZA that were to be used in the treatment arms of the Phase 1b Expansion and randomised Phase 2 stages of the study.

AG-120 expansion stage

Subjects enrolled in the AG-120 expansion were to receive AG-120 + AZA at the RCD.

**Objectives**

The primary objectives of the study, focusing on ivosidenib treatment, were:

Phase 1b Dose-finding Stage

- To assess the safety and tolerability of oral AG-120 when administered with SC AZA and oral AG-221 when administered with SC AZA in subjects with newly diagnosed AML with an IDH1 or an IDH2 mutation, respectively, who were not candidates to receive intensive IC.
- To establish the RCD of oral AG- 120 and oral AG-221 when administered with SC AZA.

Phase 1b AG-120 Expansion Stage

- To assess the safety and tolerability of oral AG-120 when administered with SC AZA in subjects with newly diagnosed AML with an IDH1 mutation, who were not candidates to receive intensive IC.

**Results**

**Participant flow**

Seven subjects were enrolled in the AG-120 + AZA group during the Phase 1b Dose-finding Stage and 17 subjects were enrolled in the AG-120 + AZA group during the Phase 1b Expansion Stage.

All 7 subjects enrolled in the Phase 1b Dose-finding Stage initiated treatment with AG-120 +AZA and 16 of 17 subjects who enrolled in the Phase 1b Expansion Stage initiated treatment with AG-120+ AZA.

Of the 23 subjects overall receiving treatment with AG-120 +AZA, 16 (69.6%) subjects discontinued from treatment and 7 (30.4%) subjects were still receiving treatment at the time of the data cutoff. The most common reasons for treatment discontinuation were AE (4 subjects), withdrawal by subject (4 subjects), and disease relapse (3 subjects).

**Analysis sets**

The Full Analysis Population (FAP) included all subjects who were enrolled and received at least 1 dose of study treatment. Subjects were classified according to the assigned dose level and schedule. The FAP was the primary analysis population and was the default analysis set for all analyses except the safety analyses, unless otherwise specified. This population was defined for Phase 1b only.

For Phase 1b, the Evaluable Analysis Population (EAP) included all subjects in the FAP for whom the baseline response assessment and at least 1 post-baseline response assessment at Day 28 or later were available and evaluable. The clinical activity of AG-221/AG-120 combined with AZA was primarily assessed in the FAP.

**Baseline data**

**Table 22.** Demographics, Study AML-005 Phase 1b FAP

| Parameter | AG-120 + AZA 75 mg/m$^2$ | | |
|---|---|---|---|
| | AG-120 500 mg + AZA in Dose-finding (N = 7) | AG-120 500 mg + AZA in Expansion (N = 16) | AG-120 500 mg + AZA Total (N = 23) |
| Age (years) | | | |
| Median | 81.0 | 74.0 | 76.0 |
| Min, Max | 72, 88 | 61, 79 | 61, 88 |
| Age Categories (years), n (%) | | | |
| < 65 | 0 | 3 (18.8) | 3 (13.0) |
| ≥ 65 to < 75 | 2 (28.6) | 6 (37.5) | 8 (34.8) |
| ≥ 75 | 5 (71.4) | 7 (43.8) | 12 (52.2) |
| Sex, n (%) | | | |
| Male | 4 (57.1) | 7 (43.8) | 11 (47.8) |
| Female | 3 (42.9) | 9 (56.3) | 12 (52.2) |
| Race, n (%) | | | |
| Asian | 0 | 1 (6.3) | 1 (4.3) |
| White | 7 (100.0) | 13 (81.3) | 20 (87.0) |
| Not collected or reported | 0 | 2 (12.5) | 2 (8.7) |
| Ethnicity, n (%) | | | |
| Hispanic or Latino | 1 (14.3) | 0 | 1 (4.3) |
| Not Hispanic or Latino | 6 (85.7) | 14 (87.5) | 20 (87.0) |
| Not reported | 0 | 2 (12.5) | 2 (8.7) |

AZA = azacitidine; FAP = Full Analysis Population; Max = maximum; Min = minimum.
Percentages were based on the number of subjects enrolled in each dose cohort group.

**Table 33.** Baseline disease characteristics - Study AML-005 Phase 1b FAP

| Parameter | AG-120 + AZA 75 mg/m$^2$ | | |
|---|---|---|---|
| | AG-120 500 mg + AZA in Dose-finding (N = 7) | AG-120 500 mg + AZA in Expansion (N = 16) | AG-120 500 mg + AZA Total (N = 23) |
| IDH Mutation Type, n (%) | | | |
| IDH1 Positive | 7 (100.0) | 16 (100.0) | 23 (100.0) |
| Not Eligible for Intensive Chemotherapy[a], n (%) | | | |
| Age | 7 (100.0) | 11 (68.8) | 18 (78.3) |
| Comorbidities | 2 (28.6) | 5 (31.3) | 7 (30.4) |
| Performance status | 0 | 2 (12.5) | 2 (8.7) |
| Unfavorable cytogenetics | 0 | 1 (6.3) | 1 (4.3) |
| Subject decision | 0 | 3 (18.8) | 3 (13.0) |
| Other | 0 | 1 (6.3) | 1 (4.3) |
| ECOG Performance Status, n (%) | | | |
| Grade 0 | 0 | 5 (31.3) | 5 (21.7) |
| Grade 1 | 7 (100.0) | 7 (43.8) | 14 (60.9) |
| Grade 2 | 0 | 4 (25.0) | 4 (17.4) |

| Parameter | AG-120 + AZA 75 mg/m$^2$ | | |
|---|---|---|---|
| | AG-120 500 mg + AZA in Dose-finding (N = 7) | AG-120 500 mg + AZA in Expansion (N = 16) | AG-120 500 mg + AZA Total (N = 23) |
| Bone Marrow Blasts Aspirate, Local | | | |
| Median (Min, Max) | 62.0 (27, 86) | 54.0 (13, 92) | 60.0 (13, 92) |
| Bone Marrow Blasts Aspirate Category I, Local, n (%) | | | |
| < 20% | 0 | 2 (12.5) | 2 (8.7) |
| ≥ 20% to < 30% | 1 (14.3) | 3 (18.8) | 4 (17.4) |
| ≥ 30% to < 50% | 0 | 2 (12.5) | 2 (8.7) |
| ≥ 50% | 6 (85.7) | 9 (56.3) | 15 (65.2) |
| Peripheral Blood Blasts, Local (%) | | | |
| Median (Min, Max) | 20.0 (0, 39) | 11.0 (0, 96) | 15.5 (0, 96) |
| Cytogenetic Risk Status, Local, n (%) | | | |
| Intermediate risk | 7 (100.0) | 9 (56.3) | 16 (69.6) |
| Normal | 4 (57.1) | 3 (18.8) | 7 (30.4) |
| Poor risk | 0 | 5 (31.3) | 5 (21.7) |
| Failure | 0 | 1 (6.3) | 1 (4.3) |
| Missing | 0 | 1 (6.3) | 1 (4.3) |
| Hemoglobin (g/L) | | | |
| Median (Min, Max) | 93.5 (78, 141) | 89.5 (65, 111) | 89.5 (65, 141) |
| Platelets (x $10^9$/L) | | | |
| Median (Min, Max) | 92.5 (21, 179) | 33.0 (11, 200) | 42.0 (11, 200) |
| ANC (x $10^9$/L) | | | |
| Median (Min, Max) | 0.2 (0, 0) | 0.3 (0, 3) | 0.3 (0, 3) |
| WBC (x $10^9$/L) | | | |
| Median (Min, Max) | 2.7 (1, 15) | 1.6 (1, 25) | 1.8 (1, 25) |
| WBC, n (%) | | | |
| < 15 x $10^9$/L | 5 (71.4) | 15 (93.8) | 20 (87.0) |
| ≥ 15 to < 30 x $10^9$/L | 1 (14.3) | 1 (6.3) | 2 (8.7) |
| Missing | 1 (14.3) | 0 | 1 (4.3) |

| Parameter | AG-120 + AZA 75 mg/m$^2$ | | |
|---|---|---|---|
| | AG-120 500 mg + AZA in Dose-finding (N = 7) | AG-120 500 mg + AZA in Expansion (N = 16) | AG-120 500 mg + AZA Total (N = 23) |
| GFR, Estimated (mL/min/1.73 m$^2$) | | | |
| Median (Min, Max) | 76.0 (65, 91) | 81.5 (53, 132) | 81.0 (53, 132) |
| GFR, Estimated (mL/min/1.73 m$^2$); n (%) | | | |
| ≥ 45 to < 60 | 0 | 3 (18.8) | 3 (13.0) |
| ≥ 60 | 5 (71.4) | 13 (81.3) | 18 (78.3) |
| Missing | 2 (28.6) | 0 | 2 (8.7) |
| Number of RBC Transfusions[b] | | | |
| Median (Min, Max) | 0.0 (0, 3) | 1.0 (0, 4) | 1.0 (0, 4) |
| Number of Platelet Transfusions[b] | | | |
| Median (Min, Max) | 0.0 (0, 5) | 0.0 (0, 10) | 0.0 (0, 10) |
| LVEF % | | | |
| Median (Min, Max) | 60.0 (56, 70) | 63.0 (45, 73) | 61.5 (45, 73) |

ANC = absolute neutrophil count; AZA = azacitidine; ECOG = Eastern Cooperative Oncology Group; FAP = Full Analysis Population; GFR = glomerular filtration rate; IC = intensive chemotherapy; IDH = isocitrate dehydrogenase; IDH1 = isocitrate dehydrogenase 1; LVEF = left ventricular ejection fraction; Max = maximum; Min = minimum; RBC = red blood cell; WBC = white blood cell.

[a] Subjects may have had more than 1 reason for ineligibility for IC.

[b] Number of transfusions within 8 weeks prior to the start of study treatment.

Percentages were based on the number of subjects in each dose cohort group. Baseline was the last nonmissing value on or prior to first dose of study drug.

**Outcomes and estimation**

ORR and DOR

The summaries of investigator-assessed ORR and duration of response for the Phase 1b FAP in subjects treated with AG-120 +AZA are presented in Table38 and Table 339 respectively.

**Table 34.** Summary of Overall Response Rate – Study AML-005 Phase 1b FAP

| Parameter | AG-120 + AZA 75 mg/m$^2$ | | |
|---|---|---|---|
| | AG-120 500 mg + AZA in Dose-finding (N = 7) | AG-120 500 mg + AZA in Expansion (N = 16) | AG-120 500 mg + AZA Total (N = 23) |
| Best Response Rate, n (%) | | | |
| CR[a] | 5 (71.4) | 8 (50.0) | 13 (56.5) |
| CRi/CRp | 0 | 2 (12.5) | 2 (8.7) |
| PR | 1 (14.3) | 0 | 1 (4.3) |
| MLFS | 1 (14.3) | 1 (6.3) | 2 (8.7) |
| SD | 0 | 3 (18.8) | 3 (13.0) |
| PD | 0 | 1 (6.3) | 1 (4.3) |
| Missing | 0 | 1 (6.3) | 1 (4.3) |
| Overall Response Rate, n (%)[b] | 7 (100.0) | 11 (68.8) | 18 (78.3) |
| 95% CI for Overall Response[c] | (59.0, 100) | (41.3, 89.0) | (56.3, 92.5) |
| CR Rate, n (%)[a] | 5 (71.4) | 8 (50.0) | 13 (56.5) |
| 95% CI for CR[c] | (29.0, 96.3) | (24.7, 75.3) | (34.5, 76.8) |

AZA = azacitidine; CI = confidence interval; CR = morphologic complete remission; CRc = cytogenetic complete remission; CRi = morphologic complete remission with incomplete neutrophil recovery; CRp = morphologic complete remission with incomplete platelet recovery; FAP = Full Analysis Population; MLFS = morphologic leukemia-free state; PD = progressive disease; PR = partial remission; SD = stable disease.

[a] CRc is counted as CR.

[b] CR + CRi + CRp + PR + MLFS.

[c] Clopper-Pearson CIs.

The ORR results for the Phase 1b EAP were generally similar to those for the Phase 1b.

**Table 35.** Summary of Duration of Response – Study AML-005 Phase 1b FAP

| Parameter | AG-120 + AZA 75 mg/m$^2$ | | |
|---|---|---|---|
| | AG-120 500 mg + AZA in Dose-finding (N = 7) | AG-120 500 mg + AZA in Expansion (N = 16) | AG-120 500 mg + AZA Total (N = 23) |
| Total Number of Subjects Who Achieved CR/CRi/CRp/PR/MLFS, n (%) | 7 (100.0) | 11 (68.8) | 18 (78.3) |
| Relapsed/Progressed[b] | 0 | 4 (36.4) | 4 (22.2) |
| Died without Relapse/Progression[b] | 1 (14.3) | 0 | 1 (5.6) |
| Censored[b] | 6 (85.7) | 7 (63.6) | 13 (72.2) |
| Duration of Response[c] (months) | | | |
| Median (95% CI) | NA (0.5, NA) | NA (7.6, NA) | NA (10.3, NA) |
| Kaplan-Meier DOR (%) | | | |
| 3 Months | 83.3 | 100 | 94.1 |
| 6 Months | 83.3 | 90.9 | 88.2 |
| 9 Months | 83.3 | 80.8 | 81.9 |
| 12 Months | 83.3 | 70.7 | 75.6 |

AZA = azacitidine; CI = confidence interval; CR = morphologic complete remission; CRi = morphologic complete remission with incomplete neutrophil recovery; CRp = morphologic complete remission with incomplete platelet recovery; DOR = duration of response; FAP = Full Analysis Population; MLFS = morphologic leukemia-free state; NA = not available; PR = partial remission.

[a] Percentages were based on the number of subjects in each dose cohort.

[b] Percentages were based on the number of subjects in each dose cohort who achieved CR/CRi/CRp/PR/MLFS.

[c] Duration of response was calculated as the date of the first documented response to the date of the first documented disease relapse, progression, or death due to any cause, whichever occurred first. Median estimate of DOR was from an unstratified Kaplan-Meier analysis.

Response was evaluated by the Investigator according to the 2003 revised IWG criteria for AML or the 2006 modified IWG criteria for MDS.

The median duration of response was NE because 13 (72.2%) of 18 subjects had not relapsed or progressed as of the cutoff date.

Time to response

The time to response for the Phase 1b FAP for subjects treated with AG-120 + AZA is summarised in Table 36.

**Table 36.** Summary of Time to Response – Study AML-005 Phase 1b FAP

| Parameter | AG-120 + AZA 75 mg/m$^2$ | | |
|---|---|---|---|
| | AG-120 500 mg + AZA in Dose-finding (N = 7) | AG-120 500 mg + AZA in Expansion (N = 16) | AG-120 500 mg + AZA Total (N = 23) |
| Total Number of Subjects Who Achieved CR/CRi/CRp/PR/MLFS, n (%) | 7 (100.0) | 11 (68.8) | 18 (78.3) |
| Time to Response[a] (months) | | | |
| n | 7 | 11 | 18 |
| Median (Min, Max) | 1.78 (0.9, 3.5) | 1.88 (0.7, 3.8) | 1.83 (0.7, 3.8) |
| Time to Response by Cycle, n (%) | | | |
| Cycle 1 | 0 | 0 | 0 |
| Cycle 2 | 1 (14.3) | 4 (25.0) | 5 (21.7) |
| Cycle 3 | 4 (57.1) | 6 (37.5) | 10 (43.5) |
| Cycle 4 | 0 | 0 | 0 |
| Cycle 5 | 1 (14.3) | 1 (6.3) | 2 (8.7) |
| Follow-up | 1 (14.3) | 0 | 1 (4.3) |

AML = acute myeloid leukemia; AZA = azacitidine; CR = morphologic complete remission; CRi = morphologic complete remission with incomplete neutrophil recovery; CRp = morphologic complete remission with incomplete platelet recovery; FAP = Full Analysis Population; IWG = International Working Group; Max = maximum; Min = minimum; MLFS = morphologic leukemia-free state; PR = partial remission.

[a] Time to response was defined as time from first dose date of study drug to first documented CR/CRi/CRp/PR/MLFS according to modified IWG AML response criteria.

Source: Table 14.2.6.1.

Time to remission

The median time to remission for combined subjects in the Dose-finding and Expansion stages was 3.49 months. Of the 13 (56.5%) subjects who achieved CR, 6 of 13 subjects achieved remission by Cycle 3, 5 of 13 subjects achieved remission during Cycle 5, and 2 of 13 subjects achieved remission during Cycle 7 or later.

Duration of remission

The median duration of remission was NE for subjects treated with AG-120 + AZA in the Dose-finding and Expansion stages because 10 (76.9%) of 13 subjects had not relapsed or progressed as of the cut-off date.

Overall survival

The summary of OS for the Phase 1b FAP for subjects treated with AG-120 + AZA is presented in Table 37.

**Table 37.** Summary of Overall Survival– Study AML-005 Phase 1b FAP

| Parameter | AG-120 + AZA 75 mg/m$^2$ | | |
|---|---|---|---|
| | AG-120 500 mg + AZA in Dose-finding (N = 7) | AG-120 500 mg + AZA in Expansion (N = 16) | AG-120 500 mg + AZA Total (N = 23) |
| Number of Subjects with Events, n (%) | 1 (14.3) | 6 (37.5) | 7 (30.4) |
| Number of Subjects Censored[a], n (%) | 6 (85.7) | 10 (62.5) | 16 (69.6) |
| Duration of OS[b] (months) | | | |
| Median (95% CI) | NA (2.3, NA) | 24.2 (14.5, NA) | NA (17.0, NA) |
| Kaplan-Meier OS (%) | | | |
| 1 Month | 100 | 100 | 100 |
| 3 Months | 85.7 | 93.8 | 91.1 |
| 6 Months | 85.7 | 87.1 | 86.3 |
| 9 Months | 85.7 | 80.4 | 81.5 |
| 12 Months | 85.7 | 80.4 | 81.5 |

AZA = azacitidine; CI = confidence interval; FAP = Full Analysis Population; NA = not evaluable; OS = overall survival.

[a] Subjects alive were censored at the last date known to be alive or a prespecified data cutoff date. Subjects who only had a baseline record were censored at the first dose date.

[b] Overall survival was calculated as the time from the first dose to the date of death due to any cause. Median percentile estimate of OS was from an unstratified Kaplan-Meier analysis.

If a value is unable to be computed, it is presented as "NA."

The median duration of OS was NE for subjects treated with AG-120 +AZA in the Dose-finding Stage because 6 (85.7%) of the 7 subjects were still participating in the study as of the cutoff date. The median duration of OS was 24.2 months for subjects treated with AG-120 +AZA in the Expansion Stage.

Event-free survival

The summary of EFS for the Phase 1b FAP for subjects treated with AG-120 + AZA is presented in Table 38.

The definition of EFS was different from the pivotal study. Here EFS was the time to documented morphologic relapse, progression according to modified IWG AML response criteria, or death from any cause, whichever occurs first.

***Table 38.*** *Summary of EFS- Study AML-005 Phase 1b FAP*

| Parameter | AG-120 + AZA 75 mg/m$^2$ | | |
|---|---|---|---|
| | AG-120 500 mg + AZA in Dose-finding (N = 7) | AG-120 500 mg + AZA in Expansion (N = 16) | AG-120 500 mg + AZA Total (N = 23) |
| Number of Events, n (%) | 1 (14.3) | 6 (37.5) | 7 (30.4) |
| Relapsed/Progressed | 0 | 5 (31.3) | 5 (21.7) |
| Died without Relapse/Progression | 1 (14.3) | 1 (6.3) | 2 (8.7) |
| Censored[a], n (%) | 6 (85.7) | 10 (62.5) | 16 (69.6) |
| Duration of EFS[b] (months) | | | |
| Median (95% CI) | NA (2.3, NA) | NA (5.7, NA) | NA (9.9, NA) |
| Kaplan-Meier EFS (%) | | | |
| 3 Months | 83.3 | 85.7 | 85.4 |
| 6 Months | 83.3 | 77.9 | 80.1 |
| 9 Months | 83.3 | 77.9 | 80.1 |
| 12 Months | 83.3 | 60.6 | 68.7 |

AML = acute myeloid leukemia; AZA = azacitidine; CI = confidence interval; EFS = event-free survival; FAP = Full Analysis Population; IWG = International Working Group; MDS = myelodysplastic syndrome; NA = not evaluable.

[a] Subjects who had no postbaseline response were censored at date of the first dose.

[b] Event-free survival was calculated as the interval from the date of the first dose to the date of documented relapse, progression, or death due to any cause, whichever occurred first. Median percentile estimate of EFS was from an unstratified Kaplan-Meier analysis.

Response was evaluated by the investigator according to the 2003 revised IWG criteria for AML or the 2006 modified IWG criteria for MDS.

Follow-up medications and procedures

*Subsequent stem cell transplants*

For subjects treated with AG-120 + AZA during Phase 1b, 1 (4.3%) subject with a disease status of CR at the time of HSCT had a subsequent allogeneic stem cell transplant for AML.

## 2.7.6. Discussion on clinical efficacy

***Design and conduct of clinical studies***

This application is mainly based on efficacy and safety results from:

- the pivotal study AG120-C-009 in subjects with previously untreated IDH1+ AML and ineligible for intensive induction chemotherapy (IC)
- the supportive study AG-221-AML-005, a phase 1b/2 study in newly diagnosed AML subjects with an IDH1 or an IDH2 mutation not candidates for intensive IC.

According to the applicant, both studies were GCP-compliant. At time of submission, no GCP inspection had been requested nor taken place and no inspection was planned.

Based on these studies, the indication sought for Tidhesco was in combination with azacitidine for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive intensive induction chemotherapy. The CHMP requested a small amendment to this by replacing "intensive" with

"standard" in line with recent approvals in the same disease setting which was accepted by the applicant.

**Pivotal study, AG120-C-009 (AGILE)**

Subjects eligible for study treatment were randomised 1:1 to receive oral ivosidenib or matched placebo on each day of the 4-week cycle, both administered in combination with subcutaneous (SC) or intravenous (IV) azacitidine for the first week (7 days) (or on a 5-2-2 schedule) of each 4-week (28-day) cycle.

The final study design limited enrolment to patients with previously untreated AML, excluding patients which were candidates to intensive induction chemotherapy (also considering stem cell transplantation). Overall, eligibility criteria were globally in line with AML guidelines and scientific advice given to the applicant.

The initial objectives and endpoints chosen for this superiority trial were consistent with recommendations from scientific advice and AML guidelines. However, since its initiation (original protocol dated 06 January 2017) the study was amended 9 times. A critical revision was amendment 5 (09 January 2020); at that time 117 patients were already recruited. With protocol amendment 5, the primary endpoint was changed from OS to EFS, OS was added as a key secondary endpoint and the corresponding statistical analyses were updated. This modification was not supported by the CHMP (EMEA/H/SA/3403/3/2018/PA/II) since EFS is not considered a validated surrogate for OS in AML.

In addition, the number of subjects to be enrolled in the study were reduced from 392 to 200 based on updated sample size estimations. The number of study-centres and countries was increased. The planned interim analyses for efficacy were removed. Despite the double-blind design of the study, which is partially reassuring, all these changes were considered by the CHMP as potentially compromising the integrity of the trial. Demographics and disease characteristics were presented at baseline for subjects randomised before and after protocol amendment 5 and were found to be generally similar, with observed differences not thought to have a meaningful impact on efficacy outcomes. The applicant also provided EFS and OS analyses at the effective date of protocol amendment 5. While the treatment effect estimates for EFS and OS were respectively slightly larger and smaller than at the final analysis, results can be considered relatively consistent overall, especially considering the increased variability and the less mature database at the time of protocol amendment 5.

After observing an imbalance in the number of deaths, a request was made by the IDMC to obtain additional data, including unblinded efficacy results. Based on these data, a recommendation was made to halt the recruitment. The applicant followed the IDMC recommendation and then discontinued the recruitment, which led to the early reporting of study results. It is noted that the IDMC considered this recommendation to be based on a safety concern, for ethical reasons. Given that the imbalance in deaths was in favour of the ivosidenib arm (i.e., not a safety concern for the experimental arm), the discontinuation of the study can be interpreted as an unplanned early stopping based on efficacy which raised further concerns about the trial integrity.

The applicant highlighted the precautions that were taken to protect the study integrity. Only a small team was unblinded to handle interactions with IDMC and FDA, while the rest of the study team remained blinded. In addition, a blinded statistician derived the updated significance boundaries prior to database lock. The applicant concluded that, because of these steps taken prior to database lock, the internal validity of the study remains intact.

The precautions that were taken by the applicant are acknowledged and appear to have limited the damage to the study integrity. However, they do not resolve the main issue of the prior decision to halt the recruitment and perform an analysis that could lead to study discontinuation. Indeed, this decision

was made by an unblinded team who had access to efficacy analyses performed by the IDMC. This opportunity to stop the trial early for efficacy was not planned by the amended protocol, i.e., there was no planned type I error control for it. Consequently, the applicant removed the p-values from all endpoints which are presented in the SmPC.

The ad hoc set of statistical boundaries used the O'Brien-Fleming alpha spending function (Lan-DeMets method), and was defined in a document separate from the SAP and dated 10-Jul-2021, by the blinded study statistician however this was done after the review of unblinded efficacy data by the unblinded team and after the decision to halt recruitment and perform the analysis. The proposed O'Brien-Fleming boundaries would only be acceptable if the unblinded look at efficacy (which led to trial discontinuation) had been prospectively planned in the study protocol. It is acknowledged that Lan-DeMets O'Brien-Fleming boundaries are commonly used for group sequential testing strategies, and that the method was initially planned in the original protocol, when the primary endpoint was OS, and before interim analyses were removed (with amendment 5). Nevertheless, other types of adjustment of sequential testing would have been possible. As requested, the applicant has provided updated Lan-DeMets O'Brien-Fleming boundaries when accounting for all past IDMC meetings as additional interim analyses. Even though this does still not provide formal control of the study type I error (due to lack of prospective planning), it is noted that p-values remain below the updated significance thresholds, thereby providing some reassurance regarding the robustness of the statistical results.

It was also acknowledged that the reported results suggest a large treatment effect and are further supported by a number of additional sensitivity analyses. Together with the information provided about the measures to preserve the integrity of the trial offers the CHMP was reassured that it could rely on the results of the study to determine the benefit/risk balance of ivosidenib in the claimed indication.

The censoring rules of the primary EFS strategy are not in line with the general recommendations in Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man (CHMP/27994/2008 Rev. 1), as they do not closely follow the ITT principle. Nevertheless, it is noted that several sensitivity analyses were planned for EFS, including an analysis considering events regardless of subsequent therapy or more missing disease assessments. This should allow the assessment of the primary analysis under different assumptions.

Statistical methods for primary and secondary endpoints (stratified log-rank tests for EFS and OS, stratified CMH tests for response endpoints) are generally deemed appropriate.

**Supportive study AG-221-AML-005**

Approximately 24 subjects were planned for enrolment in Study AML-005 (start date: 03 June 2016) for the Phase 1b AG-120 + AZA combination. As of the study DCO of 19 August 2019, 23 subjects have been enrolled, 7 in the dose-finding stage and 16 in the expansion stage of the Phase 1b.

The eligibility criteria established for the supportive trial adequately frame the inclusion of treatment-nave subjects with IDH1 or IDH2 AML.

The phase 1b dose finding stage was based on the standard 3+3 design. The primary aim of this supportive study was to determine the RCD for the treatment of IDH-mutated AML subjects based on the tolerability data of the tested doses. ORR, CR and sponsor-derived CRh were secondary endpoints of the study, while PD was an exploratory endpoint. These endpoints were appropriate to assess the suitability of AG-120 + AZA for both efficacy and safety.

***Efficacy data and additional analyses***

**AG120-C-009 (AGILE)**

A total of 146 patients was randomised, including 72 in ivosidenib + azacitidine arm (71 received the treatment), and 74 in placebo + azacitidine arm (73 received the treatment).

Clinically relevant improvement in the primary endpoint of EFS was observed following treatment with ivosidenib + azacitidine with a 67% reduction in the risk of progression/relapse or death compared to the placebo + azacitidine arm (HR = 0.33; 95% CI: 0.16-0.69). Results of the sensitivity analysis were consistent with these primary analysis results.

The third quartile of EFS shows that EFS was highly superior in ivosidenib + azacitidine arm (23.98 months; 95% CI: 14.78-NE months) compared to placebo + azacitidine arm (0.03 months; 95% CI: 0.03, 11.30 months).

As part of secondary endpoints, the CR rate in the FAS was higher in ivosidenib + azacitidine arm compared to placebo + azacitidine arm: 47.2% (95% CI: 35.3-59.3) versus 14.9% (95% CI: 7.7-25.0) with an odds ratio of 4.76 (95% CI: 2.15-10.50).

Medians OS of 24.0 months (95% CI: 11.3-34.1 months) in ivosidenib + azacitidine arm and 7.9 months (95% CI: 4.1-11.3 months) in placebo + azacitidine arm were observed. Median follow-up time was approximately 15 months for both treatment arms. Although OS is immature, clinically relevant improvement in OS was shown for subjects in ivosidenib + azacitidine arm compared to placebo + azacitidine arm (HR = 0.44; 95% CI: 0.27-0.73 which is highly superior to the HR of 0.71 assumed in the initial sample size assumptions).

Subgroup analysis on EFS and OS did not retrieve discrepancies between subgroups.

A Restricted Mean Survival Time (RMST) analysis has been provided regarding the primary endpoint EFS. The reported results supported the primary analysis. A RMST has been provided for OS, supporting the main OS analysis and the relevance of the effect in this endpoint.

The CR+CRh rate was higher in ivosidenib + azacitidine arm than in placebo + azacitidine arm (52.8% [95% CI: 40.7-64.7] versus 17.6% [95% CI: 9.7-28.2]; odds ratio of 5.01 [95% CI: 2.32-10.81]).

ORR was achieved in 62.5% (95% CI: 50.3-73.6) of the subjects in ivosidenib + azacitidine arm and 18.9% (95% CI: 10.7-29.7) of the subjects in placebo + azacitidine arm. ORR was higher in the ivosidenib + azacitidine arm than in the placebo + azacitidine arm (odds ratio of 7.15 [95% CI: 3.31-15.44]).

Median DOCR were non evaluable in both arms at the data cutoff date. However, durability of the treatment effect was observed in the ivosidenib + azacitidine arm in 93.3, 88.4, 88.4, 78.6 and 58.9% of patients at 6, 9, 12, 18 and 24 months, respectively.

Quality of life data was collected as part of the study. Even if HRQoL analyses are rather exploratory, it should be noted that more than 90% of subjects in each treatment arm completed baseline EORTC QLQ-C30 and EQ-5D-5L questionnaires. Compliance decreased over the course of treatment cycles (80% at cycle 5 versus 70% at cycle 19 with no data for the placebo + azaciditine group). For similar baseline scores, a clinically meaningful improvement was observed in the experimental arm characterised by less fatigue and better general condition.

Regardless of baseline transfusion status, a greater proportion of subjects in the ivosidenib + azacitidine arm experienced post-baseline RBC and platelet transfusion independence compared with the placebo + azacitidine arm (56.9% versus 37.8%).

Five subjects underwent an allogeneic HSCT (alloHSCT), including four from the experimental arm (5.6%) – two of them had progressive disease. Based on the narratives provided for each subject, alloHSCT was performed based on investigator's judgement and mean overall survival was 24.05 months at data cut-off.

*In vitro* biomarker analyses suggested that neither baseline co-mutation nor IDH1 R132 variant presence are anticipated to lead to primary treatment resistance, including primary resistance pathways identified from the ivosidenib monotherapy clinical studies.

**AG-221-AML-005**

A total of 23 subjects were included and treated with ivosidenib + azacitidine.

Three of the seven subjects enrolled in the dose-finding stage discontinued treatment either due to an adverse event, withdrawal of consent or transition to a marketed treatment (1 subject each, 14.3%).

Thirteen of the 17 subjects of the Expansion Phase discontinued treatment, most frequently following an AE, withdraw of consent or disease relapse. At data cut-off, only 7 subjects remained on treatment.

Due to the small sample sizes, it was not possible to make meaningful comparisons between the dose finding and expansion stages. The assessment of efficacy results was therefore be based on the pooled results of these two steps of the Phase 1b.

The investigator-assessed ORR for the combined subjects was 78.3% (95% CI: 56.3, 92.5) for 18 subjects. The overall CR rate was 56.5% (95% CI: 34.5, 76.8) for subjects who received treatment with AG-120 + AZA with a median time to remission (CR) of 3.49 months (range: 0.5-15.7).

The sponsor-derived CR/CRh response was 65.2% (95% CI: 42.7, 83.6) for 15 of 23 subjects who achieved a response of CR/CRh and the median time to response was 1.83 months (range: 0.7-3.8).

These results support what was observed in AGILE study: a clinically meaningful improvement of ORR, CRR, CR/CRh, time to remission and time to response in subjects from the ivosidenib + azacitidine arm compared to the control arm.

## 2.7.7. Conclusions on the clinical efficacy

The clinical efficacy data submitted in this MAA support the benefit of ivosidenib + azacitidine in the final agreed indication.

## 2.7.8. Clinical safety

### *2.7.8.1. Patient exposure*

The characterisation of the safety profile of ivosidenib in combination with azacitidine in AML is primarily based on the ongoing pivotal phase 3 study AG120-C-009 (AGILE). The applicant during the procedure submitted updated safety data with a new cut-off date of 1st of October 2021 and which are presented in this section along the initial cut-off date of 18th of March 2021 unless otherwise stated.

Patients included had newly diagnosed AML with an IDH1 mutation and were considered ineligible to intensive induction therapy. Patients were treated with ivosidenib 500mg QD or matching placebo + azacitidine 75 mg/m²/day SC or IV for 7 days of each 4-weeks cycle, which is the intended posology. A summary of study treatment duration is presented in *Table* 39.

**Table 39.** Summary of study treatment duration in study AG120-C-009, Safety Analysis Set

| | sNDA (Data cutoff date: 18 March 2021) | | Safety Update (Data cutoff date: 01 October 2021) | |
|---|---|---|---|---|
| | IVO + AZA (N=71) | PBO + AZA (N=73) | IVO + AZA (N=72) | PBO + AZA (Before crossover) (N=74) |
| **Treatment Duration (months)** | | | | |
| n | 71 | 73 | 72 | 74 |
| Mean (SD) | 8.80 (8.086) | 4.73 (4.971) | 11.07 (9.832) | 5.37 (5.528) |
| Median (Q1, Q3) | 5.98 (1.74, 15.08) | 2.76 (1.38, 5.59) | 7.84 (2.17, 18.66) | 3.19 (1.41, 8.61) |
| Min, Max | 0.1, 33.5 | 0.1, 19.8 | 0.1, 40.0 | 0.1, 26.3 |
| **Treatment Duration Category (months) n (%)** | | | | |
| >0 - ≤4 | 25 (35.2) | 44 (60.3) | 23 (31.9) | 41 (55.4) |
| >4 - ≤8 | 17 (23.9) | 14 (19.2) | 13 (18.1) | 12 (16.2) |
| >8 - ≤12 | 6 (8.5) | 8 (11.0) | 7 (9.7) | 13 (17.6) |
| >12 - ≤16 | 7 (9.9) | 3 (4.1) | 6 (8.3) | 3 (4.1) |
| >16 - ≤20 | 9 (12.7) | 4 (5.5) | 8 (11.1) | 4 (5.4) |
| >20 - ≤24 | 5 (7.0) | 0 | 8 (11.1) | 0 |
| >24 - ≤28 | 0 | 0 | 3 (4.2) | 1 (1.4) |
| >28 - ≤32 | 1 (1.4) | 0 | 2 (2.8) | 0 |
| >32 | 1 (1.4) | 0 | 2 (2.8) | 0 |

Abbreviations: Q1 = first quartile; Q3 = third quartile; SD = standard deviation.
Notes: Treatment duration (months) = (end date of the study treatment - start date of the study treatment + 1)/30.4375.

The median duration of treatment was >2 times longer in the IVO + AZA arm than in the PBO+ AZA arm, and the median relative dose intensity of IVO experienced by subjects randomised to the IVO + AZA arm was similar to the PBO + AZA arm for both cut-off dates (

Table 40).

**Table 40.** Summary of exposure to ivosidenib in study AG120-C-009, Safety Analysis Set

| | sNDA (Data cutoff date: 18 March 2021) | | Safety Update (Data cutoff date: 01 October 2021) | |
|---|---|---|---|---|
| | IVO + AZA (N=71) | PBO + AZA (N=73) | IVO + AZA (N=72) | PBO + AZA (Before crossover) (N=74) |
| **Duration of Exposure (days)** | | | | |
| n | 71 | 73 | 72 | 74 |
| Mean (SD) | 264.7 (245.93) | 143.6 (150.40) | 330.8 (297.98) | 162.3 (167.30) |
| Median (Q1, Q3) | 180.0 (53.0, 459.0) | 84.0 (42.0, 170.0) | 227.5 (66.0, 549.5) | 95.5 (43.0, 261.0) |
| Min, Max | 4, 1019 | 3, 588 | 4, 1216 | 3, 796 |
| **Duration of Exposure Category (weeks) n (%)** | | | | |
| >0 - ≤4 | 12 (16.9) | 15 (20.5) | 11 (15.3) | 14 (18.9) |
| >4 - ≤8 | 6 (8.5) | 13 (17.8) | 6 (8.3) | 12 (16.2) |
| >8 - ≤12 | 5 (7.0) | 9 (12.3) | 4 (5.6) | 8 (10.8) |
| >12 - ≤16 | 1 (1.4) | 7 (9.6) | 1 (1.4) | 7 (9.5) |
| >16 - ≤20 | 4 (5.6) | 4 (5.5) | 3 (4.2) | 5 (6.8) |
| >20 - ≤24 | 6 (8.5) | 6 (8.2) | 5 (6.9) | 5 (6.8) |
| >24 | 37 (52.1) | 19 (26.0) | 42 (58.3) | 23 (31.1) |
| **Cumulative Dose (mg)** | | | | |
| n | 71 | 73 | 72 | 74 |
| Mean (SD) | 112394.4 (107966.45) | 66054.8 (71715.64) | 139493.1 (129797.23) | 72787.2 (77488.64) |
| Median (Q1, Q3) | 78250.0 (25500.0, 175750.0) | 36500.0 (17500.0, 83500.0) | 90875.0 (31000.0, 232750.0) | 43500.0 (19500.0, 112500.0) |
| Min, Max | 2000, 509500 | 1500, 284500 | 2000, 608000 | 1500, 324250 |

| | sNDA (Data cutoff date: 18 March 2021) | | Safety Update (Data cutoff date: 01 October 2021) | |
|---|---|---|---|---|
| | IVO + AZA (N=71) | PBO + AZA (N=73) | IVO + AZA (N=72) | PBO + AZA (Before crossover) (N=74) |
| **Actual Dose Intensity (mg/day)** | | | | |
| n | 71 | 73 | 72 | 74 |
| Mean (SD) | 446.05 (81.411) | 457.18 (68.862) | 443.43 (84.294) | 450.67 (77.440) |
| Median (Q1, Q3) | 491.80 (427.54, 500.00) | 488.31 (446.43, 500.00) | 484.30 (431.65, 500.00) | 487.51 (443.61, 500.00) |
| Min, Max | 230.3, 501.2 | 137.3, 500.0 | 230.3, 500.8 | 137.3, 500.0 |
| **Relative Dose Intensity (%)** | | | | |
| n | 71 | 73 | 72 | 74 |
| Mean (SD) | 89.21 (16.282) | 91.44 (13.772) | 88.69 (16.859) | 90.13 (15.488) |
| Median (Q1, Q3) | 98.36 (85.51, 100.00) | 97.66 (89.29, 100.00) | 96.86 (86.33, 100.00) | 97.50 (88.72, 100.00) |
| Min, Max | 46.1, 100.2 | 27.5, 100.0 | 46.1, 100.2 | 27.5, 100.0 |

Abbreviations: Q1 = first quartile; Q3 = third quartile; SD = standard deviation.
Notes: Duration of Exposure (days) = (date of last dose - date of first dose + 1); Cumulative dose (mg) = sum of the actual doses; Planned Dose Intensity (mg/day) = 500; Actual Dose Intensity (mg/day) = Cumulative dose (mg)/ Duration of Exposure(day);Relative Dose Intensity (%) = 100×Actual Dose Intensity (mg/day)/Planned Dose Intensity (mg/day).

Supportive safety data relevant for the combination are provided by the ongoing phase 1b/2 study AG-221-AML-005 in which 23 patients with newly diagnosed AML harbouring IDH1 mutation and not eligible to induction therapy received the combination at the intended dose.

Additional safety data are provided by the ongoing phase I study AG120-C-001 in patients with advanced haematologic malignancies with an IDH1 mutation. This was the pivotal study for the previous Application of ivosidenib in monotherapy for patients with R/R AML with IDH1 mutation. 34 patients with newly diagnosed AML received ivosidenib in monotherapy at the intended dose (500mg QD).

Finally, 2 other studies provide more limited information on ivosidenib safety: study AG120-221-C-001 in patients with newly diagnosed AML with IDH1/2 mutation who received ivosidenib 500mg QD in combination with induction and consolidation therapy, and study CS3010 in Chinese patients with advanced haematologic malignancies who received ivosidenib 500 mg QD as monotherapy.

#### *2.7.8.2. Adverse events*

Almost all subjects included in the safety analysis set experienced a Treatment-Emergent Adverse Event (TEAE) as seen in Table 41.

**Table 41.** Overall Summary of Treatment-Emergent Adverse Events in study AG120-C-009 (Safety Analysis Set)

| Number of Subjects with | sNDA (Data cutoff date: 18 March 2021) | | Safety Update (Data cutoff date: 01 October 2021) | |
|---|---|---|---|---|
| | IVO + AZA (N=71) n (%) | PBO + AZA (N=73) n (%) | IVO + AZA (N=72) n (%) | PBO + AZA (Before crossover) (N=74) n (%) |
| **Any TEAE** | 70 (98.6) | 73 (100.0) | 71 (98.6) | 74 (100) |
| **Treatment-related TEAE** | | | | |
| Related to IVO or PBO only | 27 (38.0) | 18 (24.7) | 28 (38.9) | 22 (29.7) |
| Related to AZA only | 40 (56.3) | 37 (50.7) | 42 (58.3) | 38 (51.4) |
| Related to both IVO or PBO and AZA | 42 (59.2) | 36 (49.3) | 43 (59.7) | 37 (50.0) |
| **Grade ≥3 TEAE** | 66 (93.0) | 69 (94.5) | 66 (91.7) | 71 (95.9) |
| **Grade ≥3 treatment-related TEAE** | | | | |
| Related to IVO or PBO only | 11 (15.5) | 8 (11.0) | 11 (15.3) | 9 (12.2) |
| Related to AZA only | 22 (31.0) | 22 (30.1) | 23 (31.9) | 24 (32.4) |
| Related to both IVO or PBO and AZA | 32 (45.1) | 22 (30.1) | 33 (45.8) | 23 (31.1) |

| Number of Subjects with | sNDA (Data cutoff date: 18 March 2021) | | Safety Update (Data cutoff date: 01 October 2021) | |
|---|---|---|---|---|
| | IVO + AZA (N=71) n (%) | PBO + AZA (N=73) n (%) | IVO + AZA (N=72) n (%) | PBO + AZA (Before crossover) (N=74) n (%) |
| **Serious TEAE** | 49 (69.0) | 60 (82.2) | 49 (68.1) | 62 (83.8) |
| **Serious treatment-related TEAE** | | | | |
| Related to IVO OR PBO only | 5 (7.0) | 3 (4.1) | 5 (6.9) | 3 (4.1) |
| Related to AZA only | 5 (7.0) | 5 (6.8) | 5 (6.9) | 5 (6.8) |
| Related to both IVO or PBO and AZA | 16 (22.5) | 9 (12.3) | 16 (22.2) | 10 (13.5) |
| **TEAE leading to discontinuation of study drug** | | | | |
| Discontinuation of IVO or PBO only | 3 (4.2) | 2 (2.7) | 3 (4.2) | 3 (4.1) |
| Discontinuation of AZA only | 2 (2.8) | 1 (1.4) | 2 (2.8) | 1 (1.4) |
| Discontinuation of both IVO or PBO and AZA | 19 (26.8) | 19 (26.0) | 19 (26.4) | 19 (25.7) |
| **TEAE leading to dose reduction of study drug** | | | | |
| Dose reduction of IVO or PBO only | 10 (14.1) | 6 (8.2) | 12 (16.7) | 6 (8.1) |
| Dose reduction of AZA only | 9 (12.7) | 4 (5.5) | 10 (13.9) | 4 (5.4) |
| Dose reduction of both IVO or PBO and AZA | 4 (5.6) | 0 | 4 (5.6) | 1 (1.4) |
| **TEAEs leading to interruption of study drug** | | | | |
| Interruption of IVO or PBO only | 20 (28.2) | 28 (38.4) | 21 (29.2) | 29 (39.2) |
| Interruption of AZA only | 19 (26.8) | 17 (23.3) | 20 (27.8) | 18 (24.3) |
| Interruption of both IVO or PBO and AZA | 37 (52.1) | 28 (38.4) | 38 (52.8) | 30 (40.5) |
| **TEAE leading to death** | 10 (14.1) | 21 (28.8) | 11 (15.3) | 23 (31.1) |
| **Treatment-related TEAE leading to death** | | | | |
| Related to IVO or PBO only | 0 | 0 | 0 | 0 |
| Related to AZA only | 0 | 0 | 0 | 0 |
| Related to both IVO or PBO and AZA | 0 | 0 | 0 | 0 |

Abbreviations: TEAE = treatment-emergent adverse events.
Notes: For Brazilian subjects, the relatedness to Azacitidine was not assessed; MedDRA Version 23.1 and Version 24.0 and CTCAE Version 4.03 are used

**Common adverse events**

A summary of the most common TEAEs in study AG120-C-009 is displayed in Table 42.

**Table 42.** Summary of Most Common (⩾10% of Subjects in Either Treatment Arm) Treatment-Emergent Adverse Events by Preferred Term in study AG120-C-009 (Safety Analysis Set)

| | sNDA (Data cutoff date: 18 March 2021) | | Safety Update (Data cutoff date: 01 October 2021) | |
|---|---|---|---|---|
| **Preferred Term** | **IVO + AZA (N=71) n (%)** | **PBO + AZA (N=73) n (%)** | **IVO + AZA (N=72) n (%)** | **PBO + AZA (Before crossover) (N=74) n (%)** |
| **Any event** | 70 (98.6) | 73 (100.0) | 71 (98.6) | 74 (100) |
| Nausea | 30 (42.3) | 28 (38.4) | 32 (44.4) | 29 (39.2) |
| Vomiting | 29 (40.8) | 19 (26.0) | 29 (40.3) | 20 (27.0) |
| Diarrhoea | 25 (35.2) | 26 (35.6) | 25 (34.7) | 29 (39.2) |
| Pyrexia | 24 (33.8) | 29 (39.7) | 25 (34.7) | 32 (43.2) |
| Anaemia | 22 (31.0) | 21 (28.8) | 23 (31.9) | 23 (31.1) |
| Febrile neutropenia | 20 (28.2) | 25 (34.2) | 20 (27.8) | 25 (33.8) |
| Neutropenia | 20 (28.2) | 12 (16.4) | 22 (30.6) | 16 (21.6) |
| Thrombocytopenia | 20 (28.2) | 15 (20.5) | 20 (27.8) | 15 (20.3) |
| Constipation | 19 (26.8) | 38 (52.1) | 22 (30.6) | 39 (52.7) |
| Pneumonia | 17 (23.9) | 23 (31.5) | 17 (23.6) | 24 (32.4) |

| Preferred Term | sNDA (Data cutoff date: 18 March 2021) | | Safety Update (Data cutoff date: 01 October 2021) | |
|---|---|---|---|---|
| | IVO + AZA (N=71) n (%) | PBO + AZA (N=73) n (%) | IVO + AZA (N=72) n (%) | PBO + AZA (Before crossover) (N=74) n (%) |
| Electrocardiogram QT prolonged | 14 (19.7) | 5 (6.8) | 15 (20.8) | 5 (6.8) |
| Insomnia | 13 (18.3) | 9 (12.3) | 13 (18.1) | 9 (12.2) |
| Asthenia | 11 (15.5) | 24 (32.9) | 11 (15.3) | 25 (33.8) |
| Decreased appetite | 11 (15.5) | 19 (26.0) | 12 (16.7) | 21 (28.4) |
| Dyspnoea | 11 (15.5) | 9 (12.3) | 11 (15.3) | 10 (13.5) |
| Hypokalaemia | 11 (15.5) | 21 (28.8) | 11 (15.3) | 21 (28.4) |
| Differentiation syndrome | 10 (14.1) | 6 (8.2) | 10 (13.9) | 6 (8.1) |
| Pain in extremity | 10 (14.1) | 3 (4.1) | 10 (13.9) | 4 (5.4) |
| Fatigue | 9 (12.7) | 10 (13.7) | 9 (12.5) | 10 (13.5) |
| Haematoma | 9 (12.7) | 1 (1.4) | 10 (13.9) | 1 (1.4) |
| Arthralgia | 8 (11.3) | 3 (4.1) | 12 (16.7) | 4 (5.4) |
| Headache | 8 (11.3) | 2 (2.7) | 8 (11.1) | 2 (2.7) |
| Leukocytosis | 8 (11.3) | 1 (1.4) | 8 (11.1) | 2 (2.7) |
| Oedema peripheral | 8 (11.3) | 16 (21.9) | 9 (12.5) | 17 (23.0) |
| Platelet count decreased | 8 (11.3) | 6 (8.2) | 9 (12.5) | 6 (8.1) |
| Rash | 7 (9.9) | 9 (12.3) | 7 (9.7) | 10 (13.5) |
| Cough | 6 (8.5) | 11 (15.1) | 6 (8.3) | 12 (16.2) |
| Haemorrhoids | 5 (7.0) | 8 (11.0) | 5 (6.9) | 8 (10.8) |
| Weight decreased | 4 (5.6) | 12 (16.4) | 4 (5.6) | 12 (16.2) |
| Pruritis | 7 (9.9) | 4 (5.5) | 8 (11.1) | 4 (5.4) |
| Hyponatraemia | 3 (4.2) | 1 (1.4) | 5 (6.9) | 8 (10.8) |

Abbreviations: TEAE = treatment-related adverse events.
Notes: Adverse events leading to interruption of study treatment are those leading to interruption of both study drugs that are part of the combination treatment; Summarised in order of decreasing frequency of subjects with events based on the frequencies observed for ivosidenib + azacitidine; Subjects with multiple adverse events within a preferred term are counted only once in that preferred term.

**Grade ≥ 3 Adverse events**

The most common severe TEAEs (Grade 3 and above according to the Common Terminology Criteria for Adverse Event (CTCAE) in study AG120-C-009 are summarised in Table 43.

**Table 43.** Summary of Most Common (⩾5% of Subjects in Either Treatment Arm) Grade 3 or Higher Treatment-Emergent Adverse Events by Preferred Term in study AG120-C-009 (Safety Analysis Set)

| Preferred Term | sNDA (Data cutoff date: 18 March 2021) | | Safety Update (Data cutoff date: 01 October 2021) | |
|---|---|---|---|---|
| | IVO + AZA (N=71) n (%) | PBO + AZA (N=73) n (%) | IVO + AZA (N=72) n (%) | PBO + AZA (Before crossover) (N=74) n (%) |
| **Any event** | 66 (93.0) | 69 (94.5) | 66 (91.7) | 71 (95.9) |
| Diarrhoea | 1 (1.4) | 5 (6.8) | 1 (1.4) | 6 (8.1) |
| Anaemia | 18 (25.4) | 19 (26.0) | 19 (26.4) | 20 (27.0) |
| Febrile neutropenia | 20 (28.2) | 25 (34.2) | 20 (27.8) | 25 (33.8) |
| Neutropenia | 19 (26.8) | 12 (16.4) | 22 (30.6) | 16 (21.6) |
| Thrombocytopenia | 17 (23.9) | 15 (20.5) | 17 (23.6) | 15 (20.3) |
| Pneumonia | 16 (22.5) | 21 (28.8) | 16 (22.2) | 22 (29.7) |
| Electrocardiogram QT prolonged | 7 (9.9) | 2 (2.7) | 7 (9.7) | 2 (2.7) |
| Asthenia | 0 | 5 (6.8) | 0 | 6 (8.1) |
| Decreased appetite | 1 (1.4) | 6 (8.2) | 1 (1.4) | 6 (8.1) |
| Hypokalemia | 2 (2.8) | 6 (8.2) | 2 (2.8) | 7 (9.5) |
| Platelet count decreased | 6 (8.5) | 6 (8.2) | 8 (11.1) | 6 (8.1) |
| Leukopenia | 5 (7.0) | 2 (2.7) | 5 (6.9) | 2 (2.7) |
| Neutrophil count decreased | 6 (8.5) | 5 (6.8) | 6 (8.3) | 5 (6.8) |
| Hyponatraemia | 3 (4.2) | 5 (6.8) | 3 (4.2) | 6 (8.1) |
| Hypotension | 0 | 4 (5.5) | 0 | 4 (5.4) |
| Pulmonary embolism | 4 (5.6) | 1 (1.4) | 4 (5.6) | 1 (1.4) |
| Sepsis | 2 (2.8) | 6 (8.2) | 2 (2.8) | 6 (8.1) |

Notes: The table includes TEAEs that occurred in ≥5% of subjects in any column at the PT level; "Subjects with Any Grade ≥3 TEAE" are summarised for all TEAEs. Summarised in order of decreasing frequency of subjects with events in any grade based on the frequencies observed for ivosidenib + azacitidine; Subjects with multiple adverse events within a PT are counted only once in that PT; For subjects with multiple occurrences of an adverse event, the adverse event with the worst CTCAE grade is included in the summary; MedDRA Version 23.1 and CTCAE Version 4.03 are used.

In supportive study AG-221-AML-005, drug related TEAE with grade ≥ 3 severity were overall consistent with pivotal study. However, one patient in that study experienced a grade ≥ 3 tumour lysis syndrome.

Following a review and a discussion of all TLS cases observed in patients treated with ivosidenib, a significant incidence of TLS (7.4% of treated patients) in the monotherapy study AG120-C-001 compared to the pivotal AG120-C-009 (one case of TLS in control arm, none in ivosidenib arm) and the supportive studies was highlighted.

### *2.7.8.3. Serious adverse event/deaths/other significant events*

**Serious adverse events**

A summary of the most frequently reported serious TEAEs reported in study AG120-C-009 is provided in Table 44.

**Table 44.** Summary of Serious Treatment-Emergent Adverse Events Related to both ivosidenib or Placebo and Azacitidine by System Organ Class and Preferred Term - Newly Diagnosed AML in study AG120-C-009 (Safety Analysis Set)

| System Organ Class Preferred Term | sNDA (Data cutoff date: 18 March 2021) | | Safety Update (Data cutoff date: 01 October 2021) | |
|---|---|---|---|---|
| | IVO + AZA (N=71) n (%) | PBO + AZA (N=73) n (%) | IVO + AZA (N=72) n (%) | PBO + AZA (Before crossover) (N=74) n (%) |
| **Any events** | 16 (22.5) | 9 (12.3) | 16 (22.2) | 10 (13.5) |
| **Blood and lymphatic system disorders** | 7 (9.9) | 5 (6.8) | 7 (9.7) | 5 (6.8) |
| Febrile neutropenia | 5 (7.0) | 5 (6.8) | 5 (6.9) | 5 (6.8) |
| Neutropenia | 1 (1.4) | 0 | 1 (1.4) | 0 |
| Thrombocytopenia | 1 (1.4) | 0 | 1 (1.4) | 0 |

| System Organ Class<br>Preferred Term | sNDA<br>(Data cutoff date: 18 March 2021)<br>IVO + AZA<br>(N=71) n (%) | <br><br>PBO + AZA<br>(N=73) n (%) | Safety Update<br>(Data cutoff date: 01 October 2021)<br>IVO + AZA<br>(N=72) n (%) | <br><br>PBO + AZA<br>(Before crossover)<br>(N=74) n (%) |
|---|---|---|---|---|
| **Infections and infestations** | 5 (7.0) | 4 (5.5) | 6 (8.3) | 5 (6.8) |
| Bronchopulmonary aspergillosis | 1 (1.4) | 0 | 1 (1.4) | 1 (1.4) |
| Enterococcal infection | 1 (1.4) | 0 | 1 (1.4) | 0 |
| Pneumonia | 1 (1.4) | 0 | 1 (1.4) | 0 |
| Pneumonia pseudomonal | 1 (1.4) | 0 | 1 (1.4) | 0 |
| Pneumonia respiratory syncytial viral | 1 (1.4) | 0 | 1 (1.4) | 0 |
| Sepsis | 1 (1.4) | 0 | 1 (1.4) | 0 |
| Urinary tract infection | 0 | 0 | 1 (1.4) | 0 |
| Enterococcal sepsis | 0 | 1 (1.4) | 0 | 1 (1.4) |
| Escherichia sepsis | 0 | 1 (1.4) | 0 | 1 (1.4) |
| Influenza | 0 | 1 (1.4) | 0 | 1 (1.4) |
| Lower respiratory tract infection | 0 | 1 (1.4) | 0 | 1 (1.4) |
| Pneumonia staphylococcal | 0 | 1 (1.4) | 0 | 1 (1.4) |
| **General disorders and administration site conditions** | 2 (2.8) | 0 | 2 (2.8) | 0 |
| Fatigue | 1 (1.4) | 0 | 1 (1.4) | 0 |
| Pyrexia | 1 (1.4) | 0 | 1 (1.4) | 0 |
| **Gastrointestinal disorders** | 1 (1.4) | 1 (1.4) | 1 (1.4) | 1 (1.4) |
| Lower gastrointestinal haemorrhage | 1 (1.4) | 0 | 1 (1.4) | 0 |
| Diverticular perforation | 0 | 1 (1.4) | 0 | 1 (1.4) |
| **Investigations** | 1 (1.4) | 0 | 1 (1.4) | 0 |
| Blast cell count increased | 1 (1.4) | 0 | 1 (1.4) | 0 |

| System Organ Class<br>Preferred Term | sNDA<br>(Data cutoff date: 18 March 2021) | | Safety Update<br>(Data cutoff date: 01 October 2021) | |
|---|---|---|---|---|
| | IVO + AZA<br>(N=71) n (%) | PBO + AZA<br>(N=73) n (%) | IVO + AZA<br>(N=72) n (%) | PBO + AZA<br>(Before crossover)<br>(N=74) n (%) |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | 1 (1.4) | 1 (1.4) | 1 (1.4) | 1 (1.4) |
| Differentiation syndrome | 1 (1.4) | 1 (1.4) | 1 (1.4) | 1 (1.4) |
| **Nervous system disorders** | 1 (1.4) | 1 (1.4) | 1 (1.4) | 1 (1.4) |
| Cerebral infarction | 1 (1.4) | 0 | 1 (1.4) | 0 |
| Dementia | 0 | 1 (1.4) | 0 | 1 (1.4) |
| **Respiratory, thoracic and mediastinal disorders** | 1 (1.4) | 0 | 1 (1.4) | 0 |
| Pneumonitis | 1 (1.4) | 0 | 1 (1.4) | 0 |
| **Renal and urinary disorders** | 0 | 1 (1.4) | 1 (1.4) | 1 (1.4) |
| Renal failure | 0 | 1 (1.4) | 0 | 1 (1.4) |
| Renal disorder | 0 | 0 | 1 (1.4) | 0 |

Abbreviations: SAE = serious adverse events.
Notes: Summarised in order of decreasing frequency of subjects with events based on the frequencies observed for ivosidenib + azacitidine.

Data of supportive study AG-221-AML-005 were overall consistent with pivotal study data.

**Deaths**

On-treatment death was defined as death that occurred after the start of study treatment and within 28 days after the last dose of study treatment. A summary of the TEAEs leading to death is presented Table 45.

***Table 45.*** *Summary of Treatment-Emergent Adverse Events Leading to Deaths by System Organ Class and Preferred Term in study AG120-C-009 (Safety Analysis Set)*

| System Organ Class<br>Preferred Term | sNDA (Data cutoff date: 18 March 2021) | | Safety Update (Data cutoff date: 01 October 2021) | |
|---|---|---|---|---|
| | IVO + AZA (N=71) n (%) | PBO + AZA (N=73) n (%) | IVO + AZA (N=72) n (%) | PBO + AZA (Before crossover) (N=74) n (%) |
| **Subjects with Any TEAE Leading to On-Treatment Death**[1] | 10 (14.1) | 21 (28.8) | 11 (15.3) | 23 (31.1) |
| **Nervous system disorders** | 4 (5.6) | 0 | 4 (5.6) | 0 |
| Haemorrhage intracranial | 2 (2.8) | 0 | 2 (2.8) | 0 |
| Ischaemic stroke | 1 (1.4) | 0 | 1 (1.4) | 0 |
| Seizure | 1 (1.4) | 0 | 1 (1.4) | 0 |

| System Organ Class<br>Preferred Term | sNDA<br>(Data cutoff date: 18 March 2021) | | Safety Update<br>(Data cutoff date: 01 October 2021) | |
|---|---|---|---|---|
| | IVO + AZA<br>(N=71) n (%) | PBO + AZA<br>(N=73) n (%) | IVO + AZA<br>(N=72) n (%) | PBO + AZA<br>(Before crossover)<br>(N=74) n (%) |
| **Infections and infestations** | 3 (4.2) | 14 (19.2) | 4 (5.6) | 15 (20.3) |
| COVID-19 | 1 (1.4) | 0 | 1 (1.4) | 0 |
| Pneumonia | 1 (1.4) | 5 (6.8) | 2 (2.8) | 6 (8.1) |
| Septic shock | 1 (1.4) | 2 (2.7) | 1 (1.4) | 2 (2.7) |
| Abdominal infection | 0 | 1 (1.4) | 0 | 1 (1.4) |
| Bronchopulmonary aspergillosis | 0 | 1 (1.4) | 0 | 1 (1.4) |
| COVID-19 pneumonia | 0 | 1 (1.4) | 0 | 1 (1.4) |
| Corynebacterium sepsis | 0 | 1 (1.4) | 0 | 1 (1.4) |
| Pneumonia bacterial | 0 | 1 (1.4) | 0 | 1 (1.4) |
| Sepsis | 0 | 2 (2.7) | 0 | 2 (2.7) |
| **General disorders and administration site conditions** | 1 (1.4) | 3 (4.1) | 1 (1.4) | 3 (4.1) |
| Multiple organ dysfunction syndrome | 1 (1.4) | 1 (1.4) | 1 (1.4) | 1 (1.4) |
| General physical health deterioration | 0 | 2 (2.7) | 0 | 2 (2.7) |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | 1 (1.4) | 0 | 1 (1.4) | 0 |
| Adenocarcinoma | 1 (1.4) | 0 | 1 (1.4) | 0 |
| **Respiratory, thoracic and mediastinal disorders** | 1 (1.4) | 2 (2.7) | 1 (1.4) | 3 (4.1) |
| Pulmonary embolism | 1 (1.4) | 0 | 1 (1.4) | 0 |
| Haemoptysis | 0 | 0 | 0 | 1 (1.4) |
| Lung disorder | 0 | 1 (1.4) | 0 | 1 (1.4) |
| Respiratory failure | 0 | 1 (1.4) | 0 | 1 (1.4) |

| System Organ Class<br>Preferred Term | sNDA (Data cutoff date: 18 March 2021) | | Safety Update (Data cutoff date: 01 October 2021) | |
|---|---|---|---|---|
| | IVO + AZA (N=71) n (%) | PBO + AZA (N=73) n (%) | IVO + AZA (N=72) n (%) | PBO + AZA (Before crossover) (N=74) n (%) |
| **Blood and lymphatic system disorders** | 0 | 1 (1.4) | 0 | 1 (1.4) |
| Febrile neutropenia | 0 | 1 (1.4) | 0 | 1 (1.4) |
| **Psychiatric disorders** | 0 | 1 (1.4) | 0 | 1 (1.4) |
| Delirium | 0 | 1 (1.4) | 0 | 1 (1.4) |

In supportive study AG120-AML-005, 3 other deaths from infectious origin were also reported (Enterobacter bacteraemia, Enterococcal infection, and Sepsis). None was assessed as related to study treatment.

In additional study AG120-C-001 within patients with *newly diagnosed AML* who received ivosidenib monotherapy, 5 subjects (14.7%) had a TEAE leading to on-treatment death, including 3 subjects related to infectious events (Pneumonia, Febrile neutropenia and Infection), and 1 to haemorrhage (Retroperitoneal haemorrhage).

**Adverse events of special Interest**

- QT prolongation

Incidence of electrocardiogram QT prolonged was higher in ivosidenib + azacitidine arm (19.7%) than in placebo + azacitidine arm (6.8%). Among these, 9.9% (7 patients) in ivosidenib + azacitidine arm and 2.7% (2 patients) in placebo + azacitidine arm met the definition of AESI. In addition, one patient experienced a grade 3 syncope in placebo + azacitidine arm. There were no Grade 4 or Grade 5 TEAEs of Electrocardiogram QT prolonged, torsades de pointes, or fatal arrhythmias in either treatment arm. With an additional 6.5 months of follow-up since the first data cut-off, there was only 1 newly reported AESI of serious Grade 3 Syncope reported in the ivosidenib + azacitidine arm (and none on the placebo+ azacitidine arm) which was assessed by the Investigator as not related to both study drugs.

Median (min, max) time to first TEAE of electrocardiogram prolonged, assessed in study AG-120-C-009, was 29.0 days (1-561 days) with 26.7 % of first events that occurred > 60 days showing that event of QT prolonged can occur weeks after reaching the concentration at steady state (Css). Median time to first event was consistent in supportive study and other additional studies.

ECG QT prolonged led to interruption of treatment in 5 patients (6.9%), to dose reduction in 7 patients (9.7%) and to treatment discontinuation in one patient (1.4%).

Supportive study AG-221-AML-005 confirmed the high frequency of events of QT prolongation (30%, 7 patients) with 17% (4 subjects) who had a grade 3 event and no grade ≥ 4 observed.

Moreover in monotherapy study AG120-C-001, 9% of patients had a grade 3 event of ECG QT prolongation and one patient developed a ventricular fibrillation considered related to ivosidenib.

- Leukocytosis

In study AG120-C-009 (AGILE), any event of leukocytosis assessed as Grade ≥3, irrespective of seriousness, was to be reported as an AESI. No leucocytosis event was ≥ grade 3 therefore no AE met the definition of AESI. Up to the first cut-off date, leucocytosis of any grade occurred in 11.3% (8 patients) vs 1.4% (1 patient) in ivosidenib + azacitidine and placebo + azacitidine arm respectively. With an additional 6.5 months of follow-up to the second cut-off date, there was only one new nonserious event of Grade 3 leukocytosis reported in the placebo + azacitidine arm.

Grade 3 events remained rare in supportive and additional studies.

In Study AG120-C-009, Median (range) time to first onset of leucocytosis was 20 days (9-33 days) for patients in ivosidenib + azacitidine arm and 22 days (22 to 22 days) in placebo + azacitidine arm.

- Differentiation syndrome

The overall incidence of Differentiation syndrome in the ivosidenib + azacitidine and placebo + azacitidine arms was 10 (14.1%) vs. 6 (8.2%) subjects, respectively. Incidence of serious TEAEs of differentiation syndrome was also higher in experimental arm (8.5%) than in control arm (1.4%). No patients died from Differentiation syndrome in either study arm.

In 8 subjects in the experimental arm and 5 subjects in the control arm, differentiation syndrome was assessed by the Investigator as related to ivosidenib. The incidence was higher in AG-221-AML-005 (17.4%), including some SAEs. Incidences were similar in the rest of studies.

The median number of days to first onset of the PT of Differentiation syndrome was for the subjects who received treatment with ivosidenib + azacitidine, 19.5 days (range: 3 to 33 days) and for the subjects who received treatment with azacitidine + placebo, 44 days (range: 4 to 86 days). Here again, differentiation syndrome due to azacitidine may explain the difference in number of days to first onset between both arms. Nevertheless, the incidence in experimental arm was double than in control arm.

**Additional adverse events of clinical importance**

- Guillain-Barré syndrome

While no events of Guillain Barré syndrome were observed in pivotal study AG120-C-009 (AGILE) and supportive study AG-221-AML-005, 2 cases of Guillain-Barré syndrome occurred in study AMG-C-001 (ivosidenib monotherapy at 500mg QD) and were considered as related to the study treatment by the investigator. In addition, 3 cases of Guillain-Barré syndrome were retrieved in Eudravigilance database including 2 post marketing cases in US and one case in an indication of leukaemia relapse prophylaxis at an unspecified dose from a compassionate use in France.

Searches using the MedDRA HLTs of acute polyneuropathies, chronic polyneuropathies, led to the identification of several cases of peripheral neuropathy in supportive study AG-221-AML-005 (2 patients), in the post-marketing setting (4 patients) and in the pivotal study (2 patients whose event were considered related to ivosidenib).

- Leukoencephalopathy

Regarding Progressive multifocal leukoencephalopathy (PML), while no event was reported in the pivotal and supportive studies, two events were reported in one subject with R/R AML in the monotherapy study AG120-C-001, 225 and 302 days after treatment initiation. The first event resolved within 2 days with sequelae without interruption of study treatment. The treatment was interrupted on study day 305 during the second event due to the neurological symptoms. JC virus was detected in the CSF on D309 and treated with BK virus cytotoxic T lymphocyte cells, then study treatment was

resumed on D331. Both events were considered as not related to study treatment by the investigator. At the data cut off, the subject remained on study treatment and the PML was ongoing. The patient had previously received cladribine which is a confounding factor.

Concerning Posterior reversible encephalopathy syndrome (PRES), one case was retrieved in a patient who did not receive any previous therapy 94 days after treatment initiation in the same study AG120-C-001. The treatment was permanently discontinued on day 94 patient and the event of PRES was considered resolved with sequalae on study day 106. The SAE was considered as possibly related to study treatment by the investigator.

No such cases were retrieved in the pivotal and in the supportive study AG-221-AML-005 in which the search strategy for leukoencephalopathies events was more restrictive (only PT Progressive multifocal leukoencephalopathy and Posterior reversible encephalopathy syndrome). A thorough analysis of data from the pivotal study AG120-C-009, the supportive study AG-221-AML-005 and post-marketing data with the search strategy applied for study AG120-C-001 was provided by the applicant which did not identify additional cases of PML and PRES.

**Other adverse events of Interest**

- Infections

The incidence of events within SOC infection and infestation was high in both treatment arms but was lower in experimental arm (72.2%) than in control arm (79.7%). The overall incidence of Infections of any grade was lower in ivosidenib + azacitidine arm (30.6%) than in placebo + azacitidine (51.4%) as well as Grade ≥3 TEAEIs of infection (21.1% vs 30.1%), serious TEAEIs of infection (16.9% vs 23.3%), fatal TEAEIs of infection (2.8% vs 9.6%), and discontinuations of both ivosidenib or placebo and azacitidine due to infection (4.2% vs 9.6%).

The applicant provided an analysis on the number of fungal infections in each arm which do not suggest an increase of fungal infection in patient receiving ivosidenib with regards to the high incidence of neutropenia and neutropenia grade ≥ 3 events.

- Bleeding

TEAE of bleedings of any grade occurred more frequently in ivosidenib + azacitidine arm (41.7%) than in placebo + azacitidine arm (31.1%). The applicant noted that grade ≥ 3 events and serious bleeding events were comparable in both treatment arms. However, among the 3 SAE related to bleeding events which occurred in experimental arm, 2 events were grade 5 haemorrhage intracranial while no fatal event occurred in control arm. The 3rd SAE was a grade 3 lower gastrointestinal haemorrhage. This latter patient had platelets at 15x10^9g/L 6 days before the report of the event of lower gastrointestinal haemorrhage.

In one of the fatal cases reported, the patient died of an intracranial haemorrhage 17 days after the last dose of ivosidenib (study day 139). There was no supporting evidence which confirmed this diagnosis as an autopsy was not performed. The Investigator considered the event of Haemorrhage intracranial related to concomitant medication or disease and clarified that epilepsy and acute cerebrovascular disease were not excluded. However, mean terminal half-life of ivosidenib is 98 hours, meaning elimination occurs about 20 days after the last administration. It is therefore difficult to definitely rule out ivosidenib as a cause of the haemorrhage intracranial that occurred 17 days after the last dose.

Another patient was diagnosed with an SAE of haemorrhage intracranial on study day 110, 26 days after the last dose of ivosidenib. This patient had thrombocytopenia grade 4 at D111 (1.10^9/L). The investigator considered the event of haemorrhage intracranial as not related to ivosidenib but notably associated with thrombocytopenia, which is recognised as an ADR of ivosidenib.

In addition, listing of adverse events leading to on treatment death of study AG120-C-001 describes that in patients with *R/R AML* receiving ivosidenib monotherapy at 500mg QD (Arm 1 expansion phase) one patient died of a cerebral haemorrhage, one patient died of a subarachnoid haemorrhage, one patient died of a CNS haemorrhage. Additionally, one patient died of haemorrhage intracranial in escalation phase at 100 mg BID.

Furthermore, a higher incidence of haematoma in experimental arm (12.7%) compared to control arm (1.4%) was observed in the pivotal study.

- Covid-19

Overall, less patients experienced a TEAE of COVID-19 in experimental arm (2.8%, 2 patients) than in control arm (6.8%, 5 patients). SAE were observed in both patients in experimental arm and in 1 patient in control arm. Number of events that led to discontinuation or interruption was comparable in both treatment arms. 1 event in each arm led to death. The low number of cases of COVID-19 does not allow to draw any conclusions.

#### *2.7.8.4. Laboratory findings*

- Haematology parameters

Overall laboratory abnormalities were consistent with that expected within newly diagnosed AML population and safety profile of both ivosidenib and azacytidine.

- Clinical chemistry parameters

In the pivotal study, AST elevations of any grade were higher in the experimental arm (36.6%) than in control arm (23.3%). Conversely, ALT elevations of any grade were higher in the control arm (31.5%) than in the experimental arm (18.3%). No transaminases grade 3-4 elevation were observed. In addition, although any grade bilirubin elevation was similar between groups (22.5% and 21.9% for the experimental and control treatment arms respectively), grade 3/4 bilirubin elevation was observed only in the experimental arm (4.2%). Considering the low number of cases, no firm conclusion on causal association could be drawn.

- Coagulation analysis

The combination of ivosidenib + azacitidine did not seem to have a major impact on Activated Partial Thromboplastin Clotting Time (aPTT) with similar newly occurring or worsening event of any grade in both treatment arms in the pivotal study (18.2%, 12/66 patients in the experimental arm and 14.3%, 9/63 patients in control arm) and 1 case of newly occurring or worsening to grade 3 aPTT in each treatment arm and no grade 4 events.

#### *2.7.8.5. Vital signs, physical findings and other observations related to safety*

Vital signs abnormalities were comparable between both arms although a numerical higher incidence of hypertension (9.9%) in the experimental arm compared to the control arm (6.8%) was noted.

In addition, for all the QTcF parameters prolongation assessed, incidence was higher in ivosidenib + azacitidine arm than in placebo + azacitidine, confirming the high incidence of QT prolongation. Supportive studies confirm this observation.

#### *2.7.8.6. In vitro biomarker test for patient selection for safety*

Not applicable.

### *2.7.8.7. Safety in special populations*

**Table 46.** Summary of selected Treatment Emergent Adverse Events by Age-Before Crossover on Study AG120-C-009, Safety Analysis Set

| MedDRA Terms | <65 years | | 65 – 74 years | | 75 – 84 years | | ≥ 85 years | |
|---|---|---|---|---|---|---|---|---|
| | Placebo + Azacitidine N=4 n (%) | Ivosidenib + Azacitidine N=4 n (%) | Placebo + Azacitidine N=27 n (%) | Ivosidenib + Azacitidine N=30 n (%) | Placebo + Azacitidine N=34 n (%) | Ivosidenib + Azacitidine N=38 n (%) | Placebo + Azacitidine N=9 n (%) | Ivosidenib + Azacitidine N=0 n (%) |
| Number of Total TEAEs | 4 (100) | 4 (100) | 27 (100) | 29 (96.7) | 34 (100) | 38 (100) | 9 (100) | 0 |
| Serious TEAEs – Total | 3 (75.0) | 3 (75.0) | 22 (81.5) | 18 (60.0) | 29 (85.3) | 28 (73.7) | 8 (88.9) | 0 |
| Fatal | 1 (25.0) | 1 (25.0) | 7 (25.9) | 6 (20.0) | 13 (38.2) | 4 (10.5) | 3 (33.3) | 0 |
| Hospitalisation/prolong existing hospitalisation | 3 (75.0) | 3 (75.0) | 19 (70.4) | 17 (56.7) | 28 (82.4) | 28 (73.7) | 8 (88.9) | 0 |
| Life-threatening | 0 | 0 | 3 (11.1) | 5 (16.7) | 8 (23.5) | 5 (13.2) | 1 (11.1) | 0 |
| Disability/incapacity | 0 | 0 | 2 (7.4) | 1 (3.3) | 0 | 0 | 0 | 0 |
| Other medically significant | 0 | 0 | 5 (18.5) | 1 (3.3) | 5 (14.7) | 6 (15.8) | 0 | 0 |
| TEAEs leading to drop-out [1] | 0 | 1 (25.0) | 6 (22.2) | 4 (13.3) | 5 (14.7) | 7 (18.4) | 2 (22.2) | 0 |
| Psychiatric disorders | 2 (50.0) | 1 (25.0) | 5 (18.5) | 10 (33.3) | 10 (29.4) | 11 (28.9) | 3 (33.3) | 0 |
| Nervous system disorders | 0 | 3 (75.0) | 8 (29.6) | 9 (30.0) | 10 (29.4) | 13 (34.2) | 3 (33.3) | 0 |
| Accidents and injuries | 0 | 0 | 3 (11.1) | 3 (10.0) | 4 (11.8) | 8 (21.1) | 2 (22.2) | 0 |
| Cardiac disorders | 2 (50.0) | 1 (25.0) | 7 (25.9) | 4 (13.3) | 8 (23.5) | 7 (18.4) | 1 (11.1) | 0 |
| Vascular disorders | 2 (50.0) | 1 (25.0) | 6 (22.2) | 8 (26.7) | 9 (26.5) | 15 (39.5) | 2 (22.2) | 0 |
| Cerebrovascular disorders | 0 | 1 (25.0) | 1 (3.7) | 3 (10.0) | 0 | 4 (10.5) | 0 | 0 |
| Infections and infestations | 2 (50.0) | 4 (100) | 22 (81.5) | 19 (63.3) | 28 (82.4) | 29 (76.3) | 7 (77.8) | 0 |
| Anticholinergic syndrome | 2 (50.0) | 3 (75.0) | 16 (59.3) | 13 (43.3) | 21 (61.8) | 22 (57.9) | 5 (55.6) | 0 |
| Quality of life decreased | 0 | 0 | 0 | 0 | 3 (8.8) | 1 (2.6) | 0 | 0 |
| Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures | 2 (50.0) | 0 | 6 (22.2) | 5 (16.7) | 9 (26.5) | 11 (28.9) | 0 | 0 |

The denominator used to calculate percentages is N, the number of subjects in the safety analysis set within each column.
1] TEAE leading to drop-out is defined as AE leading to discontinuation of AG-120/Placebo regardless of azacitidine.
Source: AG120-C-009 MAA D120 Listing 16.6.1-1.1[f, Table 14.6-3.1c (Data cutoff date 01OCT2021)

### *2.7.8.8. Immunological events*

Not applicable.

### *2.7.8.9. Safety related to drug-drug interactions and other interactions*

***Discontinuation due to adverse events***

**Discontinuation**

The number of patients who discontinued ivosidenib or placebo only due to a TEAE were low in both treatment arms (4.2%, i.e. 3 patients and 4.1%, i.e. 3 patients in the experimental and control arm respectively). The reported PTs (one each) for these discontinuations were anaemia, ECG QT prolonged and insomnia in the experimental arm and thrombocytopenia, pneumonia, sepsis and myalgia for the control arm.

The number of patients who discontinued azacitidine only were also low in both treatment arms (2.8%, i.e. 2 patients and 1.4%, i.e. 1 patient in experimental and control arm respectively). The TEAE leading to discontinuation of azacitidine were all within the SOC Blood and lymphatic system disorders: febrile neutropenia (one in each treatment arm) and thrombocytopenia.

Dose interruption

Occurrences of dose interruption were higher in the ivosidenib + azacitidine arm (38 patients or 52.8%) than in placebo + azacitidine arm (30 patients or 40.5%) as well as mean (SD) (12.2 days (11.9) vs 7.4 days (10.1) and median (Q1, Q3) number of days with dose interruptions 7.0 days (3.0, 14.0) vs 3.0 (1.0, 10.0). These differences should be considered in the context of a longer treatment duration in experimental arm.

Overall, events leading to treatment interruption related to haematological toxicity (neutropenia and thrombocytopenia) and infections.

Dose reduction

In the pivotal study AGILE, the number of subjects with any cause reduction of ivosidenib or placebo was higher in experimental arm (12 patients or 16.7%) than in control arm (6 patients or 8.1%). This was expected in the context of a more than doubled median exposure duration in the active group (5.98 vs 2.76 months). Overall in the ivosidenib + azacitidine arm, events that led to dose reduction were related to haematological toxicity.

#### *2.7.8.10. Post marketing experience*

Cumulatively, as of 31 December 2021, approximately 3084 patients have been exposed to ivosidenib in the post-approval setting.

No new safety findings from marketing experience have arisen through 16 January 2022.

## 2.7.9. Discussion on clinical safety

The pivotal safety data for ivosidenib in combination with azacitidine are from the ongoing pivotal phase 3 study AG120-C-009 (AGILE) in patients who received the combination at the intended dose.

Even though this safety data base is limited, the intended target population is also quite small and limited to a small subset of AML patients who are ineligible to receive intensive chemotherapy and are harbouring IDH1 mutation. Thus, the size of the safety database is considered acceptable.

Baseline characteristics in the pivotal study were overall consistent with expected AML patient characteristics and balanced between both treatment arms except for platelets count which makes difficult any analysis of bleeding events.

The median duration of exposure to ivosidenib/placebo was twice longer in the ivosidenib + azacitidine arm than in the placebo + azacitidine arm, and more than twice patients received ivosidenib for more than 24 weeks in ivosidenib + azacitidine arm than in placebo + azacitidine arm.

The incidence of TEAEs, as well as grade 3 TEAEs, was similar between the experimental and the control arm in the pivotal trial.

As could be expected, more patients experienced a treatment-related TEAE to ivosidenib/placebo alone in ivosidenib + azacitidine arm than in placebo + azacitidine arm or to both ivosidenib/placebo and azacitidine. Nevertheless, Grade ≥ 3 TEAE related to ivosidenib/placebo alone or to azacitidine alone were comparable in experimental and control arm respectively.

Although serious TEAE were less frequent in ivosidenib + azacitidine arm than in placebo + azacitidine arm, more patients experienced serious treatment related TEAE to both ivosidenib and azacitidine than to both placebo and azacitidine.

TEAE leading to death were lower in ivosidenib + azacitidine arm than in placebo + azacitidine arm (15.3 % and 31.1% respectively) and none of them were considered related to any of the study treatments.

**Treatment Emergent Adverse Events**

In the pivotal study AGILE, common TEAE in experimental arm were mainly related to haematological and gastrointestinal toxicities. Indeed, the most frequently reported AE in experimental arm were PT of nausea (42.3%), vomiting (40.8%), diarrhoea (35.2%), pyrexia (33.8%), anaemia (31.0%), febrile neutropenia (28.2%), neutropenia (28.2%), thrombocytopenia (28.2%), constipation (26.8%) and pneumonia (23.9%). In addition, electrocardiogram QT prolongation (19.7%) and differentiation syndrome (14.1%) were also frequently observed.

The most frequently reported treatment related TEAE to ivosidenib and azacitidine pertained to SOC Gastrointestinal disorders (36.6%) and Blood and lymphatic system disorders (28.2%).

Regarding haematological toxicities, the PTs of neutropenia (28.2% vs 16.4%), thrombocytopenia (28.2% vs 20.5%) and leucocytosis (11.3% vs 1.4%) were more frequently reported in ivosidenib + azacitidine arm than in placebo + azacitidine arm respectively. Although azacitidine is known to be associated with haematological toxicity, differences between both treatment arms suggest that ivosidenib is also associated with neutropenia and thrombocytopenia. Furthermore, within experimental arm, the more frequent grade ≥ 3 TEAEs included febrile neutropenia (28.2%), neutropenia (26.8%), anaemia (25.4%), thrombocytopenia (23.9%) and pneumonia (22.5%), thus relating to haematological and infectious events.

The leucocytosis events that were reported did not appear to be life-threatening, and seemed to be manageable with hydroxyurea. The SmPC of ivosidenib recommends a periodic blood count as well as dose modifications and management in section 4.2 if leucocytosis occurs which are deemed adequate considering data from pivotal study. Neutropenia and thrombocytopenia are also described as ADRs in the SmPC for the AML indication.

A higher incidence of bleeding events was observed in the experimental arm (40.8%) compared to control arm (28.8%) including 2 events of fatal intracranial haemorrhage. Incidence of haematoma was also higher in experimental arm (12.7%) than in control arm (1.4%). Additional analysis meant to highlight confounding factors for events of haemorrhage are hampered as mentioned by the imbalance in platelet count at baseline between the treatment groups. Nevertheless, haemorrhage will be closely monitored in PSURs.

With regards to the risk of infection, although neutropenia any grade and grade 3 neutropenia were more frequent in experimental arm than in control arm, incidence of febrile neutropenia was lower in experimental arm compared to control arm. The incidence of events within the SOC Infections and infestations was high in both treatment arms but was lower in experimental arm (70.4%) than in control arm (79.5%). The incidence of Infections of any grade was lower in ivosidenib + azacitidine arm (28.3%) than in placebo + azacitidine (49.3%) as well as Grade ≥3 TEAEIs of infection, serious TEAEIs of infection, fatal TEAEIs of infection, and discontinuation of both ivosidenib or placebo and azacitidine due to infection. Therefore, the risk of infection does not seem to be increased by the combination.

Regarding PT related to gastrointestinal toxicities, incidences were similar between both treatment arms except for the PT of vomiting which was higher in experimental arm (40.8%) than in control arm (26.0%). Although azacitidine is also associated with gastrointestinal toxicities (diarrhoea, vomiting, constipation, nausea, abdominal pain), here again the difference between both treatment arms suggests than ivosidenib is associated with vomiting. Vomiting is described as an ADR without further

warning or recommendation which is endorsed as gastrointestinal toxicities were of low grade in general.

Other commonly reported TEAE were observed more frequently in the experimental arm compared to the control arm: insomnia, pain in extremities, arthralgia, headache, dizziness, oropharyngeal pain and back pain. These events are described as ADRs in the SmPC.

**Adverse Event of Special Interest**

Incidence of Electrocardiogram QT prolongation was higher in ivosidenib + azacitidine arm (19.7% with 9.9% of grade≥ 3) than in placebo + azacitidine arm (6.8% with 2.7% of grade≥ 3). Thus, QT prolongation was frequent and with high grade in half of the cases. ECG QT prolonged led to interruption of treatment in 4 cases (5.6%), to dose reduction in 6 cases (8.5%) and to treatment discontinuation in one case (1.4%).

Median (min, max) time to first AESI of electrocardiogram prolonged, assessed in study pivotal study AGILE (AG-120-C-009), was 29.0 days (1-141 days) with 21.4 % of first events that occurred > 60 days showing that event of QT prolonged can occur several weeks after reaching the concentration at steady state (Css).

Based on these observations, ivosidenib is contraindicated in patients with congenital long QT syndrome, familial history of sudden death or polymorphic ventricular arrythmia or a QT/QTc interval > 500 msec, regardless of the correction method.

In addition, ECG QT prolonged has been listed in section 4.8 of the SmPC, and currently, to mitigate the risk, it is recommended to monitor ECG prior initiation of the treatment, at least weekly for the first 3 weeks and then monthly. Recommendation to avoid concomitant treatment known to prolong the QTc interval or moderate or strong CYP3A4 inhibitors is also provided. Dose modifications are further recommended in case of grade 2, 3 and 4 ECG QT prolongation and in case administration of a strong CYP3A4 inhibitor is unavoidable (section 4.2 of the SmPC). In addition, a warning regarding QT prolongation is provided in section 4.4 with the recommendation to closely monitor patients with congenital long QTc syndrome, congestive heart failure or electrolyte abnormalities.

Considering that patients were carefully selected (QT <450 ms, no cardiac disease) in clinical studies which will not be the case in post-marketing setting and that dose-exposure relationship is highly variable, with a large proportion of patients exposed to potentially critical concentration with respect to QT interval prolongation, the recommendations were further strengthened to ensure better prevention and management of the risk. In addition, as QT prolongation is considered as an important identified safety concern in the RMP, events will be closely monitored in PSURs.

Incidence of differentiation syndrome was higher in experimental arm (14.1% with 9.9% Grade 2, 4.2% Grade 3) than in control arm (8.2% with 4.1% Grade 2, 2.7% Grade 3, and 1.4% Grade 4). The median number of days to first onset of Differentiation syndrome was 19.5 days (range: 3 to 33 days) in the experimental arm and 44 days (range: 4 to 86 days) in control arm.

Differentiation syndrome has been listed in section 4.8 of the SmPC. In addition, a warning describing the symptoms of differentiation syndrome and a recommendation to administer corticosteroids and initiate haemodynamic monitoring until resolution is provided. Treatment with Hydroxycarbamide is recommended in case of leucocytosis, by leukapheresis if clinically indicated and interruption of ivosidenib is required in case of grade 3 events (sections 4.2 and 4.4).

Although AML patients will be closely monitored at the beginning of the treatment, differentiation syndrome occurred at a high frequency, is a potential-life threatening event and can induce non-specific symptoms. In addition, given the oral administration of ivosidenib, patients will be mostly without HCP supervision whilst on treatment. Therefore, a patient alert card was considered necessary

for patients with AML, in order to alert patients on the symptoms of differentiation syndrome and the importance of seeking medical advice.

Additional events of clinical importance

Guillain Barré Syndrome: Although no event of Guillain Barré syndrome were observed in the pivotal study AGILE (AG120-C-009) or the supportive study AG-221-AML-005, 2 cases were reported in study AMG-C-001 (ivosidenib monotherapy at 500mg QD) and were assessed as related to the study treatment by the investigator. Moreover, 3 additional cases (2 post-market in US and 1 in France from compassionate use in another indication) were retrieved from EudraVigilance albeit with limited information. The applicant agreed to closely monitor cases of Guillain Barré in PSURs.

Leukoencephalopathy: 1 patient developed PRES in the monotherapy study AMG-C-001. This patient had previously been treated with cladribine which is a confounding factor, however the event was considered as possibly related to ivosidenib by the investigator. The applicant confirmed that these events will be closely monitored in post-marketing setting through PSURs.

Tumour Lysis Syndrome: 7.4% of treated patients in the monotherapy study AG120-C-001 experienced TLS but only one case of TLS was reported in the control arm of the pivotal study (and none in the ivosidenib. This apparent discrepancy could be explained by the investigators were aware about the risk of TLS in the pivotal study and had taken precautionary measures to mitigate its occurrence. TLS is described in the SmPC as a potential symptom of differentiation syndrome and cases of TLS will be closely monitored throughout PSURs.

**Safety in special populations**

The Analysis in special populations did not identify any trend but the limited number of patients in each sub-group does not allow any conclusion.

As the safety and efficacy of ivosidenib has not been established in patients with severe renal impairment (eGFR < 30 mL/min/1.73 $m^2$) or in patients with moderate and severe hepatic impairment (Child Pugh class B and C). Ivosidenib should be used with caution in these patients who should be closely monitored.

Given the limited information available in patients with organ impairment the applicant will conduct a study to evaluate the pharmacokinetics, safety and tolerability of ivosidenib in patients with haematologic malignancies with an IDH1 mutation with moderate hepatic impairment, severe hepatic impairment or severe renal impairment as described in the RMP.

## 2.7.10. Conclusions on the clinical safety

The size of the safety database used to characterise the safety profile of ivosidenib in combination with azacitidine in AML is acceptable due to the limited intended target population. Importantly the pivotal study for this application was a phase 3 study randomised and controlled versus azacitidine + placebo which allows to differentiate the toxicity due to ivosidenib.

The safety profile of ivosidenib in combination with azacitidine in patients with newly diagnosed AML is mainly related to QT prolongation, differentiation syndrome, haematological and gastrointestinal toxicity.

All these risks are managed through appropriate wording in the product information, most notably for QT prolongation which is contraindicated in patients with relevant medial history and detailed warnings on precautions to be taken prior to administration, monitoring and management of this risk.

Patients will be given a patient alert card to recognise the symptoms and highlight the importance of seeking medical advice if experiencing differentiation syndrome. A patient survey cross-sectional study will assess the effectiveness of the patients' alert card for ivosidenib in AML patients (see RMP).

## *2.8. Risk Management Plan*

### 2.8.1. Safety concerns

The applicant proposed the following summary of safety concerns in the RMP:

**Table 47.** Summary of safety concerns

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

### 2.8.2. Pharmacovigilance plan

**Table 48**. On-going and planned additional pharmacovigilance activities

| **Study Status** | **Summary of objectives** | **Safety concerns addressed** | **Milestone** | **Due dates** |
|---|---|---|---|---|
| **Category 1** - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation | | | | |
| None | | | | |
| **Category 2** – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances | | | | |
| None | | | | |
| **Category 3** - Required additional pharmacovigilance activities | | | | |

| Study Status | Summary of objectives | Safety concerns addressed | Milestone | Due dates |
|---|---|---|---|---|
| Organ impairment substudy of AG120-C-001<br><br>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<br><br>**Status:** Ongoing | To evaluate the pharmacokinetics, safety and tolerability of ivosidenib in patients with haematologic malignancies with an IDH1 mutation with moderate hepatic impairment, severe hepatic impairment or severe renal impairment. | • Use in patients with moderate and severe hepatic impairment<br>• Use in patients with severe renal impairment | Final report available | Planned for Q4 2025. |
| Patients survey study to assess the effectiveness of the additional risk minimisation measures.<br><br>Cross-sectional study to assess the effectiveness of the patients' alert card for ivosidenib in AML patients.<br><br>**Status:** Planned | To evaluate the effectiveness of the PAC for awareness of differentiation syndrome in AML patients, using process indicators for awareness, receipt of the material, utility and knowledge. | • Differentiation Syndrome in the AML indication. | Protocol submission | Within 3 months following EC decision |
| | | | Final report available | Planned for Q4 2025 |

## 2.8.3. Risk minimisation measures

## Table 43. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| Differentiation Syndrome in patients with AML (Important identified risk) | Routine risk minimisation measures:<br>*SmPC section 4.2, 4.4 and 4.5 where advice is given for monitoring and management of differentiation syndrome along with its treatment and temporary interruption of ivosidenib.*<br>*SmPC section 4.4 and PL section 2 where warning is given in that differentiation syndrome may be life-threatening or fatal if not treated along with description of symptoms.*<br>*SmPC section 4.8.*<br>*PL section 4 where advice is given to seek urgent medical attention if patient experiences side effects/symptoms corresponding to differentiation syndrome.*<br>Legal status: Prescription only medicine.<br>Treatment to be initiated by experienced oncologist.<br>Additional risk minimisation measures:<br>Patient Alert Card | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• Differentiation syndrome follow-up questionnaire.<br>Additional pharmacovigilance activities:<br>• Cross-sectional study to assess the effectiveness of the patients' alert card for ivosidenib in AML patients.<br>• Final report due date: Planned for Q4 2025. |
| QT prolongation<br>(Important identified risk) | Routine risk minimisation measures:<br>*SmPC section 4.3 and PL section 2 where contraindications are listed for patients with increase risk of QTc prolongation*<br>*SmPC section 4.2 and 4.4 where guidance is given on regular, and when required continuous, ECG monitoring and management of QTc interval prolongation, also reflected in the PL section 2.*<br>*SmPC section 4.2, 4.4 and 4.5. where advice is given for monitoring and management of concomitant administration of moderate or strong CYP3A4 inhibitors (leads to increase in plasma concentrations of ivosidenib) and medicines that prolong QT interval.* | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>None<br>Additional pharmacovigilance activities:<br>None |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| | *SmPC section 4.4 where warning is given that QTc interval prolongation has been reported following treatment with ivosidenib. Patients with congestive heart failure or electrolyte abnormalities should be monitored closely, with periodic monitoring of ECGs and electrolytes, during treatment with ivosidenib. Ivosidenib should be used with caution in patients with albumin levels below the normal range and underweight patients.*<br><br>*SmPC section 4.8.*<br><br>*PL section 2 and 4 where warning is given that ivosidenib can cause a serious condition known as QTc interval prolongation which can be life threatening. Advice is given to seek urgent medical attention if patient experiences side effects/symptoms corresponding to QTc interval prolongation*<br><br>*PL section 2 where patient is advised to talk to the doctor if the patient has heart problems or have problems with abnormal electrolytes levels or patient is taking any medicines that affects the heart, along with advice on regular ECG monitoring.*<br><br>Legal status: Prescription only medicine.<br><br>Treatment to be initiated by experienced oncologist<br><br>Additional risk minimisation measures:<br><br>None | |
| Embryo-foetal toxicity<br><br>(Important potential risk) | Routine risk minimisation measures:<br><br>*SmPC section 4.4, 4.6 and PL section 2 where warning is given that woman of childbearing potential should have a pregnancy test done prior to start of therapy and the women of childbearing potential and males with female partners of childbearing potential should use effective contraception during treatment with ivosidenib and for at least 1 month after the last dose.* | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>• Pregnancy follow-up questionnaire.<br><br>Additional pharmacovigilance activities:<br><br>None |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| | *SmPC section 4.4, 4.5, 4.6 and PL section 2 where caution is advised that ivosidenib may decrease the systemic concentrations of hormonal contraceptives and, therefore, concomitant use of a barrier method of contraception is recommended.*<br><br>*SmPC section 4.6 where advice is given that ivosidenib is not recommended for use during pregnancy and in women of childbearing potential not using effective contraception; if a patient (or female partner of a treated male patient) becomes pregnant during treatment or during the one-month period after the last dose, they should be informed of the potential risk to the foetus.*<br><br>*PL section 2 where advice is given that ivosidenib is not recommended during pregnancy as it may harm the unborn baby. Furthermore, patient should consult doctor if the patient is pregnant, thinks she might be pregnant or is planning to have a baby, before taking ivosidenib.*<br><br>Legal status: Prescription only medicine.<br><br>Treatment to be initiated by experienced oncologist<br><br>Additional risk minimisation measures:<br><br>None | |
| Use in patients with moderate and severe hepatic impairment<br><br>(Missing information) | Routine risk minimisation measures:<br><br>*SmPC section 4.2 and 4.4 where warning is given that the safety and efficacy of ivosidenib have not been established in patients with moderate and severe hepatic impairment (Child Pugh classes B and C respectively), therefore ivosidenib should be used with caution and this patient population should be closely monitored.*<br><br>*SmPC section 4.8.*<br><br>*PL section 2 where advice is given to talk to the doctor if the patient has any liver problem before taking ivosidenib.* | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br><br>None<br><br>Additional pharmacovigilance activities:<br><br>• Organ impairment substudy of AG120-C-001. |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| | Legal status: Prescription only medicine.<br>Treatment to be initiated by experienced oncologist<br>Additional risk minimisation measures:<br>None | • Final report due date: Planned for Q4 2025. |
| Use in patients with severe renal impairment<br>(Missing information) | Routine risk minimisation measures:<br>*SmPC section 4.2 and 4.4 where warning is given that the safety and efficacy of ivosidenib have not been established in patients with severe renal impairment (eGFR < 30 ml/min/1.73 $m^2$) therefore, ivosidenib should be used with caution and this patient population should be closely monitored.*<br>*PL section 2 where advice is given to talk to the doctor if the patient has any kidney problem before taking ivosidenib.*<br>Legal status: Prescription only medicine.<br>Treatment to be initiated by experienced oncologist<br>Additional risk minimisation measures:<br>None. | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>None<br>Additional pharmacovigilance activities:<br>• Organ impairment substudy of AG120-C-001.<br>• Final report due date: Planned for Q4 2025. |

### 2.8.4. Conclusion

The CHMP considers that the risk management plan version 1.0 is acceptable.

## *2.9. Pharmacovigilance*

### 2.9.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

### 2.9.2. Periodic safety update reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD

to determine the forthcoming data lock points.

## *2.10. Product information*

### 2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

### 2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Tidhesco (ivosidenib) is included in the additional monitoring list as it contains a new active substance.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

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

Acute myeloid leukaemia is characterised by uncontrolled proliferation of clonal neoplastic 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).

### 3.1.2. Available therapies and unmet medical need

The standard treatment strategy for newly diagnosed AML includes the option of standard Induction Chemotherapy (IC) and consolidation chemotherapy, or non-intensive treatment. Consolidation therapy for patients in complete response after IC consists of either chemotherapy, autologous haematopoietic stem cell transplantation (HSCT) or allogeneic HSCT.

Hypomethylating agents (HMA) such as azacitidine and decitabine are still considered options for patients who are not candidates for intensive chemotherapy.

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

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

### 3.1.3. Main clinical studies

The main evidence of efficacy is based on the AGILE study (n=146), a Phase 3, multicentre, double-blind, randomised, placebo-controlled clinical trial to evaluate the efficacy and safety of ivosidenib + azacitidine vs placebo + azacitidine in adult subjects with previously untreated IDH1-mutated AML and who are considered appropriate candidates for non-intensive therapy. A total of 146 patients were randomised, including 72 in the ivosidenib + azacitidine arm, and 74 in the placebo + azacitidine arm. The treatment arms were balanced in terms of demographics and baseline characteristics.

## *3.2. Favourable effects*

An improvement in the primary endpoint of EFS was observed following treatment with ivosidenib + azacitidine with a 67% reduction in the risk of progression/relapse or death compared to the placebo + azacitidine arm (HR = 0.33; 95% CI: 0.16-0.69). Results of the sensitivity analysis were consistent with these results.

The CR+CRh rate was higher in ivosidenib + azacitidine arm than in placebo + azacitidine arm (52.8% [95% CI: 40.7-64.7] versus 17.6% [95% CI: 9.7-28.2]; odds ratio of 5.01 [95% CI: 2.32-10.81]).

The CR rate in the FAS was higher in ivosidenib + azacitidine arm compared to placebo + azacitidine arm: 47.2% (95% CI: 35.3-59.3) versus 14.9% (95% CI: 7.7-25.0) with an odds ratio of 4.76 (95% CI: 2.15-10.50).

Medians OS of 24.0 months (95% CI: 11.3-34.1 months) in ivosidenib + azacitidine arm and 7.9 months (95% CI: 4.1-11.3 months) in placebo + azacitidine arm were observed. Median follow-up time was approximately 15 months for both treatment arms. Clinically relevant improvement in OS was shown for subjects in ivosidenib + azacitidine arm compared to placebo + azacitidine arm (HR = 0.44; 95% CI: 0.27-0.73 which is highly superior to the HR of 0.71 assumed in the initial sample size assumptions). This was confirmed by an updated median OS was 29.3 months in the treatment arm (HR = 0.42; 95% CI: 0.27-0.65) as of 30 June 2022.

ORR was achieved in 62.5% (95% CI: 50.3-73.6) of the subjects in ivosidenib + azacitidine arm and 18.9% (95% CI: 10.7-29.7) of the subjects in placebo + azacitidine arm. ORR was higher in the ivosidenib + azacitidine arm than in the placebo + azacitidine arm (odds ratio of 7.15 [95% CI: 3.31-15.44]).

Duration of complete remission was observed in the ivosidenib + azacitidine arm in 93.3, 88.4, 88.4, 78.6 and 58.9% of patients at 6, 9, 12, 18 and 24 months, respectively.

Quality of life data was collected as part of the study. More than 90% of subjects in each treatment arm completed baseline EORTC QLQ-C30 and EQ-5D-5L questionnaires. For similar baseline scores, a clinically meaningful improvement was observed in the experimental arm characterised by less fatigue and better general condition. Although these data are not statistically significant, they can be considered supportive of the observed clinical benefit.

No significant difference in transfusion requirement was observed between the two treatment arms during the study, regardless of the baseline transfusion status. The fact that the combination does not increase the need for transfusion is reassuring from both an efficacy and safety point of view.

## 3.3. Uncertainties and limitations about favourable effects

The main uncertainty regarding the combination of ivosidenib and azacitidine efficacy is related to the magnitude of the treatment effect due to the critical changes to the protocol made during the conduct of the study, including the change of the primary endpoint from OS to EFS. Together with the change in primary endpoint, the planned sample size was reduced (from 392 to 200) and the initially planned interim analysis was removed from the protocol. The discontinuation of the study based on an unplanned analysis of unblinded efficacy data raised further concerns about the trial integrity, and specifically about the inflation of the type I error. In the absence of any pre-specified interim analysis rules, and despite the implementation of post-hoc boundaries, the type I error cannot be considered to be formally controlled.

At the request of the CHMP the applicant provided a detailed discussion of the major changes introduced by protocol amendments, as well as supplementary analyses. Based on this information there seems to be a limited impact on the reported results from these major changes to study design and analysis plan. Nevertheless, the lack of type I error resulting from the unplanned early stop of the trial remains an issue, regardless of initial or updated post-hoc adjustments, and cannot be resolved retrospectively. Consequently, the applicant removed the p-values from all endpoints which are presented in the SmPC. On the other hand, it is acknowledged that the results are strong and further supported by a number of additional sensitivity analyses. This together with the evidence provided that the most concerning amendments in the study were implemented when the applicant was still blinded, offers reassurance about the reported results.

HRQoL analyses remain exploratory and should be interpreted with caution especially as compliance decreased over the course of treatment cycles (80% at cycle 5 versus 70% at cycle 19 with no data for the placebo + azacitidine group).

## 3.4. Unfavourable effects

In the pivotal AGILE study, the incidence of TEAE as well as grade 3 TEAE were similar between experimental and control arm.

TEAE in experimental arm were mainly related to haematological and gastrointestinal toxicities. In addition QT prolongation and differentiation syndrome were also frequently observed.

Regarding haematological toxicities, neutropenia (28.3% vs 16.4%), thrombocytopenia (28.2% vs 20.5%) and leucocytosis (11.3% vs 1.4%) were more frequently reported in ivosidenib + azacitidine arm than in placebo + azacitidine arm respectively and include frequent grade ≥ 3 toxicities. Although azacitidine is known to be associated with haematological toxicity, differences between both treatment arms suggest that ivosidenib is also associated with neutropenia and thrombocytopenia. Overall, haematological toxicities were managed with treatment interruption or dose reductions which are described extensively in the product information

On the other hand, gastrointestinal toxicities were similar between both arms except for vomiting (40.8% in experimental arm vs 26.0% in control arm). Azacitidine is also known to be associated with gastrointestinal toxicity but ivosidenib appears to be associated mostly with vomiting. Unlike haematological event, gastrointestinal events were mainly low grade.

The major risk of ivosidenib is the risk of QT prolongation, occurring in 19.7% of patients with 9.9% of grade≥ 3. Thus, QT prolongation was frequent and occurred at high grade in half of the cases, with the potential risk of ventricular arrhythmias.

Furthermore, incidence of differentiation syndrome was higher in experimental arm (14.1% with 9.9% Grade 2, 4.2% Grade 3) than in control arm (8.2% of subjects with 4.1% Grade 2, 2.7% Grade 3, and 1.4% Grade 4). The median number of days to first onset of the PT of Differentiation syndrome was longer in experimental arm with 19.5 days (range: 3 to 33 days) than in experimental arm and 44 days (range: 4 to 86 days) in control arm.

## *3.5. Uncertainties and limitations about unfavourable effects*

The main limitation in the characterisation of the safety profile of ivosidenib is the size of the safety database which is very small (71 patients in the pivotal study + 23 patients in the supportive study), although acceptable considering the very specific target population which is a subpopulation of patients with AML and the larger safety database in monotherapy provided by post-marketing data in the US; moreover, a direct comparison with the control group allows to discriminate AE due to ivosidenib.

Concerns are raised about the risk of haemorrhage considering that a higher incidence of bleeding events was observed in the experimental arm (41.7%) compared to control arm (31.1%) although grade 3 haemorrhage were similar (6.9% and 8.1% in the experimental and control arm respectively). A higher incidence of haematoma was also observed in the experimental arm compared to the control arm (12.7% and 1.4% respectively). The evaluation of the risk of haemorrhage related to the treatment is difficult as baseline characteristics showed that median platelets count was lower in experimental arm compared to control arm. As thrombocytopenia is already listed in the SmPC no further measures for this risk were considered necessary but will remain under close monitoring in the post0marketing setting.

Moreover, although no events of Guillain-Barré syndrome or leukoencephalopathy were observed in the pivotal study or the supportive study AG-221-AML-005, a small number of these events were reported in the monotherapy study in patients with R/R AML and from the post-marketing setting. Information on these events is limited but the applicant agreed to set up a close monitoring of these in the PSURs.

Finally, no conclusion can be drawn from description in safety in special groups and populations related to limited number of patients in each subgroup and this is reflected in the product information.

## *3.6. Effects Table*

**Table 49.** Effects Table for Tidhesco in newly diagnosed IDH1-mutated AML (data cut-off: 18 March 2021)

| Effect | Short description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| EFS | Events (%) | n (%) | 46 (63.9) | 62 (83.8) | HR = 0.33<br>95% CI: 0.16, 0.69 | Study AG120-C-009 |
| OS | Median | months | 24.0 | 7.9 | HR = 0.44<br>95% CI: 0.27, 0.73 | |
| CR+CRh | Rate of complete remission | n (%) | 38 (52.8) | 13 (17.6) | HR = 5.01<br>95% CI: 2.32, 10.81 | |
| **Unfavourable Effects** | | | | | | |
| Leukocytosis | Incidence | % | 11.3 | 1.4 | | Study AG120-C-009 |
| ECG QT prolonged | | % | 19.7 | 6.8 | | |
| Thrombocytopenia | | % | 28.2 | 220.5 | | |

| Effect | Short description | Unit | Treatment | Control | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| Neutropenia | | % | 28.2 | 16.4 | | |
| Differentiation syndrome | | % | 14.1 | 8.2 | | |

Abbreviations: EFS: event free survival; HR: hazard ratio; CI: confidence interval; OS: overall survival, CR: complete remission; CRh: complete remission with partial haematologic recovery; ECG: electrocardiogram

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

The most important efficacy effects were the clinically relevant improvements in EFS, OS and CR/CRh in the treatment group compared to the control group. Overall survival is considerably prolonged in patients who received the combination: this 16-month improvement indicates a meaningful clinical benefit in these fragile and poor-prognosis subjects.

These survival data, along with the EFS and remission results are considered encouraging despite statistical considerations on the reporting of the results.

The major risk of ivosidenib is the risk of QT prolongation, which was frequently observed and occurred at high grade in half of the cases, with the potential risk of ventricular arrhythmias. This risk is managed by restricting the use of the product in patients at high risk for these events and extensive warnings in the product information. In addition, events of QT prolongation will be closely monitored through PSURs.

Furthermore, a high incidence of differentiation syndrome was observed in association with ivosidenib use. A warning describing the symptoms of differentiation syndrome and a recommendation to administer corticosteroids and initiate haemodynamic monitoring until resolution is included in the product information. To further mitigate this risk, a patient alert card describing the symptoms and the need to seek medical advice will be given to patients.

### 3.7.2. Balance of benefits and risks

The benefit/risk balance of ivosidenib use is positive for the treatment in combination with azacitidine of adult patients with newly diagnosed acute myeloid leukaemia (AML) with an isocitrate dehydrogenase-1 (IDH1) R132 mutation who are not eligible to receive standard induction chemotherapy.

## *3.8. Conclusions*

The overall benefit/risk balance of Tidhesco is positive, subject to the conditions stated in section 'Recommendations'.

# 4. Recommendations

***Similarity with authorised orphan medicinal products***

The CHMP by consensus is of the opinion that Tidhesco is not similar to Dacogen, Rydapt, Mylotarg,

Vyxeos liposomal, Xospata and Daurismo within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

***Outcome***

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Tidhesco is favourable in the following indication:

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

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

***Conditions or restrictions regarding supply and use***

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

***Other conditions and requirements of the marketing authorisation***

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

***Conditions or restrictions with regard to the safe and effective use of the medicinal product***

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

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

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

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

The patient information pack:

- Patient information leaflet
- Patient alert card:

o Information for patients with AML that Tidhesco treatment may cause differentiation syndrome.

o Description of signs or symptoms of the safety concern and when to seek medical care if differentiation syndrome is suspected.

o A warning message for healthcare professionals treating the patient at any time, including in conditions of emergency, that the patient is using Tidhesco.

o Contact details of the treating physician who has prescribed Tidhesco.

o Need to be carried all the time and presented to any healthcare professional.

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

***Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States***

Not applicable.

***New Active Substance Status***

Based on the CHMP review of the available data, the CHMP considers that ivosidenib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.