CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA Multidisciplinary Review and Evaluation

Application Number	**NDA 211192**
Application Type	Original 351(a)
Priority or Standard	Priority Expedited
Submit Date	12/21/2017
Received Date	12/21/2017
PDUFA Goal Date	8/21/2018
Division/Office	DHP/OHOP
Review Completion Date	
Applicant	Agios Pharmaceuticals, Inc.
Established Name	Ivosidenib
(Proposed) Trade Name	Tibsovo
Pharmacologic Class	Isocitrate dehydrogenase-1 inhibitor
Formulations	Tablet (250 mg)
Dosing Regimen	500 mg taken orally once daily
Applicant Proposed Indication/Population	For the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test.
Recommendation on Regulatory Action	Regular approval
Recommended Indication/Population	For the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test

Addendum Clinical Pharmacology

In the Clinical Pharmacology section of the finalized review, the following appears under "Outstanding Issues":
We have issued one PMR, as presented in the PMR/PMC Section above. There are no other outstanding issues.

It should be corrected to:
We hve issued two PMRs, as presented in the PMR/PMC Section above. There are no other outstanding issues.

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

WENCHI HSU
07/20/2018

GENE M WILLIAMS
07/20/2018

NDA Multidisciplinary Review and Evaluation

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Application Type	Original 351(a)
Priority or Standard	Priority Expedited
Submit Date	12/21/2017
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Division/Office	DHP/OHOP
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Glossary

2-HG	2-hydroxyglutarate
α-KG	alpha-ketoglutarate
AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
a-fib	atrial fibrillation
AKI	acute kidney injury
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APL	acute promyelocytic leukemia
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
ATRA	all-trans retinoic acid
BID	twice daily
BLA	biologics license application
BM	bone marrow
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBC	complete blood count
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CK	creatine kinase
CMC	chemistry, manufacturing, and controls
CMML	chronic myelomonocytic leukemia
CMP	comprehensive metabolic panel
CMV	cytomegalovirus
CNS	central nervous system
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete remission
CRF	case report form
CRh	Complete remission with partial hematologic recovery
CRi	Complete remission with incomplete hematologic recovery

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CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CSF	cerebrospinal fluid
CTCAE	Common Terminology Criteria for Adverse Events
CXR	chest x-ray
DHOT	Division of Hematology Oncology Toxicology
DLT	dose limiting toxicity
DMC	data monitoring committee
DOCR	duration of CR
DOR	duration of response
DS	differentiation syndrome
ECG	electrocardiogram
eCTD	electronic common technical document
EFS	event-free survival
EMG	electromyography
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GBS	Guillain-Barre syndrome
GCP	good clinical practice
GRMP	good review management practice
GVHD	graft versus host disease
HLH	hemophagocytic lymphohistiocytosis
HSCT	hematopoietic stem cell transplantation
ICH	International Conference on Harmonization
IDH	isocitrate dehydrogenase
IND	Investigational New Drug
IRB	Institutional Review Board
IRC	Independent Review Committee
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LP	lumbar puncture
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MLFS	morphologic leukemia-free state
mOS	median overall survival
MRD	minimal residual disease

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MTD	maximum tolerated dose
MUGA	multi-gated acquisition
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NR	normal range
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	overall response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report PD pharmacodynamics
PD	progressive disease
PE	pulmonary embolism
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PML	progressive multifocal leukoencephalopathy
PMR	postmarketing requirement
PO	by mouth
PP	per protocol
PPI	patient package insert
PR	partial remission
PREA	Pediatric Research Equity Act
PRES	posterior reversible encephalopathy syndrome
PRO	patient reported outcome
PS	performance status
PSUR	Periodic Safety Update report
RAEB	refractory anemia with excess blasts
RBCs	red blood cells
REMS	risk evaluation and mitigation strategy
RP2D	recommended phase 2 dose
R/R	relapsed or refractory
RVR	rapid ventricular response
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SD	stable disease
SE	standard error
SGE	special government employee
SMQ	Standardized MedDRA Query

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SOC	standard of care
TEAE	treatment emergent adverse event
ULN	upper limit of normal
UTI	urinary tract infection
VAF	variant allele frequency
WBC	white blood cell

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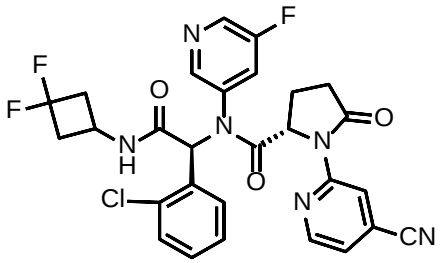
1 Executive Summary

1.1 Product Introduction

Proposed Trade Name:	TIBSOVO®
Established Name:	ivosidenib
Also Known As:	AG-120, AGI-16678
Chemical Name:	(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
Molecular Formula:	$C_{28}H_{22}ClF_3N_6O_3$
Molecular Weight:	583 g/mol
Dosage Forms:	Tablets, 250 mg
Therapeutic Class:	Antineoplastic
Chemical Class:	Small molecule
Pharmacologic Class:	Isocitrate dehydrogenase-1 (IDH1) inhibitor
Mechanism of Action:	Inhibition of the IDH1 enzymes with gain-of-function mutations decreases 2-hydroxyglutarate (2-HG) levels and induces myeloid differentiation.

Chemical Structure:



Ivosidenib is a new molecular entity. NDA 211192 was submitted for the proposed indication of treatment of adults with relapsed or refractory acute myeloid leukemia with an IDH1 mutation using a dose of 500 mg daily.

1.2 Conclusions on the Substantial Evidence of Effectiveness

The review team recommends regular approval of ivosidenib under 21 CFR 314.105 for the indication "treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test" using a dose of 500 mg daily. The recommendation is based on the finding of durable complete remission with complete or partial hematopoietic recovery (CR/CRh) and conversion to transfusion independence in Study AG120-C-001 (NCT02074839).

Safety during long-term use and appropriate dosing for patients with hepatic impairment remain to be determined in postmarketing studies.

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Study AG120-C-001 was an open-label, nonrandomized, multicenter, two-part, multi-arm clinical trial of ivosidenib for adults with AML and other myeloid neoplasms having an IDH1 R132 mutation; the design included a Phase 1 (dose-escalation and dose-expansion) portion and a Phase 2 portion that included two groups (Arms 1 and 4) for patients with relapsed or refractory (R/R) AML. The dose of 500 mg daily used in the pivotal analysis population was based on results from the Phase 1 portion which showed a) exposure was essentially over-lapping for doses ≥ 500 mg, b) maximal suppression of 2-hydroxyglutarate was achieved using ivosidenib doses ≥ 500 mg, c) similar response rates were observed at doses ≥ 500 mg, d) cohorts at doses > 500 mg had dose-limiting toxicities, and e) there was a higher predicted risk of QT prolongation with doses > 500 mg.

The primary efficacy endpoint of Study AG120-C-001 was investigator-assessed CR + sponsor-derived CRh in all patients in Arm 1 and in Arm 1-eligible patients from the escalation phase treated with ivosidenib 500 mg (Arm1+ population). The analysis was to be performed when at least 125 subjects completed 6 months of treatment or discontinued earlier. The sample size had 89% power to identify a 20% response rate while excluding a 10% response rate with a 2-sided alpha of 0.05. Additional assessments of transfusion requirements were also planned. In the Arm1+ population, the applicant reported that a CR or CRh was achieved by 38 subjects (30.4%; 95% CI 22.5%-39.3%), so the primary objective of the study was met.

FDA sought to assess efficacy in the broadest population available. Study AG120-C-001 enrolled 179 subjects identified by the applicant as having R/R AML with an IDH1 mutation treated with ivosidenib 500 mg daily. FDA excluded enrolled subjects who did not have documentation of relapse at study entry and subjects who were not confirmed positive for IDH1 R132 mutation using the proposed companion diagnostic assay. Using the updated data set with a cut-off of 11/10/2017, FDA identified 174 subjects for analysis. The study population had a median age of 67 years (range, 18-87 years), 64% were at least 65 years old, 51% were male, and 62% were white. The median number of prior therapies was 2 (range, 1-6), 37% were in untreated relapse, 37% were primary refractory, and 26% had a refractory relapse. Forty (23%) subjects had a prior stem cell transplantation.

The CR/CRh rate as adjudicated by the clinical reviewer was 33% (95% CI: 26% - 40%). The median time to response was 2 months (range, 0.9 - 5.6 months), and the median duration of response was 8.2 months (95% CI: 5.6 - 12 months). Responses were seen across demographic and disease status subgroups. Among the 110 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 41 (37%) became independent of RBC and platelet transfusions during any 56-day postbaseline period. Of the 64 patients who were independent of both RBC and platelet transfusions at baseline, 38 (59%) remained transfusion-independent during any 56-day postbaseline period.

It is concluded that the durable CR or CRh associated with transfusion-independence induced by ivosidenib constitutes substantial evidence of effectiveness.

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1.3 Benefit-Risk Assessment

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• With supportive care alone, patients with R/R AML survive only weeks.	R/R AML is a fatal disease.
Current Treatment Options	• For R/R AML with IDH1 mutations, the reported CR or CRi rates using current available therapy for 2nd or later salvage are 36-40% with a median survival of 4-6 months. The CR rate is unknown. • Most elderly patients with R/R AML would not tolerate combination chemotherapy.	There is a need for an effective agent for treatment of R/R AML, especially a treatment that would be tolerated by older patients.
Benefit	• In Study AG120-C-001, a single-arm trial, 174 adults with IDH1-mutated R/R AML were treated with ivosidenib 500 mg daily orally. • CR or CRh was achieved by 33% (95% CI: 26% - 40%). • Conversion to transfusion independence was achieved by 37%, and 59% maintained transfusion independence. • Median OS was 9.1 months (95% CI 7.4-10.2 months)	There is substantial evidence of effectiveness for ivosidenib as a palliative treatment of R/R AML with IDH1 mutation. There are no data that suggest long-term disease control.
Risks and Risk Management	• The most common adverse reactions (≥20%) included fatigue, leukocytosis, arthralgia, diarrhea, dyspnea, edema, nausea, mucositis, electrocardiogram QT prolonged, rash, pyrexia, cough and constipation. • Differentiation syndrome (DS), QT interval prolongation and Guillain-Barre syndrome that was life-threatening or fatal occurred. Early diagnosis and intervention are needed to prevent treatment-related mortality. • Dosing modifications for patients with hepatic impairment have not been established. • The protocol included monitoring for risks and instructions for intervention. With this in place, serious DS could be avoided. A dose reduction for toxicity was required for 3% of subjects and discontinuation for 13%.	The overall short-term safety profile of ivosidenib is acceptable for patients R/R IDH1-mutated AML. Long-term safety information and guidance for dosing with hepatic impairment is needed. A patient medication guide is required to inform and educate patients of the risk of DS and when to seek immediate medical attention. Labeling should include a warning for the serious risks, instructions for monitoring, and dose modifications for toxicities.

Patients with R/R IDH1-mutated AML that has relapsed or that is refractory to induction therapy have a devastating prognosis. In Study AG120-C-001, 33% (95% CI: 26% - 40%) of the study subjects treated with ivosidenib achieved a CR or CRh, conversion to transfusion-independence was achieved by 37%, and 59% maintained transfusion independence. Follow-up is too short to determine whether there is a long-term benefit or substantial effect on survival from use of this differentiating agent. Instead, FDA chose to base the finding of effectiveness on durable CR/CRh and transfusion independence, which even in the short-term provides a meaningful benefit for patients. Of note, given that there are IDH1 mutations that do not confer the pathogenic gain of function or that are not inhibited by ivosidenib (Intlekofer, Shih, et al. 2018), labeling should clarify that approval is specifically for patients with susceptible mutations (i.e., pathogenic and inhibited by ivosidenib).

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In the current era, intensive chemotherapy is the usual treatment approach for patients with R/R AML, but many of these patients are elderly and will not tolerate such treatment. In the safety population for AG221-C-001, only 13% of the study subjects terminated therapy due to an adverse reaction. The results provide substantial evidence that ivosidenib at least short-term is tolerable for most patients.

The major safety issues identified were differentiation syndrome (DS), QT prolongation and Guillain-Barre syndrome. Investigators identified DS in 11% of subjects, but the incidence may be as high as 40% based on an algorithmic approach. Two deaths due to DS was identified in the safety population. QT prolongation occurred in 9-14%, and ventricular arrhythmias were observed. Neuropathy was reported for 12%, and Guillain-Barre syndrome occurred in 2 (<1%). With procedures in place for early detection and intervention, fatal toxicities in the pivotal population were limited. The seriousness of these risks warrants a boxed warning and specific instructions to patients regarding the risks and need for early intervention, especially for DS.

Given the potential to avoid transfusions short-term using ivosidenib in addition to the tolerability of this drug, and with the safety mitigation plan in place, the clinical benefit appears to outweigh the risks of ivosidenib for patients with R/R AML with susceptible IDH1 mutations who are not seeking treatment with curative intent.

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application

☐	The patient experience data that was submitted as part of the application, include:	Section
	☐ Clinical outcome assessment (COA) data, such as	
	☐ Patient reported outcome (PRO)	
	☐ Observer reported outcome (ObsRO)	
	☐ Clinician reported outcome (ClinRO)	
	☐ Performance outcome (PerfO)	
	☐ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐ Patient-focused drug development or other stakeholder meeting summary reports	
	☐ Observational survey studies designed to capture patient experience data	
	☐ Natural history studies	
	☐ Patient preference studies (e.g., submitted studies or scientific publications)	
	☐ Other: (Please specify)	
X	No patient experience data were submitted in the application.	

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Cross-Disciplinary Team Leader

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2 Therapeutic Context

2.1 Analysis of Condition

Acute myeloid leukemia (AML) is a heterogeneous group of hematopoietic neoplasms characterized by a clonal proliferation of myeloid precursors with limited ability to differentiate into more mature myeloid cells. These blasts replace normal hematopoietic tissue in the bone marrow (BM), resulting in pancytopenia. According to the National Cancer Institute's SEER database, it is estimated that there were 21,380 new cases of AML and 10,590 deaths from AML in the United States in 2017. AML occurs in children and adults of all ages, but is primarily a disease of older adults, with a median age at diagnosis of 67 years. AML is more common in men than women (5.2 vs 3.6 new cases per 100,000 persons per year) and does not have a strong racial or ethnic predilection (Howlader N 2017). AML is universally fatal without treatment, with a median survival of approximately two months (Oran & Weisdorf 2012).

Isocitrate dehydrogenases (IDH) catalyze the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG) during cellular metabolism. Mutations of the IDH1 isoform are found in 6-16% of patients with AML (Im et al. 2014). These mutations are typically heterozygous and confer a new ability of the enzyme to catalyze the production of 2-hydroxyglutarate (2-HG). Increased cellular 2-HG levels contribute to epigenetic mechanisms of pathogenesis by inhibiting α-KG-dependent enzymes important for normal DNA methylation. IDH1 mutations are associated with older age, higher platelet levels, normal cytogenetics, NPM1, and FLT3-ITD mutations (DiNardo et al. 2015; Im et al. 2014). They are thought to be mutually exclusive with TET2 and WT1 mutations. There is conflicting information available regarding the prognostic significance of IDH1 mutations in AML, and no prospective studies have addressed this question. In one large retrospective analysis (Dinardo et al, 2015), 65% of patients with newly diagnosed IDH1+ AML achieved a complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) after induction therapy, compared to 69% of those with IDH wild-type (IDH^{WT}) AML, and median overall survival (mOS) was similar (13 months vs 15.3 months, p=0.59). Patients with relapsed IDH1+ AML had a 40% CR/CRi rate with first salvage therapy compared to 41% of those with IDH^{WT} AML, with a mOS of 5.9 months vs 7.7 months (p=0.44). For patients receiving third line or higher therapy, rates of CR/CRi were 36% for IDH1+ disease and 27% for IDH^{WT} disease, with mOS 4.0 months vs. 4.8 months (p=0.16).

2.2 Analysis of Current Treatment Options

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lists drugs with FDA approval for the treatment of AML. For patients in first relapse who are fit for intensive therapy, the standard of care is treatment with a combination chemotherapy regimen followed by HSCT. About half will achieve a second complete remission, in the absence of prior allogeneic HSCT, and 5-year survival of patients who achieve a second remission and

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undergo HSCT is about 40% (Dohner et al. 2017). However, many patients cannot tolerate intensive re-induction chemotherapy. In large, phase 3 studies of with control arms of high-dose cytarabine or investigator's choice (e.g., hypomethylating agents, multiagent chemotherapy, cytarabine, hydroxyurea, or supportive care) in primary refractory AML or AML that has relapsed after 1 or more prior regimens, the rate of CR ranges from 12 to 18%, and median OS ranges from 3.3 to 6.3 months (Faderl et al. 2012; Roboz et al. 2014). There is a clear need for new treatments for patients with relapsed or refractory (R/R) AML.

Table 1: Currently Available Treatments for Acute Myeloid Leukemia

Agent	Excerpted Indication
Azacitidine	Indicated for myelodysplastic syndrome (MDS), including refractory anemia with excess blasts in transformation (i.e., 20-30% blasts), which is now classified as AML per contemporary classification systems
Cyclophosphamide	Indicated for the treatment of leukemias
Cytarabine	Indicated in combination with other approved anticancer drugs for induction in acute non-lymphocytic leukemia of adults and children
Daunorubicin	Indicated in combination with other approved anticancer drugs for remission induction in acute non-lymphocytic leukemia of adults
Daunorubicin and cytarabine liposome injection	Indicated for the treatment of adults with newly-diagnosed therapy-related AML or AML with myelodysplasia-related changes
Decitabine	Indicated for myelodysplastic syndrome (MDS), including refractory anemia with excess blasts in transformation (i.e., 20-30% blasts), which is now classified as AML per contemporary classification systems
Dexamethasone	For the palliative management of leukemias and lymphomas
Doxorubicin	Doxorubicin has been used successfully to produce regression in disseminated neoplastic conditions, including acute myeloblastic leukemia
Enasidenib	Indicated for the treatment of adults with relapsed or refractory AML with an IDH2 mutation
Gemtuzumab ozogamicin	Indicated for the treatment of newly-diagnosed CD33-positive AML in adults and indicated for the treatment of relapsed or refractory CD33-positive AML in adults and pediatric patients 2 years and older.
Hydrocortisone	For palliative management of leukemias and lymphomas in adults, acute leukemia of childhood.
Idarubicin	Indicated in combination with other approved anti-leukemic drugs for the treatment of AML in adults
Methylprednisolone	For palliative management of leukemias and lymphomas in adults, acute leukemia of childhood
Midostaurin	Indicated for newly diagnosed, FLT3+ AML in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation.
Mitoxantrone	Indicated in combination with other approved drug(s) in the initial therapy of acute non-lymphocytic leukemia in adults
Prednisone	For palliative management of leukemias and lymphomas in adults, acute leukemia of childhood
Thioguanine	Indicated for remission induction and remission consolidation treatment of acute non-lymphocytic leukemias, with higher remission rates in combination with other chemotherapy agents
Vincristine	Indicated in acute leukemia

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3 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

Ivosidenib is currently not marketed in the United States.

3.2 Summary of Presubmission/Submission Regulatory Activity

The trials included in this application were conducted under IND 119341, which was submitted on December 20, 2013. The IND has never been placed on clinical hold.

The FDA granted Fast Track Designation to ivosidenib for the treatment of patients with AML that harbors an IDH1 mutation on May 13, 2015.

The FDA granted Orphan Drug Designation to ivosidenib for the treatment of acute myelogenous leukemia on June 9, 2015.

A Type C meeting was held on 7/29/2015 to discuss the development of AG-120 for use as a single-agent treatment of patients with AML that harbor an IDH1 mutation.

(b) (4)

(b) (4)

A Type C written response only meeting was held on 12/15/2016 to provide feedback on the adequacy of the proposed dataset from the ongoing clinical trial AG120-C-001 to support the initial registration of AG-120 for the treatment of patients with R/R-AML with an IDH1 mutation.

(b) (4)

FDA provided written responses for a Type B pre-NDA meeting on September 14, 2017. The FDA agreed that the preliminary efficacy and safety results from Study AG120-C-001 justified the submission of an NDA. However, whether the results were clinically meaningful would be assessed during the review.

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This NDA was submitted on December 21, 2017, in its entirety, using a data cut date of May 12, 2017. The Applicant requested priority review, which was granted by the FDA on February 15, 2018. The Applicant provided updated efficacy and safety data on all patients treated with ivosidenib at the time of the 90-day safety update, using a data cut date of November 10, 2017. This was agreed to by the FDA at the time of the pre-NDA meeting.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1 Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) conducted inspections for Study AG-120-C-001 at clinical sites in Villejuif, France (Institut Gustave Roussy), Houston, TX (MD Anderson Cancer Center), Boston, MA (Dana Farber Cancer Institute and Massachusetts General Hospital) and New York, NY (Memorial Sloan-Kettering Cancer Center). These sites had the highest accrual, greatest impact on the primary endpoint, and/or financial conflicts of interest. Inspection review of the New York site identified minor regulatory deficiencies related to adverse event reporting (failure to report 2 adverse events and failure to report serious adverse events within the mandatory reporting period). A Form 483 was issued to the Investigator, and the classification was Voluntary Action Indicated. The Applicant updated the study data files to include the additional adverse events identified at the inspection. The classification of the other sites was No Action Indicated. The Applicant (Agios) was also audited. The classification for the Applicant inspection is No Action Indicated. Based on these inspection results, the study data derived from the inspected clinical sites as amended by the Applicant were considered reliable in support of the requested indication.

4.2. Product Quality

Ivosidenib drug product (Tibsovo) is presented as a blue, oval-shaped, film-coated tablet for oral use containing 250 mg ivosidenib. The tablets are debossed with “IVO” on one side and “250” on the other side. Inactive ingredients include colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose and sodium lauryl sulfate. The tablet coating includes FD&C blue #2, hypromellose, lactose mono-hydrate, titanium dioxide and triacetin. All excipients are compendial-compliant. The drug product may contain genotoxic impurities, but all impurities are expected to be within the maximal acceptable limits for the intended population in accordance with ICH M7 and ICH Q3A. The drug product is supplied in bottles of 60 tablets with an expiry of 24 months when stored at USP controlled room temperature.

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The Applicant indicated that the commercial tablet formulation is the similar to the 250 mg clinical trial tablet formulation used in Study AG120-C-001, differing only in the film coating and debossing. Based on the data submitted, the Biopharmaceutics reviewer concluded that the clinical trial and commercial formulations were comparable, so the data from Study AG120-C-001 were acceptable for use in the assessment of efficacy and clinical safety.

There were no outstanding safety issues identified for the manufacturing process or from the facilities inspections. The Applicant claimed a categorical exclusion from the requirement for an environmental assessment, and the claim was accepted under 21 CFR 25.31(b). Approval of the NDA was recommended by the Product Quality review team.

4.3 Devices and Companion Diagnostic Issues

The Applicant is seeking an indication for patients with relapsed or refractory AML limited to those who have an IDH1 mutation, which is the target of ivosidenib. In Study AG120-C-001, patients were selected based on detection of an IDH1 mutation in the local laboratory, and the results were confirmed by testing in a central laboratory. It was determined that a device to select patients for therapy would be required for safe use of ivosidenib when marketed. The applicant cross-referenced PMA P170041 for the Abbott RealTi*me* ™ IDH1 mutation assay. A bridging study was conducted using the Abbott RealTi*me* ™ IDH1 mutation assay, which identifies the following IDH1 mutations: R132C, R132G, R132H, R132L and R132S. At the time of completion of this review, the Center for Devices and Radiologic Health (CDRH) had not yet made a final regulatory determination for the PMA.

(b) (4) The CDRH consultant indicated that the data submitted was not sufficient to establish analytical validation of the assay (b) (4) This is discussed further in Section 8.1.1 of this review.

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5 Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

Ivosidenib (also known as AG-120 and AGI-16678) is a small molecule inhibitor of isocitrate dehydrogenase 1 (IDH1). The metabolic enzyme isocitrate dehydrogenase plays an important role in the tricarboxylic acid cycle. The IDH1 and IDH2 are homodimeric NADP+-dependent enzymes that catalyze the oxidative decarboxylation of isocitrate to alpha-ketoglutarate (α-KG), producing nicotinamide adenine dinucleotide phosphate (NADPH) in the process. Some mutant forms of IDH enzymes alter the catalytic activity of the enzymes such that they produce high levels of a metabolite, (R)-2-hydroxyglutarate [(R)-2-HG], which is normally found at very low levels in cells.[1] 2-HG consumes NADPH and impairs differentiation of hematopoietic stem cells into mature blood cells, contributing to oncogenesis.[2,3] 2-HG is elevated in several tumor types, including subsets of AML.[4] Inhibition of IDH1 mutants can suppress 2-HG production and induce myeloid cell differentiation. These effects may provide therapeutic benefit to patients with AML with certain IDH1 mutations. The established pharmacological class for ivosidenib is an isocitrate dehydrogenase-1 inhibitor.

Ivosidenib inhibits a variety of IDH1 R132 mutants [IDH1 (R132C), (R132G), (R132H), (R132S), and (R132L)] at much lower concentrations than wild-type IDH1 enzymes in vitro. Ivosidenib showed no inhibition of IDH2 mutant or IDH2WT enzymes at concentrations >100 µM. In vitro studies in cell lines expressing either endogenous IDH1 (R132C/H/2) mutant forms or overexpressing these mutant forms showed that ivosidenib can reduce 2-HG with IC_{50} values ranging from 2-20 nM. In an ex vivo assay with primary human AML blast cells harboring the IDH1 (R132C) mutant, treatment with ivosidenib for up to 7 days reduced 2-HG levels by 98% relative to controls and IDH1WT, decreased the number of viable AML blast cells and induced cellular differentiation as evident by the increase in differentiation markers (CD45+/CD11b+ and CD45+/CD14+ populations). Additionally, in primary human IDH1 (R132H) mutant xenograft models, treatment with ivosidenib dose-dependently decreased 2-HG levels (>96%) in plasma, spleen, and bone marrow, and increased percentages of human CD14+ and CD15+ cells in the peripheral blood, suggesting that ivosidenib is likely associated with induced expression of cell surface proteins and cellular differentiation.

Ivosidenib inhibited the calcium and/or potassium ion channel currents with IC_{50} values > 13

[1] Losman JA1, Kaelin WG Jr. What a difference a hydroxyl makes: mutant IDH, (R)-2-hydroxyglutarate, and cancer. Genes Dev. 2013 Apr 15;27(8):836-52.
[2] Dang L, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature 462;739-744
[3] Clark O, et al. Molecular Pathways: Isocitrate Dehydrogenase Mutations in Cancer. Clinical Cancer Research 22(8) 2016
[4] Gross S, et al. Cancer associated metabolite 2-hydroxyglutarate accumulates in acute myelogenous leukemia with isocitrate dehydrogenase 1 and 2 mutations. *J Exp Med.* 2010;207(2):339-44.

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μM indicating a low potential to adversely affect ion channel currents. In the cardiovascular safety pharmacology assessment study in monkeys, single doses of ivosidenib at 45 and 135 mg/kg resulted in prolongation of the QT and QTcB intervals. In the 3-month repeat dose toxicology study in monkeys, prolongation of QTcB (>30 msec) was noted in individual animals in the 90 and 180 mg/kg/day dose groups corresponding to 0.7 and 2.3-times the AUC in patients administered ivosidenib at the recommended daily dose of 500 mg.

The rate of oral absorption of ivosidenib in animal species (rats, dogs, and monkeys) was characterized by T_{max} values ranging from 3-19 hours. The oral bioavailability was approximately 40%, 26% and 54% in rats, dogs, and monkeys, respectively. The tissue distribution of ivosidenib was widespread with the highest concentrations observed in the liver, fat, lacrimal glands, and adrenal gland in Long Evans (LE) rats. Ivosidenib crossed the blood-brain barrier. In pigmented LE rats, the concentrations in eye uveal tract and pigmented skin suggests association with melanin-containing tissues. The metabolic profiles of ivosidenib were similar in rat, dog, monkey and human liver microsomes, which generated four mono-oxygenated metabolites (M1-M4). No unique human metabolites were identified. The majority of administered [^{14}C]ivosidenib was excreted in feces in intact rats (>90%) and via the feces (59%) and the biliary (32%) route in bile duct-cannulated (BDC) rats.

Ivosidenib was evaluated in GLP-compliant repeat-dose general toxicology studies in rats and monkeys up to 90-days in duration. In the 90-day studies Sprague-Dawley rats were administered twice daily oral doses up to 250 mg/kg/dose (500 mg/kg/day) and monkeys were administered twice daily doses via nasogastric or gastric intubation up to 90 mg/kg/dose (180 mg/kg/day). Ivosidenib-related toxicities in the 90-day rat study occurred in the liver (elevated transaminases, increased weights, diffuse hepatocellular hypertrophy, and subcapsular fibrosis and hepatocellular necrosis), thyroid (higher thyroid/parathyroid weights and follicular cell hypertrophy/hyperplasia), marrow (increased hematopoiesis) and spleen (brown pigment and extramedullary hematopoiesis).

In the 28-day rat toxicology study, animals were administered twice daily doses up to 1000 mg/kg/dose (2000 mg/kg/day). A total of 5/24 males and 9/24 females in the 2000 mg/kg/day group were found dead or euthanized in extremis. Liver toxicity accompanied by hemorrhage was considered the predominant cause of death/moribundity. Other noteworthy target organs of toxicity were the glandular and nonglandular stomach, kidney, spleen, thymus and bone marrow.

In the 90-day monkey study, ivosidenib-related toxicities were noted in the liver and heart. Liver findings included dose-dependent increased incidence of minimal hepatocellular hypertrophy associated with increased liver weights. Prolongation of QTcB intervals were noted in individual animals in the 90 and 180 mg/kg/day dose groups, and these effects were not observed in the recovery period. Additionally, in the 28-day monkey study, ventricular bigeminy was observed in one male and one female as well as a prolonged QTcB interval in females at

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the 135 mg/kg/dose level (270 mg/kg/day).

Dedicated studies to assess ivosidenib treatment-related effects on fertility and pre- and postnatal development (PPND) were not conducted. These studies are not needed for the current indication. Embryo-fetal development (EFD) studies were conducted in pregnant rats and rabbits. Ivosidenib (10, 50, or 250 mg/kg twice daily) administered orally during organogenesis to female rats, from gestation day (GD) 6 through 17, resulted in fetal developmental toxicities at 500 mg/kg/day. Fetal developmental findings were limited to decreased mean fetal body weights, and skeletal variations (reduced ossification of the rib and unossified sternebrae). The mean systemic exposures in high dose rats ($AUC_{0\text{-}24hr}$ of 234 µg·hr/mL) was 2-times the human exposure at the recommended daily dose of 500 mg ($AUC_{0\text{-}24hr}$ = 117 µg.hr/mL).

Ivosidenib (15, 45, or 90 mg/kg/twice daily) was administered orally during organogenesis to rabbits on GDs 7 through 20, and cesareans were performed on GD 29. One animal at high dose aborted on GD 21. Treatment with ivosidenib resulted in maternal toxicities including, decreased mean gestational body weight gain and decreased food consumption at 180 mg/kg/day and the maternal toxicity may have contributed to the fetal developmental findings of decreased fetal weights, skeletal variations, and visceral variations at 180 mg/kg/day. Systemic exposure at the high dose ($AUC_{0\text{-}24hr}$ = 460 µg·hr/mL) in rabbits was 3.9-times the human exposure at the recommended daily dose 500 mg.

Ivosidenib was not genotoxic in the Ames bacterial reverse mutation test, the in vitro mammalian cell micronucleus test in human peripheral blood lymphocytes (HPBL) in the presence or the absence of external metabolic activation system, or in the in vivo rat bone marrow micronucleus test. Carcinogenicity studies were not conducted and are not required for the proposed indication.

The nonclinical pharmacology and toxicology data submitted are adequate to support approval of this NDA for ivosidenib.

5.2 Referenced NDAs, BLAs, DMFs

None

5.3 Pharmacology

Enzyme kinetics experiments were conducted to study the inhibitory effects of ivosidenib against the IDH1 (R132C/G/H/S/L), IDH2 (R172K), IDH1WT, and IDH2WT in a diaphorase/resazurin coupled system (Reports AG120-N-056-R1). In this assay, characterization of ivosidenib used a discontinuous IDH1 mutant activity, where conversion of α-KG to 2-HG was measured as a function of remaining nicotinamide adenine dinucleotide phosphate (NADPH).

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Ivosidenib inhibited IDH1 mutants (R132C/G/H/S/L) with a half-maximal inhibitory concentrations (IC_{50}) of 2-17 nM at the 1 hour time point, which are concentrations that are approximately 650-fold lower than those that inhibit the IDH1WT enzyme. Ivosidenib showed no inhibition of IDH2 mutant or WT at concentrations >100 µM.

Table 2: Inhibition of IDH1 Activity by Ivosidenib

Enzyme	IC_{50} (nM)
IDH1 (R132C) at 1 hour	17
IDH1 (R132G) at 1 hour	8
IDH1 (R132H) + NADPH at 1 hour	2
IDH1 (R132H) + NADPH at 16 hours	2
IDH1 (R132H) at 1 hour	11
IDH1 (R132S) at 1 hour	12
IDH1 (R132L) at 1 hour	13
IDH1WT at 1 hour	1326
IDH1WT + NADP at 1 hour	71
IDH1WT + NADP at 16 hours	24
IDH2 (R172K) at 1 hour	>100,000 nM
IDH2WT at 1 hour	>100,000 nM

(Table excerpted from NDA 211192)

The activity and specificity of ivosidenib was assessed against cellular IDH1 and IDH2 mutations in cell based systems using the following cell lines (Report AG220-N-051-R1):

- Human glioblastoma astrocytoma (U87MG) cells transfected to overexpress IDH1 (R132C), IDH1 (R132H), or IDH2 (R140Q) mutations.
- Human erythroid leukemia (TF-1) cells were transfected to express IDH1 (R132H).
- Several human cell lines that harbor endogenous IDH1 mutations.

Overnight cell cultures seeded in microtiter plates were treated with various concentrations of ivosidenib for 48 hours. Concentrations of ivosidenib and 2-HG were determined using a quantitative liquid chromatography with tandem mass spectrometry (LC-MS/MS) assay.
The IC_{50} values for ivosidenib-mediated inhibition of 2-HG production ranged from 2-20 nM. 2-HG production was not inhibited in cells expressing IDH2 mutations.

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Table 3: Inhibition of 2-HG in IDH Mutant Expressing Cells by Ivosidenib
(Table excerpted from NDA 211192)

Cell Line	2-HG IC_{50} (nM)
COR-L105 (R132C)	10 ± 4
HCCC-9810 (R132S)	10 ± 2
RBE (R132S)	3
HT1080 (R132C)	8 ± 4
U87MG pLVX IDH1 (R132C)	4 ± 1.6
U87MG pLVX IDH1 (R132H)	20 ± 11
Neurosphere 603 (R132H)	2.4 ± 0.2
TF1 pLVX IDH1 (R132H) clone 27	20
U87MG pLVX IDH2 (R140Q)	No Fit

To study the downstream effects of IDH1 (R132H) mutations on cellular differentiation, a model system was generated by transfecting the granulocyte macrophage colony-stimulating factor (GM-CSF)-dependent erythroleukemia cell line TF-1 with the IDH1 (R132H) mutant allele using a lentivirus pLVX system (Report AG221-N-049-R1). These cells expressed the mutant enzyme in the presence of high intracellular levels of 2-HG and exhibited growth-factor independent proliferation. TF-1 pLVX (empty vector expressing TF-1 cells was used as a control cell line).

To assess reversal in the block to cellular differentiation, TF-1 pLVX and TF-1 IDH1 (R132H) cells were pretreated for 8 days with 1 µM ivosidenib in the presence of GM-CSF and then washed to remove growth factors. Cells were then induced to differentiate using erythropoietin (EPO) (2 units/mL) in the presence or absence of ivosidenib (AG-120 in Figure 1) or DMSO. Induction continued for 8 days and the cell pellets were collected and subjected to real time polymerase chain reaction (qPCR) to detect a transcription factor that regulates erythropoiesis and markers of erythroid differentiation (hemoglobin gamma 1/2 (HBG 1/2) and Kruppel-like factor 1 (KLF-1). Cells were then processed for Western blotting and 2-HG measurement.

Treatment with ivosidenib partially restored EPO-induced expression of both HBG1/2 and KLF-1 suggesting EPO-triggered TF-1 IDH1 (R132H) differentiation with concurrent decrease in the intracellular 2-HG protein levels (>99%).

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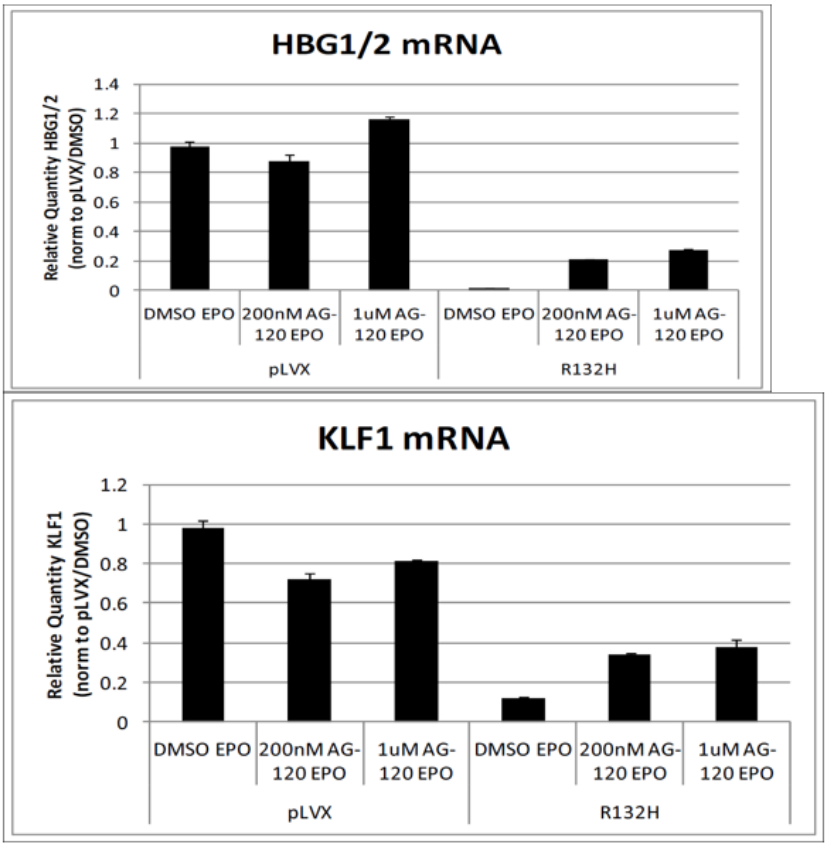
Figure 1: HBG 1/2 and KLF-1 mRNA Expression in Control and IDH1 (R132H) Mutant Cells After Treatment with EPO and Ivosidenib



(Figure excerpted from NDA 211192)

Figure 2: Intracellular 2-HG Protein Concentrations

(Figure excerpted from NDA 211192)

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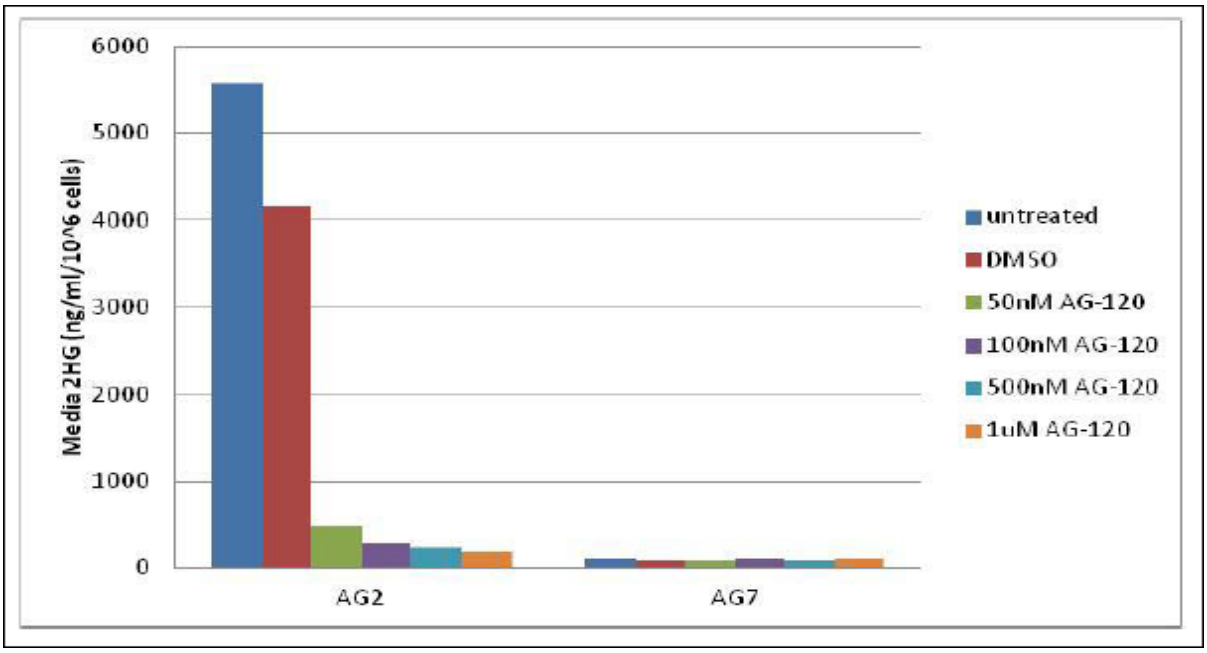
To determine the effect of IDH1 mutant inhibition in primary human AML tumor cells, primary human AML blast cells harboring IDH1 (R132C) mutations (patient AG2) or wild type (patient AG7) bone marrow samples were treated ex vivo with ivosidenib (Report AG120-N-055-R1). Cells were cultured in serum-free conditions with recombinant human cytokines in the presence of either ivosidenib or DMSO. The cells were counted at Days 0, 3, and 7. The concentrations of 2-HG in media were determined using a LC-MS/MS method on Day 3 and 7. Cell viability from both patient samples following treatment with ivosidenib was measured by trypan blue exclusion method on Day 3. FACS analysis was also conducted on the patient samples to assess for differentiation status. In the cells harboring the IDH1 (R132C) mutation, ivosidenib reduced the levels of extracellular 2-HG in a concentration dependent manner. Only very low levels of 2-HG were measured in the cells from the patient with the wild type IHD1.

Figure 3: Effects of Ivosidenib Treatment on 2-HG Concentrations in the Media of Primary Cell Cultures



(Figure excerpted from NDA 211192)

A proliferative burst was observed starting at Day 3 in samples from the patient with the IDH1 (R132C) mutation, which was not observed in the cells from the patient with wild type IDH1.

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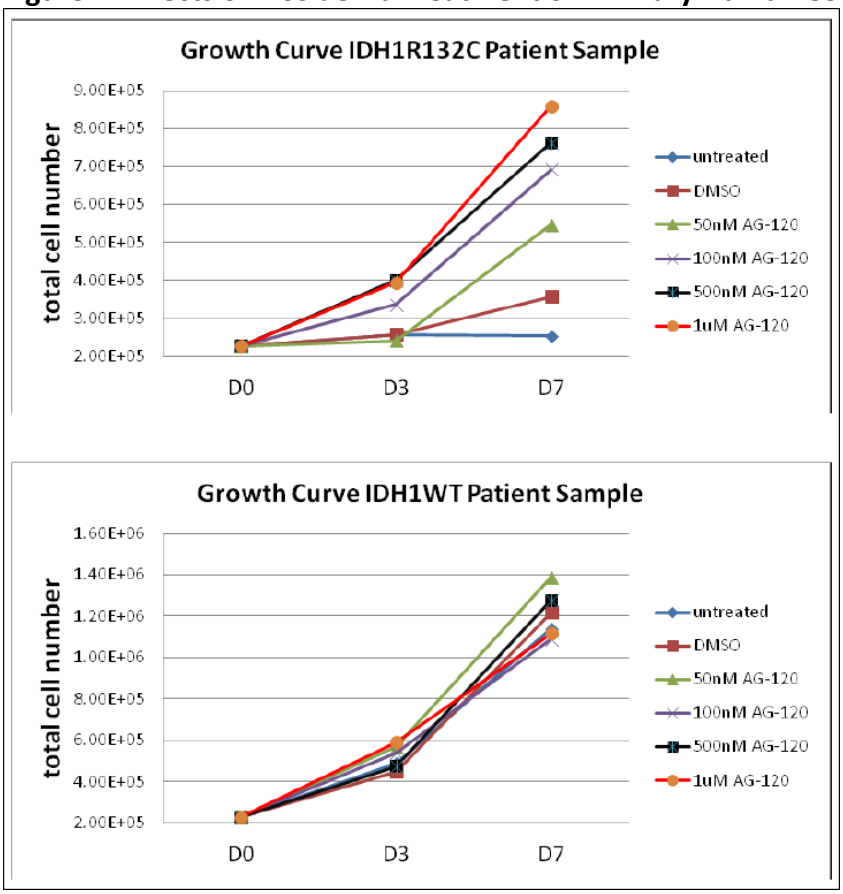
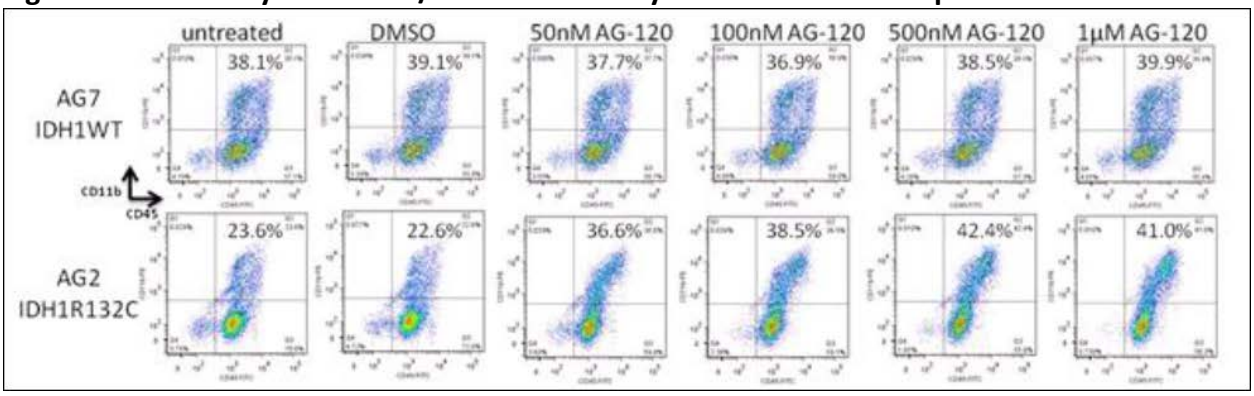
Figure 4: Effects of Ivosidenib Treatment on Primary Human Cell Numbers Over Time



(Figure excerpted from NDA 211192)

Induction of differentiation including increases in CD45+/CD11b+ and CD45+/CD14+ populations (both markers of differentiation) was observed in bone marrow blast cells with IDH1 (R132C) mutations. This was not observed in IDH1 wild type patient samples.

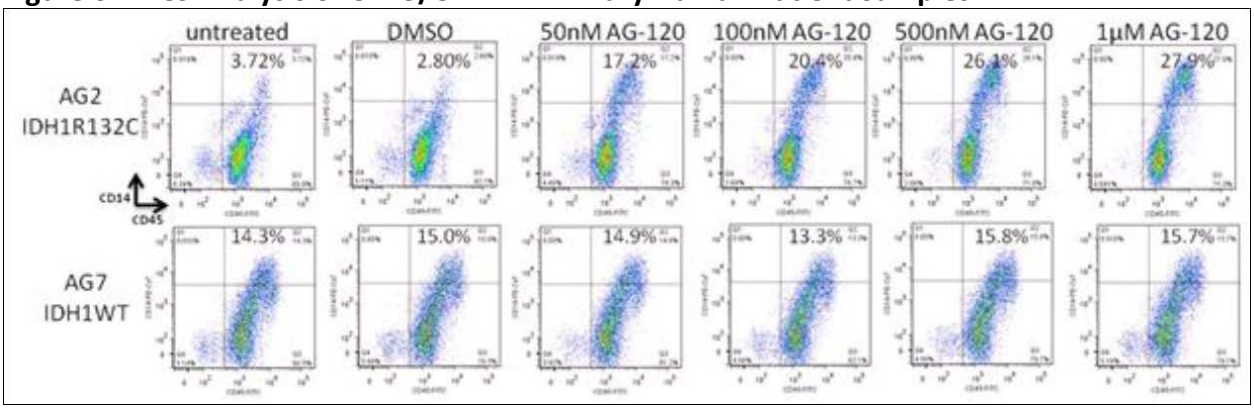
Figure 5: FACS Analysis of CD45/CD11b in Primary Human Patient Samples



(Figure excerpted from NDA 211192)

Reference ID: 4293723

Figure 6: FACS Analysis of CD45/CD14 in Primary Human Patient Samples



(Figure excerpted from NDA 211192)

A similar ex vivo study was conducted with primary AML myeloblast cells from 6 patients (2 IDH1 [R132C], 2 IDH1 [R132H], and 2 IDH WT) to measure ivosidenib induced inhibition of 2-HG production and cell differentiation (Report AG120-N-057-R1). Treatment of primary IDH1 (R132C or R132H) mutant AML cells with ivosidenib for up to 12 days reduced intracellular 2-HG levels, enhanced in vitro clonogenic activity and induced myeloblast differentiation (maturation) with increases in CD14, CD15, CD24 and MPO (myeloperoxidase) positive cells and decreased percentages of immature blasts and myeloblasts.

The in vivo activity of ivosidenib was studied in a primary human IDH1 (R132H) mutant xenograft model (Report AG120-N-093).

Primary human AML cells (TM001036) isolated from a patient with IDH1 (R132H) and FLT3 (FLT3-ITD) mutations were inoculated into female NOD/SCID mice via tail vein injection. After the engraftment reached between 5-10% of human CD33 positive cells in the peripheral blood, mice were dosed twice daily with either vehicle or ivosidenib at 50 or 150 mg/kg via oral gavage for 21 days. The quantitative analysis 2-HG protein concentrations were measured in plasma, bone marrow, and spleen samples from each treatment group after the final dose (n=3/time point) LC-MS/MS method. The mean inhibition of 2-HG production in spleen and bone marrow over 12 hours post-dose based on $AUC_{0\text{-}12hr}$ was > 96% in both ivosidenib dose groups compared to respective vehicle controls.

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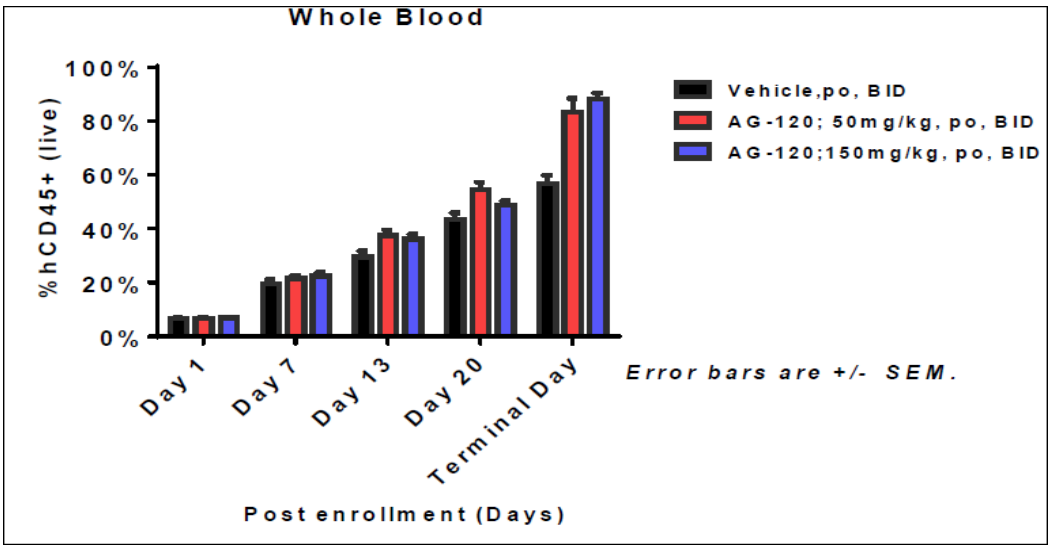
Table 4: Ivosidenib and 2-HG Exposure (AUC_{0-12hr}) and Inhibition of 2-HG in Plasma, Bone Marrow, and Spleen

	Ivosidenib AUC_{0-12hr} (hr•ng/mL)			2-HG AUC_{0-12hr} (hr•ng/mL)			Inhibition of 2-HG (%)		
Group	Plasma	Bone marrow	Spleen	Plasma	Bone marrow	Spleen	Plasma	Bone marrow	Spleen
Vehicle	NA	NA	NA	19,300	12,100,000	2,650,000	NA	NA	NA
50 mg/kg	13,600	10,800	9170	2840	449,000	151,000	99.8	97.6	96.3
150 mg/kg	28,600	25,800	19,000	2250	301,000	87,100	>99.9	98.4	98.1

(Table excerpted from NDA 211192)

Weekly FACS analysis of peripheral blood samples were conducted to assess for any differences in progression of disease burden as well as to monitor changes in differentiation between treated and untreated animals. No meaningful differences were observed in percentages of huCD45+ cells, however, treatment with ivosidenib resulted in increased percentage of human CD14+ and CD15+ cells in the peripheral blood, indicating differentiation induction.

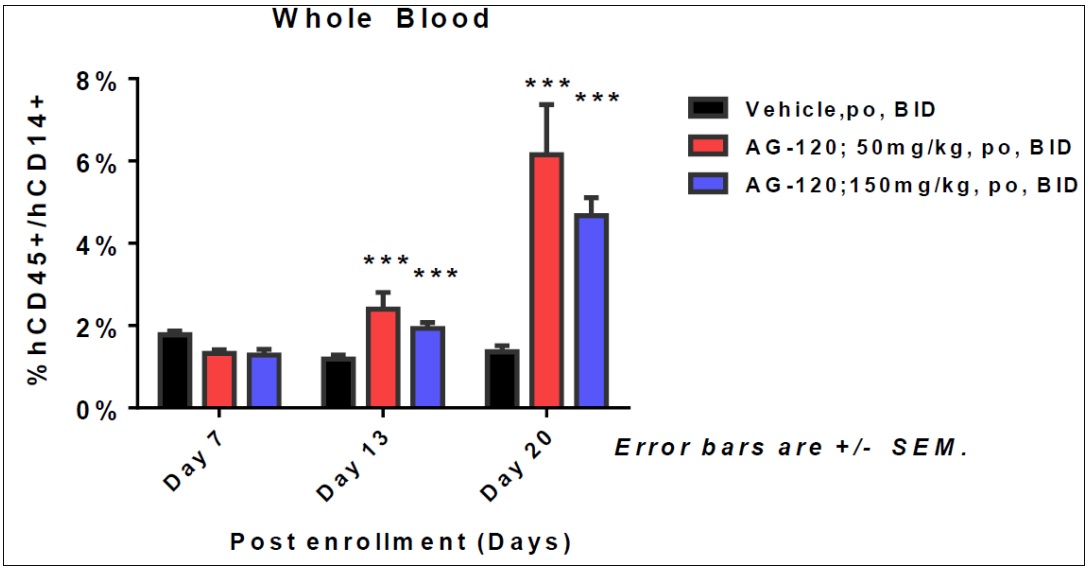
Figure 7: Mean Percentage of hCD45+ Cells Over Time



(Figure excerpted from NDA 211192)

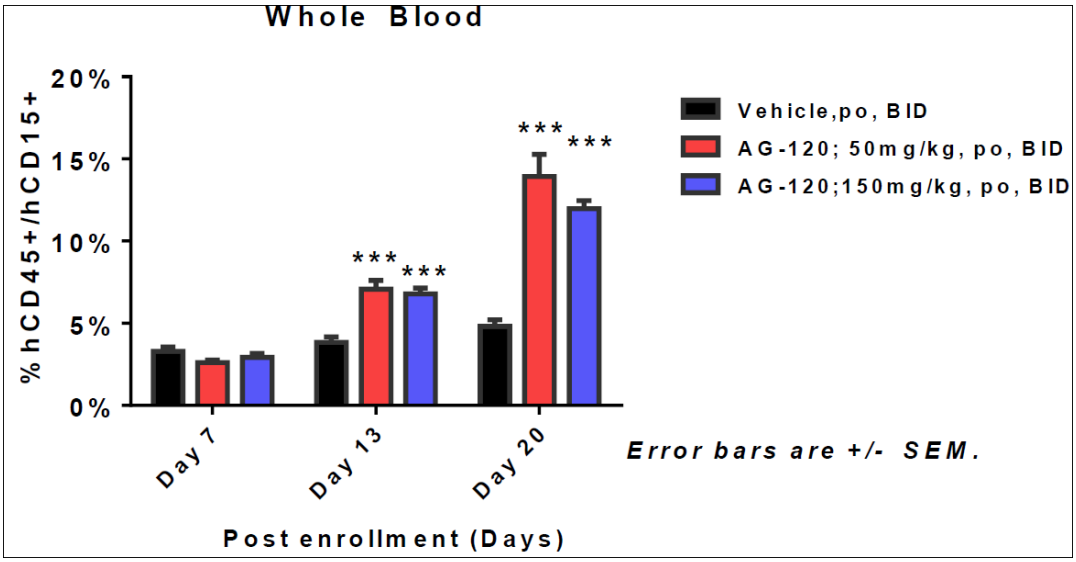
Reference ID: 4293723

Figure 8: Ivosidenib-Induced Expression of hCD14+



(Figure excerpted from NDA 211192)

Figure 9: Ivosidenib-Induced Expression of hCD15+



(Figure excerpted from NDA 211192)

Secondary Pharmacology

Ivosidenib was evaluated for its potential to inhibit binding and enzymatic activity in a panel of 80 receptors, ion channels, and enzymes (Report AG120-N-004-R1). At the single concentration of 10 µM, ivosidenib did not exhibit significant inhibition (defined as ≥ 50%) of any of the 80 targets tested.

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Safety Pharmacology

In a non-GLP in vitro study, ivosidenib was tested over a concentration range of 0.01 to 1000 µM in a manual patch clamp assay for its potential to inhibit 4 different ion channel currents: the potassium channels hKvLQT1/hminK and hERG, the sodium channel (hNAV1.5), and the calcium channel (hCaV1.2) (Report AG120-N-054-R1). Human embryonic kidney (HEK)-293 cells expressing the potassium channels and CHO cells expressing the sodium and calcium channels were used to evaluate the effects of ivosidenib. Appropriate positive controls were included for each channel. The IC_{50} values for inhibition of ion channel currents for all assays were > 13 µM for indicating a low potential to adversely affect calcium and/or IKr ion channel currents.

Table 5: Inhibition of Ion Channel Currents

Current	Ivosidenib IC_{50} (nM)
hERG (I_{Kr})	12,600[1]
hCaV1.2 (α1C/β2a/α2δ1)	>30,000
hNaV1.5	>30,000
hKvLQT1/hminK	>30,000

[1] The hERG IC_{20} value was 3000 nM, (Table excerpted from NDA 211192)

AG-120: Cardiovascular Assessment following Nasogastric Administration in Cynomolgus Monkeys (Report AG120-N-053-R1).

Conscious radiotelemetry-instrumented male cynomolgous monkeys were administered a single dose of vehicle control (b) (4) 0.1% simethicone), or 15, 45, or 135 mg/kg ivosidenib by nasogastric administration to assess cardiovascular parameters including arterial blood pressure, heart rate, body temperature, and lead II electrocardiogram (ECG). The cardiovascular parameters were collected continuously for approximately 1 hour prior to administration through approximately 24 hours post-dose. No test article-related clinical observations were noted at in any dose groups. Ivosidenib prolonged QT intervals by 12-21% and QTcB intervals by 8-12% at doses ≥ 45 mg/kg.

Reference ID: 4293723

5.4 ADME/PK

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Absorption</td><td></td></tr>
<tr><td>Study #s AG120-N-015-R1/AG120-N-22-R1/AG120-N-023-R1</td><td>Oral bioavailability of ivosidenib free base 40%, 26%, and 54% in rats, dogs and monkeys respectively.
T_{max} ranged from 3 to 19 hours in animals
$T_{1/2}$ ranged from 3 (rat) to 13 hours (monkey)</td></tr>
<tr><td>Distribution</td><td></td></tr>
<tr><td>In Vitro Assessment Of AG-120 Protein Binding in Human, Monkey, Dog, Rat, And Mouse Plasma/AG-120-N-028-R1; AG-120 Partitioning Between Blood and Plasma Human, Monkey, Dog, And Rat /AG120-N-027-R1</td><td>
Plasma Protein Binding of Ivosidenib
<table>
<tr><th rowspan="2">Matrix</th><th colspan="3">Protein Binding (% Bound)</th></tr>
<tr><th>0.2 µM AG-120</th><th>1 µM AG-120</th><th>10 µM AG-120</th></tr>
<tr><td>Mouse plasma</td><td>89.6</td><td>89.8</td><td>87.7</td></tr>
<tr><td>Rat plasma</td><td>89.2</td><td>89.3</td><td>85.4</td></tr>
<tr><td>Dog plasma</td><td>98.1</td><td>98.1</td><td>97.2</td></tr>
<tr><td>Monkey plasma</td><td>90.2</td><td>89.6</td><td>81.7</td></tr>
<tr><td>Human plasma</td><td>95.8</td><td>95.4</td><td>91.6</td></tr>
</table>
Blood Cell Partitioning of Ivosidenib
<table>
<tr><th rowspan="2">Matrix</th><th>Distribution into Blood Cells (%)</th></tr>
<tr><th>1 µM AG-120</th></tr>
<tr><td>Rat blood</td><td>0.49</td></tr>
<tr><td>Dog blood</td><td>0.10</td></tr>
<tr><td>Monkey blood</td><td>0.16</td></tr>
<tr><td>Human blood</td><td>0.41</td></tr>
</table>
</td></tr>
<tr><td>AG-120 Brain Tissue Distribution in Male Sprague-Dawley Rats After Oral Administration/AG120-N-029-R1</td><td>
Mean Concentrations of Ivosidenib Brain Tissue Distribution
<table>
<tr><th rowspan="2">PK parameters:</th><th colspan="3">Concentration</th></tr>
<tr><th>Plasma</th><th>CSF</th><th>Brain</th></tr>
<tr><td>T_{max} (hr)</td><td>4.0</td><td>4.0</td><td>4</td></tr>
<tr><td>Cmax (ng/mL)</td><td>5790</td><td>59.7</td><td>243</td></tr>
<tr><td>$AUC_{0\text{-}8hr}$ (hr•ng/mL)</td><td>36000</td><td>350</td><td>1480</td></tr>
</table>
AG-120 distributions in brain ratio (brain/plasma =4.11%) and CSF (CSF/plasma ratio =0.971%).
</td></tr>
<tr><td>Tissue Distribution of [^{14}C]Ivosidenib-Derived Radioactivity in Long Evans Rats /AG-120-N-069</td><td>Drug related radioactivity was widely distributed at 1 to 2 hours after dosing in most tissues.
The concentration of radioactivity in pituitary gland and choroid plexus was 4210 and 1510 ng eq/g at 1 hour postdose, respectively suggesting that [^{14}C]AG-120-derived radioactivity has a potential to cross the blood:brain barrier.
The concentrations in eye uveal tract and pigmented skin suggested association with melanin-containing tissues.
The highest concentrations of radioactivity were found in the liver, fat, lacrimal glands, and adrenal gland. The lowest concentrations of radioactivity were observed in olfactory lobe, bones, eye lens, vitreous humor, and eye.</td></tr>
</table>

Reference ID: 4293723

Type of Study	Major Findings
	Highest concentrations of radioactivity (>10000 ng equivalents [^{14}C]AG-120/g) were observed in the following tissues:

Concentrations of Radioactivity in Tissues

Tissue	ng equivalents [^{14}C]AG-120/g
Fat (abdominal)	12100
Fat (brown)	13000
Fat (reproductive)	11300
Fat (subcutaneous)	13100
Liver	18800

Metabolism	
In Vitro Metabolism/ AG120-N-037 In Vivo Metabolism in Rat and Monkey/AG120-N-038 Metabolism Of [^{14}C]AG-120 Following A Single Oral Administration to Rats/ AG120-N-069	The metabolic profiles of ivosidenib were similar in rat, dog, monkey and human liver microsomes which generated four mono-oxygenated metabolites (M1-M4). No unique human metabolites were identified. In a 7-day repeat toxicology study in rats and monkeys, 2 major mono-hydroxylated metabolites (M1 and M2) of ivosidenib were detected that were quantitatively similar in both species. Two additional metabolites (M5 and M6) were identified in the monkey plasma. The primary metabolic pathways for ^{14}C-ivosidenib in rats were oxidations M1, M2, M3, M4, N-dealkylation M30 and conjugation with glutathione (M22) and cysteine (M24).
Excretion	
Excretion Of [^{14}C]AG-120 Following A Single Oral Administration to Intact And Bile Duct Cannulated Rats/ AG120-N-069	**Percent Recovery of [^{14}C]ivosidenib Dose in Rats**

Species	Oral Dose	Recovery of Administered Radioactive Dose (%)			
		Urine	Bile	Feces	Total[1]
Intact Rats	10 mg/kg	7.17	NA	91.1	99.5
BDC Rats	10 mg/kg	6.91	32.4	58.8	99.2

(Table excerpted from NDA 211192)

TK data from general toxicology studies	

A 3-Month (Twice Daily) Oral (Gavage) Toxicity and Toxicokinetic Study of AG-120 in Sprague Dawley Rats with a 28-Day Recovery Period

Peak ivosidenib plasma concentrations (T_{max}) were observed at 1 to 8 hours on study Day 0 after dosing and 1 hour on study Day 90. $T_{1/2}$ values were 4-5 hours on Day 90. Exposures (C_{max} and $AUC_{0\text{-}24hr}$) were greater in females than males (female:male ratios ranging from 1.65 to 2.13 on Day 90) at MD and HD. Sex differences: Differences were noted in exposure (AUC and C_{max}) at mid dose and high dose on Day 90.

Reference ID: 4293723

Type of Study	Major Findings

Table 6: Toxicokinetics in Rats 90-Day Repeat Dose

Dosage	AUC_{0-12} (ng•hr/mL)		C_{max} (ng/mL)		T_{max} (hr)	
	Day 0	Day 90	Day 0	Day 90	Day 0	Day 90
Males						
20 mg/kg/day	13300	6880	2190	1320	1	1
100 mg/kg/day	68000	12100	8020	2770	2	1
500 mg/kg/day	173000	29000	17300	4650	8	1
Females						
20 mg/kg/day	18200	7090	2690	1580	1	1
100 mg/kg/day	67800	20000	8220	5660	2	1
500 mg/kg/day	153000	62000	14600	9710	8	1

(Table excerpted from NDA 211192

A 3-Month (Twice Daily) Oral (Nasogastric) Toxicity and Toxicokinetic Study of AG-120 in Cynomolgus Monkeys with a 28-Day Recovery Period

Peak ivosidenib plasma concentrations (T_{max}) were observed at 1.3 to 4.5 hours on study Day 0 and Day 90. $T_{1/2}$ values ranged between 15 to 38 hr study Day 0 and 6.4 to 9.0 hr on study Day 90. Exposure (C_{max} and AUC_{0-12hr}) was dose-proportional manner in males and females at 30 to 90 and 90 to 180 mg/kg/day.
Sex differences: No significant differences.

Table 7: Toxicokinetics in Monkeys 90-Day Repeat Dose

Dosage	AUC_{0-12} (ng•hr/mL)		C_{max} (ng/mL)		t_{max} (hr)	
	Day 0	Day 90	Day 0	Day 90	Day 0	Day 90
Combined Sexes						
30 mg/kg/day	23400	11800	3010	1930	1.3	1.3
90 mg/kg/day	80300	41500	8620	5750	2.6	1.8
180 mg/kg/day	118000	134000	11500	14800	4.5	2.0

(Table excerpted from NDA 211192)

TK data from reproductive toxicology studies	Rat AUC: At 30, 90, and 500 mg/kg/day the calculated AUC0-24hr (ng*hr/mL) is 19180, 41200, and 234000, respectively Rabbit AUC: At 30, 90, and 180 mg/kg/day the calculated AUC0-24hr (ng*hr/mL) is 76400, 162200, and 460000, respectively.

Reference ID: 4293723

Type of Study	Major Findings

Table 8: Toxicokinetics in Pregnant Rats Following BID Oral Administration - GD6-17

Ivosidenib Dose (mg/kg/day)	**20**	**100**	**500**
Gestation Day 6			
C_{max} (ng/mL)	2990	8860	13,600
AUC_{0-12hr} (ng*hr/mL)	23,600	78,800	141,000
Calculated AUC_{0-24hr} (ng*hr/mL)	47,200	157,600	282,000
Gestation Day 17			
C_{max} (ng/mL)	1940	4490	11,900
AUC_{0-12hr} (ng*hr/mL)	9590	20,600	117,000
Calculated AUC_{0-24hr} (ng*hr/mL)	19180	41200	234000
Mean Fetal:Maternal Plasma Ratio	0.08	0.16	0.16

(Table excerpted from NDA 211192)

Table 9: Toxicokinetic in Pregnant Rabbits Following BID Oral Administration - GD7-20

Ivosidenib Dose (mg/kg/day)	**30**	**90**	**180**
Gestation Day 7			
C_{max} (ng/mL)	1200	3390	6580
AUC_{0-12hr} (ng*hr/mL)	8100	26600	52300
Calculated AUC_{0-24hr} (ng*hr/mL)	16200	53200	104600
Gestation Day 20, 21			
C_{max} (ng/mL)	3820	8480	24600
AUC_{0-12hr} (ng*hr/mL)	38200	81100	230000
Calculated AUC_{0-24hr} (ng*hr/mL)	76400	162200	460000
Mean Fetal Maternal Ratio	0.03	0.08	0.2

(Table excerpted from NDA 211192)

5.5 Toxicology

5.5.1 General Toxicology

Study title/ Report: A 3-Month (Twice Daily) Oral (Gavage) Toxicity and Toxicokinetic Study of AG-120 in Sprague Dawley Rats with a 28-Day Recovery Period/ AG- AG120-N-058-R1

Key Study Findings

- The target organs of toxicity included liver, thyroid, marrow and spleen.

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- Liver findings included diffuse hepatocellular hypertrophy correlating with higher serum GGT values and increased liver weights; subcapsular fibrosis, subcapsular hepatocellular necrosis correlating with higher SDH and ALT values.
- Thyroid findings of follicular cell hypertrophy/hyperplasia correlated with higher thyroid/parathyroid weights.
- Spleen findings of brown pigment and extramedullary hematopoiesis and increased hematopoiesis in the femoral and sternal bone marrow were consistent with changes in red cell parameters.

Conducting laboratory and location (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 (vehicle), 0+ (b) (4) [(vehicle with an equivalent amount of (b) (4) excipient load (1:1 API to excipient load) as the high-dose Group], 10, 50, and 250mg/kg twice a day;
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4) /0.1% simethicone in deionized water
Species/Strain:	Rats/Strain: Crl:CD(SD)
Number/Sex/Group:	Main: 15/sex/group
Age:	Approximately 7 weeks old
Toxicokinetics	3/sex vehicle and vehicle (b) (4) 9 per sex at 20, 100, and 500 mg/kg/day
Deviation from study protocol affecting interpretation of results:	None

Observations and Results: changes from control

Parameters	Major findings
Mortality	No treatment related deaths. Gavage error deaths occurred in control (1F), 20 mg/kg/day (1M/1F), 500 mg/kg/day (1M/1F) in the main study; 100 mg/kg (1M) 500 mg/kg/day (1F) in the TK study.
Clinical Signs	Unremarkable
Body Weights	HD: ↓11% and ↓3.2% at terminal and recovery periods respectively vs. control (b) (4)
Ophthalmoscopy	Unremarkable
Hematology	**Terminal:** LD-HD: up to↑ 57% PT, up to ↑44% APTT vs. control MD-HD: up to ↓13%RBC, up to ↓18% HGB, up to ↓12%HCT, up to↑43% abs. retic, up to ↑17% RDW in females, up to ↑31% HDW in females vs. control+ (b) (4) HD: ↓6%MCHC vs. control + (b) (4)

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	Recovery: MD-HD: ↓9%RDW and ↓37%HDW Other changes resolved.
Clinical Chemistry	**Terminal:** LD-HD up to ↓32%K, up to ↑64%Cholesterol vs. control MD-HD up to↑13% TP, vs. control HD: ↑54%SDH, ↑9%albumin(M), ↓13% Albumin/globulin ratio (F), ↑100% GGT vs. control **Recovery:** HD: ↑53% ALT, ↑39% AST, ↑61% SDH; other changes resolved
Urinalysis	**Terminal** MD-HD: up to ↑50% K fractional excretion Recovery: Resolved.
Ophthalmology	Unremarkable
Gross Pathology	**Terminal:** MD-HD: Thyroid glands- enlarged HD: Liver-enlarged, discoloration, dark red, swollen. Recovery: Resolved except enlarged thyroid at HD
Organ Weights	**Terminal:** **Liver** LD-HD: up to ↑142% difference of the abs. organ weights vs. control **Thyroid/parathyroid (g)** LD-HD: up to ↑75% vs. control **Recovery** **Liver** LD-HD: Up to ↑29% vs. control **Thyroid/parathyroid** LD-HD: up to ↑ 85% vs. control
Histopathology **Adequate battery:** Yes	**Terminal:** **Liver:** LD-HD: minimal to severe diffuse hepatocellular hypertrophy MD-HD: minimal or mild subcapsular fibrosis and brown pigment HD: minimal hepatocellular subcapsular necrosis **Thyroid/parathyroid:** LD-HD: mild to moderate follicular cell hypertrophy/hyperplasia and moderate to severe alteration colloid **Marrow** HD: Increased minimal hematopoiesis (sternum and femur), mild myelostromal proliferation **Spleen** MD-HD: increased mild extramedullary Hematopoiesis and mild to moderate brown pigment. **Recovery:** Liver: LD-HD: minimal diffuse hepatocellular hypertrophy HD: minimal subcapsular fibrosis and brown pigment Thyroid: LD-HD: mild to moderate follicular cell hypertrophy/hyperplasia and moderate to severe alteration colloid

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	Marrow HD: Increased minimal hematopoiesis (sternum in males and femur in females) Spleen MD-HD: increased minimal to mild extramedullary Hematopoiesis and mild to moderate brown pigment.
LD: low dose; MD: mid dose; HD: high dose.	

Study title/ Report: Study title: A 3-Month (Twice Daily) Oral (Nasogastric) Toxicity and Toxicokinetic Study of AG-120 in Cynomolgus Monkeys with a 28-Day Recovery Period / AG120-N-059-R1

Key Study Findings

- Test article related toxicity was observed in liver and heart.
- Liver: Dose dependent increased incidence of minimal hepatocellular hypertrophy associated with increased liver weights.
- Heart: QTcB (> 30 msec) prolongations noted in individual animals in the 90 and 180 mg/kg/day dose groups. Similar effects were not observed in the recovery period.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0 (vehicle), 0+ (b) (4) excipient load (1:1 API to excipient load) as the high-dose group)],, 15, 45, and 90 mg/kg/dose twice a day
Route of administration:	Nasogastric (NG) or on occasion orogastric intubation route
Formulation/Vehicle:	(b) (4)/ 0.1% simethicone in deionized water.
Species/Strain:	Cynomolgus monkeys (Macaca fascicularis)
Number/Sex/Group:	Dosing period: 4/sex/group; recovery period 2/sex/group
Age:	Approximately 2-4years old
Deviation from study protocol affecting interpretation of results:	No

Reference ID: 4293723

Observations and Results: changes from control

Parameters	Major findings
Mortality	No treatment related deaths. One vehicle + (b) (4) male, one 90 mg/kg/day male, and 1 vehicle control female were found dead or euthanized in extremis during the study. The cause of death was attributed to mechanical trauma related to the dosing procedure for all 3 animals.
Clinical Signs	LD-HD: Diarrhea during the dosing period. Not observed in the recovery period.
Body Weights	Unremarkable
Ophthalmoscopy	Unremarkable
ECG	MD-HD: Prolongation of QTcB intervals (>30 msec).
Hematology	Unremarkable
Coagulation	Unremarkable
Clinical Chemistry	Unremarkable
Urinalysis	Unremarkable
Gross Pathology	Unremarkable
Organ Weights	**Terminal:** LD-HD: Liver: up to 35%↑; **Recovery:** none
Histopathology **Adequate battery:** Yes	Microscopic **LD-HD** **Liver:** Increased minimal Hypertrophy, hepatocellular

General toxicology; additional studies

Study title/ number: A 28-Day (Twice Daily Dosing) Oral Gavage Toxicity and Toxicokinetic Study of AG-120 in Sprague Dawley Rats with a 14-Day Recovery Period / AG120-N-002-R1
Ivosidenib was administered by oral gavage to Sprague Dawley rats twice daily for 28 consecutive days at doses of 50, 250, or 1000 mg/kg/dose (100, 500 or 2000 mg/kg/day). At the 2000 mg/kg/day dose level, 4/15 males and 5/15 females from toxicology groups and 1/9 males and 4/9 females from the toxicokinetic groups were found dead or euthanized in extremis. The deaths/moribundity were associated with moderate, bridging, centrilobular hepatocellular degeneration/necrosis accompanied by hemorrhage. Hemorrhages were also present in the lymph nodes, heart, and lungs, and were consistent with decreased clotting factor production in the liver. Other histological findings included tubular necrosis in the kidney; cortical and medullary tubular vacuolation in the kidney; atrophy of small intestines; hypocellularity, hemorrhage, and necrosis of the femoral and/or sternal bone marrow; and erosions of the glandular stomach; neutrophil infiltration or acute inflammation of the mandibular lymph nodes; and/or sinus histiocytosis with vacuolated macrophages in the axillary lymph nodes.

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Target organs of toxicity in the surviving rats included the liver, kidney, spleen, and thyroid at ≥100 mg/kg/day, the pituitary and glandular stomach at ≥ 500 mg/kg/day, and bone marrow, rectum, thymus, uterus, and nonglandular stomach at 2000 mg/kg/day. Liver findings included elevated absolute and relative liver weights, minimal to mild centrilobular to diffuse hepatocellular hypertrophy, and focal to multifocal hepatocellular necrosis. Kidney findings included minimal to mild tubular vacuolation and/or necrosis in the medulla. Spleen findings included minimal to mild golden brown intracellular pigment within the red pulp (globular pigment consistent with hemosiderin), and extramedullary hematopoiesis. Thyroid findings included elevated thyroid/parathyroid gland weights and minimal to moderate follicular cell hypertrophy/hyperplasia. Doses ≥500 mg/kg/day were also associated with pituitary effects (vacuolation of the pars distalis); glandular stomach effects (minimal to mild erosions); nonglandular stomach effects (subacute inflammation, minimal to mild submucosal edema, mucosal necrosis, ulceration, and hyperplasia of the limiting ridge); bone marrow effects within the medullary cavity of the sternum and/or femur (focal stromal cell hyperplasia, minimal hemorrhage, and/or necrosis).

Study title/ number: A 28-Day (Twice Daily) Oral (Nasogastric) Toxicity and Toxicokinetic Study of AG-120 in Cynomolgus Monkeys with a 14-Day Recovery Period / AG120-N-001-R1

Ivosidenib was administered via nasogastric intubation to cynomolgus monkeys twice daily for 28 consecutive days at doses of 15, 45, or 135 mg/kg/dose (30, 90, or 270 mg/kg/day). Test article-related mortality was observed in one male at the high dose associated with general malaise, poor body condition, gastrointestinal signs leading to emesis and secondary aspiration. Target organs of toxicity were liver and heart. At the HD, liver weights (absolute and relative) were increased by approximately 30% and there was evidence of hepatocellular hypertrophy. Ventricular bigeminy (Bi-Gemini), or abnormal ventricular beats occurring every other concurrent beat was observed in one male and one female, as well as a prolonged QTcB interval in females at the HD.

5.5.2 Genetic Toxicology

Study title/ number: Bacterial Reverse Mutation Assay/ AG120-N-003-R1

Key Study Findings:

- Ivosidenib was negative in the bacterial reverse mutation assay in presence and absence of S9 up to 5000 µg/plate.

GLP compliance: Yes
Test system: Salmonella typhimurium TA98, TA100, TA1535 and TA1537 and Escherichia coli WP2uvrA. Ivosidenib was tested up to 5000 µg/plate +/- S9.
Study is valid: Yes

Reference ID: 4293723

Study title/ number: In Vitro Mammalian Cell Micronucleus Assay in Human Peripheral Blood Lymphocytes (HPBL)/ AG120-N-070-R1

Key Study Findings:

- Ivosidenib was negative for the induction of micronuclei in HPBL up to the visible precipitating concentration (≥ 100 µg/mL) in the culture medium in the non-activated 4 and 24 hour exposure groups and 4 hour S9-activated exposure groups.

GLP compliance: Yes
Test system: HPBL; Method: cytokinesis-blocked proliferation index (CBPI) relative to vehicle control was used to determine the test article induced cytotoxicity. Ivosidenib was tested up to 500 µg/mL in the preliminary toxicity and up to 250 µg/mL in the definitive study. Ivosidenib induced ≥ 45% CBPI relative to the vehicle control at 500 µg/mL in the S9-activated 4 hour exposure group. Visible precipitate was observed at 150 µg/mL and 100 µg/mL in the preliminary toxicity and the definitive study, respectively. The ivosidenib highest concentrations for micronuclei analysis were selected based on the visible precipitate in the treatment medium in the absence of cytotoxicity in the non-activated and the S9-activated treatment groups at 100 µg/mL.
Study is valid: Yes

Study title/ number: CC-90007: In Vivo Mammalian Erythrocyte Micronucleus Assay in Rats/ AG120-N-071-R1

Key Study Findings:

- Ivosidenib was negative in the male rat bone marrow micronucleus assay up to 2000 mg/kg/day.

GLP compliance: Yes
Test system: Male Rat/ Sprague-Dawley (Hsd:SD); BID, oral gavage at 0, 250, 500, or 1000 mg/kg/dose (0, 500, 1000 or 2000 mg /kg/day); Animals appeared normal throughout the dosing period with the exception of sneezing at 2000 mg/kg/day.
Study is valid: Yes

5.5.3 Carcinogenicity

Not conducted per ICH S6, ICH S1, and ICH S9.

5.5.4 Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development
Studies to assess ivosidenib treatment-related effects on fertility and early embryonic development and pre- and postnatal development were not conducted.

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Embryo-Fetal Development

A Twice Daily (12 Hours Apart) Oral (Gavage) Study of the Effects of AG-120 on Embryo/Fetal Development in Rats/ AG-120-N-064-R1

Key Study Findings

- Test article related fetal developmental toxicity was observed at 500 mg/kg/day.
  - Maternal toxicity - unremarkable
  - Fetal developmental findings were limited to decreased mean fetal body weights, and skeletal variations (reduced ossification of the rib and unossified sternebrae).

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes
Methods	
Dose and frequency of dosing:	0, 10, 50, or 250 mg/kg/ twice a day (BID)
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4) /0.1% simethicone
Species/Strain:	Sexually mature, virgin female Sprague Dawley [Crl:CD(SD)] rats
Number/Sex/Group:	25 females per group
Satellite groups:	TK per group 8 Animals were administered on GD 6 through 17 (BID).
Study design:	Main Study: BID administration of ivosidenib to females from Gestation Day (GD) 6 through 17, followed by necropsy/cesarean on GD 20.

Observations and Results: Change from control

Parameters	**Major findings**
Mortality	None
Clinical Signs	There were no remarkable clinical signs.
Body Weights	There were no remarkable body weight changes compared to control
Food consumption	There were no remarkable changes compared to control

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Necropsy findings Cesarean Section Data	**Uterine and Ovarian Examinations in Rats**

Daily Dose (mg/kg/day)	**0**	**20**	**100**	**500**
Number of females with viable fetuses for examination on GD20	25	25	25	25
Number pregnant	25	25	25	25
Died while pregnant	0	0	0	0
Gravid uterine weight (g)	84	84	86	82
Mean corpora lutea	16	15	16	17
Mean implantation sites	15	15	15	15
Mean % pre-implantation loss	6	3	5	9.4
Mean % post-implantation loss	7	6	5	6
Mean litter size	14	14	14	15
Mean early resorptions (%)	1	0.9	0.7	0.8
Mean late resorptions (%)	0.3	0.0	0.0	0.0
Fetal weight change relative to control				
Male	3.9	-	-	↓10%**
Female	3.7	-	-	↓8%**
**= significantly different from the control group at 0.01				

Necropsy findings Offspring	**Fetal Developmental Findings in Rats**

Daily Dose (mg/kg/day)	**0**	**20**	**100**	**500**
Number of fetuses evaluated	354	350	354	364
Number of fetuses (litters) with malformations	0 (0)	5(4)	1(1)	1(1)
Fetal anomalies No. Fetuses/No. Litters (% per Litter)				
Gross External Anomalies	0	0	0	0.3
Visceral Anomalies	0	0.8	0	0
Skeletal Anomalies	0	0.5	0.3	0
Cervical Centrum No. 1 Ossified	83/18 (22.7)	80/17 (23.0)	62/18 17.7)	29/16 (7.8)
Reduced Ossification of the 13th Rib(s)	1/1 (0.3)	0/0 (0.0)	0/0 (0.0)	6/4 (1.4)
Sterner(e) Nos. 1, 2, 3, and/or 4 Unossified	1/1 (0.3)	1/1 (0.3)	1/1 (0.3)	6/4 (1.8)

Toxicokinetic	See section 1.4

A Twice Daily (12 hours apart) Oral (Gavage) Study of the Effects of AG-120 on Embryo/Fetal Development in Rabbits/AG120-N-067

Key Study Findings

- Test article-related adverse maternal effects included decreased mean gestation body weight gain and decreased food consumption at 180 mg/kg/day.
- Premature delivery (abortion) in one animal at 180 mg/kg/day, decreased fetal weights, skeletal variations, and visceral variations were observed.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

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Methods

Dose and frequency of dosing:	0, 15, 45, and 90 mg/kg/dose BID
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4) / 0.1% simethicone
Species/Strain:	Time-mated female New Zealand White Hra:(NZW)SPF rabbits
Number/Sex/Group:	22-244 females for main study
Satellite groups:	TK: 4 females per group dosed GD 7 through GD21
Study design:	QD administration of ivosidenib to females from Gestation Day (GD) 7 through 20, followed by necropsy/cesarean on GD 29.
Deviation from study protocol affecting interpretation of results:	None

Observations and Results: Change from control

Parameters	Major findings
Mortality	Ivosidenib-related death occurred at 180 mg/kg/day on GD 19. Gavage errors deaths occurred in two females at 30 mg/kg/day, one female at 90 mg/kg/on Day 9, and one female in control group on Day 8.
Clinical Signs	Decreased defecation and brown material around the anogenital area in females in the 180 mg/kg/day group
Body Weights	HD: BW gain GD 7-21 ↓7.3% control
Pregnancy index	Abortion HD: One animal at HD aborted on GD 21 with severe body weight losses and minimal food consumption
Food consumption	HD: Lower food consumption was observed during GD 7-21.
Necropsy findings Cesarean Section Data	**Uterine and Ovarian Examinations in Rabbits**

Daily Dose (mg/kg/day)	0	30	90	180
Number of females examined	23	24	22	22
No Pregnant	21	22	21	19
Died while pregnant	0	0	0	1
Gravid uterine weight (g)	466	483	476	374*
Mean corpora lutea	9.7	10	9.8	9.8
Mean implantation sites	8.5	8.8	9.3	8.9
Mean % pre-implantation loss	1.2	1.20	0.5	0.9
Mean % post-implantation loss	6.0	3.3	8.3	16.2
Mean early Resorptions (%)	0.4	0.2	0.5	1.0
Mean late Resorptions (%)	0.0	0.1	0.8	1.5
Fetal weight change relative to control				
Male	43	-	-	↓24%**
Female	42	-	-	↓33%**

* = significantly different from the control group at 0.05. This decrease was possibly due to the decreased mean fetal weights in this group. The mean

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	net body weight and net body weight change in this group were comparable to the control group. **= significantly different from the control group at 0.01. The values in this group were below the minimum mean values of the testing facility's historical control data and the differences from the control group were considered test article-related.
Necropsy findings Offspring	**Fetal Developmental Findings in Rabbits**

Dose mg/kg/day	0	30	90	180
No. Litters Evaluated	21	22	21	19[d]
Mean No. of Viable Fetuses	8.1	8.5	8.5	7.4
Visceral Variations [f] Small spleen	0(0)	4(3)	0(0)	12(6)
Skeletal Variations Sternebra(e) nos. 5 and/or 6 unossified	18(8))	23(8)	19(8)	38(13
Pubis unossified	0(0)	0(0)	0(0)	6(1)
Hyoid body and/or arches unossified	0(0)	0(0)	0(0)	8(5)
Reduced ossification of the skull	0(0)	0(0)	1(1)	4(1)

[d] One female had total litter resorption; therefore, for fetal body weights, male sex ratio, and fetal anomalies, N = 18 litters.
[f] Total fetuses affected (litters)

Toxicokinetics	See section 1.4

Primary Reviewer
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Team Leader
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6 Clinical Pharmacology

6.1 Executive Summary

The Applicant is seeking approval of ivosidenib for the treatment of adult patients with R/R AML with a susceptible IDH1 mutation as detected by an FDA-approved test. The proposed dosing regimen is 500 mg once daily (QD) to be taken without food (b) (4) The primary evidence of efficacy to support the proposed dosing regimen is the rate of CR + CRh demonstrated in a Phase 1, multi-center, open-label, dose-escalation/-expansion study in patients with advanced hematologic malignancies with an IDH1 mutation (AG120-C-001, N=258). In the efficacy population of 173 patients with R/R AML, treatment with 500 mg QD ivosidenib resulted in a CR + CRh rate of approximately 33%. The safety evaluation of data from patients shows ivosidenib was generally tolerable; however, there was a significant positive exposure-response relationship for QTc interval prolongation.

The Clinical Pharmacology Review evaluated the acceptability of the proposed dosing regimen as well as the food effect, drug-drug interaction, organ impairment, population PK and exposure-response analyses for safety and efficacy.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 211192. This NDA is approvable from a Clinical Pharmacology perspective. The key review issues with specific recommendations/comments are summarized below.

REVIEW ISSUE	RECOMMENDATIONS/COMMENTS
Pivotal or supportive evidence of effectiveness	The primary evidence of effectiveness comes from pivotal Study **AG120-C-001** in the target population. A CR + CRh rate of ~33% demonstrated in 119 patients with R/R AML with an IDH1 mutation whose first dose of 500 mg QD was ≥ 6 months before the data cutoff date.
General dosing instructions	The proposed dosing regimen is 500 mg QD to be taken without food (b) (4) Do not administer TIBSOVO with a high-fat meal due to an increase in ivosidenib concentrations.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The following dose modifications are recommended: ▪ **Strong CYP3A inhibitors:** Reduce dose to 250 mg QD. ▪ **Strong CYP3A inducers:** Avoid concomitant use. ▪ **Sensitive CYP3A substrates:** Avoid concomitant use. ▪ **QTc prolonging drugs:** Avoid concomitant use.
Labeling	Generally acceptable.

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Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed 250 mg tablet formulation was used in the pivotal Study **AG120-C-001**, with the exception in the non-functional film coat and debossing. Adequate bridging of formulation was established via in vitro comparative dissolution testing. Refer to Biopharmaceutics Review for details.

Post-Marketing Requirement (PMR) or Commitment (PMC)

The following issues should be addressed as PMRs:

1. Complete your ongoing Study AG120-C-012, *A Phase 1, open-label, single-dose study to evaluate the pharmacokinetics, safety, and tolerability of AG-120 in subjects with mild or moderate hepatic impairment or normal hepatic function*.

2. Conduct a clinical pharmacokinetic trial to determine an appropriate safe dose of ivosidenib in patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test with hepatic impairment (moderate) dosed with ivosidenib to steady-state vs. patients with normal hepatic function dosed with ivosidenib to steady-state. This may be performed as a sub-study in the ongoing Phase 1 Study AG120-C-001, *A Phase 1, Multicenter, Open-Label, Dose-Escalation and Expansion, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-120 in Subjects with Advanced Hematologic Malignancies with an IDH1 Mutation*. This trial should be designed and conducted in accordance with the FDA Guidance for Industry entitled *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*. Depending on the results, a clinical pharmacokinetic trial in patients with severe hepatic impairment may be required.

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

Ivosidenib is an inhibitor of the mutant IDH1 enzyme. The following is a summary of the clinical pharmacokinetics of ivosidenib:

Absorption: Median time to peak ivosidenib plasma concentration was 3 h. A high-fat meal increased ivosidenib C_{MAX} by 98% and AUC_{INF} by 25%.
Distribution: Ivosidenib is 92 to 98% bound to human plasma proteins. The mean steady-state volume of distribution was 234 L.
Metabolism: Ivosidenib is the predominant component (>92%) of total radioactivity in plasma, based on the mass balance study. Of the fraction that is metabolized, ivosidenib is primarily metabolized by CYP3A. Note that ivosidenib is an inducer of CYP3A (i.e., autoinducer of its own metabolism).

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Elimination: Following a single dose of 500 mg ivosidenib, the mean terminal elimination half-life of ivosidenib was 93 h. The steady-state apparent clearance was estimated to be 5.4 L/h, with a between-subject variability of 35%. Based on the mass balance study, 77% of the dose was recovered in the feces (67% as unchanged) and 17% of the dose was recovered in the urine (10% as unchanged).

6.2.2 General Dosing and Therapeutic Individualization

General Dosing

The recommended dosing regimen is 500 mg QD to be taken without food (b) (4) in adult patients with R/R AML with a susceptible IDH1 mutation as detected by an FDA-approved test.

Therapeutic Individualization

In regards to drug-drug interactions (DDI), the following dose modifications are recommended:

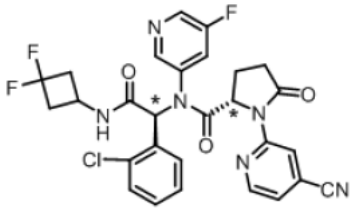
- **Strong CYP3A inhibitors:** reduce dose to 250 mg QD.
- **Strong CYP3A inducers:** avoid concomitant use.
- **Sensitive CYP3A substrates:** avoid concomitant use.
- **QTc prolonging drugs:** avoid concomitant use.

Outstanding Issues

We have issued one PMR, as presented in the PMR/PMC Section above. There are no other outstanding issues.

6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

PHYSICOCHEMICAL PROPERTIES	
Chemical structure and molecular weight	Ivosidenib (583.0 relative molecular mass)  * denotes stereocenter

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Aqueous solubility	Ivosidenib is a BCS Class II compound (low solubility, high permeability). Its aqueous solubility is pH independent; it does not contain ionizable groups under physiological conditions.
PHARMACOLOGY	
Mechanism of action	Ivosidenib is an inhibitor of mutated isocitrate dehydrogenase 1 (IDH1) (IC_{50} ≈ 2-17 nM).
Active moiety	There are no major circulating metabolites in patients with R/R AML or in healthy subjects. Based on mass balance study, ivosidenib is the predominant component (>92%) of total radioactivity in plasma.
QT/QTc prolongation	QTc prolongation is a toxicity under Warnings and Precautions. Based on concentration-QTc analysis, ivosidenib mean C_{MAX} at steady-state following the recommended dose of 500 mg QD is associated with a QTc prolongation of 17.2 msec from baseline.
GENERAL INFORMATION	
Bioanalytical assay	Validated bioanalytical assays (LC-MS/MS) were developed to measure the concentrations of ivosidenib in the clinical studies included in this NDA (see Appendix).
Patient PK vs. healthy subject (HS) PK	Patients with AML generally had longer mean terminal half-lives than HS (72-138 h following 100-1200 mg SD in patients vs. 41-77 h following 250-1000 mg SD in HS).
Steady-state exposure at the proposed dosing regimen	Steady-state is achieved within 14 d of QD dosing. At 500 mg QD at steady-state: ▪ AUC_{0-24h} ≈ 117000 ng·h/mL (50% CV) ▪ C_{MAX} ≈ 6600 ng/mL (44% CV)
Minimal effective dose or exposure	Unknown.
Maximum tolerated dose or exposure	Not reached, based on pivotal Study **AG120-C-001** in patients with IDH1-mutated hematologic malignancies (maximum dose tested = 1200 mg QD).
Dose proportionality	Following multiple-dosing, ivosidenib exposures generally increased less than dose proportionally.
Accumulation	At 500 mg QD at steady-state: ▪ AUC ≈ 1.9-fold accumulation ▪ C_{MAX} ≈ 1.5-fold accumulation
Variability	Based on pivotal Study **AG120-C-001** at 500 mg QD, inter-subject variability (%CV) was 50% and 44% for steady-state AUC and C_{MAX}, respectively.
ABSORPTION	
Bioavailability	The absolute bioavailability of ivosidenib has not been determined.
T_{MAX}	Median T_{MAX} = 3 h
Food effect	**$AUC_{0-\infty}$ (GMR, 90% CI)** / **C_{MAX} (GMR, 90% CI)** / **T_{MAX} (median)** 1.24 (1.16, 1.33) / 1.98 (1.79, 2.19) / Fed: 3.0 h Fasted: 3.0 h Ivosidenib should be administered without food (b) (4) Do not administer ivosidenib with a high-fat meal due to an increase in ivosidenib plasma concentrations.
DISTRIBUTION	
Volume of distribution (Vd)	Ivosidenib is approximately 92-96% bound to human plasma proteins. Based on population PK, Vc/F at steady-state ≈ 234 L (43% CV).
Substrate of transporter systems	Ivosidenib is a substrate of P-gp.

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ELIMINATION	
Terminal elimination half-life and clearance	Following a single dose of 500 mg ivosidenib in pivotal Study **AG120-C-001**, the mean terminal elimination half-life of ivosidenib was 93 h. The steady-state apparent clearance was estimated to be 5.4 L/h, with a between-subject variability of 35%.
Metabolism	Note that ivosidenib is primarily eliminated fecally (see **Excretion** section, directly below). Of the fraction that is metabolized, ivosidenib is primarily metabolized by CYP3A.
Excretion	Based on the mass balance study, 77% of the dose was recovered in the feces (67% as unchanged) and 17% of the dose was recovered in the urine (10% as unchanged).
Drug interaction liability	Note that ivosidenib is an autoinducer of this own metabolism (i.e., ivosidenib is an inducer of CYP3A). As a victim, ivosidenib exposure may be affected by CYP3A modulators and P-gp inhibitors. As a perpetrator, ivosidenib may decrease exposure of concomitant CYP3A, CYP2B6, CYP2C8, CYP2C9 substrates and may increase exposure of concomitant OAT3 and P-gp substrates.

6.3.2 Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. Support for evidence of effectiveness was obtained from pivotal Study **AG120-C-001**.

Study **AG120-C-001** is a Phase 1, multi-center, open-label, dose-escalation/-expansion study to evaluate the safety, PK, PD, and clinical activity of ivosidenib in patients with advanced hematologic malignancies with an IDH1 mutation (N=258). Ivosidenib was initially administered without regard to food, however once food effect Study **AG120-C-004** results became available, an amendment was made to the Protocol to avoid a high-fat meal (Amendment 5, n=6 patients enrolled). The study included 173 patients in the R/R AML Efficacy Set, with 153 patients in the Original Efficacy Set. Complete remission (CR) plus complete remission with only partial hematologic recovery (CRh) rates were 33% and 31% in the R/R AML and Original Efficacy Sets, respectively.

Effect of IDH1 mutation type on efficacy: Patients in study AG120-C-001 were selected based on the presence of an IDH1 mutation in a blood or bone marrow sample as determined by local testing with retrospective central confirmation (dose escalation) or by central testing (dose expansion). The proposed Abbott RealTime IDH1 companion diagnostic (CDx) is a polymerase chain reaction (PCR) based assay that is designed to detect a total of five IDH1 mutations at R132 (CGT) [R132C (TGT), R132H (CAT), R132G (GGT), R132S (AGT), and R132L (CTT)].

The distribution of IDH1 mutations in both the Primary and the R/R AML Efficacy Sets is provided in **Table 10.** The predominant IDH1 mutations were R132C and R132H, which is consistent with the two most commonly reported IDH1 mutations in AML (COSMIC). Ivosidenib showed clinical activity across the IDH1 R132 mutation subgroups in both the Primary and the R/R AML Efficacy Sets, with the highest CR+CRh rate found in the subgroup of patients with R132C mutation (40%) and the lowest CR+CRh rate found in the subgroup of patients with

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R132H mutation (11-19%) **(Table 10)**.

Table 10. Distribution of and Response Rates by IDH1 R132 Mutation Type in the Primary and R/R AML Efficacy Sets

	IDH1 Mutation*	N (%)	Response, N (%)		
			CR	CRh	CR+CRh
Original Efficacy Set (N=153)	R132C	91 (59)	26 (29)	10 (11)	36 (40)
	R132H	35 (23)	3 (9)	1 (3)	4 (11)
	R132G	11 (7)	3 (27)	0	3 (27)
	R132S	10 (7)	1 (10)	1 (10)	2 (20)
	R132L	6 (4)	2 (33)	0	2 (33)
R/R AML Efficacy Set (N=173)	R132C	102 (59)	30 (29)	11 (11)	41 (40)
	R132H	42 (24)	7 (17)	1 (2)	8 (19)
	R132G	12 (7)	3 (25)	1 (8)	4 (33)
	R132S	10 (6)	1 (10)	1 (10)	2 (20)
	R132L	7 (4)	2 (29)	0	2 (29)

*As detected by the proposed CDx assay. Source: Reviewer exploratory analysis.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the Applicant's **proposed dosing regimen of 500 mg QD (without food** (b) (4) **is appropriate** for the intended patient population of adult patients with R/R AML with a susceptible IDH1 mutation as detected by an FDA approved test. The proposed dosing regimen is supported by the observed PK, safety and efficacy data from pivotal Study **AG120-C-001**, as described below.

Dose Selection Rationale

Dose selection was based on results of the dose-escalation part of Study **AG120-C-001**, which evaluated ivosidenib dosing regimens of 100 mg BID (starting dose) and 300 to 1200 mg QD in adult patients with IDH1-mutated hematologic malignancies (n=78, 41 evaluable at the time of dose selection) (1 cycle = 28 d). Following evaluation of the first cohort (100 mg BID), BID regimen was discontinued based on emerging PK data in favor of QD dosing. Across the evaluated dose range, ivosidenib PK generally increased less than dose proportionally, however with overlapping exposures from 500 to 800 mg QD **(Table 11)**. In regards to the PD marker 2-HG (2-hydroxyglutarate, which is overexpressed in patients with IDH1 mutation and contributes to the oncogenesis of AML), 500 mg QD showed near maximal 2-HG inhibition in blood and bone marrow by Cycle 2, Day 1 with no additional 2-HG inhibition at doses > 500 mg QD, while lower inhibition was observed at doses < 500 mg QD. Overall PD data including data from 500 mg QD dose expansion cohorts are shown in **Table 12**. Although the MTD was not reached, one

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DLT was observed at 800 mg QD (Gr3 ECG QTc prolongation) and one DLT was observed at 1200 mg QD (Gr3 rash). Therefore, 500 mg QD was selected as the expansion dose for further evaluation based on the following:

- **PK:** overlapping ivosidenib exposures from 500 to 800 mg QD
- **PD:** near maximal inhibition of 2-HG at 500 mg QD, with no additional increases in inhibition at doses > 500 mg QD
- **Safety:** no DLTs at 500 mg QD, with DLTs observed at doses > 500 mg QD

Table 11. Summary of ivosidenib PK parameters following multiple dosing on Cycle 1, Day 15 and Cycle 2, Day 1 (dose-escalation)

PK Parameters	Summary Statistic[1]									
	Cycle 1, Day 15					Cycle 2, Day 1				
	100 mg BID (n=4)	300 mg QD (n=4)	500 mg QD (n=40)	800 mg QD (n=14)	1,200 mg QD (n=5)	100 mg BID (n=4)	300 mg QD (n=4)	500 mg QD (n=39)	800 mg QD (n=10)	1,200 mg QD (n=3)
$AUC_{0\text{-}10hr}$ (hr•ng/mL)	23,621 (37.3) n=3	47,469 (30.3) n=3	59,014 (42.7) n=37	62,063 (50.7) n=12	91,767 (29.5) n=4	22,761 (38.7) n=4	52,063 (11.6) n=4	56,212 (35.8) n=32	59,275 (38.8) n=10	96,865 (17.4) n=3
$AUC_{0\text{-}tau}$ (hr•ng/mL)	39,597 (88.7) n=4	105,363 (26.2) n=4	133,453 (44.8) n=39	125,935 (53.1) n=13	202,767 (25.8) n=5	28,305 (45.3) n=4	111,888 (18.3) n=4	123,150 (39.2) n=38	131,344 (34.6) n=9	224,063 (19.2) n=3
C_{max} (ng/mL)	4,253 (70.7) n=4	5,583 (27.9) n=4	7,108 (38.8) n=40	7,266 (44.2) n=14	10,850 (23.1) n=5	2,743 (29.2) n=4	6,633 (14.3) n=4	6,710 (36.2) n=39	7,280 (34.7) n=10	11,808 (15.2) n= 3
T_{max}[2] (hr)	1.46 (0.00, 4.08) n=4	3.40 (2.00, 4.03) n=4	3.00 (0.88, 8.13) n=40	2.58 (1.00, 6.08) n=14	3.08 (2.00, 6.00) n=5	2.48 (0.50, 4.00) n=4	1.92 (1.00, 2.98) n=4	2.95 (1.00, 6.00) n=39	2.53 (0.97, 4.03) n=10	4.00 (3.90, 4.00) n=3
CL_{ss}/F (L/hr)	2.53 (88.7) n=4	2.85 (26.2) n=4	3.75 (44.8) n=39	6.35 (53.1) n=13	5.92 (25.8) n=5	3.53 (45.3) n=4	2.68 (18.3) n=4	4.06 (39.2) n=38	6.09 (34.6) n=9	5.36 (19.2) n=3
R_{acc}(AUC)	3.46 (66.2) n=4	2.89 (13.7) n= 4	1.99 (47.9) n=12	1.77 (54.1) n=11	2.07 (42.2) n=5	2.47 (35.2) n=4	3.07 (16.2) n=4	2.01 (48.7) n=12	1.73 (48.1) n=9	1.74 (36.8) n=3
$R_{acc}(C_{max})$	3.09 (64.8) n=4	1.79 (13.3) n=4	1.46 (49.9) n=12	1.43 (49.0) n=12	1.62 (26.8) n=5	1.99 (31.5) n=4	2.13 (6.28) n=4	1.55 (47.5) n=12	1.37 (47.4) n=10	1.51 (26.0) n=3

Source: Report AG120-C-001-PKPD, Table 17. Data Cutoff Date: 12 May 2017.
Abbreviations: $AUC_{0\text{-}10hr}$ = area under the concentration × time curve from time 0 to 10 hours postdose; $AUC_{0\text{-}tau}$ = area under the concentration × time curve from time 0 to the end of the dosing interval; BID = twice daily; CLss/F = apparent clearance at steady state; C_{max} = maximum concentration; GeoCV = geometric coefficient of variation; QD = once daily; R_{acc}(AUC) = accumulation ratio (based on AUC), calculated as $AUC_{0\text{-}tau}$ (C1D15 or C2D1)/$AUC_{0\text{-}12}$ or $AUC_{0\text{-}24}$ (Day -3); $R_{acc}(C_{max})$ = accumulation ratio (based on C_{max}), calculated as C_{max} (C1D15 or C2D1)/C_{max} (Day -3); T_{max} = time to maximum concentration.
[1] Geometric Mean (GeoCV%), unless otherwise specified.
[2] Median (min, max).

Source: Table 67 of Applicant's AG120-C-001 CSR

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Table 12. Summary of plasma 2-HG percent inhibition at Cycle 2, Day 1 based on average concentration following ivosidenib administration (dose-escalation/-expansion combined)

Dose Group	n	2-HG Percent Inhibition				
		Mean	StDev	Minimum	Median	Maximum
<500 mg	8	69.3	40.0	2.46	88.8	98.0
500 mg	160	90.6	12.3	28.1	95.2	99.7
>500 mg	13	82.7	37.7	-41.4	93.3	99.3

Source: Report AG120-C-001-PKPD, Table 36. Data cutoff date: 12 May2017.
Abbreviations: 2-HG = 2-hydroxyglutarate; C2D1 = Cycle 2, Day 1; C_{avg} = average concentration; QD = once daily; StDev = standard deviation.
Note: 114 out of 160 subjects (71%) at 500 mg QD, with percent inhibition based on C_{avg} (%) ≥90%; 137 out of 160 subjects (86%) at 500 mg QD, with percent inhibition based on C_{avg} (%) ≥80%.
Source: Table 71 of Applicant's AG120-C-001 CSR

Primary Efficacy and Safety Profile
The dose-expansion part of Study **AG120-C-001** evaluated 500 mg QD ivosidenib in patients with IDH1-mutated hematologic malignancies in the following arms based on disease type:

- **Arm 1:** R/R AML (n=126)
- **Arm 2:** untreated AML (n=25)
- **Arm 3:** other advanced hematologic malignancies (n=11)
- **Arm 4:** relapsed AML not eligible for Arm 1 (n=18)

The efficacy population for this NDA consists of combined patients with R/R AML from dose-escalation/-expansion whose first dose of 500 mg QD ivosidenib was ≥ 6 months before data cutoff date (n=173). In the efficacy population, treatment with 500 mg QD ivosidenib resulted in a CR + CRh rate of approximately 33% **(Table 33).**

The safety profile was generally tolerable **(pg 114)**, however QTc interval prolongation was a significant risk (see below). Common TEAEs included fatigue (39%), leukocytosis (38%), nausea/vomiting (37%), arthralgias (36%), diarrhea (34%), and dyspnea (33%) **(Table 52).**

Exposure-Response (E-R) Analyses
The applicant performed E-R analyses for efficacy and safety using data from study **AG120-c-001**. See Pharmacometrics Review in Appendix for details of the analyses.

For efficacy, logistic regression was conducted on the primary and secondary efficacy endpoints (complete response with complete hematologic response, complete response and overall response) with the steady-state AUCss. There appears to be no clear trend of correlation with efficacy at the evaluated exposures (Figure 31).

Exposure-safety analyses were conducted for safety endpoints including rash, gastrointestinal events, liver dysfunction, hepatic enzyme elevation, leukocytosis, acute renal failure, IDH

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differentiation syndrome, tumor lysis syndrome and polyneuropathy. Logistic regression analysis indicated that the incidence of events for all safety endpoints was not associated with ivosidenib exposure (AUCss). For All Grade ALT and All Grade AST AEs, the incidence was lower in Q1 compared to Q2, Q3 and Q4. However, the trends were not evident with new or worsening ALT and AST AEs ≥Grade 2, suggesting these trends for All Grade AEs was mainly driven by Grade 1 events.

QT/QTc Prolongation

QTc prolongation is a significant clinical risk for ivosidenib. Based on the Applicant's concentration-QTc analysis **(Report AG120-C-META-CQT)**, ivosidenib mean C_{MAX} at steady-state following the recommended dose of 500 mg QD in pivotal **Study AG120-C-001** is associated with a QTc prolongation from baseline of 17.2 msec (90% CI: 14.9, 19.7 msec). The predicted QTc prolongation from baseline is 16.1 msec (90% CI: 13.3, 18.9 msec) when including only the target R/R AML population from Study **AG120-C-001** (n=136). Overall, there was a concentration-dependent increase in QTc prolongation. Refer to the QT-IRT review for details. Co-administration of moderate or strong CYP3A inhibitors is expected to further increase QTc prolongation from baseline due to increase in ivosidenib exposure **(Figure 10)**.

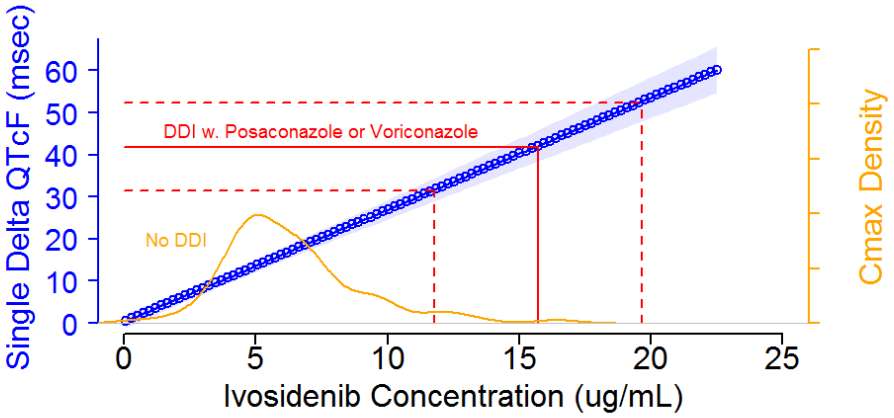

Figure 10: Effect on QT Interval

There is a significant increase in the QT interval prolongation with higher ivosidenib concentrations. The blue open circles and gray shaded region are the model prediction and 90% CI for the QT-IRT established model. The yellow line is the density plot for the Cmax values from patients who did not receive strong CYP3A4 inhibitors in study AG120-C-001. The solid and dashed red lines are the mean and 90% CI for the predicted Cmax values based on the PBPK simulation for patients receiving strong CYP3A4 inhibitors.

This relationship is developed with clinical QT data from study AG120-C-001 and supported by the observed magnitude of QT-prolongation in patients receiving different concomitant strong CYP3A4 inhibitors. A total of 50 subjects receiving either fluconazole, voriconazole or posa-conazole experienced QT prolongation between 30 – 60 ms. A total of 16 subjects receiving at least one of these three concomitant medications experienced QT prolongation of greater than 60 ms.

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Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No. Population PK analysis indicated that age, sex, race, body weight, or ECOG performance status are not significant covariates for ivosidenib clearance. No dose adjustment is needed based on these patient factors. In addition, no dose adjustment is proposed in patients with hepatic or renal impairment. Based on an exploratory analysis, patients with a greater number of mutations co-occurring with IDH1 R132 mutations tended to have lower CR+CRh rate as compared to patients with fewer co-occurring mutations.

Hepatic Impairment (HI)
Population PK analysis did not show a clinically meaningful effect of mild HI (NCI-ODWG criteria: total bilirubin ≤ ULN and AST > ULN, or total bilirubin > 1.0-1.5 x ULN and any AST) on the systemic exposure of ivosidenib (n=25, from Study **AG120-C-001**). Due to limited number of patients with moderate or severe HI enrolled, there was not enough data to evaluate the effect of moderate or severe HI on ivosidenib PK.

At this time, no dose adjustment is recommended for patients with mild H. A study to evaluate single-dose PK of ivosidenib in subjects with mild or moderate HI is currently ongoing; a PMR will be issued to ensure that this study is completed and a final clinical study report submitted. Since ivosidenib autoinduces its own metabolism, another PMR will be issued to determine an appropriate safe dose of ivosidenib in patients with R/R AML with a susceptible IDH1 mutation with moderate HI dosed with ivosidenib to steady-state vs. patients with normal hepatic function dosed with ivosidenib to steady-state (depending on the results, a trial in patients with severe HI may be required).

Renal Impairment (RI)
Population PK analysis indicated that there was no clinically meaningful effect of mild or moderate RI (MDRD formula: eGFR ≥ 30 to < 90 mL/min/1.73 m^2) on the systemic exposure of ivosidenib (n=74 mild RI, 36 moderate RI, from **AG120-C-001**). Due to limited number of patients with severe RI enrolled (n=2), there was not enough data to evaluate the effect of severe RI on ivosidenib PK. However, based on the mass balance study, renal elimination plays a minor role in the overall elimination of ivosidenib (<20%).

No dose adjustment is needed in patients with RI.

Mutations co-occurring with IDH1 R132
Blood and/or bone marrow samples were collected during study AG120-C-001 for exploratory analyses of co-occurring mutations using two next-generation sequencing (NGS) panels; the FoundationOne Heme® panel (covers 405 genes) in the dose escalation portion (N=30) and the Brigham and Woman's Hospital (BWH) Rapid Heme Panel (covers 95 genes) in the dose expansion portion of the study (N=143). All patients from the R/R AML Efficacy Set had results

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available from samples collected at screening. The IDH1 mutations identified (R132C N=99, R132H N=42, R132G N=12, R132S N=11, and R132L N=7) were generally consistent with results from the CDx assay. Two patients from the dose escalation portion did not have IDH1 R132 mutations based on the exploratory NGS results, and three patients were found to have two mutations in IDH1 (R132C+R132G, G131A+R132C, and R132Y+R132L).

Table 13. Number of Responses (CR+CRh) by Number of Co-Occurring Mutations

Dose Escalation										
Response, N	**Number of Co-Occurring Mutations***									
	0 N=1	1 N=3	2 N=2	3 N=8	4 N=8	5 N=2	6 N=1	7 N=0	8 N=3	Total N=28
CR	1	2	0	2	1	0	0	0	0	6
CRh	0	0	0	1	1	0	0	0	1	3
CR+CRh	1	2	0	3	2	0	0	0	1	9
Dose Expansion										
Response, N	**Number of Co-Occurring Mutations***									
	0 N=18	1 N=24	2 N=36	3 N=23	4 N=18	5 N=14	6 N=8	7 N=1	8 N=1	Total N=143
CR	7	10	11	2	4	2	1	0	0	37
CRh	3	1	3	1	2	1	0	0	0	11
CR+CRh	10	11	14	3	6	3	1	0	0	48

*Number of mutations co-occurring with IDH1 R132 mutation as detected by NGS panels. Source: Reviewer exploratory analysis. Two patients from the R/R AML Efficacy Set that were enrolled in the dose escalation study were negative for IDH1 R132 mutation and were excluded from this analysis. Mutations included were classified by the applicant as being known or likely oncogenic mutations and had variant types reported of deletion, frameshift, insertion, missense, nonsense, short-variant, or splicing. Unique "known or likely oncogenic mutations" in the same gene were added when the number of co-occurring mutations per patient was calculated.

Overall, patients were found to harbor 0 to 8 co-occurring mutations in addition to their IDH1 mutation **(Table 13)**. Although a consistent pattern of co-occurring mutated gene(s) or specific single gene mutation(s) was not identified in patients who achieved CR or CRh, responses were generally more common in patients with fewer co-occurring mutations. The genes most frequently identified as having co-occurring mutations were DNMT3A, NPM1, SRSF2, RUNX1, NRAS, ASXL1, and TP53. Patients with mutated NPM1, which is associated with favorable prognosis in AML with normal cytogenetics when found in the absence of FLT3 internal tandem duplication (ITD), had a CR+CRh rate of 32% (14/44) and is consistent with the response rate observed in the R/R AML and Original Efficacy Sets. In general, mutations in the receptor tyrosine kinase (RTK) pathway genes (e.g., NRAS, FLT3, KRAS, PTPN11) occurred more frequently in nonresponders relative to patients who achieved CR or CRh as a best response.

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Patients with mutated NRAS or FLT3 that achieved CR or CRh responses also had mutations in NPM1 (3/13 for NPM1+NRAS, 2/2 for NPM1+NRAS+FLT3). No patients with FLT3-ITD responded (N=3).

IDH1 R132 Variant Allele frequency (VAF)

The IDH1 R132 VAF was determined in bone marrow samples collected at screening using the BWH NGS platform (N=141 from dose expansion). The VAF was defined as the fraction of mutant reads relative to the total number of reads covering the variant. An exploratory analysis by the reviewer using the updated efficacy dataset (data cut date of November 10, 2017) found that patients with lower VAF tended to have higher CR+CRh rate (median VAF: 29%) as compared to nonresponders (median VAF: 39%).

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Yes, ivosidenib should be taken without food (b) (4) In regards to drug-drug interactions (DDI), the following dose modifications are recommended:

- **Strong CYP3A inhibitors:** reduce dose to 250 mg QD.
- **Strong CYP3A inducers:** avoid concomitant use.
- **Sensitive CYP3A substrates:** avoid concomitant use.
- **QTc prolonging drugs:** avoid concomitant use.

Food-Drug Studies

Food Effect

Study **AG120-C-004** was a Phase 1, open-label, 2-part study. Part 1 was a randomized, 2-period, cross-over study to evaluate the effect of a high-fat meal on the PK of a single oral dose of 500 mg ivosidenib in healthy subjects (n=27). Subjects were administered a single-dose of 500 mg ivosidenib with and without a high-fat breakfast, with a washout period of ≥ 25 d between doses. The high-fat breakfast consisted of two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash brown potatoes (fried with butter), and eight ounces of whole milk. As seen in **Table 14**, compared to the fasted condition, a high-fat meal increased ivosidenib C_{MAX} by 98% and AUC by 24%. Median T_{MAX} was not changed. Due to the increase in C_{MAX}, **ivosidenib should be taken without food** (b) (4)

Note that pivotal Study **AG120-C-001** was initially administered without regard to food. Once the results of Study **AG120-C-004** become available, an amendment was made to Protocol **AG120-C-001** to avoid a high-fat meal (Amendment 5, n=6 enrolled).

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Table 14: Summary of ivosidenib PK parameters and LSM analysis in food-effect part of Study AG120-C-004

	Ivosidenib Geometric LSM		Ivosidenib Geometric LSM Ratio (90% CI)	
	$AUC_{0-\infty}$ (ng·h/mL)	**C_{MAX} (ng/mL)**	**$AUC_{0-\infty}$**	**C_{MAX}**
Fed (n=27) Fasted (n=27)	174000 140000	4520 2290	1.24 (1.16, 1.33)	1.98 (1.79, 2.19)

Adapted from Table 11-2 in Applicant's AG120-C-004 CSR

Drug-Drug Interaction (in vivo and model-based approaches)

Effect of gastric pH modulators on ivosidenib PK

The aqueous solubility of ivosidenib is pH independent; ivosidenib does not contain ionizable groups under physiological condition. When co-administered with gastric pH modulators, ivosidenib exposures are not expected to change. The most commonly used gastric pH modulators in pivotal Study **AG120-C-00**1 were pantoprazole (7%) and famotidine (4%). Based on population PK analysis from pivotal Study **AG120-C-001**, pantoprazole or famotidine were not identified as significant covariates affecting ivosidenib exposure. Therefore, **no dose adjustment is needed in patients taking concomitant gastric pH modulators.**

Effect of itraconazole (a strong CYP3A inhibitor and P-gp inhibitor) on ivosidenib PK

Ivosidenib is metabolized by CYP3A enzymes and is a substrate of P-gp. Itraconazole was used a strong CYP3A index inhibitor to evaluate the effect of CYP3A inhibition on the PK of single-dose ivosidenib in healthy subjects (DDI Study **AG120-C-007**). Study **AG120-C-007** was a single-center, open-label, 2-period, fixed-sequence study to evaluate the effect of concomitant itraconazole on ivosidenib single-dose PK in healthy subjects (n=22). On Day 1 of each period, 250 mg ivosidenib was administered following an overnight fast. On Days -4 to 14 of Period 2, 200 itraconazole mg QD was administered about 30 min after the start of a standard breakfast (except on Day 1). The washout period was 21 d between ivosidenib dosing in Period 1 and first dose of itraconazole in Period 2. PK samples for ivosidenib were collected from pre-dose through post-dose 504 h in each period. As seen in **Table 15**, concomitant itraconazole increased ivosidenib single-dose AUC to 269% of control (90% CI: 245%, 295%) with no change in C_{MAX}. In regards to multiple-dosing, note that because ivosidenib induces the metabolism of CYP3A substrates following ivosidenib multiple dosing, itraconazole (a CYP3A substrate) is not recommended to be used concomitantly with TIBSOVO in patients. Based on the risk of QTc prolongation with higher exposure and a flat exposure-response relationship for safety, **ivosidenib dose should be reduced to 250 mg QD with concomitant strong CYP3A inhibitors.** For additional details on the effect of strong CYP3A inhibition on ivosidenib exposure, refer to the PBPK and Pharmacometrics reviews in the OCP Appendices.

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Table 15. Summary of ivosidenib PK parameters and LSM analysis in itraconazole DDI Study AG120-C-007

	Ivosidenib Geometric LSM		Ivosidenib Geometric LSM Ratio (90% CI)	
	$AUC_{0-\infty}$ (ng·h/mL)	C_{MAX} (ng/mL)	$AUC_{0-\infty}$	C_{MAX}
+Itraconazole (n=20-21)	302	2265	2.69 (2.45, 2.95)	1.02 (0.927, 1.13)
-Itraconazole (n=20-21)	113	2211		

Adapted from Table 11-3 in Applicant's AG120-C-007 CSR

Effect of fluconazole (a moderate CYP3A inhibitor) on ivosidenib PK

The Applicant developed a physiologically-based pharmacokinetic (PBPK) model of ivosidenib. The Applicant used the PBPK model to predict the effect of concomitant fluconazole on the exposure of ivosidenib. Co-administration of ivosidenib (500 mg on Day 8) and fluconazole (400 mg on Day 1, then 200 mg QD for 29 d) was predicted to increase ivosidenib single-dose AUC to approximately 173% of control with no change in C_{MAX}. In regards to ivosidenib at steady-state, co-administration of ivosidenib (500 mg QD for 15 d) and fluconazole (400 mg on Day 1, then 200 mg QD for 14 d) was predicted to increase ivosidenib steady-state AUC by 90% and C_{MAX} by 52% **(Table 16)**. **No dose adjustment is needed in patients taking concomitant moderate CYP3A inhibitors.** Refer to the PBPK review in the OCP Appendix for details.

Table 16. Predicted effect of concomitant fluconazole on ivosidenib exposure

Moderate CYP3A Inhibitor	Ivosidenib Dosing	Ivosidenib Geometric Mean Ratio (+fluconazole/-fluconazole)	
		AUC	C_{MAX}
Fluconazole (multiple-dose)	500 mg (single-dose)	1.7	1.0
	500 mg QD (steady-state)	1.9	1.5

Adapted from Tables 36 and 37 in Applicant's AG120-C-001-PBPK Report

Effect of rifampin (a strong CYP3A inducer) on ivosidenib on PK

The Applicant used PBPK modeling to predict the effect of concomitant rifampin on the exposure of ivosidenib. Co-administration of rifampin (600 mg QD for 15 d) and ivosidenib (500 mg QD for 30 d) was predicted to decrease ivosidenib steady-state AUC by 33% and C_{MAX} by 19% **(Table 17)**. Based on the decrease in ivosidenib steady-state AUC, **concomitant strong CYP3A inducers should be avoided.** Refer to the PBPK review in the OCP Appendix for details.

Table 17. Predicted effect of concomitant rifampin on ivosidenib exposure

Strong CYP3A Inducer	Ivosidenib Dosing	Ivosidenib Geometric Mean Ratio (+rifampin/-rifampin)	
		AUC	C_{MAX}
Rifampin (multiple-dose)	500 mg QD (steady-state)	0.67	0.81

Adapted from Tables 33 in Applicant's AG120-C-001-PBPK Report

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Effect of ivosidenib on itraconazole and midazolam (CYP3A substrates) PK

Ivosidenib induces CYP3A, including its own metabolism. Co-administration of ivosidenib with CYP3A substrates such as itraconazole is expected to decrease itraconazole steady-state AUC significantly, based on PBPK modeling. The Applicant also used PBPK modeling to predict the effect of ivosidenib on the exposure of midazolam (a sensitive CYP3A index substrate). Co-administration of ivosidenib (500 mg QD for 19 d) and midazolam (5 mg on Day 15) was predicted to decrease midazolam single-dose AUC by 83% and C_{MAX} by 74% **(Table 18)**. Due to the significant decrease in exposure of CYP3A substrates, **avoid concomitant use of ivosidenib with sensitive CYP3A substrates.**

Do not administer ivosidenib with itraconazole or ketoconazole (CYP3A substrates) due to expected loss of anti-fungal efficacy. Refer to the PBPK review in the OCP Appendix for details.

Table 18. Predicted effect of ivosidenib on midazolam exposure

Ivosidenib Dosing	Sensitive CYP3A Index Substrate	Midazolam Geometric Mean Ratio (+ivosidenib/-ivosidenib)	
		AUC	C_{MAX}
500 mg QD (steady-state)	Midazolam (single-dose)	0.17	0.26

Adapted from Tables 19 in Applicant's AG120-C-001-PBPK Report

Drug-Drug Interaction (other)

QTc prolonging drugs
In pivotal Study **AG120-C-007**, the protocol excluded patients taking medications that are known to prolong the QT interval. Since QTc interval prolongation is a Warning/Precaution, **concomitant drugs that are known to prolong the QTc interval should be avoided**. Note that itraconazole and ketoconazole are known to prolong the QTc interval, hence further justifying that itraconazole and ketoconazole should be avoided in this patient population.

Drug-Drug Interaction (in vitro)

CYP enzymes
Ivosidenib may induce CYP2B6, 2C8, and 2C9, and therefore may affect the PK of sensitive substrates of these enzymes (i.e., reduce their plasma concentration). Refer to PBPK review in the OCP Appendix for details.

Transporters
Ivosidenib does not inhibit BCRP, OATP1B1, OATP1B3, OAT1, or OCT2 at clinically relevant concentrations. Ivosidenib is an inhibitor of OAT3 and P-gp. Refer to PBPK review in the OCP Appendix for details.

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NDA Multidisciplinary Review and Evaluation
NDA 211192
Tibsovo (ivosidenib)

Vicky Hsu, Ph.D. Primary Reviewer	Gene Williams, Ph.D. Team Leader
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7 Sources of Clinical Data and Review Strategy

7.1 Table of Clinical Studies

Table 19: Listing of Clinical Trials Relevant to this NDA

Trial Identity	Trial Design (Primary Endpoint)	Regimen, Schedule, Route	Treatment Duration/ Follow Up	No. of patients enrolled	Countries : No. of Centers
Pivotal Study					
AG120-C-001	Phase 1, open-label study of ivosidenib in patients with IDH1+ advanced hematologic malignancies (PK, Safety, ORR)	Escalation: 200-1200 mg total daily dose PO Expansion: 500 mg PO daily	Until PD or unacceptable toxicity Minimum follow-up 6 months*	268	US: 23 France: 2
Studies to Support Safety					
AG120-221-C-001	Phase 1, open-label study of IDH inhibitors in combination with induction and consolidation therapy in newly-diagnosed AML with IDH mutation (PK, Safety, ORR)	500 mg PO daily + Induction: Ara-C 200 mg/m^2 CI d1-7, DNR 60 mg/m^2 or IDA 12 mg/m^2 d1-3 Consolidation x 1-4: Ara-C 1-3 g/m^2 bid d1-3 or d1,3,5 *or* MTZ 10 mg/m^2 + VP-16 100 mg/m^2 d1-5	Until relapse, toxicity, or HSCT, for up to 2 years	71 (27 IDH1)	Unknown (no datasets provided)
AG120-C-002	Phase 1, open-label study of ivosidenib in patients with IDH1+ advanced solid tumors (PK, Safety, ORR)	200-1200 mg total daily dose PO Expansion: 500 mg PO daily	Until PD or unacceptable toxicity	174	US: 13
AG120-C-003	Phase 1, open-label study of ivosidenib absorption, metabolism, and excretion in healthy male subjects (PK, Safety)	500 mg PO	Single dose	8	US: 1
AG120-C-004	Phase 1, two-period crossover study to assess food effect on ivosidenib exposure (PK, Safety)	500-1000 mg PO	Two doses	36	US: 1

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Trial Identity	Trial Design (Primary Endpoint)	Regimen, Schedule, Route	Treatment Duration/ Follow Up	No. of patients enrolled	Countries : No. of Centers
AG-221-AML-005	Phase 1b/2 open-label study of IDH targeted therapies plus azacitidine in newly-diagnosed AML with an IDH mutation (PK, Safety)	500 mg PO daily + azacitidine 75 mg/m^2/d x7d q28d	Until PD or unacceptable toxicity	7	Unknown (no datasets provided)
AG120-C-005	Phase 3, multi-center, randomized study of ivosidenib in previously-treated patients with nonresectable or metastatic cholangiocarcinoma with an IDH1 mutation (PFS)	500 mg PO daily	Until PD or unacceptable toxicity	4	Unknown (no datasets provided)
AG120-C-006	Phase 1, single-dose study of ivosidenib PK and safety in healthy male Japanese compared to Caucasian subjects (PK, Safety)	250-1000 mg PO	Single dose	60	US: 1
AG120-C-007	Phase 1, 2-period study on the effect of multiple doses of itraconazole on single-dose PK of ivosidenib in healthy adults (PK, Safety)	250 mg PO (periods 1 and 2) + itraconazole 200 mg daily d-4-14 (period 2)	Single dose	22	US: 1

Source: FDA synopses of individual studies provided by the applicant in the NDA submission.
*In the FAS1, a mature subset of the FAS
Abbreviations: Ara-C, cytarabine; bid, twice a day; CI, continuous infusion; d, days; DNR, daunorubicin; IDA, idarubicin; MTZ, mitoxantrone; q, every; VP-16, etoposide.

7.2 Review Strategy

The key materials used for the review of efficacy and safety included:

- NDA 211192
- Relevant published literature
- Relevant information in the public domain

Study AG120-C-001 was used for the primary analysis of efficacy and safety. The applicant submitted a complete dataset for this study, using a data cut date of May 12, 2017, at the time of the initial NDA submission. The applicant submitted an updated data set for Study AG120-C-001, using a data cut date of November 10, 2017, at the time of the 90-day safety update (submitted to eCTD March 22, 2018 as SDN 14). The updated data set from Study AG120-C-001 will form the basis for this review.

At the time of the NDA submission, the applicant submitted complete datasets from 4 completed studies in healthy volunteers, as well as a dataset from the ongoing study of ivosidenib in patients with solid tumors (Table 19). Data from these studies were used to supplement the analysis of safety.

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At the time of NDA submission, the applicant included SAE data and SAE narratives from 3 additional ongoing studies, 2 evaluating ivosidenib in combination with other antineoplastic regimens in patients with newly diagnosed AML and 1 evaluating single-agent ivosidenib versus placebo in patients with cholangiocarcinoma (Table 19). Given the limited data, the fact that two of these studies are in combination with chemotherapy, and two contributed only a small number of patients (n=7, n=4), this data was considered minimally in the context of this review.

The subjects treated on the studies in Table 19 received ivosidenib in different formulations over time. Since the Product Quality and Clinical Pharmacology Reviewers confirmed that the different formulations were comparable with respect to key attributes and PK (see Sections 4.2 and 6.3.2), pooling of data from patients who received different formulations of ivosidenib for the efficacy and safety review was considered acceptable.

Summaries of data and statistical analyses by the reviewer were performed using JMP 12.0, SAS Version 9.4 (both SAS Institute, Inc., Cary, NC) and Excel 2010 (Microsoft, Redmond, WA). MedDRA Adverse Events Diagnostic 1.7 (MAED) (FDA, Silver Spring, MD) was used to look for safety signals. Study AG120-C-001 was open-label and did not include a comparator arm, and therefore the analyses of efficacy and safety are descriptive only. Where possible, confidence intervals are provided to assist in the interpretation of the efficacy data. For additional statistical methodologies, see Section 8.1.1.

8 Statistical and Clinical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. AG120-C-001

A Phase 1, Multicenter, Open-Label, Dose-Escalation and Expansion, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-120 in Subjects with Advanced Hematologic Malignancies with an IDH1 Mutation

INVESTIGATIONAL PLAN

Trial Design and Endpoints

Study AG120-C-001 was a phase 1, multicenter, open-label, dose-escalation and expansion study of ivosidenib in patients with advanced hematologic malignancies harboring an IDH1 mutation. The study included a dose escalation phase utilizing a standard 3+3 design to determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) followed by expansion arms to further evaluate the safety, tolerability, and clinical activity of AG-120 in different patient populations.

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The primary objectives were to assess the safety and tolerability of treatment with ivosidenib administered continuously as a single agent dosed orally on days 1 to 28 of a 28-day cycle in patients with advance hematologic malignancies, to determine the MTD and/or RP2D, and to assess the clinical activity of ivosidenib in patients with R/R AML with an IDH1 mutation enrolled in Arm 1 of the expansion phase. The primary efficacy endpoint for this objective was the rate of CR + CR with partial hematologic recovery (CRh), where CR was based on investigator assessment of response and CRh was derived by the Applicant from relevant data, including investigator-collected BM and hematology data among responders.

CR:
- BM blasts < 5%
- No blasts with Auer rods
- No extramedullary disease
- ANC > 1000/µL and platelets > 100,000/µL

CRh:
- All of the above criteria, except ANC > 500/µL and platelets > 50,000/µL

The secondary objectives of the study were to describe the dose-limiting toxicities (DLTs), characterize the pharmacokinetics (PK) of ivosidenib, characterize the pharmacodynamic relationship of ivosidenib to 2-HG, and to characterize the clinical activity associated with ivosidenib in patients with advanced hematologic malignancies. Secondary efficacy endpoints included CR rate, overall response rate (ORR), duration of CR+CRh, duration of CR (DOCR), duration of response (DOR), OS, event-free survival (EFS), time to CR+CRh, time to CR, time to response, and transfusion independence. Toxicity was per the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

ORR:
- Rate of CR, CRi/CR with incomplete platelet recovery (CRp), morphologic leukemia-free state (MLFS), and partial remission (PR)

CRi:
- All of the above CR criteria, except for residual neutropenia (ANC < 1000/µL)

CRp:
- All of the above CR criteria, except for residual thrombocytopenia (platelets < 100,000/µL)

MLFS:
- BM blasts < 5%
- No blasts with Auer rods

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- No extramedullary disease
- No hematologic recovery required

PR:
- Decrease of BM blast percentage to 5-25%
- Decrease of pretreatment BM blast percentage by at least 50%
- All hematologic criteria of CR

Relapse:
- Defined only for patients who have previously attained CR, CRi, CRp, or MLFS
- BM blasts ≥ 5% or reappearance of blasts in the blood or development of extramedullary disease

Duration of CR+CRh:
- Calculated as the date of the first documented CR or CRh to the date of the first documented confirmed relapse or death, whichever occurs first
- Responders without confirmed relapse or death censored at date of last adequate response assessment prior to the date of alternative anti-cancer therapy

DOCR:
- Calculated as the date of the first documented CR to the date of the first documented confirmed relapse or death, whichever occurs first
- Responders without relapse or death will be censored at the last response assessment date

DOR:
- Among subjects who had a response of CR, CRi, CRp, MLFS, or PR
- Calculated as the date of first occurrence of any response to the date of first documented confirmed disease relapse, progression, or death, whichever comes first
- Patients without relapse, progression or death will be censored at the last response assessment date

OS:
- Time from first dose to date of death dur to any cause
- Patients alive at the analysis cutoff date will be censored at the last contact date

EFS:
- Calculated from the date of the first dose to the date of first documented confirmed relapse/progression or death, whichever occurs first
- Patients without confirmed relapse or progression or death event will be censored at the last response assessment that is stable disease (SD) or better prior to the start of

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alternative anti-cancer therapy

Time to CR+CRh:

- Assessed from the date of first dose to the date of first occurrence of CR or CRh

Time to CR:

- Assessed from the date of first dose to the date of first occurrence of CR

Time to response:

- Assessed from the date of first dose to the date of first occurrence of response, which includes CR, CRi, CRp, MLFS, and PR

Baseline transfusion dependence:

- Transfusions of red blood cells (RBCs) or platelets within 56 days prior to the first dose of treatment

Post-baseline transfusion independence (summarized the following 2 ways):

- No transfusion during any 28 consecutive day period during treatment
- No transfusion during any 56 consecutive day period during treatment

Ivosidenib was administered orally once daily (QD) or twice daily (BID) on Days 1 to 28 of continuous 28-day cycles until disease progression, development of unacceptable toxicity, confirmed pregnancy, undergoing a HSCT, death, withdrawal of consent, lost to follow-up, or Sponsor ending the study. There were no designated inter-cycle rest periods.

Subjects had the extent of their disease assessed, including examination of BM biopsies and/or aspirates and peripheral blood, at screening, on day 15 (dose escalation phase only) and on day 29, every 28 days through Month 12, and every 56 days thereafter while on treatment, independent of dose delays and/or dose interruptions, and/or at any time when progression of disease was suspected. Response to treatment and treatment decisions in all subjects with AML were determined by the investigators based on the modified International Working Group (IWG) criteria for AML (Cheson et al. 2003), or other appropriate response criteria for the malignancy under study.

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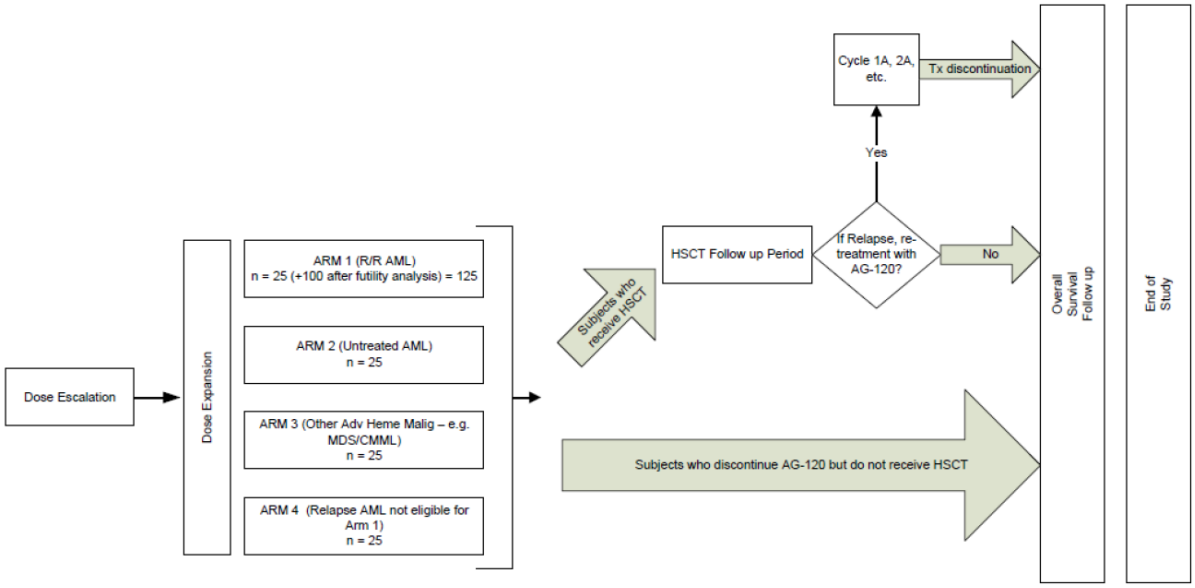
Figure 11: Study Diagram



Source: Module 5.3.5.2

The protocol defines the end of the study as the time at which all subjects discontinued treatment with ivosidenib and have been followed for survival for at least 12 months, or have died, been lost to follow-up, or withdrew consent prior to 12 months of follow-up.

Key Eligibility Criteria

<u>Inclusion Criteria</u>:

1. ≥ 18 years of age
2. Advanced hematologic malignancy, including:
   Dose Escalation Phase:
   - Relapsed and/or primary refractory AML as defined by WHO criteria; or
   - Untreated AML, ≥ 60 years of age and not candidates for standard therapy due to age, performance status (PS), and/or adverse risk factors, according to the treating physician and with approval of the Medical Monitor
   - Myelodysplastic syndrome (MDS) characterized by refractory anemia with excess blasts (RAEB-1 or RAEB-2), or considered high-risk by the Revised International Prognostic Scoring System, that is recurrent or refractory, or the subject is intolerant to established therapy known to provide clinical benefit for their condition (i.e., subjects must not be candidates for regimens known to provide clinical benefit), according to the treating physician and with approval of the Medical Monitor

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- Other relapsed and/or refractory hematologic cancers, for example chronic myelomonocytic leukemia (CMML), who fulfill the inclusion/exclusion criteria may be considered on a case-by-case basis, with approval of the Medical Monitor

Expansion Phase:

- Arm 1: R/R AML defined as:
  - Subjects who relapse after transplantation;
  - Subjects in second or later relapse;
  - Subjects who are refractory to initial induction or reinduction treatment;
  - Subjects who relapse within 1 year of initial treatment, excluding subjects with favorable-risk status according to NCCN guidelines, version 1.2015
- Arm 2: Untreated AML who are not candidates for standard therapy due to comorbid condition, PS, and/or adverse risk factors, according to the Investigator and with approval of the Medical Monitor
- Arm 3: Other non-AML IDH1-mutated R/R advanced hematologic malignancies, where no standard of care treatment option is available. Such as:
  - MDS that is recurrent or refractory after having failed hypomethylating agent(s) and with the approval of the Medical Monitor
  - Relapsed and/or primary refractory CMML with approval or Medical Monitor
  - Other non-AML IDH-mutated R/R advanced hematologic malignancy, that have failed standard of care or no standard of care treatment option is available according to the Investigator and with approval of the Medical Monitor
- Arm 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, PS, and/or adverse risk factors, according to the Investigator and with approval of the Medical Monitor

3. Subjects must have documented IDH1 R132 gene-mutated disease:
   - For patients in the dose escalation phase, IDH1 mutation may be based on local evaluation (centralized testing performed retrospectively)
   - For patients in the expansion phase, central testing of IDH1 gene-mutated disease is required during screening to confirm eligibility
4. Subjects must be amenable to serial BM sampling, peripheral blood sampling, and urine sampling during the study.
   The diagnosis and evaluation of AML or MDS will be made by BM aspiration and biopsy. If an aspirate is unobtainable (i.e., a “dry tap”), the diagnosis may be made from the core biopsy.
5. Patient must be able to understand and willing to sign an informed consent. A legally authorized representative may consent on behalf of a subject who is otherwise unable to provide informed consent, if acceptable to and approved by the site and/or site's Institutional Review Board (IRB).
6. Eastern Cooperative Oncology Group PS 0 to 2.

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7. Platelet count ≥ 20,000/µL (transfusions to achieve this level are allowed). Subjects with a baseline platelet count of < 20,000/µL due to underlying malignancy are eligible with Medical Monitor approval.
8. Subjects must have adequate hepatic function as evidenced by:
   - Serum total bilirubin ≤ 1.5 x upper limit of normal (ULN), unless considered due to Gilbert's disease or leukemic disease;
   - Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) ≤ 3 x ULN, unless considered due to leukemic disease.
9. Subjects must have adequate renal function as evidenced by:
   - Serum creatinine ≤ 2 x ULN

     OR
   - Creatinine clearance > 40 mL/min based on the Cockcroft-Gault glomerular filtration estimation
10. Subjects must be recovered from any clinically relevant toxic effects of any prior surgery, radiotherapy, or other therapy intended for the treatment of cancer. (Subjects with residual Grade 1 toxicity, for example Grade 1 peripheral neuropathy or residual alopecia, are allowed with approval of the Medical Monitor.)
11. Female subjects with reproductive potential must agree to undergo medically supervised pregnancy test prior to starting study drug. The first pregnancy test will be performed at screening (within 7 days prior to first study drug administration), and on the day of the first study drug administration and confirmed negative prior to dosing and Day 1 before dosing all subsequent cycles.
12. Female subjects with reproductive potential must have a negative serum pregnancy test within 7 days prior to the start of therapy. Subjects with reproductive potential are defined as sexually mature women who have not undergone a hysterectomy, bilateral oophorectomy or tubal occlusion or who have not been naturally postmenopausal (i.e., who have not menstruated at all) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Females of reproductive potential as well as fertile men and their partners who are female of reproductive potential must agree to abstain from sexual intercourse or to use 2 highly effective forms of contraception from the time of giving informed consent, during the study and for 90 days (females and males) following the last dose of AG-120. A highly effective form of contraception is defined as hormonal oral contraceptives, injectables, patches, intrauterine devices, double-barrier method (e.g., synthetic condoms, diaphragm, or cervical cap with spermicidal foam, cream, or gel), or male partner sterilization.

Exclusion Criteria:

1. Subjects who previously received prior treatment with a mutant-specific IDH1 inhibitor and progressed on therapy.
2. HSCT within 60 days prior to the first dose of ivosidenib, or subjects on immunosuppressive therapy post HSCT at the time of screening, or with clinically significant graft-versus-host

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disease (GVHD). The use of a stable dose of oral steroids post HSCT and/or topical steroids for ongoing skin GVHD is permitted with Medical Monitor approval.

3. Systemic anticancer therapy or radiotherapy < 14 days prior to the first dose of ivosidenib. Hydroxyurea allowed prior to enrollment and after the start of ivosidenib for control of peripheral leukemic blasts in subjects with WBC counts > 30,000/µL.
4. Subjects who received an investigational agent < 14 days prior to their first day of ivosidenib. In addition, the first dose of ivosidenib should not occur before a period ≥ 5 half-lives of the investigational agent has elapsed.
5. Subjects taking CYP3A4 substrate medications are excluded from the study unless they can be transferred to other medications within ≥ 5 half-lives prior to dosing, or unless the medications can be properly monitored during the study.
6. Patients taking P-glycoprotein transporter-sensitive substrate medications are excluded from the study unless they can be transferred to other medications within ≥ 5 half-lives prior to dosing, or unless the medications can be properly monitored during the study.
7. Subjects for whom potentially curative anticancer therapy is available.
8. Pregnant or breastfeeding
9. Subjects with an active severe infection that required anti-infective therapy or with an unexplained fever > 38.5°C during screening visits or on their first day of study drug administration (at the discretion of the Investigator, subjects with tumor fever may be enrolled).
10. Known hypersensitivity to any of the components of ivosidenib
11. The following cardiac conditions: New York Heart Association Class III or IV congestive heart failure, left ventricular ejection fraction < 40% by echocardiogram or multi-gated acquisition (MUGA) scan obtained within approximately 28 days of cycle 1 day 1, history of myocardial infarction within the 6 months prior to screening, uncontrolled angina pectoris, history of severe and/or uncontrolled ventricular arrhythmias, QTc ≥ 450 msec, or with other factors that increase the risk of QT prolongation or arrhythmic events (e.g. heart failure, hypokalemia, family history of long QT syndrome) at screening. Subjects with bundle branch block and a prolonged QTc interval should be reviewed by the Medical Monitor for potential inclusion.
12. Subjects taking medications that are known to prolong the QT interval unless they can be transferred to other medications within ≥ 5 half-lives prior to dosing or unless the medications can be properly monitored during the study.
13. Patients with known infection with human immunodeficiency virus or active hepatitis B or C.
14. Subjects with any other medical or psychological condition, deemed by the Investigator to be likely to interfere with a subject's ability to sign informed consent, cooperate, or participate in the study.
15. Subjects with known dysphagia, short-gut syndrome, gastroparesis, or other conditions that limit the ingestion or gastrointestinal absorption of drugs administered orally.

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16. Clinical symptoms suggesting active central nervous system (CNS) leukemia or known CNS leukemia. Evaluation of cerebrospinal fluid is only required if there is a clinical suspicion of CNS leukemia during screening.
17. Subjects with immediately life-threatening, severe complications of leukemia such as uncontrolled bleeding, pneumonia with hypoxia or shock, and/or disseminated intravascular coagulation.

Treatment Plan

The first 3 subjects in each cohort of Dose Escalation received a single dose of ivosidenib on Day -3 for PK and pharmacodynamic testing (2-HG levels) over 72 hours. All subjects then received ivosidenib daily as monotherapy in continuous, 28-day cycles starting on Cycle 1 Day 1 and continuing until PD, unacceptable toxicity, confirmed pregnancy, HSCT, death, withdrawal of consent, loss to follow-up, or end of study. After Amendment 3, subjects who experienced PD who were, in the opinion of the Investigator, benefitting from treatment, were allowed to continue on study drug with the approval of the Medical Monitor. Subjects who achieved an adequate response to ivosidenib and met other criteria for HSCT were allowed to proceed to HSCT after discontinuation of study therapy. Subjects who relapsed with IDH1-mutant disease following HSCT were eligible to restart ivosidenib with Medical Monitor approval.

Subjects on the Dose Escalation phase of the study were assigned to receive 200 mg to 1200 mg of ivosidenib total per day. The initial dosing regimen was 100 mg BID; however, based on emerging PK data showing that ivosidenib has a long half-life, a qday dosing schedule was implemented after Cohort 1. Subjects on the expansion phase were assigned to receive 500 mg ivosidenib daily.

Intra-patient dose escalation was allowed on the study. Patients enrolled in Dose Escalation could be escalated to a higher dose that was determined to be safe (i.e. following safety review of that cohort there were < 2 of 6 [or 0 of 3] subjects with DLTs), with approval of the Medical Monitor. Intra-subject dose escalations were not permitted in the expansion phase.

In the dose escalation and expansion phases, dose reductions to a dose approved by the Medical Monitor and/or interruption of dosing were allowed for toxicities that were possibly or probably related to treatment with ivosidenib. Escalation back to the starting dose and/or an intermediate dose could be permitted with Medical Monitor approval. Patients who experienced persistent grade ≥ 3 toxicity that were assessed as possibly or probably related to treatment with ivosidenib who were, in the opinion of the Investigator, benefiting from treatment, could continue on study drug with approval of the Medical Monitor. If the time required for recovery from toxicities, i.e. return to at least baseline levels, was more than 28 days, the patient would be discontinued from treatment and would enter the survival follow-up phase of the study.

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DLTs were evaluated during Cycle 1 of treatment and were defined as follows:

- All non-hematologic toxicities CTCAE grade ≥ 3
- Prolonged myelosuppression with the persistence of grade ≥ 4 neutropenia or thrombocytopenia in the absence of leukemia (blast count < 5%) at least 42 days after the initiation of Cycle 1 therapy

Dosing for individual subjects would be discontinued permanently for any DLT unless the subject was benefitting from study drug treatment per the Investigator and with approval of the Medical Monitor. Dose reductions could be considered.

Specific management guidelines were provided for QT prolongation. For patients with Grade ≥ 2 QTc (> 480 msec), patients should be promptly evaluated for causality and managed according to the following guidelines:

- Check electrolytes (potassium, calcium and magnesium) and supplement to correct values outside the normal range
- Review concomitant therapies and adjust as appropriate for medications with known QT prolonging effects
- If no other cause is identified and the Investigator believes it is appropriate, particularly if the QTcF remains elevated after the above measures, study drug may be interrupted and an ECG should be rechecked in approximately 1 week after the QTcF prolongation was first observed, or more frequently as clinically indicated.
- If QTcF recovered or improved and the Investigator believes it is safe, consider re-challenge with ivosidenib
- ECG should be conducted at least weekly for 2 weeks following QTcF reduction ≤ 480 msec

Grade 2 (QTcF > 480 and ≤ 500 msec):

- Reduced dose to a level approved by the Medical Monitor without interruption of dosing
- Re-escalate to the prior dose in ≥ 14 days after QT prolongation decreased to ≤ Grade 1

Grade 3 (QTcF > 500 msec)

- Hospitalization for continuous cardiac monitoring and evaluation by a cardiologist should both be considered
- Interruption of ivosidenib is required
- If QTcF decreased to within 30 msec of baseline or < 450 msec within 14 days, treatment could resume at a lower dose
- Ivosidenib could not be re-escalated following dose reduction for Grade 3 QTcF prolongation unless the prolongation was associated with an electrolyte abnormality or

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concomitant medication

Grade 4 (QTcF > 500 msec or > 60 msec change from baseline with Torsade de Pointes or polymorphic ventricular tachycardic or signs/symptoms of serious arrhythmia)

- Admit to the hospital for continuous cardiac monitoring and discharge only after review by a cardiologist
- Permanently discontinue ivosidenib

Specific management guidelines were also provided for suspected differentiation syndrome (DS) through Protocol Amendment 3: prompt administration of corticosteroids at a suggested dose of 10 mg dexamethasone IV every 12 hours until disappearance of symptoms and signs, and for a minimum of 3 days, prompt initiation of hydroxyurea at a suggested dose of 2 to 3 grams PO 2 or 3 times daily (in the case of leukocytosis), initiation of furosemide if clinically indicated, and prompt initiation of leukapheresis if required. They recommended temporary hold of ivosidenib if the clinical features could not be medically managed with the above measures. Once the signs and symptoms resolved, ivosidenib could be reinitiated if held, with the dose discussed with the medical monitor.

Prompt administration of hydroxyurea at a suggested dose of 2-3 grams PO BID was recommended for subjects with an elevated WBC count (Table 20). Initiation of leukapheresis was recommended if clinically required. Ivosidenib could be withheld if symptoms could not be medically managed. Once the signs and symptoms resolved, ivosidenib could be reinitiated after discussing dose with the Medical Monitor.

Table 20: Guidelines on administration of hydroxyurea for leukocytosis

Hydroxyurea dose and regimen	Total WBC count	Absolute increase in total WBC count from baseline
1000 mg QD	25-50K	15K-29K
2000 mg BID	51-75K	30K-49K
3000 mg BID	≥ 76K	≥ 50K

Source: Module 5.3.5.2

The following medications were to be avoided during the study:

- Hydroxyurea, aside from use prior to enrollment, for control of peripheral blasts in patients with leukocytosis (e.g. WBC > 30,000/µL) and/or for the treatment of suspected IDH DS with approval from the Medical Monitor.
- Corticosteroids (except topical cutaneous, ophthalmic, nasal, and inhalational steroids). Short courses of steroids were permitted to treat co-morbidities (e.g., DS)
- Medications known to prolong the QT interval

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- Sensitive CYP3A4 substrate medications
- P-glycoprotein transporter-sensitive substrate medications

The following medications were to be administered under careful monitoring:

- Fluoroquinolones, such as ciprofloxacin and moxifloxacin
- Azole antifungals such as fluconazole and posaconazole
- Serotonin (5-HT3) antagonists such as granisetron and ondansetron

The use of G-CSF, GM-CSF and erythropoiesis stimulating agents was permitted under appropriate circumstances. The use of other supportive care medications (e.g. analgesics or anti-nausea agents) was permitted.

Schedule of Assessments

BM and peripheral blood samples for confirmation of disease status and IDH1 mutation screening were obtained during the screening period for all patients. Patients were enrolled to dose escalation on the basis of local IDH1 testing and patients in the expansion phase were enrolled on the basis of central testing at (b) (4) All R/R AML patients with a starting dose of 500 mg qday had 1 or more specimens for retrospective testing of IDH1 mutation status using the Abbott RealTi*me* IDH1™ companion diagnostic test. Patients were considered to be IDH1+ by the Abbott RealTi*me* IDH1™ mutation assay if a mutation was detected in either the blood or the BM.

History and physical exam, including height, weight, performance status, and adverse event assessment were collected at the time of screening (within 28 days prior to study start). Screening laboratory assessments consisted of complete blood counts with differential (CBC), a comprehensive metabolic panel (CMP), coagulation studies, and a pregnancy test for women of childbearing potential. An assessment of left ventricular ejection fraction by MUGA scan or echocardiogram and a 12-lead ECG were also collected at screening.

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Table 21: Schedule of Assessments Escalation Phase

Visit/Cycle:	Scrn	Day -3[1,2]	Cycle 1				Cycle 2		Cycle 3 and Beyond		End of Treatment[3]	Follow-up	Follow-up HSCT[4]	Survival Follow-Up
Study Day:	**D -28**		**D1[2]**	**D8**	**D15[2]**	**D22**	**D1[2]**	**D15**	**D1**	**D15**		**D +28**		
Informed Consent	X													
Review Entry Criteria	X													
Demographics	X													
Medical and Surgical History	X													
Medication History	X													
Complete Physical Exam	X										X			
Limited Physical Exam		X	X	X	X		X		X					
Height[5] and Weight	X	X	X		X		X		X		X			
ECOG PS	X	X	X		X		X		X		X	X		
Vital Signs[6]	X	X	X	X	X		X	X	X		X			
12-lead ECG	Refer to Table 5 for ECG schedule													
ECHO/MUGA for LVEF[7]	X								X		X			
Gene Mutation Analysis[8]	X													
Laboratory Evaluations:														
Hematology[9]	X	X	X	X	X	X	X	X	X	X[10]	X			
Serum Chemistry[11]	X	X	X	X	X	X	X	X	X	X[10]	X			
Coagulation Studies[12]	X	X	X		X		X		X		X			
Urinalysis[13]	X	X	X		X		X		X		X			
Pregnancy Test[14]	X	X	X				X		X					
Bone Marrow Biopsy and/or Aspirate for molecular and functional studies of blasts and plasma[15,16]	X				X		X		X		X			

Visit/Cycle:	Scrn	Day -3[1,2]	Cycle 1				Cycle 2		Cycle 3 and Beyond		End of Treatment[3]	Follow-up	Follow-up HSCT[4]	Survival Follow-Up
Study Day:	**D -28**		**D1[2]**	**D8**	**D15[2]**	**D22**	**D1[2]**	**D15**	**D1**	**D15**		**D +28**		
Peripheral blood for molecular and functional studies of blasts, plasma, and neutrophils[16]	X			X	X		X		X		X			
Evaluate Extent of Disease and Response to Treatment[16,17]	X				X		X		X		X[18]		X[19]	
Single-dose Study Drug Administration		X[20,21]												
Study Drug Administration[22]			X[22]	X[22]	X[22]	X[22]	X[22]	X[22]	X[22]	X[10,22]				
Compliance Assessment[23]				X	X	X	X	X	X	X[10]	X			
PK/PD Assessments	Refer to Table 5 for sampling schedule[24]													
Adverse Events	X	X	X	X	X	X	X	X	X	X[9]	X	X[25]		
Concomitant Medications / Procedures	X	X	X	X	X	X	X	X	X	X[9]	X	X	X[19]	
Survival Status												X[26]	X[26]	X[26]
New Antineoplastic Therapy[27]												X	X	X

Source: Module 5.3.5.2

Reference ID: 4293723

Table 22: Schedule of Assessments Expansion Phase

Visit/Cycle:	Scrn	Cycle 1				Cycle 2		Cycle 3 and Beyond		End of Treatment[1]	Follow-up	Follow-up HSCT[2]	Survival Follow-up
Study Day:	**D -28**	**D1[3]**	**D8**	**D15**	**D22**	**D1[3]**	**D15**	**D1**	**D15**		**D +28**	**> D+28**	
Informed Consent	X												
Review Entry Criteria	X												
Demographics	X												
Medical and Surgical History	X												
Medication History[4]	X												
Complete Physical Exam	X									X			
Limited Physical Exam		X	X	X		X		X					
Height[5] and Weight	X	X		X		X		X		X			
ECOG PS	X	X		X		X		X		X	X		
Vital Signs[6]	X	X	X	X		X	X	X		X			
12-lead ECG	Refer to Table 6 for ECG schedule												
ECHO/MUGA for LVEF[7]	X							X		X			
Gene Mutation Analysis[8]	X												
Laboratory Evaluations:													
Hematology[9]	X	X	X	X	X	X	X	X	X[10]	X			
Serum Chemistry[11]	X	X	X	X	X	X	X	X	X[10]	X			
Coagulation Studies[12]	X	X		X		X		X		X			
Urinalysis[13]	X	X		X		X		X		X			
Pregnancy Test[14]	X	X				X		X					
Bone Marrow Biopsy and/or Aspirate for molecular and functional studies of blasts and plasma[13,16]	X					X		X		X			
Peripheral blood for molecular and functional studies of blasts, plasma, and neutrophils[16]	X		X			X		X		X			

Visit/Cycle:	Scrn	Cycle 1				Cycle 2		Cycle 3 and Beyond		End of Treatment[1]	Follow-up	Follow-up HSCT[2]	Survival Follow-up
Study Day:	**D -28**	**D1[3]**	**D8**	**D15**	**D22**	**D1[3]**	**D15**	**D1**	**D15**		**D +28**	**> D+28**	
Evaluate Extent of Disease / Response to Treatment[16,17]	X					X		X		X[18]		X[19]	
Study Drug Administration[20]		X[20]	X[20]	X[20]	X	X[20]	X	X[20]	X				
Compliance Assessment[21]			X	X	X	X	X	X	X[10]	X			
PK/PD Assessments	Refer to Table 6 for sampling schedule												
Adverse Events	X	X	X	X	X	X	X	X	X[9]	X	X[22]		
Concomitant Medications / Procedures	X	X	X	X	X	X	X	X	X[9]	X	X		
Survival Status											X[23]	X[23]	X[23]
New Antineoplastic Therapy[24]											X	X	X

Source: Module 5.3.5.2

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Table 23: PK/Pharmacodynamic Sampling and ECG Schedule – Escalation Phase

Visit/Cycle:	Scrn				Cycle 1								Cycle 2					Cycle 3				Cycle 4+					F/U
Study Day:	D -28	Day -3[1]			D 1	D8		D15			D22		D1			D15		D1			D15	D1			EOT		D +28
Assessment	Blood/ Urine/ ECG	Blood	Urine	ECG	ECG	Blood	ECG	Blood	Urine	ECG	Blood	ECG	Blood	Urine	ECG	Blood	ECG	Blood	Urine	ECG	Blood	Blood	Urine	ECG	Blood	ECG	ECG
Pre-dose[2]	X[3]	X		X	X[4]	X		X	X		X		X	X		X		X	X		X	X	X				
Post-dose																											
Anytime															X		X			X				X	X	X	X
0.5 hr		X[5]	X[6]					X[5]					X[5]														
1 hr		X[5]						X[5]					X[5]														
2 hr		X[5]						X[5]					X[5]														
3 hr		X[5]						X[5]					X[5]														
4 hr		X[5]	X[6]	X[7]	X[7]		X[7]	X[5]		X[7]			X[5]														
6 hr		X[5]						X[5]					X[5]														
8 hr		X[5]	X[6]					X[5]					X[5]														
10 hr		X[5]						X[5]					X[5]														
24 hr		X[8]																									
48 hr		X[8]																									
72 hr		X[8]																									

Source: Module 5.3.5.2

Table 24: PK/Pharmacodynamic Sampling and ECG Schedule – Expansion Phase

Visit/Cycle:	Screening	Cycle 1						Cycle 2		Cycle 3+		EOT		F/U
Study Day:	D -28	D1		D8		D15		D1		D1				D+28
Assessment	Blood/ Single ECG	Blood	Triplicate ECG[1]	Blood	Single ECG	Blood	Single ECG	Blood	Triplicate ECG[1]	Blood	Single ECG	Blood	Triplicate ECG[1]	Single ECG
Pre-dose[2]	X[3]	X	X	X		X		X	X	X	X			
Post-dose														
Anytime												X	X	X
2 hr		X[4]						X[4]						
3 hr		X[4]	X[5]					X[4]	X[5]					
4 hr		X[4]	X[5]		X[6]		X[6]	X[4]	X[5]					
6 hr		X[4]						X[4]						
8 hr		X[4]	X[5]					X[4]	X[5]					

Source: Module 5.3.5.2

Subjects had disease response assessments per BM biopsies and/or aspirates performed on day 15 (dose escalation phase only), day 29, every 28 days through month 12, and then every 56 days thereafter independent of dose delays and/or interruptions, at any time when progression of disease was suspected, and at the end of treatment visit.

During the expansion phase, subjects had an assessment of baseline transfusion requirements, defined as red blood cell or platelet transfusions within 8 weeks prior to the first dose of ivosidenib. Transfusion requirements, as well as associated hemoglobin levels and/or platelet counts, were recorded during treatment at each response assessment.

All subjects who discontinued ivosidenib were followed monthly for overall survival, HSCT conditioning, or other new anti-neoplastic therapies since discontinuation of study drug until

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death, withdrawal of consent, lost to follow-up, or the end of the study.

Statistical Analysis Plan

The statistical analysis plan for Study AG120-C-001 was submitted while the trial was ongoing, and called for a primary analysis of efficacy and safety when at least 125 expansion Arm 1 eligible subjects (including Arm 1 eligible subjects from dose escalation whose starting dose was 500 mg qday) had received at least 6 months of ivosidenib or had discontinued study therapy earlier.

The sample size for each part of the study was determined as follows:

- Dose Escalation: number of subjects required to assess 7 dose levels / schedules using 3+3 design = approximately 36 subjects
- Phase 2: approximately 25 subjects enrolled to each of the 4 arms in the expansion phase (n=100) with the possibility of enrolling an additional 100 subjects with R/R AML in Arm 1 depending on review of safety and clinical activity at the interim analysis (required ORR ≥ 15%). In the Arm 1 expansion, an observed CR+CRh rate of at least 16% in 125 treated subjects (at least 20 responses in 125 subjects) would result in an exact binomial 95% CI with a lower bound that excludes 10%. This is equivalent to testing a null CR+CRh rate of 10% compared to a target rate of 20% with 89% power and 2 sided alpha of 0.05. This was considered evidence of clinically significant activity of ivosidenib in R/R AML.

The primary efficacy endpoint of the study was the proportion of subjects with CR or CRh responses.

Reviewer comments: Durable CR is the endpoint established as reasonably likely to predict clinical benefit for patients with acute leukemia (Appelbaum et al. 2007), although this relationship was established based on data from patients treated with cytotoxic agents capable of producing minimal residual disease (MRD)-negative CRs.

The applicant is using CR+CRh as a palliative endpoint. The potential benefits have not been observed previously with traditional cytotoxic agents (e.g. transfusion independence in the presence of a continual low level of residual disease).

It is furthermore noted that the investigators set a low bar regarding "clinically significant activity of ivosidenib," requiring a CR+CRh rate of only 16%. The ultimate benefit will need to be weighed carefully against the observed safety profile.

Secondary efficacy endpoints included CR rate, overall response rate (ORR), duration of CR+CRh, DOCR, DOR, OS, EFS, time to CR+CRh, time to CR, time to response, and transfusion independence.

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The analysis sets considered for the evaluation of the study by the applicant were as follows:

- The Dose Determining Set (DDS) included all dose escalation subjects who either had a DLT during cycle 1, or who completed at least 75% of their planned cycle 1 doses (21 out of 28 days) and were considered by the clinical study team to have had sufficient safety data available to conclude that a DLT did not occur during cycle 1.
- The Safety Analysis Set (SAS) also included all patients who received at least one dose of study treatment, but subjects were classified according to the first dose level / schedule received. The SAS was used by the applicant for the analysis of safety endpoints, concomitant medications and treatment exposure.
- The Full Analysis Set (FAS) included all patients who were enrolled and received at least one dose of study treatment. The FAS was used by the applicant for the analysis of efficacy endpoints and baseline characteristics.
- The Full Analysis Set 1 (FAS1) included a subset of subjects in the FAS who received the first dose of ivosidenib at least 6 months prior to the analysis cutoff date. FAS1 was the primary efficacy analysis set for Expansion Arm 1, including any Arm 1 eligible subjects from dose escalation whose starting dose was 500 mg qday.
- The Pharmacokinetic Analysis Set (PAS) included all subjects who had at least 1 blood sample providing evaluable PK data for ivosidenib.

Of note, data from subjects in the expansion phase was pooled with data from eligible subjects in the dose-escalation phase whose starting dose was 500 mg qday. These were designated as Arm 1+, Arm 2+, Arm 3+, and Arm 4+. In this analysis set definition, all patients refer to patients in Arm 1+.

For the purposes of NDA submission and in support of the proposed indication, the applicant's primary analysis was conducted on Arm1+ subjects in the FAS1, consisting of patients with R/R-AML who were assigned to receive 500 mg total daily dose of ivosidenib. Subjects with R/R-AML were defined as follows:

- Subjects who relapse after transplantation
- Subjects in second or later relapse
- Subjects who are refractory to initial induction or reinduction treatment
- Subjects who relapse within 1 year of initial treatment, excluding subjects with favorable-risk status according to NCCN guidelines, version 1,2015

The applicant's primary analysis was planned to be conducted after 125 FAS1 subjects completed at least 6 months of ivosidenib or discontinued. There was one interim analysis at the time that the first 25 subjects on arm 1 were treated and followed for 2 cycles or discontinued earlier. If an ORR of < 15% was observed, then additional enrollment into Arm 1 was to be terminated. Based on results of the interim analysis demonstrating an acceptable safety profile and potential clinical activity in Arm 1, an additional 101 patients with IDH1 mutation positive R/R AML were enrolled.

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Efficacy Analysis

The primary efficacy analysis of the study was based on all treated Arm 1^+ FAS1 subjects whose first dose was at least 6 months prior to the data cut for the primary CSR, so that they completed at least 6 months of treatment or discontinued study drug earlier.

Supportive efficacy analyses were also performed for the following:

- Arm 1^+ subjects (FAS), including patients whose first dose was less than 6 months before the data cutoff date
- Arm 1 subjects (FAS1 and FAS) that did not include eligible dose escalation subjects
- Per protocol subset of Arm 1+ subjects using FAS1 and FAS, excluding patients with baseline blasts <5%, no IDH1 R132 gene-mutated disease, or previously received treatment with a mutant IDH1 inhibitor and progressed
- All treated R/R AML subjects across dose escalation and expansion whose starting dose was 500 mg daily (FAS1 and FAS), containing Arm 1^+ and Arm 4^+ patients

For patients who discontinued from study therapy to receive HSCT and then restarted ivosidenib after relapse, data after restarting ivosidenib was not analyzed in the primary analysis. Instead, separate listings of response assessments were produced for the period after resuming ivosidenib.

Analysis of Primary Efficacy Endpoint
The primary efficacy endpoint of CR+CRh was defined as the rate of responses including CR and CRh, where CR was based on investigator assessment of response and CRh was derived by the Applicant from relevant data, including investigator-collected BM and hematology data. The CR+CRh rate was summarized by the percentage of responses primarily in the FAS1 for Arm 1^+ subjects with 2-sided exact binomial 95% confidence interval (CI).

An observed CR+CRh rate in R/R AML subjects in the FAS1 Arm1^+ with the lower bound of the exact binomial 95% CI greater than 10% was deemed as clinically meaningful in this setting. This was considered to be evidence of clinically significant activity from ivosidenib.

Analyses of Secondary Efficacy Endpoints
Response was also summarized by the best objective response categories of CR rate and ORR (including CR, CRi/CRp, PR, and MLFS responses). CR and ORR were summarized by number and percentage with 2-sided exact binomial 95% CIs.

For duration of responses (CR+CRh, DOCR, DOR), EFS, and OS, the 25th percentile, median, and 75th percentile with 2-sided 95% CI, as well as Kaplan-Meier (KM) estimates at 3, 6, 9, and 12 months were planned. Analyses were performed in Arm 1^+ subjects using FAS1 and FAS. Censoring rules for duration of responses and EFS are per Table 25 below.

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Table 25: Censoring Rules for Time-to-Event Analyses using Response Assessments

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

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

Source: Module 5.3.5.2

Sensitivity analyses for OS were conducted for subjects who started subsequent anti-cancer therapy to censor at the start of the anti-cancer therapy. Duration of follow-up was done using the reverse KM method.

For duration of CR+CRh, in addition to analysis of Arm 1^+ subjects using FAS1 and FAS, it was summarized in the per protocol subset of Arm 1^+ subjects using FAS1 and FAS. Sensitivity analyses were performed with censoring rule variations as follows in Arm 1^+ subjects using FAS1 and FAS:

1) Subjects who undergo HSCT censored at the last adequate assessment prior to HSCT
2) Subjects who discontinue treatment due to undocumented progression considered as events on the date of last dose
3) Subjects with 2 or more consecutive missing response assessments prior to an event date (death, relapse, or disease progression) considered as events on the event date by ignoring the missing assessments

Subjects with subsequent anti-cancer therapies prior to an event date considered as events on the event date

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Time to responses included time to CR+CRh, time to response, time to CR, time to first response among CR/CRh subjects, and time to first response among CR subjects. The analyses were in Arm 1^+ subjects using FAS1 and FAS and used descriptive statistics.

RBC and platelet transfusion independence were evaluated comparing RBC and platelet transfusions pre- and post-baseline. Post-baseline transfusion independence was summarized in Arm 1^+ and Arm 1 subjects using FAS1 and FAS by best overall response of CR, CRh, non-CR/CRh responders, nonresponders, and overall. For subjects in the expansion phase Arm 1, since RBC and platelet transfusion history were captured for the 8-week period prior to first dose of the study drug, a separate analysis was to be conducted to explore transfusions over time.

Reviewer's Comments: In general, it is difficult to interpret time to event endpoints, including overall survival, in the absence of a control arm. Furthermore, the definition of EFS did not consider treatment failures, and responses of SD or better to be events (events were confirmed relapse/progression or death). Duration of CR+CRh and DOCR should be more helpful in assessing the length of meaningful response times in this patient population.

Safety analyses were descriptive. TEAEs were defined as any AEs that begin or worsen on or after the start of study drug through 28 days after the last dose of study drug. All AEs were listed. Shift tables of laboratory data from baseline to worst grade on treatment were to be presented based on CTCAE version 4.03. Shift tables would also be provided for ECOG PS from baseline to worst value on treatment.

Protocol Amendments

The original protocol was dated December 10, 2013, and the first patient entered the study on March 12, 2014. Enrollment was completed by the data cutoff of May 12 2017, with n=268 enrolled, but the study is still ongoing. The study was revised a total of 5 times between activation and the data cut-off date of May 12, 2017. Key protocol revisions are summarized as follows:

- Amendment 2 (dated May 30, 2014) added specific AML response criteria (Cheson et al. 2003), allowed patients who had previously received ivosidenib on this protocol to re-enter the study if they relapsed after HSCT, allowed concomitant use of hydroxyurea, allowed for subjects who experienced a DLT but who were benefitting from study treatment to continue on treatment with approval of the Medical Monitor, and added the recommendation to avoid the use of antacids, H1 blockers or proton pump inhibitors while taking ivosidenib based on emerging PK data.
- Amendment 3 (dated February 2, 2015) clarified that a once daily dosing schedule was implemented based on results of earlier cohorts in the dose escalation portion, further defined the expansion portion of the study to include Arms 1, 2, and 3 as defined above, increased the number of subjects to be enrolled in each expansion arm from 12 to 25,

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included an interim analysis for safety and futility to be conducted for Arm 1 of the expansion portion at the time at which the first 25 patients have been treated and followed for 2 cycles or discontinued earlier and based on this analysis an additional 100 patients could be enrolled in Arm 1, added that subjects in the expansion portion were required to have central laboratory confirmation of IDH1-mutated disease during screening prior to treatment with ivosidenib, increased response assessments (every 28 days after day 57 through month 12), specified that information on RBC and platelet transfusions would be captured for subjects in the expansion portion for the 8-week period prior to first dose of study drug and during the treatment period, added an assessment of survival status monthly after completion of the day 28 follow-up visit and for the collection of new antineoplastic therapies, added definitions for stable and progressive disease (PD) for subjects with AML, removed the requirement that treatment with hydroxyurea be administered only during the first 28 days, and added an allowance for patients who experience disease progression who were, in the opinion of the Investigator, benefitting from treatment to continue on ivosidenib with approval of the Medical Monitor. In addition, this amendment added guidelines for the management of QT prolongation and DS.

- Amendment 4 (dated August 31, 2015) removed the requirement for day 15 BM for the expansion portion, added a list of concomitant medications that can prolong QT interval and thus required careful monitoring, removed the requirement that subjects were to avoid taking antacids, H2 blockers, or proton pump inhibitors while taking ivosidenib since the solubility of ivosidenib was found not to be pH dependent, added additional detail on procedures for reporting AEs and SAEs, including DS. Amendment 5 (dated February 17, 2017) removed the independent review committee (IRC) for evaluation of clinical efficacy data for expansion portion subjects (collected all BM assessments in lieu of a formal IRC), removed the age requirement for Arm 2 of the expansion portion, primary efficacy analysis for subjects with R/R AML was changed to CR+CRh rate, leukocytosis was added as an AE of special interest and guidelines for management were incorporated, and guidelines for management of DS and QT prolongation were updated.

STUDY RESULTS

Compliance with Good Clinical Practices

The applicant provided attestation that this study was conducted in accordance with all applicable national, state, and local laws of the pertinent regulatory authorities and in accordance with good clinical practice (GCP).

Financial Disclosure

A summary of financial disclosures for Study AG120-C-001 is provided in the appendix (Section

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14.2). The applicant submitted financial disclosure information from 98% of investigators. Due diligence was attempted for the nine investigators for which financial disclosure information could not be obtained.

Two principal investigators (sites (b) (6)) and 2 sub-investigators (sites (b) (6)) had financial disclosures. Two disclosures were for consulting services/honoraria and one was for research funding, all in excess of $25,000. One disclosure was for equitable interest in Agios that exceeded $50,000 in value during the study. Lastly, two sub-investigators subsequently became employees of the Applicant (site (b) (6)). Sites (b) (6) treated a total of (b) (6) patients, respectively (including (b) (6) patients in the R/R AML Efficacy set for the primary analysis). In the R/R AML Efficacy set, sites (b) (6) reported site-specific CR+CRh rates that were higher than the rate reported for the study population as a whole. Exclusion of the (b) (6) patients enrolled at sites (b) (6) from the R/R AML Efficacy set reduces the CR+CRh rate by approximately (b) (6)%. Site (b) (6) was selected for FDA inspection (site (b) (6) was deemed to have too few patients to justify an inspection). No irregularities were identified, and the site was classified as No Action Indicated by OSI.

Data Quality and Integrity

The applicant submitted this NDA, including the data files, to the FDA CDER Electronic Document Room (EDR). The data in this submission are in Electronic Common Technical Document (eCTD) format, in accordance with FDA guidance on electronic submission. Definition files for the data sets were included. The clinical study reports and data sets are located at the following location: \\CDSESUB1\evsprod\NDA211192

All major efficacy and safety analyses conducted by the applicant were reproduced or audited. Upon further clarification from the applicant via responses to the FDA's information requests during the course of the review, the reviewers were able to:

- Reproduce the applicant's analysis and analysis results, and
- Conduct FDA's primary efficacy and safety analyses.

The integrity of the submission was supported by tracing the data in the ADAM datasets to the STDM data sets. Furthermore, responses to treatment were verified using the original data source (case report forms) and bone marrow pathology reports.

Methods

The Applicant's analyses primarily considered the Arm 1^+ subjects in FAS1 on Study AG120-C-001. The Applicant conducted additional supportive analyses, including all patients with R/R AML (Arms 1^+ and 4^+) in FAS1. The FDA conducted an independent analysis of efficacy of ivosidenib in R/R IDH1+ AML. FDA's analysis differed from the analysis provided by the

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Applicant in the original NDA submission in the following ways:

- The FDA excluded 6 subjects from the analysis who did not have an IDH1 mutation identified by the Abbott RealTi*me* IDH1™ mutation assay.

- The FDA used updated data sets, with a data cut date of November 10, 2017; this resulted in the addition of 34 subjects to the analysis as well as more matured response data.

Thus, FDA had 153 patients in their Original Efficacy Set (compared to n=125 in Arm 1^+ FAS1 per the Sponsor) and 173 patients in their R/R AML Efficacy Set (compared to n=179 per the Sponsor's All R/R AML at 500 mg QD set).

Reviewer comments: For the purposes of labeling, FDA agrees with presenting the R/R AML Efficacy set. This group had very similar results to the Original Efficacy Set across analyses and represents a broader population of R/R AML patients.

Note that the FDA did not verify responses other than CR or CRh, as other responses cannot be considered as measures of clinical benefit in R/R AML.

Patient Disposition

The first subject was enrolled on March 12, 2014. Of 368 patients screened for the study, 258 patients received at least one dose of ivosidenib on Study AG120-C-001 and were included in the applicant's FAS. 100 patients were screen failures. The most common reasons for screen failure were: IDH1-negative disease (n=38), diagnosis falling outside of the protocol-specified study population (n=15), age (n=5), active infection/unexplained fever (n=4), congestive heart failure (n=4), potentially curative therapy available (n=3), history of severe/uncontrolled ventricular arrhythmias (n=3), other medical/psychological condition (n=3), and ECOG > 2 (n=3). Of the remaining 22 screen failures, patients either failed to meet an inclusion/exclusion criterion (no more than 2 patients per criterion) and one patient did not want to enroll on the study. Ten additional patients were not screen failures, but were never treated with ivosidenib due to an adverse event (n=6), a medical condition (n=2), disease progression (n=1), or death (n=1).

Of the 258 patients in the FAS, 125 were determined by the applicant to be in the Arm 1^+ FAS1 set, and 119 of these patients had an IDH1 mutation identified by the companion diagnostic test. With the 90-day safety update, 34 additional patients were added with at least 6 months' follow-up and IDH1 positivity per the companion diagnostic, for a total of 153 patients in the FDA Original Efficacy Set. The reasons for treatment discontinuation are shown in Table 26. For the purposes of tabulating reasons for treatment discontinuation, the FDA considered death under the primary reason for discontinuation (i.e., either primary disease or adverse event). In

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addition to deaths due to primary disease, the reason "primary disease" included disposition events coded as PD or other: patient seeking alternative therapy. The reason "adverse event" included deaths due to AEs and disposition events coded as adverse event. The reason "physician decision" included physician decision and intercurrent medical condition.

Table 26: Reasons for Treatment Discontinuation

	Original Efficacy Set N=153	R/R AML Efficacy Set N=173
Therapy ongoing	14 (9%)	17 (10%)
Discontinued therapy		
Primary disease	85 (56%)	97 (56%)
Adverse event	26 (17%)	28 (16%)
HSCT	15 (10%)	17 (10%)
Physician decision	6 (4%)	6 (3%)
Withdrawal of consent	4 (3%)	5 (3%)
Subject's decision	3 (2%)	3 (2%)

Source: FDA analysis

All subjects who discontinued ivosidenib were to be followed monthly for overall survival until death, withdrawal of consent, lost to follow-up, or the end of the study. Table 27 describes the reasons for study discontinuation as determined by FDA.

Table 27: Reasons for Study Discontinuation

	Original Efficacy Set N=153	R/R AML Efficacy Set N=173
Follow-up ongoing	35 (23%)	42 (24%)
Discontinued study		
Death	107 (70%)	119 (69%)
Withdrawal of consent	6 (4%)	7 (4%)
Lost to follow-up	5 (3%)	5 (3%)

Source: FDA analysis

Protocol Violations/Deviations

A total of 1,074 deviations were reported for 153 of the 173 subjects in the FDA's R/R AML Efficacy Set on Study AG120-C-001. Table 28 lists the number of deviations by broad criterion. The most common deviations were procedure/assessment not done in 80% of patients. Multiple deviations (31% of patients) were listed under the category "Other," most of which were due to missing assessments and missing diaries. For the purposes of assessment of the primary efficacy endpoint, subjects with missing disease assessment data were considered a failure.

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Table 28: Protocol Deviations in Subjects in the R/R AML Efficacy Set (N=173)

	Minor	Major	Total
Subjects with Deviation	152 (88%)	30 (17%)	153 (88%)
Deviations by Criterion			
Procedure/assessment not done	138 (80%)	2 (1%)	138 (80%)
Visits/procedures out of window	44 (25%)	1 (1%)	45 (26%)
Study treatment administration/ dispensing/compliance	33 (19%)	20 (12%)	48 (28%)
Concomitant medication	22 (13%)	1 (1%)	23 (13%)
Inclusion/exclusion	0	1 (1%)	1 (1%)
Other	45 (26%)	7 (4%)	49 (31%)

Source: FDA analysis

The applicant identified minor deviations in 88% of patients and major deviations in 17% of patients. The majority of the major deviations were related to study treatment administration/dispensing/compliance. These included ICF procedures being incomplete or not being administered properly (n=8), SAE reporting outside of expected timelines (n=7), not holding study drug in response to grade 3 QT prolongation (n=5), and one each of inadequately maintained on-site drug accountability records and incorrect administration of study drug by site. Other causes of major deviations were development of protocol defined withdrawal criteria but not being withdrawn from the treatment, administration of a prohibited anticancer therapy (patient (b) (6) took 3 days of ivosidenib during transplant conditioning with fludarabine and busulfan), lack of mutated IDH1, or missed screening assessment.

It is notable that 13% of patients had deviations related to concomitant medications, mostly minor deviations. The most common issue was the use of QT-prolonging medications, such as haldol, chlorpromazine, amiodarone, azithromycin, ciprofloxacin, and posaconazole.

Reviewer comments: Multiple patients being on QT prolonging medications may have exacerbated some of the QT prolongation seen with ivosidenib on the trial. Do not expect an effect on efficacy. These types of medications are used very commonly in AML patients.

Table of Demographic Characteristics

Selected baseline demographic characteristics of the subjects in the FDA Original Efficacy Set and R/R AML Efficacy set are summarized in Table 29. For the R/R AML Efficacy Set, the median age of the subjects was 67 years (range: 18, 87 years), with 36% of the subjects < 65 years of age. There were 87 (50%) male subjects and most subjects (62%) were white. The majority of subjects (82%) were from the United States.

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Table 29: Demographic Characteristics

Parameter	Original Efficacy Set N=153	R/R AML Efficacy Set N=173
Sex		
Male	79 (52%)	87 (50%)
Female	74 (48%)	86 (50%)
Age		
Mean years (SD)	64.6 (13.5)	65.3 (13.0)
Median (years)	67	67
Min, max (years)	18, 87	18, 87
Age Group		
< 65 years	58 (38%)	63 (36%)
≥ 65 years	95 (62%)	110 (64%)
Race		
White	95 (62%)	108 (62%)
Black or African American	8 (5%)	10 (6%)
Asian	6 (4%)	6 (3%)
American Indian or Alaska	1 (1%)	1 (1%)
Native Hawaiian or Pacific	1 (1%)	1 (1%)
Other	6 (4%)	6 (3%)
Not provided	36 (24%)	41 (24%)
Ethnicity		
Hispanic or Latino	8 (5%)	8 (5%)
Not Hispanic or Latino	88 (58%)	100 (58%)
Not Provided	57 (37%)	65 (38%)
Region		
France	27 (18%)	31 (18%)
United States	126 (82%)	142 (82%)

Source: FDA Analysis

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Selected baseline disease characteristics are summarized in Table 30. In the R/R AML Efficacy set, most subjects had a baseline ECOG performance score of 1 (55%). The IDH1 gene mutation was in codon R132C in 59% of subjects, codon R132H in 24% of subjects, R132G in 7%, R132S in 6%, and R132L in 4%, as determined by the test used for assessing study eligibility. The majority of subjects had a cytogenetic risk status of intermediate-risk (60%) and 27% had poor-risk. No subject had favorable-risk cytogenetics, although cytogenetic analyses were missing in 13% of subjects.

All subjects received a prior systemic anticancer therapy; the majority received either 1 (42%) or 2 (28%) prior therapies.

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Table 30: Baseline Disease Characteristics

Parameter	Original Efficacy Set N=153	R/R AML Efficacy Set N=173
ECOG PS		
0	31 (20%)	36 (21%)
1	81 (53%)	96 (55%)
2	39 (25%)	39 (23%)
3	2 (1%)	2 (1%)
Gene Mutation (IDH1)		
R132C	91 (59%)	102 (59%)
R132H	35 (23%)	42 (24%)
R132G	11 (7%)	12 (7%)
R132S	10 (7%)	10 (6%)
R132L	6 (4%)	7 (4%)
R/R AML Characteristic		
Relapse after HSCT	40 (26%)	40 (23%)
Second or later relapse	25 (16%)	25 (14%)
Refractory to induction/re-induction	103 (67%)	103 (60%)
Relapsed within 1 year of therapy[1]	16 (10%)	16 (9%)
Other	0	20 (12%)
Number of Prior Anti-Cancer Therapies		
0	0	0
1	56 (37%)	72 (42%)
2	44 (29%)	48 (28%)
3	34 (22%)	34 (20%)
4	14 (9%)	14 (8%)
≥ 5	5 (3%)	5 (3%)
Median (range)	2 (1-6)	2 (1-6)
Prior Stem Cell Transplantation		
Yes	40 (26%)	40 (23%)
Allogeneic	38 (95%)	35 (88%)
Autologous	1 (3%)	1 (3%)
Missing/Other	1 (3%)	4 (10%)
No	113 (74%)	133 (77%)
Time (months) from HSCT[2] to 1st Dose		
Median (range)	16 (3-222)	16 (3-222)
Cytogenetic Risk Status		
Favorable-Risk	0	0
Intermediate-Risk	87 (57%)	103 (60%)
Poor-Risk	45 (29%)	47 (27%)
Missing	21 (14%)	23 (13%)
De novo		
Yes	105 (69)	115 (66%)
No	48 (31)	58 (34%)

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Parameter	Original Efficacy Set N=153	R/R AML Efficacy Set N=173
Bone Marrow Blasts, Local		
Mean (SD)	51 (29)	49 (29)
Median (range)	55 (0-98)	48 (0-98)
Hemoglobin (g/L)		
Mean (SD)	94 (16)	95 (16)
Median (range)	90 (67-143)	91 (67-143)
Number of RBC Transfusions[3]		
0	67 (44%)	80 (46%)
1	18 (12%)	21 (12%)
2	15 (10%)	18 (10%)
3	16 (10%)	17 (10%)
4	8 (5%)	8 (5%)
≥ 5	29 (19%)	29 (17%)
Number of Platelet Transfusions[3]		
0	72 (47%)	88 (51%)
1	22 (14%)	23 (13%)
2	8 (5%)	9 (5%)
3	7 (5%)	7 (4%)
4	5 (3%)	5 (3%)
≥ 5	39 (25%)	41 (24%)

Source: FDA analysis
[1]Of initial therapy, excluding subjects with favorable-risk status according to NCCN guidelines
[2]From most recent transplant
[3]Within the eight weeks prior to the first dose of ivosidenib, for all subjects

Reviewer comments: Overall, no clinically meaningful differences were observed in demographic and disease-related characteristics between the Original Efficacy set and the R/R AML Efficacy set. However, of the 20 additional patients in the R/R AML Efficacy set (from Arm 4+), 80% had only 1 prior therapy. Thus, the 173 total patients (Arm 1+ and 4+) have ever so slightly more favorable features, in terms of less prior therapies and less post-transplant relapses.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The median relative dose-intensity of ivosidenib was 99% (range 29-133%) of the planned dose. A median of 120 (range 2-1197) doses were administered to the 173 patients in the R/R AML Efficacy Set. Table 31 provides a summary of the treatment intensity, in terms of the number of administered doses.

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Table 31: Ivosidenib Treatment Intensity

Number of Doses Administered	Original Efficacy Set (N=153)	R/R AML Efficacy Set (N=173)
≤28	25 (16%)	27 (16%)
29-56	14 (9%)	15 (9%)
57-84	14 (9%)	15 (9%)
85-112	19 (12%)	23 (13%)
113-140	18 (12%)	20 (12%)
141-168	6 (4%)	7 (4%)
169-196	5 (3%)	8 (5%)
197-224	9 (6%)	11 (6%)
225-252	6 (4%)	6 (3%)
253-280	5 (3%)	6 (3%)
281-308	7 (5%)	8 (5%)
309-336	4 (3%)	4 (2%)
337-364	7 (5%)	8 (5%)
≥365	14 (9%)	15 (9%)

Source: FDA analysis

Table 32 provides a summary of the dose-intensity by month in the R/R AML Efficacy Set (N=173). For all months on treatment, less than or equal to 10% of the subjects received less than 80% of the planned dose. One subject (b) (6) treated in the dose escalation portion of Study AG120-C-001 received a dose intensity > 120% of the planned dose during months 3 to 6 due to intra-subject dose escalation permitted per protocol from 500 mg to 800 mg daily.

Table 32: Number of Patients with Dose Intensity <80% or >120% by Treatment Cycle

	R/R AML Efficacy Set N=173		
Month	Subjects	Dose intensity < 80%	Dose intensity > 120%
1	(b) (6)	9 (5%)	0
2		8 (6%)	0
3		6 (5%)	1 (1%)
4		5 (4%)	1 (1%)
5		7 (8%)	1 (1%)
6		5 (7%)	1 (1%)
7		4 (6%)	0
8		3 (6%)	0
9		2 (5%)	0
10		2 (5%)	0
11		3 (9%)	0
12		1 (4%)	0
> 12		2 (10%)	0

Source: Response to Information Request submitted April 20, 2018 (SDN 21)

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Efficacy Results

The primary efficacy endpoint is the proportion of patients in the primary analysis cohort who achieved complete remission (CR) or complete remission with partial hematological response (CRh). Fifty-seven out of one hundred and seventy-three patients (33%) experienced either a CR or CRh. The lower bound of 95% CI was 26%, which is higher than the pre-specified boundary of 10%. This met the applicant's pre-defined criteria for evidence of clinically significant activity. With a median follow-up time of 8.3 months (range: 0.2, 39.5), the median duration of CR+CRh was 8.2 months with 95%CI [5.6, 12.0]. The median time to CR+CRh was 2 months with range (0.9, 5.6).

Table 33: Results of the Efficacy Endpoints

	R/R AML Efficacy Set (N=173)
CR+CRh rate, n (%) [95% CI]	57 (32.9) [26.0, 40.5]
Duration of CR+CRh, median [95% CI]	8.2 [5.6, 12.0]
Time to CR+CRh, median (range)	2.0 (0.9, 5.6)
CR rate, n (%) [95% CI]	43 (24.9) [18.6, 32.0]
Duration of CR, median [95% CI]	10.1 [6.5, 22.2]
Time to CR, median (range)	2.8 (0.9, 8.3)
CRh rate, n (%) [95% CI]	14 (8.1) [4.5, 13.2]
Duration of CRh, median [95% CI]	3.6 [1, 5.5]
Time to CRh, median (range)	1.9 (1.0, 5.6)
Overall Survival, median [95% CI]	9.1 [7.4, 10.2]
Median Follow-up (Range)	8.3 (0.2, 39.5)

Source: FDA analysis

The median overall survival was 9.1 months with 95% CI [7.4, 10.2]. The Kaplan-Meier curve for survival is shown in Figure 12.

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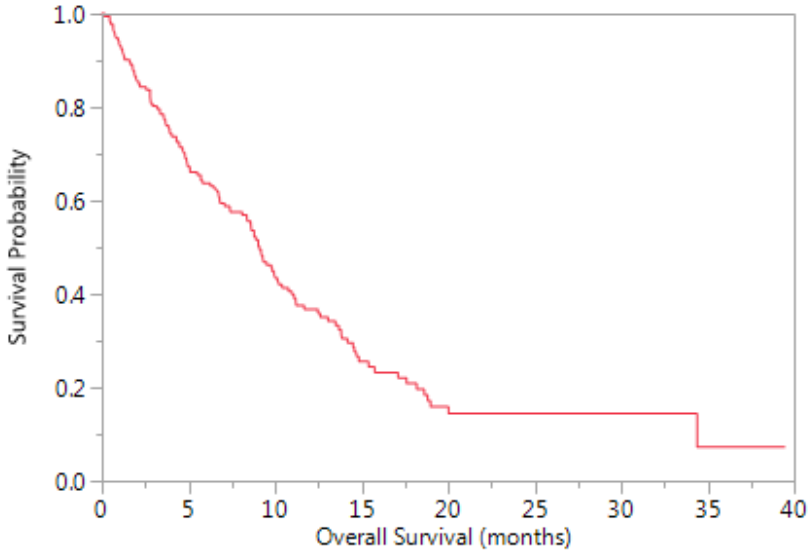
Figure 12: Overall Survival R/R AML Efficacy Set



Source: FDA analysis

Reviewer comments: Despite the demonstrated response rate, the overall survival curve indicates that very few patients will survive long-term. Thus, this therapy appears to be more palliative, as opposed to curative, in nature.

Sensitivity Analysis

The Original Efficacy Set is used as a sensitivity analysis. The results from the Original Efficacy Set agreed with the results from the R/R AML Efficacy set.

Table 34: Sensitivity Analysis

	Original Efficacy Set (N=153)
CR+CRh rate, n (%) [95% CI]	47 (30.7) [23.5, 38.7]
Duration of CR+CRh, median [95% CI]	8.2 [5.6, 14.1]
Time to CR+CRh, median (range)	2.7 (0.9, 5.6)
CR rate, n (%) [95% CI]	35 (22.9) [16.5, 30.4]
Duration of CR, median [95% CI]	10.1 [5.7, 22.2]
Time to CR, median (range)	2.8 (0.9, 8.3)
CRh rate, n (%) [95% CI]	12 (7.8) [4.1, 13.3]
Duration of CRh, median [95% CI]	3.1 [1.0, 9.2]
Time to CRh, median (range)	2.3 (1.0, 5.6)

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Overall Survival, median [95% CI]	9.0 [6.8, 10.2]
Median Follow-up (Range)	8.3 (0.2, 34.4)

Source: FDA analysis

Reviewer comments: Given that the Arm 4+ group had more favorable features than Arm 1+ overall, it is not surprising that the efficacy results appear slightly better in the full R/R AML Efficacy Set than the Original Efficacy Set shown here. Considering the Arm 4+ patients alone, the CR+CRh rate was 10/20 (50% [95% CI 28-72%]) with CR rate 8/20 (40% [95% CI 20-64%]).

FDA verified consistency across the phases of the trial as well. In the escalation phase, CR+CRh rate was 30% with median DoCR+CRh 20 months (95% CI 3, NR) and in the expansion phase was 34% with median DoCR+CRh 8.2 months (95% CI 5.6, 11.1).

Reviewer comments: The nearly equivalent CR+CRh rates in the expansion and escalation phases of the trial supports the pooling of the 2 phases. The longer DoCR+CRh in the escalation phase may partly reflect the smaller sample size and partly the increased duration of follow-up.

Subpopulations

The CR+CRh rate and its 95% of CI for subgroups based on demographic and disease characteristics are presented in the forest plot below (Figure 13 and Figure 14). Subgroups are mostly consistent with the primary analysis result. Some subgroups have wide confidence intervals due to small sample size.

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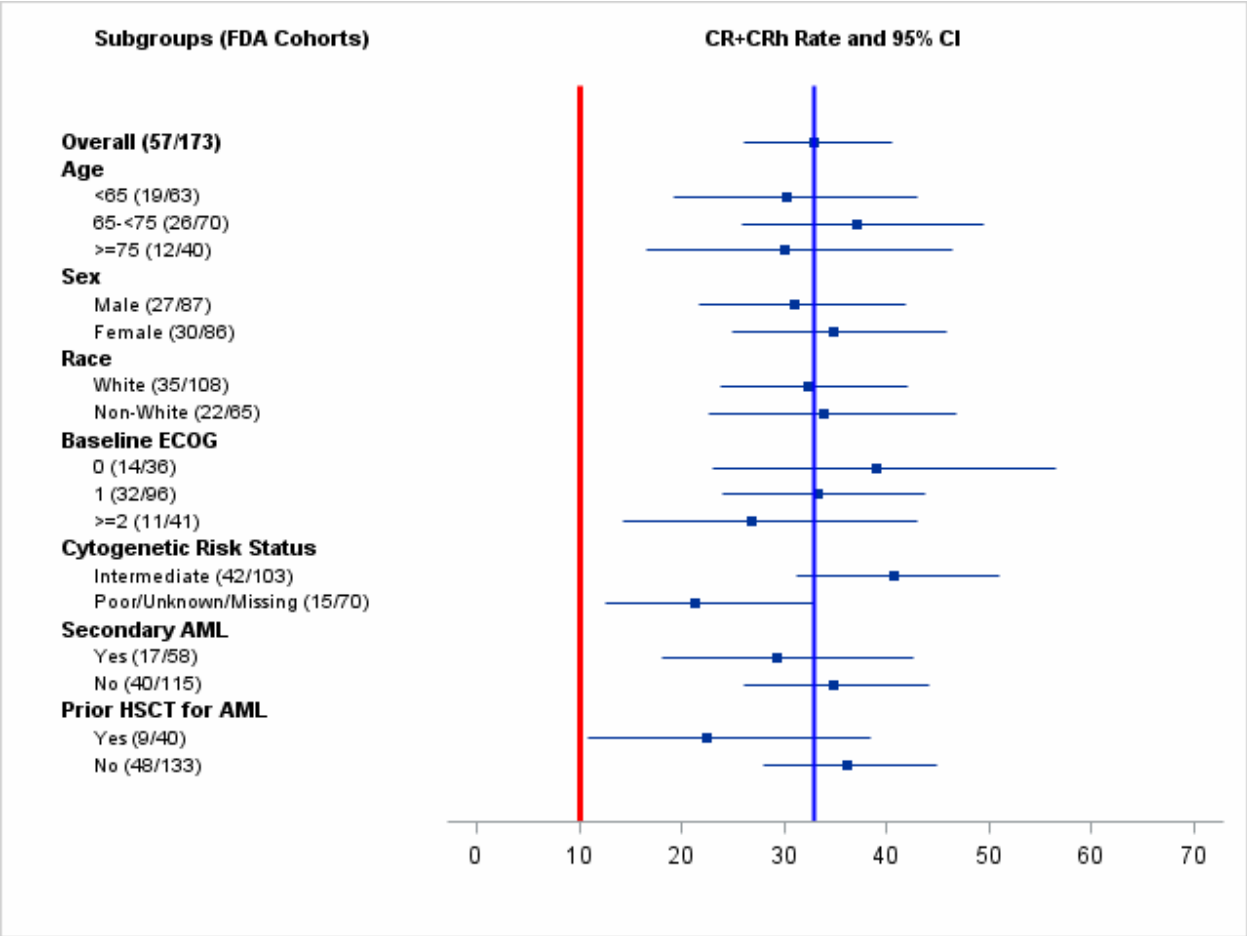
Figure 13: Forest Plot of Subgroup Analyses, Part I



Source: FDA analysis

Reviewer comments: The results indicate that traditionally poor prognostic features, such as a higher ECOG performance status, poor cytogenetics, secondary AML, and prior HSCT predict for lower response rates. In general, the results appear to be consistent across different subgroups. However, the interpretation of the subgroup results should be made with caution due to the small sample size and subgroup nature of the analyses in which potential confounding factors are not considered.

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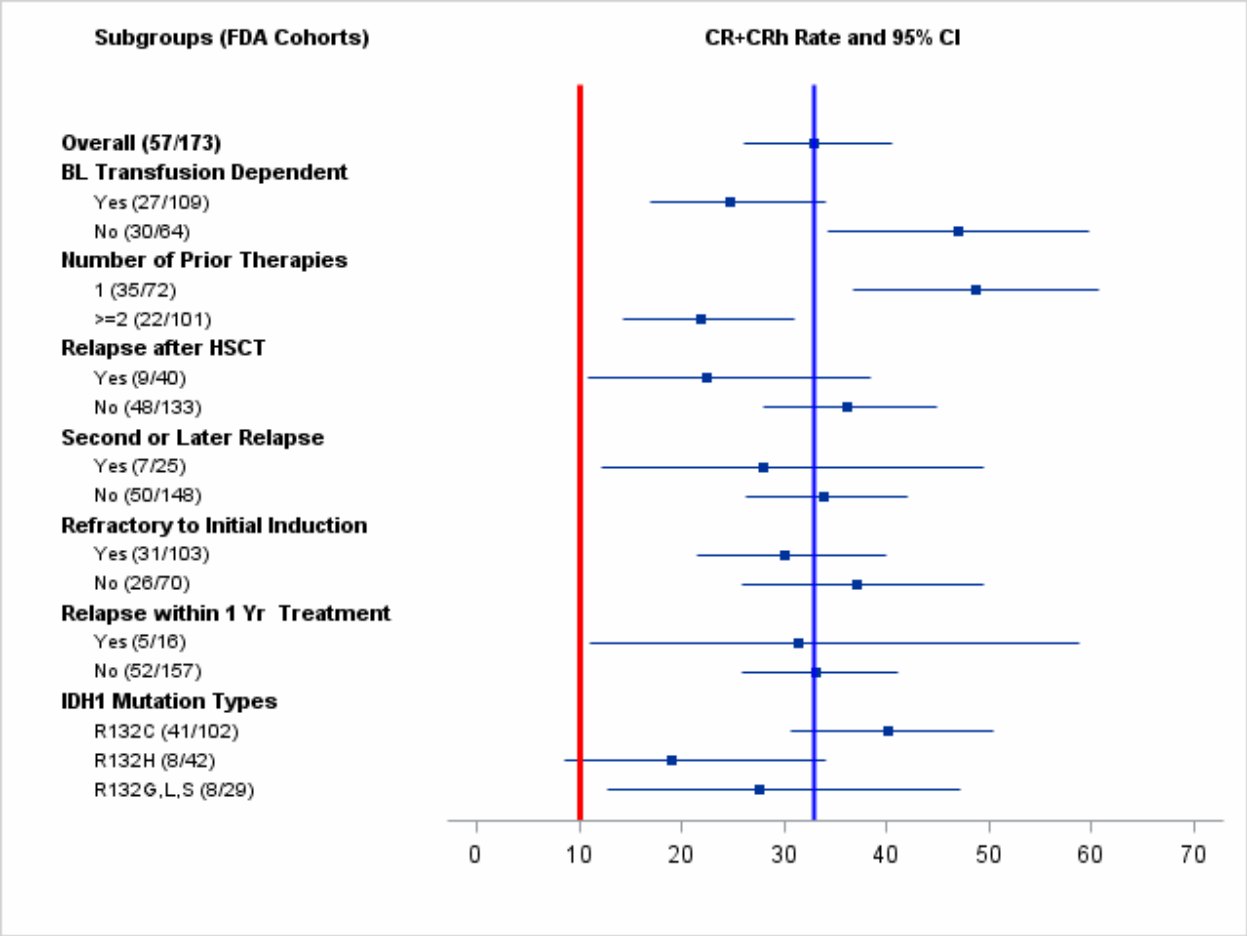
Figure 14: Forest Plot of Subgroup Analyses, Part II



Source: FDA analysis

Reviewer comments: Subgroup analysis by IDH mutation types showed a trend toward lower response rate for the R132H group. However, the confidence intervals were wide, so it is not possible to determine whether this was a true signal.

<u>MRD</u>

The Applicant provided an analysis of molecular MRD-evaluable subjects from Study AG120-C-001 (n=134; 111 R/R AML, 23 untreated AML). This included subjects with AML in the expansion portion of the study with bone marrow mononuclear cell mutant IDH1 variant allele frequency (VAF) data from baseline and at least 1 post-baseline time point. All subjects were positive for IDH1 per the companion diagnostic test. They defined molecular negativity as nondetectable mutant IDH1 VAF by digital polymerase chain reaction (≤ 0.04%) at ≥ 1 on-treatment time point.

Among the 111 molecular MRD-evaluable subjects with R/R AML in the FAS, 11 (23%) of 47 subjects who had a best response of CR or CRh achieved IDH1 mutation ≤ 0.04%. Ten of the 11

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patients with mutation clearance had a CR response and 1 had a CRh response.

Table 35: IDH1 Mutation ≤ 0.04% R/R AML MRD-Evaluable Subjects (n=111)

Best Response	n	IDH ≤ 0.04% n (%)	IDH > 0.04% n (%)
CR+CRh	47	11 (23%)	36 (77%)
CR	36	10 (28%)	26 (72%)
CRh	11	1 (9%)	10 (91%)
Other responses	64	0	64 (100%)
All responses	111	11 (10%)	100 (90%)

Source: Summary of Clinical Efficacy 90-Day Update (undated) Table 9

After consultation with CDRH, FDA determined the following about the Applicant's MRD assay (Source: Consult Memorandum, Aaron Schetter, PhD, CDRH, April 12, 2018):

- The assay is not capable of measuring MRD at a sensitivity of 0.01%
- The Applicant has not performed an appropriate Limit of Detection/ Limit of Blank study. Therefore, it is unclear if the cutoffs that have been selected for the assay are reasonable. It is possible/likely that the cutoffs will lead to high levels of false MRD(+) or MRD(-) results.
- The repeat testing of patient specimens within the trial combined with classifying a patient based on the lowest MRD value may lead to a false MRD(-) call, especially for the patients in complete remission.
- The Applicant has not performed an appropriate linearity or accuracy study to evaluate the accuracy of the quantitative measurements of the assay.
- The precision data that was included is not useful to evaluate MRD in BMMC.
- The Applicant has not indicated how much DNA has been added to the reaction; therefore, it is not possible to assess how many cells are being evaluated by their assay.
- The Applicant has not provided evidence that their assay is clinically meaningful.

Reviewer comments: Based on the lack of substantial documentation of the assay's validity, FDA is not able to make any formal assessment of the MRD responses provided in Table 35 above (b) (4)

Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

Not applicable.

Additional Analyses Conducted on the Individual Trial

Out of 173 R/R AML patients, one hundred and nine patients were transfusion dependent and sixty-four were transfusion independent at baseline. Forty-one out of these 109 transfusion

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dependent patients (38%) were independent of transfusions for at least 56-days post-baseline. Thirty-eight out of 64 transfusion independent patients (59%) remained transfusion independent for at least 56-days post-baseline. Six patients did not have post baseline transfusion data.

Table 36: Transfusion Dependency Conversion from Baseline to At Least 56 Days Post-Baseline

	Post-Baseline			
Baseline	Dependent	Independent	NE	Total
Dependent	67	41	1	109
Independent	21	38	5	64
Total	88	79	6	173

Source: FDA analysis

FDA also performed a more detailed analysis of transfusion independence in the R/R AML Efficacy Set by best overall response for platelets, red blood cells, and either red blood cells or platelets. Results are in Table 37 below.

Table 37: Transfusion Dependency by Response R/R AML Efficacy Set

Best Overall Response	Baseline Transfusion	Post-Baseline Transfusion		
		Dependent n (%)	Independent n (%)	Not evaluated n (%)
Platelets				
CR (N=43)	Dependent (N=12)	0	12 (100%)	0
	Independent (N=31)	0	31 (100%)	0
CRh (N=14)	Dependent (N=8)	2 (25%)	6 (75%)	0
	Independent (N=6)	0	6 (100%)	0
CRi/CRp/MLFS (N=18)	Dependent (N=14)	7 (50%)	7 (50%)	0
	Independent (N=4)	2 (50%)	2 (50%)	0
NR (N=98)	Dependent (N=51)	40 (78%)	10 (20%)	1 (2%)
	Independent (N=47)	18 (38%)	18 (38%)	11 (23%)
Overall (N=173)	**Dependent (N=85)**	49 (58%)	**35 (41%)**	1 (1%)
	Independent (N=88)	20 (23%)	**57 (65%)**	11 (13%)
Red blood cells				
CR (N=43)	Dependent (N=17)	2 (12)	15 (88%)	0
	Independent (N=26)	0	26 (100%)	0
CRh (N=14)	Dependent (N=9)	2 (22%)	7 (78%)	0
	Independent (N=5)	0	5 (100%)	0
CRi/CRp/MLFS (N=18)	Dependent (N=12)	7 (58%)	5 (42%)	0
	Independent (N=6)	1 (17%)	5 (83%)	0

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NR (N=98)	Dependent (N=55)	39 (71%)	14 (26%)	2 (4%)
	Independent (N=43)	18 (42%)	18 (42%)	7 (16%)
Overall (N=173)	**Dependent (N=93)**	50 (54%)	**41 (44%)**	2 (2%)
	Independent (N=80)	19 (24%)	**54 (68%)**	7 (9%)
Any platelet or red blood cell transfusion				
CR (N=43)	Dependent (N=18)	2 (11)	16 (89%)	0
	Independent (N=25)	0	25 (100%)	0
CRh (N=14)	Dependent (N=9)	3 (33%)	6 (67%)	0
	Independent (N=5)	0	5 (100%)	0
CRi/CRp/MLFS (N=18)	Dependent (N=16)	8 (50%)	8 (50%)	0
	Independent (N=2)	2 (100%)	0	0
NR (N=98)	Dependent (N=66)	54 (82%)	11 (17%)	1 (2%)
	Independent (N=32)	19 (59%)	8 (25%)	5 (16%)
Overall (N=173)	**Dependent (N=109)**	67 (62%)	**41 (38%)**	1 (1%)
	Independent (N=64)	21 (33%)	**38 (59%)**	5 (8%)

Source: Summary of Clinical Efficacy 90-Day Update (undated) Table 7

Reviewer comments: Important observations are that patients with CR responses achieve more transfusion independence than CRh responses and CRh responses achieve more transfusion independence than lesser or no responses. Another interesting observation is that, even in patients with no response, 17% converted from transfusion dependent at baseline to transfusion independent for at least a 56-day post-baseline period. The achievement or maintenance of transfusion independence in treated patients further support the clinical benefit of ivosidenib in patients with R/R AML.

Newly-Diagnosed AML

The Applicant submitted data on Arm 2+ with the 90-day safety update, which contained 25 patients with newly-diagnosed AML in the FAS IDH1+ set who received ivosidenib 500 mg daily. The following observations were made:

- CR+CRh rate 44% (95% CI 25-65%) with median DoR 7.4 months (95% CI 4.2-NR)
- CR rate 28% (95% CI 13-50%) with median DoR NR (95% CI 4.2-NR) months
- Time to CR+CRh 2.8 months (95% CI 1.9-2.8)
- Median OS 12.8 months (95% CI 4.5-NR)

Reviewer comments: The limited data in newly-diagnosed patients appears to represent slightly more effectiveness than in the R/R AML population, as expected. The CR+CRh rate of 44% compares favorably with that of azacitidine in newly-diagnosed AML on AZA-AML-001 (Dombret et al. 2015), where CR+CRi was 28% (95% CI 22-34%). The CR rate of 28% with ivosidenib also compares favorably with the CR+CRi rate on AZA-AML-001 of 20% (95% CI 15-25%). RFS on AZA-001 was 9.3 months (6.7-12.4) and median OS was 10.4 months (95% CI 5.0-

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8.6). Given that the confidence intervals cross, (b) (4)

Furthermore, we do not know how the subgroup of IDH1 mutation positive patients did on AZA-AML-001. It is possible that they may have done better than the overall study population given the epigenetic downstream effects of IDH1 mutations (Im et al. 2014).

(b) (4)

MDS

The Applicant submitted data on Arm 3+ with the 90-day safety update, which contained 9 patients with R/R MDS in the FAS IDH1+ set who received ivosidenib 500 mg daily. These patients had median 1 prior regimen (range 0-3). The following observations were made:

- CR rate 44% (95% CI 15-77%) with median DoR NR (95% CI 2.8-NR) months
- No CRh responses
- Time to CR median 1.4 months (range CI 1.0-5.6)
- Median OS NR (95% CI NR-NR) (all patients alive at last follow-up)

Clinical TL Review Comments: Although the results are supportive of the activity of ivosidenib for a disease with and IDH1 mutation, no firm conclusions can be drawn given the small sample size.

8.2 Integrated Review of Effectiveness

8.2.1 Assessment of Efficacy Across Trials

Methods

The applicant proposed the indication "For the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test" for ivosidenib. The clinical development program consisted of a single Phase 1-2 clinical trial, Study AG120-C-001.

The primary endpoint of Study AG120-C-001 was the rate of CR+CRh, as derived by the Applicant from relevant data, including investigator-collected BM and hematology data among responders. Evaluation for response, including marrow examination, was required at least on day 29, every 28 days through month 12, and every 56 days thereafter while on treatment. This frequency of efficacy assessments was considered adequate.

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Reviewer Comments: FDA usually uses CR as an endpoint reasonably likely to predict clinical benefit for patients with acute leukemia. In settings without intent to cure, FDA has considered using durable CR and CRh for regulatory-decision making on the basis of recovery of adequate blood counts to protect against infection and avoid transfusions, preferably with corroborating evidence. The Study AG120-C-001 SAP specified CR+CRh rate as the primary efficacy endpoint and transfusion-independence as an additional secondary endpoint.

There was an interim futility analysis on Study AG120-C-001 that was conducted for Arm 1 of the expansion when the first 25 subjects were treated and followed for 2 cycles or discontinued earlier. At the time of the interim analysis, demonstration of potential clinical activity (ORR ≥ 15%) allowed for enrollment of an additional 100 subjects to Arm 1 of the expansion portion, for a total of 125 subjects. The final analysis was to be performed when at least 125 expansion Arm 1 eligible subjects (including Arm 1 eligible subjects from dose escalation whose starting dose was 500 mg daily) received at least 6 months of ivosidenib or discontinued therapy earlier. An observed CR+CRh rate of at least 16% in 125 treated subjects would result in an exact binomial 95% CI with a lower bound that excludes 10%. This is equivalent to testing a null CR+CRh rate of 10% compared to a target rate of 20% with 89% power and 2-sided alpha of 0.05, which was considered evidence of clinically significant activity of ivosidenib in R/R AML. The applicant reported that a CR or CRh was achieved by 38 subjects (30.4%; 95% CI 22.5%-39.3%), so the primary objective of the study was met.

There were 258 subjects with various hematological neoplasms treated with ivosidenib on this study. For the purposes of establishing efficacy, FDA considered only the 173 subjects who a) were documented to have R/R AML at study entry, b) were treated with the 500 mg total daily dose of ivosidenib, and c) for whom the IDH1 mutation was detected by the proposed companion diagnostic (see Section 8.1.1). The demographics are shown in Table 29.

Primary Endpoint

CR/CRh: The FDA clinical reviewer adjudicated all responses and identified subjects with a CR or CRh using only ivosidenib and no additional follow-on therapies. The CR+CRh rate was 33% (95% CI 26, 41) for the R/R AML Efficacy Set and 31% (95% CI 24, 39) for the Original Efficacy Set (see Table 33 and Table 34).

Reviewer Comments: Since the populations and results are consistent between the Original Efficacy Set and the additional subjects in the R/R AML Efficacy Set, it is acceptable to pool all R/R AML data for display in the PI, even though the Arm 1+ population was originally designated as the population for the primary endpoint in the SAP.

Kinetics and Durability: The CR rate was 25% (95% CI: 19, 32) with a median duration of 10.1 months, while the CRh rate was 8% (95% CI: 5, 13) with a median duration of 3.6 months (Table 33). The duration of CR+CRh is likely to improve over time, as median time to best response of

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CR+CRh is 2 months, with some subjects experiencing best response much later.

Reviewer Comments: The results of Study AG120-C-001 show that responses to ivosidenib are delayed. The PI should be clear about the kinetics of response to ivosidenib so that healthcare providers do not discontinue use prematurely.

The duration of response (median 8.2 months) is clinically meaningful for a palliative treatment with an acceptable safety profile. Given the short follow-up and persistence of molecular positivity in most patients, the long-term benefit of treatment with ivosidenib cannot be determined.

The Applicant reported that subjects who achieved CR or CRh had lower exposure-adjusted rates of severe infection, bleeding and febrile neutropenia (Table 61).

Clinical TL Review Comment: The results of these outcomes are supportive of the clinical benefit of CR and CRh in the population of patients with relapsed or refractory AML.

Secondary and Other Endpoints

Transfusions: The applicant has also provided evidence that 38% of 109 subjects who entered study AG120-C-001 dependent on platelet or red blood cell transfusions as a consequence of their AML became transfusion-independent for at least 56 days while on treatment, and that 59% of 64 subjects who entered study AG120-C-001 independent of platelet and red blood cell transfusions remained transfusion-independent for at least 56 days while on treatment (Table 37). A total of 46% of subjects maintained or achieved transfusion-independence on ivosidenib.

Reviewer comments: Avoiding transfusions represents a notable palliative effect of ivosidenib for patients with R/R IDH1-mutated AML who seek quality of life as a short term benefit.

MRD: (b) (4)

For this endpoint, success was defined as MRD < 0.04%. The results are shown in Table 36.

Clinical TL Review Comment: There are three concerns regarding the MRD data. First, results were not provided for all subjects who achieved CR or CRh in the final efficacy population; missing data should be imputed as a failure. (b) (4) ***at the present time FDA does not consider MRD > 0.01% to be predictive of long-term efficacy for acute leukemia. Lastly, the CDRH reviewer concluded that the validation package for the assay was insufficient.*** (b) (4)

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Subpopulations

The results of the subgroup analysis for CR+CRh (Figures 13 and 14) showed that the treatment effect was largely independent of age, gender, race, performance status, or secondary AML. The CR+CRh rate was somewhat lower for patients with poor-risk cytogenetics, previous HSCT, and R132H mutation.

In an exploratory analysis of co-occurring mutations in a subgroup of study subjects, there was no consistent pattern of co-occurring mutations in patients who achieved CR or CRh. However, responses appeared to cluster in those with fewer co-occurring mutations and less responses were seen in those with co-occurring mutations in genes involved in the receptor tyrosine kinase pathways (e.g. NRAS, FLT3) (see Section 6).

Additional Efficacy Considerations

Study AG120-C-001 also had a dose-escalation portion that included 78 subjects with R/R AML treated with total daily doses of 200 mg - 1200 mg of ivosidenib. CR+CRh was achieved by 2 (25%) of 8 subjects in ivosidenib cohorts with total daily dose < 500 mg, by 13 (27%) of 48 in the 500 mg daily cohorts, and by 4 (18%) of 22 in cohorts with doses > 500 mg daily (FDA analysis). Thus, there did not appear to be a dose-response relationship. The Clinical Pharmacology reviewer also noted a relatively flat exposure-response relationship (refer to section 6).

Late-Breaking Update

In the initial submission of the NDA, Patient (b) (6) was reported as having a baseline specimen not analyzable for an IDH1 mutation. On 7/2/2018 the Applicant notified FDA that the specimen information for IDH testing for Patient (b) (6) was logged incorrectly at the testing site, and that Patient (b) (6) has confirmed IDH1 R132 mutation positivity by the companion diagnostic test. The Applicant subsequently submitted the source documentation to support the correction of this error, updated data files with this patient flagged as IDH1 positive, and reanalyzed the demographics and efficacy results including this additional patient. FDA confirmed that with the corection of the error, the R/R AML Efficacy Set would include 174 patients. FDA verified the demographic data as follows.

Table 38: Baseline Demographic and Disease Characteristics Updated R/R AML Efficacy Set

Demographic and Disease Characteristics	**Updated R/R AML Efficacy Set (N=174)**
Demographics	
Age (Years) Median (Min, Max)	67 (18, 87)
Age Categories, n (%) <65 years	 63 (36)

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≥65 years to <75 years	71 (41)
≥75 years	40 (23)
Sex, n (%)	
Male	88 (51)
Female	86 (49)
Race, n (%)	
White	108 (62)
Black or African American	10 (6)
Asian	6 (3)
Native Hawaiian/Other Pacific Islander	1 (1)
Other/Not provided	49 (28)
Disease Characteristics	
ECOG PS, n (%)	
0	36 (21)
1	97 (56)
2	39 (22)
3	2 (1)
IDH1 Mutation, n (%)	
R132C	102 (59)
R132H	43 (25)
R132G	12 (7)
R132S	10 (6)
R132L	7 (4)
Cytogenetic Risk Status, n (%)	
Intermediate	104 (60)
Poor	47 (27)
Missing/Unknown	23 (13)
Relapse Type	
Primary refractory	64 (37)
Refractory relapse	45 (26)
Untreated relapse	65 (37)
Relapse Number	
0	64 (37)
1	83 (48)
2	21 (12)
≥3	6 (3)
Prior Stem Cell Transplantation for AML, n (%)	40 (23)
Transfusion Dependent at Baseline, n (%)	110 (63)
Median Number of Prior Therapies (Min, Max)	2 (1, 6)
Type of AML, n (%)	
De novo AML	116 (67)
Secondary AML	58 (33)

Source: FDA Analysis

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The efficacy results based on the updated dataset is presented in the following table based on FDA's analysis. .

Table 39: Efficacy Results in Updated R/R AML Efficacy Set

	Updated R/R AML Efficacy Set (N=174)
CR+CRh rate, n (%) [95% CI]	57 (32.8) [25.8, 40.3]
Duration of CR+CRh, median [95% CI]	8.2 [5.6, 12.0]
Time to CR+CRh, median (range)	2 (0.9, 5.6)
CR rate, n (%) [95% CI]	43 (24.7) [18.5, 31.8]
Duration of CR, median [95% CI]	10.1 [6.5, 22.2]
Time to CR, median (range)	2.8 (0.9, 8.3)
CRh rate, n (%) [95% CI]	14 (8.0) [4.5, 13.1]
Duration of CRh, median [95% CI]	3.6 [1, 5.5]
Time to CRh, median (range)	1.9 (1.0, 5.6)
Overall Survival, median [95% CI]	9.0 [7.4, 10.2]
Median Follow-up (Range)	8.3 (0.2, 39.5)

Source: FDA Analysis

Lastly, FDA verified the transfusion dependency conversion from baseline below.

Table 40: Transfusion Dependency Conversion from Baseline to At Least 56 Days Post-Baseline with the Updated R/R AML EFficacy Set

	Post Baseline			
Baseline	**Dependent**	**Independent**	**NE**	**Total**
Dependent	68	41	1	110
Independent	21	38	5	64
Total	89	79	6	174

Source: FDA Analysis

8.2.2 Integrated Assessment of Effectiveness

The effectiveness of ivosidenib 500 mg daily for treatment of patients with R/R AML having an IDH1 mutation is established by the CR+CRh rate in Study AG120-C-001, the durability of the response, and the corroborative findings of transfusion-independence. There is insufficient information about resistant IDH1 mutations or interfering co-mutations that would warrant a limitation of use at this time. There are also no data to support an expectation of long-term benefit. Nonetheless, if the safety profile is acceptable, the effectiveness would be meaningful

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for patients seeking short-term relief from their disease.

8.3 Review of Safety

8.3.1. Safety Review Approach

Review emphasis was placed on safety data in patients with R/R AML who received 500 mg of ivosidenib daily on study AG-120-C-001 (R/R AML SAS). Patients from Phase 1 and Phase 2 were pooled for the safety analysis.

Available safety data from all patients with advanced hematologic malignancies who received ivosidenib on this study was used to support the analysis of safety in a larger patient population (SAS), and evaluate dose-toxicity relationships. In addition, safety information provided by the Applicant from the other clinical trials of ivosidenib in healthy volunteers or patients with solid tumors listed in Table 19 were summarized where relevant. Studies in Table 19 with only SAE data, including 2 studies evaluating ivosidenib in combination with other antineoplastic regimens in patients with newly diagnosed AML and 1 evaluating single-agent ivosidenib versus placebo in patients with cholangiocarcinoma were considered minimally given small numbers of patients and the preliminary nature of the data.

All safety analyses were conducted on the complete dataset provided by the Applicant for Study AG-120-C-001, which used a data cutoff date of November 10, 2017.

8.3.2. Review of the Safety Database

Overall Exposure

A total of 179 patients with R/R AML assigned a dose of 500 mg ivosidenib daily received at least one dose of ivosidenib on Study AG-120-C-001 and were included in the R/R AML SAS. An additional 79 patients with newly-diagnosed AML, other hematologic malignancies, and/or treated at other doses who received at least one dose of ivosidenib on Study AG120-C-001 were included in the SAS (n=258).

A summary of exposure to ivosidenib is provided in Table 39. In the R/R AML SAS (n=179), the median duration of exposure to ivosidenib was 3.9 months (mean 5.4 months), with a minimum exposure time of 0.07 months and a maximum exposure time of 39.4 months. In the SAS (n=258), the median duration of exposure to ivosidenib was 3.8 months (mean 5.9 months), with a minimum exposure time of 0.07 months and a maximum exposure time of 39.4 months. A total of 27 patients were exposed to ivosidenib for more than 12 months.

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Table 41: Duration of Exposure[1] to Ivosidenib in the Safety Population

	0 to 3 months	>3 to 6 months	>6 to 9 months	>9 to 12 months	> 12 months
R/R AML SAS (n=179)	66 (37%)	51 (28%)	27 (15%)	21 (12%)	14 (8%)
SAS (n=258)	95 (37%)	72 (28%)	34 (13%)	30 (12%)	27 (10%)

Source: FDA analysis
[1] Irrespective of assigned dose or regimen

Eighty-eight percent (n=228) of the patients in the SAS received a total of 500 mg of ivosidenib daily, which is the Applicant's proposed dose for marketing. Another 22 (9%) received > 500 mg daily and 8 (3%) received < 500 mg daily.

Table 42: Planned Total Daily Dose of Ivosidenib in the Safety Population

Planned total daily dose	R/R AML SAS (n=179)	SAS (n=258)
200 mg	0	4
300 mg	0	4
500 mg	179	228
800 mg	0	15
1200 mg	0	7

Source: FDA analysis

Relevant characteristics of the safety population

Demographic information for patients analyzed for safety is summarized in Table 43.

Table 43: Demographics of the Safety Population

	R/R AML SAS (n=179)	SAS (n=258)
Sex		
Male	90 (50%)	137 (53%)
Female	89 (50%)	121 (47%)
Age (years)		
Mean	65	67
Median	67	68
Min, Max	18, 87	18, 89
Age group		
18-65 years	67 (37%)	84 (33%)
≥65 years	112 (63%)	174 (67%)
ECOG Performance Status		
0	36 (20%)	56 (22%)
1	99 (55%)	144 (56%)
2	42 (23%)	54 (21%)
3	2 (1%)	4 (2%)

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	R/R AML SAS (n=179)	SAS (n=258)
Race		
White	112 (63%)	177 (69%)
Black	10 (6%)	15 (6%)
Asian	6 (3%)	6 (2%)
Other	9 (5%)	9 (3%)
Not Provided or Unknown	42 (23%)	51 (20%)
Ethnicity		
Not Hispanic or Latino	100 (56%)	152 (59%)
Hispanic or Latino	9 (5%)	12 (5%)
Not Provided	70 (39%)	94 (36%)
Underlying Disease		
R/R AML	179 (100%)	205 (79%)
Untreated AML	0	37 (14%)
MDS	0	13 (5%)
Other[1]	0	3 (1%)
Baseline Weight		
< 55 kg	21 (12%)	27 (10%)
55 to 100 kg	146 (82%)	204 (79%)
> 100 kg	12 (7%)	25 (10%)
Missing	0	2 (1%)
Trial Site		
United States	148 (83%)	223 (86%)
France	31 (17%)	35 (14%)

Source: FDA analysis
[1]CMML (n=1), essential thrombocythemia (n=1) and persistent myeloid neoplasm (n=1)

Adequacy of the Safety Database

The size of the safety database is adequate to provide a reasonable estimate of adverse reactions that may be observed with ivosidenib, and the duration of treatment is adequate to allow assessment of adverse reactions over time. Data is lacking, however, regarding long-term toxicities of ivosidenib, since the majority of patients with R/R AML have a short life expectancy. There are no randomized data regarding the safety of ivosidenib in comparison to either a standard of care agent or placebo, which would be helpful in understanding the contribution of the underlying disease to adverse reactions. The demographics of the patients included in the safety pool (Table 43) are representative of typical patients with AML that participate on clinical trials.

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8.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The quality of the safety data submitted was adequate to allow substantive primary review. The Applicant provided an analysis-ready dataset for subjects on Study AG120-C-001, as well as narratives for subjects who:

- died after the start of ivosidenib treatment until ≤ 28 days following the last dose of ivosidenib, with the exception of deaths attributed to PD
- had serious adverse events (SAEs), regardless of causality assessment, that occurred after the start of ivosidenib treatment until ≤ 28 days following the last dose of ivosidenib *or* occurred > 28 days after the last dose of ivosidenib and was considered to be related to ivosidenib by the Investigator or Sponsor
- had their study treatment permanently discontinued for any reason other than PD or death
- had DS AEs
- met Hy's Law (total bilirubin ≥ 2x the upper limit of normal and ALT or AST ≥ 3x the upper limit of normal) or had QTc prolongation ≥ Grade 3
- had ≥ Grade 3 AEs of leukocytosis

Categorization of Adverse Events

Adverse events and severe adverse events were defined according to ICH E2A guidelines. Adverse events were reported down to the investigator's verbatim term, graded by the investigator using the NCI-CTCAE for adverse events Version 4.03, and coded by the Applicant using MedDRA version 20.0. Terms that referred directly to relapse, persistence of disease, or progression of AML were excluded from the FDA's analyses. Treatment-emergent adverse events (TEAE) excluded events that started before the start of the study drug or that started more than 28 days after the last dose of ivosidenib. TEAEs were summarized by maximum grade per patient.

The FDA compared the verbatim adverse event term with the coded MedDRA preferred term for all adverse events reported on study AG120-C-001 and did not identify any irregularities. The FDA grouped some related preferred terms for all analyses; a listing of these grouped terms can be found in Appendix 14.5.1. SMQ analysis was also performed using MAED, and no additional safety signals were identified beyond those discussed below.

Routine Clinical Tests

See Section 8.1.1 for a description of the frequency of clinical testing for Study AG120-C-001. The testing was adequate to assess the risks of serious safety events such as DS, as discussed in detail below.

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8.3.4. Safety Results

Deaths

The FDA identified 174 deaths in the 258 patients who received ivosidenib on Study AG120-C-001 (67%), under half of which occurred on or within 28 days after discontinuation of ivosidenib (Table 44). For the purposes of this review, FDA focused on the evaluation of deaths in the R/R AML SAS. The all-cause mortality as calculated by the FDA for the 179 subjects in the R/R AML SAS was 7% (95% CI, 4-11%) at day 30, 15% (95% CI 10-20%) at day 60, and 20% (95% CI, 15-27%) at day 90.

Table 44: Deaths on Study AG120-C-001

	R/R AML SAS (N=179)	SAS (N=258)
All deaths	129 (72%)	174 (67%)
On-treatment deaths[1]	50 (28%)	73 (28%)
Escalation phase	10	28
Expansion phase	40	45

Source: FDA analysis
[1] On or within 28 days after the last dose of ivosidenib

The dataset provided by the applicant identified the underlying malignancy as the proximate cause of death in 23 of the 50 on-treatment deaths (46%) and in 49 of the 129 total deaths (38%) in the R/R AML SAS. However, they reported the underlying malignancy as the root cause of death in 47 (94%) and 112 (87%) of on-treatment and total deaths, respectively. Aside from the underlying malignancy, frequently reported proximate causes of on-treatment death were infection (n=13), respiratory failure (n=4), intracranial hemorrhage (n=3), and stroke (n=2).

The FDA reviewed individual patient narratives from all 50 of the on-treatment deaths that occurred in the R/R AML SAS to confirm the cause of death. Patient narratives were generally well-written. The FDA considered the root cause of death to be the primary malignancy when supported by stable or worsening of disease in the marrow or peripheral blood by blast count or flow cytometry, imaging report, or description of other objective evidence. The FDA determined that the majority (n=40, 80%) of the on-treatment deaths in R/R AML patients on Study AG120-C-001 were due to the primary malignancy.

There were 10 on-treatment deaths (5.6%) in R/R AML patients on AG120-C-001 considered by the FDA to be at least possibly related to ivosidenib (Table 45). Infection was clearly the root cause of death in 3 cases. These three subjects died of infections despite improvements in their ANC and blast counts on ivosidenib.

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Table 45: Causes of Deaths on or Within 30 Days of Treatment in the R/R AML SAS

Subject	Study Day	Days Since Last Dose	FDA Root Cause of Death	Investigator Cause of Death
(b) (6)	51	7	Respiratory failure/DS	Respiratory failure
	32	3	Aspiration pneumonia	Aspiration pneumonia
	30	17	Myocardial infarction	Myocardial infarction
	40	20	Aspergillus pneumonia	AML
	22	3	Ventricular arrhythmia	Ventricular arrhythmia
	120	3	Pneumonia	Pneumonia
	113	6	Fungal sinusitis	Subarachnoid hemorrhage
	109	4	Thrombotic stroke	Thrombotic stroke
	85	6	ARDS/DS	ARDS
	16	2	Pulmonary infection/DS	Pulmonary infection

Source: FDA analysis
Abbreviations: AML, acute myeloid leukemia; ARDS, acute respiratory distress syndrome; DS, differentiation syndrome

There were seven deaths in R/R AML patients not definitively caused by infection that were considered by the FDA to be a direct toxicity of ivosidenib:

Subject (b) (6): This 54-year-old man with R/R AML received 500 mg ivosidenib daily in the dose escalation cohort. On study day 39, he was seen in the clinic for night sweats, fevers, and lower right rib and right upper quadrant pain that worsened with breathing deeply or coughing. He had a blood pressure of 91/61, pulse of 123 bpm, respiratory rate of 18 breaths per minute, and oxygen saturation of 94%, but was afebrile. He was noted to have a log increase in his WBC count and mild renal failure. He was admitted to the hospital and treated with IV ceftazidime, vancomycin, and azithromycin for presumed healthcare-associated pneumonia. His WBC was 20.6 x 10^9/L. Cultures and viral panel were negative. The patient's oxygen requirements increased and he was diuresed due to concern for pulmonary edema, without improvement in his oxygenation. On day 43, his renal function worsened, thought to be possibly related to contrast nephropathy. On study day 45, the patient received his last dose of ivosidenib before it was discontinued due to PD. His WBC was 42.4 x 10^9/L (10% blasts) and creatinine 188.29 µmol/L. A thoracentesis was performed with removal of 500 cc of serosanguinous fluid, consistent with an exudative process. His oxygen requirements continued to increase, with the presumptive diagnosis of progression of AML. On study day 50, the patient was transferred to hospice on 35 L of 85% oxygen through a high-flow nasal cannula. His creatinine level continued to increase to 3.4 mg/dL and WBC 40.9 x 10^6/L. One day later, the patient died due to respiratory failure, which was assessed by the Investigator as due to the underlying malignancy. The Sponsor recorded the cause of death as respiratory failure, but acknowledged in the DSALL dataset that this patient possibly had DS. Based on our DS algorithm (detailed under "Significant Adverse Events" below), this patient meets the DS criteria of dyspnea, hypotension, acute kidney injury (AKI), and pulmonary infiltrates/pleuropericardial effusion, which equates

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to severe DS per Montesinos et al (Montesinos et al. 2009).

Reviewer comments: This patient was thought to have died from respiratory failure as a consequence of his AML. His WBC increased substantially around the time of his respiratory decompensation, renal failure, and hypotension. However, his peripheral blast count decreased steadily from a peak of 75% on day 18 to only 10% on day 45, arguing somewhat against progression of disease. Infection is another possibility, but cultures were all negative. In the absence of a definitive alternative, DS as the cause of death could not be ruled out.

Subject (b) (6) This 56-year-old man with R/R AML after 3 prior anti-cancer regimens including intensive and non-intensive therapies and a previous HSCT enrolled on the escalation cohort at 500 mg daily. The patient had a history of alcohol abuse, ascites, drug use, Enterobacter bacteraemia, hepatic cirrhosis, hepatitis B, hyperglycemia, intra-cerebral aneurysm operation, unilateral blindness, cellulitis, dementia, delirium, hypertension, peripheral edema, and splenomegaly. The patient was admitted to the hospital on day 19 due to grade 2 malaise, grade 4 neutropenia, and grade 3 orthostatic hypotension. The patient presented with complaints of weakness, fatigue, decreased appetite, nausea, and lightheadedness. The patient was placed on a PCA for pain, which was later transitioned to oral pain medications. The patient had episodes of desaturation and a CXR showed increased layering right pleural effusion with underlying compressive atelectasis, increasing basilar predominant interstitial opacities, and probably mild edema. On day 22, the patient was diagnosed with C diff colitis and was started on metronidazole. On day 25, the patient experienced altered mental status. Head CT showed no acute intracranial process. The patient had desaturation on room air with values in the low 80s. Required a non-rebreather mask, which improved saturations. Repeat CXR showed increase in right layering pleural effusion with adjacent compressive atelectasis with possible subpulmonic effusion. The patient started treatment with dexamethasone. Day 25, the patient missed 1 dose of ivosidenib. WBC 24 with 89% blasts. On Day 26, ivosidenib was resumed. On day 27, the patient was found taking his own Ambien and oxycodone supply and was agitated and violent with staff. Psychiatry was consulted for behavioral problems and suicidal ideation. Haldol was administered. WBC 10 with 81% blasts. On day 28, dexamethasone was discontinued and the patient continued treatment with hydroxyurea. Final dose of ivosidenib on day 30. That day, he was found lethargic. The following day, he experienced extended labored breathing with continued deterioration in his overall condition. Two days after the final dose, the patient died due to aspiration pneumonia, deemed by the investigator to be unrelated to the study treatment. Although the patient had a significant disease burden and notable co-morbidities, FDA could not rule out that ivosidenib contributed to the events of altered mental status and the ultimate aspiration event.

Subject (b) (6): This 77-year-old man with relapsed AML after one non-intensive therapy received 500 mg ivosidenib daily in the expansion cohort. Past medical history included prostate cancer status post brachytherapy, diverticulitis, hyperlipidemia, and hypertension. On study day 2, the patient presented to the ER with chest pain and was sent home. On day 14, he

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returned to the local ER with continued chest pain and was admitted. He was diagnosed with grade 2 pericarditis and myocarditis and started on steroids. Ivosidenib was discontinued. On study day 18, the patient was discharged with supplemental oxygen and dexamethasone for pericarditis. He was re-admitted 11 days after his final dose of ivosidenib for continued complaints of chest pain and was diagnosed with a grade 3 myocardial infarction. Catheterization showed 3-vessel coronary disease with thrombus in the left anterior descending artery. He was managed medically and pursued hospice care, where he died of the myocardial infarction. The investigator considered myocarditis, pericarditis, and myocardial infarction as not related to ivosidenib. Given that the patient was asymptomatic from a cardiac perspective prior to starting ivosidenib, FDA could not rule out the possibility that ivosidenib contributed to the development of pericarditis/myocarditis, which may have spurred the onset of cardiac ischemia.

Subject (b) (6) This 83-year-old woman with R/R AML after three prior anti-cancer regimens, including intensive chemotherapy, received 500 mg ivosidenib daily in the escalation phase. Past medical history included cervical cancer, brachytherapy, cardiac murmur, scarlet fever, colectomy, colostomy, radiation gastroenteritis, hypotension, non-Hodgkin's lymphoma, pneumonia, pleural effusion, and osteoporosis. Concomitant medications included fluconazole, levofloxacin, and ondansetron. On day 1, baseline QTcF was 430 msec and 4-hour post-dose QTcF was 452 msec. Potassium and magnesium levels were normal. On study day 12, the patient had a urinary tract infection (UTI). On day 20, the patient experienced syncope and presented to the ER with hypokalemia (K 2.7 mEq/L) and hypomagnesemia (Mg 1.6 mg/dL). She was admitted to the ICU. The next day, she had an SAE of ventricular fibrillation arrest (grade 4) and was resuscitated. She was intubated and started on IV amiodarone. Treatment with fluconazole and ondansetron were ongoing and electrolyte repletion began the day prior. BNP was 1885 pg/mL and creatinine was 1.9 mg/dL. The family opted for hospice care and ivosidenib was stopped after day 21. Two days after the last dose of ivosidenib, the patient died due to grade 5 ventricular arrhythmia. Per the investigator, the death was related to electrolyte abnormalities in the setting of anorexia, malnutrition, and the UTI and was not related to ivosidenib. FDA could not rule out the possibility that ivosidenib contributed to the development of the ventricular arrhythmia.

Subject (b) (6): This 67-year-old woman with R/R AML after 3 prior anti-cancer regimens received 500 mg ivosidenib daily on the expansion phase. The patient had a history of MDS and atrial fibrillation (a-fib). On study day 58, the patient experienced a prolonged episode of DS with fever, weight gain, edema, bilateral pleural effusions, and pericardial effusion. This was associated with a rising WBC count and required hydroxyurea and dexamethasone. A scan demonstrated worsening splenomegaly with signs of splenic infarction. On day 72, the patient had grade 4 sepsis requiring an ICU admission and was found to have peritoneal and peripancreatic infiltration and biliary duct dilatation with no obstruction. WBC came down and hydroxyurea and dexamethasone were discontinued. Ivosidenib was temporarily held and the patient improved with fluids, pressors, and antibiotics. On day 76, the patient resumed

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ivosidenib. The next day, she experienced a-fib with rapid ventricular response (RVR) and developed pulmonary edema. Ivosidenib was again interrupted and the a-fib improved with amiodarone. On day 79, the patient developed respiratory distress after a platelet transfusion and was transferred to the ICU with recurrent a-fib with RVR and acute pulmonary edema. The patient improved with non-invasive positive pressure ventilation and diuresis. On day 83, ivosidenib was resumed. CT showed ground glass areas in the lungs, worsening bilateral pleural effusion, pericardial effusion, intraperitoneal effusion, persistence of slight pancreatic tumefaction, but regression of the peripancreatic infiltration. On day 90, DS was considered resolved. On day 100, the patient had a grade 3 infiltrative lesion of the palate and underwent depacking surgery 3 days later. Treatment included broad antimicrobials. Digoxin was started for intermittent a-fib. The final dose of study drug was day 106. One day later, the patient had a grade 4 thrombotic stroke with complete loss of consciousness; platelets were 20,000. CT showed a complete left sylvian cerebrovascular accident. Two days later, the patient died due to the thrombotic stroke. This was assessed by the investigator as due to the underlying malignancy. However, as the bone marrow and peripheral blood blast count declined between study days 57 and 85 (last known value), the FDA could not rule out that ivosidenib contributed to the development of thrombotic stroke.

Subject (b) (6) This 72-year-old woman with R/R AML following 3 prior anti-cancer regimens and HSCT received 500 mg ivosidenib daily. She had a history of AKI, cardiac failure, hemorrhagic cystitis, cytomegalovirus (CMV) infection, GVHD of the skin, lung infection, and hypertension. Baseline WBC was 1.6 with 27% blasts and ANC 300. On study day 4, the patient developed grade 4 febrile neutropenia and non-specific infiltrates in the left lower lobe consistent with pneumonia. She received 10 days of Zosyn. CT scan showed signs of Aspergillosis, but she did not receive treatment given clinical improvement. On day 41, the patient was diagnosed with grade 2 leukocytosis (WBC 37.8) and was started on hydroxyurea. On day 78, she was hospitalized for dyspnea and fever and was found to have grade 4 pneumonia. WBC 94.5 with 18% blasts. CXR showed bilateral diffuse infectious pneumonia, but no infection was found. She was diagnosed with possible DS and dexamethasone was started. Hydroxyurea was increased. Her WBC started to come down, but her respiratory status gradually worsened and she was transferred to the ICU. She was treated empirically with broad antibiotics and developed AKI requiring dialysis. The last dose of study treatment was on day 80. The next day, the patient required mechanical ventilation. Two days later, the patient was diagnosed with grade 4 ARDS and tumor lysis syndrome. WBC was 63.5. On day 83, a bronchoalveolar lavage revealed numerous Enterococcus and Candida, which the investigator felt ruled out DS. WBC steadily came down to normal. The patient was diagnosed with Aspergillosis and voriconazole was started. Five days after the final dose of ivosidenib, the patient died due to ARDS, assessed as due to the underlying malignancy. However, bone marrow blasts declined from 45% on day 57 to 6% on day 85 and peripheral blasts declined from 38% to 1%. Also, ANC improved from 300 at baseline to 1200 on day 85. Thus, FDA could not accept that the cause of death was due to the underlying malignancy and believes that DS may have contributed. Although organisms were isolated, an inflammatory infiltrate associated

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with differentiation could have contributed to worsening of the underlying infection.

Subject (b) (6): This 62-year-old man with R/R AML after 3 prior anti-cancer regimens received 500 mg ivosidenib daily in the expansion cohort. Baseline medical history included bronchopulmonary Aspergillosis, lung infection, deep vein thrombosis, hypertension, and type 2 diabetes mellitus. The patient was hospitalized 11 days before his first dose for grade 3 febrile neutropenia, and 9 days prior, had an SAE of leukocytosis. Seven days prior, he had grade 4 Staphylococcal sepsis and grade 2 lung infection. WBC 96.6 with ANC 900. Treated with hydroxyurea. Six days prior, had grade 4 Escherichia sepsis and was admitted to the ICU. Blood cultures were positive for E. Coli and Staph and had concomitant C diff colitis. CT scan showed parenchymal lesions, but the patient was on room air. The patient was treated with multiple antibiotics and ultimately the febrile neutropenia, sepsis, and leukocytosis resolved (sepsis resolved with sequelae). Repeat blood cultures were negative. The patient, however, still had infiltrates suspicious for invasive pulmonary Aspergillosis. On day 1 of treatment, the patient had an ANC of 0. On day 7 of ivosidenib, the patient was diagnosed with a grade 3 pulmonary embolism (PE) and lung disorder. The patient was febrile, hypoxic, and polypneic and developed peripheral edema, moderate pericardial effusion, and bilateral pleural effusions. He had bilateral alveolar consolidations, mostly on the left (side of PE) with appearance of ground glass opacities in the left upper lobe compared to the prior scan. He was diagnosed with febrile bilateral pneumonia with chronic neutropenia and was treated with antibiotics. WBC 6.3 with ANC 0. Started tinzaparin for the PE and placed on 4L supplemental oxygen. On day 14, the patient developed grade 4 sepsis and lung disorder. WBC 1.7. Final dose of study treatment was day 15 and 1 day later the patient died of sepsis including pulmonary infection, assessed as due to the underlying malignancy. Of note, the patient had 97% marrow blasts at baseline and on day 8 had 83% peripheral blasts (96% peripheral blasts at baseline). Although the patient had a high burden of leukemia and possible pulmonary sepsis, no organism was identified. FDA could not rule out that the pre-existing process in the lungs may have been exacerbated by DS (concomitant fever, polypnea, pleuropericardial effusions, and peripheral edema).

Reviewer Comments: Three of the cases described above include manifestations of DS, although all the cases have other possible causes of death (e.g. infection, underlying malignancy). Due to the overlap in clinical manifestations, it is difficult to distinguish between differentiation syndrome and infection. It is also difficult to determine conclusively whether DS contributed to progression of a pre-existing or developing infection. Thus, the potential for fatal differentiation syndrome should be added to the labeling.

While there is no active comparator to determine the relative fatal toxicity of ivosidenib compared to chemotherapy combinations in general use, the early all-cause mortality for ivosidenib (7%) is modest for a relapsed/refractory population. Although statistical comparison of mortality in ivosidenib-treated patients with those reported in historical controls would not be appropriate, the early all-cause mortality observed in patients treated with ivosidenib compares favorably to the roughly 10-20% seen in patients treated with

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chemotherapy (Ramos et al. 2015).

Serious Adverse Events

A total of 137/179 (77%) of the subjects in the R/R AML SAS and 186/258 (72%) in the SAS experienced a treatment-emergent serious adverse event. The number of subjects who experienced an SAE in each SOC is shown in Table 46.

Table 46: Serious Adverse Events within 28 Days of Follow-Up

System Organ Class	R/R AML SAS (n=179)	SAS (n=258)
Any class	137 (77%)	186 (72%)
Infections and infestations	77 (43%)	95 (37%)
Blood and lymphatic system disorders	72 (40%)	95 (37%)
Respiratory, thoracic and mediastinal disorders	27 (15%)	34 (13%)
Cardiac disorders	19 (11%)	24 (9%)
Gastrointestinal disorders	19 (11%)	27 (10%)
General disorders and administration site conditions	15 (8%)	23 (9%)
Metabolism and nutrition disorders	15 (8%)	18 (7%)
Nervous system disorders	15 (8%)	20 (8%)
Investigations	14 (8%)	18 (7%)
Musculoskeletal and connective tissue disorders	8 (4%)	12 (5%)
Injury, poisoning and procedural complications	7 (4%)	9 (3%)
Renal and urinary disorders	7 (4%)	8 (3%)
Vascular disorders	6 (3%)	11 (4%)
Neoplasms, benign, malignant and unspecified	4 (2%)	7 (3%)
Skin and subcutaneous tissue disorders	4 (2%)	9 (3%)
Immune system disorders	2 (1%)	2 (1%)
Psychiatric disorders	2 (1%)	3 (1%)
Ear and labyrinth disorders	1 (1%)	2 (1%)
Hepatobiliary disorders	1 (1%)	3 (1%)

Source: FDA analysis
Note: Preferred terms were not grouped for this analysis

Among patients with R/R AML who received ivosidenib 500 mg daily (the R/R AML SAS), the most frequent (> 5%) SAEs without regard to attribution were: febrile neutropenia (n=41, 23%), sepsis (n=27, 15%), pneumonia (n=26, 15%), differentiation syndrome (n=18, 10%), leukocytosis (n=18, 10%), electrocardiogram QT prolonged (n=12, 7%), and dyspnea (n=9, 5%).

Of these serious adverse events in the R/R AML SAS, 36 were considered by the investigator to be at least possibly related to ivosidenib. The most frequent (≥ 2%) were: differentiation

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syndrome (n=16, 9%), electrocardiogram QT prolonged (n=10, 6%), and leukocytosis (n=5, 3%).

Reviewer comments: The most common SAEs reflect common consequences for patients with R/R AML, with the exceptions of differentiation syndrome, leukocytosis, and electrocardiogram QT prolonged. These three SAEs were the most common ones reported as at least possibly related to ivosidenib by investigators. However, as AG120-C-001 was a single arm trial, it is impossible to establish relatedness. Thus, all SAEs are presumed at least possibly related to ivosidenib.

Dropouts and/or Discontinuations Due to Adverse Effects

Overall, 112/258 (43%) of treated subjects had a dose interruption, dose reduction, or permanent discontinuation due to an adverse event (Table 47).

Table 47: Treatment Interruptions, Reductions, or Withdrawals

	R/R AML SAS (n=179)	SAS (n=258)
Interruption	68 (38%)	102 (40%)
Dose reduction	6 (3%)	12 (5%)
Withdrawal	24 (13%)	29 (11%)
Any of the above	76 (42%)	112 (43%)

Source: FDA Analysis

The most common TEAEs leading to interruption of ivosidenib are shown in Table 48 in decreasing order. The table includes only those events that occurred in > 2% of subjects with R/R AML who received 500 mg ivosidenib daily (R/R AML SAS).

Table 48: TEAE Leading to Dose Interruption

Preferred Term[1]	R/R AML SAS (n=179)	SAS (n=258)
Electrocardiogram QT prolonged	13 (7%)	17 (7%)
Sepsis	10 (6%)	11 (4%)
Febrile neutropenia	7 (4%)	10 (4%)
Pneumonia	7 (4%)	8 (3%)
Differentiation syndrome	6 (3%)	11 (4%)
Leukocytosis	5 (3%)	7 (3%)
Dyspnea	5 (3%)	7 (3%)

Source: FDA Analysis
[1] Includes grouped terms (see Appendix 13.5)

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The most common TEAE leading to dose reductions of ivosidenib are shown in Table 49 in decreasing order. The table includes only those events that occurred in > 1 subject on the study (SAS).

Table 49: TEAE Leading to Dose Reductions

Preferred Term[1]	R/R AML SAS (n=179)	SAS (n=258)
Electrocardiogram QT prolonged	2 (1%)	5 (2%)
Rash	0	2 (1%)

Source: FDA Analysis
[1] Includes grouped terms (see Appendix 13.5)

The most common TEAE leading to dose discontinuations of ivosidenib are shown in Table 50 in decreasing order. The table includes only those events that occurred in > 1 subject on the study (SAS).

Table 50: TEAE Leading to Discontinuations

Preferred Term[1]	R/R AML SAS (n=179)	SAS (n=258)
Sepsis	4 (2%)	5 (2%)
Fungal infection	3 (2%)	3 (1%)
Pneumonia	3 (2%)	3 (1%)
Guillain-Barre syndrome	2 (1%)	2 (1%)
Renal insufficiency	2 (1%)	2 (1%)

Source: FDA Analysis
[1] Includes grouped terms (see Appendix 13.5)

Reviewer comment: The relatively small number of reductions or discontinuations for adverse events in subjects with R/R AML who received 500 mg ivosidenib daily lends support to the tolerability of the proposed marketed dose and regimen. Dose interruptions for QT prolongation occurred in 7% of patients and differentiation syndrome, leukocytosis, dyspnea, and arrhythmia led to discontinuation in 3% of patients. Arrhythmia types included a-fib (n=3) and one each of ventricular tachycardia and ventricular arrhythmia. Guillain-Barre syndrome led to discontinuation in 2 patients. The majority of the remaining adverse events that required dose interruption, reduction, or discontinuation were related to events frequently observed in patients with AML (infections and other complications of prolonged cytopenias).

For the purposes of labeling, only adverse reactions will be listed, (b) (4)

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Significant Adverse Events

Differentiation Syndrome (DS)

The first case of possible DS was recorded on Study AG120-C-001 in June of 2014, approximately 3 months into the study. In Amendment 3 of the protocol, the Applicant added guidelines for management of DS, and in Amendment 4, they required that all events of DS be reported as SAEs. They later stipulated that any event of suspected DS of grade ≥ 2 be reported as an AE of special interest (AESI) within 24 hours.

Of the 179 subjects in the R/R AML SAS, there were 19 (11%) identified cases of DS, with 17 (9%) designated as at least possibly related to ivosidenib. Grade 3 DS occurred in 9 (5%) of patients, whereas the remaining 10 (6%) experienced grade 1-2 DS. The Applicant defined co-occurring AEs as AEs that overlapped with AEs of DS and began or worsened on or after the first dose of study treatment through 28 days after the last dose, and may be considered signs and symptoms of DS. Pertinent characteristics of the 19 cases of investigator-reported DS are as follows:

- Median time to onset 29 days (range 5-59 days)
- Co-occurring AEs included noninfectious leukocytosis (74%), peripheral edema (37%), pyrexia (26%), dyspnea and pleural effusion (21% each), hypotension (16%), AKI, fluid overload, hypoxia, pericardial effusion, pneumonia, pulmonary edema, rash, and TLS (11% each)
- Most (14, 74%) recovered without sequelae, 3 (16%) recovered with sequelae, and 2 (11%) did not recover
- CR responses seen in 5 (26%), CRi/CRp in 3 (16%), MLFS in 2 (11%), 8 had SD (42%), and 1 was not evaluated for response

In addition to investigator-reported cases of DS, FDA requested that the Applicant perform a review of DS using an algorithm based on the Montesinos et al scoring system (Montesinos et al. 2009). The Montesinos scoring system was originally devised based upon the observation of certain signs and symptoms characteristic of DS in patients with APL treated with all-trans retinoic acid (ATRA) (Frankel et al. 1992; Montesinos et al. 2009). This scoring system was later used to describe cases of DS in patients treated with the combination of ATRA and arsenic trioxide (Lo-Coco et al. 2013).

Per Montesinos et al (Montesinos et al. 2009), the diagnosis of DS is made according to the presence of the following signs and symptoms: (1) dyspnea, (2) unexplained fever, (3) weight gain greater than 5 kg, (4) unexplained hypotension, (5) acute renal failure, and (6) a chest radiograph demonstrating pulmonary infiltrates or pleuropericardial effusion. Patients with 4 or more of these features are classified as having severe DS and those with 2 or 3 features are considered to have moderate DS. No single feature is diagnostic. Patients with alternative

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explanations, such as pulmonary hemorrhage, septic shock, pneumonia, or cardiac failure are considered to not have DS. Deaths were attributed to DS when they occurred in patients with severe DS and were not explained by infection, hemorrhage, or other causes.

Reviewer comments: Although classically patients with septic shock, pneumonia, and cardiac failure are considered to not have DS, it is very difficult to make a clear distinction regarding etiology. Some patients treated with ivosidenib had several features of DS and recovering hematopoiesis in the setting of an identifiable pulmonary infection, indicating that DS may exacerbate an underlying pneumonia. This is supported by pre-clinical work showing that ATRA-differentiated cells traffic to sources of stromal cell derived factor 1, which is produced locally in the setting of pneumonia/acute lung injury (Petty et al. 2007; Zhou et al. 2010). Thus, FDA did not consider a concomitant infection as mutually exclusive with a diagnosis of DS.

FDA conducted an independent review of the safety data from the R/R AML SAS population from Study AG120-C-001 to identify subjects with possible DS based on the Montesinos et al approach (Table 51). FDA added investigator-reported IDH DS as a single criterion since investigators who reported this AE did not report the individual components of the syndrome. Furthermore, FDA added a category for multiple organ dysfunction syndrome.

Table 51: FDA Criteria for Identifying Cases of Possible DS

Part A: Report[1] of ≥ 1 of the following is considered a case of possible DS:	
Category	**Adverse event[2]**
Investigator-reported DS	IDH differentiation syndrome
Part B: Report[1, 3] of ≥ 2 of the following categories of events is considered a case of possible DS:	
Category	**Adverse event[2] or vital sign abnormality**
Dyspnea	Acute respiratory failure, cardiopulmonary failure,[4] cardio-respiratory distress, cough, dyspnoea, respiratory arrest, respiratory failure, respiratory distress[4]
Fever	Pyrexia, febrile neutropenia, or temperature ≥ 38.3°C
Weight gain	Capillary leak syndrome, fluid overload, fluid retention, generalized oedema, hydraemia, hypervolemia, oedema, oedema peripheral, or weight > 5 kg from baseline
Hypotension	Hypotension or systolic blood pressure < 90 mmHg
Acute renal failure	Acute kidney injury, anuria, cardiorenal syndrome, hepatorenal failure, prerenal failure, renal failure, renal failure acute,[4] renal impairment, renal injury, or creatinine (µmol/L) > 26.52 µmol/L above baseline or 1.5 x above baseline[4]
Pulmonary infiltrates or pleuropericardial effusion	Acute pulmonary oedema, acute respiratory distress syndrome, non-cardiogenic pulmonary edema, pulmonary congestion, pulmonary oedema, pleural effusion, pericardial effusion, acute interstitial

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	pneumonitis, acute lung injury, atypical pneumonia, lower respiratory tract infection, lower respiratory tract inflammation, lung infection, lung infiltration, pneumonia, pneumonitis, pulmonary toxicity
Multiple organ dysfunction	Multiple organ dysfunction syndrome

Source: FDA analysis
[1] Only data points occurring in the first 90 days of therapy were included
[2] All adverse event terms are listed as preferred terms
[3] A criterion from Part B must have a start date within 7 days of another criterion from Part B to be included as a case of possible DS
[4] Items that varied from the analysis FDA requested from the Sponsor at the pre-NDA meeting. Cardiopulmonary failure was incorrectly included under both "dyspnea" and "pulmonary infiltrates…" FDA assigned this term to "dyspnea." Respiratory distress and renal failure acute were added by FDA during the review. FDA requested creatinine > 0.3 mg/dL or 1.5-2.0x baseline at the pre-NDA meeting, but converted to units submitted with the review and selected for values above 1.5 x baseline.

Using the requested approach, the Applicant identified 69/179 (39%) patients with the Montesinos algorithm in the R/R AML SAS, of which they determined 30 (17%) to be at least possibly related to DS. Another 3 cases were found to be indeterminate due to insufficient information.

FDA's analysis using the Montesinos approach (results provided by Flora Mulkey, MS) identified two additional patients and the clinical reviewer identified another patient that met the Montesinos criteria based information in a death narrative (Subject (b) (6)). Thus, FDA identified 72/179 (40%) with the Montesinos algorithm. FDA reviewed narratives from all 72 patients and 34 were considered to at least possibly have DS (Table 52). Thus, the true incidence of DS in patients with R/R AML on AG120-C-001 appears to be 34/179 (19%).

Table 52: Possible Cases of DS in the R/R AML SAS

Subject	Day(s)	Severity[1]	Fatal	Leukocytosis[2]	Applicant Assessment	Alternative explanation
(b) (6)	39	Severe	Yes	Yes	Possible	Pneumonia
	11	Moderate	No	No	Possible	AML
	15	Moderate	No	Yes	Possible	None
	1	Moderate	No	Yes	Possible	Infection
	8	Moderate	No	Yes	Possible	Pneumonia
	17 & 38	Moderate	No	Yes	Possible	None
	22	Moderate	No	Yes	Possible	Infection, AML
	15	Moderate	No	Yes	Unlikely	AML
	2	Severe	No	Yes	Unlikely	Pneumonia
	21	Unknown	No	Yes	Possible	None
	24	Moderate	No	Yes	Possible	None
	38	Moderate	No	Yes	Possible	None
	23	Moderate	No	Yes	Possible	PE
	19	Severe	No	Yes	Unlikely	Infection, AML

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Subject	Day(s)	Severity[1]	Fatal	Leukocytosis[2]	Applicant Assessment	Alternative explanation
(b) (6)	53	Moderate	No	No	Possible	Pneumonia
	15	Moderate	No	Yes	Possible	None
	55	Moderate	No	Yes	Possible	Pneumonia
	15	Moderate	No	Yes	Possible	None
	43	Moderate	No	No	Unknown[5]	None
	24	Moderate	No	No	Possible	Pneumonia
	59	Unknown	No	Yes	Possible	None
	43	Moderate	No	Yes	Possible	None
	15 & 37	Moderate	No	Yes	Possible	None
	13 & 30	Moderate	No	Yes	Possible	None
	58	Moderate	No	Yes	Possible	None
	78	Severe	Yes	Yes	Unknown[5]	Pneumonia
	47	Severe	No	No	Possible	Pneumonia
	13 & 28	Moderate	No	Yes	Possible	None
	15	Moderate	No	Yes	Possible	None
	26	Moderate	No	Yes	Possible	None
	7	Moderate	No	No	Unknown[5]	Pneumonia, PE
	47	Moderate	No	No	Unlikely	None
	15	Severe	No	Yes	Possible	Pneumonia
	7	Moderate	No	Yes	Possible	AML

Source: FDA analysis
Abbreviations: AML, acute myeloid leukemia; ARDS, acute respiratory distress syndrome; DS, differentiation syndrome
[1]Per scoring system reported by Montesinos et al (Montesinos et al. 2009)
[2]WBC > 10 x 10^9/L or an AE of leukocytosis, hyperleukocytosis, or white blood cell count increased within 7 days of the first DS event
[3]Cases reported by investigators
[4]Patients with multiple episodes of DS. Defined as subsequent cases of DS separated by > 14 days.
[5]Subject not picked up in Applicant's query, but was picked up by FDA's query.

Of the 34 possible cases of DS, 9 (26%) had multiple episodes of DS. As for severity, six (18%) cases were severe and 26 (76%) were moderate. In two investigator-reported cases of DS, there were insufficient details in the narrative reports to determine severity. Cases with at least one grade 3 or higher AE occurred in 23 (68%) subjects. Two of 34 cases were fatal. Patients had concomitant leukocytosis in 27 (79%) of cases. Median time to onset of the first occurrence of DS was 18 days (range 1-78). Six of 34 (18%, 95% CI 7-35%) patients had a CR response, indicating that the occurrence of DS is not predictive of response.

Reviewer comments: Note that there was 5 CRs (26%, 95% CI 10-51%) out of the 19

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investigator-reported cases of DS. Again, there did not appear to be a significant predictive effect of having DS on response.

It is notable that all but one of the investigator reported cases of DS were associated with leukocytosis. Thus, even though leukocytosis is not a requirement for a diagnosis of DS, many clinicians may fail to consider the diagnosis in the absence of leukocytosis.

As seen in Table 52, there were 7/34 (21%) cases where FDA either disagreed with the Applicant's assessment that DS was unlikely (n=4) or FDA found additional cases of DS not found by the Applicant (n=3). These cases are described below:

Subject (b) (6) This 61-year-old woman with R/R AML following 3 prior treatment regimens including intensive and non-intensive therapies received 500 mg ivosidenib daily in the dose expansion cohort. The WBC count on day 1 was 1.1. On day 15, the patient presented with febrile neutropenia and WBC count rose to 56.5. The patient had 68% peripheral blasts, which was slightly down from 73-80% at baseline. ANC was 890, up from 30 at baseline. The patient was treated with empiric antibiotics, but cultures were all negative. She experienced a grade 1 increase in creatinine. Her fever curve came down on day 17 and was discharged home. The Sponsor cited alternative possible causes of febrile neutropenia and disease progression, assessing DS as unlikely. However, FDA could not rule out that the fever and AKI in this case could have reflected DS.

Subject (b) (6): This 53-year-old woman with R/R AML following 1 prior intensive therapy regimen and HSCT received 500 mg ivosidenib daily in the dose expansion cohort. Her WBC count on day 1 was 6.8 with 68% blasts and ANC 136. On day 7, WBC rose to 34 with 56% blasts and ANC 1700. Day 8, the patient was hospitalized for grade 2 pneumonia with right sided rib pain, low grade fever, shortness of breath, and lower extremity edema. CT chest showed consolidation and mild pericardial effusion. About 3 weeks later, the patient transferred facilities and was reportedly asymptomatic and afebrile at that time. However, chest x-ray showed evidence of multilobar patchy opacities, and so the patient was started on antibiotics. Cultures were negative. The Sponsor cited the possible alternative cause of pneumonia and the resolution without the use of corticosteroids in assessing DS as unlikely. However, FDA could not rule out that the dyspnea, fever, edema, and chest imaging findings were related to DS, particularly in the setting of her increased WBC count prior to the event.

Subject (b) (6) This 77-year-old woman with R/R AML following 1 prior investigational therapy received 500 mg ivosidenib daily on the dose escalation cohort. On day 1, her WBC count was 3.1 with ANC 0 on hydroxyurea. On day 19, she presented with complaints of fever, diarrhea, chills, and hypotension. She was admitted for grade 4 sepsis, requiring norepinephrine. Her WBC count increased to 56.7 with 46% blasts. Creatinine was up to 1.35 and CXR showed a left basilar opacity. On day 20, she received rasburicase. All cultures returned negative. Ivosidenib was interrupted on day 20 due to sepsis. Her AKI was presumed

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to be related to tumor lysis syndrome. On day 22, the CXR showed improvement in bilateral lower lobe opacities. Ivosidenib was resumed on day 23. Her last dose of treatment was on day 26 due to progressive disease. This case was confounded by multiple factors, including her disease and tumor lysis syndrome. However, given that a source of infection was not identified, DS could not be ruled out as a possible cause of the fever and hypotension.

(b) (6): This 64-year-old man with R/R AML following 2 prior therapies including HSCT received ivosidenib 500 mg daily on the dose expansion cohort. He had a history of Klebsiella sepsis, lung lobectomy, chronic obstructive pulmonary disease, obstructive sleep apnea, and osteonecrosis. On day 1, his WBC count was 3.6. On day 35, the patient was hospitalized for grade 3 failure to thrive, febrile neutropenia, and grade 4 pancytopenia. Temperature was 100.8. Initial CXR was normal and cultures were negative. The patient had recurrent fevers and was found to have an infection involving his teeth. Due to delirium, a CT of the head was done and was unremarkable. On day 41, a repeat CXR showed new patchy airspace opacities bilaterally concerning for pneumonia. He received dexamethasone for 3 days as well as Lasix. He had recorded side effects of grade 2 fluid overload on day 43 and grade 2 respiratory failure on day 46. Ivosidenib was interrupted on day 47 due to the AEs and was resumed at 500 mg after 3 days. Given lack of an alternative explanation for the CXR findings, dyspnea, and fluid overload, FDA could not rule out a diagnosis of DS.

Subject (b) (6): Case described in detail in death narratives under Section “Deaths” above. In short, this was a 72-year-old woman with R/R AML following 3 prior anti-cancer regimens and HSCT who received 500 mg ivosidenib daily. On day 78, she was hospitalized for dyspnea and fever and was found to have grade 4 pneumonia with WBC 94.5 and 18% blasts. No infection was found and she was given dexamethasone for possible DS. Her respiratory status worsened and she was transferred to the ICU. She developed AKI requiring dialysis. The last dose of study treatment was on day 80. The next day, she required mechanical ventilation. Two days later, she was diagnosed with grade 4 ARDS and tumor lysis syndrome. On day 83, a bronchoalveolar lavage revealed numerous Enterococcus and Candida. WBC steadily came down to normal. Five days after the final dose of ivosidenib, the patient died due to ARDS, assessed as due to the underlying malignancy. However, bone marrow and peripheral blood blasts declined from day 57 to day 85 and ANC improved from 300 at baseline to 1200 on day 85. Thus, FDA could not accept that the cause of death was due to the underlying malignancy and believes that DS may have contributed. Although organisms were isolated, an inflammatory infiltrate associated with differentiation could have spurred an underlying infection.

Subject (b) (6): Case described in detail in death narratives under Section “Deaths” above. In short, this was a 62-year-old man with R/R AML after 3 prior anti-cancer regimens who received 500 mg ivosidenib daily in the expansion cohort. The patient was hospitalized 11 days before his first dose for infection and leukocytosis, including bacteremia and pneumonia. He was treated with hydroxyurea and multiple antibiotics and ultimately recovered, but still had infiltrates suspicious for invasive pulmonary Aspergillosis. On day 7 of ivosidenib, the patient

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was diagnosed with a grade 3 PE and lung disorder. He was febrile, hypoxic, polypneic, and developed peripheral edema, moderate pericardial effusion, and bilateral pleural effusions. He had bilateral alveolar consolidations with appearance of ground glass opacities in the left upper lobe. He was diagnosed with bilateral pneumonia and was treated with antibiotics. WBC 6.3 with ANC 0. On day 14, the patient developed grade 4 sepsis and lung disorder. Final dose of study treatment was day 15 and 1 day later the patient died of sepsis including pulmonary infection, assessed as due to the underlying malignancy. The patient had 96% peripheral blasts at baseline and on day 8 had 83% peripheral blasts. Although the patient had a high burden of leukemia and likely pulmonary sepsis, no organism was identified. FDA could not rule out that the pre-existing process in the lungs may have been exacerbated by DS (i.e. concomitant fever, polypnea, pleuropericardial effusions, and peripheral edema). DS may have contributed to the patient's ultimate death, but FDA does not consider DS to be the primary cause of death in this patient given the pre-existing infectious issues.

Subject (b) (6): This 77-year-old woman with R/R AML following 3 prior therapies received ivosidenib 500 mg daily on the dose escalation cohort. She had a history of breast cancer and melanoma. On day 47, she had recorded AEs of grade 1 dyspnea and pulmonary edema. There was no description in the narrative for this time. She had grade 1 hypoxia 6 days prior and labs that indicate possible differentiation. On day 47, her WBC count rose from 0.8 on day 33 to 2.1, ANC rose from 160 to 1434, and peripheral blood blasts declined from 4% to 0%. Furthermore, marrow blasts declined from 59% on day 33 to 2% on day 60. Thus, in the absence of an alternative etiology for her dyspnea and pulmonary edema, this at least possibly represents a milder case of DS.

There were two cases (Subjects (b) (6)) where FDA disagreed with cases of investigator-diagnosed DS. Both subjects were given the diagnosis of DS based on a rise in WBC count. However, the narratives describe that both patients were completely asymptomatic. Thus, FDA considers that Subjects (b) (6) had AEs of ivosidenib-induced leukocytosis, but not DS. Subject (b) (6) had an episode of hypotension and AKI on day 57 (17 days after the investigator reported DS) that was picked up by the Montesinos algorithm, but FDA felt this was unlikely to represent DS as the patient was in a marrow remission at the time.

There was one case (Subject (b) (6)) picked up by the Montesinos algorithm where FDA disagreed with the Applicant's assessment of possible DS. The patient had mild AKI and weight gain in the setting of grade 4 Legionella infection, intubation, and recurrent atrial fibrillation.

In summary, investigators reported DS in 19/179 (11%) of patients, the Applicant assessed 30 (17%) to be at least possibly related to DS, and FDA assessed 34 (19%) to be at least possibly related to DS. However, given the complicated clinical nature of the diagnosis and multiple confounding factors, (b) (4) It will be essential to list the clinical features of the syndrome and to include appropriate management guidelines.

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Reviewer comments: Given the clinical nature of the DS diagnosis and the frequent comorbidities and infections seen in patients with R/R AML, it is nearly impossible to ascribe a precise incidence of this AE. The 40% of patients picked up by the algorithm clearly overestimates the incidence of DS and the 11% identified by investigators most likely underestimates the incidence. The true incidence is likely closer to 19%, particularly given that the Applicant adjudicated 17% cases that were at least possibly related to DS.

After carefully reviewing all of the cases, some distinct patterns emerged. The drug clearly has a differentiating effect and many patients had occurrence of symptoms around the same time that their WBC counts started to rise. Counts came down appropriately with hydroxyurea and steroids appeared to control the inflammatory process. Some patients experienced two episodes of DS, indicating that ivosidenib did not fully eliminate the differentiating clones. The lack of a relationship between the diagnosis of DS and response also illustrates the incomplete nature of the differentiating effect of ivosidenib in most patients.

It will be important for physicians to balance the risks and benefits of this medication in patients who develop DS since pushing through a severe episode of DS may lead to life-threatening consequences without a high degree of benefit. Thus, the label should be conservative with regards to holding therapy and instituting immediate therapy with steroids plus or minus hydroxyurea as soon as DS is suspected.

As over half of the patients with possible DS as determined by the FDA's algorithm (and slightly under half when considering investigator-reported DS) had Grade 3 or higher events, and there were at least 2 fatal cases of DS on AG120-C-001, I recommend that the USPI include a boxed warning for differentiation syndrome.

<u>QT interval prolongation</u>
QT interval prolongation is an ADR that has been associated with ivosidenib, based on both nonclinical and clinical safety findings. The applicant found that QT interval prolongation occurred in 61/258 (24%) patients in the SAS and 46/179 (26%) in the R/R AML SAS. Grade 3-4 QTc prolongation occurred in 23 (9%) of patients in the SAS and in 18 (10%) of patients in the R/R AML SAS. As per the section above on Dropouts and/or Discontinuations Due to Adverse Events, 7% of subjects in the SAS had a dose interruption and 2% had a dose reduction due to QTc prolongation. No subjects discontinued ivosidenib due to QTc prolongation.

The Applicant conducted an analysis of ECG intervals in all subjects treated on Study AG120-C-001 (n=258). The results of the applicant's analysis are shown in Table 53. They concluded that QT interval prolongation is an ADR associated with the administration of ivosidenib.

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Table 53: Maximum Postbaseline Absolute QTcF Interval

QTcF Category	R/R AML SAS (N=179)	SAS (N=258)
QTcF maximum postbaseline value		
≤ 450 msec	64 (36%)	90 (35%)
> 480 to ≤ 480 msec	78 (44%)	110 (43%)
> 480 to ≤ 500 msec	19 (11%)	35 (14%)
> 500 msec	18 (10%)	23 (9%)
QTcF maximum increase from baseline		
≤ 30 msec	78 (44%)	112 (43%)
> 30 to ≤ 60 msec	77 (43%)	110 (43%)
> 60 msec	24 (13%)	36 (14%)

Source: Applicant's ISS – 90 Day Safety Update, Section 2.1.8.2.6 (Tables 22 and 23) located in Module 5.3.5.3 and dated 22 March 2018.

Ivosidenib is a CYP3A4 substrate as per the results of their drug-drug interaction study AG120-C-007. Thus, concomitant use of ivosidenib with moderate/strong CYP3A4 inhibitors may include ivosidenib concentrations, which may increase the risk of QT interval prolongation (see Section 6 Clinical Pharmacology for details).

FDA performed an analysis of grade 3 and higher AEs by PT within the SMQ (broad) for torsades de pointes/QT prolongation. Of the 258 patients in the SAS population, 28 (11%) had a grade 3 or higher AE in this SMQ. AEs included QT prolongation (n=23), syncope (n=3), cardiac arrest (n=2), cardio-respiratory arrest (n=1), ventricular tachycardia (n=1), and ventricular arrhythmia (n=1).

The cases of cardio-respiratory arrest (Subject (b) (6) and ventricular arrhythmia (Subject (b) (6)) were fatal:

1. Subject (b) (6): Occurred on day 57, 4 days after the final dose of ivosidenib and was deemed to be related to the underlying malignancy. This subject only had one recorded elevation in QTc that was grade 1 on day 25.

2. Subject (b) (6): This case is described above in detail under the death narratives. Briefly, this was an 83-year-old woman with R/R AML on concomitant fluconazole who received 500 mg ivosidenib daily. Her baseline QTc was normal (430 msec), but her 4-hour postdose QTcF was 452 msec. On day 20, the patient experienced syncope. The next day, she had an SAE of ventricular fibrillation arrest (grade 4) and was resuscitated. She was intubated and the family opted for hospice care. Ivosidenib was stopped after day 21. Two days after the last dose, the patient died due to grade 5 ventricular arrhythmia. FDA could not rule out the possibility that ivosidenib contributed to the development of the ventricular arrhythmia.

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Reviewer comments: Subject (b) (6) had complicating features of a UTI, anorexia, and malnutrition, but FDA could not rule out the possibility that ivosidenib contributed to the development of the fatal ventricular arrhythmia.

Two cases of grade 4 cardiac arrest were in subjects (b) (6):

1. Subject (b) (6): This was a 60-year-old woman with R/R AML with a history of anxiety, asthma, hypertension, and insomnia on the expansion phase who received 500 mg ivosidenib daily. On day 113, the patient experienced prolonged QTc grade 3 while on fluconazole. Treatment was temporarily interrupted, but resumed the next day when QTc prolongation resolved. Ivosidenib was stopped on day 124 due to AKI grade 4 and altered mental status. Imaging scan of the head was normal and colonoscopy showed CMV colitis. Cardiac arrest occurred 11 days after the last dose. The patient had ventricular fibrillation with possible torsades, but had return of spontaneous circulation after 3 shocks. Of note, she received a dose of Zofran the day before the code. She was transferred to ICU intubated and had a full complex grade 2 seizure. She was placed on a cooling protocol and ultimately extubated. 24 days after last dose of ivosidenib, the patient died due to PD. AKI and altered mental status were ongoing at time of death.

2. Subject (b) (6): This was a 78-year-old woman with R/ R AML with a history of AKI, a-fib, chronic obstructive pulmonary disease, hepatic cirrhosis, peripheral venous disease, and hypertension who received 500 mg ivosidenib daily on the expansion portion of the trial. On day 72, she was found to have a left pleural effusion in the setting of a hospitalization for facial bones and femur fracture following a mechanical fall at home. She underwent an open reduction and internal fixation for the femur fracture on day 81. Five days after the last dose of ivosidenib (day 89), the patient had a grade 4 pleural effusion, pneumothorax, respiratory failure, grade 3 septic shock, a-fib with RVR, and moderate cardiomegaly. She had 0% blasts in the peripheral blood and ANC was 832. She was diagnosed with a UTI. 13 days after the last dose of ivosidenib, the patient had severe dyspnea and experienced cardiac arrest. Return of spontaneous circulation was achieved. The cause of the arrest was deemed to be hypoxia secondary to the large pleural effusion versus empyema or malignant effusion. A bronchial wash returned MRSA. QTcF was normal. The patient was ultimately discharged to a nursing facility. This was thought to most likely represent post-surgical complications.

Reviewer comments: The case of Subject (b) (6) is concerning given that the patient had grade 3 QT prolongation while on ivosidenib and concomitant fluconazole. The later occurrence of torsades occurred 11 days after the last dose and one day after a dose of Zofran, but it is possible that some amount of ivosidenib could have remained in the system at the time.

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There was one case of grade 3 ventricular tachycardia:

1. Subject (b) (6): This was a 72-year-old man with R/R AML and history of diastolic dysfunction and systolic dysfunction (EF 38-57%) treated with 3 prior anti-cancer regimens (intensive and non-intensive). Four days before starting treatment, the patient was hospitalized for Aspergillus grade 3. ECG showed premature atrial contractions and QTc 469. On study day 1, the patient had QTc prolonged grade 3 as well as multiple ECG changes (e.g. anterolateral ischemia, occasional premature ventricular contractions, marked sinus arrhythmia, a-fib). Two days later, biopsy was positive for Aspergillus and he began treatment with micafungin. QTc prolongation resolved on study day 16. Treatment was stopped after day 21. The next day, he had a 22-beat run of asymptomatic non-sustained ventricular tachycardia, which spontaneously returned to normal sinus rhythm. Prior to this episode, he was febrile to 104. The patient was placed on supportive care given his poor physical condition, which included worsening metabolic and organ dysfunction. Aspergillus PNA was ongoing at the time of death on day 40.

Reviewer comments: This case demonstrates that QTc prolongation may be exacerbated and complicated in the setting of patients with baseline cardiac dysfunction.

The median time from the first dose of ivosidenib to the first Grade 2, 3, and 4 AEs within the torsades de pointes/QT prolongation SMQ was 29 days (range 1-505 days). The highest incidence of grade 2, 3, or 4 AEs occurred within the first 30 days from the first dose (22, subjects, 60%).

Reviewer comment: I agree with the IRT reviewer that there is evidence to suggest that ivosidenib has the potential to delay ventricular repolarization. I agree to include QTc prolongation in Warnings and Precautions in the PI. I recommend adding that life-threatening arrhythmias have occurred.

<u>Hyperleukocytosis</u>
The FDA identified 92 events of leukocytosis in 68 subjects (38%) in the R/R AML SAS, and noted that Grade ≥ 3 leukocytosis was reported in 15 subjects (8%). Five subjects (3%) had a temporary interruption of ivosidenib for leukocytosis, but none permanently discontinued because of leukocytosis. Results were similar in the SAS.

The FDA reviewed all reported adverse events of Grade ≥ 3 leukocytosis in the R/R AML SAS, including laboratory data and subject narratives (where provided). Of the 15 events, the FDA found documentation of a WBC > 100 x 10^9/L in 9 patients. There were no fatal events of leukocytosis. Most events of grade 3 or higher leukocytosis were reported in conjunction with possible DS (n=6) or disease progression (n=5). The others were either isolated events (n=3) or in the context of infection (n=1). Of the 15 subjects with Grade ≥ 3 leukocytosis, 4 (27%) went

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on to have a CR or CRh, of which 3 had a CR.

The FDA identified one additional subject in the R/R AML SAS with reported treatment-emergent WBC > 100 x 10^9/L that did not have leukocytosis reported as a AE. Subject (b) (6) had hyperleukocytosis on day 21 in the setting of DS and later achieved a CR on day 127.

In the entire SAS, only two patients required leukapheresis (1%). Subject (b) (6) had R/R AML and was treated on the dose escalation phase at 300 mg daily. He experienced a jump in his WBC to 80 on day 3, which was associated with hypoxia. Treatment with leukapheresis was performed and his hydroxyurea was increased. Leukapheresis was repeated the following day, after which his WBC returned to the normal range. The second patient, Subject (b) (6) had R/R AML and was treated on the dose expansion phase. On day 8, his WBC rose to 67 with 85% blasts and underwent leukapheresis the following day. Resolved with sequelae day 13. Day 22, WBC 54.6 with 86% blasts (49% at baseline). Final dose of study treatment was on day 21 due to PD. 16 days later, died of PD.

Reviewer comment: The events of leukocytosis appear to generally be related to the occurrence of DS or the underlying malignancy in the context of disease progression. There have been cases of leukocytosis in the absence of clinical signs and symptoms of DS, which likely indicates a manifestation of differentiation without the clinical syndrome. Leukocytosis is an expected event in patients with AML, and does not appear to be a serious or life-threatening event related to treatment with ivosidenib that warrants a warning in the USPI, outside of the context of DS. However, specific dose modification and management guidelines are warranted.

Tumor lysis syndrome

The FDA identified 15 events of tumor lysis syndrome (TLS) in 14 subjects (8%) in the R/R AML SAS. Grade 3 or higher events of TLS occurred in 11 (6%) of patients and none led to permanent discontinuation. Only one subject temporarily interrupted ivosidenib for TLS. Findings were similar in the SAS.

To further understand the relationship between ivosidenib and TLS, the FDA reviewed the events of TLS, including narratives (where available) and compared the date of TLS onset to dates of reported WBC counts. In all but three subjects, TLS occurred in the setting of leukocytosis, some in the setting of PD (n=4) and/or DS (n=4).

Reviewer comment: The frequency and severity of tumor lysis syndrome is similar to what would be expected in the underlying population. In the case of ivosidenib, it appears to be occurring either as a consequence of leukocytosis/DS or disease progression. TLS does not appear to be a serious or life-threatening event related to treatment with ivosidenib that warrants a warning in the USPI.

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Polyneuropathy

The Applicant considers sensorimotor neuropathy to be a potential risk associated with ivosidenib based on safety findings, including 2 SAEs of Guillain-Barre syndrome (GBS) and 1 SAE of lumbosacral plexopathy. All 3 were assessed as treatment-related, but no clear mechanism of action has emerged. Case narratives are summarized below.

1. Subject (b) (6): 60-year-old woman with R/R AML following 2 prior intensive anti-cancer regimens and history of MDS, rectal cancer status post radiation, proctitis, asthma, dysarthria, and tremor treated with ivosidenib 500 mg daily on the expansion phase. On day 9, the patient experienced grade 1 vomiting, grade 2 tremor, dysarthria, and hemiface dysesthesia. Study treatment was interrupted, but resumed the following day. On day 15, the patient was hospitalized for grade 3 asthenia. On day 16, she experienced grade 2 GBS. She had a "sensitive neuropathy peripheral and deep" with tingling in the feet, extremity, and calf. The patient decided not to take her ivosidenib that day. Two days later, she had paresthesia involving her arms, legs, hands, and feet. MRI of the head was performed due to the recent onset of cerebellar syndrome in the context of AML refractory to chemotherapy. Results were unremarkable. Meanwhile, blood cultures were positive for Corynebacterium tuberculostearicum. On day 18, the she experienced grade 2 peripheral sensory neuropathy and grade 3 ataxia. She was also diagnosed with a nonserious AE of vitamin B12 deficiency (157 ng/L [NR: 180-914 ng/L]). Electromyography (EMG) showed abnormalities consistent with polyradiculoneuritis and nerve conduction delay in the lower limbs. She could not hold a cup, had difficulty standing, and could not walk alone because of the sensory deficit (no motor weakness). The patient was treated with vitamin B12, vitamin B1, and pyridoxine. Cerebrospinal fluid (CSF) analysis showed no evidence of malignancy, infection, or abnormal protein fractions. Her last dose of study treatment was on day 19, after which it was discontinued due to the event of GBS. Afterwards, the patient experienced grade 3 leukocytosis with significant peripheral blasts. She was treated with hydroxyurea and received intravenous immunoglobulin for the GBS. 21 days after the last dose of ivosidenib, the patient died of PD with asthenia, peripheral sensory neuropathy, ataxia, and GBS ongoing at the time of death.

2. Subject (b) (6): 82-year-old woman with R/R AML following 2 prior non-intensive anti-cancer regimens with history of psoriatic arthropathy who received ivosidenib 500 mg daily on the expansion phase. On day 31, bone marrow showed persistent AML. On day 71, peripheral sensory neuropathy and peripheral motor neuropathies were recorded as toxicities. Her last dose of study therapy was on day 71. Two days later, she was admitted for peripheral motor and sensory neuropathy. She could not stand without maximum assistance. She reported progressive distal extremity numbness and weakness over the last 1-2 weeks. Lab tests, including B12 were normal. Strength was slightly reduced in the triceps, biceps, wrist, hand muscles, iliopsoas, hamstrings, quadriceps, dorsiflexion, and plantar flexion bilaterally. There was diffuse muscle

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atrophy and reduced sensation up to the knees bilaterally. She had no vibration sense at the toes, ankles, or knees bilaterally. Neurologic exam revealed distal symmetric quadriparesis and large fiber sensory loss with hyporeflexia. This was most concerning for acute inflammatory demyelinating polyradiculoneuropathy (GBS). MRI of the brain and neck showed an old meningioma. There was no evidence of cord compression. Lumbar puncture showed few blasts (thought to be due to a traumatic tap), negative cytology, slightly elevated glucose and protein (73 and 49, respectively), and no evidence of infection or multiple sclerosis. She received 5 days intravenous immunoglobulin with no improvement. The investigator noted her symptoms correlated with a rise and normalization in neutrophils and thought that perhaps cytokine release as part of differentiation stimulated her immune system. About a month later, the patient reported improvement in her neuropathy. She died 74 days after the final dose of study treatment due to PD.

3. Subject (b) (6): 72-year-old man with untreated AML and history of MDS, acute kidney injury, cardiac failure, prostate cancer status post radiotherapy, peripheral neuropathy, and obstructive sleep apnea who received 500 mg ivosidenib on the expansion phase. On day 55, the patient developed 9/10 lower back pain and inability to walk. Two weeks earlier, he had several hours of back pain that was relieved with a heat pack. After a week, he developed gradual onset low back pain associated with right thigh pain and gradual lower extremity weakness that progressed to a complete inability to walk. He also had worsening numbness on the top and sole of his foot. Strength was reduced in the knees and dorsi/plantar flexion, worse on the right. There was decreased distal sensation to light touch on the right greater than left lower extremity. Reflexes were absent in the lower extremities. He was started on dexamethasone and pain medications. MRI showed no cord abnormalities, but showed diffuse enhancement of the lumbosacral paraspinous musculature and bilateral gluteus, iliacus, and psoas muscles. Also, there was abnormal enhancement of bilateral exiting L3, L4, and L5 nerve roots as they coursed near these muscles. CSF showed no WBCs, glucose 76, and protein 109. Cytology showed a single immature monocyte with blast-like characteristics. Infectious studies were negative. EMG showed diffuse action potential slowing with evidence of neurogenic changes with axonal loss in the lower extremities. It was hard to differentiate between lumbar polyradiculopathy, diabetic neuropathy, and acute or subacute sensorimotor polyneuropathy. Bone marrow showed a decrease in blasts from 73% to 2.5%. MRI neurogram showed abnormal contrast enhancement and edema of several lumbar nerves and lumbosacral plexus, thought to be consistent with leukemic, toxic, or idiopathic/inflammatory plexopathies. There was an additional signal abnormality of pelvic muscles (right more than left), considered likely early denervation. The patient started treatment with immunoglobulin, but had no improvement. Testing for IgG GD1a antibody was negative, excluding GBS and motor neuropathy. The patient was started on prednisone for possible DS affecting the nervous system with subjective improvement. Treatment was only temporarily held on day 55 for 2 days. His final dose

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was day 123 and permanently discontinued due to proceeding to a bone marrow transplant. The event of lumbosacral plexopathy was reported to be ongoing at last follow-up. The patient's best response was a CRp.

Reviewer comments: Based on the three cases of serious polyneuropathies, 2 of which retained the diagnosis of GBS, I agree with the Applicant to include GBS in Warnings and Precautions in the PI.

Hemophagocytic Lymphohistiocytosis (HLH)

On study AG120-C-001, there were 2 events of "histiocytosis haematophagic." HLH is a rare and life-threatening disorder of excessive immune activation characterized by fever, hepatosplenomegaly, cytopenias, lymphadenopathy, rash, icterus, and neurologic symptoms (Akyay et al. 2013). The disease has a familial form and a secondary form, which is associated with infections, autoimmune diseases, immune deficiencies, metabolic diseases, drugs, or malignancies.

HLH associated with AML is rare and mostly reported at the case report level (Akyay et al. 2013; Wang et al. 2010; Yamazaki et al. 2011). However, a recent series suggested that the condition may be more common in AML, yet is underrecognized (Delavigne et al. 2014). This single institution study showed that 32/343 (9%) patients treated with intensive chemotherapy for AML developed HLH. An important limitation was a lack of adherence to HLH-2004 diagnostic guidelines.

Given 2 cases of HLH on study AG120-C-001, the incidence of HLH in both the R/R AML SAS and the SAS was 1%. One was grade 4 and one was grade 2. Brief narratives are summarized below:

Subject (b) (6): 36-year-old woman enrolled to the dose escalation portion of AG120-C-001 had a diagnosis of R/R AML and baseline ECOG of 2, having received 5 prior anti-cancer regimens. Of note, she was negative for the IDH1 mutation. She received only 2 doses of ivosidenib at 500 mg daily, and then presented to the ER on study day 3 due to complaints of weakness and fatigue that resulted in multiple falls. CT of the head showed brain parenchymal hemorrhage, subarachnoid hemorrhage, and subdural hematoma. Two days after her last dose of ivosidenib, a brain MRI revealed multifocal sites of brain parenchymal leukemic infiltration and suspected dural leukemic infiltration. Three days later, lumbar puncture (LP) results revealed malignant cells in the cerebrospinal fluid consistent with CNS leukemia. Results from repeated LPs over the next 2 weeks showed persistent CNS leukemia, despite intrathecal cytarabine administration. Her condition continued to deteriorate due to fever, coagulopathy, transaminitis, and altered mental status. Twelve days after the last dose of ivosidenib, grade 4 HLH was diagnosed based on LP results showing 79% histiocytoid cells, serum ferritin of 235,450, and lactate dehydrogenase of 22,834. At the time of diagnosis, the patient had ongoing grade 3 acute sinusitis, grade 3 bilateral pneumonia, grade 3 rhinovirus and upper respiratory infection, and grade 4 mucositis. Treatment of HLH included etoposide and

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tocilizumab. She was ultimately switched to comfort measures only. Nineteen days after the last dose of ivosidenib, the patient died, with the cause of death reported as progressive leukemia evidenced by hematologic failure, extensive leukemic infiltration in the CNS that was complicated by persistent intracranial hemorrhage and HLH. The investigator deemed HLH as not related to ivosidenib.

Subject (b) (6): 73-year-old woman enrolled into the expansion portion of study AG120-C-001 with a diagnosis of R/R AML, having received 2 prior anti-cancer regimens. Prior to the AE of macrophage activation syndrome, the investigator reported a response of SD on study day 58, with ANC 0.2 and 49% bone marrow blasts. On study day 67, the patient was hospitalized for treatment of grade 3 febrile neutropenia and stomatitis. On study day 68, due to an increased ferritin > 10,000, HLH was suspected (reported as a non-serious AE of suspected macrophage activation syndrome) and the patient's dexamethasone dose was increased. At the time of diagnosis of suspected HLH, the patient had an ongoing grade 2 portacath infection. On study day 70, CT of the chest showed an increase in bilateral pneumonia and a new antibiotic was started the next day. Despite these treatments, the patient continued to deteriorate, which led to her decision to pursue palliative measures. She received a total of 75 days of treatment with ivosidenib before being discontinued due to the SAE of stomatitis, which was assessed by the investigator as not related to ivosidenib. Ten days after her last dose of ivosidenib, the patient died of "febrile neutropenia," which was considered by the investigator to be related to the underlying malignancy and not related to ivosidenib. The investigator assessed the AE of HLH as not related to ivosidenib.

Reviewer comments: It is difficult to discern the diagnostic validity and causality of these 2 listed cases of HLH. The first case seems more convincing as a true diagnosis of HLH, based on presence of fever, cytopenias, coagulopathy, hemophagocytosis, and elevated ferritin. Regarding the cause, malignancy has been associated with HLH, although relatively rare in AML. This patient had a high level of disease burden. Whether the treatment with ivosidenib could have led to differentiation that set off a chain of immune activation is unclear. This is unlikely, however, since the patient lacked an IDH1 mutation and her leukocyte count decreased post-treatment.

Regarding the second patient, the diagnosis of HLH is less clear. The patient had a fever and high ferritin, but other diagnostic criteria for HLH are not mentioned. Fever and high ferritin levels alone cannot be diagnostic of HLH. Furthermore, this patient had a high level of leukemia in her BM and appears to have died from complications of her leukemia.

In conclusion, the data are inconclusive to determine whether HLH is a true ADR of ivosidenib. I favor these events as being unrelated. However, vigilance in the post-marketing setting will be required.

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Leukoencephalopathy

On Study AG120-C-001, there were 3 (1%) cases of leukoencephalopathy in the SAS, per the grouped term defined in Appendix 14.5.1. One subject experienced a nonserious AE of encephalopathy, one experienced posterior reversible encephalopathy syndrome (PRES), and one had progressive multifocal leukoencephalopathy (PML). The nonserious AE of encephalopathy was in a R/R AML patient in the setting of babesiosis and PD and was thought to be unrelated to ivosidenib. The cases of PRES and PML are summarized below.

Subject (b) (6): 66-year-old man with R/R AML after 2 prior intensive therapy regimens (including cladribine) who received ivosidenib 500 mg QD during the expansion portion of the study. On day 225, the patient experienced a first instance of PML Grade 3. His symptoms included new slurred speech that had been getting worse for approximately 2 weeks. Results from an MRI showed no abnormal parenchymal or leptomeningeal enhancement. PML was considered resolved with sequelae on Day 227. Study treatment was not held for this event. On Day 302, the subject had a second SAE of PML (Grade 3) with worsening neurologic symptoms. Results from an MRI of the brain showed ring-like diffusion restriction with hyperperfusion. There was an area of subcortical and deep white matter abnormality within the left posterior frontal lobe which had progressed since the previous examination. Ivosidenib was held temporarily. The subject was hospitalized on Day 309 for further evaluation because of symptoms of Grade 2 gait disturbance, right sided hemiparesis, and progressive slurred speech. A bone marrow aspiration was performed, and the differential results showed 5% bone marrow blasts. The subject's cerebrospinal fluid was positive for JC virus and the Sponsor provided approval for the subject to receive BK virus cytotoxic T lymphocyte cells on a compassionate use protocol (95% homology between BK and JC viral sequences). Lumbar punctures were negative for leukemic cells. On Day 331, ivosidenib was resumed at the previous dose of 500 mg QD after being held for 26 days. Despite some initial improvement with rehabilitation, the patient's condition declined around day 372, with inability to repeat words, communicate during the exam, or ambulate without assistance. WBC was 20 with 3% blasts. On day 375, he received his final dose of ivosidenib per his decision. Five days later, he transitioned to hospice care. When he withdrew his consent, the PML was ongoing with persistent dysphagia and hemiparesis, as well as high levels of JC virus DNA detected in the plasma. Per the investigator, the PML was not related to the ivosidenib, but to the underlying AML. His best response on therapy was a CRh.

Reviewer comments: It is concerning that this patient continued to receive ivosidenib after developing such a serious toxicity. I am also concerned since this drug has been associated with GBS, which may lead to diagnostic delays for patients with PML. For this reason, I favor listing this case in Section 6.1 of the label.

Subject (b) (6): 81-year-old woman on the escalation cohort with newly diagnosed AML and history of MDS, essential thrombocythaemia, breast cancer, hypertension, coronary artery disease, diastolic dysfunction, and diabetes mellitus who received 500 mg ivosidenib daily. Her

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WBC on Day 1 was 6 with 90% blasts. She experienced leukocytosis on day 11 and DS on day 43 (resolved day 67) and was treated with hydroxyurea and prednisone. On day 94, she presented to the hospital with bilateral upper extremity weakness, including difficulty holding objects and dropping glasses. She also had a headache with blood pressure 183/85 and platelet count 920,000. She began yelling out stating she was cold and suffocating. She developed numbness in all extremities and was thrashing in bed. MRI of the head was suspicious for atypical PRES with atypical infection or diffuse ischemia being less likely. She was treated with carvedilol, captopril, and nifedipine. She was not answering questions and appeared to have seizure activity with bilateral hand twitching and abdominal contractions. She was given Ativan and Keppra. She was then noted to have T-wave inversion on telemetry and troponin was elevated to > 14. Echo showed ejection fraction of 45%. Her final dose of ivosidenib was on day 94. One day later, her platelet count dropped to 309. She exhibited myoclonus in the fingers and feet. Her left arm was flaccid on exam and she was not arousable to sternal rub. Later noted to be obtunded with spasticity of the right arm, forearm, and contracture of the right hand. ECG showed PACs, occasional PVCs, T-wave inversions V3-V6, and prolonged QTc 492 msec. EEG showed moderate encephalopathy with focal neuronal dysfunction. On day 100, the patient started to improve. Medical management was pursued for the patient's coronary artery disease. She was ultimately discharged to an acute rehabilitation facility. She still had right hand grasp weakness that was improving, but prevented her from feeding herself. Her leftward gaze remained impaired as well. 688 days after her last dose, she died due to PD. Her best response on therapy was CRh.

Reviewer comments: It is interesting that both patients who developed leukoencephalopathy had a CRh response. This case of PRES was in the setting of hypertension and myocardial infarction in a patient with multiple comorbidities including hypertension and coronary artery disease. It is unclear if the recent leukocytosis and DS could have spurred the onset of PRES in this delicate patient. Given that the PRES led to permanent discontinuation of ivosidenib, and given the varied neurological conditions that have been seen in patients treated with ivosidenib, I recommend inclusion of this event in Section 6.1 of the label.

Treatment Emergent Adverse Events and Adverse Reactions

Common (in ≥ 10% of patients) TEAEs occurring either on ivosidenib or within 28 days after discontinuation of ivosidenib are summarized by preferred term in Table 54. No new common AEs were detected in the analysis of the SAS.

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Table 54: Common All-Grade TEAEs (≥ 10%)

Preferred Term[1]	R/R AML SAS (n=179)	SAS (n=258)
Fatigue	69 (39%)	104 (40%)
Leukocytosis	68 (38%)	96 (37%)
Nausea/vomiting	66 (37%)	97 (38%)
Arthralgias	64 (36%)	92 (36%)
Diarrhea	60 (34%)	94 (36%)
Dyspnea	59 (33%)	81 (31%)
Edema	57 (32%)	80 (31%)
Febrile neutropenia	52 (29%)	66 (26%)
Mucositis	51 (28%)	77 (30%)
Electrocardiogram QT prolonged	46 (26%)	61 (24%)
Rash	46 (26%)	65 (25%)
Pyrexia	41 (23%)	57 (22%)
Anemia	40 (22%)	61 (24%)
Cough	40 (22%)	54 (21%)
Constipation	35 (20%)	51 (20%)
Hypokalemia	34 (19%)	49 (19%)
Decreased appetite	33 (18%)	53 (21%)
Myalgias	33 (18%)	49 (19%)
Pneumonia	33 (18%)	42 (16%)
Arthralgia	32 (18%)	46 (18%)
Epistaxis	31 (17%)	41 (16%)
Sepsis	30 (17%)	34 (13%)
Abdominal pain	29 (16%)	42 (16%)
Dizziness	29 (16%)	42 (16%)
Thrombocytopenia	29 (16%)	41 (16%)
Headache	28 (16%)	37 (14%)
Renal Insufficiency	27 (15%)	39 (15%)
Upper respiratory tract infection	26 (15%)	38 (15%)
Hepatic injury	25 (14%)	42 (16%)
Pleural effusion	23 (13%)	26 (10%)
Atrial arrhythmia	22 (12%)	31 (12%)
Chest pain	22 (12%)	36 (14%)
Hypomagnesemia	22 (12%)	35 (14%)
Hypotension	22 (12%)	31 (12%)
Neuropathy	21 (12%)	26 (10%)
Hyperuricemia	20 (11%)	28 (11%)
Urinary tract infection	20 (11%)	30 (12%)
Differentiation syndrome	19 (11%)	30 (12%)
Fungal infection	19 (11%)	25 (10%)
Insomnia	14 (8%)	27 (10%)
Pruritus	16 (9%)	26 (10%)

Source: FDA Analysis [1] Includes grouped terms (see Appendix 14.5.1)

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Given that many patients on AG120-C-001 were on concomitant hydroxyurea (94/179 [53%] in the R/R AML SAS), FDA performed an analysis to see if the TEAE of mucositis (frequently associated with hydroxyurea) could be related to concomitant hydroxyurea administration. Of the 51 patients with mucositis in the R/R AML SAS, 30 (59%) were either on hydroxyurea prior to the onset of mucositis (n=27) or had a missing data point for the date of onset of mucositis or initiation of hydroxyurea (n=3). Thus, it is possible that the true incidence of mucositis attributable to ivosidenib is much lower than reported. However, given that 21/51 cases (41%) of cases of mucositis occurred outside of the context of hydroxyurea, mucositis is likely still an ADR of ivosidenib. Furthermore, the non-clinical data demonstrated erosions and mucosal inflammation in rats, supporting plausibility (see Section 5.5.1).

Another common AE was hepatic injury in 14% of patients. This is consistent with nonclinical data, which demonstrated hepatic toxicity in rats and monkeys (see Section 5.5.1).

Common (in ≥ 5% of patients) grade ≥ 3 TEAEs occurring either on ivosidenib or within 28 days after discontinuation of ivosidenib are summarized by preferred term in Table 55. In the analysis of the SAS, fungal infection just met the threshold of ≥ 5%, thus meeting the criterion for a common grade ≥ 3 TEAE.

Table 55: Common Grade ≥ 3 TEAEs (≥ 5%)

Preferred Term[1]	R/R AML SAS (n=179)	SAS (n=258)
Febrile neutropenia	52 (29%)	65 (25%)
Anemia	36 (20%)	50 (19%)
Sepsis	29 (16%)	32 (12%)
Pneumonia	27 (15%)	34 (13%)
Thrombocytopenia	26 (15%)	35 (14%)
Electrocardiogram QT prolonged	18 (10%)	23 (9%)
Dyspnea	16 (9%)	22 (9%)
Neutropenia	16 (9%)	23 (9%)
Leukocytosis	15 (8%)	20 (8%)
Tumor lysis syndrome	11 (6%)	15 (6%)
Differentiation syndrome	9 (5%)	14 (5%)
Hypophosphatemia	9 (5%)	14 (5%)
Fungal infection	8 (4%)	13 (5%)

Source: FDA Analysis
[1] Includes grouped terms (see Appendix 14.5.1)

Common (all-grade in ≥ 5% of patients) TEAEs suspected to be possibly or probably related to ivosidenib by the investigator are summarized by preferred term in Table 56. No new suspected related adverse events were detected in the analysis of the SAS.

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Table 56: TEAEs Suspected to Be Possibly or Probably Related to Ivosidenib

Preferred Term[1]	R/R AML SAS (n=179)		SAS (n=258)	
	All grades	Grade 3-5	All grades	Grade 3-5
Nausea/vomiting	31 (17%)	0	45 (17%)	2 (1%)
Electrocardiogram QT prolonged	26 (15%)	14 (8%)	33 (13%)	18 (7%)
Fatigue	24 (13%)	1 (1%)	37 (14%)	3 (1%)
Diarrhea	19 (11%)	1 (1%)	34 (13%)	3 (1%)
Leukocytosis	18 (10%)	3 (2%)	25 (10%)	4 (2%)
Decreased appetite	17 (10%)	1 (1%)	25 (10%)	2 (1%)
Differentiation syndrome	17 (10%)	7 (4%)	28 (11%)	12 (5%)
Rash	10 (6%)	2 (1%)	19 (7%)	4 (2%)

Source: FDA Analysis
[1] Includes grouped terms (see Appendix 14.5.1)

Reviewer comments: Given that Study AG120-C-001 is a single arm trial in a population of patients with R/R AML, it is difficult to discern causality. Investigators infrequently attributed AEs to ivosidenib. Overall, the spectrum, frequency, and severity of TEAEs observed on Study AG120-C-001 are consistent with those expected in the general R/R AML population, with some notable exceptions, such as QT prolongation and DS (which can be associated with hypotension, dyspnea, hepatic injury, edema, and leukocytosis).

Although dyspnea, edema, hypotension, renal insufficiency, fever, and effusions are seen in the context of DS, it is notable that these AEs were often seen at higher incidences than would be explained by the investigator-reported cases of DS. In particular, dyspnea, edema, pyrexia, and renal insufficiency appeared to occur with ivosidenib outside of the context of DS.

Gastrointestinal side effects, fatigue, decreased appetite, and rash were frequently attributed to therapy by investigators and are believed to be ADRs. Low-grade myalgias and mucositis also emerged from FDA's analysis, although these were often considered by investigators to be unrelated.

In attempt to discern causality of TEAEs, FDA performed a review of TEAEs from the solid tumor study AG120-C-002 (Solid set) and the healthy volunteer studies AG120-C-003, AG120-C-004, AG120-C-006, and AG120-C-007 (Healthy set). Demographics for these two populations are displayed in Table 57.

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Table 57: Demographics of the Solid Tumor and Healthy Volunteer Studies

	Solid set (n=168)	Healthy set (n=126)
Sex		
Male	80 (48%)	102 (81%)
Female	88 (52%)	24 (19%)
Age (years)		
Mean	52	36
Median	54	33
Min, Max	21, 88	19, 56
Age group		
18-65 years	135 (80%)	126 (100%)
≥65 years	33 (20%)	0
Race		
White	132 (79%)	77 (61%)
Black	2 (1%)	11 (9%)
Asian	2 (1%)	34 (27%)
Other	2 (1%)	4 (3%)
Not Provided or Unknown	30 (18%)	0
Ethnicity		
Not Hispanic or Latino	121 (72%)	102 (81%)
Hispanic or Latino	8 (5%)	24 (19%)
Not Provided	39 (23%)	0
Underlying Disease		
Cholangiocarcinoma	73 (44%)	0
Chondrosarcoma	21 (13%)	0
Glioma	66 (39%)	0
Others solid tumor	8 (5%)	0
None	0	126 (100%)

Source: FDA analysis

Duration of exposure on the solid tumor and healthy volunteer trials is shown in Table 58 below. Median duration of exposure for solid tumor trial AG120-C-002 was 3.7 months (range 0.4-31.9 months). The healthy volunteer trials were only single dose trials, with the exception of Study AG120-C-004, which included 2 doses.

Table 58: Duration of Exposure[1] to Ivosidenib in Solid Tumor Patients and Healthy Volunteers

	0 to 3 months	>3 to 6 months	>6 to 9 months	>9 to 12 months	> 12 months
Solid set (n=168)	75 (45%)	24 (14%)	13 (8%)	13 (8%)	43 (26%)
Healthy set (n=126)	126 (100%)	0	0	0	0

Source: FDA analysis
[1] Irrespective of assigned dose or regimen

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Table 59 shows common (in ≥ 10% of patients) TEAEs occurring either on ivosidenib or within 28 days after discontinuation of ivosidenib, summarized by preferred term for the solid tumor and healthy volunteer studies.

Table 59: Common (≥ 10%) All-Grade TEAEs Solid Tumors and Healthy Volunteers

Preferred Term[1]	Solid set (n=168)	Healthy set (n=126)
Fatigue	59 (35%)	1 (1%)
Nausea/vomiting	58 (35%)	3 (2%)
Diarrhea	43 (26%)	3 (2%)
Arthralgias	33 (20%)	0
Hepatic injury	33 (20%)	1 (1%)
Myalgias	33 (20%)	2 (2%)
Headache	32 (19%)	10 (8%)
Abdominal pain	31 (18%)	1 (1%)
Decreased appetite	30 (18%)	0
Upper respiratory tract infection	23 (14%)	2 (2%)
Edema	20 (12%)	0
Neuropathy	19 (11%)	0
Anemia	18 (11%)	0
Cough	18 (11%)	3 (2%)
Dyspnea	17 (10%)	0

Source: FDA Analysis

Reviewer comments: The occurrence of fatigue, nausea/vomiting, diarrhea, hepatic injury, myalgias, and abdominal pain in both the healthy volunteer and solid tumor studies support these TEAEs as true ADRs. Note also that edema, neuropathy, anemia, and dyspnea were common in solid tumor patients, supporting them as ADRs.

Atrial arrhythmia was seen in only 6% of patients with solid tumors and no healthy volunteers compared to 12% of patients with R/R AML. The pre-clinical data indicated more of an effect on ventricular arrhythmia. Grade 3-4 atrial arrhythmia in R/R AML patients was only 4%. Thus, I believe it is unlikely that atrial arrhythmia is a true ADR of ivosidenib.

Note that mucositis was seen less commonly in the solid tumor patients, but was still seen in 11 (7%) patients, suggesting that it is a true adverse drug reaction. Pyrexia was seen in 8% of solid tumor patients, but no healthy volunteers. Renal insufficiency was seen in 2% of solid tumor patients and 1 (1%) healthy volunteer. The non-clinical data supports a possible effect on the kidneys based on medullary tubular vacuolation and tubular necrosis in the renal medulla in rats (see Section 5.5.1).

In general, adverse events were uncommon on the healthy volunteer studies (n=126). The most common TEAE was headache in 10 (8%) patients. Other AEs in more than 1 patient each

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included cough, diarrhea, nausea/vomiting (3 patients each [2%]), myalgias, upper respiratory tract infection, dizziness, and viral infection (2 patients each [2%]). Notable AEs in only one patient each included fatigue, hepatic injury, and renal insufficiency.

Given that myalgias occurred in 2 healthy volunteer patients, FDA performed a more detailed review of this TEAE. One healthy volunteer (USUBJID AG120-C-007-(b) (6)) developed musculoskeletal pain in his right shoulder. The other subject (USUBJID AG120-C-007-(b) (6)) developed grade 4 blood creatine phosphokinase increased (peaked at 20,843 IU/L) while on concomitant ivosidenib and itraconazole. This was a 31-year-old man who had a concomitant grade 2 AST elevation. Labs resolved within 2 weeks of onset. The elevated creatine phosphokinase was deemed related to itraconazole.

On Study AG120-C-001, the incidence of the grouped term myalgias was 18% in the R/R AML SAS, but grade 3 or higher myalgias were seen in only 1%. All-grade TEAEs included muscular weakness (n=11), myalgia (n=11), musculoskeletal pain (n=10), and musculoskeletal chest pain (n=6). The one grade 3 event was a case of muscular weakness.

Reviewer comments: The TEAEs of myalgias are common, but generally of mild severity. Given the elevation in CPK in a healthy volunteer, it will be important to monitor this AE further in the post-marketing setting.

Fatigue appears to be an ADR based on the high incidence of 69/179 (39%) in the R/R AML SAS, in 35% of solid tumor patients, and in 1 healthy volunteer. However, fatigue is commonly reported in end-stage cancer patients. FDA performed an analysis of fatigue in the R/R AML SAS and found that over half of cases of fatigue (40/69, 58%) occurred in the first 30 days of therapy. Of 19 patients with more than one reported AE of fatigue on therapy, 11 (58%) experienced worsening fatigue over the course of the study, 6 (32%) experienced decreased fatigue, and 2 (11%) experienced stable fatigue. Review of fatigue across dose levels did not reveal a clear dose toxicity relationship (100% at 100 mg bid, 25% at 300 mg daily, 39% at 500 mg daily, 47% at 800 mg daily, and 29% at 1200 mg daily).

Reviewer comments: Although fatigue can be subjective, I favor inclusion of this AE given that it was seen across trials and often worsened over the course of the study. Furthermore, and importantly, investigators frequently attributed this AE to ivosidenib, as seen in Table 56.

Dizziness is another TEAE that appeared to be an ADR based on the high incidence of 29/179 (16%) in the R/R AML SAS, in 7% of solid tumor patients, and 2 (2%) of healthy volunteers. However, given that this AE is common in end-stage cancer patients and can be subjective, FDA performed an analysis of dizziness in the R/R AML SAS. The median time to onset of the first event of dizziness was 47 days (range 1-393 days). Of the 8 patients with multiple reported AEs of dizziness, only 2 had worsening dizziness over the course of the trial, whereas the remainder maintained the same grade. Only one patient with R/R AML had grade 3 dizziness. Review of

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dizziness across dose levels revealed no dose toxicity relationship (0% at 100 mg bid, 25% at 300 mg daily, 17% at 500 mg daily, 13% at 800 mg daily, and 14% at 1200 mg daily).

Reviewer comments: Given the relatively low incidence of this low-grade, sometimes subjective AE, I believe it is unlikely that dizziness is a true AE associated with ivosidenib. This is supported by the lack of a dose toxicity relationship.

(b) (4) ***other AEs listed in the tables above for Study AG120-C-001 were considered individually regarding their attribution to ivosidenib. For example, based on the lack of notable infection and bleeding in the solid tumor and healthy volunteer trials, as well as ivosidenib's positive impact on neutrophil and platelet counts over time in responders, FDA did not attribute cases of febrile neutropenia, pneumonia, fungal infection, sepsis, urinary tract infection, upper respiratory tract infection, thrombocytopenia, or epistaxis to ivosidenib.***

When available as lab findings (e.g. anemia, hyperuricemia), AEs were not listed in the label, but rather, included as new or worsening laboratory abnormalities.

Laboratory Findings

For standard clinical laboratory test results, the applicant provided summaries of absolute values over time, and for a subset of the laboratory tests, shifts in toxicity grade from baseline to worst treatment-emergent value. The following observations were made with respect to laboratory findings:

- A tendency for improvement in platelet count was evident after 3 treatment cycles, with mean values increasing by > 40 x 10^9/L by Cycle 6.
- Neutrophils started to improve during the first cycle on treatment, showing mean increases of > 0.5 x 10^9/L by Cycle 2 and of > 1.0 x 10^9/L by Cycle 3.
- Hemoglobin mean values were stable to slightly lower following treatment initiation and showed steady improvements to > 10 g/dL by Cycle 6.
- Bone marrow blasts mean values dropped by almost 20% by cycle 2 and continued to decline to a mean value of around 10-15% after 4-6 cycles.
- There were no significant mean changes from baseline for blood chemistry parameters during the study
- Shift analyses demonstrated that magnesium values decreased in 68 (38%) of patients, all to grade 1 or 2 hypomagnesemia
- Potassium levels decreased in 54 (30%) of patients, with 11 (6%) decreasing to grade 3 or 4 hypokalemia
- Uric acid increased in 57 (32%) of patients, with 11 (6%) increasing to grade 3 or 4 hyperuricemia

Additional detail was provided by the applicant with respect to changes in hematologic

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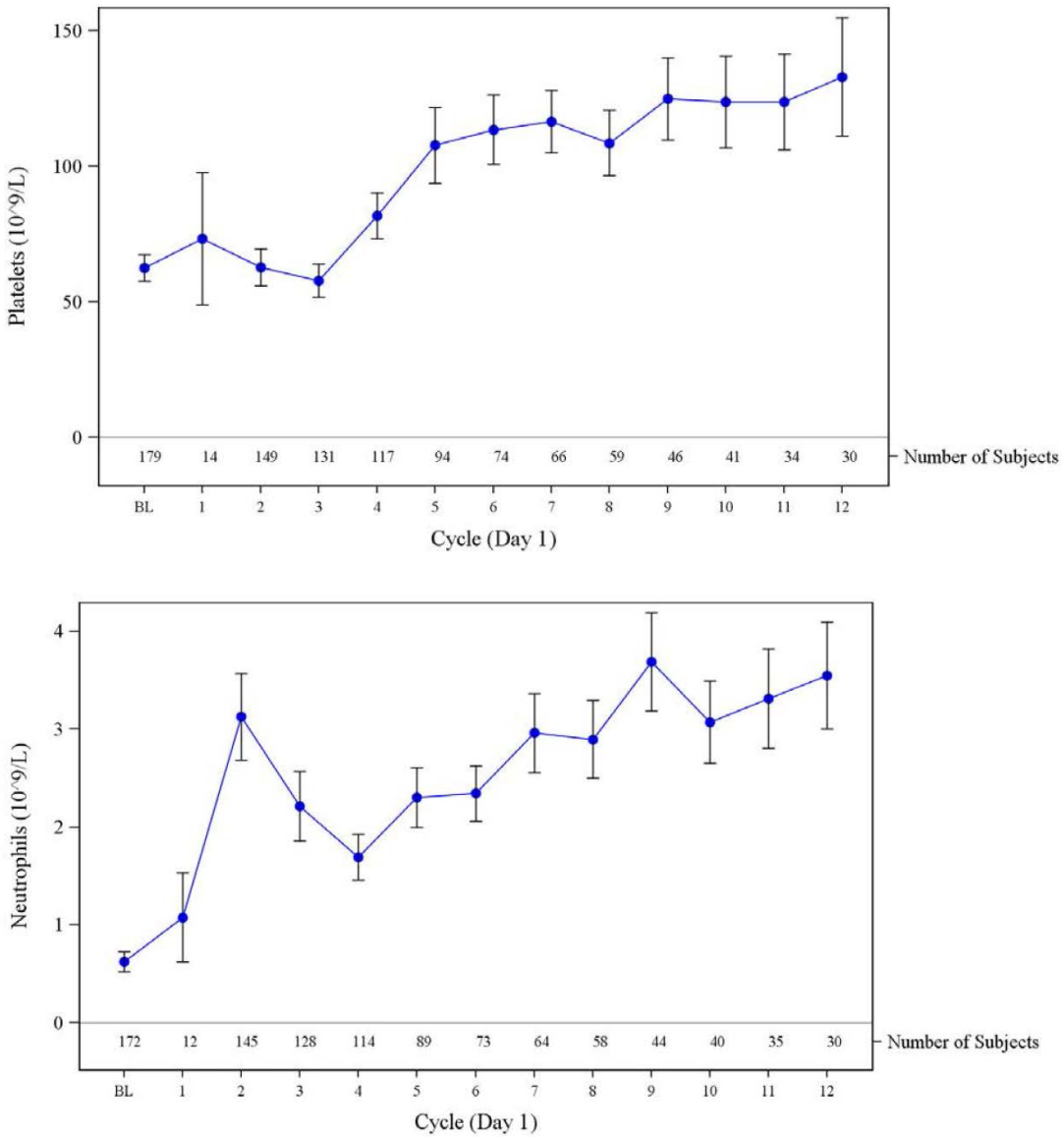
parameters over time in the lab value versus cycle graphs provided in Figure 15.

Figure 15: Mean (±SE) Platelets, ANC, and Hemoglobin for R/R AML SAS



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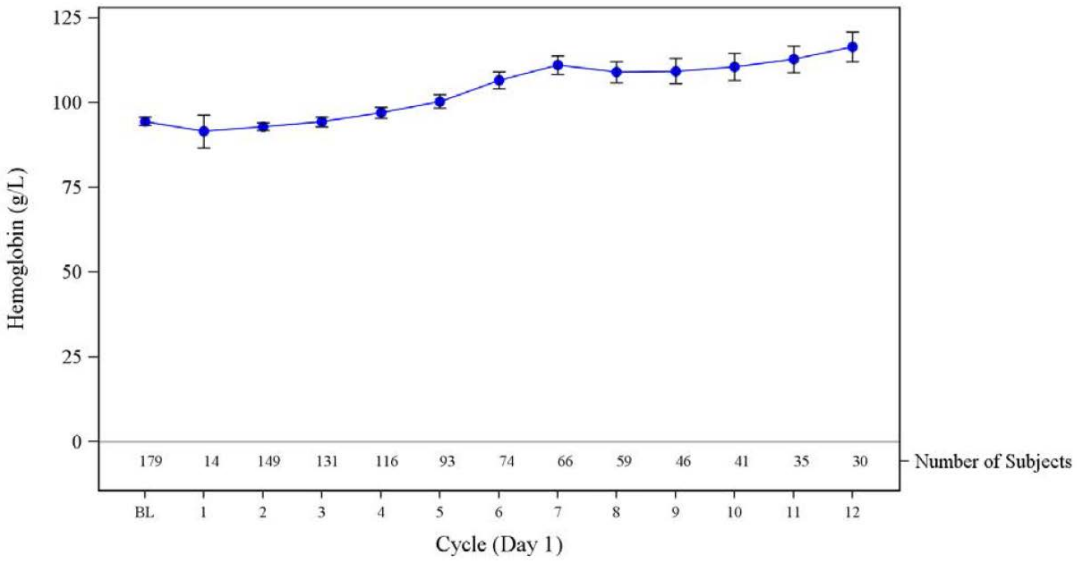

Source: Module 5.3.5.3 ISS 90 Day Safety Update Section 3

Reviewer comments: The hematologic lab value versus time graphs are biased because over time, the denominator is enriched for patients who are responding to ivosidenib. However, it appears that there is no treatment-related adverse impact of ivosidenib on platelet and neutrophil counts. Hemoglobin appeared to take a slight dip in the first cycle, after which time slow, moderate increases were observed.

In terms of liver toxicity, there were no potential Hy's law cases. Shift analyses of liver parameters demonstrated the following:

- ALT increased from grade 0 to grade 1 in 23 (13%) patients, grade 2 in 1 (1%), and grade 3 in 2 (1%)
- AST increased from grade 0 to grade 1 in 43 (24%) patients, grade 2 in 1 (1%), and grade 3 in 1 (1%); grade 1 to grade 2 in 3 (2%)
- ALP increased from grade 0 to grade 1 in 39 (22%), grade 2 in 2 (1%); grade 1 to grade 2 in 7 (4%); grade 3 to grade 4 in 1 (1%)
- Total bilirubin increased from grade 0 to grade 1 in 15 (8%), grade 2 in 6 (3%), grade 3 in 1 (1%); grade 1 to grade 2 in 6 (3%)

Reviewer comments: Based on the shift table data, it appears that low-grade liver toxicity is a common AE associated with ivosidenib. Many factors in R/R AML patients can contribute to liver toxicity, but attribution to ivosidenib cannot be disputed in a single arm trial.

Shift analyses of renal parameters demonstrated the following:

- Serum creatinine increased from grade 0 to grade 1 in 26 (15%), grade 2 in 11 (6%), and grade 3 in 1 (1%); grade 1 to grade 2 in 3 (2%), and grade 2 to grade 3 in 1 (1%)

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The Sponsor performed an analysis showing that renal AEs occurred in the setting of polypharmacy, DS, infections, and/or progressive disease.

Reviewer comments: It appears that low-grade renal insufficiency is a common AE in patients treated with ivosidenib. Although AML patients tend to be on multiple concomitant medications and have infectious issues, there is a clear effect on the kidneys in the context of DS.

Based on the SAE of blood creatine phosphokinase increased in a healthy subject on Study AG120-C-007 (Subject (b) (6)), increased creatinine phosphokinase was selected by the Applicant as an AE of clinical importance. On Study AG120-C-006 in healthy subjects, creatinine phosphokinase was evaluated regularly as part of scheduled serum chemistry evaluations. There were 2 subjects with abnormal creatine kinase (CK) lab results. Subject (b) (6) was a 32-year-old man with a baseline CK of 335 U/L (NR: 20-200 U/L). On day 4 after receiving a single dose of 250 mg ivosidenib, CK level rose to 634 and later peaked at 3,518 (Grade 4) on day 15. AST and ALT also rose to 75 and 90 U/L. On day 22, CK declined to 212 and AST/ALT returned to normal. Subject (b) (6) was a 30-year-old man with a baseline CK of 278. On day 22, his CK was 5,682. AST and ALT were mildly elevated. All labs returned to normal by day 34.

Note that CK levels were not a routine laboratory parameter evaluated on AG120-C-001. Only 13 patients had CK levels checked post-baseline and all levels were within normal limits. Across the entire ISS, there were 74 patients with post-baseline CK levels checked, from healthy volunteer studies AG120-C-006 (n=60), AG120-C-007 (n=1), and the 13 patients on AG120-C-001. Of these 74 patients, 16 (22%) had elevated CK levels post-baseline, all from the healthy volunteer studies. Aside from Subjects (b) (6) mentioned above, the highest post-baseline CK elevations were grades 1 (n=14) and 2 (n=6). Median time to first elevation was 15 days (range 4-22).

Reviewer comments: The incidence of 3 separate cases of grade 4 elevated CK on healthy volunteer studies is quite concerning. The frequent low-grade CK elevation in healthy volunteers is also troubling. Given that routine monitoring of CK levels was not done on the clinical studies, the true frequency of this AE and its possible contribution to cases of renal insufficiency and transaminase elevation are unknown. It will be important for clinicians to monitor CK levels in patients on ivosidenib to mitigate the potential risk of rhabdomyolysis. Weekly for the first month should be adequate given that the CK elevations developed within 2 weeks of a single dose on the healthy volunteer studies.

Vital Signs

The applicant did not identify any unexpected trends or clinically meaningful post-baseline findings in vital sign parameters. The most common AEs (≥ 5%) associated with vital signs were

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pyrexia (23%), hypotension (12%), hypertension (8%), and weight decreased (6%).

The FDA noted that potentially clinically significant post-baseline systolic blood pressure elevations, defined as value ≥ 160 mmHg, were observed in 15% (n=26) of subjects in the R/R AML SAS and 15% (n=38) of subjects in the SAS (Table 60). Hypertension was reported as an adverse event in 8% (n=14) of subjects in the R/R AML SAS, and was Grade ≥ 3 in 4% (n=8).

The FDA noted that potentially clinically significant post-baseline systolic blood pressure decreases, defined as value < 90 mmHg, were observed in 4% (n=8) of subjects in the R/R AML SAS and 5% (n=14) of subjects in the SAS (Table 60). A total of 23 events of hypotension (using grouped preferred term, see Appendix 14.5.1 for grouping) were reported as an AE in 12% (n=22) of subjects in the R/R AML SAS. Grade ≥ 3 hypotension was reported in 4% (n=7) of subjects.

FDA noted that post-baseline fever, defined as temperature ≥ 38.3°C, were observed in 7% (n=12) of subjects in the R/R AML SAS and 7% (n=18) of subjects in the SAS (Table 60). A total of 51 events of pyrexia were reported as a TEAE in 23% (n=41) of subjects in the R/R AML SAS. Grade ≥ 3 pyrexia was reported in 1% (n=2) of subjects.

Table 60: Post-Baseline Vital Sign Abnormalities

	R/R AML SAS (n=179)	SAS (n=258)
SBP ≥ 160 mm Hg	26 (15%)	38 (15%)
SBP < 90 mm Hg	8 (4%)	14 (5%)
DBP ≥ 100 mm Hg	3 (2%)	4 (2%)
Heart rate < 50 bpm	1 (1%)	4 (2%)
Heart rate > 120 bpm	22 (12%)	31 (12%)
Temperature ≥ 38.3°C	12 (7%)	18 (7%)

Source: FDA analysis
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; bpm, beats per minute

Reviewer comment: The hypotension observed in patients on ivosidenib rarely occurred in isolation and appears generally secondary to sepsis and/or DS.

Fevers by temperature were less frequent than TEAEs of pyrexia, likely due to different cutoffs (e.g. grade 1 fever in CTCAE is 38.0) and AEs that occurred outside of regularly scheduled clinical appointments. Based on a higher incidence of fever compared to the incidence of DS, it is thought that fever is a true AE of ivosidenib. Some fevers may be related to DS or infection, but it is impossible to distinguish from another inflammatory reaction to the ivosidenib outside of the context of full blown DS.

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QT/Electrocardiograms (ECGs)

ECGs were obtained in triplicate on Day 1 of Cycles 1 and 2 and at the end of treatment visit. Single 12-lead ECGs were obtained at screening, 4 hours post-dose on Days 8 and 15 of Cycle 1, on Day 1 of every cycle beginning with Cycle 3, and at the follow-up visit.

Atrial arrhythmias (grouped term in Appendix 14.5.1) occurred in 31 (12%) of patients in the SAS. The most frequently reported arrhythmias were tachycardia (n=11), atrial fibrillation (n=8), and sinus tachycardia (n=7).

Reviewer comments: The findings of atrial arrhythmia are similar to what would be expected in the underlying patient population. No safety signal was identified for atrial arrhythmias on review of adverse events related to ECG findings.

Ventricular arrhythmias (grouped term in Appendix 14.5.1) occurred in 4 (2%). Ventricular arrhythmias included ventricular tachycardia (n=2), ventricular extrasystoles (n=1), and ventricular arrhythmia (n=1).

A detailed review of QT prolongation and ventricular arrhythmias is provided in the subsection entitled “Significant Adverse Events” above.

Immunogenicity

Not pertinent to this review.

8.3.5 Analysis of Submission-Specific Safety Issues

As ivosidenib is a new molecular entity, there are no submission-specific safety issues. All adverse events are discussed in Section 8.3.4.

8.3.6 Safety Analyses by Demographic Subgroups

Reporting of race and ethnicity was incomplete on trial AG120-C-001, and few subjects were non-white or Hispanic and Latino. However, the applicant conducted an analysis of TEAEs by race and identified some potential differences (source: ISS Section 5.1.1):

- More Grade ≥ 3 AEs in the blood and lymphatic system disorders SOC in non-white patients (49% for white versus 64% other)
    - Grade ≥ 3 anemia 14% white versus 30% other races
    - Grade ≥ 3 thrombocytopenia 10% white versus 22% other
    - Grade ≥ 3 neutropenia 4% white versus 18% other

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Reviewer comments: It is unclear why non-white patients had more cytopenias on the trial. It is difficult to make firm conclusions based on the sample size and the amount of missing data.

The applicant conducted an analysis of TEAEs by age on the R/R AML SAS and identified only two SOCs with a difference in incidence across the age groups (source: ISS Section 5.1.1):

- More Grade ≥ 3 AEs in the blood and lymphatic system disorders SOC in subjects < 65 years (64%) compared with those who were 65 to < 75 and ≥ 75 years (49% and 50%). This may be related to the increased number of prior regimens associated with myelotoxicity in younger subjects.
- More Grade ≥ 3 AEs in the gastrointestinal disorders SOC in subjects who were < 65 years (16%) compared to those who were 65 to < 75 and ≥ 75 years (7% and 8%).

Reviewer comments: The lack of increased Grade ≥ 3 AEs in older adults supports the Sponsor's labeling claim in Section 8.5 that there were no overall differences in safety between patients 65 years and older and younger patients. In fact, most of the patients on the trial (67%) were over the age of 65.

The applicant conducted an analysis of TEAEs by sex and found no clinically relevant differences in the spectrum or severity of TEAEs by sex, except that males had less TEAEs in the infections and infestations SOC (37% versus 51%) (source: ISS Section 5.1.1).

The applicant also conducted an analysis of grade ≥ 3 AEs in the R/R AML SAS based on region (source: ISS Section 5.2.1). Results are summarized as follows:

- Patients in France had more Grade ≥ 3 AEs than subjects in the US (90% versus 81%)
- More Grade ≥ 3 AEs in the blood and lymphatic system disorders SOC in France (77% versus 50%)
- More Grade ≥ 3 AEs in the nervous system disorders SOC in France (19% versus 7%)

Reviewer comments: It is difficult to draw conclusions from the analysis of AEs by country given that the sample size was much smaller in France and most patients in France were enrolled at a single site.

The applicant conducted an analysis of grade ≥ 3 AEs in the R/R AML SAS based on the number of prior regimens (source: ISS Section 5.2.2). Results are summarized as follows:

- More Grade ≥ 3 AEs in patients with 2 versus 1 prior regimen (85% versus 79%)
- Similar number of Grade ≥ 3 AEs in patients with 2 and 3 or more prior regimens (85% versus 88%)
- Less Grade ≥ 3 AEs in the blood and lymphatic system disorders SOC with 1 prior regimen (48% versus 67% with 2 prior and 52% for 3 or more prior regimens)
- Febrile neutropenia lower in subjects with 1 prior (21%) versus 2 and 3 prior (40% and 30%, respectively)

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- Anemia lower in patients with 1 prior regimen (15%) compared to subjects with 2 and 3 prior regimens (27% and 20%, respectively)

The Applicant investigated the exposure-adjusted incidence rates of infections, bleeding, and febrile neutropenia by response in the R/R AML Efficacy Set (n=173) to demonstrate a measure of clinical benefit. Table 61 shows their results.

Table 61: Infections, Bleeding, and Febrile Neutropenia by Response

R/R AML Efficacy Set					
	CR (n=43)	**CRh (n=14)**	**CRi/CRp/MLFS (n=18)**	**NR (n=98)**	**Overall (n=173)**
Grade ≥3 infection and infestations SOC					
AEs per 100 person-months (95% CI)	2.6 (1.5, 4.6)	6.4 (3.1, 13.5)	13.1 (7.6, 22.6)	21.5 (16.9, 27.2)	10.2 (8.4, 12.4)
Grade ≥3 bleeding events[1]					
AEs per 100 person-months (95% CI)	0.4 (0.1, 1.7)	0	0	2.2 (1.1, 4.6)	0.9 (0.5, 1.8)
All-grade febrile neutropenia[2]					
AEs per 100 person-months (95% CI)	2.0 (1.0, 3.8)	3.7 (1.4, 9.8)	6.1 (2.7, 13.5)	12.0 (8.7, 16.5)	5.8 (4.5, 7.5)

Source: Summary of Clinical Efficacy – 90 Day Update (Module 2.7.3)
[1]Haemorrhage terms (excluding laboratory terms) SMQ
[2]PTs of febrile neutropenia and febrile bone marrow aplasia

Reviewer comments: It is not surprising to see that patients with increasing responses to therapy experienced less infections, bleeding, and febrile neutropenia.

8.3.7 Clinical Outcomes Assessments Informing Tolerability/Safety

There were no measured quality of life or patient reported outcomes on this trial.

8.3.8 Specific Safety Studies/Clinical Trials (including dose-related safety)

Study AG120-C-001 included a dose-escalation portion in which patients were treated with ivosidenib total daily doses of 200 mg - 1200 mg. There were 2 DLTs, one at the 800 mg daily dose (Grade 3 QT prolongation) and one at the 1200 mg daily dose (Grade 3 rash). An MTD was not identified per the protocol-specified definition. Furthermore, there were no DLTs on the solid tumor Study AG120-C-002.

For all 258 subjects treated on Study AG120-C-001, the applicant provided an analysis of adverse events by dose level. There were no notable differences in overall AEs, Grade ≥ 3 AEs, treatment-related AEs, SAEs, AEs leading to permanent discontinuation, interruption, or on-

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treatment death. A dose reduction was required for 0% vs 4% vs 9% in the cohorts with ivosidenib total doses < 500 mg, 500 mg or > 500 mg, respectively (FDA analysis).

There was no dedicated QT study or dedicated study in patients with hepatic or renal impairment. See Section 6 for a discussion of QT data from Study AG120-C-001 and for a discussion of data in patients with mild hepatic impairment who received ivosidenib.

8.3.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

A formal human carcinogenicity study was not conducted for ivosidenib. Neoplasms (identified using the Neoplasms, Benign, Malignant and Unspecified SOC) were rare on Study AG120-C-001. A second primary neoplasm was identified in 9 subjects (3%) in the SAS. Of these, 2 patients developed benign tumors (lipoma, hemangioma and cholesteatoma) and 4 patients developed skin cancers that are typically resectable (1 basal cell carcinoma, 2 squamous cell carcinoma of the skin, and 1 malignant melanoma). The remaining 3 developed endometrial cancer (n=2) and metastatic squamous cell carcinoma (n=1). The spectrum and frequency of second primary malignancies identified on this trial are similar to that of the baseline patient population. Based on these data, no secondary cancer signal was identified.

Pediatrics and Assessment of Effects on Growth

There were no data submitted that addressed short-term or long-term safety in pediatric patients.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

On Study AG120-C-001, 5 subjects accidentally took a dose that was higher than their assigned dose. The subjects were enrolled in the 300 mg daily (n=1), 500 mg daily (n=2), and 1200 mg daily (n=2) groups. The patient in the 300 mg group took 350 mg for one day. Both subjects in the 500 mg group took 1000 mg for 1 day. One subject in the 1200 mg group took 2400 mg for one day and the other took 1600 mg for one day. Subject (b) (6) in the 1200 mg dose group had an AE of vomiting on the same day as the overdose; they vomited within 15 minutes of taking their scheduled dose and took another dose afterwards. None of the subjects with accidental overdose experienced a new AE within 24 hours of the overdose.

Ivosidenib does not have abuse potential.

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8.3.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Ivosidenib is not marketed in any country, and there is no postmarket experience.

Expectations on Safety in the Postmarket Setting

Safety in the postmarket setting is expected to be similar to that observed on the clinical trials reviewed in this application. It is possible that there will be more cases of rare side effects, such as GBS, PML, and PRES. HLH is not believed to be an ADR, but will remain vigilant to any potential cases in the post-marketing setting. Lastly, no cases of rhabdomyolysis were reported in the clinical trials, but the healthy volunteer data showing elevations in CK predict that rhabdomyolysis may be seen in the post-marketing setting.

8.3.11 Integrated Assessment of Safety

The safety of ivosidenib was evaluated in detail in 179 patients with R/R AML who were assigned to receive 500 mg daily. The median duration of exposure was 3.9 months (range 0.07 to 39.4). The 30-day and 60-day mortality rates observed were 7% (12/179) and 15% (26/179), respectively.

Four adverse reactions merit close consideration:

- *Differentiation syndrome*: Some patients treated with ivosidenib developed differentiation syndrome; the signs and symptoms included noninfectious leukocytosis (74%), peripheral edema (37%), pyrexia (26%), dyspnea and pleural effusion (21% each), hypotension (16%), AKI, fluid overload, hypoxia, pericardial effusion, pneumonia, pulmonary edema, rash, and TLS (11% each). Differentiation syndrome occurred as early as 5 days and at up to 59 days after the start of ivosidenib. Based on investigator-reported and algorithmic case ascertainment, along with careful narrative review, the incidence appears to be 11-19%. About half of cases appear to be Grade ≥ 3. The management practices recommended during the conduct of the clinical trial suggest that DS is manageable and non-fatal in most subjects.

Reviewer Comments: Since DS can be fatal, this adverse reaction merits a boxed warning in the PI. Since most treatment will be in the outpatient setting, a Medication Guide for the patients will also be needed.

- *QT prolongation*: Ivosidenib caused QT prolongation in roughly a quarter of R/R AML patients, with grade 3-4 QT prolongation in about 10%. Dose interruptions (7%) and

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reductions (1%) were required. Three cases of ventricular arrhythmias have occurred, one of which was fatal.

Reviewer comments: The frequent occurrence of QT prolongation and the cases of ventricular arrhythmia warrant listing QT prolongation in Warnings and Precautions in the PI. Close monitoring of ECGs is required, along with recommendations for dose adjustments.

- *Hyperleukocytosis*: Leukocytosis was noted in 38% of patients with R/R AML, but grade 3 or higher leukocytosis was uncommon at 8%. Most cases of hyperleukocytosis with ivosidenib resulted from either DS or progression of AML. Hyperleukocytosis was managed with hydroxyurea, with only 2 subjects requiring leukapheresis.

Reviewer Comments: Although hyperleukocytosis may be alarming, treatment interruption was rarely required. The PI should provide clear instructions on management of leukocytosis.

- *Polyneuropathy*: Sensorimotor neuropathy SAEs, including 2 cases of GBS and 1 case of lumbosacral plexopathy were observed in patients treated with ivosidenib. Time to onset was as early as day 16 and as late as day 71. Both cases of GBS led to permanent discontinuation of ivosidenib.

The most common adverse reactions (≥20%) of any grade were fatigue, leukocytosis, nausea/vomiting, arthralgias, diarrhea, dyspnea, edema, mucositis, QT prolongation, rash, pyrexia, anemia, and constipation.

Serious adverse reactions were reported in 77% of patients with R/R AML treated with ivosidenib 500 mg daily. The most frequent serious adverse reactions (≥2%) were leukocytosis (10%), DS (10%), QT prolongation (7%), dyspnea (5%), renal insufficiency (4%), arthralgias (3%), respiratory failure (3%), mucositis (3%), pyrexia (3%), TLS (3%), nausea/vomiting (2%), and rash (2%).

Overall, 68 of 179 patients (38%) required a dose interruption due to an adverse reaction. The most common adverse reactions leading to dose interruption were QT prolongation (7%), DS (3%), dyspnea (3%), and leukocytosis (3%). Five of 179 patients (3%) required a dose reduction due to an adverse reaction. Adverse reactions that required dose reduction included QT prolongation (1%), diarrhea (1%), nausea (1%), decreased hemoglobin (1%), and increased transaminases (1%). Twenty-four of 179 patients (13%) permanently discontinued TIBSOVO due to an adverse reaction. Adverse reactions leading to permanent discontinuation included GBS (1%), rash (1%), stomatitis (1%), and creatinine increased (1%).

Reviewer Comments: Although DS and QT prolongation can be life-threatening and potentially fatal, there were few discontinuations due to adverse reactions, suggesting that ivosidenib 500 mg daily was tolerable in this population.

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SUMMARY AND CONCLUSIONS

8.4 Statistical Issues

- The major issue in this application is a single arm study and only treatment effect may be estimated and no inference can be drawn.
- Follow-up time in the expansion phase is limited.

8.5 Conclusions and Recommendations

The efficacy of ivosidenib was established on the basis of the CR/CRh rate, the duration of CR/CRh, and the rate of conversion from transfusion-dependence to transfusion-independence in Study AG120-C-001. With a median follow-up of 8.3 months, the 174 adults with IDH1-mutated R/R AML treated with 500 mg ivosidenib daily had a CR/CRh rate of 33% (95% CI 26, 40), the median duration of response was 8.2 months, and 37% of transfusion-dependent patients achieved transfusion-independence for at least a 56-day period. These endpoints reflect short-term benefits; long-term outcomes are not available. Nonetheless, such short-term benefit is clinically meaningful for patients seeking quality of life, even in the absence of curative intent. Ivosidenib was well-tolerated with only a minority of patients discontinuing due to adverse reactions. Serious risks, such as DS and QT prolongation, can likely be mitigated with appropriate labeling. In view of the immediate clinical benefit reflected by count recovery and transfusion-independence in addition to the tolerability of this drug, the review team recommends regular approval of ivosidenib.

Lola Luo, PhD Primary Statistical Reviewer	Yuan-Li Shen, DrPH Statistical Team Leader
Kelly Norsworthy, MD Primary Clinical Reviewer	Donna Przepiorka, MD, PhD Clinical Team Leader

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9 Advisory Committee Meeting and Other External Consultations

This Application was not presented to the Oncologic Drug Advisory Committee or any other external consultants.

10 Pediatrics

Ivosidenib has Orphan Designation for the treatment of patients with AML and is therefore exempt from pediatric studies under the Pediatric Research Equity Act (PREA). There are no data regarding the use of ivosidenib in children.

11 Labeling Recommendations

11.1 Prescribing Information

The following are recommended major changes to the Prescribing Information proposed by the applicant based on this review:

- **1 INDICATIONS AND USAGE**: Clarify approval only for patients with a susceptible mutation in IDH1.

- **2 DOSAGE AND ADMINISTRATION:** Update dose modifications for toxicities to provide more specific and detailed guidance for the physician. Add dose modifications for concurrent use with strong CYP3A4 inhibitors. Add monitoring for CPK.

- **5 WARNINGS AND PRECAUTIONS:** Add occurrence of ventricular arrhythmias to QTc prolongation warning. Delete (b) (4)

- **6 ADVERSE REACTIONS:** Revise list of adverse reactions to add adverse events at least possibly related to ivosidenib. Characterize laboratory abnormalities separately from adverse reactions.

- **8 USE IN SPECIFIC POPULATIONS**: Delete (b) (4)

- **12 CLINICAL PHARMACOLOGY:** Include a description of susceptible mutations based on both gain of function and inhibition by ivosidenib.

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- **14 CLINICAL STUDIES:** (b) (4)

- **17 PATIENT COUNSELING INFORMATION:** Revised this section to update the list of adverse reactions.

11.2 Patient Labeling

The only major change to the Medication Guide was to update the list of side effects and pre-existing conditions to report to the healthcare provider.

12 Risk Evaluation and Mitigation Strategies (REMS)

The risks of ivosidenib, including DS, can be adequately managed in the post-marketing setting through product presentation and labeling. No additional risk management strategies are recommended. The Division of Risk Management in the Office of Surveillance and Epidemiology concurred with this assessment.

12.1 Safety Issue(s) that Warrant Consideration of a REMS

None.

12.2 Conditions of Use to Address Safety Issue(s)

Not applicable.

12.3 Recommendations on REMS

REMS is not required.

13 Postmarketing Requirements and Commitments

PMR-1
Characterize the long-term safety of ivosidenib in patients with relapsed or refractory acute myeloid leukemia (AML). Submit the final study report and data set with 3 years of follow-up from ongoing Study AG120-C-001, *A Phase 1, Multicenter, Open-Label, Dose-Escalation and Expansion, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-120 in Subjects with Advanced Hematologic Malignancies with an IDH1 Mutation*. Include data from approximately 205 patients with relapsed or refractory AML. Include in the final study report the exploratory subgroup analyses and corresponding subject-

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level data related to pre- and post-treatment cytogenetics, specific IDH1 mutations, and mutation analyses for other genes as obtained under the trial protocol. Desired milestones:

PMR-2
Complete your ongoing Study AG120-C-012, *A Phase 1, open-label, single-dose study to evaluate the pharmacokinetics, safety, and tolerability of AG-120 in subjects with mild or moderate hepatic impairment or normal hepatic function*.

PMR-3
Conduct a clinical pharmacokinetic trial to determine an appropriate safe dose of ivosidenib in patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test with hepatic impairment (moderate) dosed with ivosidenib to steady-state vs. patients with normal hepatic function dosed with ivosidenib to steady-state. This may be performed as a sub-study in the ongoing Phase 1 Study AG120-C-001, *A Phase 1, Multicenter, Open-Label, Dose-Escalation and Expansion, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-120 in Subjects with Advanced Hematologic Malignancies with an IDH1 Mutation*. This trial should be designed and conducted in accordance with the FDA Guidance for Industry entitled *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*. Depending on the results, a clinical pharmacokinetic trial in patients with severe hepatic impairment may be required.

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14 Appendices

14.1 References

Akyay, A, T Celkan, G Iskender, A Tukun, C Ogan, & L Olcay. (2013). Two acute myeloblastic leukemia cases concomitant with hemophagocytic lymphohistiocytosis and review of the literature. Ann Clin Lab Sci, 43(1), 85-90.

Appelbaum, FR, D Rosenblum, RJ Arceci, WL Carroll, PP Breitfeld, SJ Forman, RA Larson, SJ Lee, SB Murphy, S O'Brien, J Radich, NS Scher, FO Smith, RM Stone, & MS Tallman. (2007). End points to establish the efficacy of new agents in the treatment of acute leukemia. Blood, 109(5), 1810-1816.

Burnett, A, M Wetzler, & B Lowenberg. (2011). Therapeutic advances in acute myeloid leukemia. J Clin Oncol, 29(5), 487-494.

Burnett, AK. (2002). Acute myeloid leukemia: treatment of adults under 60 years. Rev Clin Exp Hematol, 6(1), 26-45; discussion 86-27.

Cheson, BD, JM Bennett, KJ Kopecky, T Buchner, CL Willman, EH Estey, CA Schiffer, H Doehner, MS Tallman, TA Lister, F Lo-Coco, R Willemze, A Biondi, W Hiddemann, RA Larson, B Lowenberg, MA Sanz, DR Head, R Ohno, CD Bloomfield, SoRCTO International Working Group for Diagnosis, & L Reporting Standards for Therapeutic Trials in Acute Myeloid. (2003). Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol, 21(24), 4642-4649.

Delavigne, K, E Berard, S Bertoli, J Corre, E Duchayne, C Demur, V Mansat-De Mas, C Borel, M Picard, M Alvarez, A Sarry, F Huguet, & C Recher. (2014). Hemophagocytic syndrome in patients with acute myeloid leukemia undergoing intensive chemotherapy. Haematologica, 99(3), 474-480.

DiNardo, CD, F Ravandi, S Agresta, M Konopleva, K Takahashi, T Kadia, M Routbort, KP Patel, B Mark, S Pierce, G Garcia-Manero, J Cortes, & H Kantarjian. (2015). Characteristics, clinical outcome, and prognostic significance of IDH mutations in AML. Am J Hematol, 90(8), 732-736.

Dohner, H, E Estey, D Grimwade, S Amadori, FR Appelbaum, T Buchner, H Dombret, BL Ebert, P Fenaux, RA Larson, RL Levine, F Lo-Coco, T Naoe, D Niederwieser, GJ Ossenkoppele, M Sanz, J Sierra, MS Tallman, HF Tien, AH Wei, B Lowenberg, & CD Bloomfield. (2017). Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel.

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Blood, 129(4), 424-447.

Faderl, S, M Wetzler, D Rizzieri, G Schiller, M Jagasia, R Stuart, S Ganguly, D Avigan, M Craig, R Collins, M Maris, T Kovacsovics, S Goldberg, K Seiter, P Hari, J Greiner, N Vey, C Recher, F Ravandi, ES Wang, M Vasconcelles, D Huebner, & HM Kantarjian. (2012). Clofarabine plus cytarabine compared with cytarabine alone in older patients with relapsed or refractory acute myelogenous leukemia: results from the CLASSIC I Trial. J Clin Oncol, 30(20), 2492-2499.

Fernandez, HF, Z Sun, X Yao, MR Litzow, SM Luger, EM Paietta, J Racevskis, GW Dewald, RP Ketterling, JM Bennett, JM Rowe, HM Lazarus, & MS Tallman. (2009). Anthracycline dose intensification in acute myeloid leukemia. N Engl J Med, 361(13), 1249-1259.

Frankel, SR, A Eardley, G Lauwers, M Weiss, & RP Warrell, Jr. (1992). The "retinoic acid syndrome" in acute promyelocytic leukemia. Ann Intern Med, 117(4), 292-296.

Howlader N, NA, Krapcho M, Garshell J, Miller D, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z,Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). (2017). SEER Cancer Statistics Review, 1975-2014, National Cancer Institute.

Im, AP, AR Sehgal, MP Carroll, BD Smith, A Tefferi, DE Johnson, & M Boyiadzis. (2014). DNMT3A and IDH mutations in acute myeloid leukemia and other myeloid malignancies: associations with prognosis and potential treatment strategies. Leukemia, 28(9), 1774-1783.

Intlekofer AM, Shih AH, Wamg B, et al. (2018) Acquired resistance to IDH inhibition through trans or cis dimer-interface mutations. Nature 559:125-129.

Lo-Coco, F, G Avvisati, M Vignetti, C Thiede, SM Orlando, S Iacobelli, F Ferrara, P Fazi, L Cicconi, E Di Bona, G Specchia, S Sica, M Divona, A Levis, W Fiedler, E Cerqui, M Breccia, G Fioritoni, HR Salih, M Cazzola, L Melillo, AM Carella, CH Brandts, E Morra, M von Lilienfeld-Toal, B Hertenstein, M Wattad, M Lubbert, M Hanel, N Schmitz, H Link, MG Kropp, A Rambaldi, G La Nasa, M Luppi, F Ciceri, O Finizio, A Venditti, F Fabbiano, K Dohner, M Sauer, A Ganser, S Amadori, F Mandelli, H Dohner, G Ehninger, RF Schlenk, U Platzbecker, dA Gruppo Italiano Malattie Ematologiche, G German-Austrian Acute Myeloid Leukemia Study, & L Study Alliance. (2013). Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med, 369(2), 111-121.

Montesinos, P, JM Bergua, E Vellenga, C Rayon, R Parody, J de la Serna, A Leon, J Esteve, G Milone, G Deben, C Rivas, M Gonzalez, M Tormo, J Diaz-Mediavilla, JD Gonzalez, S Negri, E Amutio, S Brunet, B Lowenberg, & MA Sanz. (2009). Differentiation syndrome in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and anthracycline chemotherapy: characteristics, outcome, and prognostic factors. Blood, 113(4), 775-783.

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Oran, B, & DJ Weisdorf. (2012). Survival for older patients with acute myeloid leukemia: a population-based study. Haematologica, 97(12), 1916-1924.

Petty, JM, V Sueblinvong, CC Lenox, CC Jones, GP Cosgrove, CD Cool, PR Rai, KK Brown, DJ Weiss, ME Poynter, & BT Suratt. (2007). Pulmonary stromal-derived factor-1 expression and effect on neutrophil recruitment during acute lung injury. J Immunol, 178(12), 8148-8157.

Ramos, NR, CC Mo, JE Karp, & CS Hourigan. (2015). Current Approaches in the Treatment of Relapsed and Refractory Acute Myeloid Leukemia. J Clin Med, 4(4), 665-695.

Roboz, GJ, T Rosenblat, M Arellano, M Gobbi, JK Altman, P Montesinos, C O'Connell, SR Solomon, A Pigneux, N Vey, R Hills, TF Jacobsen, A Gianella-Borradori, O Foss, S Vetrhusand, & FJ Giles. (2014). International randomized phase III study of elacytarabine versus investigator choice in patients with relapsed/refractory acute myeloid leukemia. J Clin Oncol, 32(18), 1919-1926.

Wang, LX, XM Fei, YL Lu, XF Shi, Q Jiang, HY You, R Ba, & Y Zhu. (2010). Acute myeloid leukemia initially presenting as hemophagocytic lymphohistiocytosis--a case report and review of the literature. Leuk Res, 34(1), e46-49.

Yamazaki, S, F Nakamura, R Nasu, Y Nannya, M Ichikawa, & M Kurokawa. (2011). Haemophagocytic lymphohistiocytosis is a recurrent and specific complication of acute erythroid leukaemia. Br J Haematol, 153(5), 669-672.

Zhou, J, L Hu, Z Cui, X Jiang, G Wang, GW Krissansen, & X Sun. (2010). Interaction of SDF-1alpha and CXCR4 plays an important role in pulmonary cellular infiltration in differentiation syndrome. Int J Hematol, 91(2), 293-302.

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14.2 Financial Disclosure

Covered Clinical Study (Name and/or Number): AG120-C-001

Was a list of clinical investigators provided:	Yes X	No (Request list from Applicant)
Total number of investigators identified: 382		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 2		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	No (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 9		
Is an attachment provided with the reason:	Yes X	No (Request explanation from Applicant)

14.3 Nonclinical Pharmacology/Toxicology

None.

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14.4 OCP Appendices

SUMMARY OF BIOANALYTICAL METHOD VALIDATION AND PERFORMANCE

Ivosidenib concentrations in human plasma or urine were assayed in clinical trials. As outlined in **Table 62**, three LC-MS/MS methods were developed and validated. All sample analyses were performed within the established storage stability for ivosidenib. All bioanalytical methods appeared to be validated appropriately and met in-study performance criteria recommendations per FDA Guidance for Industry on Bioanalytical Method Validation. Detailed performance parameters to support validation of ivosidenib in human plasma, which was used for all clinical studies in this NDA submission, are summarized in **Table 63**.

Table 62. Validated bioanalytical methods for ivosidenib in human biological samples

Agios Method Number (CRO Method Number)	Agios Report Number (CRO Report Number)	Matrix (Anti-Coagulant/ Additive)	Assay Performance[1]						Studies Supported
			Calibration Range (ng/mL)	Precision (%CV)		Accuracy (%RE)		Long-Term Storage Stability in Matrix	
				Intra-assay	Inter-assay	Intra-assay	Inter-assay		
AG120-Q-001 ([(b) (4)]13-100)	AG120-Q-001 ([(b) (4)]13-100)	Human plasma (K_2EDTA)	1 to 1,000	≤5.0	≤3.5	±3.4	±2.8	26 days (−20°C/80°C)	AG120-C-001 AG120-C-002
AG120-Q-010 ([(b) (4)]14-032)	AG120-Q-010-R1 ([(b) (4)]14-032), AG120-Q-010-R1-ADD1 ([(b) (4)]14-032ADD1), AG120-Q-010-R1-ADD2 ([(b) (4)]14-032ADD2)	Human plasma (K_2EDTA)	50 to 50,000	≤3.1	≤2.9	±4.7	±2.0	411 days (−20°C) 838 days (−80°C)	AG120-C-001 AG120-C-002 AG120-C-003 AG120-C-004 AG120-C-006 AG120-C-007
AG120-Q-00 ([(b) (4)]13-166)	AG120-Q-00 ([(b) (4)]13-166), AG120-Q-00-R1 ([(b) (4)]13-166ADD1), AG120-Q-00-R2 ([(b) (4)]13-166ADD2)	Human urine (0.5% CHAPS)	1.00 to 1,000	≤5.5	≤3.6	±3.0	±1.8	1,157 days (−80°C) (with 0.5% CHAPS) 1,157 days (−80°C) (without CHAPS)	AG120-C-001 AG120-C-003

Abbreviations: CHAPS = 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate; CRO = contract research organization; CV = coefficient of variance; K_2EDTA = dipotassium ethylenediaminetetraacetic acid; LC-MS/MS = liquid chromatography with tandem mass spectrometry; RE = relative error
[1] The assay performance data were from the assay validation report based on 4 levels of analytical quality controls.
Source: Table 5 from Applicant's Summary of Biopharmaceutic Studies and Associated Analytical Methods

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Table 63. Analytical Methods and validation reports for ivosidenib in human plasma (high range)

Analyte: Ivosidenib			
Report numbers: AG120-Q-010-R1 ([(b) (4)]14-032), AG120-Q-010-R1-ADD1 ([(b) (4)]14-032ADD1), AG120-Q-010-R1-ADD2 ([(b) (4)]14-032ADD2)			
Method: Protein precipitation extraction, LC-MS/MS		**Regression model:** linear $1/X^2$ $r^2 \geq 0.9980$	
Species: Human	**Anticoagulant:** K_2EDTA	**Matrix:** Plasma	**Stabilizer:** None
Identification of Sample	**Concentration (ng/mL)**	**Method Performance**	
		Precision (%CV)	**Accuracy (%RE)**
Calibration range	50.0 to 50,000	≤3.9	±2.0
Intra-day QC	50.0 (LLOQ QC)	≤6.2	±5.0
	150, 4,000, 20,000, 40,000 (Analytical QC)	≤3.1	±4.7
Inter-day QC	50.0 (LLOQ QC)	≤5.7	±1.4
	150, 4,000, 20,000, 40,000 (Analytical QC)	≤2.9	±2.8
Benchtop stability 25 hours 30 minutes at RT	150 and 40,000	≤1.4	±3.3
Freeze-thaw stability: 4 cycles; stored at −20°C and thawed at RT	150 and 40,000	≤1.6	±3.3
Freeze-thaw stability: 4 cycles; stored at −80°C and thawed at RT	150 and 40,000	≤2.1	±3.5
411 days long-term storage at −20°C[1]	150 and 40,000	≤4.8	±2.7
838 days long-term storage at −80°C[2]	150 and 40,000	≤1.3	±4.7
Whole blood stability 2 hours at RT	~20,000	Diff% from control within ±1.1%	
Whole blood stability 2 hours on ice	~20,000	Diff% from control within ± 2.3%	

Analyte: Ivosidenib			
Analyte Solution Stability			
Identification of Sample	**Concentration (µg/mL)**	**Method Performance**	
		Precision (%CV)	**Accuracy (%RE)**
Solution stability in ACN/H_2O (50/50, v/v) for 180 days at −20°C[1]	1.00	Diff% from control within ±1.9%	
Solution stability in DMSO for 366 days at −20°C[1]	5.0	Diff% from control within ±0.3%	
Other Tests			
Hemolysis	No significant impact in samples evaluated with up to 2.0% hemolysis		
Hyperlipidemia	No significant impact in samples with hyperlipidemic human plasma		
Cross-validation between low-range and high-range assay	In Study [(b) (4)]14-002, 16 samples were chosen from a total of 101 samples analyzed at the beginning of the study using a low range method ([(b) (4)]13-100 at 1.00 ng/mL to 1,000 ng/mL) and re-extracted as ISRs with exactly the same dilution factors, but using the high range method [(b) (4)]14-032 at 50.0 ng/mL to 50,000 ng/mL). All of the samples met the acceptance criteria. It can therefore be concluded that both the low and high range methods were successfully cross-validated. The test was done in Run 168 under study [(b) (4)]14-002 (Study AG120-C-001) and the results are presented in method validation report AG120-Q-010-R1-ADD1 ([(b) (4)]14-032ADD1), Appendix D.		

Abbreviations: ACN = acetonitrile; CV = coefficient of variance; ISR = incurred sample reanalysis; K_2EDTA = dipotassium ethylenediaminetetraacetic acid; LC-MS/MS = liquid chromatography with tandem mass spectrometry; LLOQ = lower limit of quantitation; N/A = not applicable; QC = quality control; RE = relative error; RT = room temperature

[1] Report AG120-Q-010-R1-ADD1 ([(b) (4)]14-032ADD1).
[2] Report AG120-Q-010-R1-ADD2 ([(b) (4)]14-032ADD2).

Source: Table 6 from Applicant's Summary of Biopharmaceutic Studies and Associated Analytical Methods

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BIOPHARMACEUTICS OF IVOSIDENIB TABLET FORMULATIONS

An overview of the tablet formulations used in ivosidenib clinical development is presented in **Table 64**.). Two tablet presentations (non-debossed) were used during clinical development:

1) Uncoated tablets (50, 200, 250 mg)
2) Blue film-coated tablets (250 mg)

The intended to-be-marketed formulation is a blue film-coated 250 mg tablet (debossed with "IVO" on one side of the tablet and "250" on the other side. The intended commercial tablet formulation is the same as the 250 mg tablet formulation used in the pivotal Study **AG120-C-001**, with the exception in the non-functional film coat and debossing. To bridge the formulations (50 + 200 mg vs. 250 mg strength, un-coated vs. film-coated, non-debossed vs. debossed, formulations used in pivotal study vs. proposed commercial formulation), the Applicant conducted in vitro comparative dissolution testing. Adequate bridging between the formulations was demonstrated. Refer to the Biopharmaceutics Review for details and results.

Table 64. Tablet formulations used in ivosidenib clinical development

Study	Brief Description	Dosage Form/Tablet Presentation	Clinical Bulk Lot Number	Clinical Labelled Lot Number	NDA Summary Section
Phase 1 Studies that Define PK Characteristics in Healthy Subjects					
Radiolabeled ivosidenib AME (CSR AG120-C-003)	Healthy males Dose: Single oral dose of ~500 mg ivosidenib	Suspension containing [^{14}C]ivosidenib (~200 µCi)	AG01-022-171-A-20150610-HPE	NA[1]	Module 2.7.1 Module 2.7.2
Food effect (CSR AG120-C-004)	Healthy males and females Dose: Part 1: Single oral dose of 500 mg ivosidenib Part 2: Single oral dose of 1,000 mg ivosidenib	250 mg Blue film-coated tablet	TTZV	P133187-0023L002	Module 2.7.1 Module 2.7.2
PK in Japanese relative to Caucasians (CSR AG120-C-006)	Healthy males Dose: Single oral dose of 250, 500, and 1,000 mg ivosidenib	250 mg Blue film-coated tablet	VBVS	P133187-0044L001	Module 2.7.2
Clinical DDI study with itraconazole (CSR AG120-C-007)	Healthy males and females Dose: Single oral dose of 250 mg ivosidenib; itraconazole 200 mg QD for 18 days	250 mg Blue film-coated tablet	TTZV	P133187-0041L001	Module 2.7.2

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Key Phase 1 Studies in Subjects With Advanced Hematologic Malignancies or Advanced Solid Tumors With an IDH1 Mutation					
Ivosidenib safety, PK, PD, and clinical activity (primary clinical study, CSR AG120-C-001)	Dose escalation: Subjects with advanced hematologic malignancies Dose: Single and multiple oral doses at daily dose from 100 mg BID to 1,200 mg QD	50 and 200 mg Uncoated tablets	Numerous; see Module 3.2.P.5.4_Ivosidenib Tablets, 250 mg	Numerous; see Module 3.2.P.5.4_Ivosidenib Tablets, 250 mg	Module 2.7.2
	Expansion: Dose: Single and multiple oral doses at 500 mg QD	50, 200, 250 mg Uncoated tablets			
Ivosidenib safety, PK (AG120-C-002 NDA Safety/PK Report)	Dose escalation: Subjects with advanced solid tumors Dose: Single and multiple oral doses at daily doses from 100 mg BID to 1,200 mg QD	50, 200, 250 mg Uncoated tablets	Numerous; see Module 3.2.P.5.4_Ivosidenib Tablets, 250 mg	Numerous; see Module 3.2.P.5.4_Ivosidenib Tablets, 250 mg	Module 2.7.2
	Expansion: Dose: Single and multiple oral doses at 500 mg QD				

Abbreviations: AME = absorption, metabolism, excretion; DDI = drug-drug interaction; IDH1 = isocitrate dehydrogenase, isoform 1; NA = not applicable; NDA = New Drug Application; PD = pharmacodynamic; PK = pharmacokinetic; QD = once daily
[1] The radioactive material was provided in bulk directly to the clinical site and was prepared on site; therefore, there is no labelled lot number.

Source: Table 1 from Applicant's Summary of Biopharmaceutic Studies and Associated Analytical Methods

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PHYSIOLOGICAL-BASED PHARMACOKINETIC MODELING REVIEW

1. Study objectives

The objective of this review is to evaluate the adequacy of Applicant's ivosidenib physiologically-based pharmacokinetic (PBPK) model to 1) predict the effect of CYP3A4 inhibitors/ inducers on the exposure of ivosidenib; 2) predict the DDI potential of ivosidenib as a perpetrator in various drug-drug interaction (DDI) mechanisms including [CYP3A4, CYP2B6, CYP2C8, CYP2C9, OATP1B1/OATP1B3, P-gp and OAT3]; 3) provide dosing recommendations based on the predicted DDI potential.

This review evaluates the adequacy of Applicant's PBPK model to support its proposed US prescription information [USPI] in section 12.3:

"Based on physiologically based pharmacokinetic (b) (4)*, co-administration* (b) (4) *ivosidenib* (b) (4) *moderate CYP3A4 inhibitor (fluconazole) is predicted to increase ivosidenib steady-state Cmax* (b) (4) *and AUC* (b) (4) *"*

" (b) (4) *co-administration* (b) (4) *ivosidenib* (b) (4) *a strong CYP3A4 inducer (600 mg rifampin once daily for 15 days) is predicted to decrease ivosidenib steady-state AUC by 33%"*

"Ivosidenib does not inhibit (b) (4)*, BCRP, OATP1B1, OATP1B3, OAT1, and OCT2 at clinically relevant concentrations. Ivosidenib is an inhibitor of OAT3.* (b) (4)

2. Executive Summary

The Applicant used a PBPK modeling approach to investigate the induction effect of ivosidenib on CYP3A4, and to predict the effects of repeated doses of itraconazole (a strong CYP3A4 inhibitor) on the exposure of ivosidenib following a single dosing of 250 mg ivosidenib in healthy subjects. The PBPK model was then used to evaluate the DDI between ivosidenib and multiple CYP3A4 modulators and CYP3A4 substrates under different dosing scenarios. PBPK analysis predicted an 83% decrease in midazolam AUC when co-administrated with repeated doses of 500 mg ivosidenib once daily. FDA PBPK model analysis predicted a 281% increase in ivosidenib AUC at steady state after administration of multiple doses of ivosidenib with a strong CYP3A4 inhibitor till steady state. PBPK model simulation also suggested that, due to the induction of the ivosidenib on CYP3A4 enzyme, the model predicted an approximately 90% decrease in steady state AUC of itraconazole when itraconazole was co-administered with ivosidenib.

These analyses are adequate to support DDI dosing recommendation for ivosidenib in USPI,

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including:

- Reduce TIBSOBO dose with strong CYP3A4 inhibitors. Monitor patients for increased risk of QTc interval prolongation (2.4, 5.2, 7.1, 12.3).
- Avoid concomitant use of sensitive CYP3A4 substrates with TIBSOVO (7.2, 12.3)
- Do not administer TIBSOVO with itraconazole or ketoconazole (CYP3A4 substrates) due to expected loss of anti-fungal efficacy.

3. Background

Ivosidenib (AG-120 International Nonproprietary Name; also formerly known as AGI-16678) is a potent, selective, orally active small molecule inhibitor of mutated isocitrate dehydrogenase-1 (IDH1), with no significant off-target activity observed. It is being developed for the treatment of patients with IDH1-mutated cancers, including relapsed or refractory acute myeloid leukemia (R/R AML).

The following PBPK reports and supporting documents were submitted to support the review of this NDA:

- Report AG120-C-001-PBPK: Physiologically-Based Pharmacokinetic (PBPK) Model Development for AG-120 and Assessment of Victim and Perpetrator Drug-Drug Interaction (DDI) Potential due to Cytochrome P450 (CYP) Induction and Transporter Inhibition
- On 12/21/2017, the applicant submitted supporting files for the physiologically based pharmacokinetic (PBPK) model development and model performance assessment (Sequence # 0001).
- On 2/9/2018, the applicant submitted additional Simcyp result files and model definition file that supported the development of the PBPK model (Sequence # 0009).
- On 3/19/2018, the applicant submitted their response to an IR issued on 03/9/2018. FDA agreed with most of the answers they provided to FDA's questions, except their justification for derivation of in vivo CYP3A4 induction using blood 4β-OH-cholesterol (4β-OHC) data.
- On 3/30/2018, the applicant submitted their response to an IR issued on 3/23/2018. The derivation of in vivo CYP3A4 induction using clinical PK data of ivosidenib was acceptable.
- On 5/18/2018, the applicant submitted their response to an IR issued on 5/14/2018. The typographical error in CYP3A4 IndC50 value presented in the PBPK report was corrected. The associated PBPK model files have been updated accordingly (Sequence # 0027), which was acceptable.

Clinical PK studies of ivosidenib that were utilized for model development and verification were summarized below:

Study AG120-C-001 is a Phase 1 study. Plasma concentration-time profiles of ivosidenib following the administration of 100 mg BID, 300mg QD, 500 mg QD, 800 mg QD and 1200 mg QD

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for 19 days (SD on day 1 with plasma sampling for 72 hours followed by QD dosing on Days 4-19) was collected. Biomarker data on 4β-hydroxy-cholesterol (4β-OHC) was used to characterize CYP3A4 induction by ivosidenib.

Study AG120- C-004 is a Phase 1 study in 2 parts. Part 1 investigated the effect of food (high-fat meal) on the PK of a single oral dose of 500 mg ivosidenib in healthy subjects. Part 2 investigated the safety and PK of a single oral dose of 1,000 mg ivosidenib in healthy subjects. PK data of 500 mg ivosidenib from Part 1 was used for PBPK model development.

Study AG120-C-007 is a Phase 1 study to investigate the effects of multiple oral doses of itraconazole on the PK of a single oral dose of ivosidenib in healthy subjects. Subjects received a single dose of 250 mg ivosidenib on Day 1 of both Period 1 and Period 2, after an overnight fast. In Period 2, subjects also received 200 mg QD itraconazole on Days −4 to 14. There was a washout period between Period 1 and Period 2.

In vitro metabolism of ivosidenib in HLMs and recombinant human CYP enzymes suggested that ivosidenib is mainly metabolized by CYP3A4 (98%), with minor contributions (2%) from CYP2B6 and CYP2C8. Based on in vitro CYP inhibition studies, ivosidenib appears to be a weak inhibitor of CYP2C8, CYP2C19, CYP2D6, and CYP3A4/5 (testosterone 6β-hydroxylation and midazolam 1'-hydroxylation) with the concentrations of drug that achieved half maximal inhibition (IC50) values greater than 50 µM. There was little or no evidence of direct inhibition of CYP1A2, CYP2B6, or CYP2C9 by ivosidenib. There was little or no evidence of time-dependent or metabolism-dependent inhibition by ivosidenib for any of the CYP enzymes evaluated. On the other hand, ivosidenib induced CYP2B6, CYP2C8, CYP2C9, and CYP3A4 messenger ribonucleic acid (mRNA) levels in cultured human hepatocytes. Ivosidenib showed little or no induction of CYP1A2. The effect of ivosidenib on CYP2C19 mRNA levels in cultured human hepatocytes was inconclusive.

4. Methods

4.1 Modeling development overview

The models were developed in Simcyp (version 15.1; Simcyp Ltd., a Certara Company, Sheffield, United Kingdom). A flow chart of modeling strategy is summarized below by the applicant **(Figure 16)**. The Applicant's justification of using blood 4β-OH-cholesterol (4β-OHC) level to derive the autoinduction effect of ivosidenib on CYP3A4 was not accepted, as the clinical observations of 4β-OHC didn't exhibit significant dose-response relationship between ivosidenib dose and blood 4β-OHC levels. Per FDA's request, the applicant derived CYP3A4 auto induction parameters by comparing the steady state (Cycle 1 Day 15) vs. single dose (Day -3) Cmax and $AUC_{0\text{-}Tau}$ ratios of ivosidenib using a sensitivity analysis, and the result was accepted.

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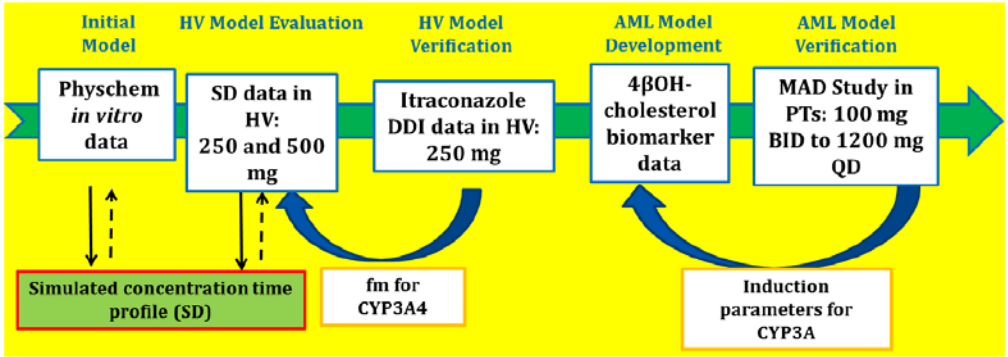

Figure 16. Summary of applicant's PBPK model building strategy
Refence: Study report AG120-C-001-PBPK Figure 2.

4.2 Model development

The PBPK model was developed using a modified Sim-NEurCaucasian population by matching the age distribution of the oncology population. This single modification accounted for the older age of the disease population used in clinical studies compared to the default file settings. Applicant stated that this change was important since age impacts drug clearance, with an increased age associated with reduced clearance.

Two PBPK models for ivosidenib (AG-120) that incorporated in vitro ADME, physicochemical and observed oral clearance were developed. Specifically:

- A model for AG-120 was developed based on the HV data obtained at 250 mg dose, in which the CLint input was back-calculated from the observed CL/F of 2.31 L/h in Study AG120-C-007 and calculated relative fa*Fg value of 89%. Fg was assumed to be 1 due to the low CL of the drug. Model input parameters for healthy volunteers are presented in Appendix 1.

- A separate model for AG-120 was developed based on the AML patient data, in which the CLint input was back-calculated from the observed CL/F of 1.63 L/h (estimated from popPK with plasma sample collection time up to 72 h) in Study AG120-C-001 and the assumed relative fa*Fg value of 69% (Appendix 2). Because in the patient study, food intake was allowed, the value of 69% as estimated from the food effect study conducted in the HVs in the fed state was used. Model input parameters for AML patients are presented in Appendix 2.

In this PBPK model, the dose-dependent absorption of AG-120 as well as food effect were not investigated in a mechanistic manner. Rather, dose-dependent fa values derived from the clinical data were used to simulate the kinetics of AG-120 at different dose levels. Additionally, it was assumed that the absorption of AG-120 was expected to be similar between HVs and patients at the same dose level. The Applicant justified their assumption by the following observation: AG-120 has high passive permeability and the estimated fa from the human AME study is moderate-to-high. Such justification appears to be acceptable.

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A fa value of 32.6% for ivosidenib was estimated from the human mass balance study in healthy volunteers with oral suspension (Study AG120-C-003) on the basis that 71.5% of the drug was recovered in the feces as unchanged parent drug, the fa values used in the model for healthy volunteers from other studies were estimated by multiplying the fa from the human AME study to those of ratios of respective plasma exposures **(Table 65)**. The fa values of ivosidenib using tablet formulation were 89.1%, 58.9% and 68.6%. Fa is assumed to be similar between patients with AML and healthy volunteers at the same dose.

Fg and Fh was assumed to be 1 due to the low CL of the drug. Subsequently, the observed 1.4- to 2.1-fold difference in CL/F (2.31 or 3.49 L/h vs. 1.63 L/h) between healthy volunteers (Study AG120-C-007 and Study AG120-C-004) and AML patients (Study AG120-C-001-PPK) was attributed to the difference in CL because of the disease and/or age effect. Thus, two PBPK models for AG-120 were developed: one model for AG-120 was developed based on the HV data and a separate model was developed based on the AML patient data. The Applicant's justifications appear to be acceptable.

Table 65. Observed single-dose CL/F of AG-120 obtained with different formulations administered to the healthy volunteers (HV) and to patients (AML)

Study	Study AG120-C-003 (Fasted HV)	Study AG120-C-007 (Fasted HV)	Study AG120-C-004 (Fasted HV)	Study AG120-C-004 (Fed HV)	Study AG120-C-001 (AML Patients)
Dose	491 mg	250 mg	500 mg	500 mg	500 mg
Formulation	Oral suspension	Tablet Clinical formulation	Tablet Clinical formulation	Tablet Clinical formulation	Tablet Clinical formulation
Population	HV (n=8)	HV(n=22)	HV (n=30)	HV (n=27)	AML
CL/F (L/h)	6.31	2.31	3.49	2.87	1.63
Fa or Relative F	32.6%	89.1%	58.9%	68.6%	68.6%

Reference: Table obtained from study report AG120-C-001-PBPK Table 1.

AG-120 showed very slow metabolism in the in vitro incubations using human liver microsomes and recombinant human CYP enzymes. By measuring the formation of four major metabolites M1-M4 in the recombinant systems, and by combining with chemical inhibition data generated in HLM, it was estimated that CYP3A4 contributes to 98% of the metabolism of AG-120; followed by 2% from other enzymes including CYP2B6 and CYP2C8. In the final model, it was assigned that CYP3A4 Contributes to 100% of AG-120 metabolism. The applicant's justifications appear to be acceptable.

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Applicant applied the retrograde method to calculate Clint(s) using the observed oral clearance (CL/F) in HV and AML patients.

Ivosidenib CYP inhibition/induction

The inhibition potential of ivosidenib on CYP enzymes was evaluated using the mechanistic static model recommended in FDA DDI guidance [1]. Results of the Applicant's analysis suggested that CYP inhibition by ivosidenib treatment is unlikely to be clinically significant **(Table 66)**.

Table 66. Mechanistic static model calculations for ivosidenib following oral dosing of 1200 mg

CYP Isoforms	Substrate #	F_m	F_g	IC_{50} (uM)	$K_{i,\mu}$ (uM)	AUCR
2D6	Metoprolol	0.81	0.98	>50	33.8	1.09
2C8	Repaglinide	0.64	0.86	>50	33.8	1.08
2C19	S-(+)-Mephenytoin	0.98	1.00	>50	33.8	1.1
3A4	Midazolam	0.96	0.60	>50	33.8	1.1

Reference: Table obtained from study report AG120-C-001-PBPK Table 5.
#Substrate fm and Fg values were taken from Simcyp compound library

Ivosidenib induced the mRNA and activity level of CYP2B6 and CYP3A4, but not CYP1A2 in cultured human hepatocytes (AG-120 Induction Report). In vitro Ind_{max} and EC_{50} values for CYP2B6, CYP2C8 and CYP2C9 induction were directly used in the ivosidenib PBPK model. For CYP3A, in vivo Ind_{max} and EC_{50} values for CYP3A4 were derived using the in-vitro mRNA induction data, and calibrated with positive control compound (such as rifampin). For ivosidenib, the observed E_{max} and EC50 values for CYP3A4 mRNA in vitro were 78.2-fold and 12.5 µM, respectively. The observed E_{max} of ivosidenib was calibrated against the in vitro rifampin E_{max} (58.2-fold) as well as the in vivo rifampin Ind_{max} (16-fold) to obtain an in vivo Ind_{max} of 21.25-fold for ivosidenib.

By using the induction parameters, Ind_{max} of 21.25 and IndC50 of 12.5 µM, the Applicant's PBPK model reasonably described the PK profiles of ivosidenib following a single dose of 250 and 500 mg ivosidenib in healthy volunteers. However, this PBPK model cannot describe ivosidenib PK profiles following multiple doses of ivosidenib in AML patients. Thus, the Applicant refined IndC50 value of ivosidenib using the clinical PK data in AML patients.

In the initially submitted PBPK report, the Applicant used the changes of blood 4β-OHC level in AML patients receiving 200 to 1200 mg daily dose of ivosidenib (Study AG120-C-001) to derive IndC50 value in the AML patients. 4β-OHC is an endogenous biomarker of hepatic CYP3A4 activity. As shown in **Figure 17**, the observed increase in 4β-OHC levels as a function of ivosidenib dose showed significant interindividual variability, and didn't exhibit a significant dose-response relationship.

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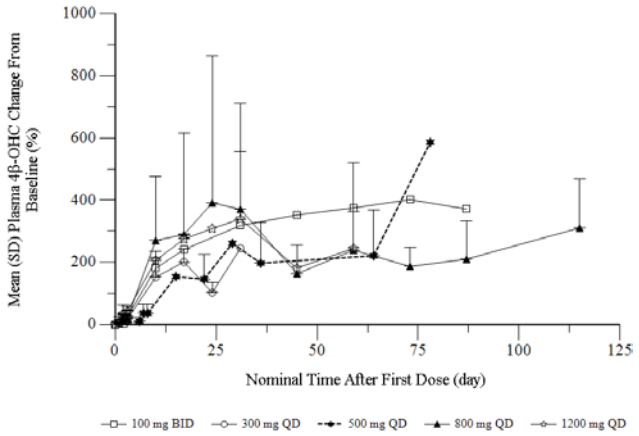

Figure 17: Observed mean (+SD) % increase in 4β-OHC levels as a function of AG-120 dose (Study AG120-001)

Reference: Figure obtained from study report AG120-C-001-PBPK Figure 3.

Therefore, the Applicant's justification in derivation of CYP3A4 autoinduction parameter, IndC50, in AML patients using 4β-OHC level was not accepted. FDA recommended the Applicant to conduct a sensitivity analysis to confirm the optimal CYP3A4 induction parameters by comparing the simulated ratios of Cmax and $AUC_{0\text{-}Tau}$ of ivosidenib at steady state (Cycle 1 Day 15) vs. single dose (Day -3) over a range of CYP3A4 induction parameters (e.g. IndC50: 0.125 to 12.5 µM), with those observed in clinical PK data (Study AG120-C-001). Applicant acknowledges the Agency's comment and conducted a sensitivity analysis using 4 clinical PK datasets collected for ivosidenib at 300, 500, 800, 1200 mg QD in Study AG120-C-001. The twice daily (BID) regimen (100 mg BID) was not included in this analysis. The predicted versus observed $AUC_{0\text{-}tau}$ and Cmax ratios of ivosidenib (300-1200 mg QD) are summarized in **Table 67** and **Table 68**, respectively. By using CYP3A4 IndC50 of 2.5 µM, the model can recover the observed $AUC_{0\text{-}tau}$ and Cmax accumulation ratios in the dose range of 300 mg to 1200 mg QD.

Table 67: Observed and Predicted Accumulation Ratio ($AUC_{0\text{-}tau,\,ss}/AUC_{0\text{-}tau,\,Day\,-3}$) of Ivosidenib (300-1200 mg QD) Over a Range of CYP3A4 Induction Parameters (IndC50: 0.125-12.5 µM)

Dose (mg)	$AUC_{0\text{-}tau,ss}/AUC_{0\text{-}tau,Day\,-3}$						
	Observed	CYP3A4 Induction Parameters ($IndC_{50}$) Used for Modeling					
		12.5 µM	5 µM	2.5 µM	1 µM	0.5 µM	0.125 µM
300	2.89 (n=4)	3.82	3.07	2.82	1.88	1.51	1.025
500	1.99 (n=12)	3.64	2.79	2.30	1.67	1.36	0.96
800	1.77 (n=11)	3.15	2.37	1.96	1.43	1.17	0.85
1200	2.07 (n=5)	2.81	2.10	1.85	1.27	1.06	0.79

Abbreviations: $AUC_{0\text{-}tau,Day\,-3}$ = area under the concentration-time curve from time 0 to the end of the dosing interval at Day -3; $AUC_{0\text{-}tau,ss}$ = area under the concentration-time curve from time 0 to the end of the dosing interval at steady state; CYP = cytochrome P450; $IndC_{50}$ = inducer concentration that supports half maximal induction.
Source: Report AG120-C-001-PKPD (observed data); Module 5.3.5.4 PBPK Simulation Files (predicted data)

Reference: Table obtained from applicant's response to IR received on 3/23/2018. Table 1

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Table 68: Observed and Predicted Accumulation Ratio ($C_{max,ss}/C_{max,Day\ -3}$) of Ivosidenib (300-1200 mg QD) Over a Range of CYP3A4 Induction Parameters (IndC50: 0.125-12.5 µM)

Dose (mg)	$C_{max,\ ss}/C_{max,Day-3}$						
	Observed	CYP3A4 Induction Parameters ($IndC_{50}$) Used for Modeling					
		12.5 µM	5 µM	2.5 µM	1 µM	0.5 µM	0.125 µM
300	1.79 (n=4)	2.38	2.05	1.98	1.50	1.32	1.069
500	1.46 (n=12)	2.35	1.96	1.72	1.42	1.26	1.04
800	1.43 (n=12)	2.13	1.77	1.57	1.3	1.16	0.98
1200	1.62 (n=5)	1.96	1.62	1.49	1.21	1.1	0.94

Abbreviations: $C_{max,Day-3}$ = maximum plasma concentration at Day -3; $C_{max,ss}$ = maximum plasma concentration at steady state; CYP = cytochrome P450; $IndC_{50}$ = inducer concentration that supports half maximal induction.
Source: Report AG120-C-001-PKPD (observed data); Module 5.3.5.4 PBPK Simulation Files (predicted data)
Reference: Table obtained from applicant's response to IR received on 3/23/2018. Table 2

Ivosidenib transporter inhibition parameters

The potential of ivosidenib in inhibiting transporters was evaluated using in vitro assays **(Table 69)**. The in-vitro inhibition parameters for P-gp, OATP1B1, OATP1B3, and OAT3 were incorporated into the developed ivosidenib PBPK model.

Table 69. Transporter inhibition parameters determined in vitro

P-gp Ki(µM)	*19.6*	*=measured IC50 as digoxin cons (10 µM) << Km Report AG120-N-026-R1*
OATP1B1 Ki (µM)	*9.56*	*=measured IC50 as Estradiol-17β-glucuronide (50 nM) << Km Report "Report AG120-N-080"*
OATP1B3 Ki (µM)	*22.8*	*=measured IC50 as Estradiol-17β-glucuronide (50 nM) << Km Report "Report AG120-N-080"*
OAT3 Ki (µM)	*0.322*	*=measured IC50 as Estrone-3-sulfate (50 nM) << Km "Report AG120-N-080"*

Reference: Table adapted from study report AG120-C-001-PBPK Table 7.

5. Results

5.1 Adequacy of the Applicant's PBPK model to describe the PK profiles of ivosidenib following a single or repeated doses of ivosidenib

The performance of the PBPK model was evaluated by comparing PBPK model simulations to observed ivosidenib PK under different clinical scenarios. FDA reviewer agreed with the applicant's overall PBPK model settings, as the final PBPK model appears to provide a reasonable characterization on ivosidenib PK following single and multiple doses, the autoinduction effect of ivosidenib, and the effects of itraconazole treatment on the single-dose PK of ivosidenib.

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(1). The performance of the PBPK model in characterizing ivosidenib PK in healthy volunteers following a single 500 mg oral dose administered under fasted condition is summarized in **Table 70**. PBPK simulation was performed in accordance to the respective clinical study design.

Table 70. Mean predicted and observed exposure of ivosidenib following the administration of a single dose of 500 mg in the fasted state

	Dose (mg)	Study	Predictions	Observations
Cmax (ng/mL)	500	AG120-C-004	3327 (3178 – 3488)	2274 ± 558
AUC (ng.h/mL)	500	AG120-C-004	160148 (149200 – 174736)	139509 ± 46064

Reference: Table obtained from applicant's response to IR received on 5/14/2018. Table 8

(2). The performance of the PBPK model to describe ivosidenib PK following the various dosing levels ranged from 100 mg BID to 1200 QD mg for 19 days (Day -3 vs. Day 15) in cancer patients under the fed condition is summarized in **Table 71** (AUC) and **Table 72** (Cmax). The PBPK model exhibited a trend of under prediction at lower doses, and over-prediction at higher doses, which may be associated with the fixed Fa value at 0.69 in AML patient PBPK model across the dosing ranges from 100 mg BID to 1200 mg QD (Appendix 2), while PK data from healthy subjects **(Table 65)** showed that the relative F of ivosidenib at 250 mg was higher than that at 500 mg (89.1% vs. 58.9%). However, the overall PBPK model performance was still acceptable. The PBPK model reasonably captured the autoinduction effect of ivosidenib on CYP3A4 **(Table 67 and Table 68)**, and described the steady-state PK profiles of ivosidenib in patients at clinically relevant exposure levels (500 mg).

Table 71. Mean predicted and observed $AUC_{0\text{-}Tau}$ of ivosidenib in Caucasian subjects receiving 100 mg to 1200 mg treatment for 19 days in cancer patients

AUC (ng.h/mL)	Dose (mg)	Study	Predictions Geomean	Observations Geomean (%CV)	Pred./Obs. Ratio
Day -3	100	AG120-C-001	6098	11442 (43.5)	0.53
	300	AG120-C-001	29143	36450 (27.6)	0.80
	500	AG120-C-001	47982	61135 (33.2)	0.78
	800	AG120-C-001	76481	84430 (54.6)	0.91
	1200	AG120-C-001	112665	96283 (41.7)	1.17
Day 15	100	AG120-C-001	31557	39597 (88.7)	0.80
	300	AG120-C-001	82046	105363 (26.2)	0.78
	500	AG120-C-001	110438	133453 (44.8)	0.83
	800	AG120-C-001	150168	125935 (53.1)	1.19
	1200	AG120-C-001	208355	202767(25.8)	1.03

Reference: Table obtained from study report AG120-C-001-PBPK Table 12 - 16

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Table 72. Mean predicted and observed Cmax of AG-120 in Caucasian subjects receiving 100 mg to 1200 mg treatment for 19 days in cancer patients

Cmax (ng/mL)	Dose (mg)	Study	Predictions Geomean	Observations Geomean (%CV)	Pred./Obs. Ratio
Day -3	100	AG120-C-001	930	1377 (44.2)	0.68
	300	AG120-C-001	2702	3117 (14.7)	0.87
	500	AG120-C-001	4595	4481 (46.6)	1.03
	800	AG120-C-001	7318	5799 (43.1)	1.26
	1200	AG120-C-001	11147	6611 (27.1)	1.69
Day 15	100	AG120-C-001	3214	4253 (70.7)	0.80
	300	AG120-C-001	5346	5583 (27.9)	0.96
	500	AG120-C-001	7924	7108 (38.8)	1.11
	800	AG120-C-001	11464	7266 (44.2)	1.58
	1200	AG120-C-001	16556	10850 (23.1)	1.53

Reference: Table obtained from study report AG120-C-001-PBPK Table 12 - 16

5.2 Clinical DDI simulation

The performance of the PBPK model in characterizing ivosidenib PK in healthy volunteers following a single 250 mg oral dose administered on Day 5 under fasted condition in the presence and absence of itraconazole treatment (200 mg QD capsules for 18 days under the fed condition) is summarized in **Table 73**. PBPK simulation was performed in accordance to the respective clinical study design. Applicant's PBPK model under-predicted the observed DDI effects with itraconazole. Applicant suggested that the under-predicted ivosidenib exposure could have resulted from the reduced renal clearance of ivosidenib by itraconazole on P-gp activity.

Table 73. Mean predicted and observed exposure ratios of ivosidenib in the presence and absence of itraconazole treatment in Caucasian subjects

	Dose (mg)	Study	Observed Ratios	Predicted Ratios	Predicted Ratios (with reduced renal clearance)
Cmax (ng/mL)	250	AG120-C-007	1.02 (0.93 – 1.13)	1.04 (1.04 – 1.04)	1.04 (1.04 – 1.05)
AUC (ng.h/mL)	250	AG120-C-007	2.69 (2.45 – 2.95)	1.94 (1.90 – 1.98)	2.14 (2.09 – 2.18)

*Table obtained from study report AG120-C-001-PBPK Table 11

5.3 Model application

(1). The DDI potential of ivosidenib as CYP enzyme inducer was evaluated by comparing the

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simulated PK of CYP enzyme substrates following a single oral dose on day 15, in the presence and absence of ivosidenib treatment at 500 mg QD or 1200 mg QD for 19 days **(Table 74)**. The default CYP substrate models within Simcyp V15.1 were used without any modification.

Table 74. Mean predicted exposure of CYP substrates in AML subjects receiving a single oral dose treatment in the presence and absence of multiple doses of ivosidenib

CYP substrates	Dose	Ivosidenib 500 mg QD for 19 days		Ivosidenib 1200 mg QD for 19 days	
		Cmax ratio	AUC ratio	Cmax ratio	AUC ratio
Bupropion (CYP2B6)	150 mg	0.92	0.90	0.89	0.85
Midazolam (CYP3A4)	5 mg	0.26	0.17	0.16	0.10
Repaglinide (CYP2C8 and CYP3A4)	0.25 mg	0.61	0.52	0.50	0.41
Warfarin (CYP2C9)	10 mg	0.99	0.84	0.98	0.77

*Table obtained from study report AG120-C-001-PBPK Table 17 - 24

(2). The DDI potential of ivosidenib as transporter inhibitor was evaluated by comparing the simulated PK of transporter substrates following a single oral dose on day 15, in the presence and absence of ivosidenib treatment at 500 mg QD or 1200 mg QD for 19 days **(Table 75)**. The default transporter substrate models within Simcyp V15.1 were used without any modification.

Table 75. Mean predicted exposure of transporter substrates in AML subjects receiving a single oral dose treatment in the presence and absence of multiple doses of ivosidenib

Transporter substrates	Dose	Ivosidenib 500 mg QD for 19 days		Ivosidenib 1200 mg QD for 19 days	
		Cmax ratio	AUC ratio	Cmax ratio	AUC ratio
Rosuvastatin (NTCP, OATP1B1 and OATP1B3)	10 mg	1.03	1.02	1.06	1.04
Methotrexate (OAT3)	200 mg/m^2	1.00	1.27	1.00	1.36

*Table obtained from study report AG120-C-001-PBPK Table 27 – 30

As the predictive power of PBPK model on transporter is less verified clinically due to insufficient clinical case, the inhibition potency of the drug on a transport substrate is primarily evaluated by comparing the ratio between local tissue concentration and the in-vitro reported Ki (see FDA in-vitro DDI draft guidance [1] for the recommended cut-off criteria). For basolateral transporters, such as OATP1B1/3 and OAT3, PBPK modeling could be used to facilitate the evaluate the DDI. Prior to using PBPK modeling to evaluate the DDI potency of an investigational drug, the applicant need to verify their PBPK models (including the substrate PBPK model) with clinical PK data (refer

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to FDA in-vitro DDI guidance [1] on suggestions for how sponsors should conduct and verify their PBPK analyses). In addition, sensitivity analyses are required to evaluate the sensitivity of the in-vitro Ki values. In the current PBPK report, the applicant has verified the PBPK model for rosuvastatin and methotrexate–as a transport substrate. Applicant's PBPK model predicted a minimal effect of ivosidenib on the PK of rosuvastatin using the in-vitro reported Ki value. By setting the both OATP1B1 and 1B3 Ki values at 1/10 of the in-vitro value, the model predicted an approximate 30% increase in exposure of rosuvastatin. For OAT3, Applicant's PBPK model predicted a 27% increase in methotrexate AUC using the in-vitro reported Ki. Applicant did not conduct the sensitivity analysis on OAT3 Ki value and FDA's analysis showed that by setting OAT3 Ki value at 1/10 of the in-vitro value, the model predicted an approximate 60% increase in exposure of methotrexate. (b) (4) (b) (4) .

The capability of the PBPK model to predict ivosidenib as a P-gp inhibitor was not evaluated because the predictive performance of PBPK for P-gp inhibition has not been fully established. In addition, the Applicant's PBPK did not include mechanism-based oral absorption model for ivosidenib. Therefore, the Applicant's PBPK model cannot be used to evaluate the inhibitory potential of ivosidenib on P-gp transporter.

(3). The DDI potential of ivosidenib as CYP enzyme substrate was evaluated by simulating PK of ivosidenib under two clinical scenarios:

Scenario 1: simulating PK of a single oral dose of 500 mg ivosidenib tablet under fed condition in the presence and absence of CYP enzyme inhibitor/inducer treatment using AML patient PBPK model (Table 76).

Table 76. Mean predicted exposure of a single oral dose of 500 mg ivosidenib in the presence and absence of CYP enzyme inhibitor/inducer treatment

CYP inhibitor/inducer	Treatment	Cmax ratio	AUC ratio
Fluconazole (Moderate CYP3A4 inhibitor)	Ivosidenib on day 8 + Fluconazole 400 mg on day 1 followed by 200 mg QD for 29 days	1.02	1.73
Fluvoxamine (Weak CYP3A4 inhibitor)	Ivosidenib on day 12 + Fluvoxamine 100 mg BID for 22 days	1.01	1.11
Rifampin (Strong CYP3A4 inducer)	Ivosidenib on day 10 + Rifampin 600 mg QD for 30 days	0.91	0.35
Efavirenz (Moderate CYP3A4 inducer)	Ivosidenib on day 10 + Efavirenz 600 mg QD for 30 days	0.94	0.50

*Table obtained from study report AG120-C-001-PBPK Table 31 – 39

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Scenario 2: simulating PK of a multiple daily oral dose of 500 mg ivosidenib tablet under fed condition in the presence and absence of CYP enzyme inhibitor/inducer treatment using AML patient PBPK model **(Table 77)**.

Table 77. Mean predicted exposure of a multiple daily oral dose of 500 mg ivosidenib in the presence and absence of CYP enzyme inhibitor/inducer treatment

CYP inhibitor/inducer	Treatment	Cmax ratio	AUC ratio
Itraconazole (Strong CYP3A4 inhibitor)[#]	Ivosidenib for 15 days + Itraconazole 200 mg QD for 15 days under fed condition	1.29	1.44
Fluconazole (Moderate CYP3A4 inhibitor)	Ivosidenib for 15 days + Fluconazole 400 mg on day 1 followed by 200 mg QD for 14 days	1.52	1.90
Fluvoxamine (Weak CYP3A4 inhibitor)	Ivosidenib for 15 days + Fluvoxamine 100 mg BID for 15 days	1.08	1.11
Rifampin (Strong CYP3A4 inducer)	Ivosidenib for 30 days + Rifampin 600 mg QD on day 15 - 30	0.81	0.67
Efavirenz (Moderate CYP3A4 inducer)	Ivosidenib for 30 days + Efavirenz 600 mg QD on day 15 - 30	0.93	0.89

Reference: Table obtained from study report AG120-C-001-PBPK Table 31 – 39
[#]Ivosidenib induces CYP3A4, including its own metabolism. Co-administration of ivosidenib with CYP3A4 substrates such as itraconazole are expected to decrease itraconazole steady-state AUC significantly. Consequently, a significant decrease in the CYP3A4 inhibitory effect of itraconazole is also expected, and model simulated result couldn't reliably reflect the effect of strong CYP3A4 inhibition on Ivosidenib at steady state.

The Applicant's PBPK simulation also suggested that co-administration of ivosidenib for 15 days significantly decreased itraconazole steady-state AUC, since itraconazole is a CYP3A4 substrates, which was associated with induction of hepatic and intestinal CYP3A4 enzymatic activity after multiple doses of ivosidenib **(Figures 18 and 19).** The simulation results indicate approximately 90% decrease in steady-state exposure of itraconazole with concomitant use with repeated doses of ivosidenib. Therefore, it was recommended that ivosidenib should not be co-administered with itraconazole or ketoconazole (both are CYP3A4 substrates) due to expected loss of anti-fungal efficacy.

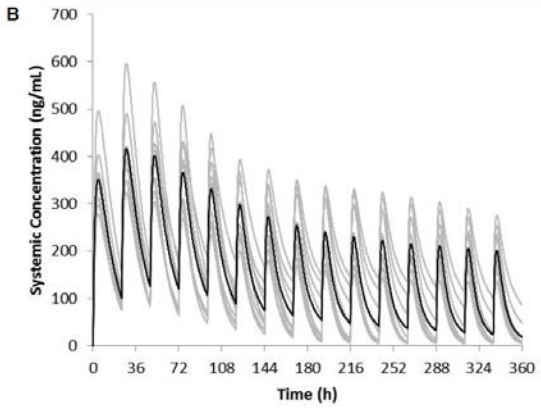

Figure 18: Simulated mean plasma concentration-time profiles of itraconazole after multiple doses of itraconazole in the presence of multiple oral doses of ivosidenib

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Reference: Figure obtained from study report AG120-C-001-PBPK Figure 38.

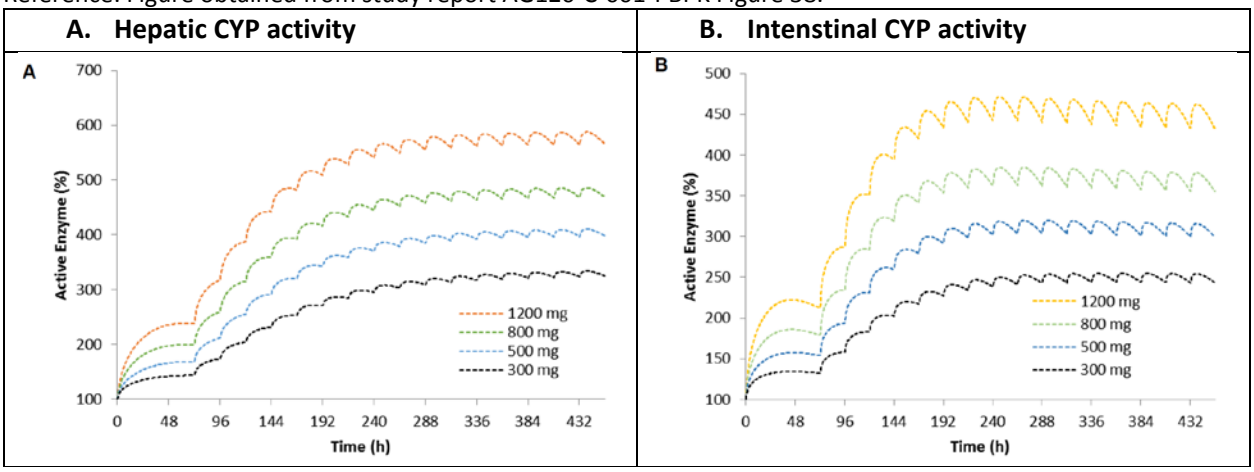

Figure 19: Simulated mean hepatic and intestinal CYP3A4 activity profiles following the administration of 300 mg to 1200 mg QD for 19 days.

Reference: Figure obtained from study report AG120-C-001-PBPK Figure 16.

(4). The DDI potential of between ivosidenib and strong CYP3A4 inhibition.

Since ivosidenib induces CYP3A4, and would significantly reduce the exposure of itraconazole and ketoconazole (both are index strong CYP3A4 inhibitors). FDA reviewer conducted additional PBPK simulations to evaluate the DDI interaction between ivosidenib and a strong CYP3A4 inhibitor which is not primary metabolized by CYP3A4 pathway.

A hypothetical strong CYP3A4 inhibitor (Compound X) was constructed by modifying the default fluconazole (a moderate CYP3A4 inhibitor) model in Simcyp V15.1. Reviewer adjusted the CYP3A4 inhibitory potency (Ki), and CLiv of Compound X till the simulated CYP3A4 inhibitory profile of Compound X following 200 mg QD for 15 days is similar to those simulated with itraconazole [2]. The fitted Ki values were 0.0017 µM while CLiv was 15 L/hr. Reviewer used Compound X PBPK model to assess the magnitude of DDI between ivosidenib and a strong CYP3A4 inhibitor which is not a substrate of CYP3A. The model predicted a 2.52 and 3.81-fold increase in the steady state Cmax and AUC of ivosidenib, respectively, following co-administration ivosidenib 500mg QD with Compound X for 15 days **(Table 78)**.

Table 78. Mean predicted exposure of a multiple daily oral dose of 500 mg ivosidenib in the presence and absence of a hypothetical strong CYP3A4 inhibitor treatment

CYP inhibitor/inducer	Treatment	Cmax ratio	AUC ratio
Hypothetical strong CYP3A4 inhibitor	Ivosidenib for 15 days + Hypothetical strong CYP3A4 inhibitor 200 mg QD for 15 days	2.52	3.81

*Table obtained from FDA simulation "Hypothetical strong CYP3A4 inhibitor_200 mg_ SS-ddi-500-mg-sd.xlsx".

6. Question Based Review

When using PBPK modeling to predict the interaction potential of ivosidenib as a substrate and

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an inducer for CYP3A4, the following questions were considered:

6.1 Can the PBPK model of ivosidenib (the investigational product) describe the available clinical PK data using different dosing regimens and the autoinduction effect of ivosidenib on CYP3A4?

Yes, the proposed ivosidenib model reasonably described the plasma concentrations of ivosidenib following repeat doses of ivosidenib for 19 days at dose ranged from 100 mg BID to 1200 mg QD **(Figure 20)**.

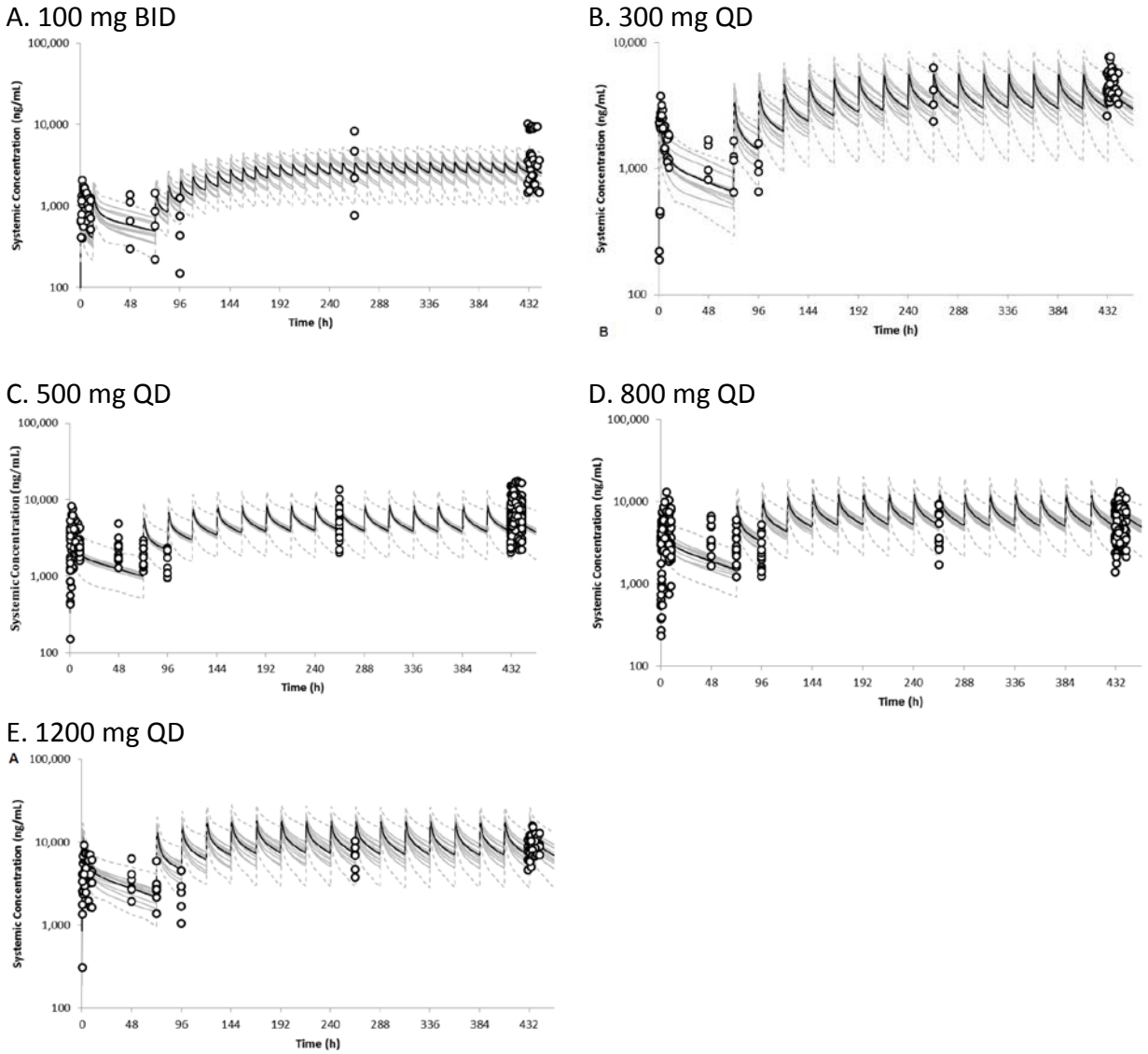

Figure 20: Simulated (lines) and observed (data points; from Study AG120- C-001) mean plasma concentration-time profiles of ivosidenib following the administration of 100 mg BID and 300 - 1200 mg QD for 19 days.

Reference: Figure obtained from study report AG120-C-001-PBPK Figure 11-15.

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The simulated mean Cmax and AUC_t reasonably agreed with the respective observed values **(Table 71 and Table 72)** as discussed Results section.

6.2 Can the proposed PBPK model be used to predict the DDIs between ivosidenib and CYP3A4 inhibitors and substrates?

Yes, the final PBPK model reasonably predicted the clinical DDI result between CYP3A4 inhibitor itraconazole with a single dose of ivosidenib in Study AG120-C-007. The predicted AUCR of a single dose of ivosidenib with itraconazole is 2.14 **(Table 73)**. The final PBPK model also predicted the clinical DDI between CYP3A4 inhibitor fluconazole and fluvoxamine with a single dose of ivosidenib. The predicted AUCRs of a single dose of ivosidenib with fluconazole and fluvoxamine are 1.73 and 1.11, respectively **(Table 76)**.

The final PBPK model was also used to predict the clinical DDI results between CYP3A4 inhibitors itraconazole, fluconazole and fluvoxamine with ivosidenib at steady state. The predicted AUCRs of ivosidenib at steady state in present of itraconazole, fluconazole and fluvoxamine are 1.44, 1.90 and 1.11, respectively **(Table 77)**. The lower AUCR of ivosidenib at steady state with itraconazole (a strong CYP3A4 inhibitor) compared to those observed with fluconazole (moderate CYP3A4 inhibitor) was associated with induction of hepatic and intestinal CYP3A4 enzymatic activity by ivosidenib **(Figure 19)** and, consequently, led to the decrease in itraconazole exposure **(Figure 18)**, since itraconazole is a CYP3A4 substrates. Therefore, an additional PBPK simulation was conducted to evaluate the steady state DDI interaction between ivosidenib and a hypothetical strong CYP3A4 inhibitor that is not metabolized by CYP3A4 (as discussed Results section). The predicted AUCRs of ivosidenib at steady state with this hypothetical strong CYP3A4 inhibitor is 3.81 **(Table 78)**.

The PBPK model also predicted that, following a repeated dosing of 500 mg ivosidenib and a single dose of midazolam, the model predicted the AUC ratio of midazolam is 0.17 **(Table 74)**.

6.3 Can the proposed PBPK model be used to predict the DDIs between ivosidenib and CYP3A4 inducer?

Yes. When co-administration with repeated doses of rifampin, a strong CYP3A4 inducer, 600 mg QD, the model predicted 65 and 33% decrease in ivosidenib AUC with a single and repeat doses of 500 mg ivosidenib once daily. The model predicted 50 and 19% decrease in ivosidenib AUC when co-administrated efavirence, a moderate CYP3A4 inducer, with a single and repeat doses of ivosidenib of 500 mg ivosidenib once daily.

The applicant proposed to avoid concomitant use of strong CYP3A4 Inducers with ivosidenib.

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7. Conclusions

The Applicant's final ivosidenib PBPK model is adequate to predict the autoinduction effect of ivosidenib on CYP3A4, as well as the plasma concentrations of ivosidenib following multiple doses at dose levels ranging from 100 mg to 1200 mg for 19 days in AML patients. This PBPK model is also adequate to predict ivosidenib exposure in healthy subjects co-administered with a strong CYP3A4 inhibitor such as itraconazole. The model predicted a 114% increase in ivosidenib AUC after a single oral dose of ivosidenib with concomitant administration of 200 mg itraconazole. FDA PBPK analysis predicted a 281% increase in ivosidenib AUC at steady state following co-administration of multiple doses of ivosidenib and a strong CYP3A4 inhibitor.

For moderate CYP3A4 inhibitors, the model predicted approximately 90% increase in steady-state exposure of ivosidenib compound when the drug is co-administered with a moderate CYP3A4 inhibitor (i.e. fluconazole) For CYP3A4 inducers, the simulation results indicated approximately 33% and 19% decrease in steady-state exposure of ivosidenib compound when the drug is co-administered with a strong CYP3A4 inducer (i.e. rifampin) or a moderate CYP3A4 inducer (i.e. efavirence). For a sensitive CYP3A4 substrate, the model predicted an 83% decrease in midazolam AUC following repeated dosing of 500 mg ivosidenib once daily and a single dose of midazolam. PBPK analysis also suggested that, due to the induction of the ivosidenib on CYP3A4 enzyme, the model predicted an approximately 90% decrease in steady state AUC of itraconazole when itraconazole was co-administered with ivosidenib. For transporter DDI, PBPK analysis suggested that the clinical inhibitory potential of ivosidenib on OATP1B1/1B3 substrate (such as rosuvastatin) is not significant. The model suggested up to 60% increase in exposure of rosuvastatin when co-administrated with ivosidenib. The applicant's PBPK model cannot be used to evaluate the inhibitory potential of ivosidenib on P-gp.

These analyses are adequate to support dosing recommendation of ivosidenib under different clinical DDI scenarios, including:

- Reduce TIBSOBO dose with strong CYP3A4 inhibitors. Monitor patients for increased risk of QTc interval prolongation (2.4, 5.2, 7.1, 12.3).
- Avoid concomitant use of sensitive CYP3A4 substrates with TIBSOVO (7.2, 12.3)
- Do not administer TIBSOVO with itraconazole or ketoconazole (CYP3A4 substrates) due to expected loss of anti-fungal efficacy.

PBPK Appendices

Appendix 1. PBPK parameter values used to simulate the kinetics of AG-120 of 250 and 500 mg in the HV population in the fasted state

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Parameter Name	Value	Method/Source
Phys Chem and Blood Binding		
MW (g/mol)	582.96	Provided by Agios
logP	2.97	Measured, Report "AGI-16678_pKa and logD"
Compound type	Monoprotic base	Provided by Agios
pK_a	1.4	Predicted, Report "AGI-16678_pKa and logD"
B/P	0.556	Report "PK parameters and renal clearance from radiolabeled AME study"
fu_p	0.057	Determined at concentration of 0.2 to 10 µM by ultracentrifugation
Absorption		
fu_{gut}	0.057	Optimised via sensitivity analysis (section 2.7.2)
fa	0.89 (250 mg) or 0.59 (500 mg)	Dose-dependent, calculated from the relative bioavailability of the clinical formulation tablet formulation vs. oral suspension, the latter associated with an estimated fa value of ~33% determined in a human mass balance study.
ka (h^{-1})	1.1	Optimised to recover the observed C_{max} in Study AG120-C-007
T_{lag} (h)	0.27	Set to the same value as estimated from AML patient data using Pop-PK analysis (Report Number AG120-C-001-PPK)
Model	Full PBPK	
V_{ss} (L/kg)	2.45	Predicted (Method 2)
Elimination		
$CL_{int,CYP3A4}$ (µl/min/pmol)	0.045	Back-calculated from observed mean CL/F of 2.31L/h in Study AG120-C-007; Assign 100% of metabolism to CYP3A4
CL_R (L/h)	0.537	Report "PK parameters and renal clearance from radiolabeled AME study"
Induction		
CYP3A4 Ind_{max}	21.25	Measured in human hepatocytes and calibrated against rifampin data (AG-120 Induction report)
CYP3A4 $IndC_{50}$(µM)	12.5	Measured in human hepatocytes (AG-120 Induction report). Measured value was used in the HV model because the induction effect following a single-dose of AG-120 cannot be verified against the observed induction data obtained at steady-state

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Appendix 2. PBPK parameter values used to simulate the kinetics of AG-120 in the AML patient population in the fed state

Parameter Name	Value	Method/Source
Absorption		
fa	0.69	Assumed to be the same as the relative bioavailability of the film-coated tablet formulation at 500 mg determined from the food effect study conducted in the HV in the fed state (Study AG120-C-004)
ka(h^{-1})	1.38	Estimated from Pop-PK analysis (Report Number AG120-C-001-PPK)
T_{lag} (h)	0.27	Estimated from Pop-PK analysis (Report Number AG120-C-001-PPK)
Elimination		
CL/F (L/h)	1.63	Estimated from Pop-PK analysis (Report Number AG120-C-001-PPK)
$CL_{int,CYP3A4}$ (µl/min/pmol)	0.036	Back-calculated from observed CL/F of 1.63 L/h in Study AG120-C-007; Assign 100% of metabolism to CYP3A4
CL_R (L/h)	0.36	Predicted after correcting for the age effect on renal function. Consistent with the estimated median GFR value in the patients in Study AG120-C-001 using the Cockcroft-Gault formula, which is 65% of the normal GFR value (AG120-001_PDPK_RENAL_20NOV16).
Induction		
CYP3A4 Ind_{max}	21.25	Measured in human hepatocytes and calibrated against rifampin data (AG-120 Induction report)
CYP3A4 $IndC_{50}$(µM)	2.5	Measured value in human hepatocytes is 12.5 µM; Optimised via sensitivity analysis (section 2.7.2)

PBPK Information Request
Information request sent on March 09, 2018:

The clinical pharmacology team requests that you please respond to the following Information Request for NDA 211192:
1. Since itraconazole (a strong CYP3A inhibitor) is a CYP3A substrate, the observed DDIs with itraconazole might not represent the magnitude of DDIs between ivosidenib and a strong CYP3A4 inhibitor which is not significantly metabolized by CYP3A4. Additional analysis is required to capture the ranges of DDIs between ivosidenib and strong CYP3A4 inhibitors to support your dosing recommendation.

2. Describe the mechanism assumptions (such as additive or multiply) used to your PBPK model to predict the DDIs when multiple inducers of the same pathway (such as ivosidenib and rifampin) are coadministered together. Discuss the uncertainty of your assumptions and their impacts on your conclusions.

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3. The use of 4β-OH-cholesterol (4β-OHC) data to derive the induction potency in vivo in cancer patients was not supported by the observed 4β-OHC induction data as shown in your clinical study (Fig.3 in AG120-C-001-PBPK report). FDA recommends to use information from clinical PK studies and popPK analysis to derive CYP3A4 in vivo induction by ivosidenib.

4. Justify the use of a fixed fraction of absorption (Fa) value in your PBPK model for AML population (dosing ranges from 100 to 1200 mg), since the dose-dependent Fa for ivosidenib was observed in healthy volunteer (Table 1 in AG120-C-001-PBPK report).

5. We cannot find several reports used in your PBPK report including "PK parameters and renal clearance from radiolabeled AME study", "AG120-001_PDPK_RENAL_20NOV16" in Table 2 and 3 in your PBPK report. Please submit these reports.

Please send me the requested information via e-mail and officially to your application by 3 PM (EST) March 19, 2018.

Information request sent on March 23, 2018:

We have the following clinical pharmacology information request:
1. There is no dose‐response relationship between 4β‐OHC and ivosidenib dose level based on Study AG120‐C‐001. FDA recommend to conduct a sensitivity analysis to confirm the optimization of CYP3A4 autoinduction parameters by comparing the steady state (Day 19) vs. single dose (Day 1) Cmax and AUC0‐Tau ratios of ivosidenib over a range of CYP3A4 induction parameters (e.g. IndC50: 0.125 to 12.5 nM (should be µM)), with the observed clinical PK data from Study AG120‐C‐001.

2. Please confirm the observed AUC and Cmax reported in Table 12‐16 is Day ‐3 or Day 3.
We ask for a response by 12:00 PM (ET) on March 30, 2018. In addition to a courtesy copy via e‐mail, please also formally submit the response under the NDA.

Information request sent on May 14, 2018:

The clinical pharmacology team requests that you please respond to the following Information Request for NDA 211192:

The CYP3A4 IndC50 value, 2.5 µM (AG120-C-001-PBPK), was used in most PBPK simulations. However, a different number (4 µM, Table 6 of the PBPK report) was used in at least one PBPK simulation (c004-500 mgsd-in-hvs..wks and c004-500-mg-sd-in-hvs.xlsx). Check and correct the inconsistency throughout your PBPK report, and confirm all PBPK model simulations have been performed with the correct CYP3A4 IndC50 value. Provide a list of modification you made in the report, and submit the revised model files and simulation output.

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Please send me the requested information via e-mail and officially to your application by 3 PM Friday, May 18, 2018.

PBPK References

[1]. FDA (2017) In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies Guidance for Industry.
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM581965.pdf.

[2]. Mano Y, Sugiyama Y and Ito K. Use of a Physiologically Based Pharmacokinetic Model for Quantitative Prediction of Drug-Drug Interactions via CYP3A4 and Estimation of the Intestinal Availability of CYP3A4 Substrates. J Pharm Sci. 2015 Sep;104(9):3183-93.

Reference ID: 4293723

PHARMACOMETRICS REVIEW

1. Results of Sponsor's Analysis

1.1 Population PK

The applicant included all possible evaluable data from 255 subjects out of the 258 total in study AG120-C-001 with a total 4656 valid samples, about 18 samples per subject.

The baseline demographics of the continuous covariates, categorical covariates, and DDI covariates evaluated in the population PK analysis are shown in **Table 79 - Table 81** respectively.

Table 79. Summary of Baseline Continuous Covariates

Covariate	Mean (CV%) Median [Min, Max]					
	100 mg BID (N = 4)	300 mg QD (N = 4)	500 mg QD (N = 225)	800 mg QD (N = 15)	1200 mg QD (N = 7)	Total (N = 255)
Age (years)	66 (27%)	70 (23%)	67 (19%)	66 (18%)	67 (21%)	67 (19%)
	69 [42, 84]	74 [47, 86]	69 [18, 87]	67 [42, 81]	63 [51, 89]	68 [18, 89]
Weight (kg)	61.5 (10%)	86.2 (35%)	76 (24%)	79.2 (26%)	80.5 (24%)	76.2 (24%)
	59.6 [56.5, 70.3]	73.5 [66.3, 131.5]	74.6 [37.7, 150.4]	79.1 [50, 111.2]	77.3 [59.8, 108.9]	74.2 [37.7, 150.4]
BSA (m^2)	1.67 (8%)	2.04 (18%)	1.88 (13%)	1.94 (17%)	1.93 (14%)	1.89 (13%)
	1.63 [1.57, 1.85]	1.91 [1.77, 2.58]	1.88 [1.31, 2.61]	1.95 [1.44, 2.37]	1.88 [1.67, 2.28]	1.89 [1.31, 2.61]
CrCl (mL/min)	73 (31%)	108 (49%)	89 (42%)	98 (46%)	98 (42%)	89 (42%)
	70 [51, 102]	104 [55, 169]	81 [21, 253]	87 [28, 182]	92 [46, 169]	83 [21, 253]
Albumin (g/L)	38 (19%)	37 (7%)	36 (16%)	39 (12%)	35 (26%)	36 (16%)
	38 [29, 44]	38 [33, 39]	37 [15, 48]	41 [30, 44]	38 [23, 43]	37 [15, 48]
ALT (U/L)	33 (72%)	24 (80%)	29 (89%)	33 (120%)	48 (95%)	30 (92%)
	33 [11, 55]	18 [8, 52]	21 [4, 224]	24 [9, 168]	21 [12, 137]	21 [4, 224]
AST (U/L)	24 (52%)	23 (29%)	26 (57%)	26 (67%)	37 (93%)	27 (59%)
	24 [10, 37]	24 [15, 30]	22 [9, 90]	22 [15, 88]	20 [17, 112]	22 [9, 112]
Total bilirubin (μmol/L)	9.4 (32%)	8.1 (32%)	10.8 (64%)	10.4 (43%)	12 (39%)	10.8 (62%)
	9.4 [6.8, 12]	6.8 [6.8, 12]	8.6 [3.4, 71.8]	8.6 [5.1, 22.2]	13.7 [5.1, 17.1]	8.6 [3.4, 71.8]

ALT: alanine transaminase; AST: aspartate transaminase; BID: twice daily; BSA = Body surface area; CrCl: Creatinine clearance; CV: Coefficient of variation; Max: maximum; Min: minimum; N: number of subjects; QD: once daily

(Source: Applicant's Population PK Report, Table 6-2)

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Table 80. Summary of Baseline Categorical Covariates

Covariate	Number of Subjects, N (%)					
	100 mg BID (N = 4)	300 mg QD (N = 4)	500 mg QD (N = 225)	800 mg QD (N = 15)	1200 mg QD (N = 7)	Total (N = 255)
Sex						
Male	2 (50%)	3 (75%)	120 (53%)	9 (60%)	3 (43%)	137 (54%)
Female	2 (50%)	1 (25%)	105 (47%)	6 (40%)	4 (57%)	118 (46%)
Race						
White	4 (100%)	4 (100%)	151 (67%)	11 (73%)	5 (71%)	175 (69%)
Black	0 (0%)	0 (0%)	13 (6%)	1 (7%)	1 (14%)	15 (6%)
Asian	0 (0%)	0 (0%)	6 (3%)	0 (0%)	0 (0%)	6 (2%)
American Indian or Alaskan Native	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)
Native American or Other Pacific Islander	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)
Other	0 (0%)	0 (0%)	7 (3%)	0 (0%)	0 (0%)	7 (3%)
Missing	0 (0%)	0 (0%)	46 (20%)	3 (20%)	1 (14%)	50 (20%)
NCI Hepatic Impairment Category						
Normal	3 (75%)	4 (100%)	180 (80%)	14 (93%)	5 (71%)	206 (81%)
Mild	1 (25%)	0 (0%)	39 (17%)	1 (7%)	2 (29%)	43 (17%)
Moderate	0 (0%)	0 (0%)	2 (1%)	0 (0%)	0 (0%)	2 (1%)
Severe	0 (0%)	0 (0%)	1 (0%)	0 (0%)	0 (0%)	1 (0%)
Missing	0 (0%)	0 (0%)	3 (1%)	0 (0%)	0 (0%)	3 (1%)
Cancer Type						
Relapsed or refractory AML	4 (100%)	4 (100%)	177 (79%)	14 (93%)	4 (57%)	203 (80%)
Untreated AML	0 (0%)	0 (0%)	33 (15%)	1 (7%)	2 (29%)	36 (14%)
Other IDH1-mutated advanced hematologic malignancies	0 (0%)	0 (0%)	15 (7%)	0 (0%)	1 (14%)	16 (6%)
ECOG Performance Status						
0	1 (25%)	1 (25%)	48 (21%)	4 (27%)	2 (29%)	56 (22%)
1	2 (50%)	2 (50%)	125 (56%)	10 (67%)	3 (43%)	142 (56%)
2	1 (25%)	1 (25%)	49 (22%)	1 (7%)	1 (14%)	53 (21%)
3	0 (0%)	0 (0%)	3 (1%)	0 (0%)	1 (14%)	4 (2%)

AML: acute myeloid leukemia; BID: twice daily; ECOG = Eastern Cooperative Oncology Group; N: number of subjects; NCI: National Cancer Institute; QD: once daily.

(Source: Applicant's Population PK Report, Table 6-3)

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Table 81. Concomitant Medication Summary

Concomitant Medication	No. of Concentration Samples (%)
Voriconazole	993 (21%)
Fluconazole	825 (18%)
Posaconazole	292 (6%)
Other moderate/strong CYP3A4 inhibitors	278 (6%)
Other mild CYP3A4 inhibitors	1100 (24%)
Any CYP3A4 inhibitor	2834 (61%)
Pantoprazole	310 (7%)
Other PPI	413 (9%)
Any PPI	698 (15%)
Famotidine	178 (4%)
Other H2 antagonists	58 (1%)
Any H2 antagonists	236 (5%)

(Source: Applicant's Population PK Report, Table 6-4)

Final Population PK Model:

Diagnostic plots for the final PK model for AG-120 are presented in Figure 21. Model parameters are shown in **Table 82**.

The model in **Table 82** is a two-compartment model with steady-state apparent clearance of 5.39 L/h and an apparent volume of 234 L. The distribution clearance is 15.8 L/h and the peripheral volume is 151 L. The absorption rate constant is 1.38 per hr, and the zero-order release duration (lag-time) is 0.27 hr.

The dose-nonlinearity parameter on Frel was -0.49, suggesting less-than dose-proportional exposures. There was a 0.64-fold (36%), 0.59-fold (41%), and 0.65-fold (35%) reduction in apparent clearance when subjects were taking voriconazole, fluconazole, and posaconazole, respectively. These ratios were similar; alternative analyses grouping CYP3A4 inhibitors are summarized in a subsequent section.

Baseline body weight had a significant impact on central volume. Increasing albumin, both baseline and time-varying albumin, correlated with increased clearance and volume. The fold-change in relative bioavailability from single-dose to steady-state was 0.50, and the fold-change in apparent clearance was 1.66. The net change in apparent clearance was 3.3-fold.

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Table 82. Final Population PK Model 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.

(Source: Applicant's Population PK Report, Table 6-7)

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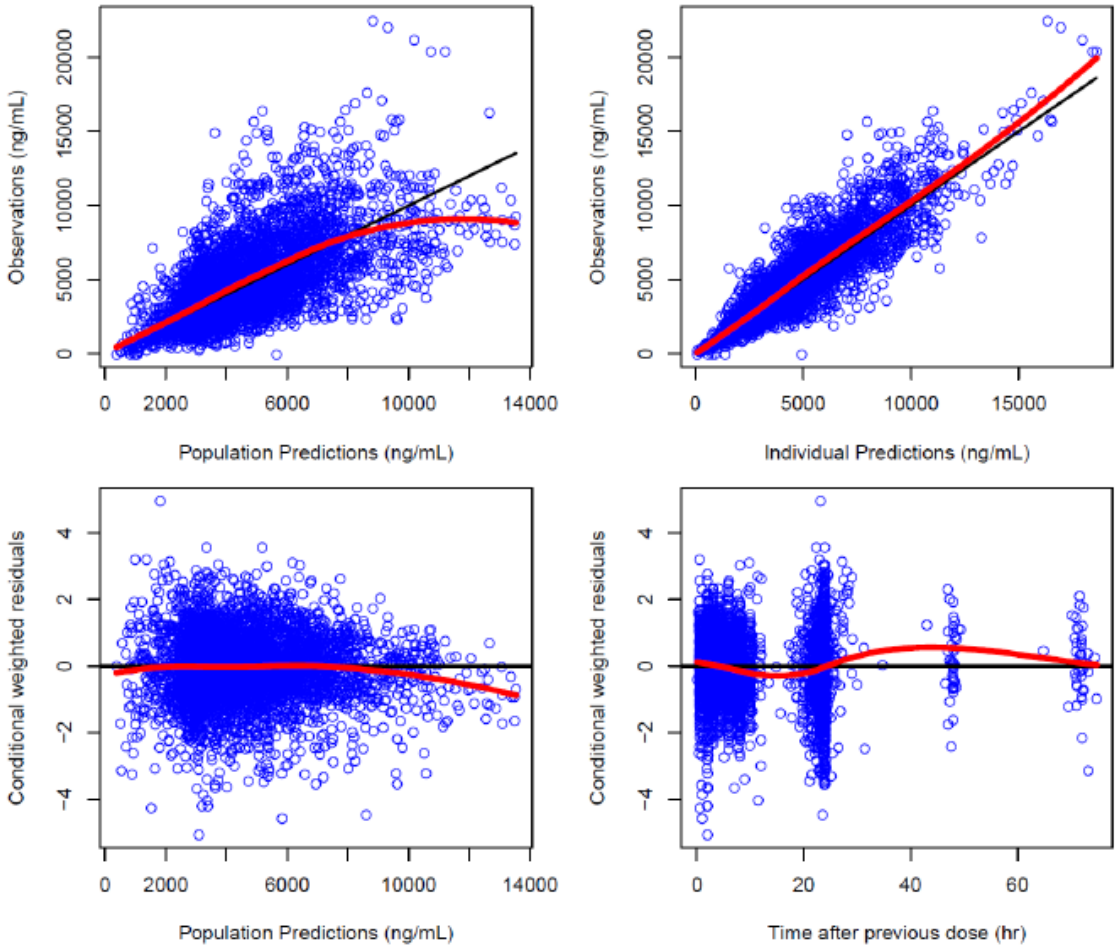
The final model equations are as follows:

$$CL/F = 5.39 \times (\text{Alb Baseline}/37)^{0.82} \times (\text{Alb}/\text{Alb Baseline})^{0.99}$$
$$(\times\ 0.64 \text{ if voriconazole})$$
$$(\times\ 0.59 \text{ if fluconazole})$$
$$(\times\ 0.65 \text{ if posaconazole})$$
$$(\times\ 0.92 \text{ if other moderate/strong CYP3A4 inhibitors})$$
$$(\times\ 1.04 \text{ if mild CYP3A4 inhibitors})$$
$$(/\ 1.66 \text{ if time} < 96\text{-hr})$$
$$/\ F_{rel}$$

$$Vc/F = 234 \times (\text{Wt}/75\text{ kg})^{0.92} \times (\text{Alb Baseline}/37)^{0.73} \times (\text{Alb}/\text{Alb Baseline})^{1.10}$$
$$/\ F_{rel}$$

$$Frel = (\text{Dose}/500\text{ mg})^{-0.49}$$
$$(/\ 0.50 \text{ if time} < 96\text{-hr})$$

Figure 21: Goodness of Fit Plots for the Final Population PK Model.
Observations and predictions in ng/mL, time after dose in h. Black lines represent reference lines (line of identity for observations vs. predictions plots, y = 0 for conditional weighted residual plots), red lines represent locally weighted smooths to the data.



(Source: Applicant's Population PK Report, Figure 6-4)

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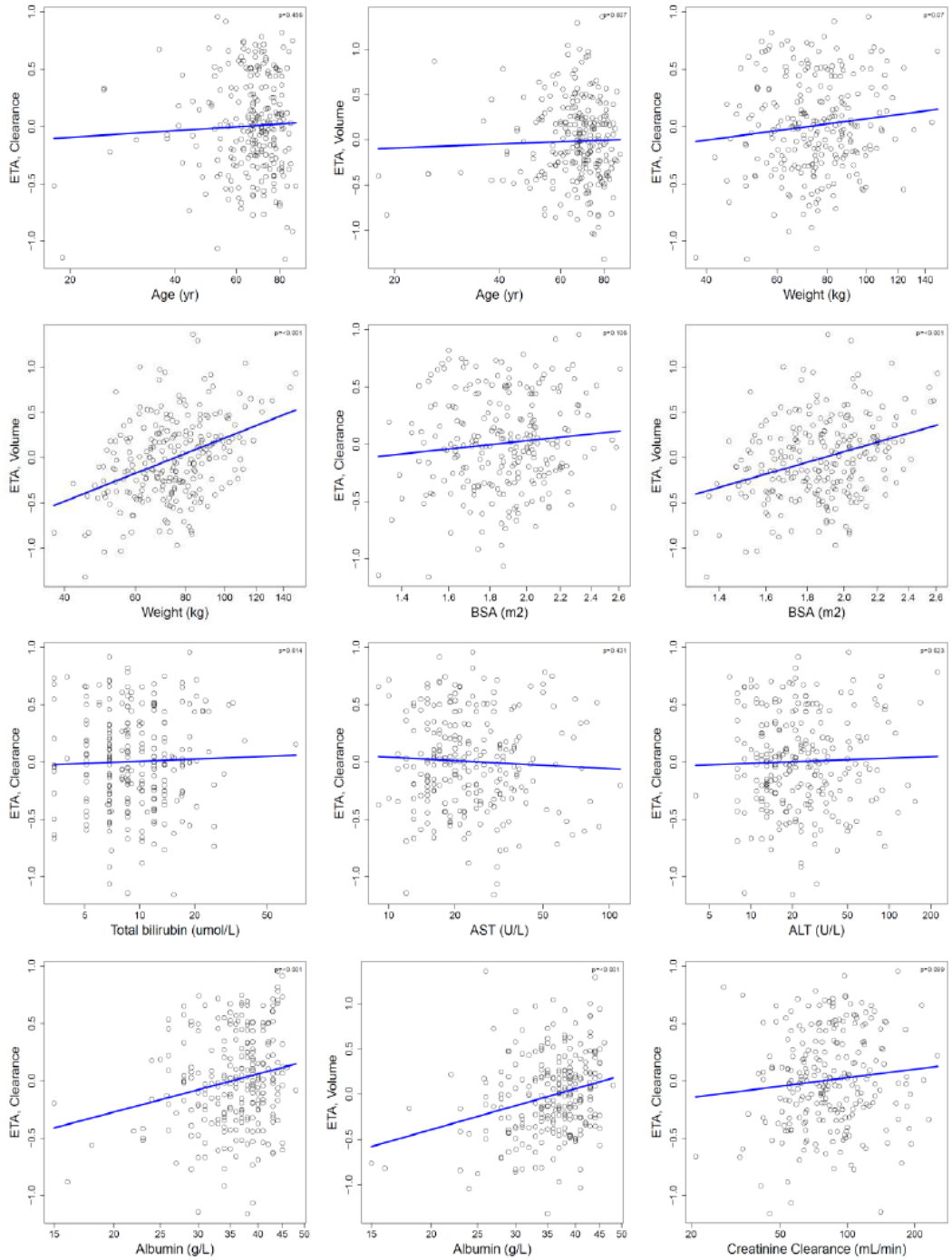
Figure 22: Base Model Random Effects versus Continuous Covariates



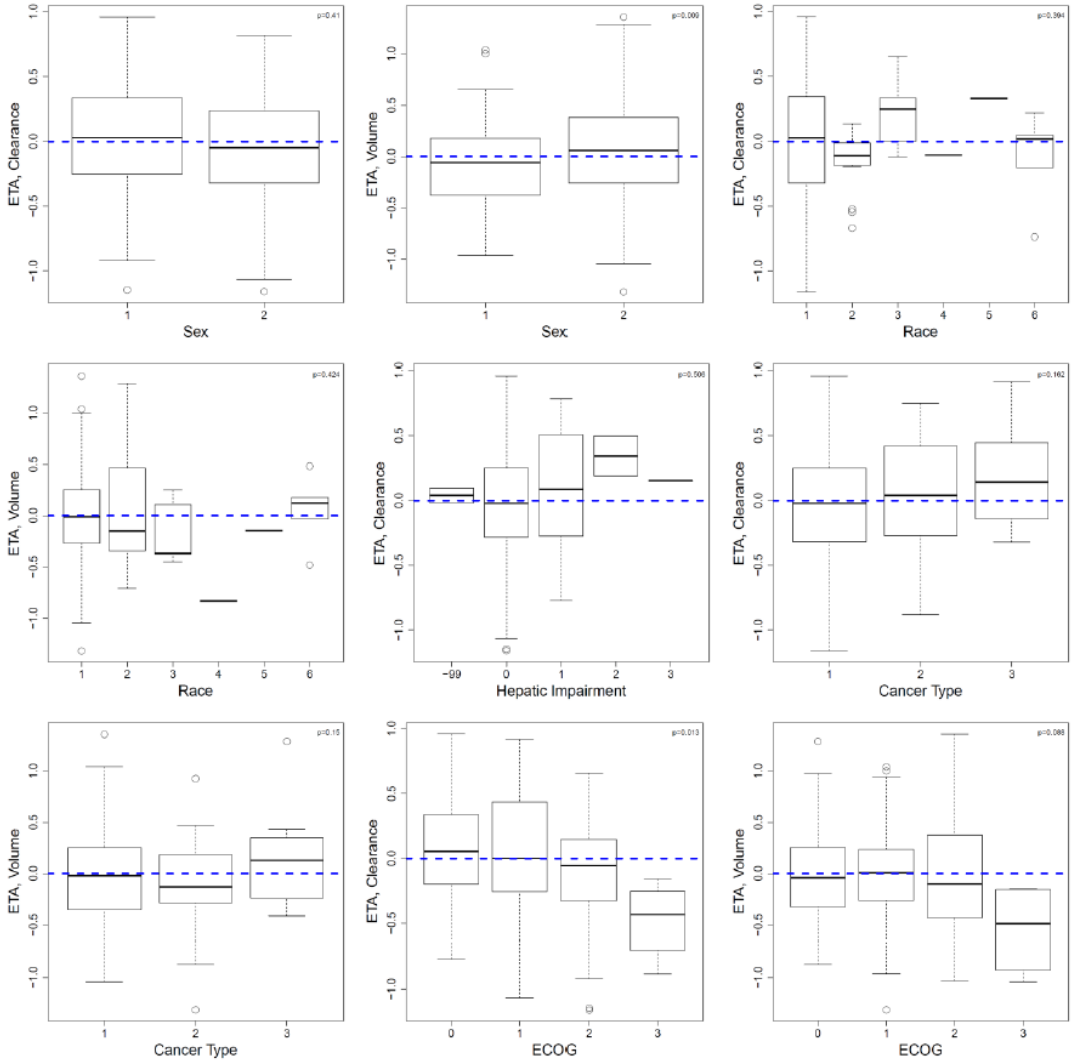
Black circles represent individual data points (one per subject). Blue lines are linear regression fits to random effects versus log-transformed covariate. The p-value for the linear fit is in the upper right corner. All correlations for p-values less than 0.05 are shown. AST: aspartate aminotransferase; ALT: alanine aminotransferase; BSA: Body surface area (m2); ETA: Random effect; p: p-value from linear regression on ETA vs. log-transformed covariate.

(Source: Applicant's Population PK Report, Figure10-5)

Reference ID: 4293723

Covariate Model Building Diagnostics:
Eta (CL) and Eta (V) plots versus categorical and continuous covariates are shown for both the base (Figures 22 and 23) and final model (Figures 24 and 25). The log of model development indicating the change in objective function with removal or addition of each covariate is shown in Table 83.

Figure 23: Base Model Random Effects versus Categorical Covariates



Blue dashed lines are zero-lines for random effects. Boxplots indicate the median and interquartile range. Whiskers indicate the furthest data point no more than 1.5 times the interquartile range from the box. Points indicate values outside the whiskers. ETA: Random effect; Sex: 1=Male, 2=Female; Race: -99=Missing, 1=White, 2=Black, 3=Asian, 4=American Indian or Alaska Native, 5=Native Hawaiian or other Pacific Islanders, 6=Other; Hepatic Impairment: -99=Missing, 0=Normal, 1=Mild, 2=Moderate, 3=Severe; Cancer Type: 1 = relapsed/refractory AML; 2=untreated AML; 3=other IDH1-mutated advanced hematologic malignancies; ECOG: Eastern Cooperative Oncology Group performance status; p: p-value from analysis of variance.

(Source: Applicant's Population PK Report, Figure 10-6)

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Table 83. Full and Final Model Development Log

Model Number	Refereren ce Model	Description	N_{param}	OFV	|ΔOFV|	|ΔDOF|	p-val significant
45	--	Base Model	13	-5374.03	--	--	--
48	45	Reparameterize at steady-state, use final dataset	13	-5374.03	--	--	--
Forward addition (p<0.01, ΔOFV>6.63 for 1 DOF)							
51	45	+ Baseline Body Weight on Vc	14	-5417.05	43.02	1	Yes
52	45	+ Baseline Albumin on CL	14	-5385.82	11.79	1	Yes
53	45	+ Baseline Albumin on Vc	14	-5393.23	19.2	1	Yes
55	45	+ Sex on Vc	14	-5380.31	6.28	1	No
57	45	+ Baseline ECOG on CL	14	-5382.01	7.98	1	Yes
58	52	+ Time-varying Albumin on CL	15	-5630.92	245.1	1	Yes
59	53	+ Time-varying Albumin on Vc	15	-5401.73	8.49	1	Yes
61	45	+ Cyp3A4 inhibitor category on CL	18	-6014.6	640.57	5	Yes
63	45	+ PPI category on CL	15	-5374.78	0.75	2	No
64	45	+ H2 antagonist category on CL	15	-5381.69	7.66	2	No
Backward elimination (p<0.001, ΔOFV>10.83 for 1 DOF)							
70	45	Full Model (BWT on Vc; BALB/ALB on CL; BECOG on CL; INH3A on CL)	24	-6300.14	926.11	11	Yes
71	70	- Baseline Body Weight on Vc	23	-6263.11	37.03	1	Yes
72	70	- Time-varying Albumin on CL	23	-6105.87	194.28	1	Yes
73	70	- Time-varying Albumin on Vc	23	-6235.6	64.54	1	Yes
74	70	- Baseline ECOG on CL	23	-6298.37	1.77	1	No
76	70	- Time-varying CYP3A inhibitors on CL	19	-5732.14	568.01	5	Yes
78	74	- Baseline body weight on V	22	-6261.31	37.06	1	Yes
79	74	- Time-varying albumin on CL	22	-6106.69	191.68	1	Yes
80	74	- Time-varying albumin on V	22	-6233.72	64.65	1	Yes
82	74	- Time-varying CYP3A on CL	18	-5730.73	567.64	5	Yes
Final model							
100	74	Final Model with cov matrix	23	-6298.37	0	0	No
112	100	Reparameterize at steady-state	23	-6298.37	0	0	--
114	100	Reparameterize at steady-state, use final dataset	23	-6298.37	0	0	--

|·| denotes absolute value; ALB = albumin; BALB = baseline ALB; BWT = body weight; CL = Apparent clearance; ΔDOF = change in degrees of freedom; ΔOFV = OFV of tested model – OFV of reference model; ECOG = Eastern Cooperative Oncology Group Performance Status; H2 = H2 antagonist; INH3A = CYP3A4 inhibitor; Nparam = number of parameters; OFV = Objective Function Value; PPI = proton pump inhibitor; Vc – central volume.

(Source: Applicant's Population PK Report, Table 10-8)

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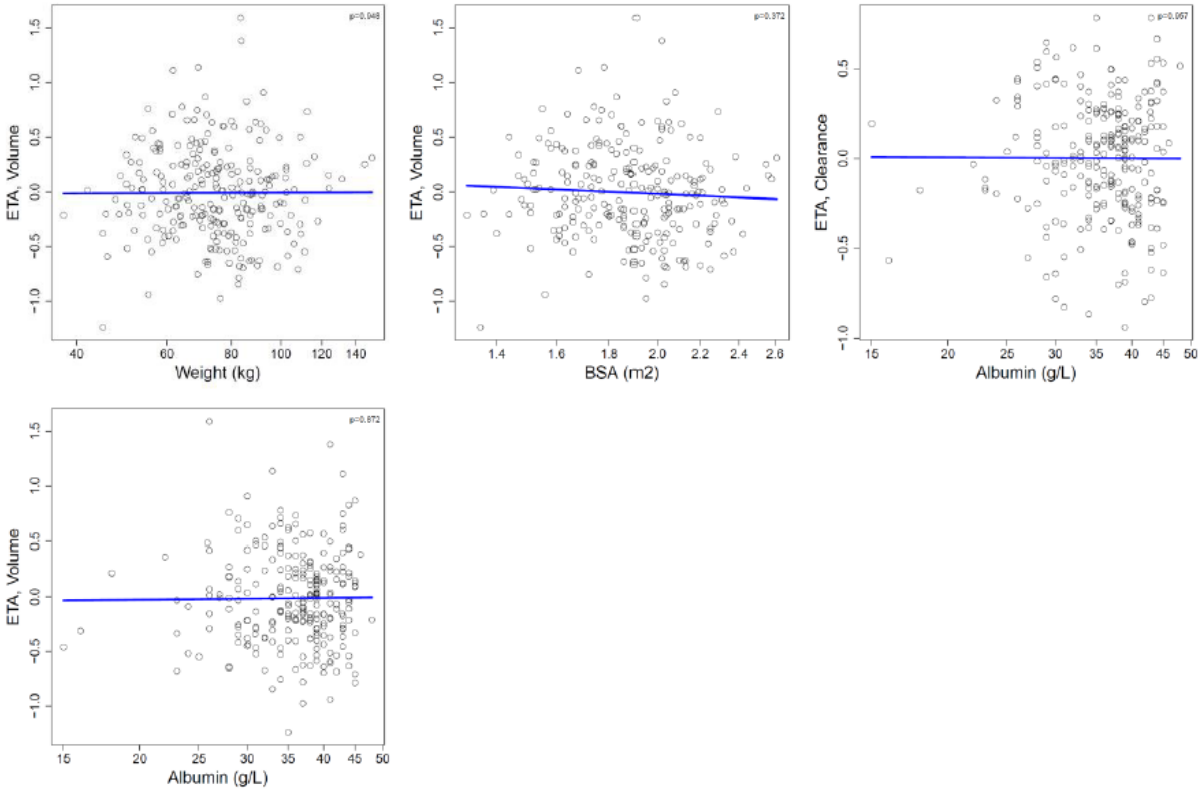
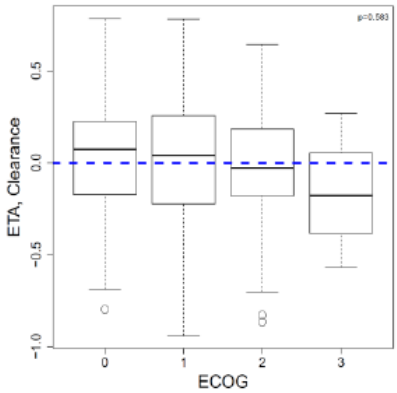
Figure 24: Final Model Random Effects versus Continuous Covariates



Black circles represent individual data points (one per subject). Blue lines are linear regression fits to random effects versus log-transformed covariate. The p-value for the linear fit is in the upper right corner. All correlations for continuous covariates in the final model are shown. BSA: Body surface area (m2); ETA: Random effect; p: p-value from linear regression.

(Source: Applicant's Population PK Report, Figure 10-9)

Figure 25: Final Model Random Effects versus Categorical Covariates



Blue dashed lines are zero-lines for random effects. Boxplots indicate the median and interquartile range. Whiskers indicate the furthest data point no more than 1.5 times the interquartile range from the box. Points indicate values outside the whiskers. All covariates for categorical covariates in the final model are shown. ETA: Random effect; Sex: 1=Male, 2=Female; ECOG: Eastern Cooperative Oncology Group performance status; p: p-value from analysis of variance.

(Source: Applicant's Population PK Report, Figure 10-10)

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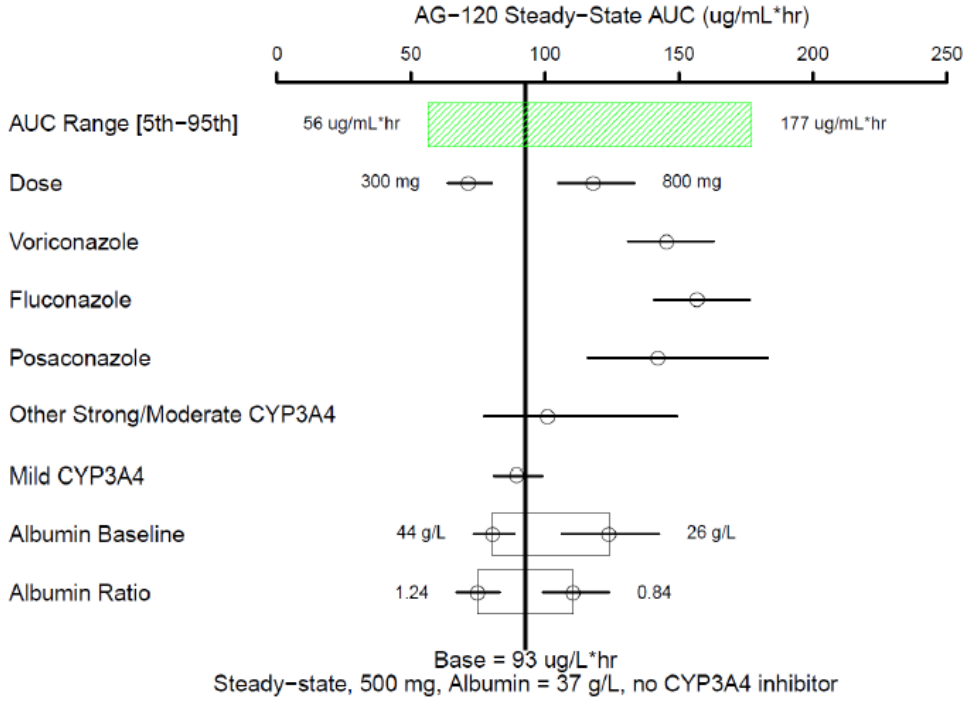
Impact of model covariates:

The applicant characterized the extent of change in AUCss and Cmax for each relevant model covariate. These are shown in Figures 26 and 27, respectively.

Figure 26: Sensitivity of AUCss to Covariates and Dose.



The vertical line represents the predicted steady-state AUC of 93 µg/mL×hr in the typical subject receiving 500 mg QD AG-120. This subject has albumin levels of 37 g/L, and is not taking a strong/moderate concomitant CYP3A4 inhibitor. The top hatched bar shows the 5th to 95th percentile of modelled AUCs across the subject population. The points show the variation in modelled AUC as covariates are changed one-at-a-time to indicated values. For continuous variables, the extreme values are 5th and 95th percentiles of the population. Horizontal lines represent 95th percentile confidence intervals of the estimate.

(Source: Applicant's Population PK Report, Table 6-9)

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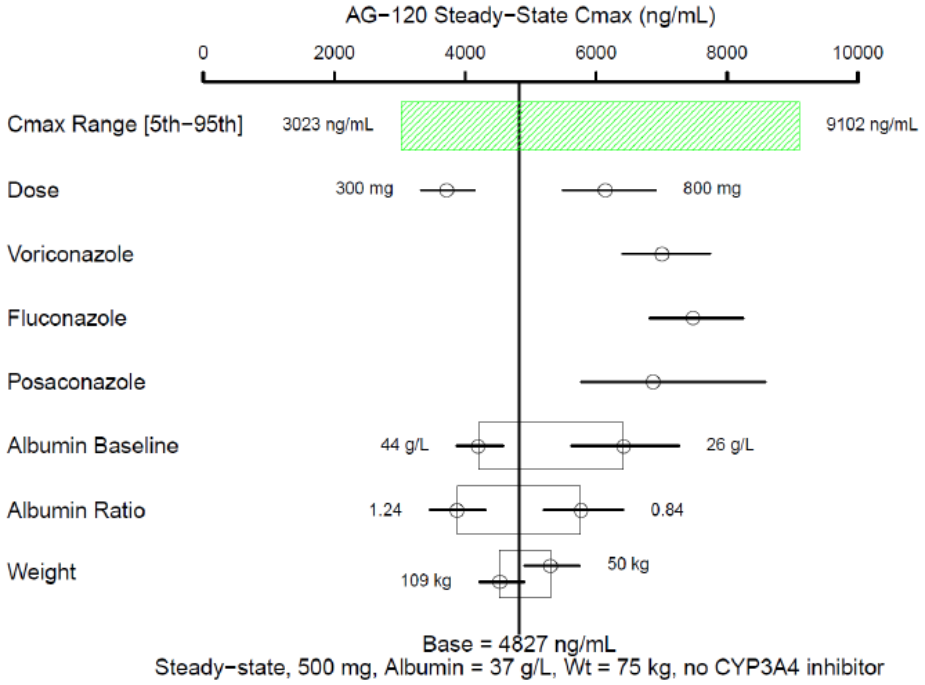
Figure 27: Sensitivity of Cmax,ss to Covariates and Dose.



The vertical line represents the predicted steady-state Cmax of 4828 ng/mL in the typical subject receiving 500 mg QD AG-120. This subject has albumin of 37 g/L and weighs 75 kg. The top hatched bar shows the 5th to 95th percentile of modelled Cmax values across the subject population. The points show the variation in modelled Cmax as covariates are changed one-at-a-time to indicated values. For continuous variables, the extreme values are 5th and 95th percentiles of the population. Horizontal lines represent 95th percentile confidence intervals of the estimate.Source: 2017-09-02-tfls-ag120-v5-qc.r

(Source: Applicant's Population PK Report, Figure 6-10)

The applicants population PK conclusions were as follows:

- AG-120 oral pharmacokinetics were described by a two-compartment model with first-order absorption.
- Steady-state apparent clearance was estimated to be 5.39 L/hr, with between-subject variability of 35%.
- The apparent clearance was estimated to be 1.63 L/hr on the first day. This estimate is uncertain, because the terminal washout after the first dose covered approximately one halflife.
- The change from day one to steady state was modeled as a 2-fold decrease in relative bioavailability and a 1.66-fold increase in clearance. The increase in clearance at steady state may be related to autoinduction.
- The dose-nonlinearity exponent on relative bioavailability is -0.49, thus a doubling of dose translates approximately to a 40% increase in exposure

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- Concomitant strong/moderate CYP3A4 inhibitors voriconazole, fluconazole, and posaconazole increased AG-120 AUC by approximately 60%. Mild CYP3A4 inhibitors, PPIs, and H2 antagonists did not have an effect on exposure.
- Baseline albumin levels of 26 g/L were associated with a 34% increase in AUC relative to a baseline albumin level of 37 g/L. The effect of time-varying albumin changes was less than 20%.
- No clearance effects of age, body weight, body mass index, sex, race, disease type, and ECOG score were detected.
- No correlations of renal function indicators (CrCl) and renal impairment category to clearance was observed, although conclusions should be interpreted with caution because there were only 2 subjects with severe renal impairment (CrCl below 30 mL/min).
- No correlation of hepatic function indicators (ALT, AST, bilirubin) and hepatic impairment category (based on NCI-ODWG criteria) to clearance was observed, although conclusions should be interpreted with caution because of the small number of subjects with moderate or severe hepatic impairment.

Reviewer's Comments:
The applicant's population PK analysis is acceptable for descriptive purposes regarding the PK of ivosidenib (i.e. labeling, deriving the exposure metrics for exposure-response analyses). The reviewer finds the labeled values regarding ivosidenib PK parameters acceptable as well as conclusions regarding intrinsic factors as potential covariates. With regard to DDI effect, the population PK analysis appears to have a sufficient amount of data, However, the effect of strong CYP3A4 inhibitors appears to have a smaller effect on clearance as compared to the results from the physiologically based PK analysis.

1.2 Exposure-Response for Efficacy

Exploratory Exposure-Efficacy Analysis Dataset:
The source analysis dataset consisted of 258 subjects, all subjects were part of the Full Analysis Set (FASFL=Y). There were 205 subjects with R/R AML in the source dataset, which includes 159 Arm 1+ subjects. After merging with post hoc exposure estimates from the final population PK model, a total of 201 subjects with R/R AML remained which includes 156 Arm 1+ subjects. The breakdown by phase of study is 59 subjects from dose escalation and 142 subjects from expansion. Four subjects ([redacted] (b) (6)) were excluded from the exposure-efficacy analysis dataset because no post hoc exposure estimates were available for these subjects.

The exposure-efficacy analysis set contained all relapsed or refractory (R/R) AML subjects in the FAS in Study AG120-C-001 for whom post hoc exposure estimates were available. The number of subjects with a response of OR, CR, CR+CRh and non-CR/CRh was 75, 43, 59 and 16, respectively.

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An overview of the numbers of subjects and response rates across doses is provided in **Table 84**.

Table 84. Number of Subjects and Response Rates by Dose Level, Subjects Included in the Exposure-Efficacy Analysis.

Dose	Total No of Subjects	Response Rate, n (%)			
		OR	CR	CR+CRh	Non-CR/CRh
100 mg BID	4	1 (25%)	1 (25%)	1 (25%)	0 (0%)
300 mg QD	4	9 (25%)	1 (25%)	1 (25%)	0 (0%)
500 mg QD	175	70 (40%)	39 (22%)	54 (31%)	16 (9%)
800 mg QD	14	2 (14%)	1 (7%)	2 (14%)	0 (0%)
1200 mg QD	4	1 (25%)	1 (25%)	1 (25%)	0 (0%)
Total	201	75 (37%)	43 (21%)	59 (29%)	16 (8%)

BID: twice daily dosing; QD: once daily dosing; n (%): Number and percentage of responders; OR: Overall response; CR: Complete remission; CR+CRh: Complete Remission plus Complete remission with partial hematological recovery; non-CR/CRh response: non-Complete Remission/Complete remission with partial hematological recovery;

(Source: Applicant's ag120-c-001-er.pdf Report, Table 6-7)

Overall, OR, CR, CR+CRh and non-CR/CRh response rates were 37%, 21%, 29% and 8%, respectively. The response rate appeared to be similar across the dose levels, but the number of observations in the 100 mg BID, 300 mg and 1200 mg QD dose groups was small and limited the power to detect dose–response relationships.

Covariate Distribution Across Exposure Quartiles:
Subject baseline and demographic covariates were summarized by AUCss quartile to investigate whether covariates were equally distributed across the exposure range. Covariate distributions for IDH1 mutation status, baseline ECOG, number of prior anti-cancer regimens, prior transplantation, cytogenetic risk, prior history of MDS, age, body weight, gender and race are provided in **Table 85**.

Covariates were evenly distributed across the AUCss quartiles, except for a slight imbalance in baseline ECOG PS. The incidence in the fourth AUCss quartile for ECOG PS = 0 appeared to be smaller and for ECOG PS = 2 appeared to be larger compared to the first, second, and third AUCss quartiles. This slight imbalance did not warrant further exploration of confounding covariates on E-R relationships.

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Table 85. Covariate Distribution Over AUCss Quartiles for all Subjects Included in the Exposure-Efficacy Analysis

AUCss Quartile	Covariate Level						
IDH1 mutation status at screening:	**No**	**Yes**					
Q1	1	50					
Q2	0	50					
Q3	0	50					
Q4	0	50					
ECOG PS at baseline:	**0**	**1**	**2**	**3**			
Q1	15	30	6	0			
Q2	12	29	9	0			
Q3	10	29	10	1			
Q4	7	23	19	1			
Prior anti-cancer regimens:	**0**	**1**	**2**	**3**	**4**	**5**	**6**
Q1	1	27	16	4	2	1	0
Q2	0	18	17	8	5	1	1
Q3	0	22	14	11	2	1	0
Q4	1	17	12	16	3	1	0
Prior transplantation:	**Missing**	**Yes**					
Q1	37	14					
Q2	36	14					
Q3	38	12					
Q4	41	9					

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AUCss Quartile	Covariate Level						
Cytogenetic risk:	**Unknown**	**Intermediate**	**Poor**				
Q1	11	25	15				
Q2	3	34	13				
Q3	7	30	13				
Q4	6	25	19				
Prior history of MDS:	**No**	**Yes**					
Q1	43	8					
Q2	41	9					
Q3	43	7					
Q4	42	8					
Race:	**White**	**Black or African American**	**Asian**	**Native Hawaiian or other Pacific islander**	**American Indian or Alaskan native**	**Other**	**Not provided**
Q1	35	0	4	0	0	1	11
Q2	28	5	0	1	1	2	13
Q3	30	4	2	0	0	3	11
Q4	37	3	0	0	0	0	10
Gender:	**Female**	**Male**					
Q1	21	30					
Q2	27	23					
Q3	24	26					
Q4	25	25					
Age cutoff:	**≤67 yrs**	**>67 yrs**					
Q1	25	26					
Q2	28	22					
Q3	24	26					
Q4	26	24					
Baseline body weight cutoff*:	**≤73.8 kg**	**>73.8 kg**					
Q1	26	25					
Q2	25	25					
Q3	25	25					
Q4	26	23					

* One subject with missing bodyweight; AML: Acute myeloid leukemia; IDH: Isocitrate dehydrogenase; MDS: Myelodysplastic syndrome; PS: Performance Status; Prior transplant missing: did not receive prior transplant; Source: EDA-efficacy.r

(Source: Applicant's ag120-c-001-er.pdf Report, Table 6-8)

Exposure Distributions for Responders and Nonresponders

Exposure distributions were explored with boxplots for responders and nonresponders for OR, CR and CR+CRh, as well as CR+CRh responders versus non-CR/CRh responders **(Figure 28)**.

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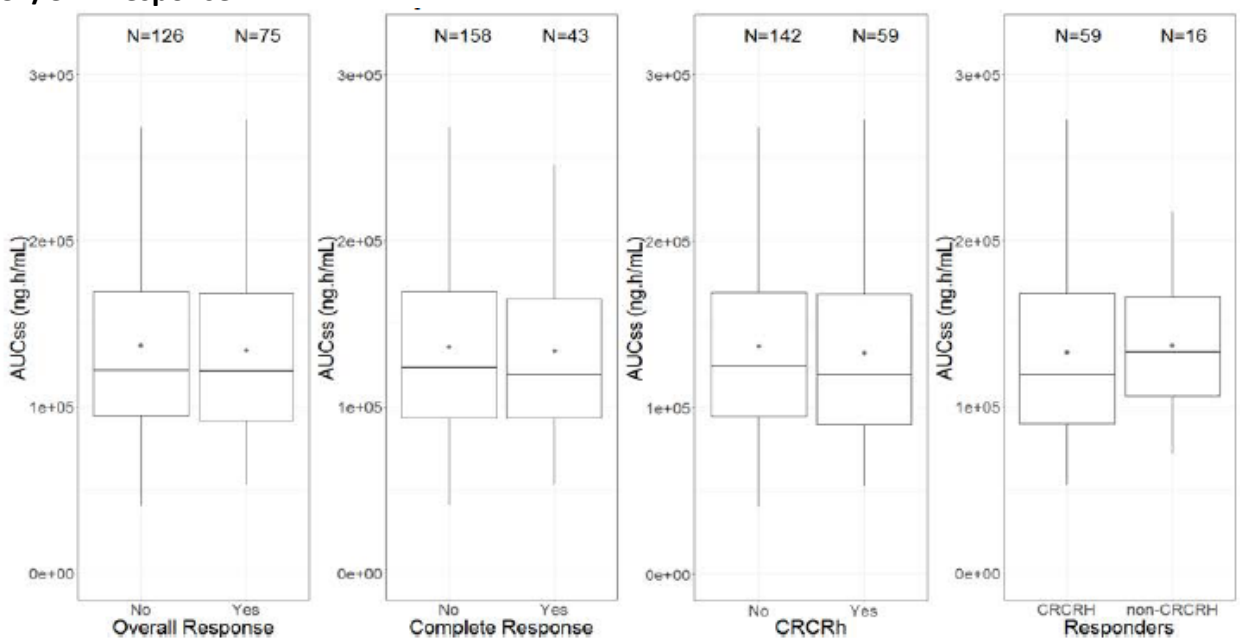
Exposure ranges were similar for responders and nonresponders for OR, CR, and CR+CRh, and for the CR+CRh and non-CR/CRh responders.

Figure 28: Post Hoc AUCss Distributions for Efficacy Endpoints OR, CR, CR+CRh and Non-CR/CRh Response.



CR/CRh: Complete Remission plus Complete remission with partial hematological recovery; Dot: Mean; Hinges: 25th, median and 75th percentile; Whiskers: extend hinges to 1.5x interquartile range; Source: EDA-efficacy.r
(Source: Applicant's ag120-c-001-er.pdf Report, Figure 6-8)

Probability of Clinical Response by Exposure Quartile, and Logistic Regression Analysis:
To further explore E-R relationships, the incidence of OR, CR and CR+CRh was stratified by AUCss quartile for **(Table 86)**. Logistic regression was applied to individual data to quantify the relationship between exposure and clinical response. Figure 29 presents the plots of incidence of clinical response by AUCss quartile, together with a linear logistic regression fit, for each of the efficacy endpoints. The slope of the effect of exposure on the incidence of clinical response and the associated p-value from the logistic regression are presented in Table 87.

The efficacy responses across exposure quartiles appeared similar; this was confirmed in the logistic regression analysis. There was no observed relationship between exposure and the probability of achieving a clinical response, exposure (AUCss) effects on the incidence of response were minimal for each of the efficacy endpoints, with p-values that ranged between 0.661 and 0.783.

Inclusion of the prognostic efficacy factors according to Breems [3] (the covariates age, cytogenetics status and prior transplantation) did not result in a meaningful difference in

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magnitude or significance of the exposure effect for OR, CR and CR+CRh.

Table 86. Incidence of Clinical Response by AUCss Quartile for All Subjects Included in the Exposure-Efficacy Analysis.

AUCss Quartile	AUCss (ng·h/mL)	No of Subjects	Incidence, n (%)		
			OR	CR	CR+CRh
Q1	40900 – 93079	51	20 (39%)	11 (22%)	17 (33%)
Q2	93393 – 121715	50	18 (36%)	12 (24%)	15 (30%)
Q3	123526 – 169509	50	18 (36%)	9 (18%)	12 (24%)
Q4	170758 – 360780	50	19 (38%)	11 (22%)	15 (30%)

n (%): Number and percentage of responders; OR: Overall response; CR: Complete remission; CR+CRh: Complete Remission plus Complete remission with partial hematological recovery; Q: Quartile; Source: EDA-efficacy.r

(Source: Applicant's ag120-c-001-er.pdf Report, Table 6-9)

Table 87. Logistic Regression Results of the AUCss Effect on the Incidence of Efficacy Endpoints for Models Including AUCss Only and AUCss + Covariates.

Table 6-10. Logistic Regression Results of the AUCss Effect on the Incidence of Efficacy Endpoints for Models Including AUCss Only and AUCss + Covariates

Endpoint	AUCss Only model		AUCss + Covariate model [1]	
	P-value AUC Effect	Slope AUC Effect	P-value AUC Effect	Slope AUC Effect
OR	0.719	-8.88E-07	0.797	-6.66E-07
CR	0.783	-8.09E-07	0.953	-1.84E-07
CR+CRh	0.661	-1.16E-06	0.808	-7.00E-07

OR: Overall response; CR: Complete remission; CR+CRh: Complete Remission plus Complete remission with partial hematological recovery; Slope expressed as the change in odds ratio (exp(slope)) for a 1 ng·h/mL change in AUC; [1] Logistic regression covariate model defined as logit(prob(response))~AUCss * slope + Age * a + cytogenetics status * b + prior transplantation * c + intercept; Missing covariate values were included as a separate "Unknown" level;

(Source: Applicant's ag120-c-001-er.pdf Report, Table 6-10)

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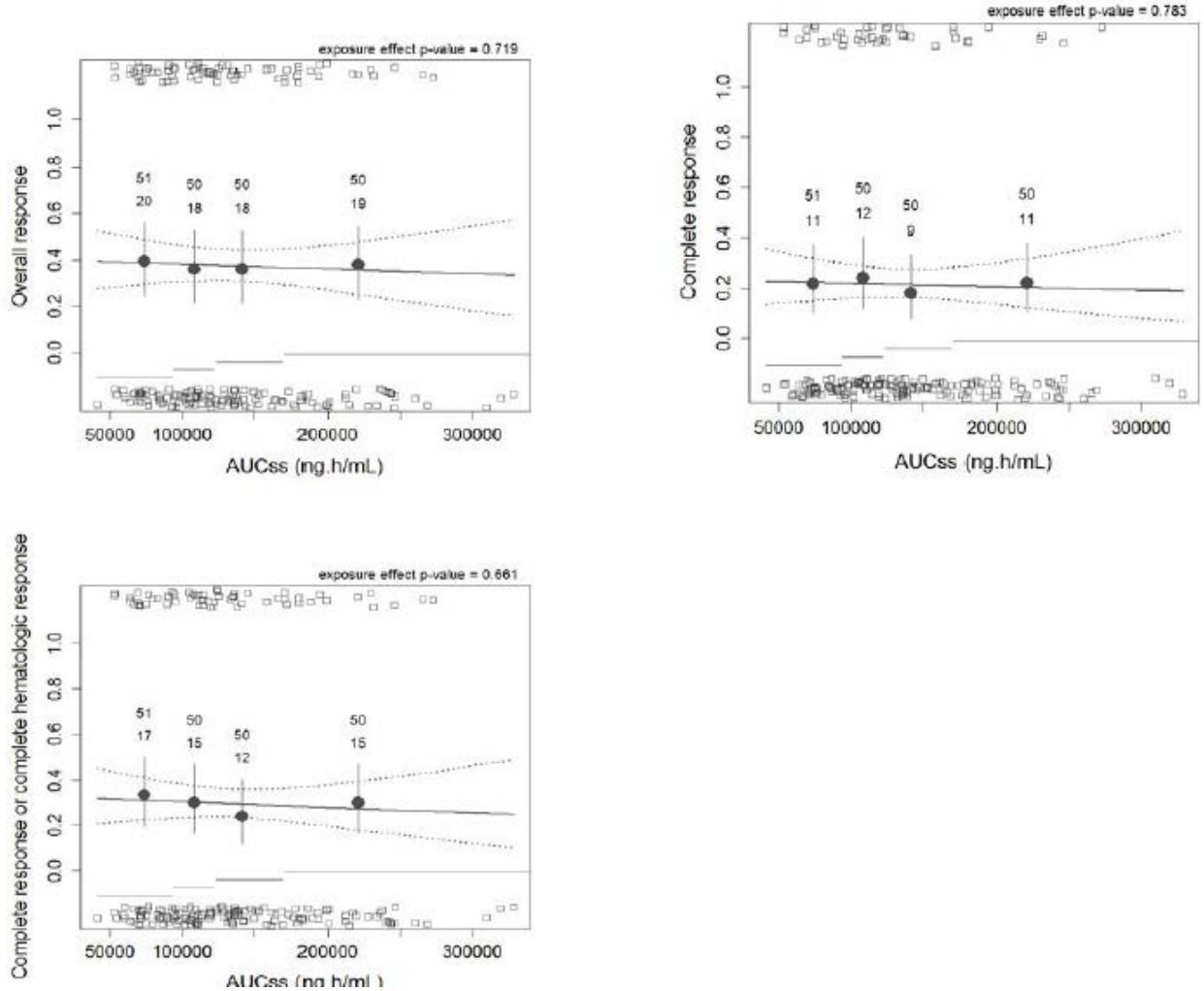
Figure 29: Quartile Plot for Post Hoc AUCss vs Incidence of Clinical Response and Linear Logistic Regression for OR, CR, and CR+CRh.
Open squares: individual values; Numbers represent total number of subjects (first row) and number of subjects with a response (second row) within corresponding quartile; Solid dot and vertical line: Incidence and 95% confidence interval of observation within quartile; Solid line: logistic regression fit of the form logit(prob(response))~AUCss * slope + intercept; Dashed lines: 95% confidence interval; Horizontal lines: width of exposure quartiles.



(Source: Applicant's ag120-c-001-er.pdf Report, Figure 6-9)

Reviewer's Comments:
The applicant's exposure-efficacy assessment is acceptable.

1.3 Exposure-Response for Safety

A QT-concentration response relationship was evident from the AG120-c-001 data. See the

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Reviewer's Analysis (Section 2) and the QT-IRT review for further details.

Safety event incidences were stratified by exposure quartile for AUCss **Table 88.** The exposure quartiles for AUCss were the same for each of the 16 safety endpoints, while the exposure quartiles for AUCavg were different for each safety endpoint. Logistic regression was applied to the individual data to quantify the relationship between exposure and incidence of safety endpoints.

Figure 30 presents plots of ALT- and AST-AE incidence by AUCss quartile together with a linear logistic regression fit. Finally, model-predicted AE incidences for the 10th, 50th and 90th percentiles of the AUCss at the AG-120 500 mg QD dose level are presented in Table 89.

Applicant's Conclusion:
The observed safety endpoint incidence by AUCss quartile did not show a clear exposure-AE relationship for any of the selected safety endpoints, except for a slight trend for the liver enzyme-related endpoints. Overall, 27% and 15% of subjects in the exposure-safety analysis population experienced an AE of new or worsening all Grade AST or new or worsening all Grade ALT, respectively. For all ALT- and AST-AEs, the lowest incidence of events was observed in the low exposure quartile, the number of events for New or Worsening ≥ Grade 2 ALT and New or Worsening ≥ Grade 2 AST was low (n=6 (2%) and n=8 (3%), respectively) and lacks the power to detect E-R trends. Although the number of events for New or Worsening All Grade ALT and New or Worsening All Grade AST (n=37 (15%) and n=68 (27%), respectively) are higher in comparison to the categories of New or Worsening ≥ Grade 2 ALT and New or Worsening ≥ Grade 2 AST (n=6 and n=8, respectively), the observed slight trend between AG-120 exposure and incidence of these AEs was mainly driven by Grade 1 events.

Logistic regression analysis illustrated that the incidence of AEs for all safety endpoints was not likely associated with AG-120 exposure (AUCss). The model-predicted AE incidence at the 10th, 50th and 90th percentiles of the AUCss at the AG-120 500 mg QD dose level illustrated the absence of meaningful exposure trends. Predicted changes over the exposure range were small and not clinically relevant Table 89. Exposure effects on the incidence of safety events based on AUCavg were consistent with the effects based on AUCss.

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Table 88. Incidence of Selected Safety Endpoints in Study AG120-c-001 Subjects Stratified by AUCss Quartiles.

	AG-120 AUCss Quartile			
Parameter, n (%)	**Q1 (N=64)**	**Q2 (N=63)**	**Q3 (N=63)**	**Q4 (N=63)**
AUCss range (ng·h/mL)	**40900 – 90601**	**90809 – 119653**	**119664 – 166334**	**166429 – 530779**
All Grade Acute Renal Failure	6 (9%)	5 (8%)	5 (8%)	7 (11%)
All Grade New or Worsening ALT	1 (2%)	13 (21%)	15 (24%)	8 (13%)
≥ Grade 2 New or Worsening ALT	0 (0%)	0 (0%)	4 (6%)	2 (3%)
All Grade New or Worsening AST	6 (9%)	22 (35%)	22 (35%)	18 (29%)
≥ Grade 2 New or Worsening AST	0 (0%)	1 (2%)	5 (8%)	2 (3%)
≥ Grade 2 Gastrointestinal events [1]	4 (6%)	9 (14%)	9 (14%)	6 (10%)
All Grade IDH differentiation syndrome	5 (8%)	9 (14%)	8 (13%)	7 (11%)
≥ Grade 3 IDH differentiation syndrome	4 (6%)	3 (5%)	5 (8%)	2 (3%)
All Grade Leukocytosis	21 (33%)	24 (38%)	25 (40%)	23 (37%)
≥ Grade 3 Leukocytosis	5 (8%)	5 (8%)	3 (5%)	7 (11%)
Liver Dysfunction	0 (0%)	0 (0%)	1 (2%)	0 (0%)
All Grade Polyneuropathy	4 (6%)	6 (10%)	2 (3%)	5 (8%)
≥ Grade 3 Polyneuropathy	0 (0%)	0 (0%)	0 (0%)	1 (2%)
All Grade Rash	11 (17%)	22 (35%)	12 (19%)	13 (21%)
≥ Grade 3 Rash	1 (2%)	1 (2%)	4 (6%)	1 (2%)
≥ Grade 3 Tumor Lysis Syndrome	5 (8%)	5 (8%)	2 (3%)	2 (3%)

[1] Gastrointestinal as category and search strategy is nausea/vomiting; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; IDH: Isocitrate dehydrogenase; Q: quartile; N: Number of subjects in exposure quartile; n (%): Number and percentage of subjects with at least one event occurrence; Source: EDA-safety.r

(Source: Applicant's ag120-c-001-er.pdf Report, Table 6-5)

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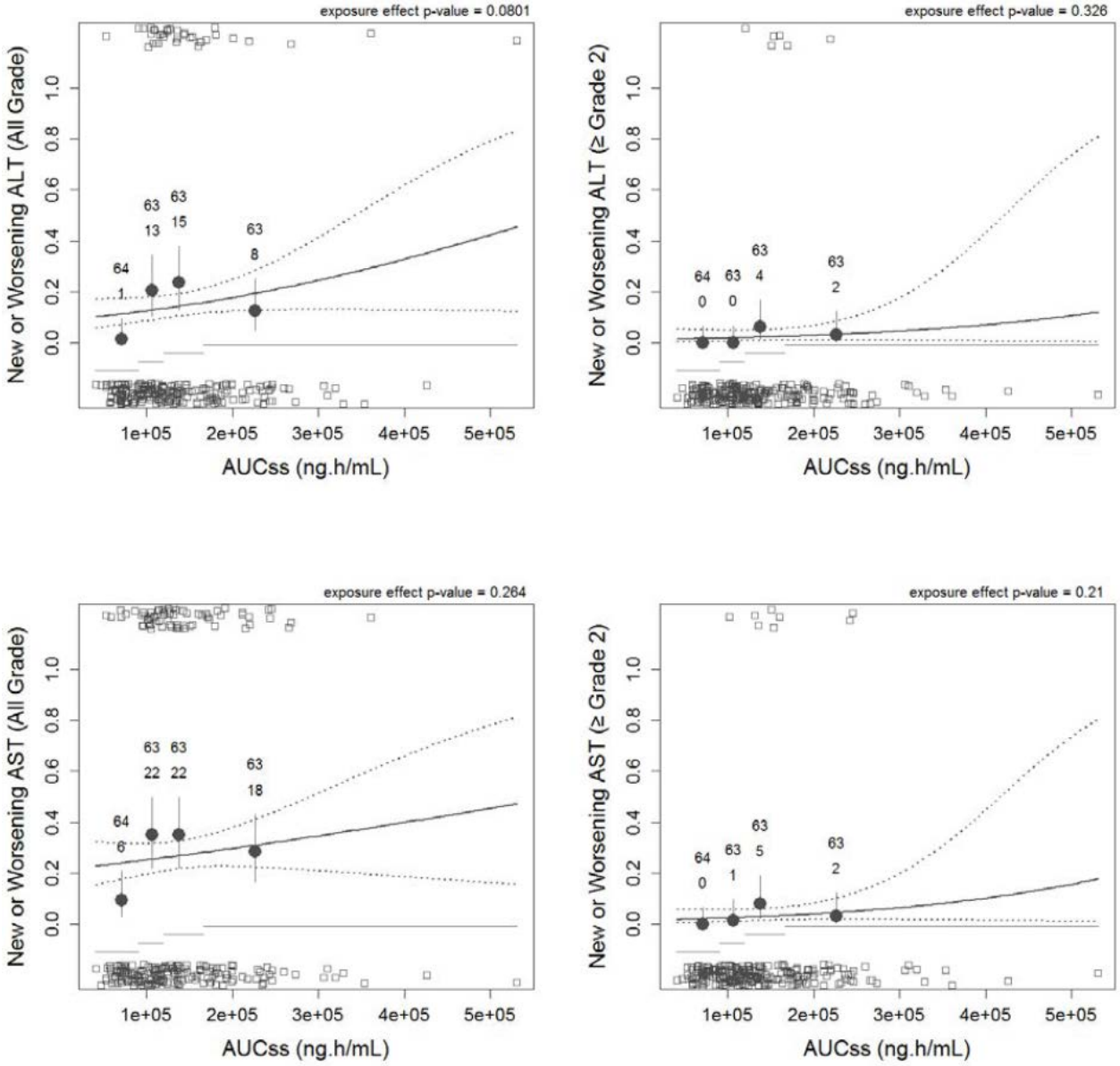
Figure 30: AE Incidence versus AUCss, with Incidence grouped by AUCss Quartile and a Linear Logistic Regression Fit for ALT – and AST – AEs.

Open squares: individual values; Numbers represent total number of subjects (first row) and number of subjects with an event (second row) within corresponding quartile; Solid dot and vertical line: Incidence and 95% confidence interval of observation at mean exposure within quartile; Solid line: logistic regression fit of the form logit(prob(event)) AUCss*slope+intercept; Dashed lines: 95% confidence interval Horizontal lines: width of exposure quartiles; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.



(Source: Applicant's ag120-c-001-er.pdf Report, Figure 6-6)

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Table 89. Model-Predicted AE Incidence at the 10th, 50th, and 90th Percentiles of AUCss at AG-120 500 mg QD, Based on Logistic Regression Parameter Estimates.

AE	Model-Predicted Incidence (95% Confidence Interval)		
	AUCss - P10	AUCss - P50	AUCss - P90
All Grade Acute Renal Failure	0.077	0.086	0.108
	(0.043 - 0.132)	(0.057 - 0.13)	(0.064 - 0.175)
New or Worsening All Grade ALT	0.113	0.135	0.185
	(0.072 - 0.174)	(0.097 - 0.185)	(0.126 - 0.264)
New or Worsening ≥ Grade 2 ALT	0.017	0.021	0.032
	(0.005 - 0.051)	(0.009 - 0.05)	(0.013 - 0.076)
New or Worsening All Grade AST	0.24	0.261	0.303
	(0.176 - 0.318)	(0.209 - 0.32)	(0.226 - 0.393)
New or Worsening ≥ Grade 2 AST	0.022	0.027	0.043
	(0.008 - 0.057)	(0.013 - 0.058)	(0.02 - 0.091)
≥ Grade 2 Gastrointestinal events [1]	0.116	0.112	0.105
	(0.07 - 0.185)	(0.078 - 0.158)	(0.059 - 0.179)
All Grade IDH differentiation syndrome	0.092	0.107	0.141
	(0.055 - 0.15)	(0.073 - 0.154)	(0.09 - 0.214)
≥ Grade 3 IDH differentiation syndrome	0.07	0.057	0.039
	(0.035 - 0.137)	(0.034 - 0.095)	(0.014 - 0.104)
All Grade Leukocytosis	0.381	0.371	0.352
	(0.301 - 0.468)	(0.312 - 0.434)	(0.267 - 0.446)
≥ Grade 3 Leukocytosis	0.075	0.078	0.084
	(0.041 - 0.133)	(0.05 - 0.12)	(0.045 - 0.15)
All Grade Polyneuropathy	0.073	0.068	0.061
	(0.038 - 0.134)	(0.043 - 0.108)	(0.028 - 0.127)
All Grade Rash	0.228	0.229	0.231
	(0.164 - 0.308)	(0.18 - 0.287)	(0.161 - 0.318)
≥ Grade 3 Rash	0.033	0.029	0.022
	(0.012 - 0.088)	(0.014 - 0.059)	(0.006 - 0.081)
≥ Grade 3 Tumor Lysis Syndrome	0.071	0.057	0.038
	(0.035 - 0.139)	(0.034 - 0.095)	(0.013 - 0.103)

(Source: Applicant's ag120-c-001-er.pdf Report, Table 6-6)

Reviewer's Comments:
The applicant's exposure-safety assessment is acceptable.

Reference ID: 4293723

2. Reviewer's Analysis

2.1 Introduction

DDI Assessment via population PK approach can underestimate the potential interaction if the time-dependent DDI variable has carryover in the PK samples collected at a time when concomitant medication was not taken. The reviewer performed a sensitivity analysis to evaluate whether points indicated as not having the concomitant medication for subjects receiving strong CYP3A4 inhibitors have an impact on the parameter estimates for the strong CYP3A4 DDI.

2.2 Objectives

The objective of reviewer's sensitivity analysis was to determine if the effect of DDI were estimated robustly with popPK analyses.

2.3 Methods

2.3.1 Data Sets
Data sets used are summarized in Table 90.

Table 90. Analysis Data Sets

Study Number	Name	Link to EDR
Ag120-c-001	Pknm.xpt	\\cdsesub1\evsprod\NDA211192\0001\m5\datasets\ag120-c-001-ppk\analysis\legacy\datasets

2.3.2 Software
NONMEM (version 7.3) was utilized to run the applicant's model and dataset.

2.3.3 Models
No new models were developed by the reviewer for this sensitivity analysis.

2.4 Results

Two model estimations were run to inform whether carryover from the time on concomitant strong CYP3A4 inhibitors into the time the patient was indicated as not being on concomitant medication impacted the estimation of the DDI effect on CL.

The first model run was the applicant's final model. This served to both confirm the applicant's results and provide a reference for the DDI evaluation. The second model run was the final model unchanged on the applicant's full dataset minus the time points from patients who had concomitant strong CYP3A4 inhibitors where they were not receiving the concomitant CYP3A4 inhibitor.

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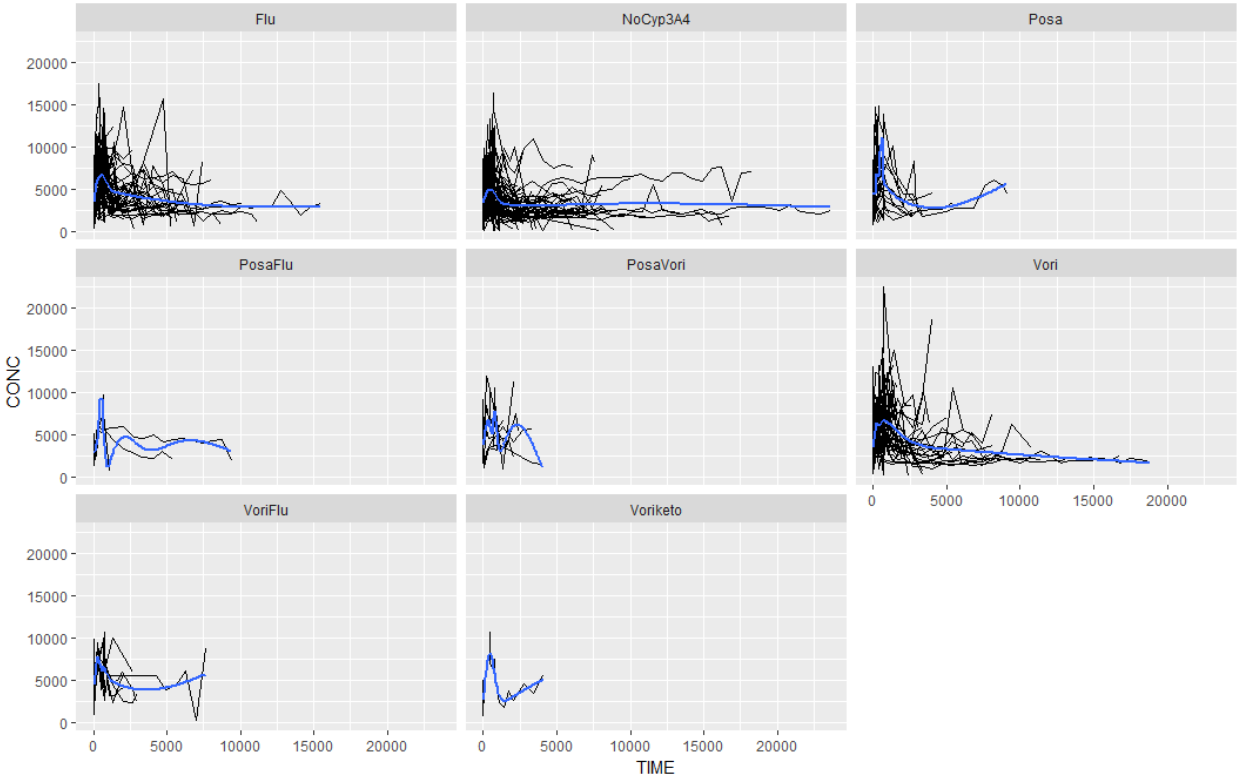
Compared the first model run, removing the data where the concomitant medication was not present during the PK sampling for patients who received strong inhibitors (second model run) yielded mildly different parameter estimates for the effect of voriconazole (3% reduction in effect on CL), fluconazole (3% reduction in effect on CL), and posaconazole (9% increase in effect) on ivosidenib clearance. The population estimate for clearance was reduced from 5.39 to 5.19 L/hr.

Additionally, the amount of data for each concomitant medication was assessed to determine if the population PK dataset if robust enough to evaluate the PK differences. The motivation came from the PBPK estimates of a 3.58-fold increase in AUC for posaconazole as compared to a 1.7-fold increase based on the popPK analyses.

Figure 31: Time Course Of Ivosidenib Concentrations Grouped By Subjects That Received Different CYP3A4 Inhibitors.
Blue lines are loess smooth lines. Black lines are individual PK profiles.



Reference ID: 4293723

Figure 32: Time Course Of Ivosidenib Concentrations Grouped By Subjects That Receive Different CYP3A4 Inhibitors

Colors indicate the presence of the comedication for each panel. Red lines are no concomitant medication, green lines indicate the presence of one CYP3A4 inhibitor, blue lines indicate the presence of two.

The review of the DDI data suggest that the popPK analyses are capable of estimating the effect of concomitant CYP3A4 inhibitor use. However, the doses of CYP3A4 inhibitor that were given concomitantly were not recorded in study AG120-C-001, so it is possible that the discrepancy with the PBPK values came from lower CYP3A4 inhibitor doses given in the study than were utilized for the PBPK analysis.

Regarding the assessment of patients with renal impairment via popPK, there did not appear to be any unresolved affect for CrCL after considering the final popPK model for ivosidenib (Figure 33). A similar trend was also observed for eGFR.

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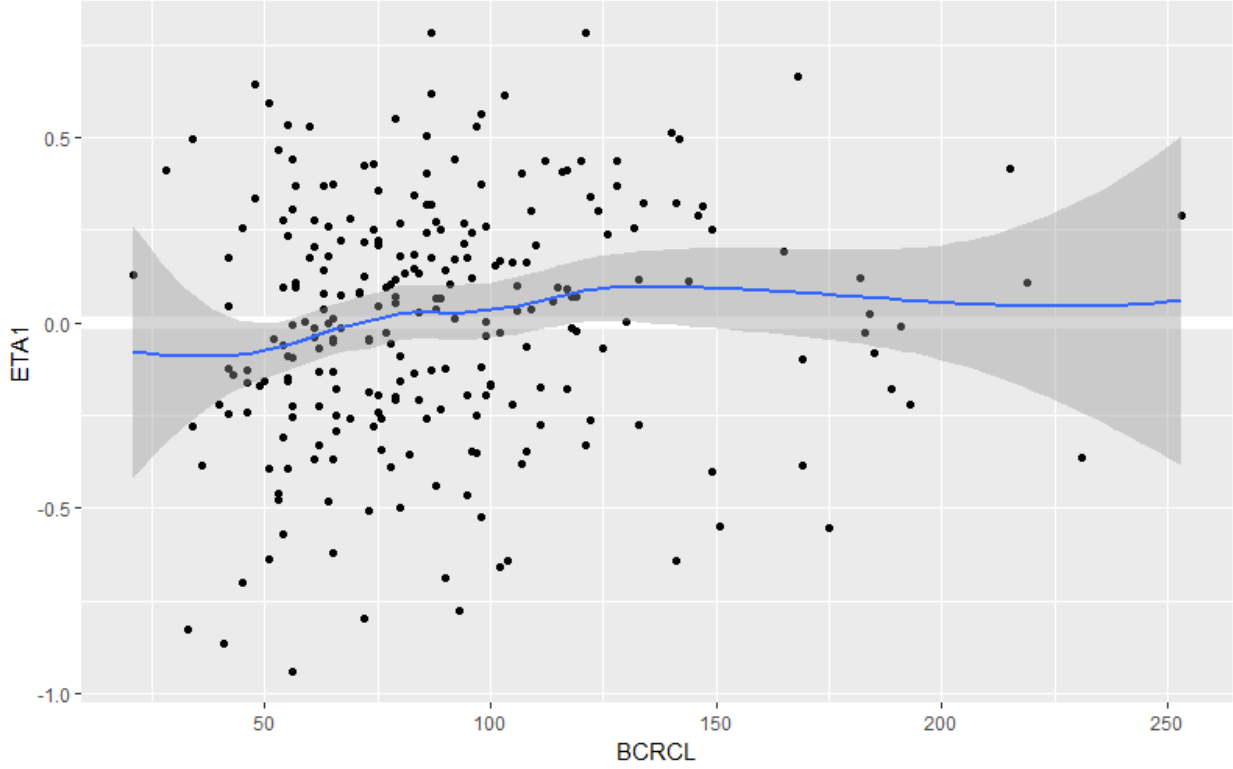
Figure 33: Eta(CL) versus baseline creatinine clearance for the data from AG120-C-001.
Black points indicate the individual post hoc etas for CL. The blue line is the Loess smooth line.



Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
DDIEval.R	Dataset Prep and QT Plots	..\Reviews\PM Review Archive\2018\Ivosidenib_NDA211192_JCE\PPK Analyses

Reference ID: 4293723

14.5 Grouped Preferred Terms

Grouped Term	Preferred Terms
abdominal pain	abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness
abscess	abdominal abscess, abdominal wall abscess, abscess, abscess bacterial, abscess drainage, abscess intestinal, abscess jaw, abscess limb, abscess neck, abscess oral, abscess soft tissue, abscess sweat gland, anal abscess, bone abscess, brain abscess, breast abscess, central nervous system abscess, genital abscess, gingival abscess, groin abscess, hepatosplenic abscess, liver abscess, lung abscess, lymph node abscess, mastoid abscess, mediastinal abscess, pelvis abscess, perihepatic abscess, perineal abscess, perirectal abscess, peritonsillar abscess, psoas abscess, rectal abscess, rectovaginal septum abscess, retroperitoneal abscess, scrotal abscess, subcutaneous abscess, tooth abscess, ureter abscess, urethral abscess
anemia	anaemia, anaemia of malignant disease, hematocrit decreased, hemoglobin decreased
arrhythmia	arrhythmia, arrhythmia supraventricular, atrial fibrillation, atrial flutter, atrial tachycardia, bradycardia, extrasystoles, junctional ectopic tachycardia, nodal arrhythmia, paroxysmal arrhythmia, sinus arrhythmia, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular tachycardia, tachycardia, tachycardia paroxysmal, ventricular arrhythmia, ventricular extrasystoles, ventricular tachyarrhythmia, ventricular tachycardia
arthralgias	arthralgia, back pain, musculoskeletal stiffness, neck pain, pain in extremity
atrial arrhythmia	arrhythmia, arrhythmia supraventricular, atrial fibrillation, atrial flutter, atrial tachycardia, bradycardia, junctional ectopic tachycardia, nodal arrhythmia, paroxysmal arrhythmia, sinus arrhythmia, sinus bradycardia, sinus tachycardia, supraventricular extrasystoles, supraventricular tachyarrhythmia, supraventricular tachycardia, tachycardia, tachycardia paroxysmal
cardiac failure	cardiac failure, cardiac failure acute, cardiac failure congestive, cardiac failure high output, diastolic dysfunction, left ventricular dysfunction, systolic dysfunction
cellulitis	anorectal cellulitis, breast cellulitis, cellulitis, cellulitis of male external genital organ, incision site cellulitis, perineal cellulitis, periorbital cellulitis, vaginal cellulitis, vulval cellulitis
chest pain	angina pectoris, chest discomfort, chest pain, non-cardiac chest pain
clostridial infection	clostridial infection, clostridium difficile colitis, clostridium difficile infection
conduction disorder	atrioventricular block, atrioventricular block complete, atrioventricular block first degree, atrioventricular block second degree, bundle branch block right, paroxysmal atrioventricular block
cough	cough, productive cough, upper airway cough syndrome
diarrhea	colitis, diarrhoea, enterocolitis, gastroenteritis, neutropenic colitis

Reference ID: 4293723

Grouped Term	Preferred Terms
dyspnea	acute respiratory failure, bronchospasm, dyspnoea, dyspnoea exertional, hypoxia, respiratory failure
edema	face oedema, fluid overload, fluid retention, generalised oedema, oedema, oedema peripheral, swelling face
eye irritation	dry eye, eye irritation, eye pain, keratitis
fatigue	asthenia, fatigue
fungal infection	anal candidiasis, anal fungal infection, aspergilloma, aspergillosis oral, bladder candidiasis, bronchopulmonary aspergillosis, candidiasis of trachea, central nervous system fungal infection, cerebral aspergillosis, cerebral candidiasis, cerebral fungal infection, cryptococcal fungaemia, fungaemia, fungal infection, fungal skin infection, gastrointestinal candidiasis, gastrointestinal fungal infection, genital infection fungal, hepatic candidiasis, hepatosplenic candidiasis, mucocutaneous candidiasis, nasal candidiasis, oesophageal candidiasis, oral candidiasis, oral fungal infection, oro-pharyngeal aspergillosis, oropharyngeal candidiasis, peritoneal candidiasis, pneumonia fungal, sinusitis fungal, splenic candidiasis, systemic candida, tongue fungal infection, upper respiratory fungal infection, vulvovaginal candidiasis, vulvovaginal mycotic infection
gastrointestinal hemorrhage	anal hemorrhage, gastrointestinal hemorrhage, haematochezia, haemorrhoidal hemorrhage, lower gastrointestinal hemorrhage, mouth hemorrhage, rectal hemorrhage, small intestinal hemorrhage, upper gastrointestinal hemorrhage
headache	headache, sinus headache
hemorrhage intracranial	cerebral haematoma, cerebral haemorrhage, haemorrhage intracranial, intracranial haematoma, subarachnoid haematoma, subarachnoid haemorrhage, subdural haematoma

Reference ID: 4293723

Grouped Term	Preferred Terms
hepatic injury	acute hepatic failure, acute on chronic liver failure, acute yellow liver atrophy, alanine aminotransferase abnormal, alanine aminotransferase increased, allergic hepatitis, ammonia abnormal, ammonia increased, ascutes, aspartate aminotransferase abnormal, aspartate aminotransferase increased, asterixis, biliary ascites, biliary cirrhosis, biliary fibrosis, bilirubin conjugated abnormal, bilirubin conjugated increased, bilirubin excretion disorder, biopsy liver abnormal, blood bilirubin abnormal, blood bilirubin increased, blood bilirubin unconjugated increased, cholestatic liver injury, chronic hepatic failure, chronic hepatitis, coagulation factor decreased, computerized tomogram liver abnormal, drug-induced liver injury, hepatic cirrhosis, hepatic congestion, hepatic encephalopathy, hepatic enzyme abnormal, hepatic enzyme increased, hepatic failure, hepatic fibrosis, hepatic function abnormal, hepatic infiltration eosinophilic, hepatic necrosis, hepatic steato-fibrosis, hepatic steatosis, hepatitis, hepatitis acute, hepatitis cholestatic, hepatitis fulminant, hepatitis toxic, hepatocellular injury, hepatorenal failure, hepatorenal syndrome, hepatotoxicity, hyperbilirubinaemia, hypertransaminasaemia, hypoalbuminaemia, hypocoagulable state, icterus index increased, international normalized ratio increased, jaundice, jaundice cholestatic, jaundice hepatocellular, liver disorder, liver function test abnormal, liver function test increased, liver injury, liver scan abnormal, mixed liver injury, portal hypertension, steatohepatitis, subacute hepatic failure, transaminases abnormal, transaminases increased, ultrasound liver abnormal, venoocclusive liver disease
herpesvirus infection	genital herpes, herpes simplex, herpes virus infection, herpes zoster, oral herpes
hyperbilirubinemia	bilirubin conjugated increased, blood bilirubin increased, blood bilirubin unconjugated increased, hyperbilirubinaemia, jaundice
hyperglycemia	diabetes mellitus, hyperglycaemia
hypersensitivity	drug hypersensitivity, hypersensitivity, urticaria
hypoalbuminemia	blood albumin decreased, hypoalbuminaemia
hypotension	blood pressure decreased, blood pressure systolic decreased, hypotension, orthostatic hypotension
leukocytosis	hyperleukocytosis, leukocytosis, white blood cell count increased
leukoencephalopathy	acute disseminated encephalomyelitis, encephalomyelitis, encephalopathy, leukoencephalomyelitis, leukoencephalopathy, posterior reversible encephalopathy syndrome, progressive multifocal leukoencephalopathy, toxic encephalopathy, toxic leukoencephalopathy
mucositis	Aphthous ulcer, gingival pain, gingivitis, glossitis, laryngeal inflammation, laryngeal pain, mouth ulceration, mucosal inflammation, oesophageal pain, oesophagitis, oral mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, proctalgia, stomatitis

Reference ID: 4293723

Grouped Term	Preferred Terms
myalgia	biopsy muscle abnormal, blood creatine phosphokinase abnormal, blood creatine phosphokinase increased, blood creatine phosphokinase MM increased, electromyogram abnormal, muscle disorder, muscle enzyme increased, muscle fatigue, muscle necrosis, muscle rupture, muscle strain, muscle twitching, muscular weakness, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal disorder, musculoskeletal pain, myalgia, myalgia intercostal, myoglobin blood increased, myoglobin blood present, myoglobin urine present, myoglobinaemia, myoglobinuria, myopathy, myopathy toxic, myositis, necrotizing myositis, rhabdomyolysis
myocardial ischemia	acute myocardial infarction, myocardial infarction, troponin increased, troponin I increased, troponin T increased
nausea/vomiting	nausea, retching, vomiting
neuropathy	Acute motor axonal neuropathy, acute motor-sensory axonal neuropathy, acute polyneuropathy, ataxia, axonal neuropathy, Bickerstaff's encephalitis, biopsy peripheral nerve abnormal, burning feet syndrome, burning sensation, cerebellar ataxia, cerebral ataxia, chronic inflammatory demyelinating polyradiculoneuropathy, demyelinating polyneuropathy, gait disturbance, Guillain-Barre syndrome, loss of proprioception, lumbosacral plexopathy, Miller Fisher syndrome, mononeuritis, mononeuropathy, multifocal motor neuropathy, myelopathy, nerve conduction studies abnormal, nerve degeneration, neuritis, neuromuscular toxicity, neuromyopathy, neuronal neuropathy, neuropathic muscular atrophy, neuropathy peripheral, paresthesia, peripheral motor neuropathy, peripheral nerve palsy, peripheral nerve paresis, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy, polyneuropathy idiopathic progressive, polyneuropathy in malignant disease, sensorimotor disorder, sensory disturbance, sensory loss, toxic neuropathy
pneumonia	lung infection, pneumonia, pneumonia aspiration, pneumonia bacterial
pneumonitis	acute interstitial pneumonitis, pneumonitis
pulmonary edema	acute pulmonary oedema, non-cardiogenic pulmonary oedema, pulmonary congestion, pulmonary oedema
rash	acute febrile neutrophilic dermatosis, butterfly rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis exfoliative, dermatitis exfoliative generalized, dermatitis psoriasiform, drug eruption, exfoliative rash, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin erosion, skin exfoliation, skin ulcer, toxic skin eruption, urticaria
renal insufficiency	acute kidney injury, acute phosphate nephropathy, acute prerenal failure, anuria, azotaemia, blood creatinine increased, continuous haemodiafiltration, dialysis, glomerular filtration rate decreased, haemodialysis, haemofiltration, hypercreatininaemia, hyponatriuria, nephropathy toxic, oliguria, peritoneal dialysis, prerenal failure, renal disorder, renal failure, renal impairment, renal tubular disorder

Reference ID: 4293723

Grouped Term	Preferred Terms
respiratory failure	acute respiratory distress syndrome, acute respiratory failure, cardiopulmonary failure, cardio-respiratory arrest, respiratory arrest, respiratory failure
sepsis	abdominal sepsis, acinetobacter bacteraemia, bacillus bacteraemia, bacteraemia, bacterial sepsis, bacteroides bacteraemia, biliary sepsis, brucella sepsis, burkholderia cepacia complex sepsis, campylobacter sepsis, citrobacter sepsis, clostridium bacteraemia, corynebacterium bacteraemia, corynebacterium sepsis, cronobacter bacteraemia, device related sepsis, enterobacter bacteraemia, enterobacter sepsis, enterococcal bacteraemia, enterococcal sepsis, escherichia bacteraemia, escherichia sepsis, granulicatella bacteraemia, haemophilus bacteraemia, helicobacter sepsis, intestinal sepsis, klebsiella bacteremia, klebsiella sepsis, listeria sepsis, meningococcal bacteraemia, meningococcal sepsis, micrococcal sepsis, neutropenic sepsis, nocardia sepsis, pelvic sepsis, pneumococcal bacteraemia, pneumococcal sepsis, post procedural sepsis, pseudomonal bacteremia, pseudomonal sepsis, salmonella bacteraemia, salmonella sepsis, sepsis, sepsis syndrome, septic shock, serratia bacteraemia, serratia sepsis, shewanella algae bacteraemia, staphylococcal bacteremia, staphylococcal sepsis, stenotrophomonas sepsis, streptococcal bacteraemia, streptococcal sepsis, urosepsis, wound sepsis, yersinia bacteraemia, yersinia sepsis
thrombosis	brachiocephalic vein thrombosis, catheter site thrombosis, cavernous sinus thrombosis, cerebral venous thrombosis, deep vein thrombosis, device related thrombosis, intracranial venous sinus thrombosis, jugular vein thrombosis, ovarian vein thrombosis, paraneoplastic thrombosis, portal vein thrombosis, portosplenomesenteric venous thrombosis, pulmonary embolism, pulmonary thrombosis, pulmonary venous thrombosis, renal vein thrombosis, splenic vein thrombosis, subclavian vein thrombosis, superior sagittal sinus thrombosis, thrombosis, thrombosis mesenteric vessel, transverse sinus thrombosis, venous thrombosis
upper respiratory tract infection	acute sinusitis, nasopharyngitis, pharyngitis, rhinitis, sinusitis, sinusitis bacterial, tonsillitis, upper respiratory tract infection, upper respiratory tract infection bacterial, viral upper respiratory tract infection
urinary tract infection	cystitis, escherichia urinary tract infection, kidney infection, pyelonephritis, urinary tract infection, urinary tract infection bacterial, urinary tract infection enterococcal, urinary tract infection pseudomonal
Ventricular arrhythmia	extrasystoles, Torsade de pointes, ventricular arrhythmia, ventricular extrasystoles, ventricular fibrillation, ventricular tachyarrhythmia, ventricular tachycardia
visual impairment	cataract, diplopia, myopia, vision blurred, visual acuity reduced, visual impairment

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15 Division Director (DHOT)

John K. Leighton, PhD
Division Director (DHOT)

Reference ID: 4293723

16 Division Director (OCP)

Nam Atiqur Rahman, PhD
Division Director (OCP)

Reference ID: 4293723

17 Division Director (OB)

Thomas E. Gwise, PhD
Deputy Director, DBV (OB)

Reference ID: 4293723

18 Division Director (DHP)

(This review was based in part on the review of Drs. Donna Przepiorka, Dr. Lola Luo, and Dr. Kelly Norsworthy).

On December 21, 2017, Agios Pharmaceuticals, Inc. submitted NDA 211192 to the FDA which requested approval for ivosidenib (Tibsovo) for the following indication: For the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA approved test. Mutational change of IDH1 is associated with higher than normal levels in the AML cells of 2-hydroxyglutarate (2HG), an oncometabolite which blocks differentiation of hematopoietic stem cells. This request relied upon study AG120-C-001, which was a Phase 1 multicenter open-label study of ivosidenib which was organized into a 3+3 dose escalation phase and an expansion phase which had 4 arms. NDA 211192 relied upon the results of treating patients with relapsed or refractory AML who were treated orally with 500 mg per day of ivosidenib.

Efficacy Results: The percent of patients with relapsed or refractory AML with mutations of IDH1 that achieved a complete response (CR) or complete disappearance of disease with partial hematological recovery: ANC > 500/µL and platelets > 50,000/µL (CRh) was 32.8% (95% CI: 25.8, 40.3) (ratio is 57/174). The duration of CR + CRh was 8.2 months (95% CI: 5.6, 12.0). The percent of patients with CR was 24.7% (95% CI: 18.5, 31.8), and the median duration of these responses was 10.1 months (95% CI: 6.5, 22.2). The median overall survival (OS) was 9.1 months (95% CI: 7.4, 10.2). Of the 68 patients who were transfusion-dependent at baseline, 41 became transfusion-independent post baseline.

Safety Results: The safety analysis sets (SAS) consisted of all patients with hematological malignancies (N=258) and with relapsed or refractory AML (N=179) who received ivosidenib on Study Ag-120-C-001. On-treatment deaths (on or within 28 days after the last dose of ivosidenib) were 28% (50/179) among patients in the relapsed/refractory AML SAS and 28% (73/258) among all patients in the advanced hematological malignancies SAS. The applicant identified the underlying malignancy as the cause of death in 23 of the 50 on-treatment deaths (46%) in the relapsed/refractory AML SAS, and in 49 of the 129 total deaths (38%) among all patients in the advanced hematological malignancies SAS. There were 10 on-treatment deaths (5.6%) in the dose-escalation phase in relapsed/refractory AML SAS patients on AG120-C-001 which were classified by the FDA review to be at least possibly related to ivosidenib. Three of the deaths included manifestations of differentiation syndrome (DS).

A total of 77% (137/179) of the subjects in the relapsed/refractory AML SAS experienced a treatment-emergent serious adverse event (SAE). Of the SAEs, 36 were considered to be at least possibly related to ivosidenib (36/179). Among these, the most frequent (≥2%) were: DS (n=16 or 9%), EKG QT prolongation (n=10 or 6%), and leukocytosis (n=5 or 3%).

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Overall, 38% (68/179), 3% (6/179) or 13% (24/179) of the relapsed/refractory AML SAS patients experienced interruption of ivosidenib, dose reduction of ivosidenib, or withdrawal from an adverse event respectively.

Benefit Risk Discussion: The 32.8% response rate based on CR + CRh with a median duration of 8 months was impressive, and the cost in terms of toxicity was relatively modest. TEAEs leading to discontinuation in the relapsed/refractory AML SAS (n=179) were 4 sepsis (2%), 3 fungal infections (2%), 3 pneumonias (2%), 2 Guillain-Barre syndrome (1%), and 2 renal insufficiencies (1%). The small number of discontinuations for adverse events in subjects with relapsed or refractory AML who received ivosidenib at 500 mg po qd suggest that the regimen used in this trial was well-tolerated and that the benefit risk ratio was favorable.

Regulatory Recommendation: This Supervisory Associate Division Director agrees with the recommendation of the review team for full approval of ivosidenib for the following indication: For the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 mutation as detected by an FDA approved test.

Albert Deisseroth, MD, PhD
Supervisory Associate Division Director (DHP)

Reference ID: 4293723

19 Office Director (or designee)

This application was reviewed under the auspices of the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. The risk-benefit of ivosidenib was also assessed by Drs. Deisseroth, Przepiorka and Norsworthy, and I concur with their recommendation to approve this drug. My signature below represents an approval recommendation for the clinical portion of this application under the OCE. My signature below also represents the approval decision of this application under CDER.

Richard Pazdur, MD
Director (OHOP)

Reference ID: 4293723

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/s/

LAURA C WALL
07/18/2018

KELLY J NORSWORTHY
07/19/2018

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07/19/2018

JOHN K LEIGHTON
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OLANREWAJU OKUSANYA on behalf of WENCHI HSU
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07/19/2018

ROSANE CHARLAB ORBACH
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GENE M WILLIAMS
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NAM ATIQUR RAHMAN
07/19/2018
I concur.

LOLA LUO
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YUAN L SHEN
07/19/2018

THOMAS E GWISE
07/19/2018

DONNA PRZEPIORKA
07/19/2018

ALBERT B DEISSEROTH
07/19/2018

RICHARD PAZDUR
07/19/2018

MEMORANDUM

Date: June 7, 2018

From: Ramadevi Gudi, PhD

Pharmacology/Toxicology Reviewer

Division of Hematology Oncology Toxicology for Division of Hematology Products

Through: Christopher Sheth, PhD

Supervisory Pharmacologist

Division of Hematology Oncology Toxicology for Division of Hematology Products

To: File for NDA 211192

Ivosidenib (AG-120 and AGI-16678)

Re: Pharmacology and Toxicology

Agios Pharmaceuticals, Inc. submitted NDA 211192 for ivosidenib, indicated to treat adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test. Mutant forms of IDH enzymes alter the catalytic activity of the IDH enzymes such that they produce high levels of a metabolite, (R)-2-hydroxyglutarate [(R)-2-HG], which is normally found at very low levels in cells. 2-HG impairs differentiation of hematopoietic stem cells into mature blood cells, contributing to oncogenesis. 2-HG is elevated in several tumor types, including subsets of AML. Inhibition of IDH1 mutants can suppress 2-HG production and induce myeloid cell differentiation. These effects may provide therapeutic benefit to patients with AML with certain IDH1 mutations. The nonclinical review is complete and has been added to the Multidisciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multidisciplinary Review and Evaluation for additional details. There are no outstanding issues from a pharmacology/toxicology perspective that would prevent approval of this application.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAMADEVI GUDI
06/07/2018

CHRISTOPHER M SHETH
06/07/2018