CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209606Orig1s000

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(s)	**NDA 209606**
Application Type	Original 505(b)(1)
Priority or Standard	Priority
Submit Date(s)	December 30, 2016
Received Date(s)	December 30, 2016
PDUFA Goal Date	August 30, 2017
Division/Office	DHP/OHOP
Review Completion Date	July 28, 2017
Applicant	Celgene Corporation
Established Name	Enasidenib
(Proposed) Trade Name	IDHIFA®
Pharmacologic Class	Isocitrate dehydrogenase 2 inhibitor
Formulation(s)	Tablets, 50mg and 100mg
Dosing Regimen	100 mg once daily
Applicant Proposed Indication(s)/Population(s)	IDHIFA is indicated for the treatment of patients with relapsed or refractory acute myeloid leukemia with an IDH2 mutation
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s)	IDHIFA is an isocitrate dehydrogenase-2 inhibitor indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia with an isocitrate dehydrogenase-2 mutation as detected by an FDA-approved test.

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DHP DDS=Division of Hematology Products Deputy Director for Safety
DMEPA=Division of Medication Error Prevention and Analysis
DMPP=Division of Medical Policy Programs
DRISK=Division of Risk Management

Glossary

2-HG	2-hydroxyglutarate
ADaM	Analysis Data Model
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice daily
BW	body weight
CBC	complete blood counts
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CDx	companion diagnostic
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CMP	comprehensive metabolic panel
CI	confidence interval
CR	complete remission
CRh	complete remission with partial hematologic recovery
CRi	complete remission with incomplete neutrophil recovery
CRp	complete remission without platelet recovery
CSR	clinical study report
CV	cardiovascular
DDS	Deputy Director for Safety
DEPI	Division of Epidemiology
DHOT	Division of Hematology Oncology Toxicology
DHP	Division of Hematology Products
DMEPA	Division of Medication Error Prevention and Analysis
DMPP	Division of Medical Policy Programs
DOR	duration of response
DRISK	Division of Risk Management
DS	Differentiation syndrome
DSRC	data safety review committee
ECG	electrocardiogram
eCTD	electronic common technical document
ECOG	Eastern Cooperative Oncology Group

EFS	event-free survival
EFT	embryo-fetal toxicity
E-R	exposure-response
FACS	fluorescence-activated cell sorting
FAS	full analysis set
FDA	Food and Drug Administration
GCP	good clinical practice
GFR	glomerular filtration rate
GLP	good laboratory practice
GVHD	graft-versus-host disease
HCP	healthcare provider
hERG	human ether-a-go-go-related gene
HSCT	hematopoietic stem cell transplantation
ICH	International Conference on Harmonization
IDH2	Isocitrate dehydrogenase-2
IND	Investigational New Drug
IWG	International Working Group
MAD	maximum administered dose
MAED	MedDRA Adverse Events Diagnostic
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MLFS	morphologic leukemia-free state
MRD	minimal residual disease
MTD	maximum tolerated dose
NDA	new drug application
OB	Office of Biostatistics
OCP	Office of Clinical Pharmacology
OPDP	Office of Prescription Drug Promotion
OPQ	Office of Pharmaceutical Quality
ORR	overall response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PD	progressive disease
PK	pharmacokinetics
PLLR	pregnancy and lactation labeling rule
PMA	pre-market approval
PMC	postmarketing commitment
PMR	postmarketing requirement
PO	by mouth
PR	partial remission

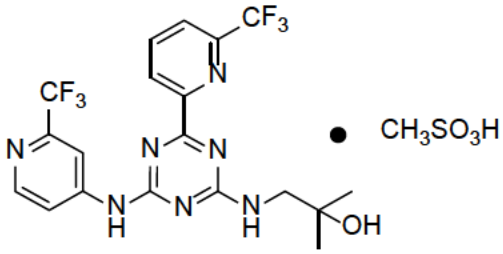
PREA	Pediatric Research Equity Act
PS	performance score
QD	once daily
RBC	red blood cell
REMS	risk evaluation and mitigation strategy
RP2D	recommended phase 2 dose
R/R	relapsed or refractory
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SD	standard deviation
SDTM	Study Data Tabulation Model
TB	total bilirubin
TEAE	treatment emergent adverse event
TK	toxicokinetic
TL	team leader
TLS	tumor lysis syndrome
ULN	upper limit of normal
USPI	United States prescribing information
WBC	white blood cell
WHO	World Health Organization
WT	wild-type

1 Executive Summary

1.1. Product Introduction

Proprietary Name:	IDHIFA®
Established Name:	enasidenib
Also Known As:	AG-221, CC-90007
Chemical Name:	2-methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl) pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate
Molecular Formula:	$C_{19}H_{17}F_6N_7O \bullet CH_3SO_3H$
Molecular Weight:	569.48 g/mol
Dosage Forms:	Tablets, 50 mg and 100 mg
Therapeutic Class:	Antineoplastic
Chemical Class:	Small molecule
Pharmacologic Class:	Isocitrate dehydrogenase 2 inhibitor
Mechanism of Action:	Inhibition of the mutant IDH2 enzyme by enasidenib decreases 2-hydroxyglutarate (2-HG) levels and induces myeloid differentiation.

Chemical Structure:



Enasidenib (IDHIFA®) is a new molecular entity. NDA 209606 was submitted for the proposed indication of treatment of patients with relapsed or refractory acute myeloid leukemia with an IDH2 mutation using a dose of 100 mg daily.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends regular approval of enasidenib under 21 CFR 314.105 for the indication "Treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test" using a dose of 100 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 AG221-C-001 (NCT01915498).

Safety during long-term use, the potential for drug-drug interactions, appropriate dosing for patients with hepatic impairment, and confirmation of the diagnostic criteria for and management of enasidenib-induced differentiation syndrome remain to be determined in postmarketing studies.

Study AG221-C-001 was an open-label, single-arm, multicenter, two-part clinical trial of enasidenib for adults with AML or higher-risk MDS; the design included a Phase 1 (dose-escalation and dose-expansion) portion and a single-arm Phase 2 portion. The dose of 100 mg daily used in the pivotal analysis was based on results from the Phase 1 portion which showed a) maximal suppression of 2- hydroxyglutarate using enasidenib doses $\geq$ 100 mg, b) similar response rates at doses $\geq$ 100 mg, and c) for doses $\geq$ 100 mg, the 100 mg cohort had the lowest proportion of subjects with dose reductions for toxicity.

The primary endpoint of Study AG221-C-001 was overall response rate (ORR, defined as CR, CRp, CRi, morphologic leukemia-free state and PR) as determined by investigator. There was no planned interim analysis in the protocol, and the final analysis was to be performed on 125 subjects in the Phase 2 portion. There was no hypothesis testing planned, but the protocol indicated that a binomial 95% CI lower bound >25% was considered clinically meaningful. FDA's analysis of the primary endpoint includes 104 subjects with relapsed or refractory (R/R) AML; the ORR for Phase 2 was 34.6% (95% CI 25.3% - 44.2%), which met the applicant's prespecified definition for clinical meaningfulness.

In presubmission meetings and correspondence with the applicant, FDA identified several deficiencies in the protocol design. These included:

- The lack of hypothesis testing and lack of justification for the sample size allowed for bias in the interpretation of the study. To overcome this challenge, FDA required that the applicant provide results only when accrual was completed for both portions of the protocol. Meaningfulness of the results would then be a review issue.
- Since the Phase 1 portion showed that patients could respond as late as with 6 cycles of treatment, FDA required that the data be submitted with at least 6 months of follow-up for the subjects in Phase 2.
- ORR was not considered an appropriate endpoint for regulatory decision-making for R/R AML. CR is usually used as a surrogate reasonably likely to predict survival. However, the applicant reported that subjects tested at best response still had minimal residual disease (MRD) including in cells other than blasts, so it was not clear that a CR induced by enasidenib, a differentiating agent, had the same prognostic value as a CR induced by cytotoxic chemotherapy. Therefore, FDA recommended that the applicant assess CR and CRh along with measures of transfusion independence to assess clinical benefit, and these were added as secondary endpoints in the protocol

Study AG221-C-001 enrolled a total of 215 subjects identified by the applicant as having R/R AML with an IDH2 mutation and who were treated with enasidenib 100 mg daily. FDA excluded enrolled subjects who did not have documentation of relapse at study entry and subjects who were not confirmed positive for the IDH2 mutation at the central laboratory. The final population used for efficacy analyses to support the indication included 101 subjects from the Phase 1 portion and 98 subjects from the Phase 2 portion. The study population had a median age of 68 years (range, 19-100 years), 62% were at least 65 years old, 52% were male, and 77%

were white. The CR/CRh rate as adjudicated by the clinical reviewer was 23% (95% CI: 18% - 30%), and the median duration of response was 8.2 months (95% CI: 4.3 - 19.4 months). The CR/CRh rate was consistent across the two portions of the study (23.8% in Phase 1 and 22.5% in Phase 2).

Of the 157 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 53 (34%) became independent of transfusions during any 56-day post baseline period. Of the 42 patients who were transfusion-independent at baseline, 32 (76%) remained transfusion-independent during any 56-day post baseline period.

It is concluded that the consistent CR/CRh rates with associated transfusion-independence across Phase 1 and Phase 2 constitutes substantial evidence of effectiveness.

1.3. Benefit-Risk Assessment

Table 1: Benefit-Risk Framework

	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 IDH2 mutations, the reported remission rate using current available therapy for 2nd or later salvage is 26% with a median survival of 5.9 months. • 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 AG221-C-001, a single-arm trial, 199 adults with IDH2-mutated R/R AML were treated with enasidenib 100 mg daily. • CR or CRh was achieved by 23% (95% CI: 18% - 30%). The results were consistent across two sequential cohorts. • Conversion to transfusion independence was achieved by 34%, and 76% maintained transfusion independence.	There is substantial evidence of effectiveness for enasidenib as a palliative treatment of R/R AML with IDH2 mutation. There are no data that suggest long-term disease control.
Risk	• The most common adverse reactions (≥20%) included nausea, vomiting, diarrhea, increased bilirubin, and decreased appetite. • Differentiation syndrome (DS) that is life-threatening or fatal occurred. Early diagnosis and intervention are needed to prevent treatment-related mortality. • Hyperleukocytosis and elevated bilirubin are on-target effects that may be confused as adverse reactions. • Nonclinical data suggest that enasidenib may cause embryo-fetal toxicity (EFT). • Dosing modifications for patients with hepatic impairment has not been established. • The effect of enasidenib on PK of drug used commonly in this population is unclear.	The overall short-term safety profile of enasidenib is acceptable for patients R/R IDH2-mutated AML. Long-term safety information is needed, dosing with hepatic impairment needs to be determined, and the potential for drug-drug interactions needs to be clarified.

Table 1: Benefit-Risk Framework

	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• The protocol included monitoring for risks and instructions for intervention. With this in place, serious DS could be avoided. Dosing was modified for more than half of the subjects. • The proposed labeling includes warnings, dose modifications and treatment of DS.	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 DS and EFT, and instructions for monitoring and dose modifications for toxicities.

Patients with R/R IDH2-mutated AML that has relapsed or that is refractory to induction therapy have a devastating prognosis. In Study AG221-C-001, 23% (95% CI: 18% - 30%) achieved a CR or CRh, conversion to transfusion-independence was achieved by 34%, and 76% 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.

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 11% of subject terminated therapy due to an adverse reaction. The results provide substantial evidence that enasidenib at least short-term is tolerable for most patients.

The major safety issue identified is differentiation syndrome (DS). The overall incidence of DS is unclear and may be as high as 33% based on an algorithmic approach. Six deaths due to DS were identified in the overall population, but with procedures in place for early diagnosis and intervention, fatal events in the pivotal population were limited. The seriousness of this risk warrants a boxed warning and instructions to patients regarding the risks and need for early intervention.

Given the tolerability of enasidenib in addition to the potential to avoid transfusions short-term and with the safety mitigation plan in place, the clinical benefit of enasidenib appears to outweigh the risks for patients with R/R IDH2-mutated AML not seeking treatment with curative intent.

Donna Przepiorka, MD, PhD
Cross-Disciplinary Team Leader

2 Therapeutic Context

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, resulting in pancytopenia. According to the National Cancer Institute's SEER database, it is estimated that there were 19,950 new cases of AML and 10,430 deaths from AML in the United States in 2016. 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 (5.0 vs 3.4 new cases per 100,000 persons per year) and does not have a strong racial or ethnic predilection. AML is universally fatal without treatment, with a median survival of approximately two months (Oran and Weisdorf, 2012).

Isocitrate dehydrogenases (IDH) catalyze the oxidative decarboxylation of isocitrate to α-ketoglutarate during cellular metabolism. Mutations of the IDH2 isoform are found in 8-19% of patients with AML (Dinardo et al, 2015). These mutations are typically heterozygous and confer a new ability of the enzyme to catalyze the production of D-2-hydroxyglutarate. The implications of this for AML pathogenesis are unknown. IDH2 mutations occur more frequently in older patients and patients with intermediate-risk cytogenetics. They frequently co-occur with FLT3-ITD and NPM1 mutations, and are thought to be nearly mutually exclusive with TET2 and WT1 mutations (Dinardo et al, 2015). There is limited information available regarding the prognostic significance of IDH2 mutations in AML, and no prospective studies have addressed this question. In one of the largest retrospective analyses (Dinardo et al, 2015), 61% of patients with newly diagnosed IDH2+ 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 (15.7 months vs 15.3 months, p=0.59). Patients with relapsed IDH2+ AML had a 50% CR/CRi rate with first salvage therapy compared to 41% of those with IDH^{WT} AML, with a mOS of 11.1 months vs 7.7 months (p=0.44). For patients receiving third line or higher therapy, rates of CR/CRi were 26% for IDH2+ disease and 27% for $IDH2^{WT}$ disease, with mOS 5.9 months vs. 4.8 months (p=0.16).

2.2. Analysis of Current Treatment Options

Combination chemotherapy regimens with or without hematopoietic stem cell transplantation (HSCT) are a mainstay of therapy for patients with newly diagnosed AML. In patients who can tolerate intensive therapy, which may be limited by factors such as age and comorbid conditions, cytarabine and daunorubicin induction followed by high-dose cytarabine consolidation is frequently used. This regimen typically results in CR rates of 60-70% and 2-year OS of approximately 50% in patients < 60 years of age (Fernandez et al, 2009). Older patients treated with intensive chemotherapy fare less well, with CR rates of approximately 50% and 2-

year overall survival of approximately 20% (summarized in Estey, 2007). Patients whose blast count remains > 5% after two cycles of intensive chemotherapy are considered primary refractory. In patients who do achieve remission, long-term disease-free survival is only 30-40% because the majority will eventually relapse.

Table 2 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, and 5-year survival of patients who achieve a second remission is about 40% (Dohner et al, 2017). However, few patients can tolerate intensive re-induction chemotherapy. In large, phase 3 studies of high-dose cytarabine or investigator's choice (e.g., hypomethylating agents, multi-agent 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 16%, and median OS ranges from 3.3 to 6.3 months (Roboz et al, 2014; Faderl et al, 2012; Ravandi et al, 2015). There is a clear need for new treatments for patients with relapsed or refractory AML.

Table 2: Currently Available Treatments for Acute Myeloid Leukemia

Agent	Excerpted Indication
Cyclophosphamide	Indicated for the treatment of acute myelogenous and monocytic leukemia. Although effective alone in susceptible malignancies, is more frequently used concurrently or sequentially with other antineoplastic drugs.
Cytarabine	Indicated, in combination with other approved anticancer drugs, for remission 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.
Doxorubicin	Has been used successfully to produce regression in disseminated neoplastic conditions, including (b) (4) myeloblastic leukemia.
Idarubicin	Indicated, in combination with other approved anti-leukemic drugs, for the treatment of acute myeloid leukemia in adults. This includes FAB classifications M1 through M7.
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 drugs, in the initial therapy of acute nonlymphocytic leukemia in adults. This category includes myelogenous, promyelocytic, monocytic and erythroid acute leukemias.
Thioguanine	Indicated for remission induction and remission consolidation treatment of acute nonlymphocytic leukemias. Is not recommended for use during maintenance therapy or similar long-term continuous treatments due to the high risk of liver toxicity. Reliance upon thioguanine alone is seldom justified for initial remission induction of acute non-lymphocytic leukemias because combination chemotherapy including thioguanine results in more frequent remission induction and longer duration of remission than thioguanine alone.
Vincristine	Indicated in acute leukemia.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Enasidenib is not currently marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

The trials included in this application were conducted under IND 117631, which was opened in the United States in July of 2013. The IND has never been placed on clinical hold.

The FDA granted Orphan Drug Designation (#14-4345) to enasidenib for the treatment of acute myelogenous leukemia on June 12, 2014.

The FDA granted Fast Track Designation to enasidenib for the treatment of patients with acute myeloid leukemia that harbor an isocitrate dehydrogenase-2 (IDH2) mutation on July 31, 2014.

At a pre-NDA meeting held on July 26, 2016, the FDA agreed that subjects with relapsed or refractory AML who relapse after allogeneic transplantation, are in second or later relapse, are refractory to initial induction or re-induction treatment, who relapse within 1 year of initial treatment, and/or have failed two or more cycles of first line therapy (consisting of an intermediate intensity chemotherapy, hypomethylating agent, or low-dose cytarabine) represent a population with unmet medical need. The FDA also agreed that the rate of complete response, in combination with duration of response, is a reasonable predictor of survival in AML. However, the FDA also encouraged the Sponsor to assess other endpoints that could be used to support a claim of clinical benefit of enasidenib in patients with relapsed/refractory AML.

This NDA was submitted on December 30, 2016 in its entirety, using a data cut date of April 15, 2016. The Applicant requested priority review, which was granted by the FDA on February 28, 2017. At the time of filing, the FDA asked the applicant to provide updated efficacy and safety data on all patients treated with enasidenib at the time of the 90-day safety update, using a data cut date of October 14, 2016.

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

4.1. Office of Scientific Investigations

The Office of Scientific Investigations (OSI) conducted inspections for Study AG-221-C-001 at clinical sites in Villejuif, France (Institut Gustave Roussy), Houston, Texas (MD Anderson Cancer Center), and New York, New York (Memorial Sloan-Kettering Cancer Center). These sites had the highest accrual, highest number of protocol violations per patient, and/or greatest impact on the primary endpoint. Inspection review of the MD Anderson site identified minor regulatory deficiencies related to adverse event reporting (failure to report one adverse event, and failure to report one serious adverse event within the mandatory reporting period). A Form 483 was issued to MD Anderson describing these deficiencies, and the preliminary classification is Voluntary Action Indicated. The preliminary classification of the other two sites is No Action Indicated. The Applicant (Celgene) was also audited. The preliminary classification of the Applicant inspection is No Action Indicated. Based on the preliminary results, the study data derived from the inspected clinical sites and the Applicant are considered reliable in support of the requested indication.

4.2. Product Quality

Enasidenib drug product (Idhifa®) is presented as 50 mg and 100 mg film-coated tablets for oral use containing 60 mg and 120 mg enasidenib mesylate drug substance, respectively. The tablets are debossed with “ENA” on one side and either “50” or “100” on the other side. Inactive ingredients include colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose acetate succinate, iron oxide yellow, magnesium stearate, microcrystalline cellulose, poly-ethylene glycol, polyvinyl alcohol, sodium lauryl sulfate, sodium starch glycolate, talc, and titanium dioxide. All excipients are either compendia-compliant or controlled. The drug product may contain genotoxic impurities, but these 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 30 tablets with an expiry of 18 months when stored at 20°C - 25°C.

Several different formulations were used in the clinical trial that forms the basis of the NDA submission: Formulation 1a (F1a), Formulation 1b (F1b), Formulation 2 (F2) and Formulation 3 (F3). F1a was produced using (b) (4), whereas all later formulations used (b) (4). F3 is the only formulation that is film-coated. Relative exposure with the different formulations is discussed in detail in Section 6 of this review, but the data suggest that there was no clinically meaningful difference in exposure to enasidenib following administration of the different formulations on Study AG221-C-001. The to-be-marketed F3 was not studied in clinical trials. The clinical trial F3 and to-be-marketed F3 differ only by debossment, and the biopharmaceutics reviewer deemed these similar based on dissolution studies. It is therefore concluded that the clinical safety and

efficacy data in the NDA are applicable to the to-be-marketed drug product.

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 IDH2 mutation, which is the target of enasidenib. In Study AG221-C-001, patients were selected based on detection of an IDH2 mutation in the local laboratory, and the results were confirmed by testing in a central laboratory using the Abbott RealTime IDH2™ mutation assay, which identifies the following mutations: R140Q, R140L, R140G, R140W, R172K, R172M, R172G, R172S, and R172W. It was determined that a device to select patients for therapy would be required for safe use of this drug when marketed. The applicant cross-referenced PMA P170005 for the Abbott RealTi*m*e IDH2™ mutation assay. 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.

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5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

IDHIFA (enasidenib, also known as CC-90007, AG-221, and AGI-12910) is an isocitrate dehydrogenase 2 (IDH2) inhibitor. The IDH enzymes catalyze the oxidative decarboxylation of isocitrate to alpha-ketoglutarate (α-KG), producing nicotinamide adenine dinucleotide phosphate (NADPH) in the process via the citric acid cycle. Some mutant forms of IDH enzymes catalyze the reduction of α-KG to an oncometabolite known as 2-hydroxyglutarate (2-HG), while consuming NADPH[1,2].

2-HG is elevated in several tumor types, including a subset of AMLs[3]. Excessive accumulation of 2-HG has been associated with histone hypermethylation in vitro and a block in normal hematopoietic cellular differentiation in vitro and in vivo. This block appears to result in an expansion of immature myeloid progenitors and precursors and a decrease in differentiated mature cells; hallmarks of acute myeloid leukemia. Inhibition of IDH2 mutants (R140Q, R172K/S) and IDH1 (R132H/C) can suppress 2-HG production; reduce the level of hypermethylation, and induce myeloid cellular differentiation; effects that may provide therapeutic benefit.

In vitro pharmacology studies demonstrated enasidenib was more potent at inhibiting IDH2 R140Q, IDH2 R172K, and IDH2 172S mutants in comparison to IDH2 wild-type (IDH2WT) enzymes (> 40 fold difference). In vitro studies in cell lines over-expressing the IDH2 mutant R140Q (i.e., TF-1 and U87MG cells) showed that sub-nanomolar concentrations of enasidenib can reduce 2-HG levels by ≥ 95% in both cell lines in comparison with other IDH2 (≥50%) and IDH1 (≥20%) mutant isoforms. In TF-1 cells, enasidenib reduced histone hypermethylation and decreased the percentage of hematopoietic stem and progenitor cells relative to untreated controls, and induced cellular differentiation. In an ex vivo assay with primary human AML blast cells (including cells with IDH2 R140Q mutations), treatment with enasidenib for up to 9 days reduced 2-HG levels by 99% relative to controls, decreased the number of viable AML blast cells (55-99% by Day 6) and induced cellular differentiation as shown by changes in cell surface markers (CD14, CD15 and CD11b) associated with monocytic and granulocytic differentiation. Additionally, in IDH2 R140Q xenograft models, treatment with enasidenib dose-dependently decreased serum 2-HG levels (>95%), increased blast cell differentiation in the bone marrow, and prolonged the survival of the mice.

[1] Dang L, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature 462;739-744
[2] Clark O, et al. Molecular Pathways: Isocitrate Dehydrogenase Mutations in Cancer. Clinical Cancer Research 22(8) 2016
[3] 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.

Enasidenib and its metabolite AGI-16903 bind adenosine A1, A2A, and A3 receptors in vitro and act as functional antagonists. The most potent functional antagonist activity for both compounds was against adenosine A3 receptor, with IC_{50} values of 5.7 and 120 nM for enasidenib and the metabolite, respectively. Inhibition of the A3 receptor may have adverse cardiovascular (CV) effects. In the CV safety pharmacology study in dogs, a dose-related increase in heart rate and increase in blood pressure was observed after single oral doses of 75 and 300 mg/kg. In a 7-day repeat dose toxicology study in dogs at doses ≥30 mg/kg/day, significantly increased heart rates, decreased PR and RR intervals, and prolongation of the QT and QTcV intervals . In addition, there were histopathological changes of minimal to mild arterial degeneration/necrosis of the heart. The systemic exposure (AUC) associated with CV effects in dogs was substantially lower than the AUC in patients administered enasidenib at the recommended daily dose of 100 mg. In addition, the IC_{50} of 5.7 nM for the adenosine A3 receptor is >50 fold below the steady state free C_{max} of enasidenib in patients at the recommended daily dose of 100 mg, suggesting the inhibitory activity against the A3 receptor may be relevant at therapeutic serum concentrations of enasidenib.

The rate of absorption of oral enasidenib was moderate in monkeys with T_{max} occurring at 3-4 hours. The oral bioavailability was approximately 40%. The tissue distribution of enasidenib was widespread with the highest concentrations observed in the small intestine, liver, stomach (glandular and non-glandular), kidney cortex, adrenal gland, Harderian gland, pancreas, and adipose (brown) in Sprague-Dawley (SD) rats. Enasidenib crossed the blood-brain barrier. In pigmented Long Evens (LE) rats, the concentrations in eye uveal tract and pigmented skin suggest association with melanin-containing tissues. Enasidenib is mainly metabolized through N-dealkylation to form M1 (AGI-16903) in dogs, monkeys and humans, while hydroxylation to form M2 (AGI-17011) was the prominent pathway in rats in vitro. In humans, M1 is the most prominent metabolite but appears to be < 10% of the parent drug exposure at steady state. The majority of enasidenib was excreted in feces in intact rats and via the biliary route in bile duct-cannulated (BDC) rats (>85% in feces of intact rats and 30-40% in BDC rats), suggesting that fecal excretion is the main route of elimination with biliary excretion being the major route of elimination for absorbed enasidenib in rats.

Enasidenib was evaluated in GLP-compliant, repeat-dose general toxicology studies in rats and monkeys with twice daily oral administration of up to 90-days in duration. Enasidenib-related toxicities in rats in the 90-day study included marked to severe seminiferous tubular degeneration in the testes and marked reduction of sperm in the epididymides correlating with decreased testes and epididymides weights at the high dose of 20 mg/kg/dose. Higher dose levels were tested in the 28-day rat study, and more toxicities including mortality occurred at the high dose of 100 mg/kg administered twice daily. The systemic exposure in rats at 100 mg/kg BID ($AUC_{0\text{-}24hr}$ = 750 µg.hr/mL) is approximately 3-fold higher than the clinical exposure in patients at the recommended daily dose of 100 mg ($AUC_{0\text{-}24hr}$ = 258.5 µg.hr/mL). The cause of death was due to toxicities in multiple tissues, including effects such as hemorrhage, necrosis,

degeneration, and/or atrophy. Additional histopathological changes observed in the 28-day study included inflammation, regeneration, apoptosis, and cellular depletion of lymphoid and hematopoietic organs. Atrophy and vacuolation were noted in the hepatic and digestive systems, as well as gastrointestinal tract erosion, decreased corpora lutea, increased degeneration of ovarian follicles, atrophy of the uterus and abnormal estrous cycles.

In the 90-day monkey study, enasidenib-related toxicities were noted in the thymus (decreased weight correlating microscopically with thymic involution/atrophy), liver (increased weights correlating with increased hepatocyte cytoplasmic rarefaction), bone (moderate decreases in thickness of the distal femoral and proximal tibial physes, slight to moderate decreases in sternal bone marrow cellularity), and pancreas (moderate to marked acinar cell degranulation) with increased incidence and severity at the high dose of 6 mg/kg administered twice daily. In the 28-day monkey study, higher dose levels were tested and mortality occurred in one male at the high dose of 12 mg/kg administered twice daily. The cause of death was considered to be ulcerative inflammation of the large intestine. Other adverse effects included reductions in red blood cells (RBCs) and lineages, reduced albumin/globulin (A/G) ratios, and increases in indirect bilirubin and cholesterol at the high dose. Increases in absolute and relative heart (>10%) and liver weights (>10%), and minimal to moderate periarteritis was observed in multiple tissues including the heart, gall bladder, epididymides, and stomach in males at the high dose. Mild to severe physeal dysplasia of the femur was also observed in males treated twice daily for 28-days at 5 and 12 mg/kg.

An exploratory 7-day repeat dose toxicity study was conducted in Beagle dogs. The dogs were administered AGI-14405 (a phosphate prodrug of enasidenib) orally at 5, 15, or 50 mg/kg twice daily. Animals dosed at 50 mg/kg were euthanized in moribund condition; hypotension and tachycardia were the likely cause of the moribund condition. Markedly elevated heart rate was noted within 1 hour of the first dose on Study Day 0. Significant enasidenib-related toxicities included increased heart rate, decreased PR and RR intervals at ≥5 mg/kg twice daily and prolongation of QT and QTcV interval and arterial degeneration/necrosis in the heart at ≥15 mg/kg twice daily. The systemic exposure to AGI-14405 was less than 0.4% of the exposure to the active drug enasidenib (AGI-12910), thus the toxicities observed in dogs are likely related to enasidenib and/or its metabolites. At the maximum tolerated dose (MTD) of 15 mg/kg twice daily, on Day 6 enasidenib exposure ($AUC_{0\text{-}24hr}$) in dogs was 13.8 µg.hr/mL, approximately 20-fold lower (0.05x margin) than that of the clinical exposure in patients at the recommended daily dose of 100 mg ($AUC_{0\text{-}24hr}$ = 258.5 µg.hr/mL).

Dedicated studies to assess enasidenib 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. Enasidenib (3, 10, or 30 mg/kg twice daily) administered orally during organogenesis to female rats, from gestation day (GD) 6 through 17, resulted in maternal toxicity including thin body condition, body weight loss and decreased body weight gain at the

high dose level. Developmental toxicity included decreased gravid uterine weights, decreased litter sizes/numbers of viable fetuses, increased resorptions, increased postimplantation loss, decreased mean fetal body weights, and unossified sternebrae at the high dose level. The systemic exposure in high dose rats ($AUC_{0\text{-}24hr}$ of 418 µg·hr/mL) was 1.6 x the human exposure at the recommended daily dose of 100 mg ($AUC_{0\text{-}24hr}$ = 258.5 µg.hr/mL). Fetal plasma enasidenib concentrations were approximately 20-50% of maternal plasma concentrations over the dose range of 3 to 30 mg/kg twice daily.

Enasidenib (2, 5, or 10 mg/kg/day) was administered orally during organogenesis to rabbits on GDs 7 through 19, and cesareans were performed on GD 29. One animal each at mid dose and high dose aborted on GD 20 and 27, respectively. The percentage of abortions in the enasidenib treatment groups is 5% at the mid and high dose level. The historical control data indicate the rate of spontaneous abortion to be 0.3% in rabbits. Treatment with enasidenib resulted in maternal toxicities including, decreased mean gestational body weight gain at 5 and 10 mg/kg/day, thin body condition, and few/absent feces at 10 mg base/kg/day. Systemic exposure at the mid dose ($AUC_{0\text{-}24hr}$ = 17.6 µg·hr/mL) in rabbits was 0.07x the human exposure at the recommended daily dose 100 mg. No developmental toxicity was observed at any dose level in rabbits. Systemic exposure to the metabolite AGI-16903 was < 7% of enasidenib exposure across all doses tested. Enasidenib and AGI-16903 fetal plasma concentrations were ≤ 5% and ≤ 14% of maternal plasma concentrations, respectively.

Findings in the embryo-fetal development studies support the inclusion of a warning for embryo-fetal toxicity in the enasidenib label. In addition, enasidenib and the metabolite AGI-16903 transfer through the blood-placenta barrier. In the repeat dose general toxicity studies in rats and monkeys both the male (testes, epididymides, prostate and seminal vesicle) and female (uterus and estrous cycle) reproductive systems were adversely affected by enasidenib treatment. These findings support the inclusion of a statement in the drug label that enasidenib may impair male and female fertility. Based on the terminal half-life of enasidenib in human plasma, the Applicant proposed the duration of use of effective contraception to be during treatment with IDHIFA and for one month following the last dose, which was acceptable from a Pharmacology/Toxicology perspective.

Enasidenib was not genotoxic in the Ames bacterial reverse mutation test, the in vitro mammalian chromosome aberration test in Chinese hamster ovary cells (CHO) 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 submitted nonclinical pharmacology and toxicology data with enasidenib are adequate to support approval of this NDA for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Primary pharmacology

The Applicant conducted enzyme kinetics experiments to study the inhibitory effects of enasidenib and its metabolites (AGI-16903 and AGI-17011) against the IDH2 mutant enzymes (IDH2 R140Q and IDH2 R172K) and wild-type IDH2 in a diaphorase/resazurin coupled system at 1 and 16 hour time points (Reports AG221-N-047-R and AG221-N-081-R1). In this assay a discontinuous IDH2 activity, where conversion of α-KG to 2-HG was measured as a function of remaining nicotinamide adenine dinucleotide phosphate (NADPH). Enasidenib inhibited IDH2 R140Q with an IC_{50} of 0.77 μM at 1 hour time point that was approximately 40-fold lower concentrations than IDH2 WT. The metabolites AGI-16903 and AGI-17011 were able to inhibit IDH2 R140Q with an IC_{50} that was 75 and 18-fold lower than the other mutant form IDH2 172K, respectively at 16 hour time point.

Table 3: Inhibition of IDH2 Activity by Enasidenib and its Metabolites

Compound	Enzyme	IC50 (μM)
Ag-221	**IDH2 R140Q**	**0.77**
	IDH2 R172S	**0.155**
	IDH2 R172K	**0.214**
	IDH2 WT	**34.1**
AGI-16903	**IDH2 R140Q**	**0.016**
	IDH2 172K	**1.2**
AGI-17011	**IDH2 R140Q**	**0.205**
	IDH2 172K	**3.6**

IC_{50} = concentration providing 50% inhibition of IDH2

The potency and specificity of enasidenib against cellular IDH2 and IDH1 mutations in cell based systems was assessed (Report AG221-N-037-R1) using the following cell lines:

- U87MG and TF-1 overexpressing IDH2 R140Q
- U87MG overexpressing IDH2 R172K
- Human chondrosarcoma cells (SW1353) endogenously expressing IDH2 R172S
- U87MG overexpressing IDH1 R132H
- HT1080 endogenously expressing IDH1 R132C human erythroid leukemia (TF-1) cells.

Overnight cell cultures seeded in microtiter plates were treated with various concentrations of enasidenib for 48 hours. After a wash, the cells were allowed to incubate for another 24 hours. At 72 hours post compound addition, 10 mL/plate of Promega Cell Titer Glo reagent was added.

2-HG concentrations were measured by LC-MS/MS and cellular IC_{50}, IC_{90}, percent maximum 2-HG inhibition, and half-maximal growth inhibition (GI_{50}) were calculated.

The IC_{50} for 2-HG inhibition by enasidenib in cells lines overexpressing IDH2 R140Q was >116-fold lower compared to IDH2 R172 mutant isoforms. Maximum percent 2-HG inhibition was ≥95% for both cell lines overexpressing IDH2 R140Q in contrast with other IDH2 and IDH1 mutant isoforms.

Table 4: Enasidenib Inhibition of Isocitrate Dehydrogenase 2 Mutants

Cell-Based System	IC_{50} (µM)	IC_{90} (µM)	% Max 2-HG Inhibition	GI_{50} (µM)	% Max Growth Inhibition
TF-1 IDH2 (R140Q)	0.012	0.361	95	> 3	5
U87MG IDH2 (R140Q)	0.012	0.129	96	> 3	5.8
U87MG IDH2 (R172K)	1.4	> 3	62	> 3	10
SW1353 IDH2 (R172S)	2.1	> 3	56	> 3	3.4
U87MG IDH1 (R132H)	> 3	> 3	20	> 3	10
HT1080 IDH1 (R132C)	> 3	> 3	26	> 3	3

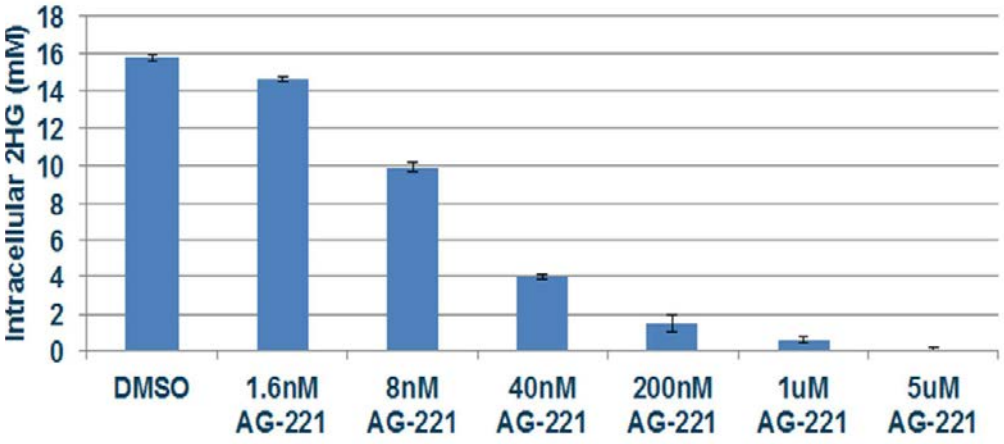
2-HG = 2-hydroxyglutarate; GI_{50} = concentration providing 50% growth inhibition; IC_{50} = concentration providing 50% inhibition of isocitrate dehydrogenase 2 activity; IC_{90} = concentration providing 90% inhibition of isocitrate dehydrogenase 2 activity; max = maximum.

(Table excerpted from NDA 209606)

The downstream effects of IDH2 R140Q mutations on cellular differentiation including histone hypermethylation was studied in a model system that was generated by transfecting the granulocyte macrophage colony-stimulating factor (GM-CSF)-dependent erythroleukemia cell line TF-1 with the IDH2 R140Q mutant allele using a lentivirus pLVX system (Report AG221-N-038-R1). The study also investigated whether inhibition of the enzymatic activity of IDH2 R140Q by enasidenib can reverse IDH2 R140Q induced hypermethylation.

TF-1 pLVX (empty vector expressing TF-1 cells used as a control) and TF-1 IDH2 R140Q cells were treated for 7 days with dimethylsulfoxide (DMSO) (control) or increasing concentrations of enasidenib. Inhibition of 2-HG production was measured using LC-MS/MS methods. Cells were lysed, protein was extracted, and histone hypermethylation was measured using Western blot analysis. Enasidenib treatment resulted in concentration-dependent reductions (> 90%) in 2-HG levels in the mutant cell line.

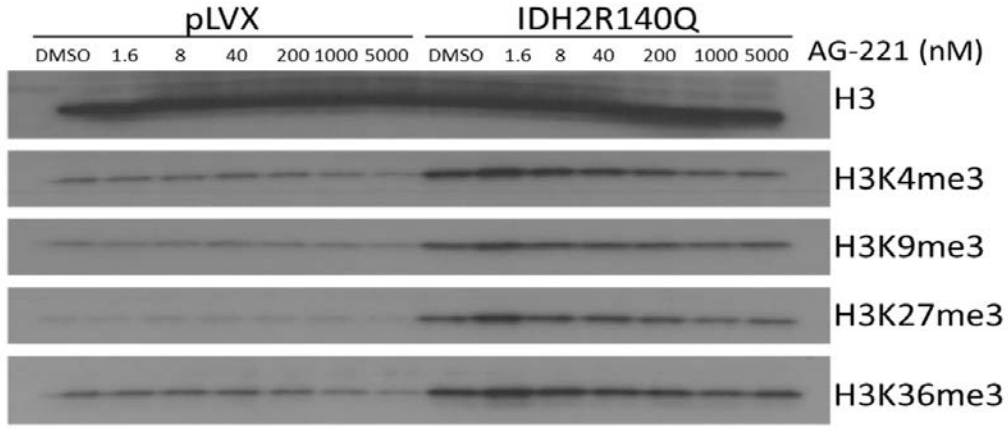
Figure 1: Enasidenib Effect on [2-HG] in TF-1 IDH2 R140Q Mutant Cells



(Figure excerpted from NDA 209606)

The Western blot analysis showed enasidenib treatment results in concentration dependent reductions in histone methylation at all 4 histone marks (H3K4me3, H3K9me3, H3K27me3, and H3K36me3) after 7 days of treatment compared to control cell line TF-1pLVX.

Figure 2: Enasidenib Reduces Histone Methylation in R140Q Mutant and Control Cells



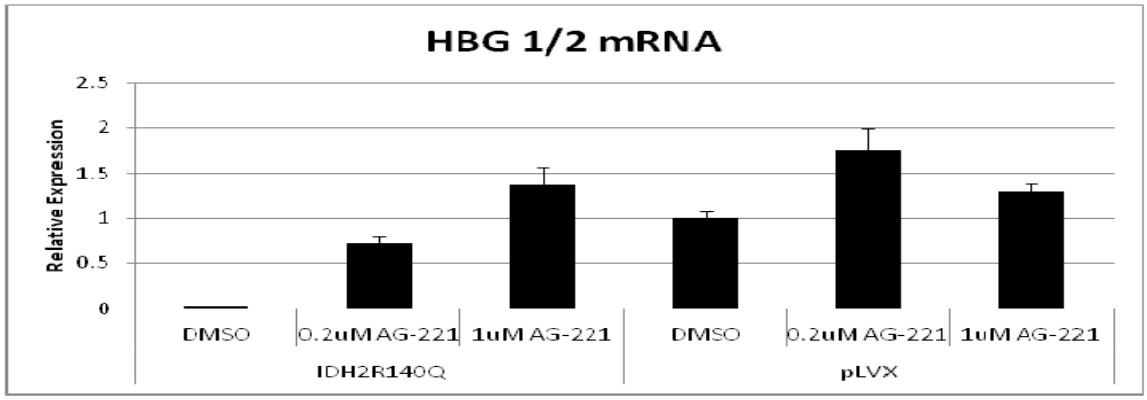
DMSO = dimethylsulfoxide; IDH2R140Q = mutant cell line; pLVX = control cell line.

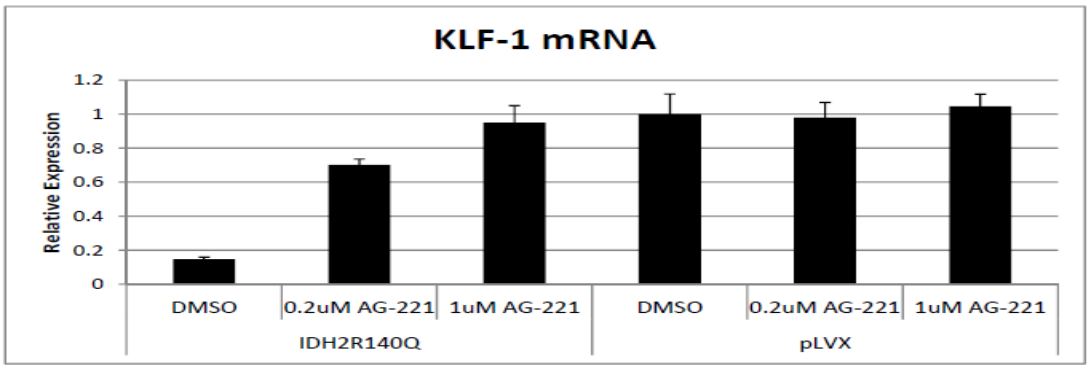
(Figure excerpted from NDA 209606)

To assess reversal in the block to cellular differentiation, TF-1 pLVX and TF-1 IDH2R140Q cells were pretreated for 9 days with 1µM enasidenib and washed to remove growth factors (GM-CSF). Cells were then induced to differentiate using erythropoietin (EPO) (2 units/mL) in the presence or absence of enasidenib or DMSO. Induction continued for 7 days and the cell pellets were collected and subjected to real time polymerase chain reaction (qPCR) to detect hemoglobin gamma 1/2 (HBG 1/2) and Kruppel-like factor 1 (KLF-1) gene expression (a transcription factor that regulates erythropoiesis and the markers of erythroid differentiation). Cells were then processed for Western blotting and 2-hydroxyglutarate (2-HG) measurement.

Treatment with enasidenib restored EPO-induced expression of both HBG 1/2and KLF-1, with reduction in intracellular HG levels following enasidenib treatment.

Figure 3: Hemoglobin G1/2 and Kruppel-like Factor-1 in TF-1 IDH2 R140Q Mutant Cells

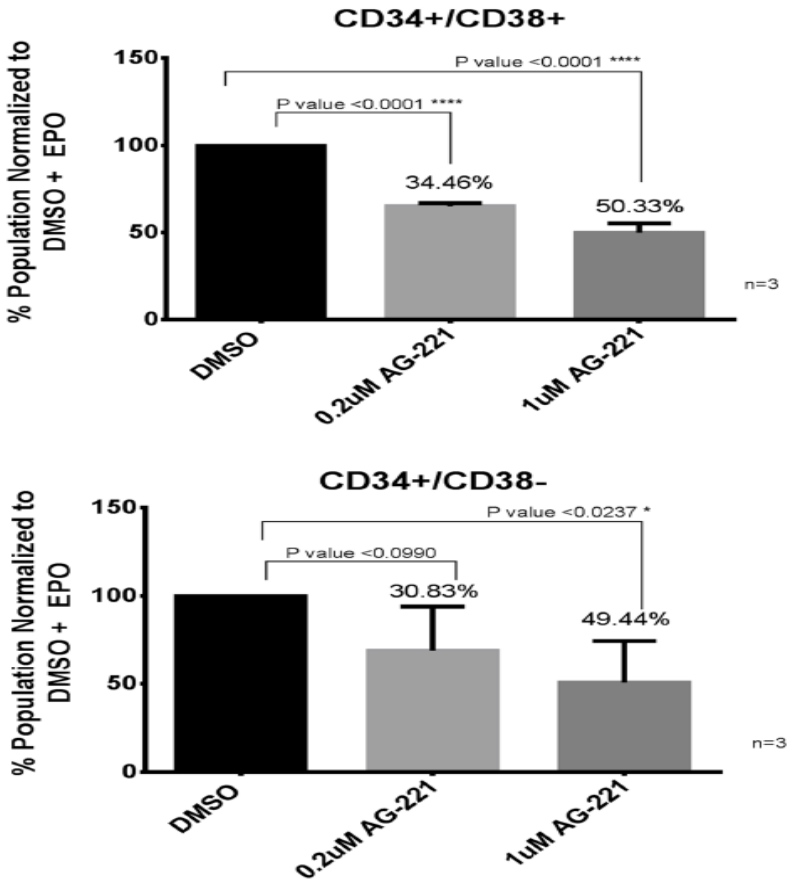




(Figure excerpted from NDA 209606)

FACS analysis was used to quantify the impact of enasidenib treatment on cell growth of hematopoietic stem (CD34+/CD38-) and progenitor (CD34+/CD38+) cell populations using TF-1 IDH2 R140Q AML cells at the end of the EPO differentiation assay (Report AG221-EF-09302016). A statistically significant ($p < 0.0001$, N=3) decrease of the progenitor cells (CD34+/CD38+) (34% and 50% at 0.2 and 1.0 µM enasidenib, respectively) and a decrease of 49% ($p < 0.0237$, N = 3) on (CD34+/CD38-) stem cells at 1.0 µM enasidenib was observed relative to untreated EPO controls, suggesting differentiation of myeloid progenitors/precursors in AML cells with IDH2 mutations.

Figure 4: Hematopoietic Progenitor and Stem Cells Respond to Treatment with Enasidenib



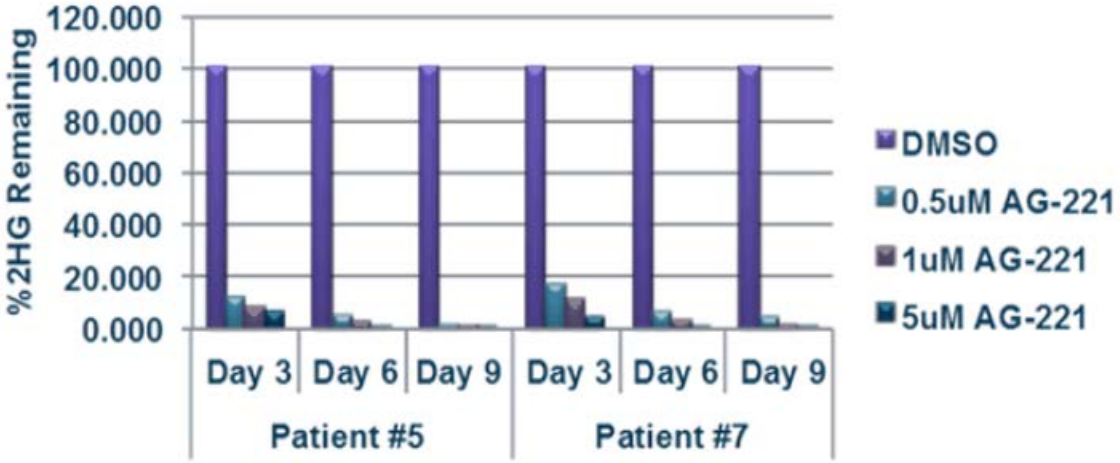
DMSO = dimethylsulfoxide; EPO = erythropoietin.
Top Panel: CD34+/CD38+ hematopoietic progenitor cells.
Bottom Panel: CD34+/CD38- are hematopoietic stem cells.
N = 3 experiments.

(Figure excerpted from NDA 209606)

An ex-vivo study (Report AG221-N-041-R) using primary human AML blast cells was conducted to characterize the activity of enasidenib on inhibition of 2-HG production and myeloblast differentiation using cytology and flow cytometry. Primary AML cells from 4 patients: including 2 with IDH2 R140Q mutations (patient# 5 and# 7) and 2 with wild-type IDH2 (patient # 1 and #3) were cultured in the presence or absence of enasidenib (0.5 µM, 1 µM, and 5 µM). Cells were counted on Days 0, 3, 6, 9, and 13 and compared to DMSO controls. Intracellular 2-HG concentrations were measured on Days 3, 6 and 9 by non-validated LC-MS/MS based method using an internal standard (13C5-2-hydroxyglutarate, 0.2 µg/mL). Morphology and differentiation status of bone marrow blasts from patient with IDH2 R140Q was analyzed by cytology on Day 9 following the ex vivo treatment.

Enasidenib reduced the level of intracellular 2-HG by 99% relative to DMSO controls at the highest concentration tested in samples from patients with the IDH2 R140Q mutation. The report states that no 2-HG was measurable in wild-type patient samples.

Figure 5: Enasidenib Decreases 2-HG in Primary Human IDH2 (R140Q) Mutant Cells

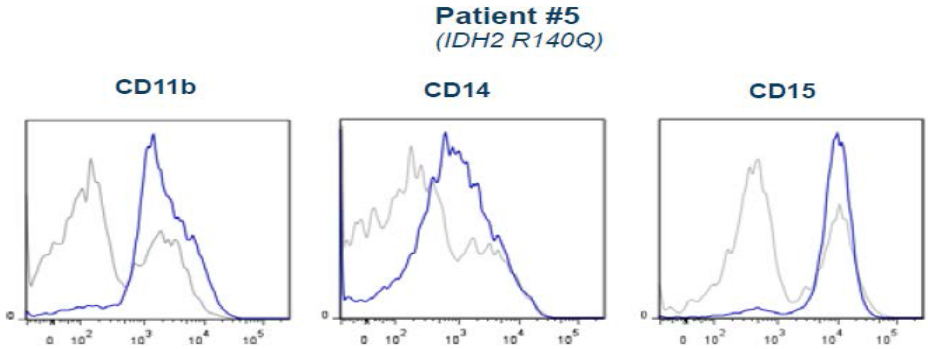


(Figure excerpted from NDA 209606)

Maturation (increased granulosity) of AML blasts was also evaluated by flow cytometry. Living cells were isolated and grown either in liquid media or in methylcellulose to evaluate their state of differentiation following treatment with enasidenib. Samples harboring the IDH2R140Q mutation grown in liquid culture showed increased granulosity (approximately 50-65%) compared to wild-type samples (approximately 30-40%) starting from Day 6 following the treatment with enasidenib.

Maturation of IDH2R140Q mutant AML blasts grown in methylcellulose were also evaluated by FACS analysis for changes in cell surface markers associated with monocytic and granulocytic differentiation (CD14, CD15, and CD11b) following treatment with enasidenib. Enasidenib treatment (blue line) increased all three cell surface markers of differentiation.

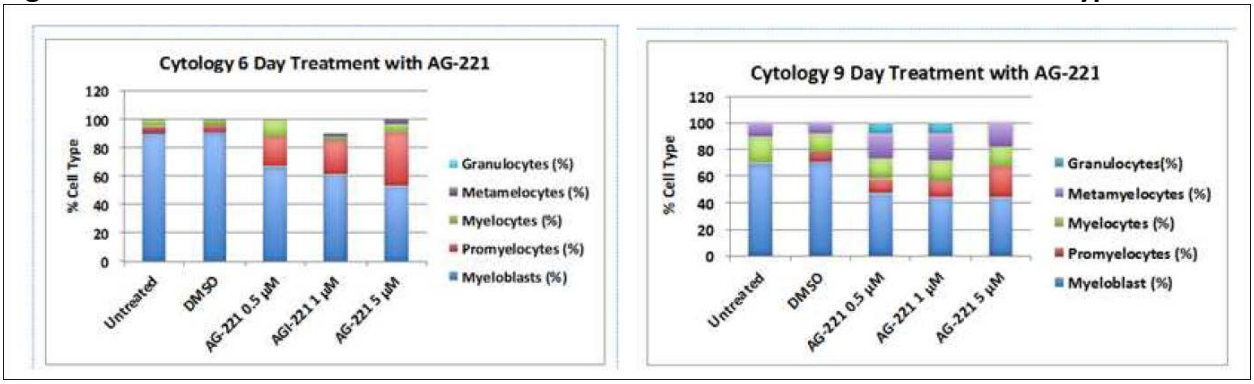
Figure 6: Maturation of Primary Human Patient IDH2 R140Q Mutant Cells



(Figure excerpted from NDA 209606)

Following 9 days of treatment *ex vivo*, the bone marrow blasts of primary samples from a patient with the IDH2R140Q mutation were analyzed for morphology and differentiation status in the presence or absence of enasidenib. The cytologic analysis was blinded with regard to treatment. Cytology revealed that the percentage of blast cells decreased from 90% to 55% by Day 6 and was further reduced to 40% by Day 9 of treatment with enasidenib. Cytology confirmed that enasidenib induced a maturation of blasts in ex vivo culture.
On Day 9 of treatment ex vivo, the bone marrow blasts of primary samples from a patient harboring the IDH2 R140Q mutation were analyzed for morphology and differentiation status.

Figure 7: Effects of Enasidenib on Maturation of Human AML Bone Marrow Cell Types



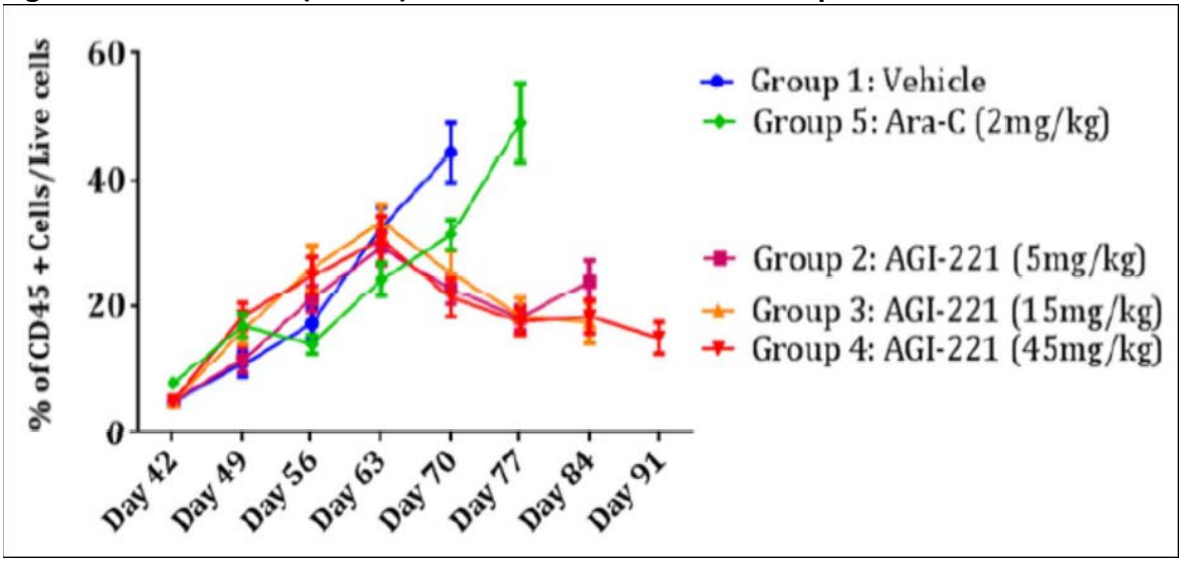
(Figure excerpted from NDA 209606)

The in vivo activity of enasidenib was studied in a primary human IDH2 (R140Q) mutant xenograft model (Report AG221-N-090-R1) and in a multi-genic mouse model (Report PM06152016RJ).

Report AG221-N-090-R1: Bone marrow AMM-7577 cells (isolated from a patient with leukemia harboring an IDH2 R140Q mutation) were placed into female non-obese diabetic severe combined immunodeficiency (NOD-SCID) mice intravenously via tail vein injection. FACS analysis was performed weekly beginning 3 weeks post inoculation to assess the percentage of human CD45+ cells in the peripheral blood as a measure of tumor engraftment and disease progression. When huCD45+ cells reached approximately 10% in peripheral blood, mice were treated with vehicle control, low-dose cytarabine (AraC), or twice-daily doses of enasidenib at 5, 15, or 45 mg/kg. The dosing with vehicle and enasidenib continued until termination.

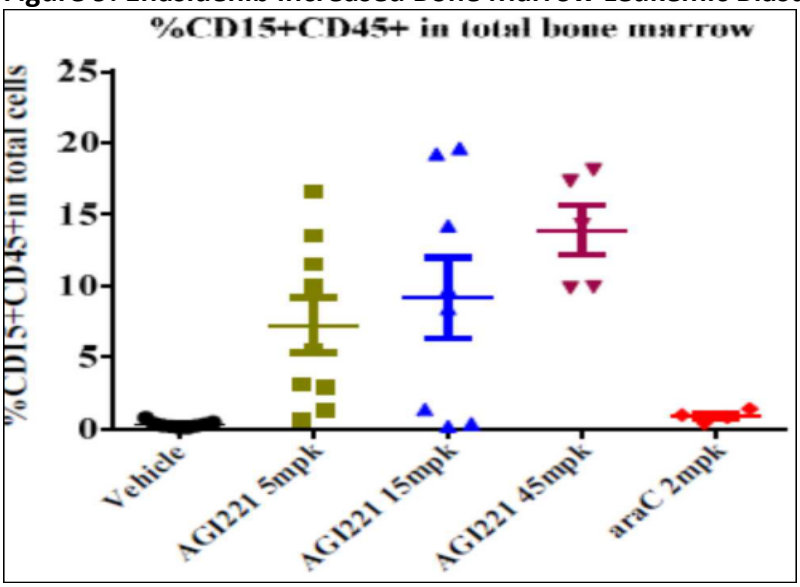
Weekly FACS analysis of peripheral blood samples was performed to assess for the percentage of huCD45+ cells. At the end of the study, bone marrow cells were harvested smears were made for cytological evaluation of differentiation. Treatment with enasidenib resulted in decreased numbers of human IDH2 R140Q mutant CD45+ leukemia cells in the peripheral blood of the mice, evidence of increased bone marrow blast differentiation (CD15+ CD45+) and increased overall survival, when compared to vehicle-treated controls or to mice administered AraC.

Figure 8: Human IDH2 (R140Q) Leukemic Blasts in Mouse Peripheral Blood



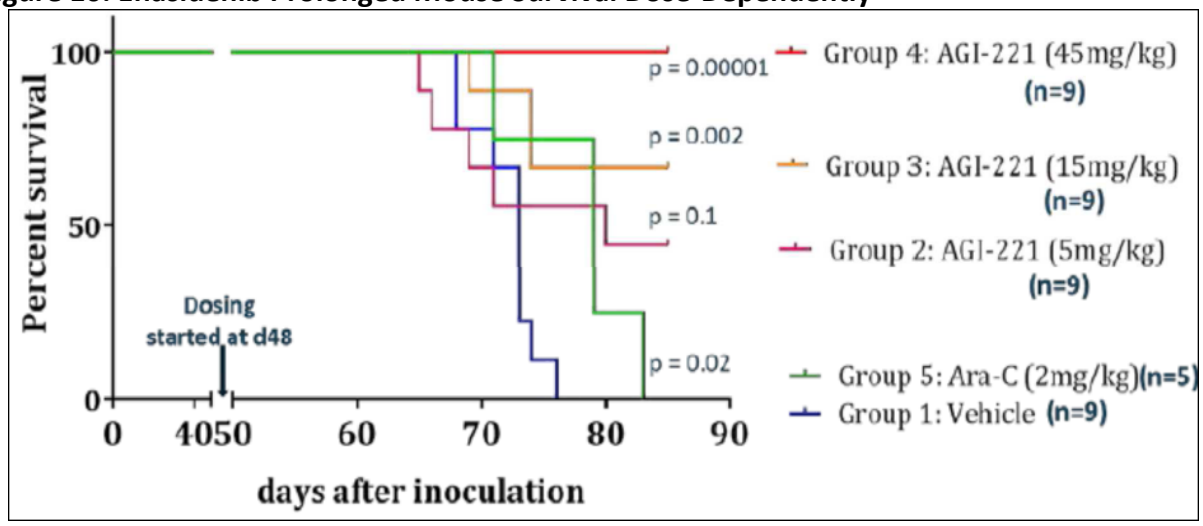
(Figure excerpted from NDA 209606)

Figure 9: Enasidenib Increased Bone Marrow Leukemic Blast Cell Differentiation



(Figure excerpted from NDA 209606)

Figure 10: Enasidenib Prolonged Mouse Survival Dose-Dependently

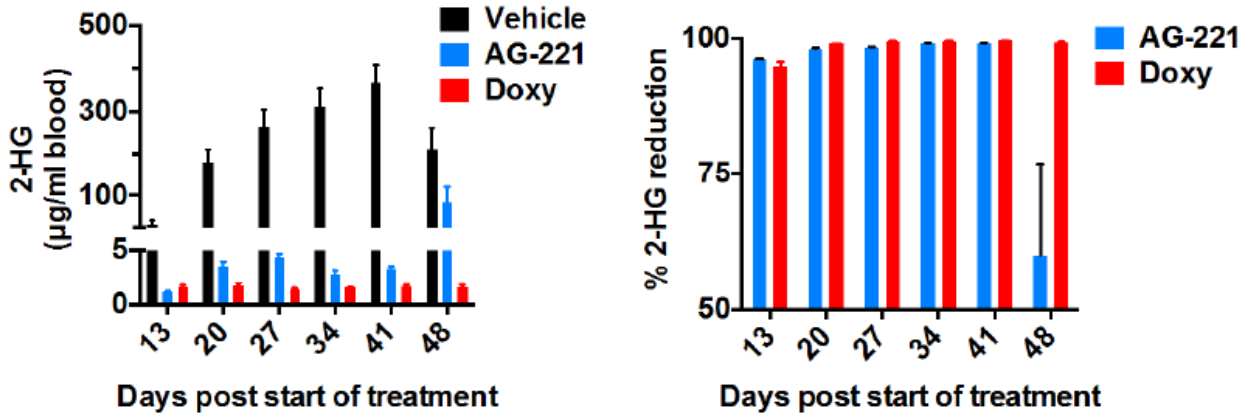


(Figure excerpted from NDA 209606)

Report PM06152016RJ: A multi-genic murine acute myeloid leukemia (AML) model with inducible expression of IDH2 R140Q was developed to study the inhibitory effects of enasidenib on mutant IDH2 Murine leukemias were generated by transplanting transduced fetal liver cells (into sub-lethally irradiated wild-type C57BL/6, congenic C57BL/6.SJL-Ptprca (Ptprca) mice via intravenous tail-vein injection. Primary recipients rapidly developed a lethal myeloid leukemia, characterized by anemia, leukocytosis, and gross splenomegaly. Antitumor activity of enasidenib was studied in secondary recipients.

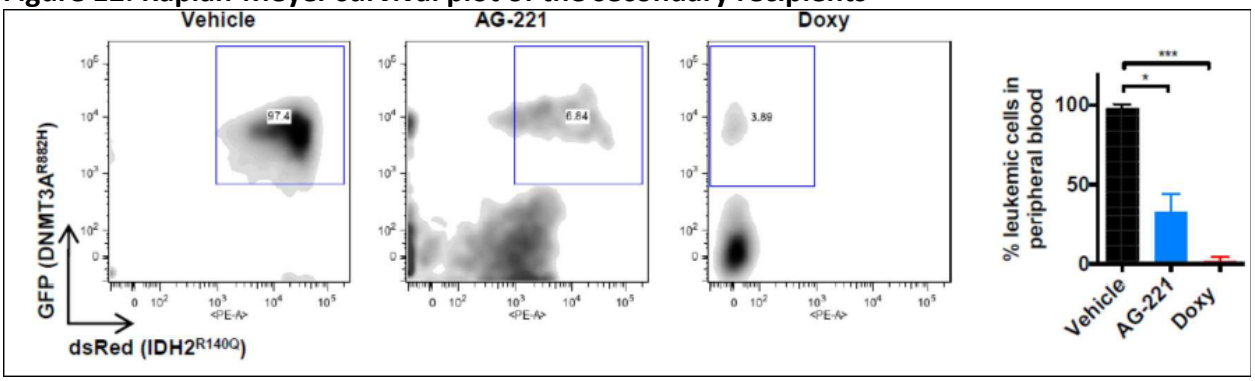
Following transplantation of leukemic cells into secondary recipients, mice were administered with vehicle, enasidenib at 40 mg/kg twice daily (BID), or doxycycline at 600 mg/kg (doxycycline ensure at 1:1 ratio of crushed doxycycline pellets in water). The levels of 2-HG in the blood of the mice were measured and recorded on a weekly basis. Enasidenib treatment reduced blood 2-HG levels by >95% through Day 41 of the experiment. Treatment with enasidenib also resulted in reduced levels of leukemic cells in the peripheral blood (40 days post-transplant) comparable to doxycycline treatment. Doxycycline appears to have higher activity in the reduction of leukemic cells and survival time compared to AG-221 in this mouse model.

Figure 11: 2-HG Blood Concentrations and Percent Reduction in Inducible IDH2 (R140Q) AML



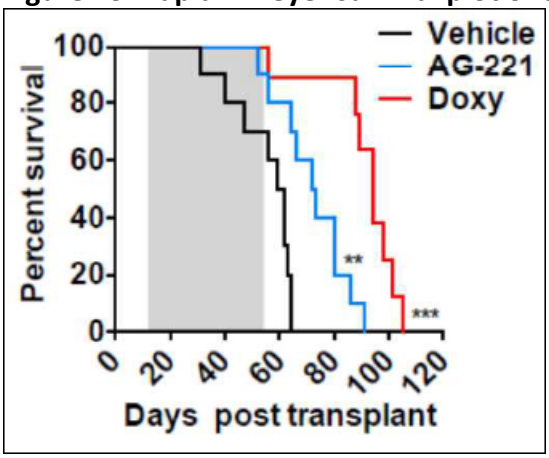
(Figure excerpted from NDA 209606)

Figure 12: Kaplan-Meyer survival plot of the secondary recipients



(Figure excerpted from NDA 209606)

Figure 13: Kaplan-Meyer survival plot of the secondary recipients



(Figure excerpted from NDA 209606)

Secondary Pharmacology

Enasidenib and its metabolite AGI-16903 were evaluated for their potential to inhibit binding and enzymatic activity in a panel of 69 (enasidenib) or 80 (AGI-16903) receptors, ion channels, transporters, and enzymes (including 26 kinases) (Reports AG221-N-064-R1, AG221-N-065-R1, AG221-N-066-R1, AG221-N-067-R1, and AG221-N-072-R1).

Enasidenib and AGI-16903 were shown to bind adenosine A1, A2A, and A3 receptors and act as functional antagonists. The strongest antagonistic activity for both enasidenib and AGI-16903 was against the adenosine A3 receptor with IC_{50} values of 5.66 and 120 nM, respectively. The IC_{50} of 5.66 nM for A3 receptor is >50 fold below the steady state free C_{max} of enasidenib in patients at the daily dose of 100 mg (free C_{max} in humans/IC_{50}), suggesting that the inhibitory activity against A3 receptor may occur at therapeutically relevant concentrations of enasidenib.

Table 5: Inhibition of Adenosine Receptor Functions by Enasidenib and AGI-16903

Target	**AG-221**	**AGI-16903**
Adenosine receptor/transporter	**% binding inhibition at 10 µM**	**% binding inhibition at 10 µM**
A_1	96	69
A_{2A}	63	72
A_3	Not determined	98
Transporter	87	64
Adenosine receptor/transporter binding	**IC_{50} (nM)**	**IC_{50} (nM)**
A_1	930	2880
A_{2A}	4650	3160
A_3	0.69	28
Transporter	320	Not determined
Adenosine receptor functional antagonism	**IC_{50} (nM)**	**IC_{50} (nM)**
A_1	3080	23,900
A_{2A}	4670	9580
A_3	5.66	120

IC_{50} = 50 %inhibitory concentration.

(Table excerpted from NDA 209606)

Table 6: IC50s at Adenosine Receptors versus Steady-State Free Cmax in Patients

Target (functional antagonism)	Enasidenib (IC_{50})	Fold difference [1,2]	AGI-16903 (IC_{50})	Fold difference [1,3]
A_1	3080 nM (1756 ng/mL)	0.1	23900 nM (13623 ng/mL)	0.003
A_{2A}	4650 nM (2651 ng/mL)	0.07	9580 nM (5461 ng/mL)	0.007
A_3	5.66 nM (3.24 ng/mL)	59	120 nM (68 ng/mL)	3

[1]Based on human free C_{max} (ng/mL)/ IC_{50} (ng/mL)
[2]Enasidenib free C_{max} of 191 ng/mL was calculated based on a total C_{max} of 12800 ng/mL in patients at 100 mg daily (enasidenib-C001-PKPD). In vitro enasidenib is 98.5% protein bound (AG221-N-004-R1).
[3]AGI-16903 free C_{max} of 40ng/mL was calculated based on total C_{max} of 1171 ng/mL in patients at 100 mg daily (enasidenib-C001-PKPD). In vitro AGI-16903 is approximately 96.6% protein bound (AG221-N-004-R1).

Safety Pharmacology

In non-GLP studies, enasidenib and the two metabolites AGI-16903 and AGI-17011 were tested over a concentration range of 0.3 to 30 µM at room temperature in manual patch clamp assays for their potential to inhibit 4 different ion channel currents, including the sodium channel (hNAV1.5), calcium channel (hCaV1.2), delayed rectifier potassium channels IKs (hKCNQ1) and I_{Kr} (hERG) (Reports AG221-N-048-R1, AG221-N-049-R1, AG221-N-050-R1, AG221-N-051-R1, AG221-N-058-R1, AG221-N-059-R1, AG221-N-060-R1, and AG221-N-061-R1).

Human embryonic kidney (HEK)-293 cells expressing hNaV1.5 and hCaV1.2 (α1C/β2a/α2δ1) and Chinese hamster ovary (CHO) cells expressing IKs and I_{Kr} (hERG) channels were used to evaluate the effects of enasidenib and the two metabolites AGI-16903 and AGI-17011. Positive controls were tetracaine (hNAV1.5), nifedipine (hCaV1.2), chromanol 293B (hKCNQ1), and amitriptyline (hERG). The IC_{50} values for inhibition of ion channel currents for all assays were > 9 µM for enasidenib and the two metabolites AGI-16903 and AGI-17011 indicating they have a low potential to adversely affect calcium and/or I_{Kr} ion channel currents.

Table 7: Inhibition of Ion Channel Currents

Current	Inhibition of Ion Channel Currents		
	IC_{50} (µM)		
	AG-221	AGI-16903	AGI-17011
I_{Kr} (hERG)	9.02	> 30	> 30
hCaV1.2 (α1C/β2a/α2δ1)	16.8	10.7	> 30
hNAV1.5	> 30	> 30	> 30
hKCNQ1/minK	> 30	> 30	> 30

I_{Kr} (hERG) = human ether-à-go-go related gene; IC_{50} = 50 % inhibitory concentration.

(Table excerpted from NDA 209606)

Dog study: In a non-GLP study, a toxicokinetic and cardiovascular assessment of enasidenib (AG-12910) following oral gavage administration in female beagle dogs was conducted (Report AG221-N-057-R1).

The first phase of this study was to assess the tolerability and toxicokinetic (TK) profile of enasidenib following oral (gavage) administration in non-implanted dogs. The second phase assessed for the potential of enasidenib to have acute effects on arterial blood pressure, heart rate, body temperature, and electrocardiograms (ECGs) in conscious radiotelemetry-instrumented dogs.

For the toxicokinetic phase, a single dose of enasidenib formulated in two different vehicles was administered by oral gavage to 2 dogs at 100 mg/kg (Vehicle 1) and 3 dogs at either 100 mg/kg (in Vehicle 2) or 300 mg/kg (in Vehicle 2). Blood samples were collected prior to dosing (within approximately 2 hours), and at 1, 3, 6, 12, and 24 hours following enasidenib administration. Clinical observations were recorded at the time of blood collection (post-dosing).

For the cardiovascular (CV) phase, a single dose of AGI-12910 in Vehicle 2 was administered by oral gavage to 2 groups of 3 female Beagle dogs/group at 75 and 300 mg/kg. Heart rate, arterial blood pressure, pulse pressure, body temperature, and ECG waveforms were collected continuously for approximately 1 hour prior to administration of AGI-12910 through approximately 24 hours post-dosing.

No test article-related clinical observations were noted at 100 mg/kg in Vehicle 1. Administration of enasidenib in Vehicle 2 at all dose levels resulted in clinical signs of toxicity, including altered feces (mucoid, diarrhea, soft feces) and emesis, and impaired muscle coordination at 300 mg/kg. There was no change in body temperature at any dose level.

Table 8: TK Parameters for Oral Enasidenib in Female Dogs

Dose (mg/kg)	Vehicle	N	$AUC_{0\text{-}12hr}$ (ng•hr/mL)	$AUC_{0\text{-}24hr}$ (ng•hr/mL)	C_{max} (ng/mL)	T_{max} (hr)
100	1	2	24000	38000	2410	2.0
100	2	3	21300 ± 2330	35300 ± 6200	2030 ± 165	5.3 ± 5.86
300	2	3	40300 ± 2600	73200 ± 9890	3810 ± 310	9.0 ± 5.20

$AUC_{0\text{-}12hr}$ = area under the concentration-time curve from time zero to 12 hours; $AUC_{0\text{-}24hr}$ = area under the concentration-time curve from time zero to 24 hours; C_{max} = maximum observed concentration; CMC-Na = carboxymethylcellulose sodium; T_{max} = time to C_{max}.
Vehicle 1 was 1% sodium citrate in 1% CMC-Na.
Vehicle 2 was 5% pluronic F68 with 1% sodium citrate in 1% CMC-Na.
Values are mean ± standard deviation (SD). Where no SD is given, the mean is comprised of fewer than 3 observations.

(Table excerpted from NDA 209606)

- Dose-related higher heart rate (45 and 67 beats/minute [bpm] increase vs. pretest) approximately 5 and 9 hours post-dosing was seen following administration of 300 and 75 mg/kg and appeared to remain elevated for 22 to 24 hours.
- Initial decreases in blood pressure (systolic, diastolic, and mean) up to 5 hours pose-dose (9.1% and 16.3% maximal decrease) and subsequent increase (19.9% and 22.2% higher than baseline) through 24 hours pose-dose was observed at 75 and 300 mg/kg, respectively.
- The durations of PR, RR, and QT intervals were reduced coincident with increase in heart rate.
- Prolonged QTcV was noted at both dose levels with an onset of approximately 12 hours post-dose and persisting through 24 hours post-dose.
- Systemic exposure (AUC) associated with CV effects in dogs was substantially lower than those reported for patients administered enasidenib 100 mg daily (AUC0-24hr in dogs/SS AUC0-24hr in AML patients; 73200/258506 ng*h/mL).

Monkey study: A non-GLP toxicokinetic and cardiovascular assessment of enasidenib following nasogastric administration in cynomolgus monkeys was conducted (Report AG221-N-062-R1).

For the cardiovascular (CV) phase, a single dose of either Vehicle 2 or AGI-221 in Vehicle 2 at 10 mg/kg was administered by nasogastric intubation to 3 male cynomolgus monkeys/group. Heart rate, blood pressure (systolic, diastolic, mean arterial pressure, and pulse pressure), body temperature, and ECG waveforms (from which ECG intervals PR, QRS, RR, QT, and heart rate corrected QT [QTcB] were derived), were collected continuously for approximately 1 hour prior to administration of enasidenib through approximately 24 hours post-dosing. In the CV phase, administration of 10 mg/kg enasidenib in Vehicle 2 did not affect heart rate, blood pressure, pulse pressure, body temperature, ECG intervals (PR, QRS, RR, QT, or QTcB), ECG waveform morphology, or the clinical condition of the animals.

5.4. ADME/PK

Type of Study	Major Findings
Absorption	
Pharmacokinetics of single (Report AG221-N-018-R1) or multiple (AG221-N-022-R1) oral doses of enasidenib in male cynomolgus monkeys	The rate of absorption was moderate in monkeys. T_{max} occurred at 3-4 hours. Oral bioavailability was approximately 40%. Oral exposure to enasidenib was lower in fed monkeys (AG221-N-018-R1). Exposure increased with repeat dosing (> 2fold), suggesting accumulation of enasidenib (AG221-N-022-R1)

Table 9: Monkey PK Parameters Following Administration of Enasidenib

Route	PO (fasted)	PO (fasted)	PO (fed)	PO (fasted)	PO (fasted)
Dose (mg/kg)	10	10	10	5 BID (Day 1)	5 BID (Day 5)
Sample	plasma	plasma	plasma	plasma	plasma
Analyte Enasidenib	FB	MS	MS	MS	MS
$AUC_{0\text{-}24hr}$ (hr*µg/mL)	23.4	NA	NA	NA	51.4
$AUC_{0\text{-}\infty}$ (hr*µg/mL)	NA	33.9	18.2	14.7	69.5
T_{max} (hr)	4.0	4.0	3.0	4.0	4.0
C_{max} (µg/mL)	31.1	30.1	14.5	17.8	36.8
F (%)	36.5	ND	ND	ND	ND

FB = freebase; MS= mesylate salt

Distribution

Distribution study with [14C] enasidenib in rats following a single 10 mg/kg oral dose/Report AG-221-DMPK-1955

The tissue distribution of a single oral 10 mg/kg [^{14}C] enasidenib was investigated in male Long Evans (LE) rats as well as male and female SD rats. SD rats were sacrificed and processed for quantitative whole body autoradiography (QWBA) at 1, 2, 4, 8, 24, 48, 96, and 168 hours post dose, and male LE rats were sacrificed and processed for QWBA at 4, 8, 24, 48, 96, and 168 hours post-dose. In SD rats, the tissue distribution of enasidenib-derived radioactivity was widespread with the highest concentrations observed in the small intestine, liver, stomach (glandular and non-glandular), kidney cortex, adrenal gland, harderian gland, pancreas, and adipose (brown). Elimination was nearly complete at 168 hours post dose, with the radioactivity content below the quantification limit by 96 hours post dose for most tissues.

Report AG221-N-013-R1

In pigmented LE rats, the concentrations in eye uveal tract and pigmented skin suggested association with melanin-containing tissues. The highest concentrations were observed in the Liver, kidney cortex, stomach (glandular), and adrenal gland. Elimination was nearly complete at 168 h post-dose with the only concentrations remaining in skin (pigmented), liver, and eye uveal tract.

Enasidenib crossed the blood:brain barrier: Following a single oral dose of enasidenib at 50 mg/kg in rats, enasidenib exhibited low cerebral spinal fluid (CSF) penetration (0.3%) and

	modest brain penetration (10%).Enasidenib and the metabolite AGI-16903 were highly bound to plasma proteins in the human, monkey, dog, rat, and mouse plasma (92-99%) and (93 to 97%), respectively. The binding was independent of concentration in all five species for both enasidenib and AGI-16903.

Table 10: Percent Plasma Protein Binding of AG-221 in Various Species

Species	Plasma Protein Binding (%)							
	AG-221				AGI-16903			
	0.2 µM	1 µM	10 µM	Overall Mean	0.2 µM	1 µM	10 µM	Overall Mean
Human	98.7	98.6	98.3	98.5	96.6	96.8	96.4	96.6
Monkey	93.4	93.7	92.6	93.2	91.9	93.4	92.0	92.4
Dog	92.9	92.7	92.3	92.6	93.9	92.2	92.2	92.8
Rat	90.2	90.0	89.6	89.9	91.5	91.2	90.9	91.2
Mouse	95.8	95.1	95.1	95.3	95.6	94.2	93.8	94.5

n = 3.

Metabolism	
In Vitro Metabolism of AGI-12910 in the Presence of Cryopreserved Sprague-Dawley Rat, Beagle Dog, Cynomolgus Monkey and Human Hepatocytes/Report AG221-N-36-R	Enasidenib is mainly metabolized through N-dealkylation, oxidation, butyl hydroxylation, direct glucuronidation, and a combination of oxidation and glucuronidation. In vitro data indicate that N-dealkylation to form M1 (M401) is the prominent pathway in dogs, monkeys and humans, while hydroxylation to form M2 (M489b) is the prominent pathway in rats.
In Vivo Metabolism of AGI-12910 in Sprague-Dawley Rats, Beagle Dogs and Cynomolgus Monkeys: Plasma Profiles and Quantitation of Metabolites/Report AG221-N-035-R1	The metabolism of enasidenib was qualitatively similar but quantitatively different across species. The predominant drug-related species were the parent (enasidenib) with major amounts of the N-dealkylation metabolite (M1 or AGI-16903) and trace amounts of the oxidation metabolite (M2 or AGI-17011) in dog and monkey following single doses. Metabolites (M1 and M2) were found in trace amounts in rat (<1%) following 5-day repeated oral administration. No unique metabolites were identified in plasma of these three species. In humans M1 (AG-AG16903) is the major metabolite, present at <10% of the parent drug.

Table 11: Comparative Metabolic Profile in Animals

Species (Dose)	AG-221 (ng/mL)	M1 (AGI-16903) (% of Parent)	M2 (AGI-17011) (% of Parent)
Rat (80 mg/kg/day 5 days)	ND	< 1% [a]	< 1% [a]
Dog (10 mg/kg single dose)	139	41%	2%
Dog (75 mg/kg single dose)	263	34%	2%
Monkey (fasted, 10 mg/kg single dose)	543	90%	4%
Monkey (fed, 10 mg/kg single dose)	899	53%	4%

(Table excerpted from NDA 209606)

Excretion

Pharmacokinetics of single or multiple oral doses of enasidenib in male cynomolgus monkeys

Reports AG221-N-015-R1, AG221-N-018-R1, and AG221-N-022-R1

Table 12: Monkey PK Parameters Following Administration of Enasidenib

Route	**PO (fasted)**	**PO (fasted)**	**PO (fed)**	**PO (fasted)**	**PO (fasted)**
Dose (mg/kg)	10	10	10	5 BID (Day 1)	5 BID (Day 5)
Sample	plasma	plasma	plasma	plasma	plasma
Analyte Enasidenib (FB or MS)	FB	MS	MS	MS	MS
CL/F (L/hr/kg)	NC	0.336	0.656	NA	NA
$t_{1/2}$ (hr)	NC	5.6	4.9	5.5	11.4

FB = freebase; MS= mesylate salt

Metabolite Profiling and Structure Characterization of $^{[14C]}$-AG-221 in Sprague-Dawley Rats Following a Single 10 mg/kg Oral Administration

Report AG-221-DMPK-2038

The majority of $^{[14C]}$enasidenib-derived radioactivity was excreted as the parent drug in feces (43% to 73% of dose), likely representing unabsorbed fraction of drug.

The absorbed drug was metabolized and excreted via the biliary route and to a limited extent in the urine.

The prominent metabolites in rats included oxidation metabolites (M2 and M6 (M489a)), a glutathione conjugate (M4), a direct glucuronide (M10), and M13 that was formed through N-dealkylation and oxidation, while the N-dealkylation product M1 was a minor metabolite.

Table 13: Excretion of Enasidenib and Metabolites Following a Single 10 mg/kg Oral Administration

Intact Rats	Male (% of Dose)				Female (% of Dose)			
Metabolite/ Metabolic Pathway	[redacted]	Urine	Feces	total	[redacted]	Urine	Feces	Total
Total/NA		11	85	96		3.7	88	91
Enasidenib/ Parent		0.26	53	53		0.22	73	73
M1/ N-dealkylation		D	0.71	0.71		D	1.1	1.1
M2/ Oxidation		0.86	21	22		0.17	8.6	8.8
M6/ Oxidation		9	0.83	9.8		3.3	1.2	4.5
BDC Rats	**Bile**	**Urine**	**Feces**	**total**	**Bile**	**Urine**	**Feces**	**total**
Total/NA	34	11	52	97	41	8.2	47	95
Enasidenib/ Parent	2.7	0.26	44	47	4.3	0.37	43	47
M1/ N-dealkylation	0.90	D	0.43	1.33	0.46	0.017	D	0.48
M2/ Oxidation	1.2	0.75	7.2	9.1	0.58	0.26	4	4.9
M4/ Glutathione	4.3	ND	ND	4.3	3.9	ND	ND	3.9
M10/ Glucuronidation	10	0.065	ND	11	18	ND	ND	18
M13/ N-Dealkylation +oxidation	0.76	D	D	0.76	0.38	D	ND	0.38

BDC= Bile Duct-Cannulated, ND=metabolite not detectable by mass spectrometry or radiometric detector, D = metabolite detectable by mass spectrometry, but undetectable by radiometric detector

TK data from general toxicology studies	Refer to Section 5.5
TK data from reproductive toxicology studies	Refer to Section 5.5
TK data from Carcinogenicity studies	No carcinogenicity studies have been conducted.

5.5. Toxicology

5.5.1. General Toxicology

All toxicity studies were conducted with enasidenib mesylate salt

Study title/ Report: Enasidenib: A 90-Day Oral (Gavage) Toxicity Study in Rats/ AG-221-TOX-1911

Key Study Findings

- Administration of enasidenib for 90 consecutive days to male and female rats

was tolerated at 5 and 20 mg/kg twice daily.

- Enasidenib toxicities included minimal to severe seminiferous tubular degeneration in the testes at ≥5 mg/kg and marked reduction of sperm in the epididymides at 20 mg/kg.
- Mean steady state (ss) exposure margin from low dose male rat to human is approximately 0.1x (doubling the mean ss-$AUC_{0\text{-}24hr}$ 25 µg.hr/mL for the twice daily dosing in animals).

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

Methods

Dose and frequency of dosing:	0, 5 and 20 mg/kg twice a day
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% Methylcellulose [400cps], 5% vitamin E TPGS, and 5% Hydroxypropylmethylcellulose acetate succinate, pH 6.5 ± 1.5 in deionized water
Species/Strain:	Rats/Strain: Crl:CD(SD) CD® IGS
Number/Sex/Group:	Main: 10/sex/group
Age:	Approximately 9 weeks old
Satellite groups/ unique design:	3/sex control, 4 male and 6 female at 5 and 20 mg/kg BID
Deviation from study protocol affecting interpretation of results:	None

Observations and Results: changes from control

Parameters	**Major findings**
Mortality	No treatment related deaths. One male and one female rat each in control and low dose were found dead or euthanized due to gavage error or unknown reasons.
Clinical Signs	Unremarkable
Body Weights	HD: males (↓ 6%) and females (↓11%) vs. control
Ophthalmoscopy	Unremarkable
Hematology	HD: up to ↓40% Eosinophils; Hematology changes did not correlate with histopathology
Clinical Chemistry	HD: ↑120% in males and ↑280% females in total bilirubin vs. controls LD: ↑55% in females vs. controls
Gross Pathology	HD: small, soft testes and soft epididymides

Organ Weights	HD: absolute weight ↓48% testes, ↓31% epididymides vs. controls
Histopathology **Adequate battery:** Yes	**Testes:** LD: minimal degeneration, seminiferous tubules HD: marked to severe degeneration, seminiferous tubules **Epididymides** HD: marked reduction, intraluminal sperm **Pancreas** LD: minimal to slight atrophy, acinar cell HD: minimal vacuolation with apoptosis, acinar Cells

Table 14: Toxicokinetics in Rats following 90-Day Repeat Dosing with Enasidenib

	Toxicokinetic Parameters	
Dose	**5 mg/kg BID**	**20 mg/kg BID**
C_{max} (ng/mL)	1540	16200
$AUC_{0\text{-}12hr}$ (ng·hr/mL)	13900[a]	166000[b]

$AUC_{0\text{-}12hr}$ = area under the plasma concentration-time curve from time zero to 12 hours post first daily dose; BID = twice daily; C_{max} = maximum plasma concentration.
[a] Male = 12500 ng·hr/mL, Female = 15200 ng·hr/mL.
[b] Male = 155000 ng·hr/mL, Female = 177000 ng·hr/mL.
All toxicokinetic parameters were measured on Day 90.

(Table excerpted from NDA 209606)

Dose proportionality: greater than dose-proportional manner in males and females (12-fold) in the enasidenib dose range of 5 to 20 mg/kg BID.
Sex differences: no significant differences.

LD: low dose; MD: mid dose; HD: high dose.

Study title/ Report: Study title: Enasidenib: A 90-Day Nasogastric Gavage Toxicity Study in Cynomolgus Monkeys / AG-221-TOX-1912

Key Study Findings

- Administration of enasidenib twice daily for 90 consecutive days to male and female monkeys was tolerated at 2 and 6 mg/kg twice daily (BID).
- Mean steady state exposure margin from high dose at 6 mg/kg twice daily to human (estimated $AUC_{0\text{-}24hr}$ at 100 mg QD 258.5 µg.hr/mL) is 0.34 (doubling the combined mean ss-$AUC_{0\text{-}24hr}$ 88.8 µg.hr/mL for the twice daily dosing in animals).

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

Methods
Dose and frequency of dosing: 0, 2 and 6 mg/kg twice a day

Multidisciplinary Review and Evaluation
NDA 209606
IDHIFA® (enasidenib)

Route of administration:	Nasogastric (NG) or on occasion orogastric intubation route
Formulation/Vehicle:	0.5% Methylcellulose [400cps], 5% vitamin E TPGS, and 5% Hydroxypropylmethylcellulose acetate succinate, pH 6.5 ± 1.5 in deionized water
Species/Strain:	Cynomolgus monkeys (Macaca fascicularis)
Number/Sex/Group:	Main: 3/sex/group
Age:	Approximately 2 to 3 years old
Satellite groups/ unique design:	3/sex/group
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	**Major findings**
Mortality	No treatment related deaths. One female at 2 mg/kg BID was found dead. The cause of death was attributed to incidental aspiration pneumonia. This animal was replaced and dosed until day 90.
Clinical Signs	HD: Female, thin appearance
Body Weights	LD: ↓13% males HD:↓19% males and females
Ophthalmoscopy	Unremarkable
ECG	Unremarkable
Hematology	HD: Lymphocytes ↓53%,Monocytes ↓58%, Eosinophils ↓ 55% vs. controls
Coagulation	Unremarkable
Clinical Chemistry	HD: ↑95% in males and ↑165% females in total bilirubin vs. controls LD and HD: A/G ratio ↓28% males vs. controls
Urinalysis	Unremarkable
Gross Pathology	Unremarkable
Organ Weights	Thymus LD: ↓58% males HD↓65% males, ↓22% females vs. control Liver: HD: ↑9% males
Histopathology **Adequate battery:** Yes	Microscopic findings in thymus, liver, femur (including joint), sternal bone marrow, and pancreas: LD and HD: minimal to marked involution/atrophy in thymus

	HD: ↑ hepatocyte cytoplasmic rarefaction LD and HD: moderate to marked decreases in thickness of the distal femoral and proximal tibial physes HD: ↓slight to moderate decreases in sternal bone marrow cellularity HD: moderate to marked acinar cell degranulation in pancreas

Table 15: Toxicokinetics in Monkeys following 88-Day Repeat Dosing with Enasidenib

	Toxicokinetic Parameters	
Dose	**2 mg/kg BID[a]**	**6 mg/kg BID**
C_{max} (ng/mL)	398	5270
$AUC_{0\text{-}12hr}$ (ng·hr/mL)	2540	44400

$AUC_{0\text{-}12hr}$ = area under the plasma concentration-time curve from time zero to 12 hours post first daily dose; BID = twice daily; C_{max} = maximum plasma concentration.
[a] Toxicokinetic parameters were measured on Day 88 for all animals except Day 60 for the replacement female at 2 mg/kg BID.

(Table excerpted from NDA 209606)

Enasidenib:
Dose proportionality: greater than dose-proportional manner for enasidenib in males and females (13.8- and 25.3-fold increase, respectively)
Sex differences: no significant differences.

LD: low dose; MD: mid dose; HD: high dose.

General toxicology; additional studies

Study title/ Report: A 28-Day (Twice Daily Dosing) Oral Gavage Toxicity and Toxicokinetic Study of AG-221 in Sprague Dawley Rats with a 14-Day Recovery Period/AG221-N-002

Enasidenib was administered orally at 0, 10, 30, or 100 mg/kg BID for 28-days to Sprague-Dawley rats.

- Significant early deaths/moribundity occurred at HD in 10 of 24 males, 12 of 24 females. The cause of death was multi-tissue toxicities including hemorrhage, necrosis, degeneration, and/or atrophy.
- Significantly lower body weights (>10%) at MD and HD compared to controls.
- Clinical pathology changes at HD included cytopenias, ↑A/G ratio, and↓ total protein, albumin, and globulin correlated with bone marrow hypocellularity, muscle atrophy and wasting; ↑creatine kinase (CK) likely correlated with skeletal muscle degeneration and necrosis.
- Target organs included: salivary glands, gastrointestinal tract, pancreas, kidney, adrenal gland, urinary bladder, hematopoietic and lymphoid organs, skeletal muscle, pituitary, and reproductive organs (male and female) at MD and HD.

  - Findings included: atrophy, depletion, hypocellularity, vacuolation, degeneration/regeneration, inflammation, hemorrhage, erosion, necrosis, and/or apoptosis.
- Degeneration and hypertrophy of the liver correlated with higher liver weights and liver enzymes.
- Reproductive organs: degeneration in testes, edema, granuloma, hypospermia in epididymis, atrophy in prostate and seminal vesicle, and atrophy in uterus and vagina and abnormal estrous cycle.
- Decreased body weight gain and changes observed in testes and epididymides at 30 mg/kg BID were present in the recovery period.
- The exposure on Day 27 was greater than the exposure on Day 0 with accumulation ratios for C_{max} ranging from 2.35 to 3.24 and for $AUC_{0\text{-}12hr}$ ranging from 2.68 to 5.90.

Study title/ Report: A 28-Day (Twice Daily) Oral (Nasogastric) Toxicity Study of enasidenib in Cynomolgus Monkeys with a 14-Day Recovery Period/AG-221-N-001

Enasidenib was administered orally (nasogastric) at 0, 2, 5, or 12 mg/kg BID for 28-days to cynomolgous monkeys. One male at HD was euthanized in extremis. The cause of moribundity was ulcerative inflammation of large intestine.

- Clinical signs of toxicity included tremor, emesis, thin appearance, inappetence, soft/mucoid feces, diarrhea, red facial area, and/or brown material in the anogenital area in the surviving animals at HD and all animals at MD as well as emesis and soft feces at LD.
- There was significant loss of at least 10% of body weights at HD compared to control.
- Clinical pathology changes included ↓RBC, ↓hemoglobin, ↓hematocrit, ↓A/G ratio, ↑total and indirect bilirubin, ↓urea nitrogen, ↓GGT and ↑cholesterol at HD.
- Increases in absolute and relative heart (>10%) and liver weights (>10%) in males at high dose.
- Minimal to moderate periarteritis in multiple tissues (heart, gall bladder, epididymides, gallbladder, stomach) in males at high dose.
- Physeal dysplasia (mild to severe) of the femur was seen in males at MD and HD.
- Decreased body weight gain, increased serum globulin, decreased BUN, and one incidence of periarteritis (epididymides) were present at 12 mg/kg BID during the recovery period.

A 7-Day (BID) Oral Gavage Toxicity/Toxicokinetic Study of AGI-14405 in Male Beagle Dogs/AG221-N-054-R1

Beagle dogs were orally administered the enasidenib phosphate prodrug, AGI-14405 at 0, 5, 15, and 50 mg/kg twice daily for 7-days.

- All (3/3) animals dosed at 50 mg/kg were euthanized on Day 1 (following two doses on Day 0 and one dose on Day 1) due to moribund clinical signs, hypotension, and

tachycardia with prolonged QT intervals. Clinical pathology parameters were abnormal. Microscopic changes were noted in the arteries (arterial medial degeneration/necrosis), pancreas (increased apoptosis), and intestines (neutrophil infiltrate); other changes included lymphoid depletion in lymph nodes, and Peyer's patches, neutrophilic infiltrates in spleen and necrosis in thymus.

- At 15 mg/kg twice daily, ↑bilirubin (direct and total) and ↑ phosphorus values were noted. Liver, kidney, and adrenal gland weights were increased and spleen weights were decreased at 15 mg/kg twice daily.
- Higher heart rates and shorter PR and RR intervals occurred at ≥5 mg/kg twice daily and shorter QT intervals at ≥15 mg/kg twice daily were noted on study Day 0.
- Microscopic changes:
  - ≥15 mg/kg twice daily: heart (arterial medial degeneration/necrosis, hemorrhage, and/or acute inflammation) and spleen (lymphoid depletion).
  - ≥5 mg/kg twice daily: adrenal cortex (increased vacuolation), liver (hepatocellular cytoplasmic clearing), and bone marrow (hypercellular, single cell necrosis, and/or hypocellular).
- Systemic exposure of AGI-14405, the prodrug, was less than 0.4% of the exposure to the active drug, AGI-12910. Systemic exposure to AGI-12910 (active) was associated with CV effects in dogs at 15 mg/kg twice daily on day 6.

5.5.2. Genetic Toxicology

Study title/ number: Bacterial Reverse Mutation Assay/AG221-N-046
Key Study Findings:

- Enasidenib is non-cytotoxic and negative in 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. Ag-221 was tested up to 5000 ug/plate; +/- S9.
Study is valid: Yes

Study title/ number: In Vitro Mammalian Chromosome Aberration Assay in Chinese Hamster Ovary (CHO) Cells/AG-221-TOX-2063
Key Study Findings:

- Enasidenib was cytotoxic and negative for the induction of chromosome aberrations in CHO cells.

GLP compliance: Yes
Test system: Chinese hamster ovary (CHO) cells; AG-221 was tested up to 100 µg/mL in the non-activated 4-hour treatment group; up to 40 µg/mL in the S9-activated 4-hour treatment group; up to 20 µg/mL in the non-activated 20-hour treatment group. The AG-221 concentrations were selected based on cell growth inhibition compared to respective controls.
Study is valid: Yes

Study title/ number: CC-90007: In Vivo Mammalian Erythrocyte Micronucleus Assay in Rats/ CC-90007-TOX-2136

Key Study Findings:

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

GLP compliance: Yes

Test system: Rat/ Sprague-Dawley (Hsd:SD); single oral gavage (0, 20, 100, 500 or 2000 mg base/kg); diarrhea in animals treated at 100 mg base/kg, and piloerection and diarrhea in animals treated at 500 and 2000 mg base/kg.
Study is valid: Yes

Other Genetic Toxicity Studies

Bacterial Reverse Mutation Assays with enasidenib Process-related Impurities

The mutagenic potential of 13 process-related impurities, were tested in 3 bacterial reverse mutation assays using 4 Salmonella typhimurium tester strains (TA98, TA100, TA1535, and TA1537) and Escherichia coli strain WP2 uvrA in the presence and absence of an exogenous metabolic activation. Under the conditions of these studies, these 13 process-related impurities were negative in the non-GLP bacterial reverse mutation assays.

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 enasidenib treatment-related effects on fertility and early embryonic development and pre- and postnatal development were not conducted.

Embryo-Fetal Development
CC-90007: An Oral (Gavage) Study of the Effects on Embryo Fetal Development in Rats Including a Toxicokinetic Evaluation/ CC-90007-TOX-2105

Key Study Findings

- Test article related maternal and fetal developmental toxicity was observed at 30 mg/kg BID.
    - Maternal toxicity - multiple incidences of thin body condition, body weight loss and decreased body weight gain, and decreased food consumption.

- Developmental toxicity - decreased gravid uterine weights, decreased litter size/number of viable fetuses, increased resorptions, increased postimplantation loss, decreased mean fetal body weights, and sternebrae not ossified.

- Mean steady state exposure margin from high dose in rats at 30 mg/kg/BID to human (estimated $AUC_{0\text{-}24hr}$ at 100 mg QD 258.5 µg.hr/mL) is 1.6x (doubling the combined mean ss-$AUC_{0\text{-}24\ hr}$ 418 µg.hr/mL for the twice daily dosing in animals).

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

Methods

Dose and frequency of dosing:	0, 3, 10, or 30 mg/kg twice a day (BID)
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/v) methylcellulose (400cps), 5% (w/v) vitamin E TPGS, and 5% (w/v) hydroxypropylmethylcellulose acetate succinate, grade AS-MF, in deionized water, (pH 6.5 ± 1.5)
Species/Strain:	Time-mated female CD® [Crl:CD®(SD)] rats
Number/Sex/Group:	25 females per group
Satellite groups:	TK: 3 in control and 6 in each test article groups. Animals were administered on GD 6 through 18 (BID).
Study design:	Main Study: BID administration of enasidenib mesylate salt 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	Thin body condition in multiple animals at 30 mg/kg BID
Body Weights	HD: BW gain ↓65% at the end of dosing vs. control
Food consumption	HD: Mean gestation food consumption↓65%

Necropsy findings
Cesarean Section Data

Table 16: Uterine and Ovarian Examinations In Rats

Dose mg/kg/BID	**0**	**3**	**10**	**30**
No evaluated	**F:25**	**F:25**	**F:25**	**F:25**
Pregnancy Index (%)	96	100	100	100
Gravid Uterine Weight (g)	75.3	-	-	54**
Final Body Weight (g)	371	-	-	308**
Adjusted Final Body Weight (g)	295	-	-	255**
* = p < 0.05; ** = p < 0.01.				

Necropsy findings
Offspring

HD: Mean fetal BW↓ 26%;
HD: ↑fetal skeletal developmental variation of sternebrae not ossified (17 (89.5%) vs. 13 (54.2%) control
HD: ↓ mean number of viable fetuses and litter size per animal.

Table 17: Rat Fetal Evaluations

Dose mg/kg/BID	**0**	**3**	**10**	**30**
No evaluated	**F:25**	**F:25**	**F:25**	**F:25**
Least Square Mean Fetal Body Weight (g)	3.94	-	-	2.92**
Mean No. Viable Fetuses per Animal	12.8	-	-	9**
Fetal Sex Ratio % Males per Animal	45.0	-	-	57*
Mean % Postimplantation Loss per Animal	3.38	-	-	35**
Litter Size Mean No. per Animal per Animal	12.8	-	-	9**
Mean No. Resorptions: Early + Late per Animal	0.5	-	-	4**
Mean No. Viable Fetuses per Animal	13	-	-	9**
No. Litters/No. Fetuses Evaluated	24/153	25/151	25/150	19/104
Sternebra(e), Not ossified				
No. Litters (%)	13 (54.2)	14 (56.0)	20 (80.0)	17 (89.5)*
No. Fetuses (%)	38 (24.8)	34 (22.5)	52 (34.7)	77 (74.0)

Table 18: Summary of Toxicokinetics Parameters in Rats

	Toxicokinetic Parameters		
Dose	**3 mg/kg BID**	**10 mg/kg BID**	**30 mg/kg BID**
GD 6			
C_{max} (ng/mL)	286	1480	4650
AUC_{0-t} (ng·hr/mL)	2790	14700	36800
GD 17			
C_{max} (ng/mL)	556	3720	18500
AUC_{0-t} (ng·hr/mL)	4720	39400	209000
GD18			
Maternal Conc. (ng/mL), 2 hr postdose	674	3760	17800
Fetal Conc. (ng/mL), 2 hr postdose	113	961	7950
Fetal/Maternal Conc. Ratio	0.176	0.256	0.493

AUC_{0-t} = area under the plasma concentration-time curve from time zero to the last quantifiable concentration post first daily dose; BID = twice daily; C_{max} = maximum plasma concentration; Conc. = concentration.

(Table excerpted from NDA 209606)

Enasidenib:
Dose proportionality: approximately dose-proportional manner on GD 6 (13- fold) and in a greater than dose-proportional manner on GD 17 (44-fold) over the dose range of 3 to 30 mg base/kg twice daily.
The GD 17 to GD 6 exposure ratios were 2:6 with increasing enasidenib dose.
Sex differences: no significant differences.
GD18 fetal to maternal plasma enasidenib concentration
3 mg/kg BID:18%
10 mg/kg BID:26%
30 mg/kg BID: 49%
AG-16903
There was no notable maternal or fetal exposure to AGI-16903 following BID oral administration of AG-221 to female pregnant rats at the doses tested.

Enasidenib: An Oral (Gavage) Study of the Effects on Embryo Fetal Development in Rabbits Including a Toxicokinetic Evaluation/CC90007-TOX-2149

Key Study Findings

- Test article-related adverse maternal effects of thin body condition and few/absent feces, along with decreased mean gestation body weight gain and decreased food consumption were observed at 10 mg base/kg/day.
- Premature delivery (abortion) in one animal each at 5 and 10 mg/kg/day

- Mean steady state exposure margin in rabbits at 5 mg/kg/day (AUC_{0-24} 17.6 µg.hr/mL) to human (estimated AUC_{0-24hr} at 100 mg QD 258.5 µg.hr/mL) is 0.07x.

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

Methods

Dose and frequency of dosing:	0, 2, 5, 10 mg/kg/day once daily
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% (w/v) methylcellulose (400cps), 5% (w/v) vitamin E TPGS, and 5% (w/v) hydroxypropylmethylcellulose acetate succinate, grade AS-MF, in deionized water, (pH 6.5 ± 1.5)
Species/Strain:	Time-mated female New Zealand White Hra:(NZW)SPF rabbits
Number/Sex/Group:	23 females for main study
Satellite groups:	TK: 4 females per group dosed through GD20
Study design:	QD administration of enasidenib mesylate salt to females from Gestation Day (GD) 7 through 19, 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	None related to test article. Females at control (3), 2 mg/kg (4) and 10 (1) mg/kg/day were found dead or euthanized due to deteriorated conditions related gavage errors.
Clinical Signs	Soft feces at 2,5, 10 mg/kg/day, fewer/absent feces at 10 mg/kg/day and red material at 5 and 10 mg/kg/day with severely reduced food consumption. HD: Feces few/absent, thin body condition in multiple animals at 10 mg/kg/day
Body Weights	MD: BW gain GD 7-10↓ 85% vs. control HD: BW gain GD 7-10 ↓ (195 % vs. control) GD 7-19↓ (62% vs. control)
Pregnancy index	Abortion MD and HD: One animal at MD and HD aborted on GD 20 and GD 27, respectively with severe reduced food consumption (≤ 10 g/animal/day) for several days prior to aborting. The frequency of abortions is 5% which is higher than the historical control data of 0.3%.

Food consumption	MD: GD 7-10↓ 14% compared to controls HD: GD 7-10 ↓ 40%, GD 10-13 ↓50%, GD 13-16 ↓31%. Over all dosing period GD 7-19 ↓35% and the entire study period GD 0-29 ↓15% compared to controls.
Necropsy findings Cesarean Section Data	HD: ↑ Postimplantation loss 8 vs. 3 in control and within the HCD range (2 to 10) HCD= historical control data **Table 19: Uterine and Ovarian Examinations In Rabbits**

Dose mg/kg/day	**0**	**2**	**5**	**10**
No evaluated	**F:23**	**F:23**	**F:23**	**F:23**
No. Pregnant	23	20	21	21
Pregnancy Index (%)	100	87	91	91
No. Abortions	0	0	1	1
Mean No. Viable Fetuses	9.3	8.8	8.4	8.6
Mean % Postimplantation Loss	3	2.7	3.4	7.8
Litter Size Mean No. per Animal	9.3	8.8	8.4	8.6
Mean No. Resorptions: Early + Late	0.3	0.2	0.4	0.8

Necropsy findings Offspring	Mean fetal body weight (g): ↓7-8% but within the HCD No developmental toxicity was observed up to 10 mg base/kg/day. No adverse external, visceral and skeletal changes noted.

Table 20: Enasidenib: Summary of Mean Toxicokinetic Parameters in Rabbits

	Toxicokinetic Parameters		
Dose	**2 mg/kg/day**	**5 mg/kg/day**	**10 mg/kg/day**
GD 7			
C_{max} (ng/mL)	137	438	1060
AUC_{0-t} (ng·hr/mL)	1440	5260	15700
GD 19			
C_{max} (ng/mL)	287	1030	2690
AUC_{0-t} (ng·hr/mL)	4170	17600	44300
GD 20			
Maternal Conc. (ng/mL), 2 hr postdose	218	753	2410
Fetal Conc. (ng/mL), 2 hr postdose	6.30	23.8	123
Fetal/Maternal Conc. Ratio	0.0293	0.0301	0.0490

AUC_{0-t} = area under the plasma concentration-time curve from time zero to the last quantifiable concentration post first daily dose; C_{max} = maximum plasma concentration; Conc. = concentration.

(Table excerpted from NDA 209606)

Systemic exposure (AUCt) for enasidenib increased in a greater than dose-proportional manner in the dose range of 2 to 10 mg/kg/day on GD 7 and GD 19.
On GD 20, enasidenib fetal plasma concentrations at 2 hours post-dose were ≤ 4.9% of the maternal plasma concentrations.
Systemic exposure to AGI-16903 was < 7% of the exposure to enasidenib in pregnant rabbits and ≤ 14.1% fetal plasma concentrations at 2 hours post-dose.

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6 Clinical Pharmacology

6.1. Executive Summary

Enasidenib, a first in class inhibitor of the mutant isocitrate dehydrogenase 2 (IDH2) enzyme, is proposed for the treatment of patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) with an IDH2 mutation. The proposed dose of enasidenib is 100 mg orally once daily with or without food. The key review issue from a clinical pharmacology perspective is the appropriateness of the enasidenib dose in the proposed population.

The Office of Clinical Pharmacology has reviewed the information contained in NDA 209606. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations and comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The safety and effectiveness of enasidenib in patients with R/R AML with an IDH2 R140 or R172 mutation was supported by the results from study AG221-C-001. Exposure-response (E-R) for efficacy provided supportive evidence of effectiveness.
General dosing instructions	The proposed dose of 100 mg once daily without regard to food is effective and appears to be safe given the available data. Food is not anticipated to affect efficacy or safety.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No alternative dosing is recommended for age, body weight, sex, race, or renal impairment. No drug interactions are anticipated with the concomitant use of cytochrome P450 (CYP) or uridine 5'-diphosphate glucoglucuronosyltransferase (UGT) modulators, as enasidenib is metabolized by multiple CYP and UGT enzymes. Exposure-response (E-R) for safety analyses supports a dose reduction for patients with Grade 3 or higher bilirubin elevation. A post market requirement (PMR) is requested to evaluate dosing in patients with hepatic impairment.
Labeling	Labeling language is generally acceptable with changes to the specific content and formatting from the review team reflected in the final approved labeling.
Bridge between the to-be-marketed and clinical trial formulations	No dedicated bioequivalence study was conducted. Comparative pharmacokinetic (PK) data was provided for bridging between the to-be-marketed formulation (F3) and the formulations used during clinical development formulations (F1 and F2). For additional details, see section 6.3.2 and the CMC/Biopharmaceutics review.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Enasidenib is an IDH2 enzyme inhibitor that exhibited dose proportional increases in exposure across the evaluated dose range. Following a total daily dose of 100 mg, steady state was generally achieved within 29 days. One active metabolite, M2 (AGI-16903), comprises about 10% of the drug in circulation. No large mean effects (e.g. 20 ms) are anticipated with the observed steady state of enasidenib at a dose of 100 mg once daily. The following is a summary of the clinical PK of enasidenib.

Absorption: Enasidenib exposure increases with a dose up to 450 mg once daily. The median time to the maximum concentration (T_{max}) was approximately 4 hours. Absolute bioavailability was approximately 57%. An increase of 64% in maximum concentration (C_{max}) and 50% in area under the curve (AUC) was observed with a high-fat meal (as defined by the FDA in Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies, December 2002).

Distribution: The estimated volume of distribution is 55.8 L [coefficient of variation (CV%), 29%]. Plasma protein binding was 98.5% in human plasma. Enasidenib is not a substrate for P-glycoprotein (P-gp) or breast cancer resistant protein (BCRP), while its metabolite AGI-16903 is a substrate of both P-gp and BCRP.

Elimination: Enasidenib is metabolized by multiple CYP and UGT enzymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A1, UGT1A3, UGT1A4, UGT1A9, UGT2B7, and UGT2B15) in vitro. The dose is primarily eliminated in the feces (89%) as compared to the urine (11%). Enasidenib represents 34% of the dose in the feces.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dose and administration of enasidenib is 100 mg once daily with or without food. Study AG221-C-001 evaluated enasidenib at the proposed total daily dose under fasted conditions in 207 patients with R/R AML. The proposed dose appears to be effective and has a manageable safety profile. The maximum administered dose (MAD), elimination half-life and the effect of food on the bioavailability of enasidenib support the administration with or without food. Clinical studies in patients with hepatic impairment have not been conducted; a PMR is proposed to evaluate the appropriateness of a dose of 100 mg once daily in this patient population.

Therapeutic Individualization

No therapeutic individualization for intrinsic or extrinsic factors is recommended at this time.

Outstanding Issues

Two PMRs will be issued from Clinical Pharmacology: (1) a trial to determine an appropriate dose of enasidenib in patients with hepatic impairment; (2) a trial to evaluate the effect of enasidenib on the PK of sensitive substrates of multiple metabolic enzymes and transporters. Refer to the Post-Marketing Requirements and Commitments (Section 12) for additional details.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacology		
Mechanism of Action	Enasidenib is an IDH2 inhibitor (R140Q IC_{50} = 0.067µM, R172K IC_{50} = 0.21 µM, Wildtype IC_{50} = 3.0 µM).	
Active Moieties	Enasidenib and its active metabolite AGI-16903 account for 89% and 10% of the total plasma radioactivity. AGI-16903 is 3 times less potent compared to the parent as an inhibitor of R140Q.	
QT Prolongation	Enasidenib did not result in clinically meaningful mean changes in heart rate and other ECG intervals (e.g. PR and QRS).	
General Information		
Bioanalysis	Enasidenib and AGI-16903 were measured using validated LC/MS/MS methods. A summary of the method validation reports is included as an appendix.	
Healthy vs. Patients	The exposure following a single dose is higher in patients compared to healthy subjects (3.4-fold, cross study-comparison).	
Drug Exposure at Steady State Following the Therapeutic Dosing Regimen	The $AUC_{0\text{-}10h}$ was 106 mcg.h/mL and C_{max} was 13 mcg/mL in patients at a dose of 100 mg once daily.	
Range of Effective Dose or Exposure	Only one dose level was studied for safety and efficacy in the proposed patient population.	
Maximally Tolerated Dose or Exposure	Not reached with doses evaluated up to 650 mg.	
Dose Proportionality	Dose proportional within the range of 50 mg to 450 mg once daily in patients.	
Accumulation	Mean accumulation ratio 9- to 11-fold at steady state.	
Variability	CV% for C_{max}: 46.3 and $AUC_{0\text{-}10h}$: 47.7.	
Absorption		
Bioavailability	57%	
T_{max} [oral]	4 hours	
Food Effect (High-Fat) Geometric Mean Ratio (90% CI)	**$AUC_{0\ to\ inf}$**	**C_{max}**
	1.5 (90% CI: 1.4, 1.7)	1.6 (90% CI: 1.4, 1.9)

Distribution	
Volume of Distribution	55.8 L (CV% 29%)
Plasma Protein Binding	98.5%
Substrate of Transporters [*in vitro*]	Enasidenib is not a substrate for P-gp, BCRP, MRP2, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2. AGI-16903 is a substrate of both P-gp and BCRP, but is not a substrate of MRP2, OAT1, OAT3, OATP1B1, OATP1B3, or OCT2.
Elimination	
Terminal Elimination Half-Life	137 hours
Metabolism	
Primary Metabolic Pathway(s) [*in vitro*]	Enasidenib metabolism is mediated by multiple CYP enzymes (e.g., CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4), and by multiple UGTs (e.g., UGT1A1, UGT1A3, UGT1A4, UGT1A9, UGT2B7, and UGT2B15). Metabolism of the metabolite AGI-16903 is also mediated by multiple enzymes (e.g. CYP1A2, CYP2C19, CYP3A4, UGT1A1, UGT1A3, and UGT1A9).
Excretion	
Primary Excretion Pathways (% dose)	89% (34% unchanged enasidenib) in the feces and 11% (0.4% unchanged enasidenib) in the urine. The renal route appears to be a minor elimination pathway.
Interaction liability (Drug as perpetrator)	
Inhibition/Induction of Metabolism [*in vitro*]	Enasidenib inhibits the activity of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and UGT1A1. AGI-16903 inhibits the activity of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. Enasidenib induces CYP2B6 and CYP3A4.
Inhibition/Induction of Transporter Systems [*in vitro*]	Enasidenib inhibits P-gp, BCRP, OAT1, OATP1B1, OATP1B3, and OCT2, but not MRP2 or OAT3. AGI-16903 inhibits BCRP, OAT1, OAT3, OATP1B1, and OCT2, but not P-gp, MRP2, or OATP1B3.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. A significant E-R relationship for efficacy in patients with an R140 mutation and a trend of increase in response with increase in exposure for patients with R172 mutation provides supportive evidence of effectiveness of enasidenib in this patient population. At the proposed dose of 100 mg once daily, enasidenib suppressed 2-hydroxyglutarate (2-HG) levels in peripheral blood with a median steady state rate of 92.8% in patients with R140 mutations and 27.6% in patients with R172 mutations. The similar clinical responses across the mutation types support effectiveness of the proposed dose despite the difference of 2-HG suppression between patients with R140 and R172 mutations.

Summary of efficacy: Study AG221-C-001 was a multicenter, open-label study of enasidenib in patients with advanced hematologic malignancies with an IDH2 mutation. The study included Phase 1 dose escalation, Phase 1 expansion, and Phase 2 portions. The Phase 1 dose escalation portion assessed doses of 50 mg to 650 mg QD and 30 mg to 150 mg twice daily (BID) (N = 113). A MTD was not reached. A 100 mg once daily dose was selected for the Phase 1 expansion portion (N = 126) and the Phase 2 portion (N = 106). Of these patients, 199 patients with R/R AML were included in the Final FDA Efficacy Analysis Set and the complete remission (CR)/complete remission with only partial hematologic recovery (CRh) rate was 23.1% (See Section 7 for additional details).

Effect of IDH2 mutation type on efficacy: Patients in study AG221-C-001 were selected based on the presence of an IDH2 mutation in blood or bone marrow as determined by local testing with retrospective central confirmation (Phase 1) or by central testing (Phase 2). The proposed Abbott RealTime IDH2 companion diagnostic (CDx) is a polymerase chain reaction (PCR) based assay that is designed to detect a total of ten substitutions at R140 [R140Q (CAG), R140L (CTG), R140G (GGG), R140W (TGG)] and R172 [R172K (AAG), R172M (ATG), R172S (AGT and AGC), R172G (GGG), and R172W (TGG)]. Table 21 shows the distribution of IDH2 mutations in the Final FDA Efficacy Analysis Set based on the proposed CDx test. When both blood and bone marrow were assessed by the CDx and found to be discordant, the result of blood is reported. The predominant IDH2 mutations were R140Q (75.4%) and R172K (20.1%), which correspond to the most commonly reported IDH2 mutations in AML (My Cancer Genome, COSMIC).

Table 21: Distribution of IDH2 Mutations as Detected by the Proposed Companion Diagnostic Test (Final FDA Efficacy Analysis Set)

IDH2 Mutation (CDx)	Phase 1 N = 101	Phase 2 N = 98	Phase 1/2 Combined N = 199
R140L	1 (1.0%)	0	1 (0.5%)
R140Q	78 (77.2%)	72 (73.5%)	150 (75.4%) [a,b]
R140W	2 (2.0 %)	2 (2.0%)	4 (2.0%)
R172K	19 (18.8%)	21 (21.4%)	40 (20.1%) [c]
R172W	1 (1.0%)	3 (3.1%)	4 (2.0%)

Patients with discordant IDH2 mutation calls between blood and bone marrow samples are presented in the table based on the blood result such that: [a] 1 patient had CDx result of R140Q in bone marrow and R140W in blood, [b] 2 patients had CDx results of R140Q in bone marrow and R172K in blood, [c] 1 patient had CDx result of R172K in bone marrow and R140Q in blood.
Source: Reviewer analysis.

Enasidenib showed clinical activity across the IDH2 R140 and R172 mutation subgroups, although a higher CR, CRh, and CR/CRh rate was generally observed in the subgroup of patients with R172 mutations (Table 22). All patients with CR or CRh had R140Q or R172K.

Table 22: Best Response by IDH2 R140 or R172 Mutation (Efficacy Evaluable Population)

Response	Phase 1		Phase 2		Phase 1/2 Combined	
	R140 N = 81	R172 N = 20	R140 N = 74	R172 N = 24	R140 N = 155	R172 N = 44
CR	15 (18.5%)	4 (20.0%)	13 (17.6%)	5 (20.8%)	28 (18.1%)	9 (20.5%)
CRh	2 (2.5%)	3 (15.0%)	4 (5.4%)	0	6 (3.9%)	3 (6.8%)
CR/CRh	17 (21.0%)	7 (35.0%)	17 (23.0%)	5 (20.8%)	34 (21.9%)	12 (27.3%)

Source: Reviewer analysis.

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

Yes. The proposed dose of 100 mg QD is effective and appears to have a manageable safety profile. The E-R for efficacy and safety provide further insights into dose selection as summarized below.

Exposure-response for efficacy: Based on the E-R for efficacy (Figure 14), there was a strong relationship between steady state exposure (AUC_{ss}) and ORR (ORR is defined as the rate of responses including complete response [CR], CR with incomplete neutrophil recovery [Cri], CR with incomplete platelet recovery [CRp], partial response [PR], marrow CR [mCR, for MDS], and morphologic leukemia-free state [MLFS, for AML], based on investigator assessment) for patients with IDH2 R140 mutations (N = 131, p-value = 0.02 for multi-covariate logistic regression) over the exposure range. There was also an apparent positive relationship between AUC_{ss} and ORR for patients with R172 mutations (N= 46, p-value=0.07 for multi-covariate logistic regression). The E-R relationship for patients with R172 mutations appears to be steeper than for patients with R140 mutations suggesting that increasing the dose for patients with an R172 mutation may offer more benefit. This is consistent with the observations in which greater inhibition of IDH2 (as measured by 2-HG suppression) occurred at a dose of 100 mg once daily for R140 mutations as compared to R172 mutations; however, the following limitations of the data preclude us from recommending a higher dose for patients with R172 mutations.

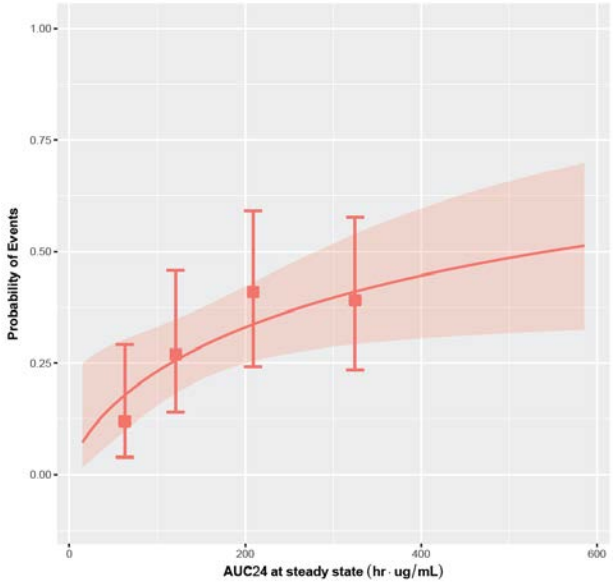
- Data for E-R analysis was available primarily from a dose of 100 mg (75% of total data).
- The sample size in the R172 mutation types is limited (N=46).
- Based on the multivariate E-R analysis for R172 mutations, while other factors were strongly associated with response.
- It is difficult to differentiate the effect of exposure and various risk factors on efficacy in the absence of control arm.

Thus, sufficient evidence is not available to support that a higher dose may provide better efficacy in patients with R172 mutations. (b) (4)

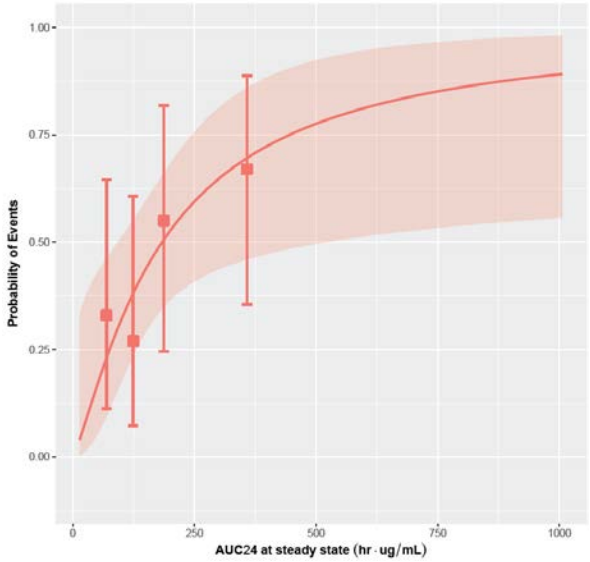
(b) (4)

Figure 14: Exposure-efficacy Relationships for Objective Response Rate

ORR: in R140 R/R AML (N=131)



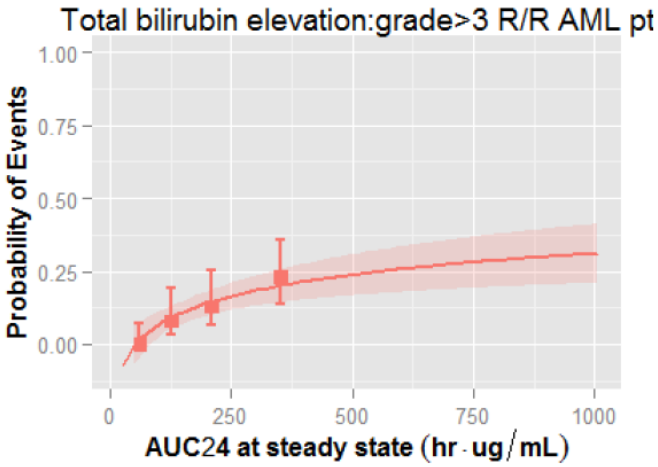
ORR: in R172 R/R AML (N=46)



Source: Reviewer's Analysis.

Exposure-response for safety: Based on E-R for safety, a strong relationship between enasidenib steady state exposure (AUC_{ss}) and total bilirubin elevation (all Grade, and Grade 3 and Grade 4) in plasma was observed (Figure 15). The total bilirubin elevation was not associated with increases in transaminases. The isolated bilirubin elevation may be the result of an inhibitory effect of enasidenib on UGT1A1, which is responsible for the metabolism of bilirubin. There was no apparent relationship between enasidenib steady state exposure and anemia, febrile neutropenia, leukocytosis, tumor lysis syndrome or IDH differentiation syndrome. Enasidenib exhibited a manageable safety profile based on the relatively low incidence of dose interruptions or dose reductions.

Figure 15: Exposure-Safety Relationship for Grade 3 and Grade 4 Total Bilirubin Elevation (N=242)



Source: Response to FDA Clinical Pharmacology Information Request on 09 Mar 2017.

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

No. The available data show that age (range: 19 years to 100 years), body weight (range: 38.6 kg to 136.1 kg) or body surface area, sex, race and renal impairment do not have clinically meaningful effect on enasidenib steady state exposure. Insufficient data are available to ascertain the effects of hepatic impairment on steady state exposure. Based on an exploratory analysis, patients with more co-occurring mutations tended to have lower CR/CRh rate as compared to patients with less co-occurring mutations.

Hepatic Impairment: Based on a population pharmacokinetic (PPK) analysis that included 45 patients with mild hepatic impairment [total bilirubin (TB) ≤ upper limit of normal (ULN) and aspartate transaminase (AST) > ULN or TB < 1 to 1.5 times ULN and any AST as defined by the National Cancer Institute Organ Dysfunction Working Group], mild hepatic impairment had no effect on the exposure of enasidenib when compared to patients with normal hepatic function. No dose adjustment is necessary in patients with mild hepatic impairment. Since enasidenib is primarily metabolized in the liver, hepatic impairment has the potential to increase enasidenib exposure and the risk for adverse reactions. A PMR will be issued to determine an appropriate dose in patients with hepatic impairment.

Renal Impairment: No dedicated study was conducted in patients with renal impairment, as only 0.4% unchanged enasidenib was excreted in the urine. Based on the PPK analysis, mild [estimated glomerular filtration rate (eGFR) 60 mL/min/1.73m^2 to 89 mL/min/1.73m^2, N=116] and moderate (eGFR 30 mL/min/1.73m^2 to 59 mL/min/1.73m^2, N=58) renal impairment had no effect on the exposure of enasidenib. No dose adjustment is being recommended for patients

with renal impairment, since renal clearance appears to be a minor elimination pathway for enasidenib.

Co-occurring Mutations: The Applicant conducted exploratory analyses of co-occurring known or likely somatic mutations using the FoundationOne Heme® panel in a subset of 100 patients with IDH2 mutation positive R/R AML enrolled in the Phase 1 portions of study AG221-C-001. Of the 100 patients tested, 98 had IDH2 mutations including W21S (N = 1), R140H (N = 1), R140Q (N = 76), R140W (N = 1), R172K (N = 19), and D225N (N = 1). One patient had two IDH2 mutations (R140Q and D225N). A total of 42 patients included in the Final FDA Efficacy Analysis Set (See Sections 6.3.2 and 7) were assessed for the number and pattern of co-occurring mutations. Patients were identified as having IDH2 mutations (R140Q N = 38, R172K N = 3, and R140Q+D225N N = 1) and 0 to 9 co-occurring mutations in addition to their IDH2 mutation (median: 3). In this subset, the CR/CRh rate was 23.8%. The number of patients with R172 compared to R140 mutations was too small to draw any conclusions. No consistent pattern of co-occurring mutations was identified in patients who achieved CR or CRh; however, responses appeared to cluster in the subgroup of patients with fewer co-occurring mutations (Table 23). In addition, patients identified as having co-occurring mutations in either NPM1 or FLT3 (NPM1 (N = 6), FLT3 (N = 4), NPM1 and FLT3 (N = 2)) did not achieve a CR or CRh. The relevance of these findings remains to be investigated.

Table 23: Number of Patients Achieving CR/CRh by Number of Co-Occurring Mutations

	Number of Known or Likely Somatic Mutations									
	0 (N = 1)	1 (N = 7 [a])	2 (N = 5 [b])	3 (N = 10)	4 (N = 6)	5 (N = 6)	6 (N = 5 [c])	8 (N = 1)	9 (N = 1)	Total (N = 42)
CR	1	3	2	0	1	0	0	0	0	7
CRh	0	1	0	0	1	1	0	0	0	3
CR/CRh	1	4	2	0	2	1	0	0	0	10

[a] Includes 1 patient with R172K. [b] Includes 2 patients with R172K. [c] Includes 1 patient with R140Q/D225N.
Source: Reviewer exploratory analysis.

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

No. The administration with food is unlikely to have a clinically meaningful effect on steady state exposure given the available data including the MAD, the elimination half-life, and the effect of food on enasidenib exposure. The labeling will recommend that IDHIFA be taken with or without food.

The coadministration of drugs known to inhibit or induce the enzymes that metabolize enasidenib or proteins that transport enasidenib are unlikely to have a clinically meaningful effect on the steady state exposure of enasidenib, as enasidenib is metabolized by multiple CYP and UGT enzymes; however, enasidenib and its active metabolite may inhibit or induce multiple enzymes. A PMR will be issued to evaluate the effects of enasidenib on the exposure of sensitive substrates of multiple drug metabolizing enzymes and transporters. The ability of enasidenib to inhibit UGT1A1 may be responsible for the marked elevations in bilirubin noted, as bilirubin is primarily metabolized by this enzyme; this potential inhibitory effect further supports the recommendation to conduct a trial to determine the effect of enasidenib on the exposure of multiple sensitive substrates.

Food-Drug Interactions: The Applicant conducted a randomized, two-way crossover study (AG221-C-002) to evaluate the effect of food on the exposure of enasidenib. A single oral dose of 100 mg was administered following a 10-hour overnight fast or within 30 minutes after a high-fat breakfast (defined as listed in the FDA Guidance for Industry on food effect studies). An increase in enasidenib exposure was observed in the fed state (Table 24). The increased exposure is not expected to be clinically relevant based on the MAD, E-R analyses, and elimination half-life.

Table 24: Effect of a High-Fat Meal on the Bioavailability of Enasidenib

Parameter	Geometric LSM[a]		% Ratio of LSM[b] (90% CI)	Intra-subject CV%
	Treatment B (Fed)	Treatment A (Fasted)		
AUC_t	80.0	53.5	150 (135, 166)	23.3
AUC_∞	80.3	53.8	149 (135, 166)	23.1
C_{max}	1.35	0.827	164 (144, 186)	29.1

ANOVA = analysis of variance; AUC = area under the plasma concentration time curve; AUC_∞ = AUC from zero to infinity; AUC_t = AUC from zero to the time of last quantifiable concentration; CI = confidence interval; C_{max} = maximum observed concentration in plasma; CV% = coefficient of variation; LSM = least-squares means

[a] Geometric LSM are the LSM from ANOVA presented following back transformation to the original scale. The 90% CIs are presented following back transformation to the original scale.

[b] Ratio of Fed (Treatment B) / Fasted (Treatment A)

Source: Study AG221-C-002 Clinical Study Report Table 9.

Drug-Drug Interactions: The Applicant has not conducted clinical drug interaction studies. Based on in vitro studies, enasidenib is metabolized by multiple CYP and UGT enzymes (e.g., CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A1, UGT1A3, UGT1A4, UGT1A9, UGT2B7, and UGT2B1), and the metabolite AGI-16903 is metabolized by multiple enzymes (e.g. CYP1A2, CYP2C19, CYP3A4, UGT1A1, UGT1A3, and UGT1A9). Given that enasidenib and AGI-16903 are metabolized by multiple CYP and UGT enzymes, coadministration of drugs that inhibit enzymes that metabolize enasidenib are unlikely to have a clinically meaningful effect on the steady state exposure of enasidenib.

In vitro studies suggest that enasidenib and AGI-16903 may inhibit multiple enzymes (e.g., CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and UGT1A1) and enasidenib may induce several enzymes (e.g., CYP2B6 and CYP3A4) based on the ratio of the steady state concentrations to the half maximal inhibitory concentration (IC_{50}). Enasidenib and AGI-16903 may also inhibit multiple transporters (e.g., P-gp, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, and OCT2). Given the potential for enasidenib to alter exposure of other coadministered drugs, a PMR will be issued to evaluate the effects of enasidenib on the exposure of sensitive substrates of multiple drug metabolizing enzymes and transporters.

Enasidenib does not demonstrate pH dependent solubility. It is unlikely that the coadministration of acid reducing agents (ARA), such as proton pump inhibitors (PPI) or histamine 2 receptor antagonists (H2RA), will affect steady state exposure.

Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

No. The Phase 1 portions of Study AG221-C-001 primarily used formulation 2 (F2, non-coated tablet) and the Phase 2 portion used the to-be-marketed formulation (F3, coated tablet). The Applicant provided a tabular comparison of PK data, which suggests that there is no clinically meaningful difference in exposure of enasidenib following administration of the F2 and F3 formulations (Table 25). This data support the pooling of all available data for these formulations to describe the PK and assess safety and efficacy. For additional details, see also the CMC/Biopharm review.

Table 25: Relative Bioavailability of Enasidenib Following the Administration of Two Formulations

Pharmacokinetic Parameter (unit)	Formulation	N	Geometric Mean	Ratio (%) of Geometric Means (F3/F2)	90% CI of Ratio of Geometric Means
C_{max} (ng/mL)	F3	36	11751.1	89.4	(77.5, 103.2)
	F2	90	13145.8		
$AUC_{0\text{-}8}$ (ng•h/mL)	F3	27	76971.0	89.8	(75.9, 106.3)
	F2	86	85704.8		

Source: Response to FDA Information Request Dated 24 Apr 2017

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7 Statistical and Clinical Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

Table 26: 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					
AG221-C-001	Phase 1, open-label study of enasidenib in patients with IDH2+ advanced hematologic malignancies (PK, Safety, ORR)	Escalation: 50-650 mg total daily dose PO Expansion: 100 mg PO daily	Until PD or unacceptable toxicity Minimum follow-up 6 months	345	US: 15 France: 2
Studies to Support Safety					
AG221-C-003	Phase 1/2, open-label study of enasidenib in patients with IDH2+ advanced solid tumors (PK, Safety)	100 mg or 150 mg PO daily	Until PD or unacceptable toxicity	21	US: 11 France: 1
AG221-C-002	Phase 1, two-way crossover study to assess food effect on enasidenib exposure (PK, Safety)	100 mg PO	Two doses	30	US: 1
AG-221-CP-001	Phase 1, open-label study of enasidenib in healthy adult Japanese male subjects (PK, Safety)	50 to 300 mg PO	Single dose	62	US: 1
AG-221-CP-002	Phase 1, open-label study of enasidenib bioavailability, metabolism and excretion in healthy male adult subjects (PK, Safety)	100 mg PO	1 or 2 doses	14	US: 1

Source: FDA synopses of individual studies provided by the applicant in the NDA submission.
Abbreviations: PD, progressive disease; PK, pharmacokinetics; PO, by mouth; ORR, overall response rate.

7.1.2. Review Strategy

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

- NDA 209606
- Relevant published literature
- Relevant information in the public domain

Study AG221-C-001 was used for the primary analysis of efficacy and safety. The applicant submitted a complete data set for this study, using a data cut date of April 15, 2016, at the time of the initial NDA submission. At the request of the FDA, the applicant submitted an updated data set for Study AG221-C-001, using a data cut date of October 14, 2016, at the time of the 90-day safety update (submitted to eCTD May 10, 2017 as SDN 27). The updated data set from Study AG221-C-001 formed the basis for this review.

The applicant also submitted complete data sets from the 3 completed studies in healthy volunteers, as well as data in the form of tables, listings, graphs, and analysis from the completed study of enasidenib in patients with solid tumors (Table 26) at the time of the initial NDA submission. Data from these studies were used to supplement the analysis of safety.

At the time of NDA submission, (b) (4)
data from these studies were not considered relevant for this review.

The subjects treated on the studies in Table 26 received enasidenib 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 enasidenib 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 1.3 (MAED) (FDA, Silver Spring, MD) was used to look for safety signals. Study AG221-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 7.2.2.

Data and Analysis Quality

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\NDA209606

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 from a randomly selected subset of patients to the STDM data sets and then to the original data source (case report forms). The data provided by the applicant in the ADAM datasets was traceable to the original data source in all cases; no anomalies were identified.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

AG221-C-001

Study Design and Objectives

Study AG221-C-001 was a Phase 1/2, open-label study of enasidenib in patients with advanced hematologic malignancies harboring an IDH2 mutation. The study was conducted in three stages: Dose Escalation, Phase 1 Expansion, and Phase 2.

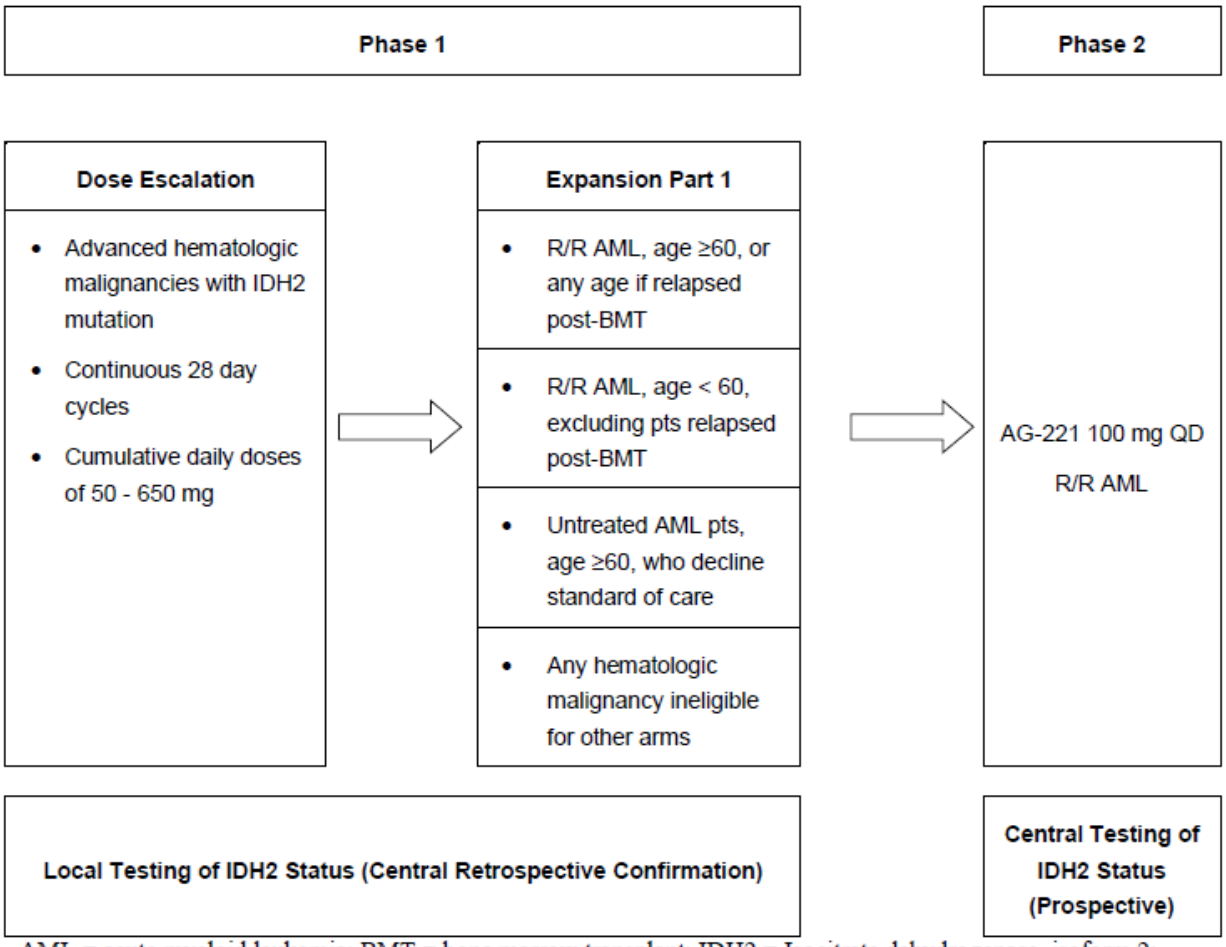
Dose Escalation was conducted using a standard 3+3 design. The primary objective of Dose Escalation and Phase 1 Expansion was to assess the safety and tolerability of enasidenib as monotherapy, and to determine the recommended Phase 2 dose (RP2D) for further testing in patients with IDH2+ hematologic malignancies. Phase 2 was conducted using a single-arm design. The primary objective of Phase 2 was to assess the efficacy of enasidenib as treatment for subjects with relapsed or refractory AML with an IDH2 mutation.

The secondary objectives of the study were to describe the dose-limiting toxicities, evaluate the safety profile, and characterize the pharmacokinetics (PK) of enasidenib, and to characterize the pharmacodynamic (PD) relationship of enasidenib to 2-hydroxyglutarate (2-HG).

Enasidenib was administered orally once daily (QD) or twice daily (BID) on Days 1 to 28 of continuous 28-day cycles until disease progression, the development of unacceptable toxicity, or withdrawal of consent. There were no designated inter-cycle rest periods.

Subjects had the extent of their disease assessed (including examination of bone marrow biopsies and/or aspirates and peripheral blood) on protocol-specified study days while on study drug 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 2003 modified International Working Group (IWG) criteria for AML (Cheson et al, 2003).

Figure 16: Study Diagram



AML = acute myeloid leukemia; BMT = bone marrow transplant; IDH2 = Isocitrate dehydrogenase, isoform 2; pts = patients; QD = once daily; R/R = relapsed/refractory.

Source: Applicant CSR Figure 1

The protocol and statistical analysis plan define the end of the study as the time at which either: a) all subjects had discontinued treatment with enasidenib and had been followed for survival for at least 12 months, or have died, been lost to follow-up, or withdrew consent, or b) the last data point from the last subject that was required for primary, secondary and/or exploratory analysis was received, whichever was later.

Key Eligibility Criteria

Subjects with the following conditions were eligible for Dose Escalation:

- Refractory or relapsed AML
- Untreated AML with age ≥ 60 years, if not candidates for standard therapy

- Myelodysplastic syndrome (MDS) characterized by refractory anemia with excess blasts (RAEB) or considered high-risk by the Revised International Prognostic Scoring System (IPSS-R), if recurrent or refractory and not a candidate for regimens known to provide clinical benefit
- Other relapsed or refractory hematologic cancers, with approval of the Medical Monitor

Subjects with the following conditions were eligible for Phase 1 Expansion:

- Arm 1: relapsed or refractory AML with age ≥ 60 years, or AML that has relapsed following HSCT regardless of age
- Arm 2: relapsed or refractory AML with age < 60 years, excluding AML that has relapsed following HSCT
- Arm 3: untreated AML with age ≥ 60 years, if decline standard of care chemotherapy
- Arm 4: advanced hematologic malignancies not eligible for Arms 1-3

Phase 2 enrolled subjects with relapsed or refractory AML who either:

- Relapsed after allogeneic HSCT,
- Were in second or later relapse,
- Were refractory to initial induction or re-induction treatment, or
- Relapsed within 1 year of initial treatment, excluding patients with favorable-risk cytogenetics according to NCCN guidelines (NCCN 2015)

All subjects on AG221-C-001 were required to have IDH2-mutated disease as determined by local or central testing.

Relapsed AML was defined per IWG criteria, as bone marrow blasts ≥ 5%, or reappearance of blasts in the blood, or development of extramedullary disease. Resistant AML was defined per IWG criteria as failure to achieve CR or CRi following completion of initial treatment, with evidence of persistent leukemia by blood and/or bone marrow examination.

Other key eligibility criteria included:

1. ECOG performance score of 0 to 2
2. Platelet count ≥ 20,000/μL (transfusions allowed) unless due to underlying malignancy
3. Serum total bilirubin ≤ 1.5 x ULN unless due to Gilbert's disease, a gene mutation in UGT1A1, or leukemic organ involvement
4. AST, ALT and alkaline phosphatase ≤ 3.0 x ULN unless due to underlying malignancy
5. Serum creatinine ≤ 2.0 x ULN or creatinine clearance > 40 mL/min based on the Cockroft-Gault formula
6. No CNS leukemia
7. No HSCT within 60 days prior to the first dose of enasidenib, no requirement for post-HSCT immunosuppressive therapy at screening, and no clinically significant GVHD

8. No systemic anticancer therapy or radiotherapy within 14 days prior to the first dose of enasidenib (hydroxyurea allowed for control of peripheral leukemic blasts in subjects with WBC > 30,000/μL)
9. None of the following cardiac conditions: New York Heart Association Class III or IV congestive heart failure, left ventricular ejection fraction < 40%, history of myocardial infarction within the 6 months prior to screening, uncontrolled hypertension (SBP > 180 mmHg or DBP > 100 mm Hg), uncontrolled angina pectoris, history of severe ventricular arrhythmias, or QTcF ≥ 450 msec
10. Not pregnant and not nursing, and willing to use highly effective method of birth control
11. No prior treatment with an IDH2 inhibitor (Phase 2 only)

Treatment Plan

The first 3 subjects in each cohort of Dose Escalation as well as the first 15 subjects on each arm of Phase 1 Expansion received a single dose of enasidenib on Day -3 for PK testing. All subjects then received enasidenib daily as monotherapy in continuous, 28-day cycles starting on Cycle 1 Day 1 and continuing until unacceptable toxicity, progressive disease, or withdrawal of consent. After Amendment 4, subjects who experienced disease progression 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 until confirmation of progression upon repeat evaluation 28 days later. Subjects who achieved an adequate response to enasidenib and met other criteria for HSCT were allowed to proceed to HSCT after discontinuation of study therapy. Subjects who relapsed following HSCT were eligible to restart enasidenib with Medical Monitor approval provided they continued to meet other eligibility criteria and had received no other anti-cancer therapies after the last dose of enasidenib (except those used as part of the HSCT itself).

Subjects on the Dose Escalation phase of the study were assigned to receive 50 to 650 mg of enasidenib total per day. The initial dosing regimen was BID; however, based on emerging PK data showing that enasidenib has a long half-life, a QD dosing schedule was implemented in Protocol Amendment 3. Subjects on the Phase 1 expansion or Phase 2 were assigned to receive 100 mg enasidenib daily.

Intra-patient dose escalation was allowed on the study. Patients enrolled in Dose Escalation could be escalated to any higher dose that did not exceed the maximum tolerated dose (MTD), with approval of the Medical Monitor. Patients enrolled in Phase 1 Expansion could be escalated to a higher dose one time, if they had suboptimal response at the first clinical response assessment or later, or evidence of relapse on enasidenib after a response in either the peripheral blood or marrow. Patients enrolled in Phase 2 could be escalated to 200 mg daily if any of the following occurred:

- ANC < 0.5 x 10^9/L after being on enasidenib for the first cycle without Grade ≥ 3 adverse events suspected by the investigator to be related to enasidenib; or

- No partial remission (PR) or better achieved after being on enasidenib for at least 2 cycles without Grade ≥ 3 adverse events suspected by the investigator to be related to enasidenib; or
- Evidence of morphologic relapse or progressive disease.

Dose reductions, in 50 mg increments, were allowed for toxicity. Any subject unable to tolerate 50 mg enasidenib daily was removed from study treatment.

Specific management guidelines were provided for QT prolongation: For patients with Grade 2 QTcF, dose reduction was recommended, and re-escalation permitted after at least 14 days if QTcF decreased to Grade ≤ 1. For patients with Grade 3 QTcF, interruption of enasidenib was required. If QTcF decreased to within 30 msec of baseline or < 450 msec within 14 days, treatment could resume at a lower dose. For patients with Grade 4 QTcF, permanent discontinuation of enasidenib was required.

Specific management guidelines were also provided for differentiation syndrome through Protocol Amendments 4 and 6: 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, was recommended for patients with suspected differentiation syndrome.

Hydroxyurea at a suggested dose of 2-3 g PO twice or three times day was recommended for subjects with elevated WBC. Initiation of furosemide and/or prompt initiation of leukapheresis were recommended if clinically required. Enasidenib could be withheld at the investigator's discretion.

The following medications were not permitted during the study:

- Other anti-neoplastic therapy (except hydroxyurea)
- Corticosteroids (except topical cutaneous, ophthalmic, nasal, and inhalational steroids). Short courses of steroids were permitted to treat co-morbidities (e.g., differentiation syndrome)
- Medications known to prolong the QT interval
- Sensitive CYP substrate medications that have a narrow therapeutic range
- P-gp and BCRP transporter-sensitive substrates digoxin and rosuvastatin
- Antacids, H2 blockers, and proton pump inhibitors

The following medications were restricted during the study and were only allowed if medically necessary:

- Drugs that are substrates for UGT1A1
- Drugs that are substrates for OAT, OATP1B or OCT2
- Drugs that are substrates for CYP2C8, 2C9, 2C19, 2D6, 3A4 or 1A2
- Drugs that are substrates for P-gp or BCRP

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

Schedule of Assessments

Bone marrow and peripheral blood samples for confirmation of disease status and IDH2 mutation screening were obtained during the screening period for all patients. Patients were enrolled to Dose Escalation, Phase 1 Expansion, and the initial portion of Phase 2 on the basis of local IDH2 testing; IDH2 mutation status in these patients was confirmed retrospectively by central testing using the Abbott RealTi*m*e IDH2™ mutation assay. The majority of patients on Phase 2 were enrolled on the basis of central testing using the Abbott RealTi*m*e IDH2™ mutation assay. Patients were considered to be IDH2+ by Abbott RealTi*m*e IDH2™ mutation assay if a mutation was detected in either the blood or the bone marrow.

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), creatine kinase, cardiac troponin, amylase, lipase, coagulation studies, a fasting lipid panel, and a pregnancy test for women of childbearing potential. An assessment of left ventricular ejection fraction by multi-gated (MUGA) scan or echocardiogram and a 12-lead ECG were also collected at screening.

For all subjects, physical exam, and adverse event assessment were repeated on days 1, 8 and 15 of Cycle 1, then on the first day of each subsequent cycle. Creatine kinase, cardiac troponin, amylase, lipase, and coagulation studies were repeated on the first day of each cycle. For subjects in Dose Escalation or Phase 1 expansion, CBC and CMP were repeated weekly during Cycle 1, and every other week for the remainder of enasidenib treatment, and a fasted lipid panel was repeated every 6 months. For subjects in Phase 2, CBC and CMP were repeated approximately every other week throughout enasidenib treatment. Peripheral blood and urine were collected for PK and PD assessments at multiple time points throughout the study, as were time-matched 12-lead ECGs.

Subjects enrolled in Dose Escalation or Phase 1 Expansion had disease response assessments performed on C1D15, C2D1, C3D1 and every 28 days (peripheral blood) or 56 days (bone marrow biopsies and/or aspirates) thereafter while on enasidenib. Subjects enrolled in Phase 2 had disease response assessments performed on C2D1, every 28 days after that through 12 months, and every 56 days after that for the remainder of study treatment. Additional response assessments were performed at any time when progression of disease (PD) was suspected, and 28-days after an assessment of PD to confirm the progression.

Subjects on Dose Escalation and the Phase 1 Expansion had an assessment of baseline transfusion requirements, defined as red blood cell or platelet transfusions within 4 weeks prior

to and 4 weeks after the first dose of enasidenib. Subjects on Phase 2 also had an assessment of baseline transfusion requirements, but defined as red blood cell or platelet transfusions within 8 weeks prior to the first dose of enasidenib. All subjects were evaluated for red blood cell (RBC) and platelet requirements as well as associated hemoglobin levels and platelet counts at each disease response assessment time point.

All subjects who discontinued enasidenib were followed monthly for disease status, overall survival and initiation of non-study anti-neoplastic therapy until death, withdrawal of consent, or the end of the study, whichever occurred first.

Statistical Analysis Plan

The statistical analysis plan for Study AG221-C-001 was submitted while the trial was ongoing, and called for a primary analysis of efficacy and safety after all patients had received at least 6 cycles of enasidenib or had discontinued study therapy. Phase 1 (Dose Escalation and Phase 1 Expansion) was intended to be analyzed separately from Phase 2.

As Phase 2 was originally intended to be the pivotal portion of the study, the sample size for each part of the study was determined as follows:

- Dose Escalation: number of subjects required to assess 13 dose levels / schedules using 3+3 design = approximately 66 subjects
- Phase 1 Expansion: 25 subjects per arm yields 93% probability of detecting 1 or more adverse events with a true rate of 5%
- Phase 2: An overall response rate (ORR) of at least 33% in 125 subjects will result in an exact binomial 95% confidence interval (CI) with a lower bound greater than 25%, which the sponsor felt was clinically meaningful in this setting, and exceeded the ORR expected with available therapies (e.g., Roboz et al, 2014)

The primary efficacy endpoint of the study was the proportion of subjects who achieved an overall response, defined as complete remission (CR), complete remission with incomplete platelet recovery (CRp), complete remission with incomplete neutrophil recovery (CRi), morphologic leukemia-free state (MLFS), or partial remission (PR) by investigator assessment. The response rate was to be reported with 95% 2-sided confidence intervals.

Reviewer comment:

- *Overall response rate is not an accepted predictor of clinical benefit in patients with AML (Appelbaum et al, 2007).*

Key secondary efficacy endpoints were:

- Rate of CR/CRh (complete remission with incomplete hematologic recovery), derived by the sponsor using programmatic assessment of trial data supplemented by clinical review based on the modified IWG criteria as follows:

  - CR was defined as < 5% blasts in the bone marrow and full recovery of peripheral blood counts (platelets > 100 x 10^9/L and ANC > 1.0 x 10^9/L)
  - CRh was defined as < 5% blasts in the bone marrow and partial recovery of peripheral blood counts (platelets > 50 x 10^9/L and ANC > 0.5 x 10^9/L)
- Duration of response, defined as the date of the first documented response to the date of the first documented disease relapse, progression, or death due to any cause, whichever occurs first, in subjects with a response of CR, CRi, CRp, PR or MLFS by investigator assessment (or CR, CRh, PR or MLFS by sponsor assessment). Subjects without relapse, progressive disease, or death due to any cause were censored at the date of the last adequate response assessment;
- Rate of CR according to modified IWG criteria (the statistical analysis plan did not specify investigator-assessed versus applicant-derived); and
- OS, defined as the time from first dose to the date of death due to any cause. Subjects alive were censored at the last date known to be alive or the data cut-off date, whichever is earlier.

Other efficacy endpoints included event-free survival (EFS), duration of complete response (DOCR), time to response (TTR), time to best response (TTBR), and time to complete response (TTCR).

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 agents capable of producing minimal residual disease (MRD)-negative CRs.*

- *The predictive value of morphological remission with only partial hematologic recovery (CRh) is less clear, and may vary by clinical setting (Appelbaum et al, 2007). While CRh should not be used alone for regulatory decision making, durable CRh in relapsed/refractory leukemia may be considered evidence of disease palliation.*

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

- The Full Analysis Set (FAS) included all patients who 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 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 Evalulable Analysis Set (EAS) was used by the applicant for a sensitivity analysis of efficacy endpoints. It included all patients in the FAS for whom the baseline efficacy parameters (e.g., hematologic and bone marrow assessments) and at least 1 post-

baseline response assessment at Day 28 or later are available and evaluable and who have experienced no major protocol violations, defined as:

- Subject does not have an advanced hematologic malignancy
- Subject does not have documented IDH2 gene-mutated disease
- Subject received concomitant treatment for their malignancy other than enasidenib

For the purposes of NDA submission and in support of the proposed indication, the applicant's primary analysis was conducted on a subset of the FAS (Applicant Efficacy Analysis Set) consisting of patients with relapsed or refractory AML who were assigned to receive 100 mg total daily dose of enasidenib. Subjects with relapsed AML were defined as follows:

- Subjects who relapse after allogeneic transplantation
- Subjects in second or later relapse
- Subjects who relapse within 1 year of initial treatment, excluding subjects with favorable-risk status according to NCCN Guidelines (2015)

Subjects with refractory AML were defined as follows:

- Subjects who are refractory to initial induction or re-induction treatment
- Subjects who have failed 2 or more cycles of first-line therapy (consisting of an intermediate intensity chemotherapy, hypomethylating agent, or low-dose cytarabine)

The applicant's primary analysis was planned to be conducted after all subjects had completed at least 6 cycles of enasidenib or discontinued. The results of Phase 1 (Dose Escalation and Phase 1 Expansion) and Phase 2 were planned to be analyzed separately, and there was no planned interim analysis. Although the applicant originally intended Phase 2 to be the pivotal portion of the study, their analysis of data from Phase 1, with a data cut date of April 15, 2016, was submitted as the basis for the NDA to support the proposed indication due to the high unmet need in this patient population. During the course of the review, the FDA asked the applicant to analyze updated data from Phase 1 and Phase 2 together, and the applicant submitted additional information to comply with this request.

Efficacy Analysis

All efficacy analyses were performed on the FAS unless otherwise specified.

Efficacy analyses were primarily presented for the FAS for Phase 1 dose escalation by total daily dose groups, Part 1 expansion by cohorts, and the combined Phase 1 (Phase 1 dose escalation+Phase 1 expansion) by malignancy type and by total daily dose of < 100 mg, 100 mg, and > 100 mg in R/R AML.

Sensitivity analyses for key efficacy results were also performed in the FAS combined Phase 1, for subjects who finished at least 6 cycles of treatment or discontinued early, to assess the impact of the length of follow-up on efficacy results.

Analysis of Primary Efficacy Endpoint
The primary efficacy endpoint of ORR is defined as the rate of responses including complete response (CR), CR with incomplete neutrophil recovery (CRi), CR with incomplete platelet recovery (CRp), partial response (PR), marrow CR (mCR) (for MDS), and morphologic leukemia-free state (MLFS) (for AML), based on investigator assessment. The ORR in Phase 1 was summarized by the percentage of responses primarily in the FAS with 2-sided exact binomial 95% confidence interval (CI).

Response was also summarized by the best objective response categories following the hierarchical order of CR, CRi/CRp, PR, mCR/MLFS, stable disease, progressive disease/failure, and not evaluable (NE). The best response of CRi and CRp are of the same rank and thus, was reported as a single category. The best response of progressive disease (PD) and failure was grouped as PD.

An observed ORR in R/R AML subjects in the combined Phase 1 with the lower bound of the exact binomial 95% CI greater than 25% was deemed as clinically meaningful in this setting and exceeded the ORR expected with available therapies. This was considered to be evidence of clinically significant activity from AG-221.

Sensitivity Analyses
To assess the robustness of the primary analysis, the following sensitivity analyses were performed:

(1) ORR in the EAS for the combined Phase 1 and Phase 2.
(2) ORR in the FAS who have completed at least 6 cycles of treatment or have discontinued study treatment early.
(3) Sponsor-derived ORR in the FAS.

Analyses of Secondary Efficacy Endpoints
Kaplan-Meier (KM) method was utilized to estimate duration of responses and OS. Counts and percentages were used to describe categorical variables. Mean (standard deviation [SD]), median, and range were provided to descriptively summarize continuous variables.

Reviewer's Comments:
In general, OS is not interpretable in single arm studies.

Changes in the Planned Analyses
Changes which occurred after the final protocol amendment are described below.

- Interim analyses: As per Protocol Amendment 6, no formal interim analysis was planned. However, as of the cutoff date of April 15, 2016, almost all (173 out of 176) subjects with R/R AML have completed at least 6 cycles of treatment or discontinued earlier, which is the pre-specified duration of follow up for the primary analysis in protocol

- Secondary endpoints of CR/CRh and CR/CRh/PR were added.
- The investigators' overall ECG interpretation data were not summarized; these data are provided in a listing.

Efficacy analyses in this single-arm study are aimed to provide treatment effect estimates. Thus, multiplicity is not of concern for this study and time-to-event endpoints are not interpretable.

Key Protocol Amendments

The original protocol was dated June 3, 2013, and the first patient entered the study on September 20, 2013. Enrollment was completed in April 2016, with n=411 enrolled, but the study is still ongoing. The study was revised a total of 6 times between activation and the data cut-off date of October 14, 2016. Key protocol revisions are summarized as follows:

- Amendment 3 (dated April 16, 2014) added the Phase 1 expansion cohorts, added specific AML response criteria (Cheson et al, 2003), allowed patients who had previously received enasidenib on this protocol to re-enter the study if they relapsed after HSCT, and added the recommendation to avoid the use of antacids, H1 blockers or proton pump inhibitors while taking enasidenib based on emerging PK data.
- Amendment 4 (dated February 2, 2015) added Phase 2 to the study, and specified that information on red blood cell and platelet transfusions would be captured for subjects on Phase 2 for the 8-week period prior to first dose of study drug and during the treatment period. This amendment added an allowance for subjects who experience disease progression to continue on study drug if they are, in the opinion of the investigator, benefiting from treatment, and added guidelines for the management of QT prolongation and differentiation syndrome.
- Amendment 6 (dated October 14, 2015) added additional guidance for differentiation syndrome in cases in which subjects were affected by presumed infections requiring hospitalization that did not respond to anti-infective treatments or worsened in the first 48 hours.

7.2.2. Study Results

Compliance with Good Clinical Practices

The applicant provided attestation that this study was conducted in accordance with U.S. regulations governing the protection of human subjects, institutional review boards, and the obligations of clinical investigators in accordance with good clinical practice (GCP).

Financial Disclosure

A summary of financial disclosures for Study AG221-C-001 is provided in the appendix (Section 13.2). The applicant submitted financial disclosure information from 100% of investigators. Two principal investigators (sites (b) (6) and (b) (6) and 1 sub-investigator (site (b) (6) had financial

disclosures. All three disclosures were for grants in excess of $25,000 from the study sponsor to the investigator to fund ongoing research. Sites (b) (6) enrolled a total of (b) (6) patients, respectively. Site (b) (6) reported site-specific CR rates that were higher than the rates reported for the study population as a whole. Exclusion of the (b) (6) patients enrolled at that site from the primary efficacy analysis reduces the CR rate by approximately (b) (6)% and the CR/CRh rate by approximately (b) (6)%. This site was thus selected for FDA inspection. No irregularities were identified, and the site was classified as No Action Indicated by OSI. One additional sub-investigator at site (b) (6) from March 26, 2014 through July 31, 2014, became a full-time employee of the sponsor as of August 4, 2014. Although this site enrolled (b) (6) patients, the majority (n= (b) (6)) enrolled after July 31, 2014. Exclusion of the patients enrolled at sites (b) (6) from the primary efficacy analysis positively impacted the CR and the CR/CRh rates, and thus it does not appear that enrollment of patients by these investigators biased the outcome of the study in favor of enasidenib.

Methods

The FDA conducted an independent analysis of efficacy of enasidenib in relapsed or refractory IDH2+ AML using data from Study AG221-C-001, which was described in detail in Section 7.2.1. The FDA's analysis differed from the analysis provided by the applicant in the original NDA submission in the following ways:

- The FDA excluded 7 subjects from the analysis who did not have an IDH2 mutation identified by the Abbott RealTi*m*e IDH2™ mutation assay.
- The FDA used updated data sets, with a data cut date of October 14, 2016; this resulted in the addition of 7 subjects to the analysis as well as more matured response data from Phase 2, which had only a short duration of follow-up time in the original NDA.
- The FDA excluded CR/CRh responses that occurred only after HSCT.

Reviewer comments:

- *Due to the substantial differences between the analyses conducted by the applicant to support the NDA and those conducted by the FDA to confirm the findings, the applicant analyses presented in the original NDA are omitted from this review.*

- *As of the October 14, 2016, data cut date, 3 of the subjects on Study AG221-C-001 had not completed at least 6 cycles of enasidenib or discontinued, which is a violation of the pre-specified statistical analysis plan. These subjects were included in all FDA analyses.*

- *The FDA did not verify responses other than CR or CRh, as other responses cannot be considered as predictors of clinical benefit in relapsed or refractory AML.*

Patient Disposition

The first subject was enrolled on September 20, 2013. Of 411 patients screened for the study, 345 patients received at least one dose of enasidenib on Study AG221-C-001 and were included

in the applicant's FAS. Fifty-seven patients were screen failures. The most common reasons for screen failure were: diagnosis falling outside of the protocol-specified study population (n=19), IDH2-negative disease (n=10) and QTcF ≥ 450 msec or other factors that increase the risk of QT prolongation or arrhythmic events (n=8). Of the remaining 9 patients screened for the study but not included in the FAS, 8 never received any enasidenib, and 1 (Subject ID 201-024) was a subject that had previously been enrolled on the study under a different subject ID number, came off study for HSCT, then re-enrolled on the study after relapsing post-HSCT.

Of the 345 patients in the FAS, 207 were determined by the applicant to have relapsed or refractory AML and an IDH2 mutation identified by the companion diagnostic test, and were assigned to receive 100 mg of enasidenib total daily dose. These 207 patients were included in the FDA Efficacy Analysis Set. The reasons for treatment discontinuation are shown in Table 27. 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). The reason "primary disease" included disposition events coded as disease progression, persistent disease, lack of response/efficacy/benefit, change in therapy, transition to hospice/comfort care, or an adverse event with a preferred term related to the primary disease. The reason "adverse event" included disposition events coded as adverse event or admission to the intensive care unit, The reason "physician decision" included disposition events coded as: investigator removal in the best interest of the patient, poor performance status, medical condition that puts the subject at risk for continuing treatment or precludes further participation, and 2-HG level report.

Table 27: Reasons for Treatment Discontinuation

	Phase 1 N=103	Phase 2 N=104	Phase 1/2 Combined N=207
Therapy ongoing	8 (8%)	20 (19%)	28 (14%)
Discontinued therapy			
Primary disease	62 (60%)	45 (43%)	107 (52%)
Adverse event	12 (12%)	23 (22%)	35 (17%)
HSCT	12 (12%)	9 (9%)	21 (10%)
Withdrawal of consent	5 (5%)	3 (3%)	8 (4%)
Physician decision	4 (4%)	3 (3%)	7 (3%)
Missing	0	1 (1%)	1 (<1%)

Source: FDA analysis

All patients were to be followed for overall survival for at least 12 months after study treatment discontinuation. Investigators appeared to inconsistently include this survival follow-up period in their assessment of the study discontinuation date and reason for study discontinuation. For this reason, Table 28 describes the reasons for study discontinuation as determined by the FDA as follows: If death date is known, reason for study discontinuation was assigned as death. All other patients with no death date and study discontinuation flagged were assigned "withdrawal or other" unless study discontinuation reason was specifically described as lost to follow-up.

Table 28: Reasons for Study Discontinuation

	Phase 1 N=103	Phase 2 N=104	Phase 1/2 Combined N=207
Follow-up ongoing	17 (17%)	45 (43%)	60 (29%)
Discontinued study			
Death	64 (62%)	56 (54%)	122 (59%)
Withdrawal or other[1]	21 (20%)	2 (2%)	23 (11%)
Lost to follow-up	1 (1%)	1 (1%)	2 (1%)

Source: FDA analysis
[1]Includes subjects who completed the protocol-specified minimum of 12 months of follow-up

Protocol Violations/Deviations

The applicant classified divergences from the protocol as deviations (i.e., minor deviations) or violations (i.e., major deviations). A total of 1843 deviations were reported for 195 of the 207 subjects in the FDA's efficacy analysis set on Study AG221-C-001. Table 29 lists the number of deviations by broad criterion. The most common deviations were missing or late assessments or procedures (83%). For the purposes of assessment of the primary efficacy endpoint, subjects with missing disease assessment data were considered a failure.

Table 29: Protocol Deviations

	Minor	Major	Total
Subjects with Deviation	194/207 (94%)	37/207 (19%)	195/207 (94%)
# of Deviations	1795/1843 (97%)	48/1843 (3%)	1843/1843 (100%)
Deviations by Criterion			
Missing or late assessment/procedure	1532 (83%)	0	1532 (83%)
GCP issues[1]	117 (6%)	12 (<1%)	129 (7%)
Treatment error	81 (4%)	0	81 (4%)
Use of prohibited concomitant med	37 (2%)	25 (1%)	62 (3%)
Ineligible	13 (<1%)	10 (<1%)	25 (%)
Informed consent issues	11 (<1%)	0	11 (<1%)
Not withdrawn despite meeting criteria	2 (<1%)	0	2 (<1%)
Other	2 (<1%)	1 (<1%)	3 (<1%)

Source: FDA analysis
Abbreviations: GCP, Good Clinical Practice
[1] Failure to report serious adverse events, source documentation missing, equipment not calibrated or validated, etc.

The applicant identified 97% of the deviations as minor and 3% as major. The majority (52%) of the major deviations were related to the use of a prohibited concomitant medication. Other causes of major deviations were issues related to Good Clinical Practice (e.g., failure to report serious adverse event in a timely manner) or failure to meet eligibility criteria.

Reviewer comments:

- *The FDA requested information from the applicant that was required to confirm the*

eligibility and clinical responses of certain patients. This information was received very late in the review process. The FDA reviewed this documentation from subjects in the FDA Efficacy Analysis Set in order to confirm that at the time of study entry, all subjects met the established definition of relapse, specifically, ≥ 5% blasts in the marrow, circulating blasts in the peripheral blood, or extramedullary disease. The FDA identified 9 subjects for whom there was insufficient evidence to confirm active relapse at screening. However, as the majority of the review had been completed at this time, only key efficacy analyses required to confirm clinical benefit were repeated with the adjusted denominator and adjudicated best responses. These analyses are presented as an addendum to the efficacy review (Section 7.2.3).

Demographic and Other Characteristics

Selected baseline demographic characteristics of the subjects in the FDA Efficacy Analysis Set are summarized in Table 30. The median age of the subjects was 68 years (range: 19, 100 years), with 39% of the subjects < 65 years of age. There were 108 (52%) male subjects and the majority of subjects (77%) were white. The majority of subjects (84%) were from the United States.

Table 30: Demographic Characteristics

Parameter	Phase 1 N=103	Phase 2 N=104	Phase 1/2 Combined N=207
Sex			
Male	45 (44%)	63 (61%)	108 (52%)
Female	58 (56%)	41 (39%)	99 (48%)
Age			
Mean years (SD)	64.0 (12.4)	66.5 (11.9)	65.3 (13.0)
Median (years)	67	69	68
Min, max (years)	19, 100	32, 89	19, 100
Age Group			
< 65 years	47 (46%)	34 (33%)	81 (39%)
≥ 65 years	56 (54%)	70 (67%)	126 (61%)
Race			
White	83 (81%)	77 (74%)	160 (77%)
Black or African American	5 (5%)	6 (6%)	11 (5%)
Asian	1 (1%)	0	1 (<1%)
Hispanic or Latino	1 (1%)	0	1 (<1%)
Native Hawaiian or Other Pacific Islander	0	1 (1%)	1 (<1%)
Unknown	1 (1%)	0	1 (<1%)
Not provided	12 (12%)	20 (19%)	32 (15%)
Ethnicity			
Hispanic or Latino	12 (12%)	8 (8%)	20 (10%)
Not Hispanic or Latino	71 (69%)	59 (57%)	130 (63%)
Not Provided	20 (19%)	37 (36%)	57 (28%)

Parameter	Phase 1 N=103	Phase 2 N=104	Phase 1/2 Combined N=207
Region			
France	15 (15%)	19 (18%)	34 (16%)
United States	88 (85%)	85 (82%)	173 (84%)

Source: FDA Analysis

Other Baseline Characteristics

Selected baseline disease characteristics are summarized in Table 31. The majority of subjects had a baseline ECOG performance score of 1 (62%). The IDH2 gene mutation was in codon R140 in 76% of subjects and codon R172 in 23% of subjects as determined by the test used for assessing study eligibility. The majority of subjects had a cytogenetic risk status of intermediate-risk (49%) or poor-risk (27%). No subject had favorable-risk cytogenetics, although cytogenetic analyses failed in 3% and were missing in 21% of subjects.

All subjects had received a prior systemic anticancer therapy; the majority of subjects had received either 1 (45%) or 2 (31%) prior regimens.

Table 31: Baseline Disease Characteristics

Parameter	Phase 1 N=103	Phase 2 N=104	Phase 1/2 Combined N=207
ECOG PS			
0	24 (23%)	24 (23%)	48 (23%)
1	64 (62%)	64 (62%)	128 (62%)
2	15 (15%)	15 (14%)	30 (15%)
Missing	0	1 (1%)	1 (<1%)
Gene Mutation (IDH2)			
R140	81 (79%)	77 (74%)	158 (76%)
R172	22 (21%)	25 (24%)	47 (23%)
Unknown	0	2 (2%)	2 (1%)
UGT1A1 Mutation Status			
Heterozygous	4 (4%)	20 (19%)	24 (12%)
Homozygous	2 (2%)	10 (10%)	12 (6%)
Wild Type	0	19 (18%)	19 (9%)
Not Available/Missing	97 (94%)	55 (53%)	152 (73%)
R/R AML Characteristic			
Relapse after allogeneic HSCT	11 (12%)	17 (17%)	28 (15%)
Second or later relapse	12 (13%)	13 (13%)	25 (13%)
Refractory to induction/re-induction	35 (39%)	28 (28%)	63 (33%)
Relapsed within 1 year of treatment[1]	25 (28%)	28 (28%)	53 (28%)
Failed ≥ 2 cycles first-line therapy[2]	22 (24%)	32 (32%)	54 (29%)

Parameter	Phase 1 N=103	Phase 2 N=104	Phase 1/2 Combined N=207
Prior Systemic Anti-Cancer Therapies			
Yes	103 (100%)	104 (100%)	207 (100%)
No	0	0	0
Number of Prior Anti-Cancer Regimen			
1	54 (52%)	40 (38%)	94 (45%)
2	26 (25%)	39 (37%)	65 (31%)
3	14 (14%)	14 (13%)	28 (14%)
4	4 (4%)	9 (9%)	13 (6%)
≥ 5	5 (5%)	2 (2%)	7 (3%)
Prior Stem Cell Transplantation			
Yes	11 (11%)	17 (16%)	28 (14%)
Autologous	1 (9%)	0	1 (4%)
Allogeneic	9 (82%)	16 (94%)	25 (89%)
Other	0	1 (6%)	1 (4%)
Missing	1 (9%)	0	1 (4%)
No	92 (89%)	87 (84%)	179 (87%)
Cytogenetic Risk Status			
Favorable-Risk	0	0	0
Intermediate-Risk	46 (45%)	56 (53%)	102 (49%)
Poor-Risk	29 (28%)	26 (25%)	55 (27%)
Failure	2 (2%)	5 (5%)	7 (3%)
Missing	26 (25%)	17 (16%)	43 (21%)
Time (month) from Last Prior HSCT to First Dose of Treatment			
N	11	14	25
Mean (SD)	18.8 (13.49)	21.4 (16.09)	20.2 (14.76)
Median	11.3	17.0	16.8
Min, Max	4.8, 39.1	6.4, 53.5	4.8, 53.5
Bone Marrow Blasts, Local			
Mean (SD)	49.0 (28.01)	47 (29.01)	47.9 (28.5)
Median	49.0	46.0	47
Min, Max	0.0, 96.0	1.0, 98.0	(0.0, 98.0)
Hemoglobin (g/L)			
Mean (SD)	94.1 (13.90)	92.1 (14.75)	93.1 (14.33)
Median	93.0	89.0	90.5
Min, Max	(69.0, 138.0)	70.0, 156.0	69.0, 156.0
Number of RBC Transfusions[3]			
0	22 (21%)	38 (37%)	60 (29%)
1	9 (9%)	19 (18%)	28 (14%)
2	15 (15%)	12 (11%)	27 (13%)
3	18 (18%)	12 (11%)	30 (15%)
4	4 (4%)	4 (4%)	8 (4%)
≥ 5	35 (34%)	19 (18%)	54 (26%)

Parameter	Phase 1 N=103	Phase 2 N=104	Phase 1/2 Combined N=207
Number of Platelet Transfusions[3]			
0	33 (32%)	45 (43%)	78 (36%)
1	10 (10%)	15 (14%)	25 (12%)
2	11 (11%)	10 (10%)	21 (10%)
3	6 (6%)	3 (3%)	9 (4%)
4	5 (5%)	5 (5%)	10 (5%)
≥ 5	38 (37%)	26 (25%)	64 (31%)

Source: FDA analysis
[1]Of initial treatment, excluding subjects with favorable-risk status according to NCCN guidelines
[2]Consisting of intermediate intensity chemotherapy, hypomethylating agent, or low-dose cytarabine
[3]Within the four weeks prior to the first dose of enasidenib, for all subjects

Reviewer's comment:

- *Overall, no clinically meaningful differences were observed in demographic and disease-related characteristics between Phase 1 and Phase 2 studies, except that the number of RBC and platelet transfusions required during the baseline assessment was numerically higher for subjects in Phase 1.*

Treatment Compliance

The median dose-intensity of enasidenib was 100% of the planned dose, regardless of cycle, across Phases 1 and 2 of the study. Table 32 provides a summary of the dose-intensity by cycle. With the exception of cycle 2, fewer than 5% of the subjects in each cycle received less than 80% of the planned dose. Subjects with dose intensity > 120% are those who underwent per-protocol dose intrapatient dose escalations, and do not represent dosing errors.

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

Cycle	Phase 1 N=103 Subjects	Phase 1 N=103 Dose intensity < 80%	Phase 1 N=103 Dose intensity > 120%	Phase 2 N=104 Subjects	Phase 2 N=104 Dose intensity < 80%	Phase 2 N=104 Dose intensity > 120%	Phase 1/2 Combined N=207 Subjects	Phase 1/2 Combined N=207 Dose intensity < 80%	Phase 1/2 Combined N=207 Dose intensity > 120%
1	103	5	0	104	4	0	207	9	0
2	94	7	1	93	10	4	187	17	5
3	82	2	12	80	3	19	162	5	31
4	73	1	24	68	3	19	141	4	43
5	61	2	24	55	2	15	116	4	39
6	51	1	21	45	4	12	96	5	33
7	42	0	18	29	3	6	71	3	24
8	31	0	12	22	2	3	53	2	15
9	26	0	9	14	1	3	40	1	12
10	23	0	8	10	1	4	33	1	12
11	21	0	7	7	1	4	28	1	11

Cycle	Phase 1 N=103 Subjects	Phase 1 N=103 Dose intensity < 80%	Phase 1 N=103 Dose intensity > 120%	Phase 2 N=104 Subjects	Phase 2 N=104 Dose intensity < 80%	Phase 2 N=104 Dose intensity > 120%	Phase 1/2 Combined N=207 Subjects	Phase 1/2 Combined N=207 Dose intensity < 80%	Phase 1/2 Combined N=207 Dose intensity > 120%
12	18	0	7	6	1	4	24	1	11
> 12	17	0	6	6	1	4	23	1	10

Source: FDA analysis

Efficacy Results – Primary Endpoint and Key Secondary Endpoints

Statistical Methodologies
All efficacy analyses were performed in the FAS unless otherwise specified. Due to short follow-up in Phase 2, all efficacy endpoints were separately analyzed for the Phase 1 and Phase 2 portions of study.

Reviewer's Comments: The investigator assessed overall response (ORR) efficacy endpoint was the primary analysis endpoint per the final SAP. However, based on current understanding, the ORR does not predict clinical benefit in patients with AML. The complete response is an accepted clinical meaningful endpoint beneficial in patients with AML. In addition, since many of the investigator responses are inconsistent with the response criteria, the FDA therefore considers the sponsor assessed CR/CRh as a primary efficacy endpoint which will be included in the labeling. The analyses of investigator assessed efficacy endpoints are considered as sensitivity analyses.

FDA pooled analysis of Phase 1 and Phase 2 study is also included in this review report. The rationale for pooling from different studies was based on consistency of demographic and baseline disease characteristics of the trial populations, same dose regimen between two trials, and consistent improvements in investigator assessed CR and durability of the response across the two trials.

The investigator-assessed CR, ORR and duration of response are presented in Table 33.

For complete response rate:

- In the Phase 1 study, treatment with 100 mg enasidenib daily resulted in CR of 18.4% with 95% CI of (11.5, 27.3), using binomial proportion Clopper-Pearson exact method.
- In the Phase 2 study, treatment with 100 mg enasidenib daily resulted in CR of 20.2% with 95% CI of (13.0, 29.2), using binomial proportion Clopper-Pearson exact method.
- After combining Phase 1 and Phase 2 studies, treatment with 100 mg enasidenib daily resulted in CR of 19.3% with 95% CI of (14.2,25.4), using binomial proportion Cloper-Pearson exact method.

For overall response (CR+CRi+CRp+PR+mCR+MLF) rate:

- In the Phase 1 study, treatment with 100 mg enasidenib daily resulted in ORR of 38.8% with 95% CI of (29.4,48.9), using binomial proportion Clopper-Pearson exact method.
- In the Phase 2 study, treatment with 100 mg enasidenib daily resulted in CR of 34.6% with 95% CI of (25.3, 44.2), using binomial proportion Clopper-Pearson exact method.
- After combining Phase 1 and Phase 2 studies, treatment with 100 mg enasidenib daily resulted in CR of 36.7% with 95% CI of (30.1, 43.7), using binomial proportion Clopper-Pearson exact method.

Table 33: Summary of Efficacy Endpoint-Investigator's Assessment

	Phase 1 N=103	Phase 2 N=104	Phase 1/2 Combined N=207
Complete Response	19 (18.4)	21 (20.2)	40 (19.3)
95% CI	(11.5, 27.3)	(13.0, 29.2)	(14.2, 25.4)
Median Duration of Response (months)	NA	6.5	8.8
95% CI	(6.6, NA)	(3.7, NA)	(5.6, NA)
Overall Response Rate	40 (38.8)	36 (34.6)	76 (36.7)
95% CI	(29.4, 48.9)	(25.3, 44.2)	(30.1, 43.7)
Median Duration of Response (months)	6.6	5.6	5.6
95% CI	(3.8, 17.1)	(2.8, NA)	(4.6, 8.8)

Reviewer's Comments:
In the population of R/R AML subjects who received 100 mg enasidenib daily and were IDH2 positive, the investigator assessed CR rate was similar between Phase 1 and Phase 2 study. The median duration of CR for the combined Phase 1 & Phase 2 study was 8.8 months with 95% CI of (5.6, NA) using KM method.

The reviewer's summary of sponsor-assessed CR, CRh, ORR and duration of response are presented in the table below.

For complete response rate:

- In the Phase 1 study, treatment with 100 mg enasidenib daily resulted in CR of 16.5% with 95% CI of (10.7, 26.2), using binomial proportion Clopper-Pearson exact method.
- In the Phase 2 study, treatment with 100 mg enasidenib daily resulted in CR of 12.5% with 95% CI of (6.8. 20.4), using binomial proportion Clopper-Pearson exact method.
- After combining Phase 1 and Phase 2 studies, treatment with 100 mg enasidenib daily resulted in CR of 14.5% with 95% CI of (10.0, 20.0), using binomial proportion Cloper-Pearson exact method.

For overall response (CR+CRi+CRp+PR+mCR+MLF) rate:

- In the Phase 1 study, treatment with 100 mg enasidenib daily resulted in ORR of 31.1% with 95% CI of (22.3, 40.9), using binomial proportion Clopper-Pearson exact method.
- In the Phase 2 study, treatment with 100 mg enasidenib daily resulted in CR of 29.8% with 95% CI of (21.2, 39.6), using binomial proportion Clopper-Pearson exact method.

- After combining Phase 1 and Phase 2 studies, treatment with 100 mg enasidenib daily resulted in CR of 30.4% with 95% CI of (24.3, 37.2), using binomial proportion Clopper-Pearson exact method.

For CRh rate:

- In the Phase 1 study, treatment with 100 mg enasidenib daily resulted in ORR of 5.8% with 95% CI of (2.2, 12.3), using binomial proportion Clopper-Pearson exact method.
- In the Phase 2 study, treatment with 100 mg enasidenib daily resulted in CR of 4.8% with 95% CI of (1.6, 10.9), using binomial proportion Clopper-Pearson exact method.
- After combining Phase 1 and Phase 2 studies, treatment with 100 mg enasidenib daily resulted in CR of 5.3% with 95% CI of (2.7, 9.3), using binomial proportion Clopper-Pearson exact method.

Table 34: Summary of Efficacy Endpoint-Sponsor's Assessment

	Phase 1 N=103	Phase 2 N=104	Phase 1/2 Combined N=207
Complete Response	17 (16.5)	13 (12.5)	30 (14.5)
95% CI	(9.9, 25.1)	(6.8, 20.4)	(10.0, 20.0)
Median Duration of Response (months)	11.5	6.5	9.7
95% CI	(5.5, NA)	(3.7, NA)	(5.5, NA)
(Range)	(1.4-16.7)	(1.0-8.4)	(1.0-16.7)
Overall Response Rate	32 (31.1)	31 (29.8)	63 (30.4)
95% CI	(22.3, 40.9)	(21.2, 39.6)	(24.3, 37.2)
Median Duration of Response (months)	5.6	5.6	5.6
95% CI	(2.6, 11.5)	(3.7, NA)	(3.7, 9.7)
CRh	6 (5.8)	5 (4.8)	11 (5.3)
95% CI	(2.2, 12.3)	(1.6, 10.9)	(2.7, 9.3)
Median Duration of Response (months)	5.1	NA	5.1
95% CI	(1.0, NA)	(0.8, NA)	(1.0, NA)
(Range)	(1.0-8.3)	(0.8-5.6)	(0.8-8.3)
CR/CRh	23 (22.3)	18 (17.3)	41 (19.8)
95% CI	(14.7, 31.6)	(10.6, 26.0)	(14.6, 25.9)
Median Duration of Response (month)	9.7	6.5	8.8
95% CI	(5.4, NA)	(3.7, NA)	(5.4, NA)
(Range)	(1.0-16.7)	(0.8-8.4)	(0.8-16.7)
Median Follow-up (month)	8.3	5.5	6.7
(Range)	(0.7, 27.7)	(0.4, 12.4)	(0.4, 27.07)

Source: FDA analysis

Reviewer's Comments:

- *In the population of R/R AML subjects who received 100 mg enasidenib daily and were IDH2 positive, there was numerical a difference for the sponsor assessed CR rates between Phase 1 (16.5%) and Phase 2 (12.5%). The median duration of CR for the combined Phase 1 & Phase 2 was 9.7 months with 95% CI of (5.5, NA) using the KM*

method. However, the estimated median durations of response were different between Phase 1 (11.5 months) and Phase 2 (6.5 months). The median follow-up times were different between Phase 1 (8.3 months) study and Phase 2 (5.5 months) study. The differences in response rates and durations of response indicate variations between the two trials. Caution should be exercised in the interpretation of the pooled results.

Efficacy Results – Secondary and other relevant endpoints

Time to First and Best Response, Duration of Treatment

Investigator Assessed Response

The time to first response, time to best response, and duration of treatment for subjects who achieved a best response of CR or an overall response (i.e. ORR) is presented in the table below

For subjects who achieved a best response of CR, the median time to first response was 1.9 months

- For both Phase 1 and combined Phase 1 and Phase 2 studies, the median time to first response was 1.9 month.
- For Phase 2 study, the median time to first response was 2.8 month.

For subjects who achieved an overall response, the median time to first response was 1.9 month for Phase 1, Phase 2 and combined Phase 1 and Phase 2 studies.

Table 35: Summary of Time to Response Analysis –Investigator's Assessment

	Phase 1 N=103		Phase 2 N=104		Phase 1/2 Combined N=207	
	CR n=17 (18.5%)	ORR n=40 (38.8%)	CR n=13 (20.2%)	ORR n=36 (35.2%)	CR n=40 (19.3%)	ORR n=76 (36.75)
Time to first response (months)						
Median	1.9	1.9	2.8	1.9	1.9	1.9
Min, Max	0.5, 7.5	0.5, 11.1	0.9, 4.6	0.9, 5.5	0.5, 7.5	0.5, 11.1
Time to best response (months)						
Median	3.7	3.7	3.7	3.7	3.7	3.7
Min, Max	0.7, 11.2	0.6, 11.2	0.9, 5.5	0.9, 5.5	0.7, 11.2	0.6, 11.2
Duration of treatment (months)						
Median	12.8	7.5	7.1	6.6	8.8	6.9
Min, Max	3.7, 23.6	1.8, 23.6	3.5, 12.3	2.1, 12.3	3.5, 23.6	1.8, 23.6

Source: FDA analysis

Sponsor Assessed Response

The reviewer's summary of the time to first response, time to best response, and duration of treatment for subjects who achieved a best response of CR, CRh and CR/CRh are presented in Table 36.

For subjects who achieved a best response of CR, the median time to first response was 1.9 months

- For both Phase 1 and combined Phase 1 and Phase 2 studies, the median time to first response was 1.9 month.
- For Phase 2 study, the median time to first response was 2.8 month.

For subjects who achieved first response of CRh, the median time to first response was 1.8 month for Phase 1, Phase 2 and combined Phase 1 and Phase 2 studies.

Table 36: Summary of Time to Response Analysis –Sponsor's Assessment

	Phase 1 N=103	Phase 2 N=104	Phase 1/2 Combined N=207
Subjects with best response CR			
Time to First Response (months)			
Median	1.9	2.8	1.9
Min, Max	0.5, 7.5	0.9, 3.8	0.5, 7.5
Time to Best Response			
Median	3.7	4.6	3.7
Min, Max	0.6, 11.2	0.9, 8.3	0.6, 11.2
Subjects with best response CRh			
Time to First Response (months)			
Median	1.8	1.8	1.8
Min, Max	0.9, 3.7	0.9, 2.8	0.9, 3.7
Time to Best Response			
Median	2.6	2.8	2.8
Min, Max	1.0, 9.2	0.9, 5.5	0.9, 9.2
Subjects with best response CR/CRh			
Time to First Response (months)			
Median	1.8	2.8	1.9
Min, Max	0.5, 7.5	0.9, 3.8	0.5, 7.5
Time to Best Response			
Median	3.7	3.7	3.7
Min, Max	0.6, 11.2	0.9, 8.3	0.9, 8.3

Source: FDA analysis

Reviewer's Comments:
In the population of R/R AML subjects who received 100 mg daily and were IDH2 positive, the median time to best response in subjects who achieved a CR was the same between Phase 1 and Phase 2 studies; the median time to first response in CR endpoint between Phase 1 and Phase 2 studies were different (1.9 month for Phase 1 study, 2.8 month for Phase 2 study).

Table 37 shows the reviewer's exploratory analysis results of sponsor's assessed CR/CRh by cycle.

Table 37: Summary of Sponsor's Assessed CR/CRh by Cycle

Cycle	Exposed n	CR n (%)	CRh n (%)	CR/CRh n (%)
1	207	2 (1.0)	0 (0.0)	2 (1.0)
2	187	2 (1.1)	2 (1.0)	4 (2.1)
3	162	2 (1.2)	1 (0.9)	5 (3.1)
4	141	1 (0.7)	2 (1.4)	3 (2.1)
5	117	9 (7.7)	1 (0.9)	10 (8.5)
6	97	4 (4.1)	1 (1.0)	5 (5.2)

Source: FDA analysis

Reviewer's Comments:
FDA's analysis results for the sponsor's assessed CR show that there is a slight trend in the improvement of response as the treatment cycle increases in the pooled data of Phase 1 study and Phase 2 study. However, such an analysis is exploratory in nature, because this is not a pre-specified analysis and it may reflect the selected subgroup results in later cycles as more patients were lost-to-follow-up or dead. In addition, there is no guarantee that the study was properly powered for such interpretations. By breaking down the results by cycle and making clinical inferences based on such analyses could be misleading. In other words, the results may be only useful as reference for future studies.

Transfusion

Baseline and post baseline RBC transfusion status during any 56-day period is summarized in the table below. In the combined Phase 1 & 2 population, 58 subjects (39.5%) who were RBC transfusion dependent at baseline became RBC transfusion independent during 56 day post baseline period.

Table 38: Summary of RBC Transfusion Status

Baseline Transfusion Status	N	Postbaseline Transfusion Status Phase 1/2 Combined (N=207) Independent N (%)	Dependent N (%)
Dependent	147	58 (39.5)	89 (60.5)
Independent	60	39 (65.0)	21 (35.0)

Source: FDA analysis

Baseline and post baseline platelet transfusion status during any 56-day period is summarized in the table below. In the combined Phase 1 & 2 population, 46 subjects (35.7%) who were platelet transfusion dependent at baseline became platelet transfusion independent during 56 day post baseline period.

Table 39: Summary of Platelet Transfusion Status

Baseline Transfusion Status	N	Postbaseline Transfusion Status Phase 1/2 Combined (N=207) Independent N (%)	Dependent N (%)
Dependent	129	46 (35.7)	83 (64.3)
Independent	78	57 (73.1)	21 (26.9)

Overall Survival

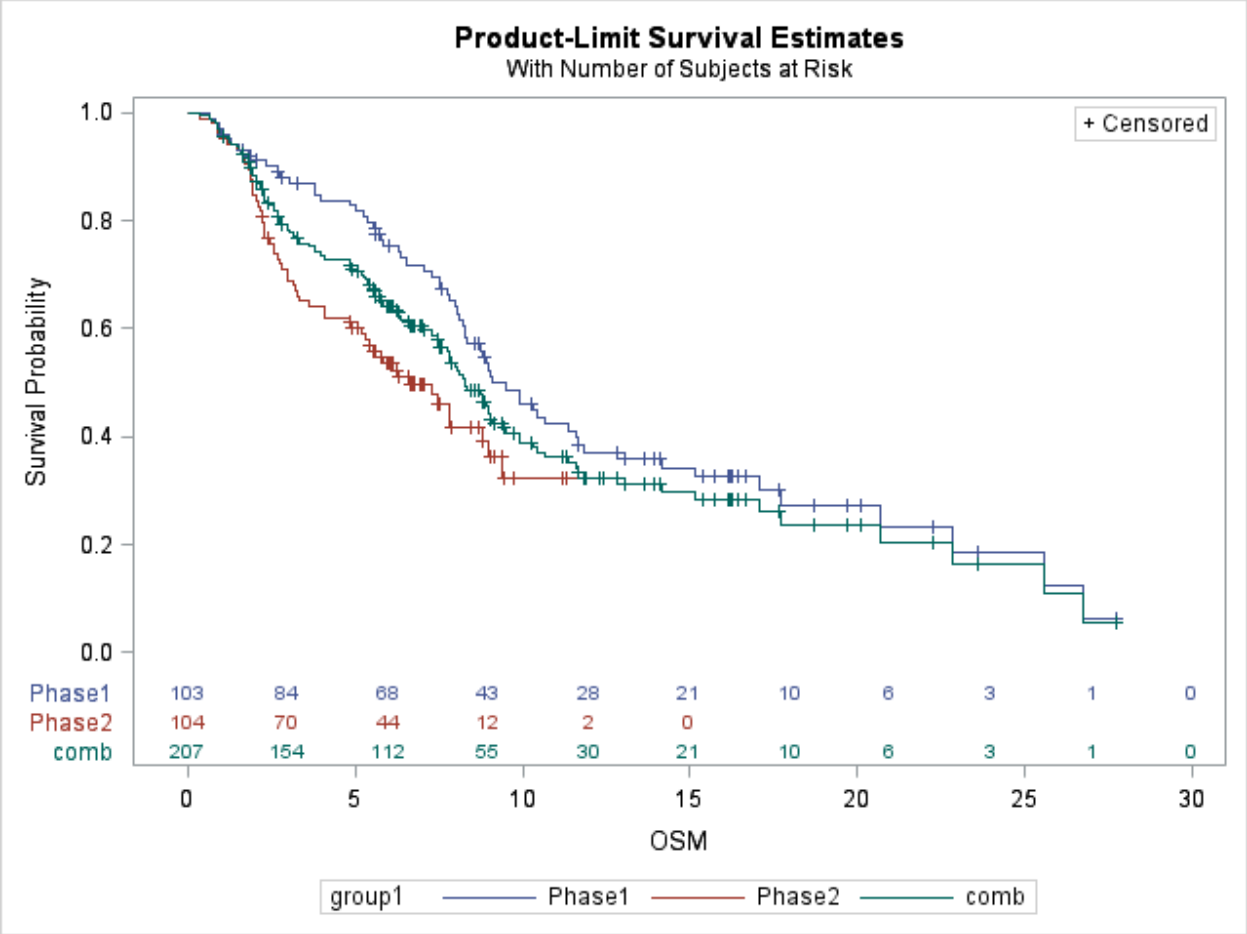
There were more deaths in Phase 1 population (63.1%) compared to those from Phase 2 population (54.8%). The estimated median OS in the Phase 2 population of 6.6 months was shorter in comparison with Phase 1 population (9.1 months) (Table 40**).**

Table 40: Summary of Analysis Results for Overall Survival

	Phase 1 N=103	Phase 2 N=104	Phase 1/2 Combined N=207
Number of deaths	65 (63.1)	57 (54.8)	122 (58.9)
Median survival time (months)	9.1	6.6	8.3
95% CI	(8.2, 11.6)	(4.9, 9.0)	(7.5, 9.4)

Figure 17 shows a Kaplan-Meier plot for OS by Phase 1, Phase 2, and combined Phase 1 & 2.

Figure 17: Kaplan-Meier Plot for Overall Survival



Source: FDA analysis

Reviewer's comments: The two survival curves of Phase 1 and Phase 2 studies suggest potential differences in follow-up and patient population. However, time-to-event endpoints such as overall survival are not interpretable in single arm studies as it includes natural history of the disease.

Subgroup Analyses

Table 41 summarizes the reviewer's subgroup analyses. The treatment effect on both investigator assessed CR and sponsor assessed CR for combined Phase 1 & 2 was investigated for the selected subgroup of age, gender, region, race, baseline ECOG PS, prior history of MDS, WHO classification of AML, prior HSCT for AML, IDH2 gene mutation type, baseline cytogenetic risk status, and number of prior AML therapies.

Table 41: Subgroup Analyses by Age, Gender, Race and Region for CR-Investigator Assessment

n/N (%)	Complete Response Rate N=199	95% CI
Age		
<=65	6/81 (7.4)	2.8, 15.4
>65	34/126 (27.0)	19.5, 35.6
Sex		
Male	22/108 (20.4)	13.2, 29.2
Female	18/99 (18.2)	11.1, 27.2
Region		
United states	31/173 (17.9)	12.5, 24.5
France	9/34 (26.5)	12.9, 44.4
Race		
White	31/160 (19.4)	13.6, 26.4
Non-White	2/15 (13.3)	1.7, 40.5
Not-Provided	7/31 (21.9)	9.3, 40.0

Source: FDA analysis

Table 42: Subgroup Analyses by Baseline Disease Characteristic for CR-Investigator Assessment

n/N (%)	Complete Response Rate N=207	95% CI
Prior History of MDS		
Yes	4/46 (8.7)	2.4, 20.8
No	36/161 (22.4)	16.2, 29.6
Prior HSCT for AML		
Yes	8/28 (28.6)	13.2, 48.7
No	32/179	12.6, 24.3
ECOG Performance Status		
O	13/48 (27.1)	15.3, 41.8
1	17/128 (13.3)	7.9, 20.4
2	9/30 (30.0)	14.7, 49.4
WHO Classification of AML		
Class 1	6/28	8.3, 41.0
Class 2	5/44	3.8, 24.6
Class 3	1/5	0.5, 71.6
Class 4	26/110 (23.6)	16.1, 32.7
Baseline Cytogenetic Risk Status		
Favorable Risk	NA	
Intermediate Risk	23/102	14.9, 31.9
Poor Risk	5/55	3.0, 20.0
Failure	3/7	9.9, 81.6
IDH2 Gene Mutation Type		
R140	29/158 (18.4)	12.7, 25.3
R172	10/47 (21.3)	10.7, 35.7

Source: FDA analysis

Table 43: Subgroup Analyses by Age, Gender, Race and Region for CR-Sponsor's Assessment

n/N (%)	Complete Response Rate N=207	95% CI
Age		
<=65	6/81 (7.4)	2.8, 15.4
>65	24/126 (19.1)	12.6, 27.0
Sex		
Male	15/108 (13.9)	8.0, 21.9
Female	15/99 (15.2)	8.7, 23.8
Region		
United states	21/173 (12.1)	7.7, 18.0
France	9/34 (26.5)	12.9, 44.4
Race		
Not Hispanic or Latino	17/130 (13.1)	7.8, 20.1
Hispanic or Latino	2/20 (10.0)	1.2, 31.7
Not-Provided	11/57 (19.3)	10.1, 31.9

Source: FDA analysis

Table 44: Subgroup Analyses by Bassline Disease Characteristic for CR-Sponsor's Assessment

n/N (%)	Complete Response Rate N=207	95% CI
Number of Prior History of MDS		
Yes	1/46 (8.7)	0.1, 11.5
No	26/161 (18.0)	12.4, 24.8
Prior HSCT for AML		
Yes	5/28 (17.9)	6.1, 36.9
No	25/179 (14.0)	9.3, 19.9
ECOG Performance Status		
O	9/48 (18.8)	9.0, 32.6
1	14/128 (10.9)	6.1, 17.7
2	7/30 (23.3)	9.9, 42.3
WHO Classification of AML		
Class 1	5/28 (17.9)	6.1, 36.9
Class 2	3/44 (6.8)	1.4, 18.7
Class 3	2/5 (40.0)	5.3, 85.3
Class 4	19/110 (17.3)	10.7, 25.7
Baseline Cytogenetic Risk Status		
Favorable Risk	NA	
Intermediate Risk	18/102 (17.7)	10.8, 26.4
Poor Risk	2/55 (3.6)	0.4, 12.5
Failure	3/7 (42.9)	9.9, 81.6
IDH2 Gene Mutation Type		
R140	21/158 (13.3)	8.4, 19.6
R172	8/47 (17.0)	7.7, 30.8

Source: FDA analysis

Reviewer's Comments:

- *In general, the sponsor assessed CRs appear to be supportive of the primary finding. A lower CR rate was observed in patients <=65 years. These are exploratory analyses and no inference may be drawn.*

- *In general, the sponsor assessed CRs are also supportive of the primary findings in various disease characteristic subgroups.*

There were several other key analyses conducted by the sponsor that contributed to the FDA's evaluation of effectiveness of enasidenib at the proposed dose of 100 mg daily:

- On Study AG221-C-001, subjects in Phase 1 Expansion or Phase 2 were allowed to increase their dose to 200 mg daily if certain criteria were met. The applicant analyzed responses over time subjects who underwent dose increase, and found that an increase to the higher 200 mg dose was not associated with better objective responses. The FDA agreed with this assessment.
- MRD was assessed by flow cytometry and variant allele frequency (by next generation sequencing, NGS) in an academic research laboratory on an exploratory basis in 8 of the subjects who achieved a CR on Study AG221-C-001. All 8 subjects were flow-MRD positive at best response, with concomitant IDH2 mutation detected by NGS.

Reviewer comments:

- *The observation that dose increases did not produce more frequent or deeper responses in patients treated with enasidenib is supported by lack of an exposure-response relationship (see Section 13.4.3). Thus, although intra-patient dose escalation occurred extensively on study AG221-C-001, there are no data to suggest that patients who are not on a clinical trial should increase the dose in the event of inadequate response.*

- *The persistence of MRD in subjects with CR is consistent with the applicant's hypothesis that enasidenib acts as a differentiating agent. As MRD was generally not assessed in studies of other agents in AML as described in Section 2.2, it is difficult to know whether the CRs produced by enasidenib are "lesser" than those produced by chemotherapy or hypomethylating agents. In the absence of such data, it seems reasonable to conclude that durable CRs on this trial should be interpreted as a reliable indicator of clinical benefit.*

7.2.3. Study Results Addendum

As stated earlier in this review, the FDA reviewed documentation from subjects in the planned efficacy population, including documentation provided by the applicant very late the review process, in order to confirm that at the time of study entry, all subjects met the established definition of relapse, specifically, ≥ 5% blasts in the marrow, circulating blasts in the peripheral

blood, or extramedullary disease. The FDA identified 9 subjects (102-003, 102-008, 102-012, 108-013, 111-053, 111-057, 113-004, 201-036, and 900-006) for which there was insufficient evidence to confirm active relapse at screening. In the process of reviewing this documentation, it was also discovered that one subject (108-003) that was originally identified by the applicant as not having an IDH2 mutation identified by the Abbott RealTi*me* IDH2™ mutation assay did, in fact, have a mutation identified by the assay.

After removing the 9 subjects without confirmed active relapse at screening, and adding back the 1 additional subject confirmed to be IDH2+ by the companion diagnostic, key efficacy analyses were repeated in the remaining 199 subjects (Final FDA Efficacy Analysis Set).

The FDA's analysis of efficacy was based on the key secondary endpoint of CR/CRh in the Final FDA Efficacy Analysis Set. As CRh is not included in the IWG response criteria and was therefore not an investigator-assessed response, subjects with best response of CRh (n=12, 6.0%) were programmatically identified by the applicant and confirmed by the FDA based on hematologic laboratory values, transfusion requirements, and bone marrow blast counts.

Forty of the 199 subjects (20.1%) in the FDA's Final Efficacy Analysis Set had a best response of CR as determined by the investigator, excluding two subjects who had a best response of CR only after HSCT. The applicant programmatically identified CR in 30 subjects (15.1%), and the FDA agreed. There were 10 subjects with discordant determinations of CR by investigator-determination compared to programmatic identification. The applicant adjudicated these discordances, and concluded that 8 represented "true" CRs, 1 a "true" CRh, and 1 a "true" SD (Table 45). The applicant provided additional supportive information (including pathology reports) upon FDA request to enable review of these adjudicated responses, and the FDA agreed with the applicant's adjudication in all 10 cases (Table 45).

Table 45: FDA Adjudication of Discordant Determinations of CR

Subject	Investigator-determined Response	Applicant-derived Response	Applicant-adjudicated Response	Reason for discrepancy and summary of supporting data	FDA Response
Phase 1					
105-016	CR	SD	CR	CR was assessed at an unscheduled visit, which was not included in programmatic derivation. FDA confirmed that on Day 91 BM blast count < 5% and Auer rods absent, and that on Day 99, platelet count was 131 and ANC 1200 without transfusions.	CR

Subject	Investigator-determined Response	Applicant-derived Response	Applicant-adjudicated Response	Reason for discrepancy and summary of supporting data	FDA Response
106-005[1]	PD	CR	CR	Per protocol, responses after PD not included in assessment of best response. Subject had initial assessment of PD (not verified by 2nd BM), but remained on enasidenib, and achieved CR after PD. FDA confirmed that on Day 116, subject met all criteria for CR.	CR
110-001	CR	CRh	CR	Met all other criteria for CR but absence or presence of Auer rods not reported. FDA confirmed that on Day 106, all other criteria for CR were met. FDA also noted that on the screening, Day 18 and Day 32 BM biopsies, blasts were present but Auer rods were reported as negative. It is unlikely that Auer rods would appear on Day 106, particularly in the absence of rising blast counts.	CR
Phase 2					
101-008	CR	SD	SD	The applicant noted that at the time of investigator-assessed CR, the BM blast count was 10%. The FDA agreed.	SD
104-058	CR	NE	CR	Baseline blast count was < 5%, below criteria for relapsed AML diagnosis. The applicant provided a pathology report demonstrating that relapse was in the form of leukemia cutis. Patients with only extra-medullary relapse were eligible for the study on Phase 2. The investigator reported that leukemia cutis resolved with treatment at Cycle 5 Day 1 (Day 113). The FDA confirmed that on Day 113, all other criteria for CR were met.	CR
106-012	CR	CRh	CR	Met all other criteria for CR but absence or presence of Auer rods not reported. FDA confirmed that on Day 113, all other criteria for CR were met. FDA also noted that on the screening and Day 57 BM biopsies, blasts were present but Auer rods were reported as negative. It is unlikely that Auer rods would appear on Day 113, particularly in the absence of rising blast counts.	CR

Subject	Investigator-determined Response	Applicant-derived Response	Applicant-adjudicated Response	Reason for discrepancy and summary of supporting data	FDA Response
108-009	CR	NE	CR	Baseline blast count was < 5%, below criteria for relapsed AML diagnosis. Applicant submitted biopsy report from screening that stated there were circulating blasts, 1%. The FDA confirmed that on Day 141, all criteria for CR were met.	CR
108-010	CR	MLFS	CR	Missing ANC at time of CR assessment. Applicant provided pathology report from BM biopsy performed on Day 115 that quotes a CBC from the same day. The FDA confirmed that on Day 115, all criteria for CR were met.	CR
114-005	CR	CRh	CRh	The applicant noted that at the time of investigator-assessed CR, the hematology criteria did not meet CR but did meet criteria for CRh. The FDA agreed and confirmed that on Day 85, all criteria for CRh were met.	CRh
900-020[1]	CR	PD	CR	Per protocol, responses after PD not included in assessment of best response. Subject had initial applicant-derived assessment of PD (SD by investigator determination), but remained on enasidenib, and achieved CR after PD. The FDA confirmed that on Day 113, the subject met all criteria for CR.	CR

Source: Applicant-provided information for late-cycle meeting dated 16 June 2017 and FDA analysis
[1] Date of relapse was adjusted for subject 106-005 to reflect PD after CR. As the initial PD for subject 900-020 was deemed SD by the investigator, no adjustment of date of relapse was required.

The final key efficacy endpoints as calculated by the FDA are shown in Table 46. Duration of response (DOR) was defined as the time since first response of CR or CRh to relapse or death, whichever is earlier. The date of best response of CR/CRh used for the calculation of DOR was that programmatically identified by the sponsor except for the 9 adjudicated subjects with CR/CRh in Table 45, for which the date of best response of CR/CRh was that confirmed by the FDA during review of the cases. None of these endpoints was the subject of hypothesis testing.

Table 46: Final FDA Analysis of Response

	Phase 1 N=101	Phase 2 N=98	Phase 1/2 Combined N=199
CR	19 (18.8%)	18 (18.4%)	37 (18.7%)
95% CI	(11.7, 27.8)	(11.3, 27.5)	(13.4, 24.7)
Median Duration of Response (months)	9.90	4.67	8.23
95% CI	(4.73, NA)	(1.90, NA)	(4.67, 19.4)
CRh	5 (5.0%)	4 (4.1)	9 (4.5%)
95% CI	(1.61, 11.1)	(1.1, 10.1)	(2.1, 8.4)
Median Duration of Response (months)	4.27	NA	9.6
95% CI	(0.93, NA)	(0.73, NA)	(0.73, NA)
CR/CRh	24 (23.8%)	22 (22.5%)	46 (23.1%)
95% CI	(15.9, 33.3)	(14.6, 32.0)	(17.5, 29.6)
Median Duration of Response (months)	9.6	5.3	8.23
95% CI	(4.27, NA)	(2.80, NA)	(4.27, 19.40)
Median Follow-up (months)	8.3	5.5	6.6
(Range)	(0.7, 27.7)	(0.4, 12.4)	(0.4, 27.7)

Source: FDA analysis

Final Subgroup Analyses

Table 47 and Table 48 summarizes the reviewer's final subgroup analyses on age, gender, race region and baseline disease characteristic for CR.

Table 47: Subgroup Analyses by Age, Gender, Race and Region –Complete Response

n/N (%)	Complete Response Rate N=199	95% CI
Age		
<=65	7/76 (7.4)	3.8, 18.1
>65	30/123 (24.4)	17.1, 33.0
Sex		
Male	20/103 (19.4)	12.3, 28.3
Female	17/96 (17.7)	10.7, 26.8
Region		
United states	28/166 (16.9)	11.5, 23.5
France	9/33 (27.3)	13.3, 45.5
Race		
White	27/153 (17.7)	12.0, 24.6
Not-Provided	7/25(21.9)	9.3, 40.0

Source: FDA analysis

Table 48: Subgroup Analyses by Baseline Disease Characteristic –Complete Response

n/N (%)	Complete Response Rate N=199	95% CI
Prior History of MDS		
Yes	2/41 (4.9)	0.6, 16.5
No	35/158 (22.2)	15.9, 29.4
ECOG Performance Status		
O	12/46 (26.1)	14.3, 40.4
1	17/124 (13.7)	8.2, 21.0
2	8/28 (28.6)	13.2, 48.7
WHO Classification of AML		
Class 1	6/28	8.3, 41.0
Class 2	5/44	3.8, 24.6
Class 3	1/5	0.5, 71.6
Class 4	26/110 (23.6)	16.1, 32.7
Baseline Cytogenetic Risk Status		
Favorable Risk	NA	
Intermediate Risk	23/98 (23.5)	15.5, 33.1
Poor Risk	4/54 (7.4)	2.1, 17.9
Failure	3/7 (42.9)	9.9, 81.6
IDH2 Gene Mutation Type		
R140	26/152 (17.1)	11.5, 24.1
R172	10/44 (22.7)	11.5, 37.8

Source: FDA analysis

In the Final FDA Efficacy Pool, 79% of the subjects (n=157) were dependent on blood or platelet transfusions at the start of the trial. Of these, 34% achieved blood and platelet transfusion independence on enasidenib. Of the 42 subjects (21%) who were independent of blood and platelet transfusions at the start of the trial, 32 (76%) remained blood and platelet transfusion independent (Table 49).

Table 49: Transfusion Dependence in Final Efficacy Pool

	Dependent on Platelet or Red Blood Cell Transfusions at Baseline	Independent of Platelet and Red Blood Cell Transfusions at Baseline
Final FDA Efficacy Pool (n=199)	157	42
Dependent on either Platelets or Red Blood Cell Transfusions Post-baseline	104 (66%)	10 (24%)
Independent of both Platelets and Red Blood Cell Transfusions Post-baseline	53 (34%)	32 (76%)

7.3. Integrated Review of Effectiveness

7.3.1. Assessment of Efficacy Across Trials

Methods

The applicant proposed the indication "For the treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with an IDH2 mutation" for enasidenib. The clinical development program consisted of a single Phase 1-2 clinical trial, Study AG221-C-001. There were 346 subjects with various hematological neoplasms treated with enasidenib on this study. For the purposes of establishing efficacy, FDA considered only the 199 subjects who a) were documented to have relapsed or refractory AML at study entry, b) were treated with the 100 mg total daily dose of enasidenib, and c) for whom the IDH2 mutation was detected by the proposed companion diagnostic (see Section 7.2.2).

Efficacy Endpoints

The primary endpoint of Study AG221-C-001 was overall response rate (ORR; defined as CR, CRp, CRi, morphologic leukemia-free state and PR) as determined by investigator. Evaluation for response, including marrow examination, was required at least on C2D1, every 28 days through 12 months, and every 56 days thereafter. This frequency of efficacy assessments was considered adequate.

There was no planned interim analysis in Study AG221-C-001, and the final analysis was to be performed on 125 subjects in the Phase 2 portion. There was no hypothesis testing planned, but the protocol indicated that a binomial 95% CI lower bound >25% was considered clinically meaningful. FDA's analysis of the primary endpoint included 104 subjects with relapsed or refractory (R/R) AML; the ORR for Phase 2 cohort was 34.6% (95% CI 25.3% - 44.2%) (Table 33), which met the applicant's prespecified definition for clinical meaningfulness. Hence, this was a positive trial.

FDA usually uses CR as an endpoint reasonably likely to predict clinical benefit. However, the applicant reported that MRD analysis by flow cytometry detected the persistence of AML in enasidenib-treated patients at CR and PR (Module 2.7.3 Summary of Clinical Efficacy Section 2.1.2.5.5), suggesting that a response with this differentiating agent might differ in quality or depth in comparison to a response induced by cytotoxic chemotherapy and perhaps not be reasonably likely to predict clinical benefit. In acute leukemia settings without intent to cure, FDA has also 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 final Study AG221-C-001 SAP dated July 7, 2016, included CR/CRh as a key secondary outcome and transfusion-independence as an additional secondary endpoint.

CR/CRh: The FDA clinical reviewer adjudicated all responses (Table 45) and identified subjects with a CR or CRh using only enasidenib and no additional follow-on therapies. The CR/CRh rate was 23.8% (95% CI 15.9, 33.3) for the 101 evaluable subjects in Phase 1 and 22.5% (95% CI 14.6, 32.0) for the 98 evaluable subjects in Phase 2 (Table 46).

TL Reviewer Comment: Since the populations and results are consistent between Phase 1 and Phase 2, it would be acceptable to pool data for display in the Prescribing Information. For the 199 subjects treated, the CR/CRh rate was 23.1% (95% CI 17.5, 29.6). The reproducibility between Phase 1 and Phase 2, completion of study accrual, and adequate follow-up for durability allay to some extent the deficiencies in the study design and potential for bias.

Kinetics and Durability: The CR rate was 18.7% (95% CI: 13.4, 24.7) with a median duration of 8.2 months, while the CRh rate was 4.5% (95% CI: 2.1, 8.4) with a median duration of 9.6 months (Table 46). The duration of CR/CRh is likely to improve over time, as median time to best response of CR/CRh is 3 months, with some subjects experiencing best response much later, and subjects on Phase 1, which had a longer follow-up time, had a longer median duration of CR/CRh than those on Phase 2 (9.6 months vs 5.3 months).

TL Reviewer Comments:

- *Unlike responses to cytotoxic chemotherapy, the results of Study AG221-C-001 show that responses to enasidenib are delayed; although this is a novel finding, the consistency between Phase 1 and Phase 2 for this observation supports its verity. The Prescribing Information should be clear about the kinetics of response to enasidenib, so that healthcare providers do not discontinue use prematurely.*
- *The duration of response (median 8.2 months) would be clinically meaningful for a palliative treatment with an acceptable safety profile.*
- *Given the short follow-up and reports of persistence of MRD, the long-term benefit of treatment with enasidenib cannot be determined*.

Transfusions: The applicant has also provided evidence that 34% of 157 subjects who entered study AG221-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 76% of 42 subjects who entered study AG221-C-001 independent of platelet and red blood cell transfusions remained transfusion-independence for at least 56 days while on treatment (Table 49). A total of 43% of subjects maintained or achieved transfusion-independence on enasidenib.

TL Reviewer Comment: Achieving or avoiding transfusions represents a notable palliative effect of enasidenib for these patients with relapsed or refractory IDH2-mutated AML who seek only quality of life in the short term.

Lastly, FDA assessed consistency between CR/CRh and the other potential measures of benefit. In addition to transfusion-independence as described above, the measures of benefit included severe infection or bleeding in the first 6 months on therapy (the assessment was limited to 6 months in order to account for differences between patients in duration of treatment). As displayed in Table 50, patients who achieve CR or CRh have a numerically lower incidence of severe infection or severe bleeding in the first 6 months on therapy, and a numerically higher rate of transfusion-independence, confirming internal consistency.

Table 50: Assessment for Consistency Between Response and Clinical Outcomes

	Response Achieved			
Outcome	CR (n=37)	CRh (n=9)	Less than CRh[a] (n=19)	SD or PD (n-118)
Grade 3-5 Infection[b]	30%	22%	53%	49%
Grade 3-5 Bleeding[b]	8%	0	11%	20%
Transfusion-independence	92%	89%	47%	29%

Source: FDA analysis
[a]Includes PR, MLFS and CR with incomplete hematological recovery less than that needed for CRh
[b]Assessment limited to the first 6 months on therapy

Subpopulations

The results of the subgroup analysis for CR (Tables 47-48) showed that the treatment effect was largely independent of gender, race, performance status, geographic region, prior HSCT or IDH2 base mutated. The CR rate was lower for patients < 65 years old, with a prior history of MDS, or with poor-risk cytogenetics. The CR/CRh rate was also consistent by IDH2 base mutated (Table 22).

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 (Table 23). In addition, none of the patients identified as having co-occurring mutations in NPM1, FLT3 or both NPM1 and FLT3 achieved a CR or CRh.

TL Reviewer Comment:

- *The small numbers limit conclusions that can be made about the low response rate in patients < 65 years old, with a prior history of MDS, or with poor-risk cytogenetics. From the results of the exploratory analysis of co-occurring mutations, one might speculate that mutations in genes other than IDH2 might interfere with the activity of enasidenib, but there is insufficient information to make such a conclusion at this time.*
- *The assessment of response by specific IDH2 mutation is limited by the fact that 2 mutations (R140Q and R172K) accounted for 95% of the study subjects, 3 mutations (R140L, R140W and R172W) accounted for about 5% of subjects, and there were no subjects with the other*

IDH2 mutations detected by the proposed companion diagnostic. The issue is complicated further by the lack of testing each of the 9 mutations for resistance in vitro. This warrants additional study in the postmarketing setting to ensure an appropriate risk:benefit for enasidenib independent of the specific IDH2 mutation.

Additional Efficacy Considerations

Study AG221-C-001 also had a dose-escalation portion that included 91 subjects with relapsed or refractory AML treated with total daily doses of 50 mg - 650 mg of enasidenib. Based on sponsor-derived determination of response, a CR was achieved by 2 (11%) of 19 subjects in enasidenib cohorts with total daily dose < 100 mg, by 9 (20%) of 46 in the 100 mg daily cohorts, and by 6 (23%) of 26 in cohorts with doses > 100 mg daily (FDA analysis). Although there appears to be a dose-response relationship, the difference in response rate between the 100 mg cohort and the cohorts with higher doses was small. The pharmacometrics reviewer also noted an exposure-response relationship (Table 82 Appendix 13.4.3); the relationship was significant only for the subjects with the R140 mutations, but a trend was seen for those with the R172 mutations. Lastly, the applicant also identified 31 subjects in the 100 mg daily dose cohorts whose dose was increased to 200 mg, usually due to lack of response at 100 mg. There was no evidence that treatment with the higher dose resulted in objective responses (Module 2.7.3 Summary of Clinical Efficacy Section 4).

TL Reviewer Comment: Although there appears to be a dose-response relationship, there does not appear to be much gained at enasidenib doses > 100 mg daily.

7.3.2. Integrated Assessment of Effectiveness

The effectiveness of enasidenib 100 mg daily for treatment of patients with relapsed or refractory AML having an IDH2 mutation is established by the CR/CRh rate in Study AG221-C-001, the durability of the response, and the corroborative finding of induction or maintenance of transfusion-independence. There is insufficient information about resistant IDH2 mutations or interfering co-mutations that would warrant a limitation of use at this time. There are also no data that support an expectation of long-term benefit. Nonetheless, if the safety profile is acceptable, the effectiveness would be meaningful for patients seeking short-term relief from the burdens of the disease.

7.4. Review of Safety

Safety Review Approach

Review emphasis was placed on safety data in patients with relapsed or refractory AML who received 100 mg of enasidenib daily on study AG-221-C-001 (Primary Safety Pool). As patients from Phase 1 and Phase 2 were all followed for a minimum of 6 months or until discontinuation of enasidenib, patients from both phases were pooled for the safety analysis. As this pooling

may underestimate the frequency of late toxicities due to the shorter follow-up time for patients on Phase 2, an additional sensitivity analysis addressing this possibility was performed (see Section 7.4.4).

Available safety data from all patients with advanced hematologic malignancies who received enasidenib on this study was used to support the analysis of safety in a larger patient population (Sensitivity Safety Pool), and evaluate dose-toxicity relationships. In addition, safety information provided by the Applicant from the other clinical trials of enasidenib in healthy volunteers or patients with solid tumors listed in Table 26 was summarized where relevant.

All safety analyses were conducted on the complete dataset provided by the Applicant for Study AG-221-C-001, which used a data cutoff date of October 14, 2016.

7.4.2. Review of the Safety Database

Overall Exposure

A total of 214 patients with relapsed or refractory AML assigned a dose of 100 mg enasidenib daily received at least one dose of enasidenib on Study AG-221-C-001 and were included in the Primary Safety Pool. An additional 131 patients with other hematologic malignancies and/or treated at other doses who received at least one dose of enasidenib on Study AG-221-C-001 were included in the Sensitivity Safety Pool.

A summary of exposure to enasidenib is provided in Table 51. In the Primary Safety Pool (n=214), the median duration of exposure to enasidenib was 5.3 months (mean 6.0 months), with a maximum exposure time of 23.6 months. In the Sensitivity Safety Pool (n=345), the median duration of exposure to enasidenib was 5.1 months (mean 6.4 months), with a maximum exposure time of 26.6 months. A total of 44 patients were exposed to enasidenib for more than 12 months.

Table 51: Duration of Exposure[1] to Enasidenib in the Safety Population

	0 to 3 months	>3 to 6 months	>6 to 9 months	>9 to 12 months	> 12 months
Primary Safety Pool (n=214)	57	69	53	16	19
Sensitivity Safety Pool (n=345)	104	97	69	31	44

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

Seventy-five percent (n=259) of the patients in the Sensitivity Safety Pool received a total of 100 mg of enasidenib daily, which is the Applicant's proposed dose for marketing. Another 63 (18%) received > 100 mg daily and 23 (7%) received < 100 mg daily (Table 52).

Table 52: Planned Total Daily Dose of Enasidenib in the Safety Population

Planned total daily dose	Primary Safety Pool (n=214)	Sensitivity Safety Pool (n=345)
50 mg	0	9
60 mg	0	7
75 mg	0	7
100 mg	214	259
150 mg	0	13
200 mg	0	24
300 mg	0	14
450 mg	0	5
650 mg	0	7

Source: FDA analysis

Relevant characteristics of the safety population:

Demographic information for patients analyzed for safety is summarized in Table 53.

Table 53: Demographics of the Safety Population

	Primary Safety Pool (n=214)	Sensitivity Safety Pool (n=345)
Sex		
Male	109 (51%)	201 (58%)
Female	105 (49%)	144 (42%)
Age (years)		
Mean	65	67
Median	68	69
Min, Max	19, 100	19, 100
ECOG Performance Status		
0	49 (23%)	79 (23%)
1	132 (62%)	204 (59%)
2	32 (15%)	61 (18%)
Missing	1 (<1%)	1 (<1%)
Race		
White	164 (77%)	267 (77%)
Black	12 (6%)	19 (6%)
Asian	1 (<1%)	4 (1%)
Other	2 (1%)	4 (1%)
Not Provided or Unknown	35 (16%)	51 (15%)
Ethnicity		
Not Hispanic or Latino	136 (64%)	234 (68%)
Hispanic or Latino	20 (9%)	27 (8%)
Not Provided	58 (27%)	84 (24%)
Underlying Disease		
R/R AML	214 (100%)	281 (81%)
Untreated AML	0	38 (11%)

	Primary Safety Pool (n=214)	Sensitivity Safety Pool (n=345)
MDS	0	17 (5%)
Other[1]	0	9 (3%)
Baseline Weight		
< 55 kg	27 (13%)	40 (12%)
55 to 100 kg	169 (79%)	274 (79%)
> 100 kg	16 (7%)	26 (8%)
Missing	2 (1%)	5 (1%)
Trial Site		
United States	178 (83%)	294 (85%)
France	36 (17%)	51 (15%)

Source: FDA analysis
[1] CMML (n=7), myelofibrosis (n=1) and blastic plasmacytoid dendritic cell 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 enasidenib, and the duration of treatment is adequate to allow assessment of adverse reactions over time. Data is lacking, however, regarding long-term toxicities of enasidenib, since the majority of patients with relapsed or refractory AML have a short life expectancy. There are no randomized data regarding the safety of enasidenib 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 53) are representative of typical patients with AML that participate on clinical trials. However, non-white patients are under-represented compared to the overall AML population in the United States.

7.4.3. 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 substantial primary review. The Applicant provided analysis-ready datasets for subjects on both phases of AG-221-C-001, as well as narratives for subjects on Phase 1 (dose escalation and initial expansion) who:

- died after the start of enasidenib treatment, whether on study or anytime thereafter, regardless of cause
- had serious adverse events (SAEs), regardless of causality assessment, that occurred after the start of enasidenib treatment until ≤ 28 days following the last dose
- had their study treatment permanently discontinued for any reason other than progressive disease
- 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 and ≥ 60 msec increase from baseline

A subset of the safety data was traced back to the primary source (individual case report forms) and no discrepancies were identified.

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 16.0. 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 enasidenib. 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 AG-221-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 13.5. SMQ analysis was also performed using MAED, and no additional safety signals were identified beyond those discussed below.

Routine Clinical Tests

See Section 7.2.1 for a description of the frequency of clinical testing for Study AG-221-C-001. The testing was adequate to assess the risks of serious safety events such as differentiation syndrome as discussed in detail below.

7.4.4. Safety Results

Deaths

The FDA identified 208 deaths in the 345 patients who received enasidenib on Study AG-221-C-001 (60%), approximately half of which occurred on or within 28 days after discontinuation of enasidenib (Table 54).

Table 54: Deaths on Study AG-221-C-001

	Primary Safety Pool (n=214)	Sensitivity Safety Pool (n=345)
All deaths	127 (59%)	208 (60%)
On-treatment deaths[1]	62 (29%)	113 (33%)
Phase 1	21	71
Phase 2	41	42

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

The dataset provided by the applicant identified the underlying malignancy as the cause of death in 45 of the 113 on-treatment deaths (40%), and in 102 of the 208 total deaths (49%). Other frequently reported causes of on-treatment death were infection (n=22), respiratory failure (n=10), multi-organ failure (n=6), intracranial hemorrhage (n=5), and cardiac arrest (n=4).

The FDA reviewed individual patient narratives from all 71 of the on-treatment deaths that occurred in patients enrolled on Phase 1 to confirm the cause of death. Patient narratives were generally well-written, although lack of availability of patient narratives from subjects enrolled on Phase 2 of the study is a limitation of this FDA review. The FDA considered the root cause of death to be the primary malignancy when supported by 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=52, 73%) of the on-treatment deaths on Phase 1 of Study AG-221-C-001 were due to the primary malignancy, and that another 4 deaths were clearly related to another underlying medical condition.

There were 15 deaths in on Phase 1 of AG-221-C-001 considered by the FDA to be at least possibly related to enasidenib (Table 55). Infection with or without neutropenia was clearly the root cause of death in 4 cases. In all cases, the subject had prior prolonged periods of neutropenia or lymphopenia that may have potentially contributed to the infection.

Table 55: Causes of Deaths Occurring On or Within 30 Days of Treatment in Phase 1

Subject	Study Day	FDA Root Cause of Death	Investigator Cause of Death
103-005	54	Leukocytosis	Gastrointestinal hemorrhage
103-007	75	Infection	Sepsis
103-015	192	Infection	Sepsis
104-013	39	Infection/DS	Sepsis
104-041	298	Infection	Respiratory failure
105-006	47	Infection/DS	Respiratory failure
105-012	54	AML/DS	Multi-organ failure
105-014	16	DS	Cardiac tamponade
106-010	173	Heart failure	Fluid overload
108-006	56	Cardiac arrest	Cardiac arrest
109-007	81	Acute MI	Failure to thrive
112-008	54	ARDS/DS	ARDS
201-005	44	Infection/DS	Sepsis
201-017	95	Pneumonitis	Pneumonitis
201-026	165	Infection	Sepsis

Source: FDA analysis
Abbreviations: ARDS, acute respiratory distress syndrome; DS, differentiation syndrome; MI, myocardial infarction

There were 11 deaths on Phase 1 not definitively caused by infection that were considered by the FDA to be a direct toxicity of enasidenib:

Subject 103-005: 72 year old man with chronic myelomonocytic leukemia (CMML) who received 75 mg enasidenib daily. On study day 25, his white blood cell (WBC) count began to rise dramatically, peaking at 147,000. On study day 30, he underwent emergent leukapheresis. Over the course of the day, however, the subject developed disseminated intravascular coagulation (DIC) complicated by bilateral subdural hematomas. On study day 31, he developed Grade 2 azotemia, Grade 2 elevated transaminases, and labored breathing that prompted intubation and mechanical ventilation. The subject stabilized and was extubated, but general condition again began to decline, and the subject developed gastrointestinal hemorrhage that resulted in death. The investigator felt that the DIC was possibly related to enasidenib and the leukocytosis was probably related to enasidenib. As there was no documentation of tumor reassessment on treatment, the FDA agreed that these adverse events could be related to blinatumomab.

Subject 104-013: 49 year old man with relapsed/refractory AML who received 100 mg enasidenib twice daily. On study day 11, the subject was hospitalized with pyrexia and Grade 3 leukocytosis, and enasidenib was interrupted. That same day he became hypoxic and short of breath, and a chest x-ray revealed bilateral pleural effusions. On study day 15, the fever resolved and enasidenib was resumed. On study day 17, the subject developed Grade 2 hyperbilirubinemia and Grade 2 ALT elevation. On study day 22, the subject developed worsening hypoxia, and CT scan showed an "infectious pulmonary process", new anasarca, and ascites. Repeat blast count was unchanged from baseline. Enasidenib was interrupted. On study day 35, the subject decompensated, suffered respiratory arrest, and was placed on mechanical ventilation. His condition continued to deteriorate and he died on study day 39. The investigator reported the cause of death as septic shock and respiratory failure secondary to *Stenotrophomonas* pneumonia. However, no culture results were reported. The subject does not appear to have received steroids during the course of treatment. The FDA noted that differentiation syndrome, manifested by fever, pleural effusions, and eventually multi-organ failure, represents a possible alternative cause of death.

Subject 105-006: 74 year old man with MDS who received 100 mg enasidenib daily. On study day 17, the subject was hospitalized for mental status changes associated with a hemoglobin of 6.8 g/dL. He was started on broad spectrum antimicrobials. On study day 28, the subject developed a fever, and a chest x-ray showed multi-focal infection and mild pulmonary edema. Antimicrobial coverage was broadened. On study day 30, the subject was transferred to the ICU for respiratory distress after a RBC transfusion, and enasidenib was discontinued. On study day 41, the subject was intubated for acute hypoxic respiratory failure, on study day 43, he developed Grade 3 hyperbilirubinemia. On study day 47 he was started on dexamethasone, but subsequently died from respiratory failure. The investigator assessed the adverse events as unrelated to enasidenib, but did not specify an alternative cause. The Differentiation Syndrome

Review Committee (DSRC) assessed the event of respiratory failure as possible differentiation syndrome, and the FDA agrees.

Subject 105-012: 77 year old man with previously untreated AML who received 100 mg enasidenib daily. On study day 44, the patient was diagnosed with pneumonia complicated by hypoxemia. CT scan on study day 48 revealed pleural effusions in addition to the pneumonia. The subject developed progressive respiratory distress and was transferred to the ICU on study day 50. The patient was empirically treated with dexamethasone for differentiation syndrome, with no improvement in symptoms. On study day 51, the patient developed multi-organ failure and he died on study day 54. All cultures were negative. The investigator considered the adverse events to be related to the subject's underlying AML. As the peripheral blast count declined between study days 15 and 35 (last known value), the FDA noted that differentiation syndrome represents a possible alternative cause of death.

Subject 105-014: 83 year old woman with previously untreated AML who received 100 mg enasidenib daily. On study day 14, the subject presented for routine infusion and was noted to have supraventricular tachycardia and a large pericardial effusion causing tamponade. She was diagnosed with differentiation syndrome and enasidenib was interrupted. The subject's status was changed to do-not-resuscitate and she did not receive any treatment or intervention and died on study day 16. No tumor reassessments on treatment were performed. The DSRC assessed the event as possible differentiation syndrome, and the FDA noted that the cause of death was most likely differentiation syndrome.

Subject 106-010: 78 year old man with previously untreated AML who received 100 mg enasidenib daily. Baseline medical history of hypertension, diabetes, coronary artery bypass, congestive heart failure and pacemaker insertion on multiple cardiac medications at baseline. Subject experienced multiple episodes of dyspnea throughout treatment which were considered to potentially be differentiation syndrome, but resolved with diuresis. Echocardiogram performed on study day 142 showed severe right ventricle dilation and markedly elevated central venous pressure, although it is not noted how this compares to baseline. On study day 173, the subject died due to fluid overload, with no further details specified. Although exacerbation of the subject's underlying cardiac condition was the likely cause of death, the FDA could not rule out a contribution by enasidenib.

Subject 108-006: 75 year old woman with relapsed/refractory AML who received 100 mg enasidenib daily. On study day 55, the subject was hospitalized for Grade 4 anemia and Grade 4 hypotension. She received transfusions of RBCs and platelets as well as dopamine and intravenous fluids, but died from cardiac arrest the following day. The investigator determined that the adverse events were not related to enasidenib, but did not provide an alternative cause. As the peripheral blast count declined between study days 15 and 30 (last known value), her death is not clearly due to the underlying malignancy, and the FDA cannot rule out a contribution by enasidenib.

Subject 109-007: 73 year old woman with refractory MDS who received 100 mg enasidenib daily. On study day 35, the patient experienced an acute myocardial infaction that required emergent stent placement. On study day 68, she was hospitalized with failure to thrive, a splenic infarct was noted, and enasidenib was permanently discontinued. She was discharged to hospice on study day 79 and died two days later. The investigator determined that the adverse events were not related to enasidenib. However, as the peripheral blast count declined steadily from baseline through study day 62 (last known value), and her platelet and neutrophil counts had also improved, her death is not clearly due to the underlying malignancy, and the FDA cannot rule out a contribution by enasidenib.

Subject 112-008: 87 year old man with previously untreated AML who received 100 mg enasidenib daily. On study day 39, the subject developed tumor lysis syndrome, was hospitalized in the ICU, and enasidenib was interrupted. The TLS resolved and enasidenib was resumed on study day 52. On study day 53, the subject developed hypoxia and dyspnea. Chest x-ray revealed bilateral perihilar opacities interpreted as pneumonia versus pulmonary edema, and BiPAP was started. The subject developed progressive ARDS followed by cardiac arrest and died on study day 54. The investigator assessed the ARDS as unrelated to enasidenib, although did not provide an alternative cause. Although the cause of the respiratory distress is unclear, given the occurrence immediately following resumption of enasidenib, the FDA noted that the cause of death could be differentiation syndrome.

Subject 201-005: 62 year old man with relapsed/refractory AML who received 75 mg enasidenib twice daily. On study day 22, the subject was hospitalized in the ICU for Grade 4 pharyngeal mucositis and Grade 4 ARDS that was thought due to an obstruction. On study day 28, the subject was diagnosed with differentiation syndrome, although the basis of this is not reported. Enasidenib was permanently discontinued, and the subject was treated with dexamethasone, antibiotics and mechanical ventilation. On study day 35, bronchoalveolar lavage (BAL) culture was positive for coagulase-negative *Staphylococcus*. The subject developed severe capillary leak syndrome, renal failure, bilateral pleural effusions and fever, and died on study day 44 with investigator-determined cause of death as sepsis. Blood culture results were not reported. The DSRC assessed the initial event of respiratory distress syndrome as possible differentiation syndrome. As blood culture results were not reported, and capillary leak syndrome is a relatively unusual consequence of pneumonia, the FDA considers that differentiation syndrome remains a possible cause of death.

Subject 201-017 : 78 year old woman with relapsed/refractory AML on 150 mg enasidenib twice daily. Prior to her first dose of study treatment, the subject was hospitalized for Grade 3 interstitial lung disease, which persisted until her death. On study day 75, the subject was hospitalized with febrile neutropenia. On study day 92, CT scan revealed left pleuropneumopathy with pleural effusions, splenic infarction, and sinusitis. She was diagnosed with Grade 4 pneumonitis, and enasidenib was interrupted. On study day 94, she developed

mental status changes which did not resolve, and she died on study day 95 with an investigator-determined cause of death of pneumonitis, unrelated to enasidenib. Insufficient detail is provided to confirm progression of pre-existing pneumonitis as the cause of death, but the FDA notes that contribution of enasidenib to the patient's death cannot be ruled out.

While narratives are not available for patients enrolled on Phase 2 of the study, the all-cause mortality as calculated by the FDA for the 214 subjects in the Primary Safety Pool was 4% (95% CI, 2-8%) at day 30 and 24% (95% CI, 19-31%) at day 90.

Reviewer Comments:

- *Six of the cases described above include manifestations of respiratory distress, pulmonary edema, and/or multiorgan dysfunction consistent with differentiation syndrome, although at least five of 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 sepsis in the absence of cultures. Although none of these patients were in the FDA's Primary Safety Pool (i.e., none were patients with relapsed or refractory AML who were assigned 100 mg enasidenib daily), the potential for fatal differentiation syndrome should be added to the labeling.*

- *Of the 109 subjects with relapsed or refractory AML who received the 100 mg daily dose of enasidenib who were treated on Phase 1 and for whom death narratives are available, only one had a fatal adverse event considered at least possibly related to enasidenib. While there is no active comparator to determine the relative fatal toxicity of enasidenib compared to chemotherapy combinations in general use, the low early all-cause mortality of 4% is encouraging. Although statistical comparison of mortality in enasidenib-treated patients with those reported in historical controls would not be appropriate, the early all-cause mortality observed in patients treated with enasidenib compares favorably to the 10-20% seen in patients treated with chemotherapy (reviewed in Ramos et al, J Clin Med 2015).*

Serious Adverse Events

A total of 166 (78%) of the subjects in the Primary Safety Pool and 270 (78%) in the Sensitivity Safety Pool experienced a treatment-emergent serious adverse event. The number of subjects who experienced an SAE in each SOC is shown in Table 56.

Table 56: Serious Adverse Events within 28 Days of Follow-Up

System Organ Class	Primary Safety Pool (n=214)	Sensitivity Safety Pool (n=345)
Any class	166 (78%)	270 (78%)
Infections and infestations	102 (48%)	166 (48%)
Blood and lymphatic system disorders	94 (44%)	133 (39%)
Respiratory, thoracic and mediastinal disorders	52 (24%)	84 (24%)
Gastrointestinal disorders	44 (21%)	74 (21%)
General disorders and administration site conditions	43 (20%)	66 (19%)
Metabolism and nutrition disorders	24 (11%)	42 (12%)
Nervous system disorders	19 (9%)	33 (10%)
Cardiac disorders	19 (9%)	32 (9%)
Renal and urinary disorders	13 (6%)	27 (8%)
Vascular disorders	15 (7%)	25 (7%)
Investigations	12 (6%)	24 (7%)
Musculoskeletal and connective tissue disorders	14 (7%)	23 (7%)
Psychiatric disorders	11 (5%)	20 (6%)
Injury, poisoning and procedural complications	11 (5%)	19 (6%)
Skin and subcutaneous tissue disorders	8 (5%)	9 (3%)
Neoplasms, benign, malignant and unspecified	5 (2%)	8 (2%)
Hepatobiliary disorders	6 (3%)	7 (2%)
Immune system disorders	3 (1%)	4 (1%)
Surgical and medical procedures	2 (1%)	3 (1%)
Congenital, familial and genetic disorders	0	2 (1%)
Eye disorders	1 (<1%)	1 (<1%)
Reproductive system and breast disorders	0	1 (<1%)
Uncoded	1 (<1%)	1 (<1%)

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

Among patients with relapsed or refractory AML who received enasidenib 100 mg daily (the Primary Safety Pool), the most frequent (> 5%) serious adverse events without regard to attribution were: febrile neutropenia (n=64, 30%), pneumonia (n=50, 23%), sepsis (n=35, 16%), dyspnea (n=26, 12%), pyrexia (n=22, 10%), leukocytosis (n=21, 10%), differentiation syndrome (n=17, 8%), fatigue (n=13, 6%), renal insufficiency (n=13, 6%), urinary tract infection (n=13, 6%), and diarrhea (n=12, 6%).

Of these serious adverse events in the Primary Safety Pool, 120 were considered by the investigator to be at least possibly related to enasidenib. The most frequent (≥ 2%) were: differentiation syndrome (n=17, 8%), dyspnea (n=8, 4%), febrile neutropenia (n=8, 4%), leukocytosis (n=8, 4%), nausea (n=7, 3%), fatigue (n=5, 2%), pyrexia (n=5, 2%), decreased

appetite (n=4, 2%), diarrhea (n=4, 2%), and vomiting (n=4, 2%).

Dropouts and/or Discontinuations Due to Adverse Effects

Overall, 61% of treated subjects had a dose interruption, dose reduction, or permanent discontinuation due to an adverse event (Table 57).

Table 57: Treatment Interruptions, Reductions, or Withdrawals

	Primary Safety Pool (n=214)	Sensitivity Safety Pool (n=345)
Interruption	114 (53%)	186 (54%)
Dose reduction	21 (10%)	53 (15%)
Withdrawal	24 (11%)	39 (11%)
Any of the above	130 (61%)	209 (61%)

Source: FDA Analysis

The most common TEAE leading to interruption of enasidenib are shown in Table 58 in decreasing order. The table includes only those events that occurred in > 2% of subjects with relapsed or refractory AML who received 100 mg enasidenib daily (Primary Safety Pool).

Table 58: TEAE Leading to Dose Interruption

Preferred Term[1]	Primary Safety Pool (n=214)	Sensitivity Safety Pool (n=345)
Hyperbilirubinemia	8 (4%)	18 (5%)
Pneumonia	8 (4%)	18 (5%)
Febrile neutropenia	12 (6%)	16 (5%)
Sepsis	9 (4%)	15 (4%)
Differentiation syndrome	8 (4%)	14 (4%)
Dyspnea	8 (4%)	13 (4%)
Leukocytosis	6 (3%)	11 (4%)
Fatigue	6 (3%)	10 (3%)
Pyrexia	7 (3%)	8 (2%)

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

The most common TEAE leading to dose reductions of enasidenib are shown in Table 59 in decreasing order. The table includes only those events that occurred in > 1 subject on the study (Sensitivity Safety Pool).

Table 59: TEAE Leading to Dose Reductions

Preferred Term[1]	Primary Safety Pool (n=214)	Sensitivity Safety Pool (n=345)
Peripheral neuropathy	3 (1%)	5 (1%)
Fatigue	2 (1%)	4 (1%)
Nausea	0	4 (1%)
Decreased appetite	1 (<1%)	3 (1%)
Hyperbilirubinemia	0	3 (1%)
Diarrhea	0	2 (1%)
GI hemorrhage	0	2 (1%)
Rash	1 (<1%)	2 (1%)
Vomiting	0	2 (1%)

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

The most common TEAE leading to dose reductions of enasidenib are shown in Table 60 in decreasing order. The table includes only those events that occurred in > 1 subject on the study (Sensitivity Safety Pool).

Table 60: TEAE Leading to Discontinuations

Preferred Term[1]	Primary Safety Pool (n=214)	Sensitivity Safety Pool (n=345)
Dyspnea	4 (2%)	8 (2%)
Sepsis	4 (2%)	8 (2%)
Intracranial hemorrhage	3 (1%)	5 (1%)
Leukocytosis	3 (1%)	5 (1%)
Hyperbilirubinemia	3 (1%)	4 (1%)
Multiorgan failure	2 (1%)	3 (1%)
Alkaline phosphatase increased	2 (1%)	2 (1%)
Cellulitis	1 (<1%)	2 (1%)
Decreased appetite	1 (<1%)	2 (1%)
GI hemorrhage	0	2 (1%)
Pneumonia	2 (1%)	2 (1%)
Tumor lysis syndrome	2 (1%)	2 (1%)

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

Reviewer comment: The relative paucity of dose reductions or discontinuations for adverse events in subjects with relapsed or refractory AML who received 100 mg enasidenib daily lends support to the tolerability of the proposed marketed dose and regimen. Dose interruptions for hyperbilirubinemia, an on-target effect of enasidenib, and differentiation syndrome each occurred in 4% of patients and should be mentioned in the product label. See below for additional analysis of these events. 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) and do not merit special mention in the label.

Significant Adverse Events

Hyperbilirubinemia

Enasidenib inhibits UGT1A1, the enzyme responsible for the metabolism of bilirubin (see Section 6.3.2 for details). In nonclinical toxicology studies, an increase in serum bilirubin was noted in all species tested (see Section 5.5.1 for details). The applicant found that bilirubin elevations occurred frequently in patients, and that higher total bilirubin levels were associated with high drug exposure. The applicant noted that 38.5% of subjects in their safety pool had at least one TEAE related to the biliary system. About two thirds of these subjects had Grade 1 or 2 events, and one third had Grade ≥ 3 events. To assess whether bilirubin elevations were isolated laboratory changes not associated with liver damage, the applicant analyzed concurrent ALT, AST and/or bilirubin elevations reported within one cycle of each other. The majority of subjects with elevations in total bilirubin did not have concurrent elevations in ALT and/or AST (Table 61).

Table 61: Post-baseline Changes in Bilirubin and Transaminases

		R/R AML 100 mg daily (n=199)		All subjects (n=330)	
Parameter	**Criteria**	**Any Visit**	**Last Visit**	**Any Visit**	**Last Visit**
ALT	≥ 3x ULN and < 5x ULN	14 (7%)	3 (2%)	19 (6%)	3 (1%)
	≥ 5x ULN and < 8x ULN	2 (1%)	0	5 (2%)	0
	≥ 8x ULN	1 (<1%)	1 (<1%)	2 (<1%)	1 (<1%)
AST	≥ 3x ULN and < 5x ULN	7 (4%)	2 (1%)	15 (5%)	3 (1%)
	≥ 5x ULN and < 8x ULN	1 (<1%)	0	3 (1%)	0
	≥ 8x ULN	1 (<1%)	1 (<1%)	3(1%)	1 (<1%)
Total bilirubin	≥ 2x ULN	67 (34%)	41 (21%)	124 (38%)	26 (8%)
	≥ 3x ULN	24 (12%)	10 (5%)	52 (16%)	26 (8%)
Total bili ≥ 2x ULN and ALT ≥ 3x ULN in the same cycle	ALT ≥ 3x ULN and < 5x ULN	4 (2%)	1 (<1%)	6 (2%)	1 (<1%)
	ALT ≥ 5x ULN and < 8x ULN	2 (1%)	0	3 (1%)	0
	ALT ≥ 8x ULN	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)
Total bili ≥ 2x ULN and AST ≥ 3x ULN in the same cycle	ALT ≥ 3x ULN and < 5x ULN	6 (3%)	1 (<1%)	8 (2%)	2 (<1%)
	ALT ≥ 5x ULN and < 8x ULN	1 (<1%)	0	1 (<1%)	0
	ALT ≥ 8x ULN	1 (<1%)	1 (<1%)	1 (<1%)	1 (<1%)

Source: Applicant's Summary of Clinical Safety (Module 2.7.4) Section 2.1.5.5.2

The FDA audited the applicant's findings using the updated data set, and got similar results.

Bilirubin elevations were reported in the majority (n=177, 83%) of subjects in the Primary Safety Pool, with 15% (n=33) of subjects reporting a Grade ≥ 3 bilirubin elevation (Table 62).

Table 62: FDA Analysis of Maximum Bilirubin Level

	Primary Safety Pool (n=214)	Sensitivity Safety Pool (n=345)
Not elevated	37 (17%)	67 (19%)
Grade 1 (> ULN – 1.5x ULN	49 (23%)	78 (23%)
Grade 2 (> 1.5X – 3X ULN)	95 (44%)	138 (40%)
Grade 3 (> 3x – 10X ULN)	32 (15%)	61 (18%)
Grade 4 (> 10X ULN)	1 (<1%)	1 (<1%)

Source: FDA analysis

While transaminase elevations occurred in 59% (n=127) of subjects in the Primary Safety Pool, Grade ≥ 3 transaminase elevations occurred in just 3 subjects (1%) (Table 6363).

Table 63: FDA Analysis of Maximum ALT/AST Level

	Primary Safety Pool (n=214)	Sensitivity Safety Pool (n=345)
Not elevated	87 (41%)	153 (44%)
Grade 1 (> ULN – 3x ULN)	106 (50%)	156 (45%)
Grade 2 (>3x – 5x ULN)	18 (8%)	27 (8%)
Grade 3 (> 5x – 20X ULN)	2 (1%)	8 (2%)
Grade 4 (> 20x ULN)	1 (<1%)	1 (<1%)

Source: FDA analysis
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

The FDA reviewed narratives from the 13 subjects who developed a total bilirubin level ≥ 2x the upper limit of normal concurrently (within the same cycle) with ALT or AST level ≥ 3x the upper limit of normal (Table 61), and did not identify any cases of apparent drug-induced liver injury. Almost all cases occurred in the setting of progressive disease, sepsis, differentiation syndrome, or rapidly rising WBC count with initiation of hydroxyurea, and the remainder represented small increases in transaminase levels over baseline that resolved by the next measurement with no interruption of study drug or other treatment.

Reviewer comment:
Hyperbilirubinemia is frequent in patients treated with enasidenib, and appears to be related to inhibition of UGT1A1. Although 4% of subjects had a temporary dose interruption for hyperbilirubinemia (Table 58), enasidenib-associated hyperbilirubinemia does not appear to be associated with hepatotoxicity or clinically significant sequellae. Information about hyperbilirubinemia should be included in the USPI so that physicians and patients are aware of this adverse reaction and how to manage it. Based on the data provided in the NDA, enasidenib does not appear to be associated with direct liver toxicity, although liver damage may occur

secondary to other events (e.g. differentiation syndrome).

Differentiation Syndrome

The first case of possible differentiation syndrome (DS) was recognized on Study AG221-C-001 in November of 2013, approximately 1 month into the study. The applicant ultimately established a Differentiation Syndrome Review Committee (DSRC) to formally review known and potential cases of DS in subjects receiving enasidenib due to the heterogeneity of clinical symptoms and lack of diagnostic procedures. This analysis was done retrospectively as follows:

1. The applicant screened their clinical and safety databases for preferred terms they considered consistent with signs and symptoms of DS, and identified 139 cases of potential DS for further evaluation.
2. The applicant reviewed the cases, and excluded 67 of them based on their conclusion that symptomatology was attributed to another cause. The remaining 72 cases were selected for DSRC review.
3. DSRC reviewers were instructed that in order to consider a case as "possible" or "probable" DS, the following criteria should be met:
    a. Patient presented with symptoms characteristic of DS
    b. Timing of the event occurred between 10 days and 3 months
    c. There was no secondary cause such as infection or heart failure
    d. There was evidence of differentiation in peripheral blood counts
4. Even if the case did not satisfy all 4 criteria, if the patient had been treated with steroids and manifested a rapid response, the event should be considered "possible" DS.

Based on this procedure, of the 214 subjects in the FDA Primary Safety Pool, the DSRC identified cases of possible or probable DS in 28 of them (13%).

The investigators on AG221-C-001 were informed about the possibility of differentiation syndrome with enasidenib and asked to report suspected cases as "retinoic acid syndrome" per the MedDRA version being used. In the FDA's Primary Safety Pool (n=214), the investigators reported retinoic acid syndrome in 29 subjects (14%). There was not complete overlap between the subjects identified as having DS by the applicant's DSRC and those identified as having DS by the investigator: for example, there were 8 subjects for whom retinoic acid syndrome was reported by the investigator, but the DSRC determined that DS was "unlikely".

The FDA conducted an independent review of the safety data to identify subjects with possible DS using the following approach:

1. The FDA reviewed narratives from subjects determined as having possible or probable DS as determined by the applicant's DSRC, as well as narratives from subjects reported to have DS according to the investigator, and available literature regarding the signs and symptoms of differentiation syndrome produced by other agents (e.g. arsenic trioxide and all-trans retinoic acid in APML) and used this information to devise an algorithm to identify cases of screen-positive DS using the AG221-C-001 data set (Table 64).
2. The FDA applied this algorithm to the Primary Safety Pool (n=214), and identified 92

possible DS events in 70 subjects (33%) (results provided by Flora Mulkey, MS). Of these 92 events, 55 (60%) were not reviewed by the applicant's DSRC, 12 (13%) were reviewed by the DSRC and considered unlikely to be DS, and the remaining 25 (27%) were reviewed by the DSRC and considered possibly or probably DS.

   a. Note that of the 12 cases reviewed by the DSRC and considered unlikely to be DS, 8 were reported as DS by the investigator. The other 4 were reported as pleural effusion (n=2), fever/cough/peripheral edema (n=1) and edema/renal failure/respiratory failure (n=1) by the investigator.

3. The FDA identified 12 additional events in 8 additional subjects that were determined to be possibly or probably DS events by the applicant's DSRC, but that were not picked up by the FDA's algorithm. Eight of these events were not picked up by the FDA's algorithm because they occurred after study day 90. The remaining 4 events occurred within the first 90 days of treatment but did not meet FDA algorithm criteria for possible DS event.

Table 64: FDA Criteria for Identifying Cases of Possible DS

Part A: Report[1] of ≥ 1 of the following categories of events is considered a case of possible DS:	
Category	**Adverse event[2]**
Investigator- reported DS	Retinoic acid syndrome
Pulmonary edema	Acute pulmonary edema, acute respiratory distress syndrome, non-cardiogenic pulmonary edema, pulmonary congestion, or pulmonary edema
Effusion	Pericardial effusion or pleural effusion
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**
Fever	Adverse event of pyrexia or Temperature ≥ 38.3°C
Edema	Adverse event of capillary leak syndrome, edema, edema peripheral, fluid overload, fluid retention, generalized edema, hydremia or hypervolemia
Hypotension	Adverse event of hypotension or Systolic Blood Pressure < 90 mmHg
Interstitial lung infiltrates or similar	Adverse event of acute interstitial pneumonitis, acute lung injury, acute respiratory failure, atypical pneumonia, cardiopulmonary failure, cardio-respiratory distress, cough, dyspnea, lower respiratory tract infection, lower respiratory tract inflammation, lung infection, lung infiltration, pneumonia, pneumonitis, pulmonary toxicity, respiratory arrest or respiratory failure
Organ failure	Acute kidney injury, anuria, cardiorenal syndrome, hepatorenal failure, multi-organ failure, renal failure, renal impairment or renal injury

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

Thus, a total of 78 subjects (36%) had possible or probable DS (as determined by either the FDA or the applicant). The FDA reviewed available supportive information (concomitant adverse event reports, laboratory data, and narratives, where available) for these subjects, but was generally unable to definitively determine on the basis of this information whether the subject had DS or an alternative cause (e.g., sepsis, disease progression) of the component signs or symptoms. While some cases occurred in the setting of rising peripheral blast counts, which would seem to indicate progression, rather than DS, in many of these cases, subjects stayed on enasidenib and peripheral blast counts fell again, making these cases difficult to interpret.

The maximum grade of possible or probable DS was determined by the FDA as the maximum grade of the component adverse event(s). Using this approach, 37 subjects (17%) had Grade 3-4 possible or probable differentiation syndrome. There was only one fatal event, which occurred in subject 111-017. However, at the time of the fatal adverse event, the subject had sharply rising blast counts after an initial period of falling peripheral blast counts, and the FDA considered disease progression the most likely cause of death.

Reviewer comments:
Differentiation syndrome has overlapping signs and symptoms of other frequent adverse events in patients with AML (e.g., sepsis) and requires a high degree of clinical vigilance and experience to recognize. It is difficult for the FDA to definitively confirm the frequency of DS in patients with relapsed or refractory AML treated with enasidenib, although it appears to be at least 13% (the frequency of retinoic acid syndrome as reported by the applicant) and probably no higher than 33% (the frequency of possible DS as determined by the FDA's algorithm).

As approximately half of the patients with possible DS as determined by the FDA's algorithm had Grade 3-4 events, as there was at least 1 fatal case of DS in a patient on AG221-C-001 (see Table 55), albeit none in the FDA's Primary Safety Pool, I recommend that the USPI include a boxed warning for differentiation syndrome. I also recommend that the sponsor be asked to further explore the frequency, severity, diagnostic features, and ideal management of DS through a PMR.

<u>Hyperleukocytosis</u>
The FDA identified 67 events of leukocytosis in 49 subjects (23%) in the Primary Safety Pool, and noted that Grade ≥ 3 leukocytosis was reported in 22 subjects (10%). Six subjects had a temporary interruption of enasidenib for leukocytosis, and 3 subjects permanently discontinued enasidenib as a result of leukocytosis. (b) (4)

The FDA reviewed all reported adverse events of Grade ≥ 3 leukocytosis, including laboratory data and subject narratives (where provided). Of the 26 events, the FDA was only able to find documentation of a WBC > 100 x 10^9/L in 4 events. Most events of leukocytosis, including the

single reported fatal event, were reported in conjunction with rising blast counts or a response evaluation of disease progression. While some subjects with Grade ≥ 3 leukocytosis continued on study drug in accordance with protocol instructions to continue enasidenib in the absence of confirmed (by 2nd bone marrow) progressive disease, none of them went on to have a CR or CRh after the event.

The FDA identified an additional 4 subjects with reported WBC > 100 x 10^9/L that did not have leukocytosis reported as an adverse event. In 3 of these patients, the elevated WBC occurred in association with a response evaluation of disease progression. In the 4th, it occurred as part of a reported event of differentiation syndrome. Enasidenib was held, WBC normalized five days later, and the subject resumed enasidenib without further leukocytosis.

Reviewer comment: The events of leukocytosis appear to generally be related to the underlying malignancy and occur in the context of disease progression. Although leukocytosis may be observed in the context of differentiation syndrome, there does not appear to be an independent effect of enasidenib on white blood cell counts. 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 enasidenib (b) (4)

Tumor lysis syndrome

The FDA identified 15 events of tumor lysis syndrome (TLS) in 13 subjects (6%) in the Primary Safety Pool. Most events (n=12) were Grade 3; there was one fatal event of tumor lysis syndrome (TLS). Enasidenib was permanently discontinued due to the TLS in 2 subjects, including the subject with a fatal event. No subject temporarily interrupted enasidenib for TLS. (b) (4)

To further understand the relationship between enasidenib 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 one subject (201-038), TLS occurred at the time of progressive disease and/or rapidly rising WBC count. In subject 201-038, WBC count rose steadily from baseline to 33.3 x 109/L over the first two weeks on enasidenib, which was followed by a steady decline over the next four weeks, during which the TLS event occurred. The subject's best response was stable disease, and the subject was taken off study at the end of cycle 5 due to disease progression.

Reviewer comment: TLS caused by enasidenib-induced cell lysis is unexpected given the mechanism of action of the drug. If present, it should be associated with falling WBC counts. The observation that almost all TLS events occurred in the setting of rising WBC counts suggests that the events of tumor lysis syndrome are related to the underlying malignancy. The frequency and severity of tumor lysis syndrome is similar to what would be expected in the underlying population. TLS does not appear to be a serious or life-threatening event related to treatment

Treatment Emergent Adverse Events and Adverse Reactions

Common (in ≥ 20% of patients with relapsed/refractory AML who received 100 mg enasidenib daily) TEAE occurring either on enasidenib or within 28 days after discontinuation of enasidenib are summarized by preferred term in Table 65. No new common adverse events were detected in the analysis of the Sensitivity Safety Pool. While febrile neutropenia was more common in the Primary Safety Pool than the broader study population (36% vs 30%), rates of infection (e.g. pneumonia, sepsis) were similar in the two pools.

Table 65: Common TEAE (All Grades)

Preferred Term[1]	Primary Safety Pool (n=214)	Sensitivity Safety Pool (n=345)
Fatigue	119 (56%)	185 (54%)
Nausea	107 (50%)	166 (48%)
Dyspnea	91 (43%)	145 (42%)
Diarrhea	90 (42%)	151 (44%)
Hyperbilirubinemia	78 (36%)	136 (39%)
Febrile neutropenia	76 (36%)	105 (30%)
Musculoskeletal pain	76 (36%)	124 (36%)
Anemia	74 (35%)	110 (32%)
Cough	73 (34%)	112 (32%)
Decreased appetite	73 (34%)	117 (34%)
Vomiting	73 (34%)	112 (32%)
Edema	72 (34%)	115 (33%)
Pneumonia	66 (31%)	102 (30%)
Rash	63 (29%)	99 (29%)
Pyrexia	62 (29%)	96 (28%)
Hypokalemia	57 (27%)	90 (26%)
Constipation	55 (26%)	93 (27%)
Mucositis	52 (24%)	91 (26%)
Headache	50 (23%)	72 (21%)
Renal insufficiency	49 (23%)	86 (25%)
Leukocytosis	48 (22%)	68 (20%)
Hepatic injury	46 (21%)	65 (19%)
Sepsis	45 (21%)	74 (21%)
Thrombocytopenia	43 (20%)	72 (21%)

Source: FDA Analysis
Note: Includes TEAE reported in ≥ 20% of patients with relapsed or refractory AML treated with 100 mg enasidenib daily (Primary Safety Pool).
[1] Includes grouped terms (see Appendix 13.5)

Common (in ≥ 5% of patients with relapsed/refractory AML who received 100 mg enasidenib daily) Grade ≥ 3 TEAE occurring either on enasidenib or within 28 days after discontinuation of

enasidenib are summarized by preferred term in Table 66. No new common Grade ≥ 3 adverse events were detected in the analysis of the Sensitivity Safety Pool. While Grade ≥ 3 febrile neutropenia was more common in the Primary Safety Pool than the broader study population (34% vs 29%), rates of Grade ≥ 3 infection (e.g. pneumonia, sepsis) were similar in the two pools.

Table 66: Common Grade ≥ 3 TEAE

Preferred Term[1]	Primary Safety Pool (n=214)	Sensitivity Safety Pool (n=345)
Febrile neutropenia	73 (34%)	100 (29%)
Anemia	57 (27%)	83 (24%)
Pneumonia	54 (25%)	84 (24%)
Sepsis	41 (19%)	68 (20%)
Dyspnea	39 (18%)	62 (18%)
Thrombocytopenia	37 (17%)	63 (18%)
Hyperbilirubinemia	22 (10%)	46 (13%)
Leukocytosis	22 (10%)	30 (9%)
Hypokalemia	19 (9%)	28 (8%)
Fatigue	17 (8%)	32 (9%)
Diarrhea	17 (8%)	24 (7%)
Urinary tract infection	17 (8%)	22 (6%)
Platelet count decreased	16 (7%)	25 (7%)
Differentiation syndrome	15 (7%)	22 (6%)
Hypotension	14 (7%)	23 (7%)
Neutropenia	14 (7%)	21 (6%)
Hyperglycemia	12 (6%)	14 (4%)
GI hemorrhage	12 (6%)	23 (7%)
Tumor lysis syndrome	12 (6%)	24 (7%)
Nausea	11 (5%)	17 (5%)
Musculoskeletal pain	11 (5%)	18 (5%)
Mucositis	11 (5%)	16 (5%)
Hepatic injury	11 (5%)	17 (5%)
Fungal infection	11 (5%)	14 (4%)
Hypophosphatemia	10 (5%)	16 (5%)
Clostridial infection	10 (5%)	17 (5%)

Source: FDA Analysis
Note: Includes TEAE reported in ≥ 5% of patients with relapsed or refractory AML treated with 100 mg enasidenib daily (Primary Safety Pool).
[1] Includes grouped terms (see Appendix 13.5)

Common (in ≥ 5% of patients with relapsed/refractory AML who received 100 mg enasidenib daily) TEAE suspected to be possibly or probably related to enasidenib by the investigator are summarized by preferred term in Table 67. No new suspected related adverse events were detected in the analysis of the Sensitivity Safety Pool.

Table 67: TEAE Suspected to Be Possibly or Probably Related to Enasidenib

Preferred Term[1]	Primary Safety Pool (n=214)		Sensitivity Safety Pool (n=345)	
	All grades	Grade 3-5	All grades	Grade 3-5
Hyperbilirubinemia	68 (32%)	14 (7%)	116 (34%)	33 (10%)
Nausea	59 (28%)	5 (2%)	93 (27%)	8 (2%)
Decreased appetite	41 (19%)	4 (2%)	61 (18%)	7 (2%)
Fatigue	39 (18%)	4 (2%)	61 (18%)	10 (3%)
Vomiting	37 (17%)	2 (1%)	52 (15%)	3 (1%)
Diarrhea	34 (16%)	3 (1%)	53 (15%)	4 (1%)
Hepatic injury	30 (14%)	6 (3%)	41 (12%)	9 (3%)
Differentiation syndrome	28 (13%)	15 (7%)	38 (11%)	22 (6%)
Rash	27 (13%)	5 (2%)	41 (12%)	6 (2%)
Dysgeusia	22 (10%)	0	34 (10%)	0
Dyspnea	22 (10%)	12 (6%)	32 (9%)	15 (4%)
Leukocytosis	16 (7%)	5 (2%)	25 (7%)	10 (3%)
Peripheral neuropathy	15 (7%)	0	23 (7%)	10 (3%)
Anemia	14 (7%)	12 (6%)	25 (7%)	19 (6%)
Pyrexia	14 (7%)	2 (1%)	16 (5%)	3 (1%)
Hyperuricemia	12 (6%)	3 (1%)	18 (5%)	5 (1%)
Renal insufficiency	11 (5%)	2 (1%)	16 (5%)	4 (1%)
Weight decreased	11 (5%)	0	15 (4%)	1 (<1%)
Edema	10 (5%)	2 (1%)	18 (5%)	2 (1%)

Source: FDA Analysis
Note: Includes TEAE reported in ≥ 5% of patients with relapsed or refractory AML treated with 100 mg enasidenib daily (Primary Safety Pool).
[1] Includes grouped terms (see Appendix 13.5)

Reviewer comment: Overall, the spectrum, frequency, and severity of TEAE observed on Study AG-221-C-001 are consistent with those expected in the general relapsed/refractory AML population with the exception of hyperbilirubinemia, and differentiation syndrome (which can be associated with hypotension, dyspnea, hepatic injury and edema), which were discussed in more detail above.

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 applicant noted the following observations with respect to laboratory findings (Module 2.5 Clinical Overview Section 5.7):

- Hemoglobin mean values were stable following treatment initiation and showed steady and sustained improvements to > 10 g/dL by Cycle 6.
- 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.

- Increases in mean uric acid, mean serum creatinine, and mean total bilirubin were noted early upon treatment initiation, with levels stabilizing by Cycle 2, Day 1 with no further clinically relevant increases observed in subsequent cycles.
- An initial increase in mean lactate dehydrogenase level (already elevated at baseline) was observed early in treatment and subsequently subsided with continuation of treatment, returning to baseline level at Cycle 4, with further trending to normalization at Cycles 5 and 6.

Additional detail was provided by the applicant with respect to changes in hematologic parameters over time in the lab value versus cycle graphs provided in Figure 18.

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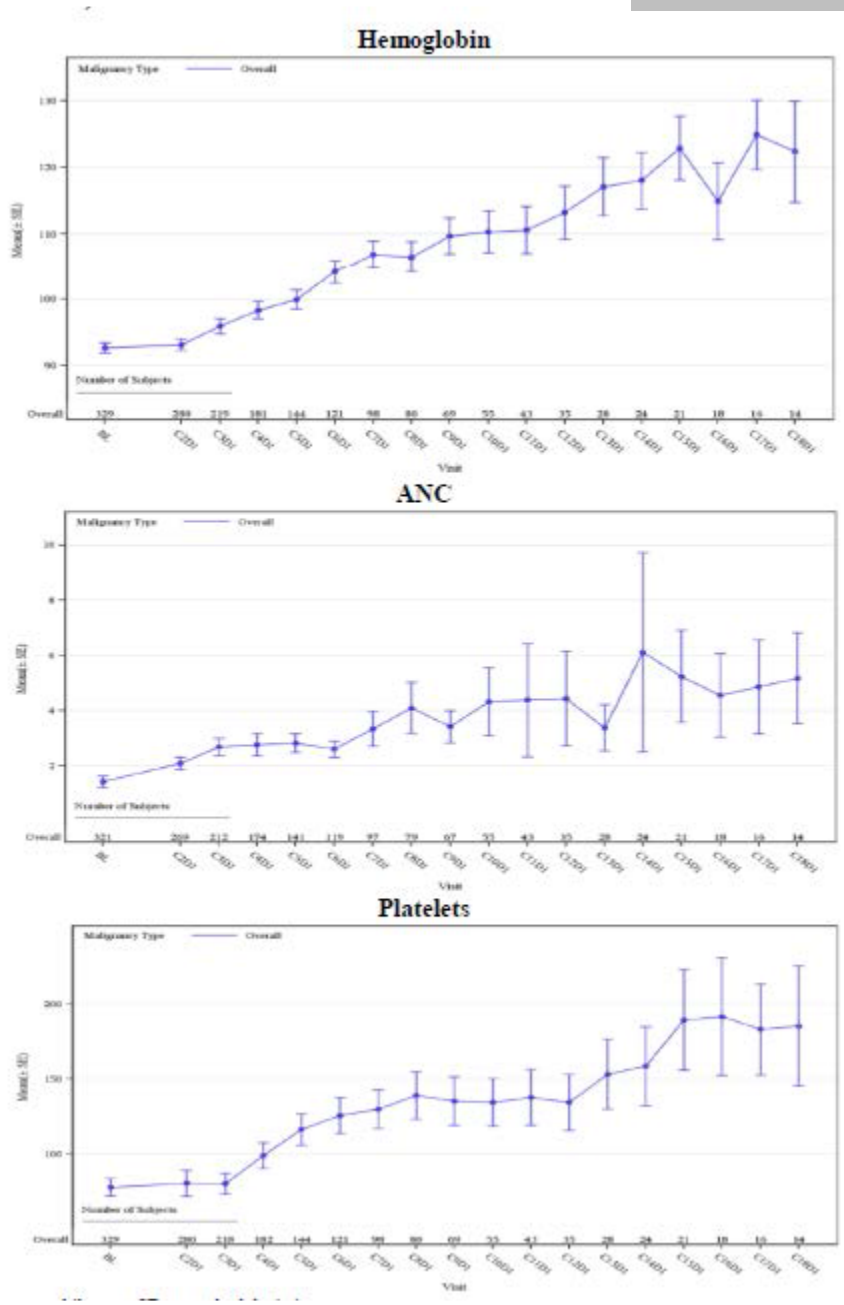
Figure 18: Mean (±SD) of Hemoglobin (g/L), ANC (10^9/L), and Platelets (10^9/L) by Visit for All Subjects on AG-221-C-001



Source: Module 2.5 Clinical Overview Section 5.7
Note: The applicant used day 1 values in each cycle for each subject

Reviewer comment: Although the hematologic lab value versus time graphs are biased because over time, the denominator is enriched for patients who are responding to enasidenib, there clearly is no treatment-related adverse impact of enasidenib on peripheral blood counts. As patients without progressive disease were advised to stay on study for at least 6 cycles given the

observation that responses to enasidenib improved with time, the observed improvements in hemoglobin, ANC and platelets in the first 6 months support the FDA's conclusion that enasidenib provides clinical benefit in patients with relapsed or refractory AML (see Section 7.3).

Vital Signs

The applicant did not identify any unexpected trends or clinically meaningful post-baseline findings in vital sign parameters.

The FDA noted that potentially clinically significant post-baseline systolic blood pressure elevations, defined as value ≥ 160 mmHg, were observed in 10.2% (n=22) of subjects in the Primary Safety Pool and 12% (n=41) of subjects in the Sensitivity Safety Pool (Table 68). Hypertension was reported as an adverse event in 5% (n=11) of subjects in the Primary Safety Pool, and was Grade ≥ 3 in 1% (n=3).

The FDA noted that potentially clinically significant post-baseline systolic blood pressure decreases, defined as value < 90 mmHg, were observed in 7% (n=15) of subjects in the Primary Safety Pool and 6% (n=21) of subjects in the Sensitivity Safety Pool (Table 68). A total of 56 events of hypotension (using grouped preferred term, see Appendix 13.5 for grouping) were reported as an adverse event in 20% (n=42) of subjects in the Primary Safety Pool. Grade ≥ 3 hypotension was reported in 5% (n=15) of subjects.

Table 68: Vital Sign Abnormalities

	Primary Safety Pool (n=214)	Sensitivity Safety Pool (n=345)
SBP ≥ 160 mm Hg	22 (10%)	41 (12%)
SBP < 90 mm Hg	15 (7%)	21 (6%)
DBP ≥ 100 mm Hg	3 (1%)	4 (1%)
Heart rate < 50 bpm	3 (1%)	6 (2%)
Heart rate > 120 bpm	17 (8%)	25 (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 enasidenib rarely occurred in isolation and appears generally secondary to sepsis and/or differentiation syndrome.

Electrocardiograms (ECGs)

ECGs were obtained in triplicate at baseline, at a number of time points on Day 1 of Cycles 1 and 2 (along with time-matched PK samples), and at the end of treatment. Additional single 12-lead ECGs were collected on Day 1 of every cycle beginning with Cycle 3. Arrhythmias occurred in 48 (14%) of patients in the Sensitivity Safety Pool. The most frequently reported arrhythmias

were tachycardia (n=17), atrial fibrillation (n=15), sinus tachycardia (n=6) and sinus bradycardia (n=5).

Reviewer comment: These findings are similar to what would be expected in the underlying patient population. No safety signal was identified based on review of adverse events related to ECG findings.

QT

The hERG assay demonstrated that enasidenib and its metabolites had low potential to adversely effect ion channel flux (see Section 5.3). There was no dedicated QT study. The applicant conducted an analysis of ECG intervals in all subjects treated on Phase 1 of Study AG-221-C-001 (n=239). The results of the applicant's analysis are shown in Table 69. They concluded that enasidenib had no effect on cardiac repolarization.

Table 69: Maximum Postbaseline Absolute QTcF Interval

QTcF Category	R/R AML 100 mg daily dose (N=109)	All Subjects (N=239)
Baseline value		
≤ 480 msec	105 (96%)	230 (96%)
> 480 to ≤ 500 msec	3 (3%)	6 (3%)
> 500 msec	1 (1%)	2 (1%)
QTcF maximum postbaseline value		
≤ 480 msec	97 (89%)	211 (88%)
> 480 to ≤ 500 msec	6 (6%)	17 (7%)
> 500 msec	6 (6%)	11 (5%)
QTcF increased from baseline		
≤ 30 msec	67 (62%)	163 (68%)
> 30 to ≤ 60 msec	36 (33%)	65 (27%)
> 60 msec	6 (6%)	10 (4%)

Source: Applicant's CSR for Study AG-221-C-001, Section 12.4.4.2 (Table 79) located in Module 5.3.5.2 and dated 16 November 2016.

The applicant also reviewed the cardiac adverse events in subjects on Phase 1 of Study AG-221-C-001 and identified a TEAE of QT prolongation in 17 subjects (7%). The applicant provided additional analysis for these cases, and concluded that all subjects were on concomitant medications known to prolong the QT interval (Source: Applicant's CSR for Study AG-221-C-001, Section 12.4.1.5.7 (Table 71) located in Module 5.3.5.2 and dated 16 November 2016).

The FDA Interdisciplinary Review Team (IRT) for QT Studies reviewed the data from Study AG-221-C-001 and found no clinically significant prolongation of QTc interval or relationship between changes in QTc and concentration of enasidenib. The IRT concluded that there is no evidence that enasidenib affects the QTc interval. See Section 6.3.1 for additional information.

Reviewer comment: I agree with the IRT reviewer that there is no evidence to suggest that enasidenib has the potential to delay ventricular repolarization.

7.4.5. Analysis of Submission-Specific Safety Issues

As enasidenib is a new molecular entity, there are no submission-specific safety issues. All adverse events are discussed in Section 7.4.4.

7.4.6. Safety Analyses by Demographic Subgroups

As reporting of race and ethnicity was incomplete on the trial, and few subjects were non-white or Hispanic and Latino, safety was not analyzed by these variables.

The applicant conducted an analysis of TEAEs by age and identified only two TEAEs with a difference in incidence across the age groups (source: SCS Section 5.1.1.1):

- Febrile neutropenia was more common (36%) in subjects with age < 70 than in subjects with age ≥ 70 (19%). This may be related to the increased number of prior regimens associated with myelotoxicity in younger subjects.
- Dyspnea was more common (34%) in subjects with age ≥ 60 than in subjects with age < 60 (14%).

The applicant conducted an analysis of TEAEs by sex and found no clinically relevant differences in the spectrum or severity of TEAEs by sex. They also found no differences in TEAEs that led to study drug discontinuation or dose modification by sex (source: SCS Section 5.1.1.2).

7.4.7. Specific Safety Studies/Clinical Trials

Study AG221-C-001 included dose-escalation portion in which patients were treated with enasidenib total daily doses of 50 mg - 650 mg. There was 1 DLT at the highest dose level, and an MTD was not identified according to the protocol-specified definition. A dose reduction was required for 17% vs 17% vs 39% in the cohorts with enasidenib total doses < 100 mg, 100 mg or > 100 mg, respectively (Study AG221-C-001 Clinical Study Report Table 42).

For all 266 subjects with relapsed or refractory AML treated on the dose-escalation portion or on any of the other portion of the Study AG221-C-001, the applicant provided an analysis of adverse events by total daily enasidenib dose < 100 mg, 100 mg, or > 100 mg. Differentiation syndrome (reported as retinoic acid syndrome) occurred in 0 vs 13% vs 13%, respectively. The only adverse reactions occurring in at least 10% of the subjects in the highest dose cohort and that appeared to be dose-related were hyperglycemia (0 vs 10% vs 21%), hyponatremia (0 vs 11% vs 17%), weight decreased (0 vs 11% vs 17%) , hypophosphatemia (0 vs 9% vs 15%), pruritus (0 vs 8% vs 13%), dyspepsia (0 vs 8% vs 13%), and dysphagia (0 vs 3% vs 10%) (Study AG221-C-001 Clinical Study Report Table 14.3.1.6.6). The exposure-safety analysis revealed a

significant relationship between exposure and bilirubin elevation (Table 83, Appendix 13.4.3); this was not associated with elevations in transaminases, so the relationship was concluded to reflect the known affect of enasidenib on UGT1A1.

There was no dedicated QT study or dedicated study in patients with hepatic or renal impairment. See Section 6.3.1 for a discussion of QT data from Study AG-221-C-001 and Section 6.3.2 for a discussion of data in patients with mild hepatic impairment who received enasidenib.

7.4.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

A formal human carcinogenicity study was not conducted for enasidenib. Neoplasms (identified using the Neoplasms, Benign, Malignant and Unspecified SOC) were rare on Study AG221-C-001. A second primary neoplasm was identified in 13 subjects (4%) in the Sensitivity Safety Pool. Of these, 3 patients developed benign tumors (lipoma, hemangioma and papilloma) and 5 patients developed skin cancers that are typically resectable (basal cell carcinoma, squamous cell carcinoma of the skin). The remaining 5 developed lung adenocarcinoma, oropharyngeal squamous cell carcinoma, breast cancer, malignant melanoma, and neoplasm not further specified. 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

The applicant was granted Orphan Designation for enasidenib for the treatment of patients with AML and is therefore exempt from pediatric studies under the Pediatric Research Equity Act (PREA).

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The applicant did not provide any reported cases of overdose of enasidenib in the AML population. Enasidenib does not have abuse potential.

7.4.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Enasidenib 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.

7.4.10. Integrated Assessment of Safety

The safety of enasidenib was evaluated in detail in 214 patients with relapsed or refractory AML who were assigned to receive 100 mg daily. The median duration of exposure was 4.3 months (range 0.3 to 23.6). The 30-day and 60-day mortality rates observed were 4.2% (9/214) and 11.7% (25/214), respectively.

Three adverse reactions merit close consideration:

- *Differentiation syndrome*: Some patients treated with enasidenib developed differentiation syndrome; the presumed signs and symptoms included hypoxemia requiring supplemental oxygen (76%), pulmonary infiltrates (73%), renal impairment (70%), dyspnea (68%), pleural effusion (45%), fever (36%), lymphadenopathy (33%), bone pain (27%), peripheral edema with rapid weight gain (21%), and pericardial effusion (18%). Hepatic, renal, and multi-organ dysfunction were also been observed. Differentiation syndrome occurred as early as 10 days and at up to 5 months after start of enasidenib. Based on multiple methods of case ascertainment, the incidence appears to be 13-33%. 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 the majority of subjects. However, the true frequency, defining characteristics, and best management practices are not fully defined.

TL Reviewer Comment: Since differentiation syndrome can be fatal, this adverse reaction merits a Warning in the Prescribing information. Since most treatment will be in the outpatient setting, a Medication Guide for the patients will also be needed. Since differentiation syndrome was recognized as an entity well after start of the study, it is not clear that the data available fully characterized the syndrome or that the optimal approach for diagnosis and mitigation are in place. This warrants further study in the postmarketing period.

- *Hyperbilirubinemia*: Enasidenib inhibits UGT1A1, thereby causing hyperbilirubinemia in animal models as well as patients. The hyperbilirubinemia is dose-dependent, stable over prolonged drug administration, not associated with other signs or symptoms of liver toxicity, and resolves when the drug is temporarily interrupted.

- *Hyperleukocytosis*: Although most cases of hyperleukocytosis resulted from progression of AML, treatment with enasidenib was associated with hyperleukocytosis without progressive disease in a small proportion of patients, frequently in association with differentiation syndrome. Hyperleukocytosis was managed with hydroxyurea and/or drug interruption in the protocol.

TL Reviewer Comment: Although hyperbilirubinemia and hyperleukocytosis may be disconcerting, treatment discontinuation is not always required. The Prescribing Information should provide clear instructions on management of these entities.

The most common adverse reactions (≥20%) of any grade were nausea, vomiting, diarrhea, elevated bilirubin and decreased appetite.

Serious adverse reactions were reported in 77% of patients. The most frequent serious adverse reactions (≥2%) were leukocytosis (10%), diarrhea (6%), nausea (5%), vomiting (3%), decreased appetite (3%), tumor lysis syndrome (5%), and differentiation syndrome (8%).

Overall, 92 of 214 patients (43%) required a dose interruption due to an adverse reaction; the most common adverse reactions leading to dose interruption were differentiation syndrome (4%) and leukocytosis (3%). Ten of 214 patients (5%) required a dose reduction due to an adverse reaction; no adverse reaction required dose reduction in more than 2 patients. Thirty-six of 214 patients (17%) permanently discontinued IDHIFA due to an adverse reaction; the most common adverse reaction leading to permanent discontinuation was leukocytosis (1%).

TL Reviewer Comment: Although differentiation syndrome can be life-threatening and is potentially fatal, overall, there were few discontinuations due to adverse reactions, suggesting that enasidenib 100 mg daily was tolerable in this population.

SUMMARY AND CONCLUSIONS

7.5. 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 draw.
- The investigator assessed CR rate and sponsor assessed CR rate are different. In pooled analysis, the investigator assessed response rate was 19.3% with 95% CI of (14.2, 25.4); the sponsor assessed CR rate 14.5% with 95% CI of (10.0, 20.0).
- Even though the demographic and baseline disease characteristics of the trial populations between Phase 1 and Phase 2 study are consistent, the sponsor assessed CR rate were different across the two trials. In the Phase 1 study, the sponsor assessed CR rate was 16.5% with 95% CI of (9.9, 25.1); while in the Phase 2 study, the sponsor assessed CR rate was 12.5% with 95% CI of (6.8, 20.4).
- There were more deaths in the Phase 1 population (63.1% compared to those from the Phase 2 population 54.8%). The median OS time in the Phase 2 population of 6.6 months was shorter in comparison with Phase 1 population of 9.1 month. However, differences in median follow-up times are noted (8.3 and 5.5 months for Phase 1 and 2, respectively).
- Follow-up time in the phase 2 study is limited.

7.6. **Conclusions and Recommendations**

The efficacy of enasidenib 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 AG221-C-001. With a median follow-up of 6.6 months, the 199 adults treated in the study had a CR/CRh rate of 23% (95% CI 18, 30), the median duration of response was 8.2 months, and 34% 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. Enasidenib was well-tolerated with only a minority of patients discontinuing due to adverse reactions. Serious risks, such as differentiation syndrome, 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 enasidenib.

Qing Xu, PhD
Primary Statistical Reviewer

Yuan-Li Shen. Dr. PH
Statistical Team Leader

Ashley Ward, MD
Primary Clinical Reviewer

Donna Przepiorka, MD, PhD
Clinical Team Leader

8 Advisory Committee Meeting and Other External Consultations

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

9 Pediatrics

The Applicant was granted Orphan Designation for enasidenib for the treatment of patients with AML and is therefore exempt from pediatric studies under the Pediatric Research Equity Act (PREA). There is no data regarding the use of enasidenib in children.

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10 Labeling Recommendations

10.1. Prescribing Information

The following are recommended major changes to the enasidenib prescribing information proposed by the applicant based on this review:

- **HIGHLIGHTS:** Add a boxed warning describing differentiation syndrome. See edits to Section 1, also reflected in Highlights.

- **1 INDICATIONS AND USAGE:** Remove [redacted] from the indication statement. Added "as detected by an FDA-approved test" to reference the method for determining IDH2 mutations. Added "adult" to indication statement to provide clear communication about the indicated populations. Removed the [redacted] from the indication statement to enhance the clarity of the indication. Removed [redacted].

- **2 DOSAGE AND ADMINISTRATION:** Add a section on patient selection that describes the companion diagnostic. Modify dose modifications for toxicities to provide more specific and detailed guidance for the physician.

- **5 WARNINGS AND PRECAUTIONS:** Add embryo-fetal toxicity. Remove [redacted]

- **6 ADVERSE REACTIONS:** [redacted] describe adverse reactions [redacted] in patients with relapsed/refractory AML who received a 100 mg daily dose [redacted]. Use a data cut date of October 14, 2016. Characterize laboratory abnormalities separately from adverse reactions. Differentiation syndrome should be defined as described in Section 7.4 of this review and the frequency adjusted accordingly. Relocated required verbatim statement from section 6 to within section 6.1 because text between main sections and numbered subsections may not be captured by electronic providers of labeling information. Changed the term [redacted] to "adverse reactions" per the Adverse Reactions labeling guidance recommendations. Removed the term [redacted] because it is not clinically meaningful. Recommended (per Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products Guidance) rounding of adverse reaction rates to whole integers. Revise list of adverse reactions and laboratory abnormalities to occur in descending order (by all grades) within each body system.

- **8 USE IN SPECIFIC POPULATIONS: 8.1 Pregnancy** Revised this section to be consistent with the PLLR Final Rule and Guidance. Per the PLLR Guidance, the risk statement based on animal data must include (§201.57(c)(9)(i)(B)(2)) the animal doses expressed in terms of human dose or exposure equivalents. Requested that the animal doses in terms of human dose or exposure equivalents be added. Replaced (b) (4) with "embryofetal mortality and alterations to growth", per PLLR Guidance, adverse developmental outcomes include these four: structural abnormalities, embryo-feta and/or infant mortality, functional impairment, and alterations to growth. Revised with 'within section cross-reference' format to *(see Data)* per the PLLR guidance.

  8.3 FEMALES AND MALES OF REPRODUCTION POTENTIAL Added text that was in 12.4 regarding the information that IDHIFA may increase or decrease the concentrations of combined hormonal contraceptives. This text is relevant to the selection of contraceptive methods in patients, and is relevant here.

- (b) (4)

- **14 CLINICAL STUDIES:** Revise this section to describe the rate of CR/CRh and duration of CR/CRh in patients with relapsed/refractory AML who received a 100 mg daily dose. Use a data cut date of October 14, 2016. Exclude (b) (4) Per OND policy, added the trial number and NCT number to ease identification of trials included in labeling.

- **17 PATIENT COUNSELING INFORMATION:** Revised this section to remove description of (b) (4) Added text regarding lactation recommendations to be consistent with Section 8.2.

10.2. Patient Labeling

A Medication Guide was not initially included in the prescribing information by the Applicant, but was requested by the FDA to convey the risks, signs and symptoms of differentiation syndrome and the importance of early communication with the healthcare provider if a patient notes any of these signs or symptoms.

10.3. Container Labeling

The Division of Medical Policy Programs (DMPP) in the Office of Medical Policy recommended changes in the container labels in regard to prominence of proprietary and established names, inclusion of important administration information, bar code, lot number and expiration number to decrease the likelihood of medication errors.

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11 Risk Evaluation and Mitigation Strategies (REMS)

The risks of enasidenib, including differentiation syndrome, 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 concurs with this assessment.

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12 Post-marketing Requirements and Commitments

One clinical study to characterize drug-induced differentiation syndrome and two clinical trials of risks of long-term use will be required under FDAAA:

1. Conduct a meta-analysis to characterize enasidenib-related differentiation syndrome, specifically incidence, appropriate diagnostic criteria, and effective treatment based on patient-level data and pooled analyses for on-going trials in patients with acute myeloid leukemia: AG221-C-001, AG-120-221-C-001, AG-221-AML-004, and AG-221-AML-005. Submit the study report and analysis data set.
2. Characterize the long-term safety of enasidenib in patients with relapsed or refractory acute myeloid leukemia (AML). Submit the final study report and data (b) (4) with 3 years of follow-up from Study AG-221-C-001, *A phase 1/2, multi-center, open-label, dose-escalation and expansion, safety, pharmacokinetic, pharmacodynamics, and clinical activity study of orally administered AG-221 in subjects with advanced hematologic malignancies with an IDH2 mutation*. Include data from approximately 280 patients with relapsed or refractory AML.
3. Conduct a trial to provide evidence sufficient to characterize the long-term safety of enasidenib compared to conventional care regimens in patients with acute myeloid leukemia (AML). Submit the final study report and data set with 3 years of follow-up from ongoing Study AG-221-AML-004, *A phase 3, multicenter, open-label, randomized study comparing the efficacy and safety of AG-221 versus conventional care regimens in older subjects with late stage acute myeloid leukemia harboring an isocitrate dehydrogenase 2 mutation*. Include data from approximately 140 patients with relapsed or refractory AML. Include in the final study report the exploratory subgroup analyses and corresponding subject-level data related to pre- and post-treatment cytogenetics, specific IDH2 mutations, and mutation analyses for other genes (e.g., IDH2, FLT3, NPM1, CEBPA, DNMT3A, NRAS) as obtained under the trial protocol or from medical history prior to trial enrollment.

Two pharmacokinetic clinical studies will be required under FDAAA:

1. Conduct clinical pharmacokinetic trials to evaluate the effect of multiple doses of enasidenib on the single dose pharmacokinetics of sensitive substrates of CYP3A4, CYP2D6, CYP2C19, CYP2C9, UGTs, P-gp, and BCRP to address the potential for excessive drug toxicity. This trial should be designed and conducted in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”
2. Conduct a clinical pharmacokinetic trial to determine an appropriate dose of enasidenib in patients with hepatic impairment. 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.”

13 Appendices

13.1. References

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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): AG221-C-001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 290		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
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: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Nonclinical Pharmacology/Toxicology

Not applicable.

13.4. OCP Appendices (Technical documents supporting OCP recommendations)

13.4.1. Summary of Bioanalytical Method Validation and Performance

Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Yes. The plasma concentrations of the parent drug enasidenib and its active metabolite M1 (AGI-16903, N-dealkylation) were measured in the clinical pharmacology and biopharmaceutics studies.

Based on the mass-balance Study AG-221-CP-002, enasidenib was the main circulating moiety in plasma (89%). The circulating metabolites included the active metabolite M1 (AGI-16903, N-dealkylation) which represented 10% of the circulating radiolabel. No major metabolites were identified. Unchanged parent drug accounted for 34% of the dose in feces and 0.4% of the dose in urine, and M1 represented approximately 16% of the dose in feces and 0.5% of the dose in urine. Table 70 lists the metabolites profile from the plasma, feces, and urine.

Table 70: Enasidenib Metabolite Profile in Human Plasma and Excreta in Study AG-221-CP-002

Radioactivity Components		Excretion (% Dose)			Plasma	
		Urine	Feces	Total	AUC_{0-24} (ng Eq*h/mL)	$\%AUC_{0-24}$ Ratio to TRA
Total % Dose in Samples Analyzed for Profiling		7.95	63.9	71.8	24200	------
AG-221	Parent	0.3	24.6	24.9	21600	89
M1	AGI-16903, N-dealkylation	0.3	11.6	11.9	2520	10
M2	AGI-17011, oxidation	ND	4.3	4.3	61.4	0.3
M5	N-dealkylation, oxidation, olucuronidation	0.5	2.9	3.4	ND	NA
M5a	N-dealkylation, oxidation, glucuronidation	0.7	ND	0.7	ND	NA
M6	Oxidation	0.4	ND	0.4	15.1	0.06
M7	Oxidation, olucuronidation	0.3	ND	0.3	NC	NA
M10	Glucuronidation	0.8	ND	0.8	NC	NA
M12	Oxidation	ND	1.6	1.6	ND	NA
M13	N-dealkylation, oxidation	< 0.1	9.6	9.6	ND	NA
M19	N-dealkylation, glucuronidation	0.3	1.6	1.9	ND	NA

[a] = Excretion data reflect measurements out to 168 hours.
AUC_{0-24}: Area under the plasma concentration-time curve from time 0 to 24 hour.
NA = not applicable; ng-Eq = nanogram equivalents; NC = not calculated; ND = not detected.
TRA: Total Radioactivity (TRA).

Source: Study AG-221-CP-002, Table 9.

For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

The total plasma concentration of enasidenib and AGI-16903 were measured in the clinical trials. It was appropriate to measure total concentration because the average binding to proteins in human plasma was independent of concentration (0.2 mcg/mL to 10 mcg/mL) and was 98.5% for enasidenib and 96.6% for AGI-16903 (Table 71).

Table 71: Protein Binding for Enasidenib (AG-221) and its Metabolite

	Percentage Protein Bound in Human Plasma			
Plasma concentration	0.2 µM	1 µM	10 µM	Average
AG-221	98.7	98.6	98.3	98.5
AGI-16903	96.6	96.8	96.4	96.6

Source: Applicant's Question Based Assessment, Table 18.

What bioanalytical methods are used to assess concentrations?

One method ((b) (4)13027) was used for the analysis of enasidenib and its active metabolite AGI-16903 (N- dealkylation) in human plasma samples collected during clinical studies. The liquid chromatography-tandem mass spectrometry (LC/MS/MS) method was validated (validation report AG221-Q-005) and used to analyze samples from studies AG-221-CP-001, AG-221-CP-002, AG-221-C-001, and AG221-C-002. The parameters described indicate that the method was adequate to estimate the concentration data. Table 72 lists the range of the standard curve and the curve fitting techniques applied to measure enasidenib and AGI-16903 in human plasma. The standard curve ranges were adequate for the purposes of determining plasma concentrations of enasidenib and AGI-16903 in the clinical studies.

Table 72: Summary of Bioanalytical Methods

Parameter	Enasidenib	AGI-16903
Method	(b) (4) 13027 ((b) (4))	(b) (4) 13027 ((b) (4))
Standard Curve		
- Range	1 to 1000 ng/mL	1 to 500 ng/mL
- Model	Linear	Linear
- Weighting Factor	$1/x^2$	$1/x^2$
Lower Limit of Quantification	1 ng/mL	1 ng/mL
Upper Limit of Quantification	1000 ng/mL	500 ng/mL
Accuracy	Intra- and inter-assay precision and accuracy	
Precision	Mean bias within ±15% (±20% at LLOQ) <15% (<20% at LLOQ)	
Sample Stability		
Freeze-Thaw		
In plasma		
- - 20 ºC	4 times	4 times
- - 70 ºC	4 times	4 times
Long-Term Solution		
- - 20 ºC	51 days	51 days
Bench-Top Solution		
- Room temperature	1 day	1 day
QC Concentrations	1 ng/mL 3 ng/mL 40 ng/mL 400 ng/mL 800 ng/mL	1 ng/mL 3 ng/mL 20 ng/mL 200 ng/mL 400 ng/mL

13.4.2. Clinical PK

Enasidenib PK was studied after a single dose in healthy subjects in three studies. The PK parameters are summarized in Table 73, Table 74, and Table 75.

- Study AG-221-CP-001: comparison between Japanese and Caucasian;
- Study AG-221-CP-002: mass balance and oral bioavailability; and
- Study AG221-C-002: effect of food

Table 73: Summary of Enasidenib Pharmacokinetics in Healthy Japanese and Caucasian Subjects

Cohort	Dose (mg)	Race	AUC_t (ng•h/mL)	AUC_∞ (ng•h/mL)	C_{max} (ng/mL)	T_{max}[a] (h)	$t_{1/2}$ (h)	CL/F (mL/h)	V_z/F (mL)
B	50	Japanese (n=10)	21800 (46.9)	21900 (46.7)	533 (41.0)	3.98 (0.98, 8.95)	21.1 (31.6)	2290 (46.7)	69700 (40.9)
		Caucasian (n=9)	17800 (55.0)	18000 (55.0)	406 (34.9)	4.00 (2.02, 24.0)	23.0 (47.4)	2780 (55.0)	92300 (44.5)
A	100	Japanese (n=11)	40500 (47.2)	40700 (47.3)	786 (27.1)	4.00 (1.97, 24.0)	19.5 (45.6)	2460 (47.3)	69000 (25.1)
		Caucasian (n=10)	49200 (27.5)	49500 (27.8)	822 (38.5)	2.99 (1.03, 9.08)	25.5 (51.4)	2020 (27.8)	74400 (41.2)
C	300	Japanese (n=10)	168000 (44.7)	170000 (44.6)	2030 (34.3)	13.4 (1.00, 48.0)	27.7 (35.6)	1760 (44.6)	70300 (15.3)
		Caucasian (n=10)	163000 (44.8)	163000 (44.9)	1780 (27.8)	10.5 (1.97, 24.0)	28.3 (32.0)	1840 (44.9)	74900 (26.9)

AUC = area under the concentration-time curve; AUC_t = AUC from time zero to time t, where t is the last measurable time point; AUC_∞ = AUC from time zero extrapolated to infinity; CL/F = apparent total plasma clearance; C_{max} = maximum observed plasma concentration; CV% = percent coefficient of variation; $t_{1/2}$ = estimate of the terminal eliminationhalf-life; T_{max} = time to C_{max}; V_z/F = apparent total volume of distribution.
[a] Median (minimum, maximum) presented for T_{max}.
Note: Cohorts: A = Single oral dose of 100 mg AG-221, B = Single oral dose of 50 mg AG-221, C = Single oral dose of 300 mg AG-221.

Source: Study AG-221-CP-001, Table 7.

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Table 74: Summary of Enasidenib Pharmacokinetics in Healthy Subjects

Treatment	$AUC_{0-\infty}$ (ng•h/mL)	AUC_{0-t} (ng•h /mL)	C_{max} (ng/mL)	T_{max}[a] (h)	$t_{1/2}$ (h)	Cl/F* (L/h)	Vz/F* (L)	F_{abs} (%)
Oral AG-221 (Dose=100 mg) N = 6	41800 (27.2)	41100 (29.5)	703 (16.4)	3.01 (3.00-24.0)	29.0 (41.4)	2.39 (27.2)	100 (45.2)	57.2 (10.8)
IV ^{14}[C]-AG-221 (Dose=0.1 mg) N = 6	73.0 (21.9)	69.7 (24.2)	2.83 (31.0)	0.117 (0.117-0.500)	28.3 (25.4)	1.37 (21.9)	55.8 (29.1)	NA

[a] T_{max} is summarized by median and range (minimum – maximum)
* F=1 for intravenous dose
N = Number of subjects; CV = Coefficient of variation; C_{max} = Maximum observed plasma concentration; T_{max} = Time to maximum plasma concentration; $t_{1/2}$ = Estimate of the terminal elimination half-life in plasma; AUC_{0-t} = Area under the plasma concentration-time curve from time 0 to the last quantifiable concentration; $AUC_{0-\infty}$ = Area under the plasma concentration-time curve from time 0 extrapolated to infinity; CL/F = Apparent total plasma clearance when dosed orally; V_z/F = Apparent total volume of distribution when dosed orally; F_{abs} = Absolute bioavailability; NA = Not applicable

Source: Study AG-221-CP-002, Table 11.

Table 75: Summary of Enasidenib Pharmacokinetics in Healthy Subjects

Parameter	Geometric Mean (GeoCV%)	
	A: 100 mg AG-221 (Fasting) (N=29)	**B: 100 mg AG-221 (Fed) (N=29)**
AUC_t (µg•h/mL)	54.0 (62.6)	79.9 (50.3)
AUC_∞ (µg•h/mL)	54.3 (62.5)	80.2 (50.2)
C_{max} (µg/mL)	0.816 (45.6)	1.34 (22.7)
t_{max}[a] (h)	4.00 (1.00, 48.08)	4.00 (2.00, 9.00)
$t_{½}$ (h)	31.2 (36.5)	32.5 (36.7)
CL/F (L/h)	1.84 (62.5)	1.25 (50.2)
V_z/F (L)	83.0 (42.6)	58.4 (33.7)

AUC = area under the plasma concentration time curve; AUC∞ = AUC from zero to infinity; AUCt = AUC from zero to the time of last quantifiable concentration; CL/F, apparent clearance, Cmax = maximum observed concentration in plasma; GeoCV% = percent geometric coefficient of variation; t½ = elimination half-life; tmax = time to maximum observed plasma concentration; Vz/F = apparent volume of distribution
[a] Median (minimum, maximum)

Source: Study AG221-C-002 Clinical Study Report Table 8.

In patients, enasidenib and AGI-16903 PK characteristics were evaluated after the first dose and after multiple doses as part of the Phase 1 portion of Study AG221-C-001. The PK parameters are summarized in Tables 76 and 77.

Table 76: Summary of Enasidenib Pharmacokinetics in Patients with Advanced Hematologic Malignancies

A) Single Dose

Plasma PK Parameters	Geometric Mean (Geometric CV%) n								
	30 mg (N=4)	50 mg (N=8)	75 mg (N=9)	100 mg (N=57)	150 mg (N=8)	200 mg (N=11)	300 mg (N=6)	450 mg (N=2)	650 mg (N=1)
AUC_{0-8} (ng*h/mL)	3364 (59.7) 4	2866 (59.9) 8	5319 (57) 9	6579 (80.1) 57	9397 (32.1) 8	11550 (49.2) 11	15268 (42) 6	15039 (NC) 2	31580 (NC) 1
AUC_{0-10} (ng*h/mL)	4120 (61.5) 4	3711 (59.6) 8	6834 (54.1) 9	8544 (77.0) 56	11819 (31.3) 8	14818 (49.2) 11	20727 (41.0) 6	19961 (NC) 2	38711 (NC) 1
AUC_{0-24} (ng*h/mL)	8987 (72.1) 4	9083 (60.8) 8	17330 (50.6) 9	21515 (55.9) 55	28989 (29.6) 8	37703 (48.3) 11	58743 (41.5) 6	60846 (NC) 2	NC 0
AUC_{0-72} (ng*h/mL)	19317 (102.0) 4	19044 (84.7) 6	39972 (55.2) 7	58381 (60.7) 49	76820 (31.2) 8	95217 (57.2) 9	160083 (12.0) 4	244130 (NC) 1	NC 0
AUC_{0-t} (ng*h/mL)	19317 (102) 4	18761 (70.1) 8	38281 (56.0) 9	52593 (74.8) 57	76820 (31.2) 8	95959 (50.5) 11	134094 (32.6) 6	157042 (NC) 2	38711 (NC) 1
C_{max} (ng/mL)	569 (45.6) 4	508 (63.8) 8	1084 (51.6) 9	1272 (56.4) 57	1624 (29.5) 8	2082 (46.5) 11	3358 (43.1) 6	3031 (NC) 2	4670 (NC) 1
T_{max}[a] (h)	1.59 (1.00 - 4.08) 4	4.94 (1.92 - 24.25) 8	3.00 (1.13 - 21.42) 9	4.00 (0.67 - 71.97) 57	3.98 (2.00 - 24) 8	4.08 (1.00 - 48.55) 11	8.89 (2.95 - 72.17) 6	18.61 (13.33 - 23.88) 2	6.17 (6.17 - 6.17) 1
T_{last}[a] (h)	72.25 (70.42 - 73.12) 4	69.04 (48.5 - 73.42) 8	71.13 (47.92 - 73.75) 9	71.75 (9.58 - 75.95) 57	71.98 (70.1 - 72.57) 8	71.57 (47.42 - 72.82) 11	71.44 (24.42 - 72.33) 6	59.88 (48.25 - 71.5) 2	10.00 (10.00 - 10.00) 1

Plasma PK Parameters	Geometric Mean (Geometric CV%) n								
	30 mg (N=4)	50 mg (N=8)	75 mg (N=9)	100 mg (N=57)	150 mg (N=8)	200 mg (N=11)	300 mg (N=6)	450 mg (N=2)	650 mg (N=1)
$t_{1/2}$ (h)	33.2 (124.6) 3	36.0 (62.1) 7	52.6 (109.5) 7	66.6 (92.6) 26	96.2 (60.1) 5	73.8 (18.8) 3	100.1 (NC) 1	NC 0	NC 0

AUC_{0-t} = area under the concentration versus time curve from time zero to the last quantifiable concentration; AUC_{0-8} = area under the concentration versus time curve from 0 to 8 h; AUC_{0-10} = area under the concentration versus time curve from 0 to 10 h; AUC_{0-24} = area under the concentration versus time curve from 0 to 24 h; AUC_{0-72} = area under the concentration versus time curve from 0 to 72 h; C_{max} = maximum concentration; CV% = percent coefficient of variation; NC = not calculated; PK = pharmacokinetic; SD = standard deviation; T_{last} = time last quantifiable concentration; T_{max} = time to reach C_{max}.

[a] Median (min - max)

Note: All subjects who received twice-daily dosing on Day -3 were excluded from the PK analyses on Day -3.

B) Multiple Dose

AG-221 PK Parameters	Geometric Mean (Geometric CV%) n												
	30 mg BID (N=4)	50 mg BID (N=7)	75 mg BID (N=5)	100 mg BID (N=2)	150 mg BID (N=4)	50 mg QD (N=5)	75 mg QD (N=4)	100 mg QD (N=102)	150 mg QD (N=5)	200 mg QD (N=11)	300 mg QD (N=7)	450 mg QD (N=5)	650 mg QD (N=3)
AUC_{0-10} (ng•h/mL)	41108 (63.2) 4	99954 (35.1) 7	126765 (34.6) 5	176539 (NC) 2	200661 (18.9) 4	61226 (117.0) 4	53067 (50.1) 4	106661 (47.7) 90	126237 (37.8) 5	132322 (51.9) 11	131523 (43.0) 7	199749 (24.0) 3	269750 (NC) 2
C_{max} (ng/mL)	5300 (71.9) 4	12538 (39.2) 7	15860 (34.5) 5	26245 (NC) 2	26715 (24.7) 4	6543 (124.9) 5	6922 (64.2) 4	13255 (46.3) 102	15734 (38.6) 5	17517 (61.2) 11	18505 (42.4) 7	28049 (23.4) 5	35269 (10.7) 3
T_{max}[a] (h)	0.50 (0.00, 3.92) 4	2.00 (0.50, 9.83) 7	0.50 (0.00, 1.00) 5	0.73 (0.48, 0.97) 2	1.54 (1.00, 9.83) 4	3.02 (0.00, 10.00) 5	4.04 (1.00, 10.08) 4	1.03 (0.00, 10.00) 102	2.13 (0.70, 9.83) 5	1.02 (0.00, 8.00) 11	5.98 (0 .00, 9.95) 7	4.08 (0.97, 6.00) 5	2.00 (1.95, 3.00) 3
AUC_{0-t} (ng*h/mL)	41108 (63.2) 4	99954 (35.1) 7	126765 (34.6) 5	176539 (36.8) 2	200661 (18.9) 4	51273 (111.1) 5	53067 (50.1) 4	102484 (49.0) 102	126237 (37.8) 5	132322 (51.9) 11	131523 (43.0) 7	202702 (17.8) 5	256155 (16.0) 3
T_{last}[a] (h)	9.92 (9.83, 10.00) 4	10.00 (9.33, 10.00) 7	9.97 (9.83, 10.00) 5	9.93 (9.90, 9.95) 2	9.98 (9.83, 10.00) 4	9.92 (7.83, 10.08) 5	10.01 (8.67, 10.08) 4	9.96 (6.00, 11.5) 102	9.83 (9.83, 10.03) 5	10.00 (9.83, 10.10) 11	9.87 (9.83, 10.00) 7	9.83 (7.88, 10.00) 5	10.00 (7.40, 10.08) 3
$R(AUC_{0-10})$[b]	8.94 (NC) 1	48.88 (NC) 1	17.07 (NC) 2	17.02 (NC) 1	14.95 (NC) 2	8.82 (48.4) 3	9.76 (NC) 2	11.82 (65.9) 35	11.85 (51.6) 5	8.62 (55.2) 7	8.07 (61.2) 4	NC 0	7.94 (NC) 1
$R(C_{max})$[b]	6.28 (NC) 1	42.4 (NC) 1	14.39 (NC) 2	18.47 (NC) 1	14.1 (NC) 2	7.73 (78.2) 3	8.28 (NC) 2	10.31 (59.7) 40	10.72 (45.2) 5	7.72 (63.5) 7	7.63 (79.2) 4	9.29 (NC) 1	8.09 (NC) 1

AUC_{0-t0} = area under the concentration-time curve calculated from time 0 to time 10 hours; AUC_{0-t} = area under the concentration-time curve calculated from time zero to the last measured time point; BID = twice daily; C_{max} = maximum concentration for each dose; NC = not calculated; PK = pharmacokinetic; QD = once daily; $R(C_{max})$ = Accumulation ratio based on Cmax; $R(AUC_{0-10})$ = Accumulation ratio based on AUC_{0-t0}; T_{max} = time to reach C_{max}.; T_{last} = time to the last measured time point.

[a] median (minimum, maximum).

[b] R(AUC) and $R(C_{max})$ were only calculated when subjects had AUC_{0-10} and C_{max} PK parameters for both the single dose administration of AG-221 on Day -3 and the multiple dose steady-state cycle for which accumulation is being computed.

Data cutoff date: 15 Apr 2016

Source: AG-221-C-001-PKPD Study Report Table 7, AG221-C-001 Phase 1 Study Report Table 23 (data cutoff 15 Apr 2016).

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Table 77: Summary of AGI-16903 Pharmacokinetics in Patients with Advanced Hematological Malignancies

A) Single Dose

Plasma PK Parameters	Geometric Mean (Geometric CV%) n								
	30 mg	50 mg	75 mg	100 mg	150 mg	200 mg	300 mg	450 mg	650 mg
	(N=4)	(N=8)	(N=9)	(N=54)	(N=8)	(N=11)	(N=6)	(N=2)	(N=1)
AUC_{0-8} (ng*h/mL)	122 (83.6) 4	179 (148) 8	276 (80.6) 9	269 (102.5) 54	558 (70.3) 8	530 (91.1) 11	526 (58.8) 6	384 (NC) 2	1470 (NC) 1
AUC_{0-10} (ng*h/mL)	162 (80.4) 4	246 (148.3) 8	383 (72.3) 9	370 (97.8) 53	735 (65.1) 8	716 (86.8) 11	757 (57.5) 6	548 (NC) 2	1893 (NC) 1
AUC_{0-24} (ng*h/mL)	474 (80.4) 4	734 (120) 8	1238 (54.4) 9	1200 (70.4) 52	2128 (54.2) 8	2159 (75.4) 11	2477 (51.5) 6	2274 (NC) 2	NC 0
AUC_{0-72} (ng*h/mL)	1403 (93.7) 4	1949 (113.6) 6	3773 (31.4) 7	4204 (58.5) 46	7188 (43.6) 8	7634 (66.2) 9	10673 (29.8) 4	17591 (NC) 1	NC 0
AUC_{0-t} (ng*h/mL)	1403 (93.7) 4	1970 (89.9) 8	3417 (50.7) 9	3698 (83.7) 54	7188 (43.6) 8	7070 (62) 11	6531 (93.9) 6	8035 (NC) 2	1893 (NC) 1
C_{max} (ng/mL)	28.6 (89.3) 4	44.7 (72.3) 8	74.3 (52.3) 9	77.5 (60.1) 54	126 (39.4) 8	138 (47.4) 11	151 (52.4) 6	188 (NC) 2	242 (NC) 1
T_{max} [a] (h)	36.38 (3.00 - 70.42) 4	16.75 (1.92 - 69.50) 8	10.00 (3.00 - 71.00) 9	48.00 (3.00 - 74.42) 54	24.12 (6.20 - 72.10) 8	47.33 (1.98 - 72.82) 11	48.10 (7.95 - 72.17) 6	59.88 (48.25 - 71.50) 2	6.17 (6.17 - 6.17) 1
T_{last} [a] (h)	72.25 (70.42 - 73.12) 4	69.04 (48.50 - 73.42) 8	71.13 (47.92 - 73.75) 9	71.75 (9.58 - 75.95) 54	71.98 (70.10 - 72.57) 8	71.57 (47.42 - 72.82) 11	71.44 (24.42 - 72.33) 6	59.88 (48.25 - 71.5) 2	10.00 (10.00 - 10.00) 1

Plasma PK Parameters	Geometric Mean (Geometric CV%) n								
	30 mg	50 mg	75 mg	100 mg	150 mg	200 mg	300 mg	450 mg	650 mg
	(N=4)	(N=8)	(N=9)	(N=54)	(N=8)	(N=11)	(N=6)	(N=2)	(N=1)
$t_{1/2}$ (h)	18.9 (NC) 1	38.2 (149.1) 3	29.0 (NC) 2	66.6 (189.1) 6	106.4 (NC) 1	NC 0	NC 0	NC 0	NC 0

AUC_{0-t} = area under the concentration versus time curve from time zero to the last quantifiable concentration; AUC_{0-8} = area under the concentration versus time curve from 0 to 8 h; AUC_{0-10} = area under the concentration versus time curve from 0 to 10 h; AUC_{0-24} = area under the concentration versus time curve from 0 to 24 h; AUC_{0-72} = area under the concentration versus time curve from 0 to 72 h; C_{max} = maximum concentration; CV% = percent coefficient of variation; NC = not calculated; PK = pharmacokinetic; SD = standard deviation; $t_{1/2}$= half-life; T_{last} = time last quantifiable concentration; T_{max} = time to reach C_{max}.
[a] Median (Min - Max)
Note: All subjects who received twice-daily dosing on Day -3 were excluded from the PK analyses on Day -3.

B) Multiple Dose

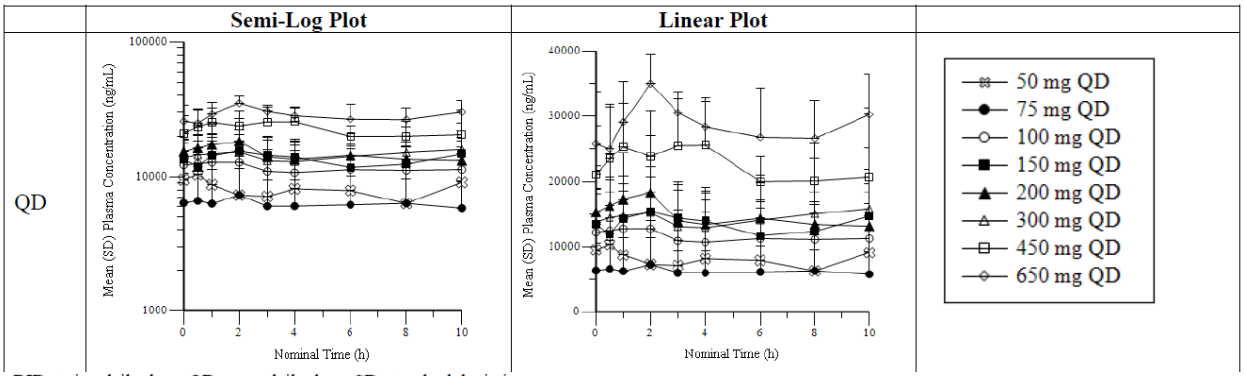
AGI-16903 PK Parameters	Geometric Mean (Geometric CV%) n												
	30 mg BID (N=4)	50 mg BID (N=7)	75 mg BID (N=5)	100 mg BID (N=0)	150 mg BID (N=4)	50 mg QD (N=5)	75 mg QD (N=4)	100 mg QD (N=102)	150 mg QD (N=3)	200 mg QD (N=11)	300 mg QD (N=7)	450 mg QD (N=5)	650 mg QD (N=3)
AUC_{0-10} (ng•h/mL)	4830 (82.9) 4	9437 (46.8) 7	9002 (60.0) 5	NC 0	20705 (16.1) 4	6502 (132.7) 4	3954 (80.6) 4	9640 (41.8) 90	13263 (40.1) 3	14270 (47.4) 11	12448 (35.0) 7	17963 (18.7) 3	22102 (NC) 2
C_{max} (ng/mL)	619 (95.0) 4	1149 (54.0) 7	1096 (62.8) 5	NC 0	2651 (13.6) 4	680 (148.1) 5	518 (99.8) 4	1220 (41.8) 102	1640 (30.2) 3	1791 (55.1) 11	1687 (37.7) 7	2415 (33.2) 5	3135 (38.8) 3
T_{max}[a] (h)	1.50 (0.00, 4.17) 4	2.00 (1.00, 10.00) 7	0.52 (0.33, 7.97) 5	NC 0	1.54 (1.00, 8.00) 4	2.92 (0.00, 3.92) 5	1.58 (1.00, 6.08) 4	1.00 (0.00, 10.00) 102	4.00 (2.00, 9.83) 3	1.00 (0.00, 8.00) 11	5.98 (0.00, 9.95) 7	2.98 (0.97, 6.00) 5	1.97 (1.95, 10.00) 3
AUC_{0-t} (ng*h/mL)	4830 (82.9) 4	9437 (46.8) 7	9002 (60.0) 5	NC 0	20705 (16.1) 4	5181 (133.1) 5	3954 (80.6) 4	9375 (42.3) 102	13263 (40.1) 3	14270 (47.4) 11	12448 (35.0) 7	17846 (33.7) 5	24187 (24.4) 3
T_{last}[a] (h)	9.92 (9.83, 10.00) 4	10.00 (9.33, 10.00) 7	9.97 (9.83, 10.00) 5	NC 0	9.98 (9.83, 10.00) 4	9.92 (7.83, 10.08) 5	10.01 (8.67, 10.08) 4	9.96 (6.00, 11.5) 102	9.83 (9.83, 10.00) 3	10.00 (9.83, 10.1) 11	9.87 (9.83, 10.00) 7	9.83 (7.88, 10.00) 5	10.00 (7.40, 10.08) 3
$R(AUC_{0-10})$[b]	11.85 (NC) 1	242.57 (NC) 1	35.82 (NC) 2	NC 0	27.08 (NC) 2	11.27 (107.6) 3	5.31 (NC) 2	23.10 (96.0) 35	17.68 (113.7) 3	15.63 (89.6) 7	17.98 (33.6) 4	NC 0	14.01 (NC) 1
$R(C_{max})$[b]	9.94 (NC) 1	46.25 (NC) 1	25.37 (NC) 2	NC 0	19.87 (NC) 2	9.06 (78.8) 3	4.56 (NC) 2	14.35 (57.6) 40	13.61 (52.9) 3	10.65 (60.7) 7	12.91 (27.4) 4	12.48 (NC) 1	12.89 (NC) 1

AUC_{0-t0} = area under the concentration-time curve calculated from time 0 to time 10 hours; AUC_{0-t} = area under the concentration-time curve calculated from time zero to the last measured time point; BID = twice daily; C_{max} = maximum concentration for each dose; NC = not calculated; PK = pharmacokinetic; QD = once daily; $R(C_{max})$ = Accumulation ratio based on C_{max}; $R(AUC_{0-10})$ = Accumulation ratio based on AUC_{0-t0}; T_{max} = time to reach C_{max}.; T_{last} = time to the last measured time point.
[a] median (minimum, maximum)
[b] R(AUC) and $R(C_{max})$ were only calculated when subjects had AUC_{0-10} and C_{max} PK parameters for both the single dose administration of AG-221 on Day -3 and the multiple dose steady-state cycle for which accumulation is being computed.
Data cutoff date: 15 Apr 2016

Source: AG-221-C-001-PKPD Study Report Tables 18, AG221-C-001 Phase 1 Study Report Table 25 (data cutoff 15 Apr 2016).

In the Phase 1 portion of Study AG-221-C-001, enasidenib plasma concentrations were measured after a single dose and after multiple doses across the dose range of 30 mg to 650 mg in patients with advanced hematologic malignancies (Figure 19).

Figure 19: Enasidenib Pharmacokinetic Profile in Patients Following Once Daily Dosing



BID: twice-daily dose; QD: once-daily dose; SD: standard deviation
Note: Concentration values not presented for timepoints where N=1.

Source: Study AG-221-C-002 Study Report Figure 7.

13.4.3. Pharmacometrics Assessments

Applicant's PPK analysis:

Objectives:

- To develop a population model describing the PK data of enasidenib and associated inter-individual variability (IIV) and residual variability (RV).
- To assess the influence of covariates of interest on the PK of enasidenib.
- To predict individual exposures for the analysis of E-R for safety and efficacy.

Data, Software, Methods: The analysis dataset had a total of 395 evaluable subjects who received various daily doses (50 mg to 650 mg) of oral enasidenib in single- or multiple-dose regimens. This dataset included 96 healthy subjects from three clinical pharmacology studies and 299 patients with advanced hematologic malignancies from study AG221-C-001 study (as of the 15 Apr 2016 data cutoff date). The summary of the studies and subject or patient distribution in different dose regimens are provided in Table 78 and Table 79.

Table 78: Summary of Studies included in PPK Analysis

Study	Disease	No. of PK Subjects	AG-221 Treatment	Intensive PK sample times
AG221-C-001 Phase 1 dose escalation, part 1 expansion and Phase 2	**Phase 1**: dose escalation and part 1 expansion. Subjects with advanced hematologic malignancies with an IDH2 Mutation **Phase 2:** subjects with relapsed or refractory AML with an IDH2 mutation	**Phase 1**: 225 **Phase 2**: 74	**Phase 1:** BID: single doses of 30, 50, 75, 100, and 150 mg. QD: 50, 75, 100, 150, 200, 300, 450, and 650 mg **Phase 2:** Multiple 100 mg QD	**Phase 1:** Following 72-hour single doses: Pre-dose, 0.5, 1, 2, 3,4, 6, 8, 10, 24, 48, and 72 hour pose-dose on C0D-3 Following multiple doses: Pre-dose, 0.5, 1, 2, 3,4, 6, 8, and 10 hour pose-dose on C1D15, C2D1, C4D1, and C8D1[a]. **Phase 2:** 0, 2, 4, 6, 8, and 24 hours post-dose on C1D1 and C2D1.
AG221-C-002	Healthy subjects	29	100 mg single dose	Pre-dose, 1, 2, 3, 4, 6, 9, 12, 18, 24, 48, 96, 168, 240, 336 and 504 hours post-dose
AG-221-CP-001	Healthy subjects	61	50, 100 and 300 mg single dose	Pre-dose, 0.5, 1, 2, 3, 4, 4.083, 4.25, 4.5, 5, 6,7,8,10, 14, 18, 24, 48, 96, 168, 240, 336, 408, 504, and 672 hours post-dose
AG-221-CP-002	Healthy subjects	6 (in Part 2)	Part 2: A single 100 mg AG-221 tablet administered orally. Four hours after the oral dose, 100 µg AG-221 containing ~300 nCi of [^{14}C]-AG-221 was given intravenously over approximately 2 minutes	Pre-dose, 0.5, 1, 2, 3, 4, 6, 9, 12, 18, 24, 48, 96, 168, 240, 336, 408, 504 and 672 hours after the oral dose

Notes: BID = twice daily; C0D-3 = Cycle 0 Day -3; C1D1 = Cycle 1 Day 1; C1D15 = Cycle 1 Day 15; C2D1 = Cycle 2 Day 1; C4D1 = Cycle 4 Day 1; C8D1 = Cycle 8 Day 1; PK = pharmacokinetic; QD = once daily[a] Only applicable for subjects treated prior to Amendment 6.

Source: Applicant's clinical PK/PD report, AG-221-MPK-001, Table 2, page 16

Table 79: Summary of Populations in Different Dose Regimens in Population Pharmacokinetic Analysis

Patients with advanced hematologic malignancies in AG221-C-001 study													
Initial multiple dose regimen	BID					QD							
Initial multiple dose (mg)	30	50	75	100	150	50	75	100	150	200	300	450	650
AG221-C-001 Phase 1[a]	7	6	7	8	4	8	7	136	6	16	9	5	5
AG221-C-001 Phase 2								74					
Healthy subject in AG221-C-002, AG-221-CP-001 and AG-221-CP-002 study													
AG221-C-002								29					
AG-221-CP-001						19		22		20			
AG-221-CP-002								6					

Notes: One subject in Phase 1 of Study AG221-C-001 had PK data only for first 3 days after single dose. There is no PK data for this subject after multiple doses in the current PPK dataset.

Source: Applicant's clinical PK/PD report, AG-221-MPK-001, Table 5, page 28

PPK modeling was performed on natural logarithm-transformed enasidenib concentration versus time profiles with NONMEM (version 7.2, ICON Development Solution, MD, US) software with the first-order condition estimation (FOCE) with INTERACTION option. IIV was modeled using exponential error model and RV was modeled using a log error model. The PPK model was developed in three stages, including structural model selection, covariate analysis, and model evaluation with goodness-of-fit criteria, visual and numeric predictive checks, and the bootstrap resampling approach. Analysis dataset preparation, data processing, and diagnostic plots were completed using SAS (version 9.2, SAS Institute, Inc., Cary, NC, US) and R (Version 2.15.0 or greater, The R Foundation for Statistical Computing, US). Individual apparent clearance was calculated through NONMEM and exposure metrics (e.g. area under concentration-time curve AUC) were calculated using R.

Enasidenib exposure measure (AUC_{ss}) was calculated based on individual estimates of apparent clearance (CL/F) from the final PPK model and used as predictor variables in the exploratory E-R (efficacy/safety) analysis for 299 patients with advanced hematologic malignancies.

Results:

PPK Parameters: The plasma enasidenib concentrations were well described by a linear one-compartment PPK model with first order absorption and elimination. The PK parameters from the final PPK model are summarized in Table 80 below.

The estimated CL/F for a typical patient with advanced hematologic malignancies was 0.74 L/hr with IIV of 71%. The terminal half-life in patients was estimated to be 137 hours. The CL/F is 3.4-fold lower in patients than in healthy subjects.

Table 80: Parameter Estimates (95% CI) for Enasidenib Final Population Pharmacokinetic Model

Parameter	Estimate	Bootstrap Estimate	95% Bootstrap CI	Shrinkage (%)
Ka for PT and HV (hr^{-1})	0.55	0.55	(0.45, 0.64)	41.9
CL/F for PT (L/hr)	0.74	0.74	(0.68, 0.79)	4.3
V/F for PT (L)	146	153	(98, 194)	25.7
CL/F ratio (HV/PT)	3.39	3.40	(3.03,3.75)	
V/F ratio (HV/PT)	0.78	0.77	(0.54, 1.02)	
Inter-Individual Variability				
ω^2 (Ka) for PT and HV	1.25	1.24	(0.97, 1.53)	
ω^2 (CL/F) for PT and HV	0.41	0.41	(0.34, 0.49)	
ω^2 (V/F) for PT and HV	1.01	1.08	(0.31, 1.71)	
Residual Variability				
δ^2 for HV	0.14	0.14	(0.11, 0.16)	10.7
δ^2 for PT	0.47	0.46	(0.39, 0.55)	3.5

Notes: CI = confidence interval; CL/F= clearance from the central compartment; CL/F ratio (HV/PT) = ratios of apparent clearance between healthy subjects and patients with advanced hematologic malignancies; Ka= first-order absorption rate; HV=healthy subjects; PT=subjects with advanced hematologic malignancies that harbor an IDH2 mutation; V/F = volume of distribution for the central compartment; V/F ratio (HV/PT) = ratios of volume distribution between healthy subjects and patients with advanced hematologic malignancies.

[a] Bootstrap confidence interval values are taken from bootstrap calculation (941 successful out of a total of 1000 bootstrap replicates)

Source: Applicant's clinical PK/PD report, AG-221-MPK-001, Table 7, page 34-35

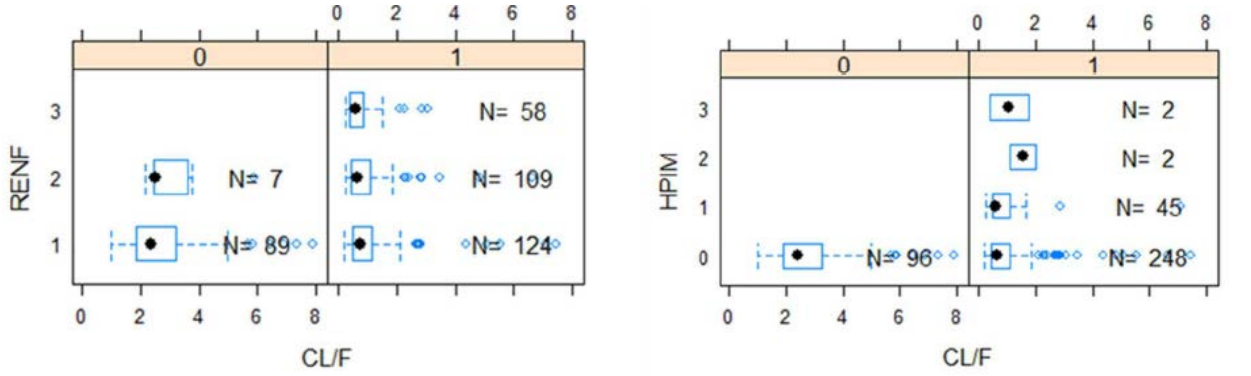
Covariate Analysis: The stepwise covariate model building tool of Perl-Speaks-NONMEM (PsN, version 3.5.3) was used for the development of enasidenib covariate model, which implemented forward selection and backward elimination of covariates to enasidenib PPK model.

The following covariates were not found to have a significant effect on AG-221 plasma exposure. Figure 20 showed no effect of mild or moderate renal impairment and mild hepatic impairment on CL/F of enasidenib.

- age (range: 19-100 years),
- body weight (range: 38.6-136.1 kg),

- body surface area (BSA),
- sex,
- race,
- mild hepatic impairment (defined as TB ≤ ULN and AST > ULN or TB < 1 to 1.5 times ULN and any AST),
- renal function (Mild Renal Impairment: eGFR 60 to 89 mL/min/1.73m^2, N=116; and Moderate Renal Impairment: eGFR 30 to 59 mL/min/1.73m^2, N= 58),
- potential drug-drug interactions (ARA, N= 18 and CYP inhibitors, N= 86)
- mutation type (R140, N=221 and R172, N=75),
- tumor type,
- bone marrow blasts burden (%), and
- formulation.

Figure 20: No Apparent Effect of Renal Impairment and Mild Hepatic Impairment on Apparent Oral Clearance

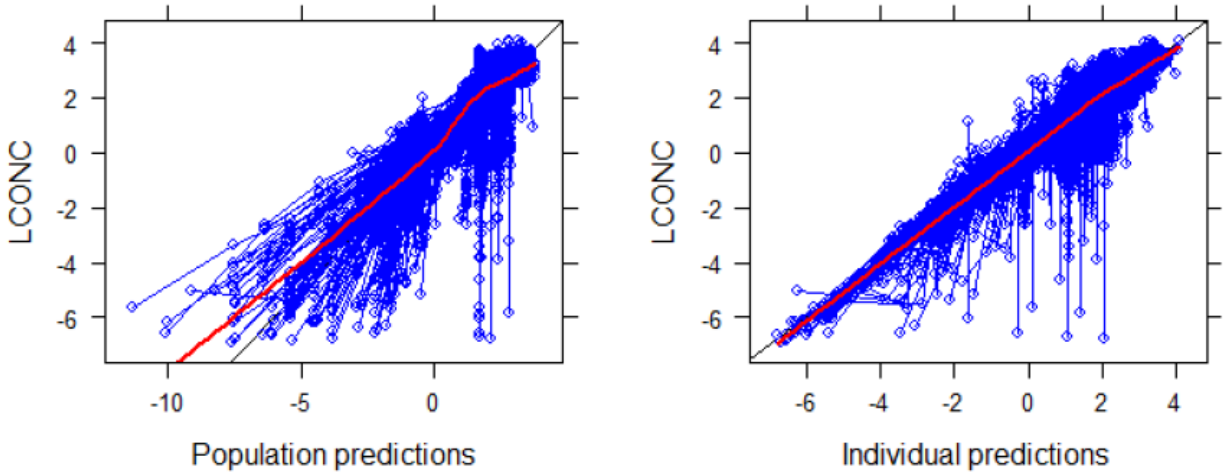


Notes: CL/F = apparent clearance (L/hr); STATUS = 0 for healthy subjects and 1 for subjects with advanced hematologic malignancies; RENF = renal impairment category. 1 = Normal If CRCL ≥ 90; 2 = Mild If 60 ≤ CRCL < 90; 3 = Moderate If 30 ≤ CRCL < 60. HPIM = hepatic dysfunction category, 0 = Normal if total bilirubin ≤ its ULN and AST ≤ its ULN;1 = Mild If (total bilirubin ≤ its ULN and AST > its ULN) or (1 * its ULN < total bilirubin ≤ 1.5* its ULN and any AST); 2 = Moderate if 1.5 * its ULN < total bilirubin ≤ 3* and any AST ; 3 = Severe if 3 * its ULN < total bilirubin and any AST; when ULN does not exist in the lab datasets, HPIM was assumed normal.

Source: Applicant's clinical PK/PD report, AG-221-MPK-001, Figure 11, page 41

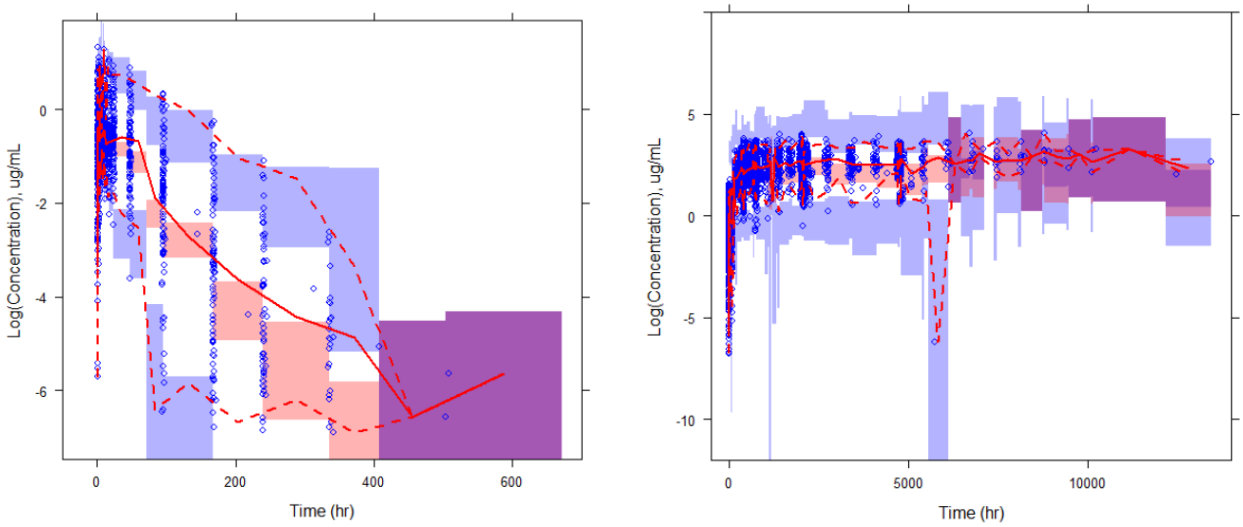
Model Evaluation: The final model was evaluated with a bootstrap re-sampling procedure and visual predictive checks (VPC). Figure 21 and Figure 22 showed the goodness-of-fit plots of the model and VPC plots from the final model for both heathy subjects and patients. The model describes the observed data relatively well, and observed data are mostly consistent with the 95% prediction intervals.

Figure 21: Goodness-of-Fit Plots of the Final Model – Population or Individual Predicted Concentrations versus Observed Concentrations



Notes: Left Panel: Population Predicted Concentration versus log scale observed concentration, Right Panel: individual Predicted Concentration versus log scale observed concentration. The solid line represents the identity line or zero line. The red line represents the locally weighted scatterplot smoothing line.
Source: Applicant's clinical PK/PD report, AG-221-MPK-001, Figure 5, page 32

Figure 22: Visual Predictive Checks for the Time Profiles of Enasidenib Concentrations in Healthy Subjects (Left Panel) and Patients (Right Panel)



Notes: Circles represent observed data. Lines represent the 5th (dashed), 50th (solid), and 95th (dashed) percentiles of the observed data. Shaded areas represent nonparametric 95% confidence intervals about the 5th (blue), 50th (pink), and 95th (blue) percentiles for the corresponding model-predicted percentiles.
Source: Applicant's clinical PK/PD report, AG-221-MPK-001, Figure 13-14, page 45-46

Reviewer's comments:

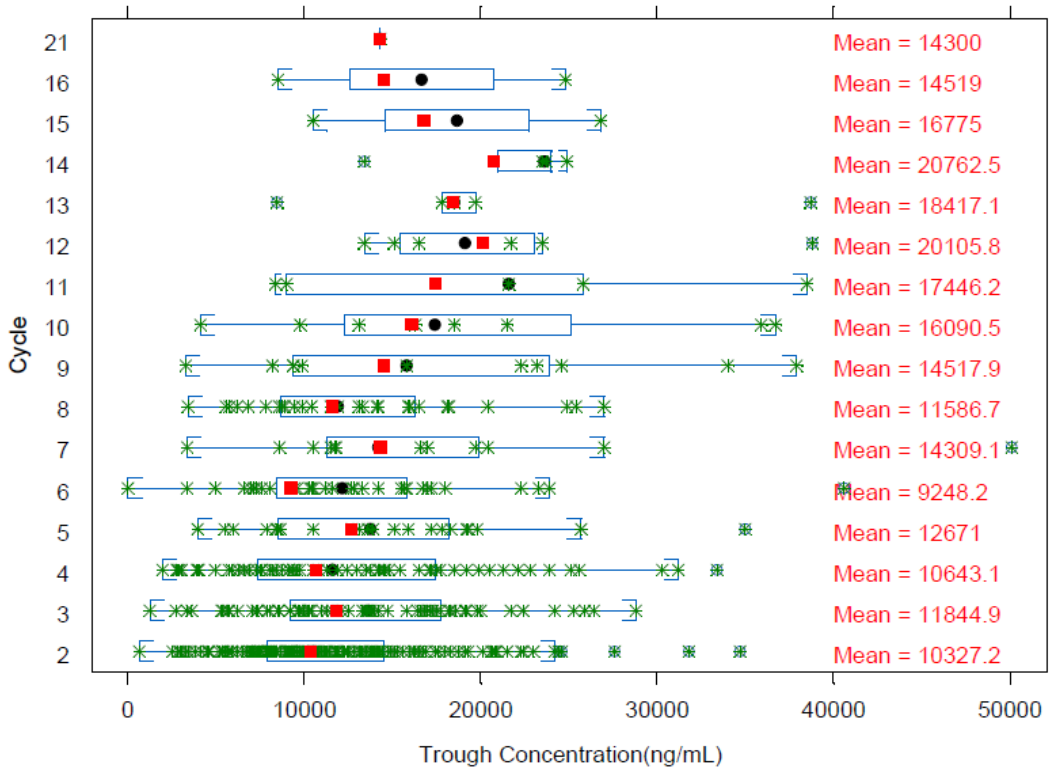
- *The final PPK model was successfully converged by FDA reviewer's independent analysis. The observed data was reasonably described by a one compartment model with shrinkage for CL and V less than 30%. There were subsets of subjects or patients in which the exposure were over predicted by the model.*
- *The underlying mechanism of the difference of exposure levels after oral dose of enasidenib between patients and heathy subjects could not be described by the model. An information request was sent to evaluate the potential for time-dependent PK in patients when comparing the steady state vs the first dose (See the time-dependent PK evaluation below).*
- *From the PPK perspective, the reviewer agrees with sponsor's conclusion that there is no clinically relevant effect of age, body weight or body surface area, sex, or race on enasidenib PK.*
- *No dose adjustment is necessary in patients with mild hepatic impairment and renal impairment. A PMR will be issued for to identify a safe dose in patients with hepatic impairment.*

Time-dependent PK Evaluation: Upon FDA reviewer's information request, the time-dependent PK evaluation was conducted with the available PK data in patients, since there was 3.4-fold lower clearance in patients when compared to healthy subjects.

Visual plot of the trough concentrations of enasidenib beyond Cycle 2 were generated and further analysis was conducted with the trough concentrations of enasidenib beyond Cycle 2 fitted into a linear mixed effect model: Trough concentration = Intercept + Time*Slope.

Figure 23 shows that after Cycle 2, enasidenib trough concentration reaches a plateau with limited fluctuation. Table 81 shows estimated parameters from the linear mixed effect modeling. The slope of enasidenib trough concentration beyond Cycle 2 versus time relationship is -0.018 with a 90% CI of [-0.68, 0.64], suggesting there is not a statistically significant correlation between enasidenib trough concentration and time. The Applicant concluded that it is unlikely that enasidenib clearance is time-dependent and that a time-dependent clearance model for the PPK analyses is not necessary.

Figure 23: Boxplots of Trough Observations Stratified by Cycles



Notes: Green stars represent the individual observations; red squares represent the geometric mean values; black diamonds are the medians.
Source: Response to FDA Information Request on 09 Mar 2017.

Table 81: Estimated Parameters for the Linear Mixed Effect Modeling

	Median[a]	Lower 90%CI[a]	Upper 90%CI[a]
Intercept (ng/mL)	12314.1	11149.96	13412.07
Slope (ng/mL/h)	-0.01791	-0.68387	0.63964

Notes: [a:] from 500 bootstraps
Source: Response to FDA Information Request on 09 Mar 2017.

Reviewer's comments: *The Applicant's analysis seems acceptable, since the steady state appeared to be reached before cycle 2 and there were limited PK sampling time points after steady state except the trough concentrations. In addition, the long half-life and high variability also limit the evaluation.*

Sponsor's Exposure-Response Analysis:

Objectives:

- To quantitatively describe the enasidenib E-R relationship in patients with advanced hematologic malignancies.

Data, Software, Methods: A total of 299 patients with advanced hematologic malignancies who participated in study AG221-C-001 and who had evaluable efficacy, safety and PK data were included in the E-R analyses.

Sponsor's Results: The E-R relationship for the clinical response (investigator-assessed and sponsor derived best response, as of the 15 Apr 2016 data cutoff date) was explored in 283 patients who received at least one dose of enasidenib and who had systemic exposure data after the first dose. The relationship between enasidenib exposure and response endpoints were explored through data visualization (graphing and fitting using locally weighted regression). The main exposure metrics were AUC_{ss} simulated or estimated from final PPK model.

Dose proportionality and PK for the different IDH2 mutation types: As shown in Figure 24, steady state exposure of enasidenib was approximately dose proportional over the dose range of 50 mg to 650 mg QD. PK exposures of BID and QD dosing regimens were generally comparable for the same total daily dose. A comparison of the steady state exposure between the mutation types (R140Q and R172K) indicated that steady state was similar between the two mutation types (Figure 24).

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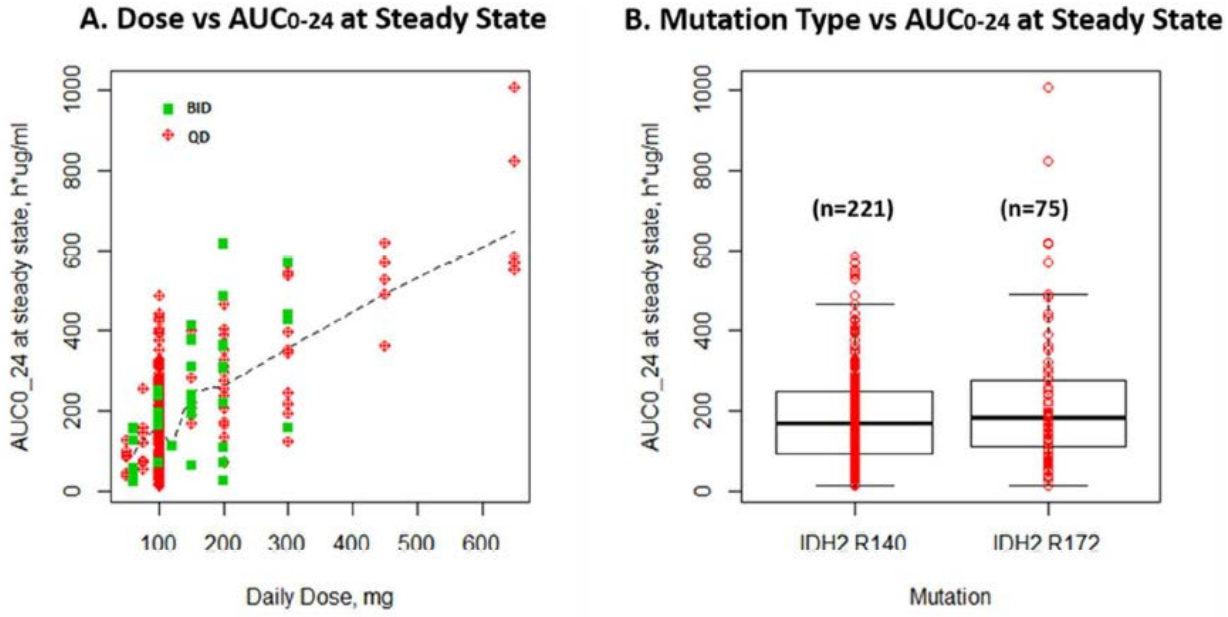
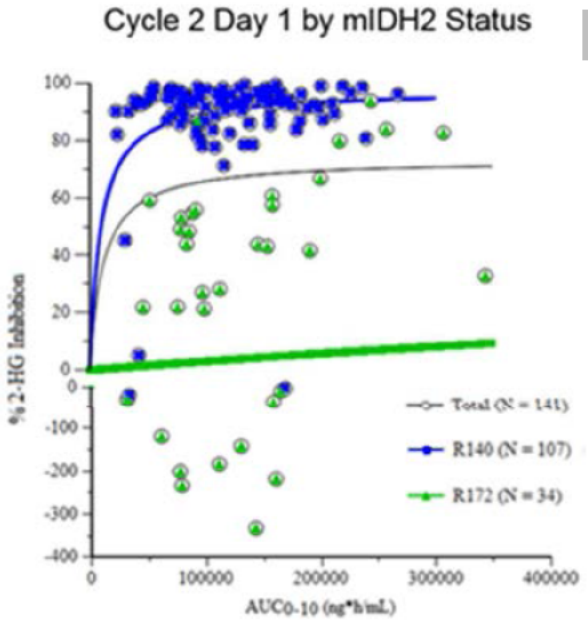
Figure 24: Correlation between Dose vs. Steady State Exposure (A) and Mutation Type vs. Steady State Exposure (B)



Notes: AUC0-24 = area under the concentration-time curve (0 to 24 hours) at steady state; PK = pharmacokinetics
There are 3 subjects with missing mutation type information.
Source: Applicant's clinical PK/PD report, AG-221-MPK-001, Figure 15, page 49

Suppression of 2-HG by IDH2 mutation types (R140 vs R172): PK/PD correlations between exposure to enasidenib ($AUC_{0\text{-}10h}$) and the extent of suppression of 2-HG at Cycle 2 Day 1 in peripheral blood was explored using a graphical display of data by IDH2 mutation type. At a daily dose of 100 mg, 2-HG was consistently suppressed at Cycle 2 Day 1 in both patients with R140 mutations (n = 66, median 92.8% inhibition [min 45.3%, max 99.4%]) and patients with the R172 mutations (n = 22, median 27.6% inhibition [min -233.7%, max 93.8%] (Figure 25). Despite the difference of 2-HG reductions in patients with R140 and R172 mutations, the clinical responses were similar across the mutation types.

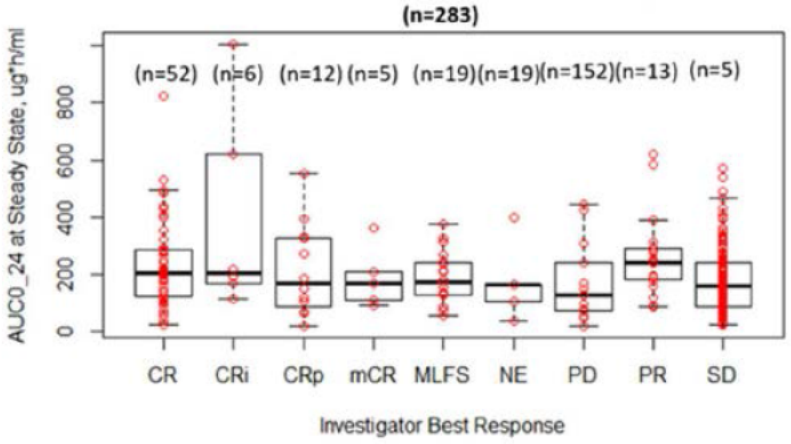
Figure 25: Percent Suppression of 2-HG vs. Steady State Exposure



Source: Applicant's clinical PK/PD report, AG-221-C-001-PKPD, Figure 33, page 165

No E-R relationship for efficacy: Figure 26 indicates that there is no apparent relationship between systemic enasidenib exposure and the clinical best responses, in the range of exposures evaluated at clinical daily doses from 50 mg to 650 mg, using investigator-assessed best response.

Figure 26: Relationship between Steady State Exposure and Investigator-assessed Best Responses in Data from Phase 1 and 2 Portions of Study AG221-C-001



Notes: AUC0-24 = area under the concentration-time curve (0 to 24 hours) at steady state; CR= complete remission; Cri = complete remission with incomplete hematologic recovery; CRp = complete remission with

incomplete platelet recovery; mCR = marrow complete remission; MLFS= morphologic leukemia-free state; NE = not evaluable; PD = progressive disease; PR = partial remission; SD = stable disease.
Source: Applicant's clinical PK/PD report, AG-221-MPK-001, Figure 16, page 51.

Reviewer comments: *The graphic visualization of data with steady state AUC stratified by best responses could not quantitatively describe the E-R relationship for efficacy. Logistic regression analysis for E-R relationship was requested through an information request during the review cycle. See the logistic regression analysis for E-R efficacy below.*

Logistic regression of E-R analysis for ORR: Upon FDA reviewer's request, logistic regression of E-R analyses with ORR as efficacy endpoint for all patients and patients with R/R AML stratified by IDH2 mutation type was conducted.

Results from the logistic regression of E-R for efficacy in patients with R/R AML stratified by IDH2 mutation type are summarized in Table 82. Logistic regression adjusted for potential prognostic factors of cytogenetic risk status, prior therapies, performance status and age shows that:

- No statistically significant relationship between enasidenib steady state exposure and ORR for patients with R/R AML with R172 mutation (N = 46) (p-value = 0.071) after adjusting for significant prognostic factors of cytogenetic risk status, prior therapies, age, and performance status;
- A statistically significant relationship between enasidenib steady state exposure and ORR for patients with R/R AML with R140 mutation (N= 131) (p-value = 0.018) after adjusting for significant prognostic factors of cytogenetic risk status, prior therapies, age, and performance status.

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Table 82: Probability of ORR in Relapsed Refractory AML Stratified by IDH2 Mutation Type

Mutation Status	Variable	Class	Estimate	Std. Error	z	P value
R140	Intercept		-4.9044	1.7211	8.1203	0.0044
	Log(AUC_{24})		0.7688	0.3247	5.607	**0.0179**
	Prior therapies	1	-0.179	0.2875	0.3877	0.5335
		2	0.3306	0.2989	1.2231	0.2687
	Cytogenetic Risk Status	Intermediate Risk	0.2385	0.2324	1.0541	0.3046
	Age	< 60	0.042	0.3459	0.0148	0.9033
		≥ 60-< 70	-0.17	0.3821	0.1978	0.6565
		≥ 70-< 75	-0.2052	0.3865	0.2819	0.5954
	ECOG	0	0.6448	0.3482	3.4289	0.0641
		1	-0.0101	0.2836	0.0013	0.9717
R172	Intercept		-11.5676	5.5261	4.3818	0.0363
	Log(AUC_{24})		1.9453	1.0754	3.2724	**0.0705**
	Prior therapies	1	0.1297	0.6775	0.0367	0.8482
		2	-0.1428	0.7455	0.0367	0.8481
	Cytogenetic Risk Status	Intermediate Risk	1.8894	0.7159	6.9656	0.0083
	Age	< 60	-2.7966	1.0299	7.374	0.0066
		≥ 60-< 70	0.793	0.9808	0.6537	0.4188
		≥ 70-< 75	1.604	1.1329	2.0044	0.1568
	ECOG	0	-0.2888	1.0959	0.0694	0.7921
		1	1.1402	0.8674	1.7277	0.1887

Notes: AUC24 = area under the concentration-time curve at 24 hours (steady state); ECOG = Eastern Cooperative Oncology Group; ORR = objective response rate; R/R AML = relapsed or refractory acute myeloid leukemia
Source: Response to FDA Information Request on 09 Mar 2017.

Reviewer's comment: *The reviewer agrees that the E-R relationship for efficacy is statistically significant for R140 mutations. The data cannot support a conclusion of the E-R relationship for R172 mutations due to the following limitations of the data.*

- *The sample size for the R172 mutation is limited (N=46) and the response is variable.*
- *Exposure was marginally insignificant while other risk factors were significantly related to response.*
- *The cytogenetic risk status (N=33 for intermediate risk at base line, and N=13 for poor risk at baseline) and age appeared to be significantly correlated to the response.*
- *Multivariate logistic regression was confirmed by reviewer's independent analysis and the plots of E-R relationship between ORR and steady state exposure were generated with stratification of IDH2 mutation type in patients with R/R AML. See Reviewer's analysis below.*

Logistic regression of E-R analysis for safety: Upon FDA reviewer's request, logistic regression of E-R analyses with safety endpoints for patients with R/R AML stratified by gene mutation type was conducted. The safety endpoints included all Grade and ≥ Grade 3 treatment emergent adverse events (TEAEs) including anemia, febrile neutropenia, leukocytosis, tumor lysis syndrome, IDH differentiation syndrome, hepatic safety, and total bilirubin elevation. The

exposure metric is logarithm transformed steady state derived from the starting dose. A total of 299 patients (with N= 242 patients with R/R AML) from Study AG221-C-001 Phase 1 and 2 portions were included in this analysis. The results are summarized below (Table 83).

- No statistically significant relationship between steady state exposure and TEAE anemia, febrile neutropenia, leukocytosis, tumor lysis syndrome or IDH differentiation syndrome.
- A statistically significant relationship between steady state exposure and total bilirubin elevation and hepatic safety.

Table 83: Results from the Logistic Regression of E-R of Grade 3 or Grade 4 Adverse Reactions for Patients with R/R AML

Safety Endpoints (≥ Grade 3)	Parameter	Estimate	Std. Error	z	p value
PT Leukocytosis	Intercept	-3.3379	1.4641	-2.28	0.0226
	$log(AUC_{24})$	0.232	0.2826	0.821	0.4117
PT Tumor lysis syndrome	Intercept	-4.6328	2.0503	-2.26	0.0238
	$log(AUC_{24})$	0.3453	0.3909	0.884	0.377
PT Febrile neutropenia	Intercept	-0.69172	0.90279	-0.766	0.444
	$log(AUC_{24})$	-0.01785	0.1779	-0.1	0.92
Lab Total bilirubin elevation	Intercept	-9.4785	1.9887	-4.766	1.88E-06
	$log(AUC_{24})$	1.3983	0.3588	3.897	**9.72E-05**
PT Anemia	Intercept	-0.66099	0.96512	-0.685	0.493
	$log(AUC_{24})$	-0.09412	0.19109	-0.493	0.622
PT IDH differentiation*	Intercept	-5.7295	1.9444	-2.947	0.00321
	$log(AUC_{24})$	0.609	0.3635	1.675	0.09388
Hepatic safety**	Intercept	-9.4785	1.9887	-4.766	1.88E-06
	$log(AUC_{24})$	1.3983	0.3588	3.897	**9.72E-05**

Notes: AUC24 = area under the concentration-time curve at 24 hours (steady state); ECOG = Eastern Cooperative Oncology Group; ORR = objective response rate; R/R AML = relapsed or refractory acute myeloid leukemia
Source: Response to FDA Information Request on 09 Mar 2017.

Reviewer's comment: *The multivariate logistic regression of the E-R for safety analysis was confirmed by reviewer's independent analysis. The total bilirubin elevation correlated with enasidenib exposure was not associated with concurrent elevations in ALT or AST and it may be due to the inhibitory effect of enasidenib on UGT1A1, which is involved in bilirubin metabolism. Enasidenib exhibited manageable safety profile via dosing hold and dose reduction.*

Reviewer's analysis:

Objective: Logistic regression of exposure-response analyses with ORR and safety endpoints for R/R AML patients and generate plots accordingly.

Data: ***\\cdsesub1\evsprod\nda209606\0015\m5\datasets\ag-221-mpk-01\analysis\legacy\datasets\adpkexpr.xpt***

Software: SAS 9.4 and R 3.2.2 were used for data handling, logistic regression, visualization and post-processing.

Results and discussion: The Applicant's E-R analysis with logistic regression was confirmed by reviewer's independent analysis and the plots of E-R relationship between ORR and steady state exposure were generated with stratification of IDH2 mutation type in patients with R/R AML. See
Figure 14 in Section 6.3.2. The analysis indicated an apparent positive relationship between AUC_{ss} and ORR for patients with R/R AML with R172 mutation types (N= 46, p-value=0.07 for multi-covariate logistic regression). The slope in the E-R analysis for efficacy in R172 mutation types appears to be steeper than for R142 mutation types indicating that increasing dose for patients with R172 mutation types may offer more benefit. This is consistent with observation in which greater suppression of 2-HG was observed at a dose of 100 mg QD dose for the patients with R140 mutation types (median 92.8% inhibition [range 45.3 to 99.4%]), as compared to the patients with R172 mutation types (median 27.6% inhibition [range -233.7 to 93.8%]); however, based on the following limitations of the data, no definitive conclusion can be drawn that a dose higher than 100 mg in patients with R172 mutation types would lead to greater suppression of 2-HG and translate to a higher level of ORR in this patient population.

- Data for E-R analysis was available primarily from a dose of 100 mg (75 % of total data).
- The sample size for R172 mutation subgroup is limited (N=46) and the response is variable.
- Based on the multivariate E-R analysis for the R172 mutation subgroup, exposure was marginally insignificant while other risk factors were significantly related to response.
- In addition, in the absence of control arm, it is difficult to differentiate the effect of exposure and various risk factors on efficacy.

(b) (4)

13.5. Grouped Preferred Terms

Grouped Term	Preferred Terms
abdominal pain	abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness
abscess	abdominal abscess, abscess bacterial, abscess limb, anal abscess, bone abscess, brain abscess, groin abscess, lung abscess, perirectal abscess, peritonsilar abscess, psoas abscess, scrotal abscess, subcutaneous abscess, tooth abscess, urethral abscess
anemia	anemia, hematocrit decreased, hemoglobin decreased
arrhythmia	arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystoles, sinus bradycardia, sinus tachycardia, supraventricular tachycardia, tachycardia, ventricular extrasystoles, ventricular tachycardia
cardiac failure	cardiac failure, cardiac failure congestive, diastolic dysfunction, left ventricular dysfunction, systolic dysfunction
cellulitis	cellulitis, cellulitis of male external genital organ, incision site cellulitis, periorbital cellulitis
chest pain	angina pectoris, chest discomfort, chest pain
clostridial infection	clostridial infection, clostridium difficile colitis, clostridium difficile infection
conduction disorder	atrioventricular block second degree, bundle branch block right
cough	cough, productive cough, upper airway cough syndrome
diarrhea	colitis, diarrhea, enterocolitis, gastroenteritis, neutropenic colitis
dyspnea	acute respiratory failure, bronchospasm, dyspnea, dyspnea exertional, hypoxia, respiratory failure
edema	face edema, generalized edema, edema, edema peripheral, fluid overload, fluid retention, swelling face
eye irritation	dry eye, eye irritation, eye pain, keritits
fatigue	asthenia, fatigue
fungal infection	aspergilloma, aspergillosis, bronchopulmonary aspergillosis, candidiasis, fungaemia, fungal infection, fungal skin infection, gastrointestinal fungal infection, genital infection fungal, oesophageal candidiasis, oral candidiasis, oral fungal infection, pneumonia fungal, sinusitis fungal, systemic candida, vulvovaginal mycotic infection
gastrointestinal hemorrhage	anal hemorrhage, gastrointestinal hemorrhage, hematochezia, hemorrhoidal hemorrhage, lower gastrointestinal hemorrhage, mouth hemorrhage, rectal hemorrhage, small intestinal hemorrhage, upper gastrointestinal hemorrhage
headache	headache, sinus headache
hemorrhage intracranial	cerebral hemorrhage, hemorrhage intracranial, intracranial hematoma, subdural hematoma
hepatic injury	acute hepatic failure, alanine aminotransferase increased, aspartate aminotransferase decreased, hepatic enzyme increased, hepatic failure, hepatic function abnormal, hepatocellular injury, hepatotoxicity, transaminases increased, venoocclusive liver disease

Grouped Term	Preferred Terms
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
hyperglycaemia	diabetes mellitus, hyperglycaemia
hypersensitivity	drug hypersensitivity, hypersensitivity, urticaria
hypoalbuminemia	blood albumin decreased, hypoalbuminaemia
hypotension	blood pressure decreased, blood pressure systolic decreased, hypotension, orthostatic hypotension
mucositis	aphthous stomatitis, esophagitis, esophageal pain, gingival pain, gingivitis, glossitis, laryngeal inflammation, laryngeal pain, mouth ulceration, mucosal inflammation, oral mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, proctalgia, stomatitis
musculoskeletal pain	back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, neck pain, pain, pain in extremity
myocardial ischemia	acute myocardial infarction, cardiac enzymes increased, myocardial infarction, troponin increased, troponin i increased, troponin t increased
peripheral neuropathy	neuropathy peripheral, paresthesia, peripheral motor neuropathy, peripheral sensorimotor neuropathy, peripheral sensory neuropathy, polyneuropathy
pneumonia	lung infection, pneumonia, pneumonia aspiration, pneumonia bacterial
pneumonitis	acute respiratory distress syndrome, pneumonitis,
pulmonary edema	acute pulmonary edema, pulmonary congestion, pulmonary edema
rash	dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis exfoliative, dermatitis psoriasiform, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, skin exfoliation, toxic skin eruption
renal insufficiency	blood creatinine increased, renal disorder, renal failure, renal failure acute, renal tubular disorder
sepsis	acinetobacter bacteremia, bacteremia, bacterial sepsis, enterobacter bacteremia, enterococcal sepsis, escherichia bacteremia, klebsiella bacteremia, klebsiella sepsis, pseudomonal bacteremia, pseudomonal sepsis, sepsis, septic shock, staphylococcal bacteremia, staphylococcal sepsis, urosepsis
thrombosis	deep vein thrombosis, jugular vein thrombosis, pulmonary embolism, splenic vein thrombosis, thrombosis
upper respiratory tract infection	acute sinusitis, nasopharyngitis, pharyngitis, pharnygitis, rhinitis, sinusitis, sinusitis bacterial, tonsillitis, upper respiratory tract infection, upper respiratory tract infection bacterial
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
visual impairment	cataracts, diplopia, myopia, vision blurred, visual acuity reduced, visual impairment

14 Division Director (DHOT)

John Leighton, PhD

APPEARS THIS WAY ON ORIGINAL

15 Division Director (OCP)

NAM Atiqur Rahman, PhD

APPEARS THIS WAY ON ORIGINAL

16 Division Director (OB)

Rajeshwari Sridhara, Ph.D.

APPEARS THIS WAY ON ORIGINAL

17 Division Director (Clinical)

Albert Deisseroth, MD, PhD

APPEARS THIS WAY ON ORIGINAL

18 Office Director (or designated signatory authority)

This application was reviewed under the auspices of the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. The risk-benefit assessment was also assessed by Drs. Deisseroth, Przepiorka and Ward who recommend approval. I also recommend approval of this application. 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

APPEARS THIS WAY ON ORIGINAL

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/s/

JENNIFER J LEE
07/28/2017

ASHLEY F WARD
07/28/2017

RAMADEVI GUDI
07/28/2017

CHRISTOPHER M SHETH
07/28/2017

JOHN K LEIGHTON
07/28/2017

SARAH E DORFF
07/28/2017

XIANHUA W CAO
07/28/2017

ROSANE CHARLAB ORBACH
07/28/2017

STACY S SHORD
07/28/2017

YANING WANG
07/28/2017

NAM ATIQUR RAHMAN
07/28/2017
I concur.

QING XU

07/28/2017

YUAN L SHEN
07/28/2017

RAJESHWARI SRIDHARA
07/28/2017

DONNA PRZEPIORKA
07/28/2017

ALBERT B DEISSEROTH
07/28/2017

RICHARD PAZDUR
07/28/2017

CROSS-DISCIPLINE TEAM LEADER MEMO

NDA	209606
Submission Type	Original
Applicant	Celgene Corp
Submission Date	December 30, 2016
Trade Name	IDHIFA
Nonproprietary Name	Enasidenib
Dosage Form and Strength	50 mg and 100 mg tablets
Route of Administration	Oral
Proposed Dosing Regimen	100 mg once daily
Proposed Indication	For the treatment of patients with relapsed or refractory acute myeloid leukemia with an IDH2 mutation
Recommended Indication	For the treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation as detected by an FDA-approved test
CDTL	Donna Przepiorka, MD, PhD

The CDTL review is incorporated into the Multidisciplinary Review and Evaluation. The recommended regulatory action is regular approval.

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/s/

DONNA PRZEPIORKA
06/30/2017

MEMORANDUM

Date:	May 30, 2017
From:	Ashley Ward, MD Clinical Reviewer Division of Hematology Products
Through:	Donna Przepiorka, MD, PhD Clinical Team Leader
To:	NDA 209606 Enasidenib (IDHIFA)
Re:	Clinical Review

Enasidenib is an isocitrate dehydrogenase 2 (IDH2) inhibitor indicated for the treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with an IDH2 mutation. Please see my clinical review in the Multi-Disciplinary Review document, which will be uploaded to DARRTS when it is finalized. There are no clinical issues that would prevent approval of this application.

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/s/

ASHLEY F WARD
05/30/2017

DONNA PRZEPIORKA
05/30/2017

MEMORANDUM

Date: May 30, 2017
From: Ramadevi Gudi, PhD
Nonclinical Reviewer
Division of Hematology Oncology Toxicology (DHOT)
for Division of Hematology Products (DHP)
Through: Christopher M. Sheth, PhD
Nonclinical Supervisor
To: NDA 209606 Enasidenib (IDHIFA)
Re: Nonclinical Review

Enasidenib is an isocitrate dehydrogenase 2 (IDH2) inhibitor indicated for the treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2 (IDH2) mutation. The nonclinical review is complete and has been added to the Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for additional details. There are no nonclinical issues that would prevent approval of this application.

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/s/

RAMADEVI GUDI
05/30/2017

CHRISTOPHER M SHETH
05/30/2017

MEMORANDUM

NDA #:	209606
Supplement #:	0001
Drug Name:	enasidenib
Indication(s):	Patients with relapsed or refractory acute myeloid leukemia (AML) with an IDH2 mutation.
Applicant:	Celgene
Date(s):	Letter Date: December 30, 2016 Stamp Date: December 30, 2016
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Qing Xu, Ph.D.

Enasidenib is an isocitrate dehydrogenase 2 (IDH2) inhibitor indicated for the treatment of patients with relapsed or refractory acute myeloid leukemia (AML) with an isocitrate dehydrogenase-2(IDH2) mutation. Please see the statistical review in the Multi-disciplinary Review document for details, which will be uploaded to DARRTs when it is finalized. There are no major statistical issues that would prevent approval of this application.

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/s/

QING XU
05/30/2017

YUAN L SHEN
05/30/2017

OFFICE OF CLINICAL PHARMACOLOGY MEMO

NDA	209606
Link to EDR	\\cdsesub1\evsprod\nda209606\
Applicant	Celgene Corp
Submission Date	December 30, 2016
Submission Type	NME (priority review)
Brand Name	IDHIFA
Generic Name	Enasidenib
Dosage Form and Strength	50 mg and 100 mg tablets
Route of Administration	Oral
Proposed Indication	IDHIFA is indicated for the treatment of patients with relapsed or refractory acute myeloid leukemia with an IDH2 mutation
Proposed Dosing Regimen	100 mg once daily
Associated INDs	117631
OCP Review Team	Sarah Dorff, Ph.D., Xianhua (Walt) Cao, Ph.D., Stacy Shord, Pharm.D., Nitin Mehrotra, Ph.D., Rosane Charlab Orbach, Ph.D.
OCP Final Signatory	Nam Atiqur Rahman, Ph.D. (Division Director)

The Office of Clinical Pharmacology (OCP) review is complete and has been added to the Multi-Disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Based on our analyses of the submitted PK, efficacy, and safety data, enasidenib is approvable from a clinical pharmacology perspective.

APPEARS THIS WAY ON ORIGINAL

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/s/

SARAH E DORFF
05/30/2017

XIANHUA W CAO
05/30/2017

ROSANE CHARLAB ORBACH
05/30/2017

NITIN MEHROTRA
05/30/2017

STACY S SHORD
05/30/2017

NAM ATIQUR RAHMAN
05/30/2017
I concur.