CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215814Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	New
Application Number(s)	215814
Priority or Standard	Standard
Submit Date(s)	February 15, 2022
Received Date(s)	February 15, 2022
PDUFA Goal Date	February 15, 2023
Division/Office	Division of Hematologic Malignancies I
Review Completion Date	November 30, 2022
Established Name	olutasidenib
(Proposed) Trade Name	REZLIDHIA
Pharmacologic Class	Isocitrate dehydrogenase-1 (IDH1) inhibitor
Code name	FT-2102
Applicant	Forma Therapeutics, Inc.
Formulation(s)	150 mg capsule
Dosing Regimen	150 mg orally every 12 hours
Applicant Proposed Indication(s)/Population(s)	For the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation.
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations

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OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GD	gestation day
GLP	good laboratory practice
GRMP	good review management practice
hERG	human ether-a-go-go related gene
IC_{50}	half-maximal inhibitory concentration
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LDAC	low dose cytarabine
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	overall response rate
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1 Product Introduction

Proposed Trade Name:	REZLIDHIA®
Established name:	olutasidenib
Also Known As:	FT-2102
Chemical Name:	(S)-5-((1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)amino)-1-methyl-6-oxo-1,6-dihydropyridine-2-carbonitrile
Molecular Formula:	C18H15ClN4O2
Molecular Weight:	354.79 g/mol
Dosage Forms:	Capsules, 150 mg
Therapeutic Class:	Antineoplastic
Chemical Class:	Small molecule
Pharmacologic Class:	Isocitrate dehydrogenase-1 (IDH1) inhibitor
Mechanism of Action:	Inhibition of the IDH1 enzymes with gain-of-function mutations decreases 2-hydroxyglutarate (2-HG) levels and induces myeloid differentiation.

Olutasidenib is a new molecular entity. NDA-215814 was submitted for the proposed indication of treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation using a dose of 150 mg twice daily.

1.2 Conclusions on the Substantial Evidence of Effectiveness

The review team recommends the regular approval of olutasidenib under 21 CFR 314.105 for the indication "treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test" using a dose of 150 mg twice daily. The recommendation is based on the finding of rates of durable complete remission with complete or partial hematopoietic recovery (CR/CRh) in Study 2102-HEM-101 (NCT02719574).

Safety during long-term use and appropriate dose for patients administered concomitant OATP1B1 substrates remain to be determined in post-marketing studies.

Study 2102-HEM-101 is an open-label, nonrandomized, multicenter, multi-arm clinical trial of olutasidenib for adults with AML or MDS having an IDH1 R132 mutation. The design included a Phase 1 (dose-escalation and dose-expansion) portion, and a Phase 2 portion that included two cohorts studying monotherapy (Cohorts 1 and 3) for patients with relapsed or refractory (R/R) AML. The dose of 150 mg twice daily used in the pivotal analysis population from Cohort 1 was based results from the Phase 1 portion that showed a) less than proportional increase in steady-state exposures between 150 and 300 mg daily b) maximal reduction in 2-hydroxyglutarate (2-HG) at the dose of 150 mg twice daily, c) similar response rates across doses from 150 mg to 300 mg daily, d) lack of dose-limiting toxicities across all dose levels, and e) highest exposure at steady state using 150 mg twice daily.

The primary efficacy endpoint of Study of 2102-HEM-101 was investigator-assessed CR + CRh in all patients in Cohort 1 treated with olutasidenib 150 mg BID. The number of patients planned for Cohort 1 was based on a group sequential design with one futility interim analysis at the time of ~33% of patients and one efficacy interim analysis at the time of ~67% of patients completing the first response assessments. If the study did not stop early for efficacy or futility, the analysis was to be performed when approximately 190 patients (to allow for 173 evaluable patients with confirmed IDH1-R132 mutation per the central test) in Cohort 1 completed 6 months of treatment or discontinued study drug. The sample size of 173 evaluable patients had 90% power to identify a 25% CR + CRh rate while excluding a 15% CR + CRh rate with a 2-sided alpha of 0.05. Assessments of conversion to transfusion independence were also planned. In Cohort 1, the Applicant reported that a CR or CRh was achieved by 41 out of 123 efficacy evaluable subjects at the time of interim analysis 2 (33%; 95% CI 25.1%-42.4%), so the primary objective of the study was met.

FDA sought to assess efficacy in the broadest population available. Study 2102-HEM-101 enrolled 153 subjects identified by the Applicant as having R/R AML with an IDH1 mutation treated with olutasidenib 150 mg BID in the pivotal Cohort 1. At the time of the initial NDA submission, follow-up for the full 153 patients was not available. However, updated efficacy data was provided at the time of the 90-day safety update, and all patients received their first dose at least 6 months before the data cutoff date. FDA excluded enrolled subjects who were not confirmed positive for IDH1 R132 mutation using the proposed companion diagnostic assay and evaluated patients for documentation of relapse at study entry. Using the updated data set with a cut-off date of June 18, 2021, FDA confirmed 147 patients for analysis. The study population had a median age of 71 years (range, 32-87), 31% were age 75 years or older, 50% were male, and 46% were white. The median number of prior treatments was 2; 55% of patients were untreated relapse, 31% were primary refractory, and 14% had a refractory relapse. Seventeen (12%) subjects had a prior stem cell transplantation.

The CR/CRh rate as adjudicated by the clinical and statistical reviewers was 35% (95% CI: 27% - 43%). The median time to response was 1.9 months (range, 0.9 – 5.6 months), and the median

duration of response was 25.9 months (95% CI: 13.5, not reached). Responses were seen across demographic and disease status subgroups, with the exception of the IDH1 R132H mutation, which had a lower CR+CRh rate of 17%. Among the 86 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 29 (34%) became independent of RBC and platelet transfusions during any 56-day postbaseline period. Of the 61 patients who were independent of both RBC and platelet transfusions at baseline, 39 (64%) remained transfusion-independent during any 56-day postbaseline period.

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

1.3 Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Patients with R/R IDH1-mutated AML that has relapsed or is refractory to prior therapy have a poor prognosis. In Study 2102-HEM-101, 35% (95% CI: 27% - 43%) of patients with R/R AML and confirmed IDH1 mutation in the pivotal cohort achieved a CR or CRh. Conversion to transfusion independence was achieved by 34% and 64% 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 based the finding of effectiveness on durable CR/CRh and transfusion independence, which even in the short-term provides a meaningful benefit for patients. Of note, given that there are IDH1 mutations that do not confer the pathogenic gain of function or that may not be inhibited by olutasidenib (Intlekofer, Shih, et al. 2018), labeling should clarify that approval is specifically for patients with susceptible mutations (i.e., pathogenic and inhibited by olutasidenib).

Intensive chemotherapy continues to be the usual treatment approach for appropriate patients with R/R AML, but many patients are elderly and will not tolerate such treatment. Ivosidenib is another IDH1 inhibitor that is FDA-approved in the patient population the Applicant is seeking. In the safety population for the pivotal Cohort of 2102-HEM-101, only 8% of patients discontinued therapy due to an adverse reaction, which is relatively similar to the incidence seen on the pivotal trial of ivosidenib (13%). The results provide substantial evidence that olutasidenib at least short-term is tolerable for most patients.

The major safety issues identified were differentiation syndrome (DS) and hepatotoxicity. Investigators identified DS in 14% of patients, but the incidence may be as high as 44% based on an algorithmic approach. FDA adjudicated that 16% of patients experienced DS, with two deaths attributed to complications from DS. The seriousness of this risk warrants a boxed warning and specific instructions to patients regarding the risks and need for early intervention. Hepatotoxicity occurred in 23% of patients in the pivotal cohort, and a case of fatal drug-induced liver injury was observed in a patient treated with olutasidenib in combination with azacitidine. With procedures in place for early detection and intervention, fatal toxicities in the pivotal population were limited.

Given the potential to avoid transfusions short-term and the relative tolerability of olutasidenib with a safety mitigation plan in place, the clinical benefits appear to outweigh the risks of olutasidenib for patients with R/R AML with susceptible IDH1 mutations who are not seeking treatment with curative intent.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• With supportive care alone, patients with R/R AML survive only weeks.	R/R AML is a fatal disease.
Current Treatment Options	• For R/R AML with IDH1 mutations, the reported CR or CRi rates using non-IDH inhibitor therapy for 2nd or later salvage are 36-40% with a median survival of 4-6 months. The CR rate is unknown. • Ivosidenib, an IDH1 inhibitor approved in 2018 for patients with R/R AML with an IDH1 mutation, has a CR/CRh rate of 33% with a median duration of response of 8.2 months. • Most elderly patients with R/R AML would not tolerate combination chemotherapy.	There is a need for another effective agent for treatment of R/R IDH1-mutated AML, especially a treatment that would tolerated by older patients.
Benefit	• In study 2102-HEM-101, a single-arm trial, 147 adult patients with confirmed IDH1-mutated R/R AML were treated with olutasidenib 150mg BID. • CR or CRh was achieved by 35% (95% CI: 27% - 43%). • Conversion to transfusion independence was achieved by 34%, and 64% maintained transfusion independence.	There is substantial evidence of effectiveness for olutasidenib as a palliative treatment of R/R AML with an IDH1 mutation. There are no data that suggest long-term disease control.
Risk and Risk Management	• The most common adverse reactions (≥20%) included nausea, fatigue/malaise, arthralgia, constipation, leukocytosis, dyspnea, rash, mucositis, diarrhea, and transaminitis. • Differentiation syndrome (DS) and hepatotoxicity that was life-threatening or fatal occurred. Early diagnosis and intervention are needed to prevent treatment-related mortality. • Dosing modifications for patients administered concomitant OATP1B1 substrates have not been established. • The protocol included monitoring for risks and instructions for intervention. With this in place, serious DS could be avoided. A dose	The overall short-term safety profile of olutasidenib is acceptable for patients with R/R IDH1-mutated AML. Long-term safety information and guidance for dosing with concomitant OATP1B1 substrates is needed. A patient medication guide is required to inform and educate patients of the risk of DS and when to seek immediate medical attention. Labeling should include a warning for the serious risks, instructions for monitoring, and dose

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	reduction for adverse reaction was required for 11% of patients and discontinuation for 8%.	modifications for toxicities.

1.4 Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include:			Section where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Section 8.1.2
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		

□	Patient experience data that was not submitted in the application, but was considered in this review.

Kelly Norsworthy, MD
Cross-Disciplinary Team Leader

2.0 Therapeutic Context

2.1 Analysis of Condition

AML is a serious and lethal hematologic malignancy characterized by accumulation of abnormal immature myeloid blasts in the bone marrow which interfere with normal hematopoiesis and accumulate in peripheral blood and other tissues and organs. AML is universally fatal without treatment, with a median survival of approximately two months (Oran 2012). The incidence of AML increases with age with a median age at diagnosis of 68 years (SEER 2021). In the US, the incidence of AML is 1.33 cases per 100,000 individuals up to the age of 50 years, 5.14 cases per 100,000 individuals aged 50 to 64 years, and 20 cases per 100,000 individuals 65 years of age or older (Howlader, et al. 2021). In 2021, the number of estimated new cases of AML in the US is 20,240 (SEER 2021). Due to advancing age of the population, the absolute number of patients with AML is anticipated to increase significantly over the next several decades. Despite advancements in the understanding of AML biology and the resultant approvals of targeted therapies, the treatment of relapsed/refractory AML remains an enormous challenge with poor response rates and a dismal prognosis with five-year overall survival (OS) of only 10% (DeWolf, Tallman 2020).

The metabolic enzyme IDH1 catalyzes the oxidative decarboxylation of isocitrate to α ketoglutarate (α-KG). Mutations of IDH1 at codon 132 imparts a neomorphic activity to the enzyme, converting α-KG to 2-hydroxyglutarate (2-HG) and thereby leads to the aberrant accumulation of 2-HG. 2-HG is an "oncometabolite" that has pleotropic effects on tumorigenesis. Excess production of 2-HG inhibits α KG-dependent enzymes involved in epigenetic regulation, collagen synthesis, and cell signaling, thereby leading to a block in normal differentiation of progenitor cells and the subsequent development of cancer (Cairns, Mak 2013; Gross, et al. 2010; Losman, et al. 2013). Therefore, inhibition of mutated IDH1 in tumor cells and the concomitant decrease in 2-HG production is expected to restore normal cellular differentiation and provide therapeutic benefit in IDH1 mutated cancers. The frequency of IDH1 mutations in AML is estimated at approximately 6% to 10% (Mardis, et al. 2009; Bullinger, et al. 2017). IDH1 mutations (IDH1m) in AML are associated with advance age, intermediate risk cytogenetics, higher platelet count, increased bone marrow blast % at diagnosis, and NPM1 and FLT3 co-mutations (Issa, DiNardo 2021; Patel, et al. 2011).

The FDA's Assessment:

The FDA agrees with the applicant's assessment on the analysis of AML. The FDA would like to comment further on the prognostication of IDH1 mutations in AML. There is conflicting information regarding the prognostic significance of IDH1 mutations in AML. A meta-analysis that examined fifteen studies covering a total of 8,121 patients in patients with newly-diagnosed AML, found that patients with an IDH1 mutation had lower complete remission rate (RR=0.90, 95% CI: 0.63-1.28, p=0.559) and inferior overall survival (HR= 1.17, 95% CI: 1.02-1.36,

p=0.029) compared to patients without an IDH1 mutation (Feng, et al. 2012). In one large retrospective analysis (Dinardo et al, 2015), 65% of patients with newly diagnosed IDH1+ AML achieved a complete remission (CR) or complete remission with incomplete hematologic recovery (CRi) after induction therapy, compared to 69% of patients without an IDH1 mutation, and median overall survival (mOS) was similar (13 months vs 15.3 months, p=0.59). Patients with relapsed IDH1+ AML had a 40% CR/CRi rate with first salvage therapy compared to 41% of those with IDHWT AML, with a mOS of 5.9 months vs 7.7 months (p=0.44). For patients receiving third line or higher therapy, rates of CR/CRi were 36% for IDH1+ disease and 27% for IDHWT disease, with mOS 4.0 months vs. 4.8 months (p=0.16). An analysis of COG, SWOG, and ECOG studies (N=3,588) showed that IDH mutation did not predict outcomes, and that patients that with IDH mutation had similar 5-year event free survival (EFS) compared to patients without an IDH mutation (40% vs 39%, p=.723). It should be noted that this retrospective analysis did not differentiate between IDH1 and IDH2 mutations (Zarnegar-Lumley, et al. 2020).

2.2 Analysis of Current Treatment Options

The Applicant's Position:

Patients with R/R AML, particularly older patients, have a lower likelihood of CR and shorter OS with IC therapy if they have higher-risk cytogenetics (Breems, et al. 2005; Weltermann, et al. 2004; Kell 2016). Certain molecular markers and cytogenetic abnormalities are associated with a poorer prognosis in AML (e.g., autosomal monosomies, complex karyotypes, FLT3, additional sex combs-like 1 [ASXL1], TP53, and runt-related transcription factor 1 [RUNX1]), while other mutations are associated with a favorable prognosis (nucleophosmin 1 [NPM1] and CCAAT/enhancer binding protein alpha [CEBPA]) (Grimwade, et al. 2016; Yu, et al. 2020). Available data suggest that the probability of achieving CR and the duration of CR decrease with each treatment failure; a CR of 8% to 13% and median OS of 1.5 to 4.8 months has been reported among patients receiving second or greater salvage therapy (DiNardo, et al. 2015; Giles, et al. 2005; Keating, et al. 1989).

Typical available therapies for RR AML include IC for younger and fit patients and nonintensive therapy with hypomethylating agents (HMAs). In large, Phase 3 studies of high-dose cytarabine or the Investigator's choice (e.g., HMAs, multi-agent chemotherapy, cytarabine, hydroxyurea, or supportive care) in primary refractory AML or AML that had relapsed after one or more prior regimens, the CR rate ranged from 12% to 16%, and median OS ranged from 3.3 to 6.3 months (Roboz, et al. 2014; Faderl, et al. 2012; Ravandi, et al. 2015). Further, a large, international, multicenter, retrospective study of the effectiveness of HMAs in R/R AML enrolled 655 patients from 12 centers who received azacitidine (57%) or decitabine (43%) (Stahl, et al. 2018). Median age at diagnosis was 65 years (range: 16-92). In total, 70% of patients had been diagnosed with de novo AML. Of the 30% who had secondary AML, 27% had therapy-related AML. The median number of prior therapies was one (range: 1-7); 26% had received two prior lines of therapy, and 18% had received three prior lines. Prior allogeneic HSCT was reported for 19% of patients. Of the 655 patients studied, 365 (56%) had relapsed and 290 (44%) had refractory

AML. Best response to HMAs was CR (11%) or CRi (5.3%). The low response rates demonstrated with IC and HMAs data illustrate the need for additional effective treatment strategies.

Over the last decade, significant advances in the biologic understanding of AML have led to the development of molecularly targeted treatment (Kantarjian, et al. 2021), most notably IDH inhibitors (the IDH1 inhibitor, ivosidenib, and IDH2 inhibitor, enasidenib), the B-cell lymphoma-2 (BCL-2) inhibitor, venetoclax, and fms-like tyrosine kinase 3 (FLT3) inhibitors (gilteritinib, midostaurin, sorafenib, quizartinib, crenolanib). While these new targeted therapies expand the treatment options for those patients with AML who decline intensive chemotherapy or who are not candidates due to comorbid conditions, older age, or impaired functional status and have actionable mutations (e.g., IDH1, IDH2, or FLT3), (NCCN 2021), AML remains a serious disease with a poor prognosis, particularly for older adults who account for over half of all diagnoses and have lower chance of long-term survival (Buege, et al. 2018).

Table 1: FDA Approved Treatment Options for Relapsed or Refractory Acute Myeloid Leukemia

Product Name	Relevant Indication
TIBSOVO (ivosidenib)	Adult patients with R/R AML with a susceptible IDH1 mutation
XOSPATA (gilteritinib)	Adult patients with R/R AML with a FLT3 mutation
IDHIFA (enasidenib)	Adult patients with R/R AML with a susceptible IDH2 mutation
MYLOTARG (gemtuzumab ozogamicin)	Relapsed or refractory CD33-positive AML in adults and pediatric patients 2 years and older

The FDA's Assessment:

The FDA acknowledges the Applicant's assessment of current treatment options for R/R AML. The FDA would like to further elaborate on treatment options for patients with R/R AML and an IDH1 mutation. Treatment options for patients with R/R AML is complex as treatment will be tailored to the patient's age, performance status, mutational status, co-morbidities, and previous treatment including allogeneic stem cell transplantation (Thol, et al. 2021). For patients that are "fit" salvage therapy typically consists of an anthracycline and high-dose cytarabine backbone with CR rates with these regimens ranging from 29-66% (Thol, et al. 2015). Patients that relapse post-HSCT and receiving donor lymphocyte infusion have an estimated two-year survival of 21% (Schmid, et al. 2021).

For patients who are less "fit", treatment with relapsed/refractory AML has typically been with hypomethylating agents or low dose cytarabine (LDAC). In a large retrospective study of 655 patients with relapsed/refractory AML that received a hypomethylating agent, the CR rate was 11% with a median overall survival of 6.7 months.

Although not FDA-approved for patients with R/R AML, venetoclax + HMA has been evaluated in numerous studies showing an overall response rate (ORR) ranging from 24%-64% (Tenold, et al. 2021; Dinardo et al. 2018; Goldberg et al,2017; Aldoss et al, 2018, Gaut et al, 2020). A systematic review of venetoclax as monotherapy or in combination with a HMA or low-dose cytarabine (LDAC) in patients with R/R AML found a composite ORR was 38.7%, with a CR rate of 19.0%, and median OS ranging from 3.0-6.6 months (Bewesdorf et al, 2020). In a very small study by Venugopal et al (2021), 3 patients with R/R AML and an IDH1 mutation treated with venetoclax and decitabine had a CR rate of 33%. Finally, a small retrospective study evaluated response to LDAC + glasgedib in 31 patients with R/R AML (Zuchenka, et al, 2021). The median OS was only 3.9 months, with only one patient proceeding to HSCT.

Ivosidenib was FDA-approved patients with R/R AML and a susceptible IDH1 mutation in 2017. Approval was based on the single-arm, open-label study (Study AG120-C-001) of 174 patients with R/R AML and an IDH1 mutation. The median age was 67 (only 36% of patients were less than 65) and 110 patients (63%) were dependent on red blood and/or platelet transfusions. Efficacy was based on the rate of complete remission (CR) plus complete remission with partial hematologic recovery (CRh). The CR rate was 25% with a CR + CRh rate of 33%. Of the 110 patients that were transfusion dependent at baseline, 41 (37.3%) became independent of RBC and platelet transfusions during the 56-day post-baseline period. Despite the approval of ivosidenib, however, there remains a clear need for new treatments for patients with R/R IDH1-mutated AML, particularly for patients who may not be able to tolerate ivosidenib.

3.0 Regulatory Background

3.1 U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Olutasidenib (also known as FT-2102) is a potent, selective, orally bioavailable, small-molecule inhibitor of mutated IDH1 proposed for use as a treatment for relapsed/refractory AML with IDH1 mutations under NDA 215814. The development of olutasidenib began with FDA interactions starting in 2015 and Forma worked closely with the Agency with frequent communication and advice meetings to ensure the development pathway was appropriate. Olutasidenib is not approved in the US and not marketed in any other country.

The FDA's Assessment:
The Applicant's position is confirmed.

3.2 Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:
A summary of key regulatory interactions related to the development program of olutasidenib in R/R AML is provided in Table 2. Key Development Aspects were discussed and agreed at the Type C meeting in July 2018 and confirmed again at the Pre-NDA meeting in May 2021, including the following.

- Adequacy of CR + CRh to demonstrate clinical benefit and provide evidence for full approval of olutasidenib for the treatment of R/R AML with IDH1 mutations in Study HEM-101 a (Phase 2 Cohort 1)
- Second interim analysis could support an NDA submission for full approval
- A safety database comprised of at least 115 patients treated at the proposed dose with 6 months of follow-up would be sufficient to support an NDA submission for full approval.
- QTc prolongation assessment via a cardiac sub-study with centrally read Holter monitoring, along with an overall integrated assessment of QT effects across studies will provide sufficient QT information to adequately characterize the risk of QT/QTc interval prolongation

The statistical analysis plan (SAP) for the pivotal HEM-101 study was submitted and reviewed multiple times (feedback received 09 Aug 2019 and 28 Apr 2020), as was the ISS SAP (feedback received on 27 Jul 2020); feedback was incorporated into the SAPs each time. CMC activities were discussed with the Agency twice during development as per the table below.

Table 2: Key Regulatory Activities: Olutasidenib Development

Date	Major Interaction/Purpose
29 September 2015	Type B Pre-IND Meeting
30 October 2015	Original IND 127313 submitted
27 April 2017	Orphan Drug Designation for AML granted
11 July 2018	Type C Meeting – Clinical Development
17 October 2018	Type C Meeting – CMC and Clinical Pharmacology
09 August 2019	Requested comments on HEM-101 SAP received
21 August 2019	Type F Pediatric Meeting

20 December 2019	Initial pediatric study plan agreed
27 July 2020	Type C Meeting regarding ISS SAP
13 May 2021	Type B Pre-NDA Meeting
21 Jun 2021	Type B CMC Pre-NDA Meeting

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

The NDA package was submitted in its entirety, with a data cut-off date of June 18th, 2020, on February 15th, 2022. The Applicant requested priority review, but this was not granted due to the availability of another FDA-approved IDH1 inhibitor with a relatively comparable efficacy and safety profile. The Applicant provided a 90-day safety update, using a data cut-off date of June 18th, 2021, on May 12th, 2022. This was agreed to by the FDA at the time of the pre-NDA meeting.

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

4.1 Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) conducted inspections for Study 2102-HEM-101 at clinical sites in Villejuif, France (Institut Gustave Roussy) and Toronto, Ontario (Princess Margaret Cancer Centre). These sites were selected given that Institut Gustave Roussy was the highest accruing French site (three French sites enrolled the most patients, but the other two had lower response rates) and Princess Margaret Cancer Centre was the fourth highest enrolling site. Inspection review of both sites led to a classification of No Action Indicated. The Applicant (Forma) was also audited. The classification for the Applicant inspection was also No Action Indicated. Based on these inspection results, the study data derived from the inspected clinical sites were considered reliable in support of the requested indication.

4.2 Product Quality

Olutasidenib drug product (Rezlidhia) is presented as an opaque white hard gelatin capsule for oral use containing 150 mg olutasidenib. The capsules are imprinted with "OLU 150." Inactive ingredients include croscarmellose sodium, magnesium stearate and microcrystalline cellulose. The capsule shell contains gelatin and titanium dioxide. Each capsule is printed with black ink containing ferrosoferric oxide, propylene glycol, and shellac. All excipients are compendial-compliant. Individual unspecified impurities are proposed to be controlled at a limit consistent with ICH Q3B(R2). The drug product is supplied in bottles of 30 capsules with an expiry of 36 months when stored at USP controlled room temperature.

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. Approval of the NDA was recommended by the Product Quality review team.

4.3 Clinical Microbiology

Not applicable.

4.4 Devices and Companion Diagnostic Issues

The Applicant is seeking an indication for patients with relapsed or refractory AML limited to those who have an IDH1 mutation, which is the target of olutasidenib. In Study 2102-HEM-101, patients were selected based on detection of an IDH1 mutation in the local laboratory, and the results were confirmed by testing in a central laboratory. It was determined that a device to select patients for therapy would be required for safe use of olutasidenib when marketed. The applicant cross-referenced PMA P170041 for the Abbott RealTi*m*e™ IDH1 mutation assay, which

identifies the following IDH1 mutations: R132C, R132G, R132H, R132L, and R132S. The Center for Devices and Radiological Health (CDRH) reviewed The Abbott Real Ti*m*e™ IDH1 mutation assay for its intended use as a companion diagnostic to identify AML patients with an IDH1 mutation for treatment with olutasidenib under P170041/S006 (MDUFA date 6/19/2022). Following review, CDRH decided that the information provided was acceptable and the sPMA is approvable pending approval of olutasidenib.

5.0 Nonclinical Pharmacology/Toxicology

5.1 Executive Summary

The nonclinical development program for olutasidenib included various in vitro and in vivo studies to evaluate the pharmacology, pharmacokinetics, general toxicology, reproductive and developmental effects, and the genotoxic potential of olutasidenib. Olutasidenib (FT-2102) is a small molecule inhibitor of mutated isocitrate dehydrogenase (IDH) 1, indicated for the treatment of adult patients with relapsed or refractory AML with a IDH1 mutation. The IDH1 catalyzes the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG). In several hematologic and solid tumor malignancies, mutated IDH1 preferentially converts α-KG to (R)-2-hydroxyglutarate (2-HG) and thereby leads to the aberrant accumulation of 2-HG, an oncometabolite that has pleotropic effects on tumorigenesis.

From in vitro studies, olutasidenib inhibited the mutated IDH1 proteins IDH1-R132H and IDH1-R132C with IC_{50} values of 24 nM and 125 nM, respectively. Olutasidenib displayed little or no inhibitory activity against wild type IDH1 or mutated IDH2 proteins. The cell lines expressing mutated IDH1 proteins (R132H, R132L, R132S, R132G, and R132C) treated with olutasidenib showed suppressed 2-HG production with IC_{50} values ranging from 8 to 116 nM. The suppression of 2-HG production was also observed in a patient-derived, IDH1-mutated anaplastic oligoastrocytoma neurospheres model with an IC_{50} value of 1.29 nM. Additionally, olutasidenib treatment suppressed 2-HG production, increased cell proliferation, and induced granulocytic/monocytic cell differentiation in primary human AML cells with IDH1 mutations.

The in vivo activity of olutasidenib was assessed by measuring 2-HG in xenograft models of cell lines engineered to express mutated IDH1. The HCT116 cell line expressing IDH1-R132H or IDH1-R132C was subcutaneously implanted into nude mice dosed with olutasidenib at 6.25, 12.5, 25, or 50 mg/kg twice daily (BID) at 12 hour intervals for a total of 3 doses (HCT116-IDH1-R132H xenograft) or 6 doses (HCT116-IDH1-R132C xenograft). The test-article dosing group showed a dose-dependent inhibition of 2-HG in tumor tissues as compared to the vehicle control group with IC_{50} values of 26 nM and 36 nM for HCT116- IDH1-R132H and HCT116-IDH1-R132C xenograft models, respectively.

Safety pharmacology studies assessed the effects of olutasidenib on the cardiovascular system. In the electrophysiological assays, olutasidenib had an inhibitory effect on the human ether-à-go-go related gene (hERG) ion channel (IC_{50} = 11.8 μM) but had less inhibitory effects against human Cav1.2 calcium (IC_{50} = 43.3 μM) and Nav1.5 sodium channels (IC_{50} = 86.1 μM). There was no effect on QT interval or any other cardiovascular parameters in the Langendorff perfused rabbit heart model. Consistent with hERG inhibition, olutasidenib was associated with a significant increase in corrected QT (QTc) interval in the 28-day toxicology study in monkeys.

The oral bioavailability of olutasidenib in mice and dogs was 83.4 % and 73.2%, respectively. The plasma protein binding for olutasidenib determined in the mouse, rat, monkey, and human ranged from 92 – 96%. The steady-state volume of distribution (Vss) following IV

administration was moderate (~1.5 L/kg) in all species tested. The blood-brain barrier penetration and unbound brain exposure of olutasidenib were investigated in vivo using male CD-1 mice. The mean brain to plasma ratio based on total concentration was determined to be 0.339 at the 7-hour time point. Olutasidenib was extensively metabolized in rats with < 0.3% of the radioactive dose recovered as unchanged test article in the urine from rats and only 6.63% of the radioactive dose recovered from bile in male bile cannulated rats. Distribution studies showed binding of olutasidenib to melanin-containing tissues and a follow up phototoxicity study in rats showed erythema in the skin of animals after 48 hours of exposure to UV light that persisted for 72 hours.

Repeat-dose studies in rats and monkeys were conducted to assess the general toxicology of olutasidenib. The drug was administered for 13 weeks in rats and monkeys via oral administration, which is consistent with the intended clinical route of administration. Overall, adverse findings included altered glucose and lipid metabolism, inflammation, electrolyte imbalance, and toxicities in the GI tract, liver, cardiovascular system, kidneys, and hematopoietic system. Phototoxicity may also occur as discussed above. In the 13-week rat study, olutasidenib was administered at 25, 100, or 250 mg/kg BID, (50, 200, or 500 mg/kg/day) with a 4-week recovery period. A total of two olutasidenib-related mortalities occurred in the high-dose (HD) group; one death may have been related to GI erosion. Toxicities included decreases in body weight gain, labored breathing, glucosuria, decreased erythrocyte parameters, increased lymphocyte, monocyte, and eosinophil counts, reduced sodium and chloride, increased cholesterol, reduced albumin and increased globulin. Microscopic findings were observed in the kidney (karyomegaly), liver (e.g. hypertrophy and necrosis), and thyroid gland. In the 13-week monkey study, olutasidenib was administered at 15, 35/25, or 75 mg/kg BID (30, 70/50, or 150 mg/kg/day) with a 4-week recovery period. Due to adverse clinical observations in the mid-dose (MD) and HD groups, the dose level in the MD group was reduced from 70 mg/kg/day to 50 mg/kg/day beginning on Day 38. Dosing in the HD group was suspended on Day 36 and the main-dosing part of the study was terminated on Day 38. Adverse olutasidenib-related clinical observations included intermittent tremors, emesis, jaundice, and thin body condition. Olutasidenib-related microscopic findings in the liver correlated with hepatobiliary injury and altered liver function. Other toxicities included the following: GI tract (emesis, villus atrophy), liver (increased ALT, AST, ALP, and GGT, and increased weight), pancreas (depletion, acinar cells), and hematopoietic system (reduced RBCs and lineages, increased WBCs and differentials, increased platelets, and lymph node cellular depletion). In the 28-day study in monkeys, animals were administered doses of 30, 100/50, or 300/200/100 mg/kg/day via oral gavage with a 28-day recovery period. The gastrointestinal effects including loose stools and vomitus/emesis were observed in a dose-dependent manner. Increases in QTc interval duration were observed in the HD group, which became progressively longer with repeated dosing.

In an embryo-fetal development study in rats, olutasidenib was administered at 25, 125, or 250 mg/kg BID (50, 250, or 500 mg/kg/day) via oral gavage to pregnant rats on gestation day (GD) 6 – 17. There were no olutasidenib-related effects on pregnancy rate or cesarean section indices, and no olutasidenib-related fetal external or visceral variations or malformations were observed. A dose-responsive and olutasidenib-related increase in supernumerary ribs was observed, which

was statistically significant at the high dose. The highest dose tested had an exposure that was 10 times the exposure at the recommended clinical dose based on the AUC values. In a pilot study, administration of olutasidenib orally to pregnant rats during organogenesis resulted in an increase in post-implantation loss at doses of 250 and 450 mg/kg/day (9 and 10 times the AUC at the clinical dose of 150 mg BID). In an embryo-fetal development study in female rabbits, olutasidenib was administered at 10, 20, or 40 mg/kg BID (20, 40, or 80 mg/kg/day) via oral gavage on GD7 – 20. The highest dose of 80 mg/kg/day resulted in maternal toxicity characterized by a reduction in body weight gain and food intake by the end of the dosing period. There were no olutasidenib-related effects on intrauterine growth and survival at any dose levels. Additionally, there were no olutasidenib-related external, visceral, and skeletal malformations or external and visceral developmental variations. An olutasidenib-related higher incidence of supernumerary thoracolumbar rib and increased post-implantation loss occurred in the HD group. The highest dose tested had exposure that was 0.68 times the exposure at the recommended clinical dose based on the AUC values.

In genetic toxicity studies, olutasidenib was not mutagenic in the in vitro bacterial reverse mutation assay. The drug was also negative for clastogenicity in both the in vitro micronucleus assay in human lymphocyte cultures and the in vivo rat bone marrow micronucleus assay.

No carcinogenicity studies have been conducted or are warranted to support the marketing of olutasidenib for the current indication.

The nonclinical pharmacology and toxicology data submitted to this NDA are adequate to support the approval of olutasidenib for the proposed indication.

5.2 Referenced NDAs, BLAs, DMFs

The Applicant's Position:

There are no referenced NDAs, BLAs, or DMFs related to nonclinical pharmacology or toxicology for olutasidenib.

The FDA's Assessment:

We concur.

5.3 Pharmacology

Primary pharmacology

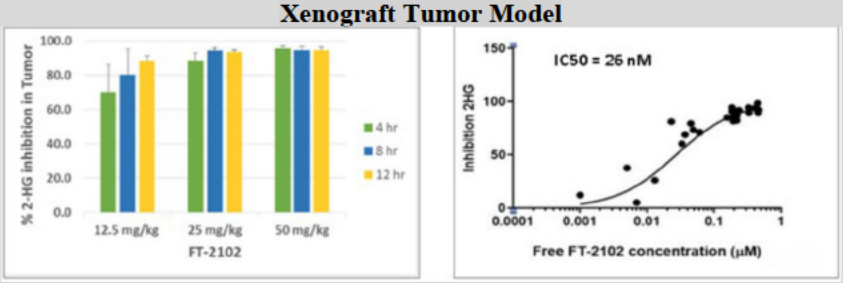
FDA's Assessment:

Study Title/Study No.	Findings
Biochemical Potency of FT-2102 in IDH1 and IDH2	Olutasidenib inhibited mutated IDH1, IDH1-R132H and IDH1-R132C, with IC_{50} values of 24.3±1.6 nM and 125.0±7.6 nM, respectively. Olutasidenib had

<table>
<tr><td>Enzymatic Assays / FT-2102-PH-001</td><td>little or no inhibitory activity against wild type (WT) IDH1or mutated IDH2 (R172K) with IC_{50} values of 22.4 µM and 27.3 µM, respectively. These results indicate that olutasidenib is an inhibitor of IDH1-R132 mutated proteins.</td></tr>
<tr><td>Cellular Potency of FT-2102 in Inhibiting 2-HG Level in mutated IDH1 Expressing Cancer Cells / FT-2102-PH-002</td><td>Olutasidenib inhibited intracellular 2-HG production in cancer cell lines expressing mutated IDH1-R132 including, R132H, R132L, R132S, R132G, and R132C, with IC_{50} values ranging from 8 - 116 nM.

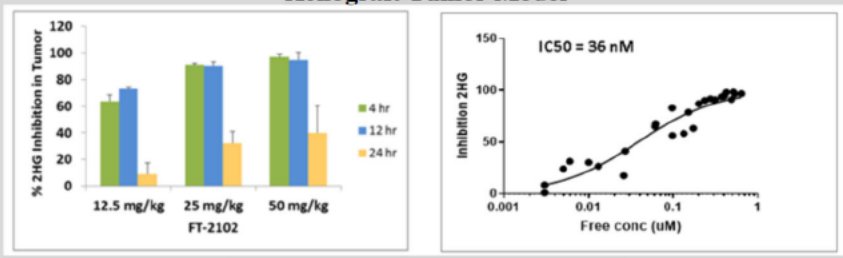
Olutasidenib Suppressed 2-HG In Vitro in Cell Lines Expressing Mutated IDH1-R132
<table><tr><th>Cell Line</th><th>2-HG IC_{50} (nM)</th></tr><tr><td>HT-1080 (IDH1-R132C/+)</td><td>80.2 (N = 1)</td></tr><tr><td>HCT-116 (IDH1-R132H/+)</td><td>27.9 ± 5.4 (N = 13)</td></tr><tr><td>HCT-116 (IDH1-R132C/+)</td><td>115.9 ± 21.2 (N = 14)</td></tr><tr><td>U87MG/IDH1-R132H</td><td>10.7 ± 1.8 (N = 9)</td></tr><tr><td>U87MG/IDH1-R132C</td><td>58.1 ± 17.3 (N = 7)</td></tr><tr><td>U87MG/IDH1-R132L</td><td>44.7 ± 9.9 (N = 4)</td></tr><tr><td>U87MG/IDH1-R132G</td><td>8.3 ± 2.5 (N = 6)</td></tr><tr><td>U87MG/IDH1-R132S</td><td>9.7 ± 2.0 (N = 3)</td></tr></table>(Excerpted from Applicant's submission)</td></tr>
<tr><td>Cellular Potency of FT-2102 in Inhibiting 2-HG Level in the BT-142 Neurosphere model / FT-2102-PH-003</td><td>Olutasidenib inhibited production of 2-HG in neurospheres formed in vitro with the BT142 tumor stem cell line with an IC_{50} value of 1.29 nM. The BT142 cell line was derived from a patient with grade III anaplastic oligoastrocytoma and harbors a heterozygous IDH1-R132H mutation.</td></tr>
<tr><td>Functional Assessment of Hematopoietic Cell Populations in IDH1 mutant AML Patient cells Treated with FT-2102 / FT-2102-C-001</td><td>The ability of olutasidenib to induce hematopoietic differentiation of bone marrow mononuclear or peripheral blood cells was assessed with cells from patients with AML with WT or mutated IDH1. The cells were cultured in the presence of olutasidenib at 0.15 - 5 µM with or without decitabine (5AZAdC). Olutasidenib suppressed 2-HG production, increased cell proliferation, and induced granulocytic/monocytic cell differentiation in primary human AML cells with IDH1 mutations. Olutasidenib in combination with 5AZAdC was shown to increase differentiation of AML cells with mutated IDH1.</td></tr>
<tr><td>In vivo Potency of FT-2102 in Inhibiting 2-HG level in the HCT-116 IDH1-R132H/+ Xenograft Tumor Model / FT-2102-PH-004

Functional Assessment of Hematopoietic Cell Populations in IDH1 mutant AML Patient cells Treated with FT-2102 / FT-2102-PH-005</td><td>The HCT-116 cell line harboring heterozygous IDH1-R132H or IDH1-R132C mutations were implanted subcutaneously in nude mice. The animals were dosed twice daily with olutasidenib at 6.25, 12.5, 25, or 50 mg/kg for a total of 3 doses (HCT116-IDH1-R132H xenograft) or 6 doses (HCT116-IDH1-R132C xenograft). The results showed a time- and a dose-dependent inhibition of 2-HG in tumor tissues.

Olutasidenib Suppressed 2-HG In Vivo in HCT-116 (IDH1-R132H/+) Xenograft Tumor Model
 

(Excerpted from Applicant's submission)</td></tr>
</table>

Olutasidenib Suppressed 2-HG In Vivo in HCT-116 (IDH1-R132C/+) Xenograft Tumor Model



(Excerpted from Applicant's submission)

IC_{50} = half-maximal inhibitory concentration

Secondary Pharmacology

The Applicant's Position:

The selectivity of olutasidenib was evaluated at concentrations up to 10 µM in a broad in vitro receptor ligand binding screen for inhibition of radiolabeled ligand specific binding using human and rat recombinant cell lines. In this screen, inhibition (or stimulation for assays run under basal conditions) of >50% was considered to represent a significant effect of a test compound. Olutasidenib displayed less than 25% inhibition of each of the 44 receptors, enzymes, and ion channels tested, except for the sodium channel (site 2) ion channel for which the mean inhibition was 27.0%. The selectivity of olutasidenib was also evaluated for binding to 59 different kinase proteins, and no significant binding activity was observed.

The FDA's Assessment:

The FDA agrees with the Applicant that olutasidenib at concentrations up to 10 µM displayed <25% inhibition of each of the 44 receptors, enzymes, and ion channels tested, except for the sodium channel (site 2) ion channel (27.0%; Study No. FT-2102-PH-006). No significant binding activity was observed in the selectivity study of olutasidenib using 59 different kinase proteins (Study No. FT-2102-PH-007).

Safety Pharmacology

The Applicant's Position:

Olutasidenib is a potent and selective inhibitor of mutated IDH1, but not wild type IDH1 or mutated IDH2. Olutasidenib displayed little or no off-target activity against a broad panel of other receptors and kinases. In safety pharmacology assessments in vitro, the only notable interaction of olutasidenib is modest inhibition of the human ether-à-go-go-related gene (hERG) ion channel (IC50 = 11.8 µM), which is 17-fold the free C_{max} of 711 nM at the efficacious dose of 150 mg BID. Consistent with hERG inhibition noted in vitro, QT interval increases were noted in the 28-day toxicology study in monkeys.

The FDA's Assessment:

The FDA agrees with the Applicant's summary for safety pharmacology. Additional details regarding the safety pharmacology assessments are provided below.

Cardiovascular System

A. The in vitro effect of olutasidenib was evaluated on three different cardiac ion channels at concentrations up to 100 μM by patch clamp studies (FT-2102-PH-008). Olutasidenib inhibited hERG potassium channels with an IC_{50} value of 11.8 μM, which is 17-fold the free C_{max} of 711 nM at the recommended clinical dose of 150 mg BID. Olutasidenib inhibited human Cav1.2 calcium and Nav1.5 sodium channels with IC_{50} values of 43.3 μM and 86.1 μM, respectively. These results indicate a predominant role of the hERG channel in the observations of QTc prolongation in the in vivo study.

B. The in vitro effect of olutasidenib was evaluated in the Langendorff perfused rabbit heart model (FT-2102-PH-009). There was no significant olutasidenib-related effect on QT interval or any other monitored parameters at concentrations up to 30 μM.

C. The in vivo cardiovascular assessments were conducted as part of a 28-day repeat-dose general toxicology study in monkeys (2336-008). Consistent with hERG inhibition, olutasidenib was associated with a significant increase in corrected QT (QTc) interval duration at the high dose (300/200/100 mg/kg/day), which became progressively longer with repeated dosing. Electrocardiogram examinations conducted at the end of the recovery period were unremarkable.

5.4 ADME/PK

The Applicant's Position:

The absorption, distribution, metabolism, excretion of olutasidenib have been well characterized.

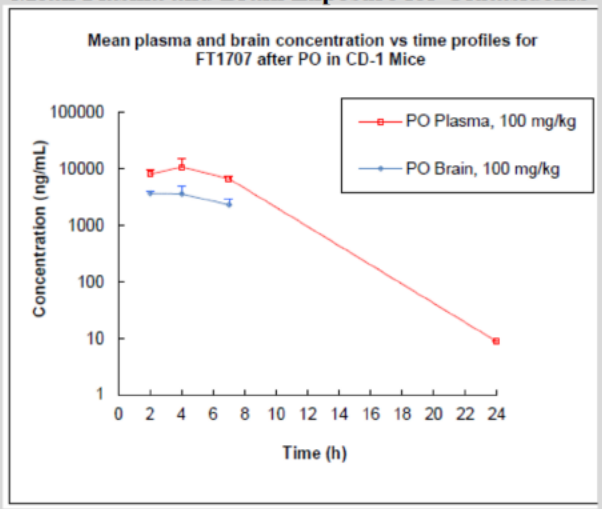
- The single-dose PK properties of olutasidenib were determined in mice, rats, dogs, and monkeys and confirm high oral bioavailability and low clearance. Repeat-dose PK properties of olutasidenib were determined after oral administration in rats and monkeys where exposure to olutasidenib increased with increasing dose with no or modest accumulation following repeat dosing. In pregnant rats olutasidenib crossed the placenta with maternal:fetal ratios from 0.808 to 0.970.
- Olutasidenib is highly protein bound across species (4.8-9.2% free) with modest red blood cell partitioning. A QWBA distribution study in rats demonstrated tissues with the highest radioactivity concentrations were small intestines, cecum, and liver. Olutasidenib crossed the blood brain barrier in rats with unbound ratios of cerebrospinal fluid to plasma and brain to plasma of 0.29 and 0.1, respectively.
- No major or human-specific metabolites of olutasidenib were identified in vitro in human, rat, dog, and monkey hepatocytes. Identified metabolites of olutasidenib in patient plasma samples were detected in at least one species from the rat and monkey 13-week toxicology studies. The circulating metabolites observed in patients after a

single dose of olutasidenib were also detected at steady state (150 mg BID), and no major circulating metabolites (> 10% relative abundance) were identified with unchanged parent as the predominant drug related component.

The FDA's Assessment:

The FDA generally agrees with the Applicant's statement. See the review below for additional details regarding the PK studies.

Type of Study	Major Findings
Absorption	
Pharmacokinetic Study of FT1706 in Cynomolgus Monkeys Following Single Intravenous (IV) and Oral (PO) Administration / FT-2102-PK-004	Male cynomolgus monkeys were given single oral or IV doses of 2 mg/kg and 1 mg/kg, respectively. • Oral bioavailability = 73.2% • $T_{1/2}$ (hours) = 14.8 following oral administration
Pharmacokinetic Study of FT3924170-1 in Male Balb/c Nude Mice Following Single Intravenous (IV) and Oral (PO) Administration / FT-2102-PK-001	Male mice were given single oral or IV doses of 5 mg/kg and 1 mg/kg, respectively. • Oral bioavailability = 83.4% • $T_{1/2}$ (hours) = 7.11 following oral administration
Distribution	
Protein Binding Measurements of 7 Forma Compounds in Plasma Using the Equilibrium Dialysis Method / FT-2102-PK-012, MC19M-0030	Plasma protein binding for olutasidenib was determined in mice (95.7%), rats (94.4%), monkeys (90.8%), and humans (92.6%).
Pharmacokinetics, Distribution, Metabolism, and Excretion of 14C-FT-2102 After a Single Oral Administration to Rats / 8362183	The distribution of olutasidenib was investigated in vivo in Sprague Dawley (SD) and Long Evans (LE) rats administered radiolabeled olutasidenib orally by using quantitative whole-body autoradiography (QWBA). Tissue distribution of radioactivity following a single oral dose of 150 mg/kg of [^{14}C]-olutasidenib with specific activity of 100 µCi/kg was evaluated through 72 hours (SD) or 168 hours (LE) after dosing. The distribution of radioactivity was moderately widespread at 0.5 hours post-dose. A notable difference was that a biphasic distribution was observed in most tissues for SD rats, but not for LE rats. Tissues with the highest radioactivity concentrations common to both rat strains were the small intestine, cecum, and liver. Radioactivity concentrations were higher in the uveal tract and pigmented skin of partially pigmented LE rats and lasted for a longer duration than for albino SD rats, indicating that there was an affinity of ^{14}C-olutasidenib - derived radioactivity for tissues containing melanin.

Type of Study	Major Findings
Pharmacokinetic Study of FT1707 in Male CD-1 Mice Following Single Oral (PO) Administration / FT-2102-PK-018	The blood-brain barrier penetration and unbound brain exposure of olutasidenib was investigated in vivo using male CD-1 mice. Blood and brain sampling was done at 2, 4, 7, and 24 hours after a single oral dose of 100 mg/kg. The mean plasma and brain concentration versus time profiles after olutasidenib administration are shown in figure below. The mean brain to plasma ratio based on total concentration measurements was determined to be 0.339 ± 0.052 at the 7-hour time point. **Mean Plasma and Brain Exposure for Olutasidenib**  (Excepted from Applicant's submission)
Metabolism	
Metabolic Stability of 4 FMA Compounds in Human, Rat, or dog Hepatocytes / FT-2102-PK-013, FT-2102-PK-020	The in vitro metabolic stability of olutasidenib has been studied across species in both hepatocytes and microsomes. Intrinsic clearance (CL_{int}) values were 25.9, 8.4, and 3.2 µL/min/10^6 cells in rat, dog, and human hepatocytes, respectively. Olutasidenib was very stable in human liver microsomes (CL_{int} < 2.49 µL/min/mg). High stability was also observed in, rat, dog, and monkey liver microsomes.
Metabolic Stability of FT1707 in Different Species of Liver Microsomes / FT-2102-PK-015	**Metabolic Stability of Olutasidenib in Human, Rat, and Dog Hepatocytes** Species Parent, Metabolism: Human | Rat | Dog Percent remaining at 120 minutes: 82.00 | 20.92 | 59.22 CL_{int} (µL/min/10^6 cells): 3.20 | 25.90 | 8.37 $t_{1/2}$ (min): 433.80 | 53.51 | 165.54 $t_{1/2}$: terminal half-life (Excerpted from Applicant's submission) **Metabolic Stability of Olutasidenib in Rat, Dog, Monkey, and Human Liver Microsomes** Species Parent, Metabolism: Rat | Dog | Monkey | Human Percent remaining at 60 minutes: 77.97 | 79.54 | 76.71 | 92.29 CL_{int} (µL/min/mg): 8.33 | 8.08 | 8.90 | 2.49 $t_{1/2}$ (min): 166.35 | 171.55 | 155.69 | 557.47 (Excerpted from Applicant's submission)

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Identify and characterize metabolites of the test compound FT1706 formed during incubation with human, rat, dog, and monkey cryopreserved hepatocytes/ FT-2102-PK-007</td><td>Cryopreserved hepatocytes from several species were incubated with olutasidenib at a final concentration of 10 µM for 120 min. Three metabolites were identified in this study, and there was no indication of human-specific metabolites. The pathways of metabolism were oxidation, hydroxylation followed by glucuronidation (major metabolite in the monkey and human), and demethylation.

Table. Metabolites of Olutasidenib in Human, Monkey, Dog, and Rat Cryopreserved Hepatocytes
<table>
<tr><th rowspan="2">Metabolite ID</th><th rowspan="2">Expected m/z</th><th rowspan="2">Mass Shift</th><th rowspan="2">RT (min)</th><th colspan="4">Area (%)</th></tr>
<tr><th>Human</th><th>Monkey</th><th>Dog</th><th>Rat</th></tr>
<tr><td>M1 – Hydroxylation + glucuronide formation</td><td>547.12</td><td>192</td><td>3.65</td><td>72.59</td><td>53.90</td><td>—</td><td>—</td></tr>
<tr><td>M2 – Demethylation</td><td>341.08</td><td>-14</td><td>3.88</td><td>—</td><td>30.90</td><td>0.74</td><td>55.34</td></tr>
<tr><td>M3 – Hydroxylation</td><td>371.09</td><td>16</td><td>4.25</td><td>—</td><td>8.85</td><td>—</td><td>21.92</td></tr>
<tr><td>M4 – Parent</td><td>355.10</td><td>0</td><td>4.68</td><td>27.41</td><td>6.36</td><td>19.52</td><td>22.73</td></tr>
</table>
ID: identification, RT: retention time. m/z: mass-to-charge ratio.
(Excerpted from Applicant's submission)</td></tr>
<tr><td>Characterization of FT-2102 Metabolites in Monkey and Rat Plasma Samples / XT190057</td><td>In vivo metabolites of olutasidenib were identified and characterized in the rat and monkey plasma samples collected from the 13-week toxicology studies. The olutasidenib components were formed by N-dealkylation, N-demethylation, oxidative decyanation, nitrile hydrolysis to yield the carboxylic acid, oxygenation, di-oxygenation, dehydrogenation, glucuronidation, or combinations. In rat plasma, no olutasidenib-related components were present at greater than 10% relative abundance. In monkey plasma, the component formed by glucuronidation was the only olutasidenib-related component formed at greater than 10% relative abundance.</td></tr>
<tr><td>Excretion</td><td></td></tr>
<tr><td>Pharmacokinetics, Distribution, Metabolism, and Excretion of 14C-FT-2102 After a Single Oral Administration to Rats/ 8362183</td><td>A single oral dose of radiolabeled olutasidenib (148 ± 1.08 mg/kg and 103 µCi/kg) was administered to SD rats (6 males and 3 females). Urine and feces were collected through 168 hours after dosing from 3 male and 3 female animals. Urine, feces, and bile were collected through 120 hours after dosing from 3 bile duct-cannulated (BDC) male animals. Olutasidenib was extensively metabolized in rats with < 0.3% of the radioactive dose recovered as unchanged in the test-article and only 6.63% of the radioactive dose recovered from the bile in male BDC rats. Therefore, renal and biliary clearance are minor routes of olutasidenib clearance in the rat.</td></tr>
</table>

5.5 Toxicology

5.5.1 General Toxicology

The Applicant's Position:

Olutasidenib is highly selective for mutated IDH1, supporting its use exclusively in patients with tumors harboring this mutation. As IDH1 mutations do not exist in noncancerous tissue, the biological target of olutasidenib is not expressed in healthy animals. Therefore, mechanism (target)-based toxicity was not expected in the toxicology program, and high dose levels [ie, up

to the 2000-mg/kg/day limit dose] were initially tested in range-finding studies in both rats and monkeys. The definitive nonclinical safety program to characterize the nonclinical safety profile comprised 28-day and 13-week studies in rats and monkeys, as well as the standard battery of genetic toxicology studies, in vitro and in vivo phototoxicity studies as well as EFD studies in rats and rabbits in accordance with regulatory guidelines (ICH, 2009a).

Toxicology studies up to 3 months in duration in rats and monkeys identified cardiovascular, GI, and hepatobiliary systems as primary organs of toxicity. These effects were likely due to off-target chemical toxicity because the pharmacologic target (mutated IDH1) is expressed in cancerous tissue but not in healthy noncancerous tissue. Effects additionally noted in the thyroid gland in rats were considered secondary to the alteration of hepatic function secondary to hepatobiliary injury. Whereas there is no clear species specificity of the cardiovascular, GI, and hepatobiliary effects to exclude human relevance, the thyroid effect is considered to be of limited relevance to human risk because the thyroid gland of humans is much less sensitive to this pathogenic phenomenon than that of rodents (Hotz, 1997). Liver and GI effects noted in rats and/or monkeys have also been noted in the clinic. However, the QTc interval prolongation effects noted in monkeys did not translate to clinically relevant QTc interval prolongation, and the thyroid effect noted in rats was secondary to altered hepatic function and has not been observed in the clinic.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's assessment; see additional information provided below for the 13-week repeat-dose toxicity studies in rats and monkeys, respectively.

13-Week Oral Gavage Toxicity and Toxicokinetic Study with FT-2102 in Rats with a 4-Week Recovery Phase / 8362179

- There were 9 unscheduled deaths; two deaths in the main study high-dose group were considered olutasidenib-related. The death of one animal was due to glandular stomach erosion and the other one was undetermined.
- The main hematological findings included decreased erythrocyte parameters and increased lymphocyte, monocyte, and eosinophil counts. Reduced sodium and chloride, and increased cholesterol were also observed.
- Other findings included glucosuria and toxicities observed in the kidney (increased weight, karyomegaly, mineralization), liver (increased weight, hypertrophy, necrosis, vacuolation), and thyroid gland.

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0 (vehicle), 25, 100, or 250 mg/kg/dose BID (0, 50, 200, or 500 mg/kg/day) for 13 weeks

Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4)% [w/v] (b) (4) in reverse osmosis water
Species/Strain:	Crl:CD (Sprague Dawley) rats
Number/Sex/Group:	Main study - 15/sex/control group and group 4; 10/sex/group 2 and group 3; Recovery study - up to 5/sex/group in control group and group 4 were designated for the recovery study from the main study
Age:	6 to 7 weeks
Satellite groups/ unique design:	TK study – 3/sex/control group; 6/sex/treatment group

Observations and Results: changes from control

Parameters	Major findings
Mortality	There was a total of 9 unscheduled deaths during the study. **0 mg/kg/day (control)**: 1 recovery female was found dead on Day 1 and the cause of death was attributed to the stress of blood collection. **200 mg/kg/day (MD)**: 1 main study female euthanized in extremis on Day 1 and 1 main study female found dead on Day 4; 1 main study male was found dead on Day 31 and the cause of death was undetermined; 1 main study male was euthanized in extremis on Day 65 with a test-article unrelated foot lesion with mixed cell inflammation. **500 mg/kg/day (HD)**: 1 TK male euthanized in extremis on Day 3 and 1 TK male found dead on Day 5; 1 main study male euthanized in extremis on Day 71; 1 main study female euthanized in extremis on Day 71. The two unscheduled deaths (1 male, 1 female) on Day 71 of the main study at the HD were considered olutasidenib-related. The male animal had a glandular stomach erosion, which was likely a secondary effect and the cause of the moribund condition. The moribund condition of the female animal could not be determined. These animals had olutasidenib-related microscopic findings including hepatocellular hypertrophy in the liver and follicular cell hypertrophy in the thyroid. The cause of mortality could not be determined for the other animals based on the lack of noteworthy pathologic findings.
Clinical Signs	Olutasidenib-related clinical observations were limited to the 1 main study male and 1 main study female in the HD group that were euthanized in extremis on Day 71. The observations included general debilitation, thin appearance, and piloerection in the male, and swollen abdomen in the female.
Body Weights	Decreases in body weight gain were noted in male and female animals at the HD up to 16% and 15%, respectively. The changes were reversible during the recovery period. No olutasidenib-related effects on food consumption were noted.
Ophthalmoscopy	Unremarkable.
Hematology	The main findings included ↓ hemoglobin, hematocrit, mean corpuscular volume, and/or mean corpuscular hemoglobin and ↑ reticulocytes at ≥ 200 mg/kg/day. ↑ lymphocytes and monocytes and ↓ eosinophils were also noted in both sexes. These changes were generally reversible by the end of the recovery period.

Hematology values by Day 92 (Week 13)

	Male			Female		
Doses (mg/kg/day)	**50**	**200**	**500**	**50**	**200**	**500**
Eosinophils (10^9/L)	-1.5	-36.4	-44.4	-42.6	-51.4	-35.6
Ery. Mean Corpuscular Hemoglobin (pg)	-2.02	-2.86	-8.24	-0.15	-3.6	-6.54
Ery. Mean Corpuscular Volume (fL)	-2.44	-3	-6.51	-1.07	-2.92	-4.69
Hematocrit (%)	-3.1	-8	-8.82	-3.2	-5.68	-5.43
Hemoglobin (g/dL)	-2.67	-7.77	-10.4	-2.18	-6.23	-7.22
Lymphocytes (10^9/L)	18.5	25.38	37.76	12.92	16.98	49.23
Monocytes (10^9/L)	26.3	71	65.56	9.62	11.06	57.37
Reticulocytes (10^9/L)	6.38	9.46	32.97	5.7	13.16	24.4

% change from the control values.

Clinical Chemistry	Animals at the HD had ↓ albumin (ALB), albumin:globulin (A:G) ratio, sodium (Na), chloride (Cl), and ↑ globulin concentration. In males, ↓ triglycerides (TRIG) concentration was observed at the HD. In females, ↓ urea nitrogen (UN) concentration was observed at the HD and ↑ cholesterol (CHOL) was observed at ≥ 50 mg/kg/day. These changes recovered at the end of the recovery period, with the exception of a lower ALB concentration in males at the HD.
Urinalysis	↑ urine volume was noted in females at the MD and HD and males at the HD. ↓ urine-specific gravity was noted in females at the HD. In males, ↑ incidence and severity of urine ketones and bilirubin were observed at the MD and HD. ↑ incidence and severity of urine glucose were also observed in males at the HD. These changes recovered at the end of the recovery period.
Gross Pathology	Unremarkable.
Organ Weights	Olutasidenib-related changes in organ weights included ↑ liver weights in animals at ≥50 mg/kg/day, ↑ kidney weights in females at ≥200 mg/kg/day, ↑ adrenal weights in males at the HD and females at ≥200 mg/kg/day, and ↓ thymus weights in animals at all dose levels. At the end of the recovery period, higher adrenal weights persisted in the HD group in both sexes and ↑ thymus weights occurred in males at the HD.

Organ weights by Day 92 (week 13)

Organ/Tissue		Male			Female		
	Dose (mg/kg/day)	**50**	**200**	**500**	**50**	**200**	**500**
GLAND, ADRENAL	Organ to Brain Weight Ratio (%)	0.47	-4.45	8.85	-1.35	20.7	42.26
GLAND, ADRENAL	Weight (g)	-2.19	-8.45	7.82	-3.56	18.43	38.79
KIDNEY	Organ to Brain Weight Ratio (%)	9.81	10.36	8.95	0.61	12.87	14.97
KIDNEY	Weight (g)	6.39	5.16	7.84	-1.83	10.57	12.16
LIVER	Organ to Brain Weight Ratio (%)	13.68	32.44	68.42	13.55	44.37	85.12
LIVER	Weight (g)	10.01	26.08	66.75	10.8	41.57	80.32
THYMUS	Organ to Brain Weight Ratio (%)	-3.68	-13.11	-35.82	-13.4	-22.3	-46.5
THYMUS	Weight (g)	-7.85	-17.69	-36.93	-15.1	-23.7	-48.03

% change from the control values.

Histopathology	Olutasidenib-related microscopic findings were observed in the kidney, liver, and thyroid. There were increased incidences of the basophilic tubules and karyomegaly in the kidney following the recovery period. All the other findings were reversible following the recovery period.

Selected microscopic parameters at the end of the dosing period

		Severity	Male				Female			
Organ/Tissue	**Finding**	**mg/kg/day**	**0**	**50**	**200**	**500**	**0**	**50**	**200**	**500**
LIVER		# Animals Examined	10	10	10	11	11	10	10	11
	Hematopoiesis, extramedullary	1 OF 5	1			2	1	1		
	Hypertrophy, hepatocellular	1 OF 5			7*	1*			10	
		2 OF 5			2	7				8
		3 OF 5				3				3
	Necrosis, hepatocyte	1 OF 5	1			2	1			
	Necrosis, individual hepatocyte	1 OF 5			2	2				
	Vacuolation, hepatocyte	1 OF 5	1	1	4	5*				4
		2 OF 5			4*	4				1
		3 OF 5				1				
KIDNEY		# Animals Examined	10	10	10	11	11	10	10	11
	Atrophy, tubule	1 OF 5		1					1	1*
	Basophilic tubule	1 OF 5	3	4	4*	8	1	1	9	9*
	Karyomegaly	1 OF 5				6		2	10	10*
	Mineralization, tubule	1 OF 5					6*	5	2	3
GLAND, THYROID		# Animals Examined	10	10	10	11	11	10	10	11
	Hypertrophy, follicular cell	1 OF 5	1	2	6	10*			1	8*

Blank cells: not toxicologically significant, 1= minimal, 2= mild, 3= moderate, 4= marked, 5= severe, * Finding was in both animal(s) with early mortality and surviving animals. Table generated from Janus Nonclinical.

Toxicokinetics	The exposures (C_{max} and AUC_{last}) were approximately 2-fold higher in females compare to males. Accumulation of the drug was observed following administration of 50 mg/kg/day. Accumulation was not observed following administration of 200 or 500 mg/kg/day after multiple doses in rats. The findings are summarized in the table below.

Summary of the FT-2102 Toxicokinetic Parameters in Rat Plasma (13 Week)

Dose (mg/kg/day)	Study Day	C_{max} (ng/mL)		AUC_{0-12} (ng·h/mL)	
		Male	Female	Male	Female
50	1	4600	8670	35,000	68,200
	91	8630	16,800	54,200	141,000
200	1	16,300	21,300	147,000	221,000
	91	16,400	30,200	116,000	236,000
500	1	16,900	27,800	165,000	250,000
	91	19,000	23,600	155,000	214,000

(Excerpted from Applicant's submission)

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

13-Week Oral Gavage Toxicity and Toxicokinetic Study with FT-2102 in Cynomolgus Monkeys with a 4-Week Recovery Phase / 8362180

- Due to adverse clinical observations in the mid- and high-dose groups, these animals had dose modifications. The dose level in the mid-dose group was reduced from 70 mg/kg/day to 50 mg/kg/day beginning on Day 38. The high-dose group was suspended after the first dose on Day 36 and terminated on Day 38; animals designated for the recovery study in this group underwent a 4-week recovery period.
- Olutasidenib-related microscopic findings in the liver correlated with hepatobiliary injury and altered liver function; altered lipid metabolism such as increased cholesterol and triglycerides were noted.
- Toxicities were observed in the GI tract (emesis, villus atrophy), liver (increased ALT, AST, ALP, and GGT, and increased weight), pancreas (depletion, acinar cells), and lymphatic and hematopoietic system (reduced RBCs and lineages, increased WBCs and differentials, increased platelets, reduced thymus weights, and depletion in lymph node).

GLP compliance: Yes

Methods	
Dose and frequency of dosing:	0 (vehicle), 15, 35, or 75 mg/kg/dose BID (0, 30, 70, or 150 mg/kg/day) for 13 weeks. MD was reduced to 50 mg/kg/day on Day 38. HD group was dosed for 36 days.
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4)% [w/v] (b) (4) in reverse osmosis water
Species/Strain:	Cynomolgus monkeys
Number/Sex/Group:	Main study - 6/sex/control group and group 4; 3/sex/group 2 and group 3; Recovery study - up to 2 animals/sex/group from the main study

	designated for recovery in control group and group 4 underwent a 4-week recovery period
Age:	35 - 47 months old
Deviation from study protocol affecting interpretation of results:	None that affected the overall interpretation of study findings nor compromised the integrity of the study.

Observations and Results: changes from control

Parameters	Major findings
Mortality	There was a total of 7 unscheduled deaths during the study. **70 mg/kg/day (MD)**: 1 male was euthanized on Day 35 due to a necrotic distal tail and thin appearance. **150 mg/kg/day (HD)**: 3 males and 2 females were euthanized early on Days 22 – 37; 1 female was euthanized on recovery Day 2 (Day 38). The animals showed poor clinical conditions (thin appearance, discolored feces) and olutasidenib-related microscopic findings in the liver.
Clinical Signs	Olutasidenib-related clinical observations in the HD group included tremors, vomitus/emesis, low food consumption, jaundice, pale mucosa, liquid feces, and/or thin body condition.
Body Weights	Unremarkable.
Ophthalmoscopy	Unremarkable.
ECG	Unremarkable.
Hematology	There were ↓ red blood cell parameters including erythrocyte, hemoglobin, and hematocrit counts in both sexes. Dose-dependent ↓ reticulocyte counts were observed in females and ↑ reticulocyte counts were observed in males at 150 mg/kg/day. ↑ leukocyte, monocyte, neutrophil, and platelet counts were observed in both sexes. The changes were reversible. Note: The recovery animals in group 4 underwent a 4-week recovery following termination of dosing period on Day 36 (until Day 64 and necropsied on Day 65).

Hematology values on Day 31 and at the end of the dosing period (Day 92)

	Study Day	Male				Female			
	Doses (mg/kg/day)	0 (mean)	30	70/50	150	0 (mean)	30	70/50	150
Erythrocytes (10^{12}/L)	31	5.97	-8.1	-20.32*	-20.3*	5.51	-9.19	-7.5	-6.65*
	92	6.04	-12.7	-20.32		5.48	-2.89	-12.63	
Hematocrit (%)	31	44.4	-3.75	-12.76*	-19.3*	42.1	-10.05	-5.93	-3.96*
	92	45.7	-8.39	-9.63		42.6	-5.01	-9.86	
Hemoglobin (g/dL)	31	13.7	-4.03	-17.95*	-22.5*	13	-9.4	-7.85	-9.4*
	92	13.8	-11.27	-16.36		12.4	-2.68	-11.8	
Leukocytes (10^9/L)	31	11.64	-37.37	21.22*	68.42*	11.69	-4.01	28.37	41.81*
	92	8.77	7.51	57.73		10.11	-4.53	60.44	
Monocytes (10^9/L)	31	0.42	-18.25	-7.14*	133.3*	0.33	-3.06	63.27	143.9*
	92	0.25	29.33	318		0.30	2.25	144.94	
Neutrophils (10^9/L)	31	5.09	-43.03	76.82*	130.3*	5.32	-7.58	84.85	132.3*
	92	3.79	52.88	93.53		4.37	4.39	118.92	
Platelets (10^9/L)	31	341	13.96	116.5*	110.7*	413	-15.17	31.96	62.15*
	92	379	21.2	91.69		431	-6.97	52.09	
Reticulocytes (10^9/L)	31	75.6	-1.86	-26.03*	29.88*	80.9	-19.23	-21.01	-28.6*
	92	55.3	83.25	17.32		74.4	-19.31	-32.62	

% change from the control values, Table generated from Janus Nonclinical, Blank: not available, * Finding was in animal(s) with early mortality and/or surviving animals.

Clinical Chemistry	Clinical chemistry changes included ↑ alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), cholesterol, and triglycerides. ↑ bilirubin was observed, which correlated with microscopic liver findings. ↓ albumin and ↑ globulin concentrations were also noted.

Clinical chemistry parameters by Day 31 and at the end of the dosing period (Day 92)

	Study Day	Male			Female		
	Doses (mg/kg/day)	30	70/50	150	30	70/50	150
Alanine Aminotransferase (U/L)	31	6.96	238.5*	213.9*	-26.53	182.1*	127.2*
	92	11.11	333.3		-32.39	120.3	
Albumin (g/dL)	31	0.69	-24.31*	-34.58*	-5.93	-10.4*	-23.7*
	92	-7.64	-22.92		-2.94	-13.24	
Alkaline Phosphatase (U/L)	31	11.11	151.7*	410.7*	-37.96	138*	288.67*
	92	-14.2	45.62		-34.06	381	
Bilirubin (mg/dL)	31	-40	300*	2044*	-25	75*	1356.2*
	92	-33.3	300		-61.9	80.95	
Cholesterol (mg/dL)	31	-20.5	34.59*	81.13*	4.79	38.17*	75.56*
	92	-24.6	27.16		8.18	56.17	
Gamma Glutamyl Transferase (U/L)	31	-10.8	355*	308.5*	115.3	627*	481.9*
	92	-24.4	293.7		104.6	661.3	
Triglycerides (mg/dL)	31	-27	372.4*	444.3*	16.36	255.5*	888.9*
	92	-3.75	140.6		-0.88	61.4	

% change from the control values, Blank: not available, * Finding was in both animal(s) with early mortality and/or surviving animals.

Urinalysis	The presence of bilirubin in the urine was observed on Day 24 of the dosing period in both sexes, which corresponded to the dark yellow, brown, amber, and rarely green color of the urine in these animals. These findings were reversible.
Gross Pathology	Olutasidenib-related macroscopic findings were observed in the liver and skin/subcutis. Black or dark red discolored liver occurred in animals in the MD and HD groups. Yellow discolored skin/subcutis occurred in animals at the HD.
Organ Weights	At the terminal sacrifice, olutasidenib-related effects on organ weight included ↑ liver and ↓ thymus weights. At the recovery sacrifice, ↑ liver weights with partial recovery were observed for the animals at the HD.

Organ weights by Day 92 (Week 13)

Organ/Tissue		Male				Female			
		0 (mean)	30	70/50	150	0 (mean)	30	70/50	150
LIVER	Organ to Body Weight Ratio (%)	1.71	12.41	69.9	125	1.79	11.2	82.65	99.38
LIVER	Weight (g)	53.64	12.1	76.5	65.07	49.05	8.66	85.73	108.3
THYMUS	Organ to Body Weight Ratio (%)	0.077	-62.5	-63.4	-85.62	0.064	2.09	-47.6	-60.73
THYMUS	Weight (g)	2.46	-64.4	-67.1	-90.05	1.75	1.3	-47.7	-60.23

% change from the control values. Table generated from Janus Nonclinical.

Histopathology	Olutasidenib-related microscopic findings were observed in the liver, thymus, mesenteric lymph node, and pancreas. The findings in the liver correlated with increased liver weight, hepatobiliary injury, altered hepatic function and inflammation. Following the recovery period, minimal hepatocyte degeneration and bile duct hyperplasia were noted. All the other findings were reversible.

Selected microscopic parameters at the end of the dosing and recovery period

Organ/Tissue	Finding	Severity	Male					Female				
		mg/kg/day	0	30	70/50	150	R	0	30	70/50	150	R
LIVER		# Animals Examined	6	3	3	4	2	6	3	3	4	2
	Degeneration, hepatocytes	1 OF 5				1*	2					1
		2 OF 5				1*				1		
		3 OF 5			2	1				2	3*	1*
		4 OF 5			1	1*					1	
	Hyperplasia, bile duct	1 OF 5			1	1*	1				2*	
		2 OF 5			1					1		
		3 OF 5			1					2		
	Infiltrate, mixed cell	1 OF 5				2	1				1*	2*
		2 OF 5			3	1	1			2	3*	
		3 OF 5				1*						
	Pigment, hepatocyte	1 OF 5			2							
LYMPH NODE, MESENTERIC		# Animals Examined	6	3	3	4	2	6	3	3	4	2
	Cellularity, decreased, lymphocytes	1 OF 5			1						3	
		2 OF 5				2*						
THYMUS		# Animals Examined	6	3	3	4	2	6	3	3	4	2
	Cellularity decreased, lymphocytes	1 OF 5		2				1	1	1	1	1
		2 OF 5				1*					1	
		3 OF 5			1	2*				1	2*	1*
		4 OF 5			1	1*						
PANCREAS		# Animals Examined	6	3	3	4	2	6	3	3	4	2
	Secretory depletion, acinar cell	1 OF 5				1*					3*	1*
		2 OF 5			1	1					1*	
LYMPH NODE, MANDIBULAR		# Animals Examined	6	3	3	4	2	6	3	3	4	2
	Vacuolation, macrophages, increased	2 OF 5				1					2	

Blank cells: not toxicologically significant, 1= minimal, 2= mild, 3= moderate, 4= marked, 5= severe, * Finding was in animal(s) with early mortality and/or surviving animals, R = recovery. Table generated from Janus Nonclinical.

Toxicokinetics	No sex difference was observed in exposures (C_{max} and AUC_{0-24}). The increases in exposure were less than dose – proportional. No accumulation of the olutasidenib was observed after multiple doses in animals administered 30 mg/kg/day. The findings are summarized in the table below.

Summary of the FT-2102 Toxicokinetic Parameters in Monkey Plasma

Dose (mg/kg/day)	Study Day	Cmax (ng/mL)		AUC_{0-24} (ng·h/mL)	
		Male	Female	Male	Female
30	1	3830	3520	58200	56300
	46	3080	3120	53800	41400
	88	3270	3150	50700	46000
70	1	6730	6510	97000	108000
50	46	4360	4560	60600	55300
	88	4990	5410	75400	73300
150	1	8750	9290	147000	159000

(Adopted from Applicant's submission)

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

Study title/Study number: FT-2102.1: A 28-day Oral Toxicity Study in Monkeys with a 28-day Recovery Period / 2336-008

The animals were administered doses of 30, 100/50, or 300/200/100 mg/kg/day via oral gavage for 28 days. The animals in all groups, including the vehicle-control group, presented GI effects (i.e., loose stools, vomitus/emesis including red vomitus at HD), which may be in part related to the Kolliphor-based vehicle. One female in the HD group was euthanized in extremis due to GI mucosal atrophy. Severity of the GI effects was generally dose-related and as a result, the dose level for the MD group was decreased from 100 to 50 mg/kg/day. The animals in the HD group were placed on a dosing holiday beginning on Day 4 through Day 11 and the dose was reduced from 300 to 200 mg/kg/day, which was further reduced to 100 mg/kg/day. Dose-related decreases in body weight gain were observed in the animals. At the HD, treatment with olutasidenib was associated with increases in QTc interval at Day 1 post-dose and at Day 28 pre-dose and post-dose. The QTc interval prolongation became progressively longer with repeated dosing, which was reversible upon cessation of dosing. The hematology findings included decreases in red cell mass, red blood cell counts, hemoglobin concentrations, and hematocrit values, and increases in reticulocyte counts. Clinical chemistry findings indicative of hepatocellular and cholestatic injury were noted in both sexes. Other olutasidenib-related findings included increased platelets and aPTT, multinucleated cells in the liver and mucosal atrophy of the intestinal tract.

5.5.2 Genetic Toxicology

The Applicant's Position:

Olutasidenib was not genotoxic in the vitro bacterial reverse mutation, human lymphocyte micronucleus, and in vivo rat bone marrow micronucleus assays.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment. Additional details regarding the studies are provided in the review below.

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)
Study title / number: FT-2102.1: Bacterial Reverse Mutation Assay / 8378157

Key Study Findings:

- Olutasidenib did not increase the number of revertant colonies in tester strains with or without metabolic activation compared to the concurrent vehicle control.
- Precipitation was observed on the test plates at concentrations of 1600 µg/plate and above, and toxicity was observed at 5000 µg/plate in strains TA1537 and TA102 in the absence and presence of S9.

GLP compliance: Yes
Test system: Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA102 in the absence or presence of induced rat liver S9 extract (up to 5000 µg/plate).
Study is valid: Yes.

In Vitro Assays in Mammalian Cells
Study title / number: FT-2102.1: In Vitro Human Lymphocyte Micronucleus Assay / 8378158

Key Study Findings:

- Olutasidenib did not induce biologically relevant increases in the frequency of micronuclei in human peripheral blood lymphocytes with or without metabolic activation.

GLP compliance: Yes.
Test system: Human peripheral blood lymphocytes with or without S9 activation. Drug concentrations of FT-2102.1 were 175 – 225 µg/mL for 3+21 hours of incubation (3 hours with 21-hour recovery) with or without S9 and 40 - 75 µg/mL for 24+24 hours of incubation (24 hours with 24-hour recovery) without S9.
Study is valid: Yes.

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)
Study title / number: FT-2102 Spray Dried Dispersion: Rat Bone Marrow Micronucleus Assay / 8382830

Key Study Findings:

- Olutasidenib did not induce micronuclei in the polychromatic erythrocytes of the bone marrow of rats when tested up to 400 mg/kg/day.

GLP compliance: Yes.

Test system: Sprague Dawley rats (Crl:CD(SD)) were administered two doses of olutasidenib Spray Dried Dispersion ranging from 25 - 400 mg/kg/day at 24 hours apart. Necropsies were conducted 24 hours after the second dose.
Study is valid: Yes.

5.5.3 Carcinogenicity

The Applicant's Position:
Carcinogenicity of olutasidenib was not evaluated in accordance with ICH S9.

The FDA's Assessment:
The FDA agrees with the Applicant's position.

5.5.4 Reproductive and Developmental Toxicology

The Applicant's Position:

Animal studies with olutasidenib have been conducted in rats and rabbits to evaluate effects on embryofetal development. Olutasidenib was administered BID at dose levels of 25, 125, or 250 mg/kg/dose (50, 250, or 500 mg/kg/day) to pregnant rats during organogenesis (gestation days 6-17) and was not associated with mortality, adverse effects on reproductive performance or Cesarean section indices, fetal external or visceral variations or malformations. A dose-responsive increase in supernumerary ribs was observed in all olutasidenib-treated groups (statistically significant at 500 mg/kg/day). This olutasidenib-related finding was considered to be a developmental variation with no impact on function and survival, and therefore, considered to be non-adverse.

Olutasidenib was administered BID at dose levels of 10, 20, or 40 mg/kg/dose (20, 40, or 80 mg/kg/day) via oral gavage to pregnant rabbits during the period of organogenesis (gestation days 7-20). All animals survived to their scheduled necropsies. No effect was seen on reproductive performance, Cesarean section indices, fetal external or visceral variations or malformations noted. An olutasidenib-related slightly higher incidence of supernumerary ribs was noted in the 80 mg/kg/day group compared to the control group. This developmental variation is considered to have no impact on function and survival, and therefore was considered non-adverse.

The FDA's Assessment:
In general, the FDA agrees with the Applicant's assessment. The FDA's review of the embryo-fetal development studies in rats and rabbits is provided below.

Embryo-Fetal Development

Study title/ number: Oral Gavage Dose Range-Finding Developmental Toxicity and Toxicokinetics Study for Effects with FT-2102 in Rats / 8382835

Key Study Findings

- Administration of olutasidenib orally to pregnant rats during organogenesis resulted in an increase in post-implantation loss at doses of 250 and 450 mg/kg/day (9 and 10 times the AUC at the clinical dose of 150 mg BID).

In a pilot study, administration of olutasidenib orally to pregnant rats during organogenesis resulted in an increase in post-implantation loss of 2.5%, 2.6%, 5.9%, and 9.3% at doses of 0, 50, 250 and 450 mg/kg/day, respectively. The values at 250 and 450 mg/kg/day exceeded the mean value in the [redacted] historical control data (5.2%) but not the maximum value (11.2 %).

Study title/ number: Oral Gavage Embryo-Fetal Development and Toxicokinetic Study For Effects with FT 2102 in Rats / 8382833

Key Study Findings

- A dose-responsive and olutasidenib-related increase in supernumerary ribs was observed at the high dose. The values at the 500 mg/kg/day dose were outside of the historical control data for fetal incidence and reached the upper limit of threshold for litter incidence.
- The exposure at 500 mg/kg/day is 10 times the clinical exposure at the recommended dose of 150 mg BID based on AUC values.

GLP compliance: Yes.

Methods

Dose and frequency of dosing:	25, 125, or 250 mg/kg/dose BID (50, 250, or 500 mg/kg/day) from Gestation Day (GD) 6 - GD17
Route of administration:	Oral gavage
Formulation/Vehicle:	[redacted]% (w/v) [redacted] in purified water
Species/Strain:	Sprague-Dawley rat
Number/Sex/Group:	Main study: 22 females/group TK study: Control: 6 females/group Olutasidenib: 9 females/group
Study design:	Pregnant rats received olutasidenib BID during GD6 through 15. Euthanization/caesarean section/necropsy were performed on GD17.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	One HD female was found in moribund condition on GD8. Necropsy findings included abnormal contents in the thoracic cavity and duodenum, and a large stomach. The cause of death was undetermined. One female at the MD died on GD16. Necropsy findings included an esophageal perforation, clear fluid in the thoracic cavity, discolored lung lobes, and green gelatinous contents in the jejunum. The death was accidental and not related to the drug treatment. One female at the MD died on GD7 due to gavage error. In the TK study, one animal at the LD was found dead and one animal at the MD died during observation. These deaths were not considered olutasidenib-related.
Clinical Signs	Unremarkable.
Body Weights	Lower body weight gains were observed in the MD group (up to 5.6%) and the HD group (up to 8.8%). The changes were reversible at the end of the dosing period. Decreases in food consumption were observed for animals in the MD and HD groups (↓13.6% and 19.7%, respectively).
Macroscopic observations	Unremarkable.
Necropsy findings	Pregnancy rate was 100, 95, 100, and 95% for controls and females administered 25, 125, or 250 mg/kg BID, respectively. Cesarean sections: no olutasidenib-related effects on cesarean section parameters were noted at any of the doses.
Fetal observations	An increase in unossified phalanx of the forelimb was observed at the LD. A dose-responsive increase in supernumerary ribs was observed in all olutasidenib-treated groups and reached significance in animals administered 500 mg/kg/day. The values at the 500 mg/kg/day dose are outside of the historical control data of 25.14% for fetal incidence and reach the upper limit of the threshold (75%) for litter incidence.

	Incidences (litters/fetuses)			
Dose (mg/kg/day)	0	50	250	500
Number Examined (litters/fetuses)	22/137	21/126	21/139	20/126
Forelimb; phalanx - unossified	1/1	6/9	3/3	1/1
Supernumerary rib	5/8	5/9	10/16	15/40

Toxicokinetic Parameters

Interval	Dose Group	Dose Level (mg/kg/ dose)	Dose Level (mg/kg/ day)	$C_{max0-24}$ (ng/mL)	SE $C_{max0-24}$ (ng/mL)	$T_{max0-24}$ (h)	AUC_{0-24} (ng·h/mL)
GD 6	2	25	50	12800	1050	13.0	140000
	3	125	250	27300	3120	13.0	411000
	4	250	500	33400	4850	13.0	409000
GD 17	2	25	50	11600	811	13.0	207000
	3	125	250	19600	176	13.0	353000
	4	250	500	25300	2350	13.0	406000

(Excerpted from Applicant's submission)

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

Study title / number: A Twice Daily (BID) Oral (Gavage) Study of the Effects of Olutasidenib (FT-2102) on Embryo/Fetal Development in Rabbits / 00325538

Key Study Findings

- Olutasidenib administered at the highest dose of 80 mg/kg/day resulted in maternal toxicity characterized by a reduction of body weight gain and food intake by the end of the dosing period.
- An increase in fetal supernumerary rib and increased post-implantation loss occurred at the high dose of 80 mg/kg/day; the exposure at the high dose is 0.68 times the clinical exposure at the recommended dose of 150 mg BID.

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 10, 20, or 40 mg/kg/dose BID (0, 20, 40, or 80 mg/kg/day) from GD7 – GD20
Route of administration:	Oral gavage
Formulation/Vehicle:	(b) (4)% [w/v] (b) (4) in reverse osmosis deionized water
Species/Strain:	Rabbit/ New Zealand White
Number/Sex/Group:	22 females/group
Satellite groups:	TK study: 4 females/group
Study design:	Pregnant rabbits were dosed BID with olutasidenib via oral gavage from GD7 through GD20. Euthanization/caesarean section/necropsy were performed on GD29.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings
Mortality	None.
Clinical Signs	Unremarkable.
Body Weights	In the MD and HD groups, lower body weight gain was observed during GD13 - GD21 and GD10 - GD21, respectively. Lower food consumption was also noted in these groups. The changes were reversible.
Necropsy findings Cesarean Section Data	Unremarkable.
Necropsy findings Offspring	The numbers of fetuses (litters) available for morphological evaluation were 180 (20), 193 (22), 201 (22), and 186 (21) in the control, 20, 40, and 80 mg/kg/day groups, respectively. An olutasidenib-related higher mean litter proportion of supernumerary thoracolumbar rib was noted in the HD group (57.02%) compared with the control group (30.21%). This difference was statistically significant and exceeded the maximum mean value in the (b) (4) (b) (4) historical control data (56.24%).

<table>
<tr><td></td><td>Increased post-implantation loss occurred with values of 1.53%, 5.39%, 5.99%, and 7.10% in the control, 20, 40, and 80 mg/kg/day groups, respectively. The values for the groups dosed with olutasidenib exceeded the mean value in the (b) (4) historical control data (4.26%) but not the maximum value (10.15%).</td></tr>
<tr><td>Toxicokinetic parameters</td><td>
<table>
<tr><th>Day</th><th>Dose[a] (mg/kg/day)</th><th>C_{max} (ng/mL)</th><th>T_{max} (h)</th><th>$AUC_{0\text{-}24}$ (ng·h/mL)</th></tr>
<tr><td rowspan="3">GD 7</td><td>20</td><td>779</td><td>2</td><td>8780</td></tr>
<tr><td>40</td><td>1770</td><td>2</td><td>19,200</td></tr>
<tr><td>80</td><td>4490</td><td>2</td><td>51,200</td></tr>
<tr><td rowspan="3">GD 20</td><td>20</td><td>1790</td><td>1</td><td>19,800</td></tr>
<tr><td>40</td><td>2150</td><td>1</td><td>15,500</td></tr>
<tr><td>80</td><td>3490</td><td>1</td><td>27,800</td></tr>
</table>
(Excerpted from Applicant's submission)</td></tr>
</table>

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

5.5.5 Other Toxicology Studies

The Applicant's Position:

In a neutral red uptake phototoxicity assay conducted in BALB/c 3T3 mouse fibroblasts, olutasidenib demonstrated phototoxic potential.

An in vivo phototoxicity study was conducted in LE pigmented rats. Oral administration of olutasidenib at dose levels of 50, 150, or 450 mg/kg/day (25, 75, or 225 mg/kg/dose BID) for 3 consecutive days followed by exposure to ultraviolet (UV) A and UVB approximately 2 hours after the final daily dose administration resulted in cutaneous phototoxicity to pigmented or nonpigmented skin at 450 mg/kg/day; however, no ocular phototoxicity was observed at this dose level. No cutaneous or ocular phototoxicity was observed at olutasidenib dose levels of ≤ 150 mg/kg/day. There were no adverse event trends in clinical studies that suggest phototoxicity (eg, rashes in sun exposure areas), although patients were advised to minimize sun exposure during the study. The use of light-protective measures should be employed to minimize the risk of phototoxicity, such as avoiding extensive sun exposure, phototherapy, or use of a tanning salon.

The FDA's Assessment:

The FDA agrees with the Applicant's summary for phototoxicity that olutasidenib at a dose of 450 mg/kg/day resulted in cutaneous phototoxicity to pigmented or nonpigmented skin (Study No. 20294440). Cutaneous signs indicative of phototoxicity were observed in 3 out of 3 surviving rats administered 450 mg/kg/day olutasidenib. On the non-pigmented and pigmented skin site, one rat exhibited erythema grade 1 (barely perceptible light redness). On the pigmented skin site, 2 rats exhibited erythema grade 1. These skin reactions were first observed 48 hours after UVR and persisted for 72 hours.

Primary Reviewer
Moran Choe, PhD

Supervisor
Brenda Gehrke, PhD

6.0 Clinical Pharmacology

6.1 Executive Summary

The FDA's Assessment:

Olutasidenib is an inhibitor of isocitrate dehydrogenase 1 (IDH1) enzyme. The Applicant is seeking approval of olutasidenib for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation. The Applicant's proposed dosing regimen is 150 mg twice daily (every 12 hours, BID) to be taken orally without food (i.e., at least 1 hour before or 2 hours after a meal).

The primary evidence for olutasidenib in the proposed indication is based on data from the Cohort 1 of pivotal Phase 2 part of Study 2102-HEM-101, an ongoing Phase 1/2, multicenter, open-label, dose-escalation and expansion study for safety, PK/pharmacodynamic, and clinical activity evaluation in patients with AML or MDS with IDH1-R132 mutations. In the efficacy population of 123 patients with R/R AML, treatment with 150 mg BID olutasidenib resulted in a CR+CRh rate of approximately 33%. The safety evaluation showed that olutasidenib was generally tolerable, however a positive trend was identified for the probability of increasing rates for Grade 3+ PI-identified differentiation syndrome and Grade ≥ 3 hepatotoxicity with increasing olutasidenib exposures. The proposed dosing regimen of 150 mg BID is deemed acceptable with favorable benefit:risk assessment.

The Clinical Pharmacology key review questions focused on the appropriateness of the proposed dosing regimen for the general patient population, dose recommendation for patients with hepatic impairment, and determining the drug-drug interaction potential for olutasidenib as a victim and as a perpetrator.

6.1.1 Recommendations

This NDA is approvable from a clinical pharmacology perspective, provided the Applicant and the FDA reach an agreement regarding the labeling language. The key review issues with specific recommendations/comments are summarized below.

Table 3. Key Clinical Pharmacology Review Issues by FDA

Review Issues	Recommendations and Comments

Pivotal evidence of effectiveness	An ongoing Phase 1/2, multicenter, open-label, dose-escalation and expansion study (2102-HEM-101) in patients with relapsed or refractory AML with IDH1-R132 mutations (Phase 2 Cohort 1).
General Dosing instructions	The recommended dosage of olutasidenib is 150 mg orally twice daily (every 12 hours) without food (i.e., at least 1 hour before or 2 hours after a meal).
Dosing in patient subgroups (intrinsic factors)	• No dose adjustment is recommended for patients with (total bilirubin ≤ULN and any AST >ULN or total bilirubin >1 to 1.5 times ULN and any AST) or moderate (total bilirubin >1.5 to 3 times ULN and any AST) hepatic impairment. The recommended dosage for use in patients with severe hepatic impairment (total bilirubin > 3 times ULN with any AST) has not been established. • No dose adjustment is recommended for patients with mild to moderate renal impairment (Creatine Clearance [CLcr] 30 to < 90 mL/min, as estimated by Cockcroft-Gault). The recommended dosage of olutasidenib has not been established in patients with severe renal impairment (CLcr 15 to 29 mL/min as estimated by Cockcroft-Gault), kidney failure (CLcr <15 mL/min, as estimated by Cockcroft-Gault), and patients on dialysis. • No dose adjustment is recommended based on age, sex, or body weight.
Drug-drug interactions	• Avoid concomitant use with strong or moderate CYP3A4 inducers. • Avoid concomitant use with CYP3A sensitive substrates. If unavoidable, closely monitor for potential loss of efficacy.
QTc Assessment	• The largest mean increase in QTc interval was 6.2 msec (upper 90% CI = 9.7 msec) in 33 patients with advanced hematologic malignancies with an IDH1 mutation following a single dose and multiple doses of the approved recommended olutasidenib dosage under fasted conditions. This increase in the QTc interval was concentration-dependent. • Increased QT prolongation is expected with increased exposures of olutasidenib under a fed condition compared to that under fasting condition. The clinical impact of this increase could not be determined because QTc intervals were not evaluated at higher olutasidenib exposures.
Bridge between the to-be-marketed and clinical trial formulations	Immediate-release capsules 50 mg and 150 mg were evaluated in the clinical development program of olutasidenib; however, only 150 mg dose strength was submitted for registration of this NDA. The to-be-marketed formulation, i.e., 150 mg capsule, was used for relevant clinical pharmacology studies and for pivotal cohort in the target patient population.

6.1.2 Post-Marketing Requirements and Commitments

The rationale and descriptions of post-marketing requirements (PMR) and commitments (PMC) are summarized in the table below. The PMC and PMRs are issued to address the drug interaction potential for olutasidenib as a victim and as a perpetrator.

Table 4. Summary of Post-Marketing Requirements and Commitments

Post-Marketing Requirement-1	
PMR Rationale	Olutasidenib is an inhibitor of OATP1B1 transporter in vitro. Co-administering olutasidenib with OATP1B1 substrates may increase the substrates' exposure, which may increase the incidence and severity of adverse reactions of the substrates. A clinical drug interaction study is required to evaluate the effect of coadministration of olutasidenib on the pharmacokinetics of OATP1B1 substrates to determine the dosage recommendations when olutasidenib is co-administered with OATP1B1 substrates. Given that olutasidenib is to be administered following repeated doses, the study is expected to be conducted in patient population. As such, FDA recommends longer time of period for the Applicant's study design, completion, and final report submission.
PMR Description	Conduct a clinical drug interaction study to evaluate the effect of repeated doses of olutasidenib on the pharmacokinetics of substrates of OATP1B1. Assess the magnitude of increased drug exposure and determine appropriate dosage recommendations when olutasidenib is administered concomitantly with OATP1B1 substrates. Design and conduct the study in accordance with the FDA Guidance for Industry titled " Clinical Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions." Draft Protocol Submission: 12/2023 Final Protocol Submission: 06/2024 Study Completion: 06/2027 Final Report Submission: 12/2027
Post-Marketing Commitment-1	
PMC Rationale	Olutasidenib is primarily metabolized by CYP3A4 in vitro. In the clinical drug-drug interaction study in healthy subjects, olutasidenib drug exposure decreased by 80% when co-administered with a strong CYP3A inducer (rifampin). The risk of

	concomitant use of moderate CYP3A inducers to decrease olutasidenib plasma exposure, leading to reduced efficacy, has not been ruled out. Given that the study could be conducted in healthy subjects, FDA recommends a shorter period of time for the Applicant's study design, completion, and final report submission.
PMC Description	Conduct a clinical drug interaction study to evaluate the effect of repeated doses of a moderate CYP3A inducer on the pharmacokinetics of olutasidenib to assess the magnitude of decreased drug exposure and determine appropriate dosage recommendations when olutasidenib is administered concomitantly with moderate CYP3A inducers. Design and conduct the study in accordance with the FDA Guidance for Industry titled " Clinical Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions." Draft Protocol Submission: 06/2023 Final Protocol Submission: 12/2023 Study Completion: 12/2024 Final Report Submission: 06/2025
Post-Marketing Commitment-2	
PMC Rationale	In vitro studies revealed that olutasidenib is an inducer of CYP3A4, 1A2, 2B6, 2C8, and 2C9. The effect of olutasidenib on decreasing plasma exposures of CYP substrates have not been ruled out. In addition, the potential of olutasidenib to induce CYP2C19 cannot be ruled out based on the results from the hepatocyte induction study because the response of the hepatocytes to the positive control rifampin was less than 2-fold and was less than the response to olutasidenib in most cases. Given that olutasidenib is to be administered following repeated doses, the study is expected to be conducted in patient population. As such, FDA recommends longer time of period for the Applicant's study design, completion, and final report submission.
PMC Description	Conduct a clinical drug interaction study to evaluate the effect of repeated doses of olutasidenib on the pharmacokinetics of substrates of CYP1A2, 2B6, 2C8, 2C9, 2C19, and 3A. Assess the magnitude of decreased drug exposures determine appropriate dosage recommendations when olutasidenib is administered concomitantly with CYP substrates. Design and conduct the study in accordance with the FDA Guidance for Industry titled " Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."

	Draft Protocol Submission:	12/2023
	Final Protocol Submission:	06/2024
	Study Completion:	06/2027
	Final Report Submission:	12/2027

6.2 Summary of Clinical Pharmacology Assessment

6.2.1 Pharmacology and Clinical Pharmacokinetics

Olutasidenib is a potent, selective, small-molecule inhibitor of mutated IDH1. In vitro, olutasidenib significantly inhibited mutated IDH1-R132H and IDH1-R132C proteins without inhibition of wild-type IDH1 or mutated IDH2 proteins. Olutasidenib inhibition of mutant IDH1 led to decreased 2-HG levels in in vitro and in vivo xenograft models. A significant and sustained decrease in 2-HG levels, and a sustained reduction in blast counts with restored normal cellular differentiation were also observed in blood of AML patients with IDH1 mutations treated with olutasidenib 150 mg twice daily in clinical studies.

Absorption:

- The median t_{max} of olutasidenib following a single oral dose of 150 mg is approximately 4 hours.
- A high-fat meal (approximately 800 to 1,000 calories, with approximately 50% of total caloric content of the meal from fat) increased olutasidenib C_{max} by 191% and AUC_{inf} by 83%.

Distribution:

- Mean (SD) apparent volume of distribution of olutasidenib is 319 (89) L. The plasma protein binding of olutasidenib is approximately 93% and the blood-to-plasma ratio is 0.5 to 0.7.

Elimination (Metabolism and Excretion):

- The mean half-life (t½) of olutasidenib is approximately 67 hours and the mean (SD) apparent oral clearance (CL/F) of olutasidenib is 4 (2.5) L/h.

Metabolism:

- Olutasidenib is primarily metabolized by CYP3A4, with minor contributions from CYP2C8, CYP2C9 and CYP2C19.
- Based on a mass balance study, olutasidenib is the predominant circulating component (92%) in plasma and no major circulating metabolites were observed. Olutasidenib metabolic pathways involve N-dealkylation, demethylation, oxidative deamination followed by oxidation, mono-oxidation with subsequent glucuronidation.

Excretion:

- Following a single oral radiolabeled olutasidenib dose of 150 mg, approximately 75% of olutasidenib was recovered in feces (35% unchanged) and 17% in the urine (1% unchanged).

Specific Populations:

- Based on a population pharmacokinetic analysis, age (28 to 90 years), sex and body weight (36 to 145 kg) do not have clinically meaningful effects on olutasidenib PK.
- In subjects with mild hepatic impairment (Child-Pugh A), AUC0-inf and Cmax of olutasidenib increased by 23% and 36%, respectively, and by 37% and 12%, respectively in subjects with moderate hepatic impairment (Child-Pugh B) relative to subjects with normal liver function. Olutasidenib plasma protein binding was similar in subjects with varying degrees of hepatic function. The unbound AUC and Cmax of olutasidenib increased by 48% and 34%, respectively, in subjects with mild hepatic impairment (Child-Pugh A), and by 118% and 42%, respectively, in subjects with moderate hepatic impairment (Child-Pugh B) relative to subjects with normal liver function. Although olutasidenib exposure was higher in subjects with hepatic impairment (HI) compared to those with normal hepatic function, the differences are not anticipated to be clinically meaningful (based on exposure-safety analysis). Population pharmacokinetic analysis using the National Cancer Institute liver dysfunction categories (n=61 mild HI and n=7 moderate HI) also showed that mild or moderate hepatic impairment do not have clinically meaningful effects on olutasidenib pharmacokinetics.

- Renal function with creatinine clearance [CLcr] ≥24 mL/min as estimated by Cockcroft-Gault had no clinically meaningful effects on olutasidenib pharmacokinetics as assessed in the population PK model (n= 82 mild RI and n= 31 moderate RI with median [min,max] baseline creatinine clearance = 83.0 [24.0, 267] mL/min). Olutasidenib pharmacokinetics in patients with CLcr <24 mL/min and patients on dialysis is unknown.

Drug-Drug Interactions:

Clinical Studies

Strong CYP3A4 Inhibitors: No clinically meaningful differences in olutasidenib pharmacokinetics were observed when co-administered with multiple doses of a strong CYP3A4 inhibitor (itraconazole).

Strong CYP3A4 Inducers: Co-administration of multiple doses of rifampin (strong CYP3A inducer) decreased the olutasidenib C_{max} by 43% and AUC by 80%.

In vitro Studies

CYP Enzymes: Olutasidenib induces CYP3A4, CYP2B6, CYP1A2, CYP2C8 and CYP2C9 and therefore may affect the pharmacokinetics of sensitive substrates of these enzymes.

Olutasidenib does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5 at clinically relevant concentrations.

Transporter Systems: Olutasidenib is a substrate of P-glycoprotein (P-gp). Olutasidenib is not a substrate of BCRP, BSEP, MRP2, MPR3, or MRP4.

Olutasidenib is an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT3, OCT2, MATE1 and MATE2K. Olutasidenib does not inhibit BSEP, MRP2, MRP3, MRP4, or OAT1.

Exposure-adverse event analysis:
The relationship between olutasidenib exposure and the probability of experiencing AEs was evaluated. Findings include:

- Increased olutasidenib exposure was correlated with the increased probability of investigator-identified differentiation syndrome and drug-related investigator-identified differentiation syndrome.
- There was an inverse relationship between olutasidenib exposure and all hepatic AE endpoints. Hepatic AE at any grade, Grade 3+ hepatic AE, and drug-related hepatic AEs were less likely to occur as olutasidenib exposure at steady state increased; the reason for this negative correlation is unknown.
- There was no apparent correlation between the olutasidenib exposure at steady state and the other AEs.

The Applicant's Position:

The clinical pharmacology of olutasidenib has been well characterized. The data included in the application consists of PK properties of olutasidenib, population PK (PopPK) and exposure/response analyses, and results from clinical pharmacology studies, all reflected in the prescribing information.

The FDA's Assessment:

FDA generally agrees with the Applicant's position that the clinical pharmacology program supports the use of olutasidenib for the treatment of R/R AML with IDH1 mutation. However, the current submission did not provide sufficient data to evaluate the drug interaction potential for olutasidenib as a victim or as a perpetrator. As a result, FDA issued one PMR and two PMCs to evaluate the effects of moderate CYP3A4 inducer on olutasidenib exposure, the effect of olutasidenib on exposures of substrates of CYP1A2, 2B6, 2C8, 2C9, 2C19, 3A4, and the effect of olutasidenib on exposures of substrates of OATP1B1. See Section 6.3.2.4 below for the detailed reviewer assessment of the drug-drug interaction potential.

The assessment of dosage recommendation for patients with hepatic impairment was made based on population PK and exposure-response analysis for patients with AML in Study 2102-HEM-101 Phase 2 Cohort 1. See Section 6.2.2.2 for the detailed reviewer assessment of hepatic impairment.

FDA disagrees with the Applicant's position for exposure-response analysis. Per FDA analysis, a positive trend was identified for the probability of increasing rates for both Grade 3+ PI-identified differentiation syndrome and Grade ≥ 3 hepatotoxicity with increasing olutasidenib

exposures. See Section 6.2.2.1 and Section 20.4.3.6 for details.

6.2.2 General Dosing and Therapeutic Individualization

6.2.2.1 General Dosing

Data:

The recommended dose of olutasidenib for adult R/R AML patients with *IDH1* mutations is 150 mg, every 12 hours, at least 2 hours after a meal or at least (b) (4) prior to the next meal.

The dose escalation portion of Study HEM-101 evaluated dosing regimens of 150 mg QD, 300 mg QD, 100 mg QD (with food), and 150 mg BID on Days 1 to 28 of each 28-day cycle. At the time of recommended phase 2 dose selection for dose expansion, there were no dose limiting toxicities (DLTs) observed at any dose among the 34 patients in the DLT-evaluable Set treated during dose escalation, and a maximum tolerated dose (MTD) was not determined. Preliminary PK data suggested a less than proportional increase in steady-state plasma olutasidenib exposures between 150 and 300 mg QD. Olutasidenib 150 mg BID resulted in the highest olutasidenib exposure at steady-state and was determined to be a well-tolerated dose. Consistent with the expected MOA of olutasidenib, 2-HG plasma concentrations were suppressed at all doses tested. By predose Cycle 2, the median 2-HG plasma concentration for the olutasidenib 150 mg BID dose was near normal range for AML patients with wild-type IDH. This response was sustained throughout treatment. Therefore, olutasidenib 150 mg BID was identified as the maximum evaluated dose from the dose-escalation stage to be evaluated in dose-expansion cohorts. The safety, PK and PD profile reported in patients treated with the olutasidenib 150 mg BID dose in the expansion cohorts was consistent with the profile of patients treated in the dose escalation.

The Applicant's Position:

Based on the totality of the data obtained from the olutasidenib clinical program, approval is being sought for olutasidenib 150 mg BID for the treatment of R/R AML patients with *IDH1* mutations. The PK and PD results in Phase 2 Cohort 1 were consistent with the results observed in Phase 1 for 150 mg BID and confirmed that this dose and schedule provided the highest olutasidenib exposure and maximal PD response. 2-HG plasma concentrations were reduced by Cycle 2 across all response categories with the lowest median levels observed in CR/CRh responders and other responders. Olutasidenib 150 mg BID was shown to provide clinically meaningful and durable efficacy and a manageable safety profile that was characteristic of symptoms or conditions frequently experienced by patients undergoing treatment for AML.

The FDA's Assessment:

FDA agrees with the Applicant's proposed dosage of olutasidenib 150 mg BID, which is supported by a favorable efficacy/safety profile in 2102-HEM-101 Phase 2 Cohort 1 (pivotal cohort), as well as additional PK and PD information in the indicated patient population with the following rationales:

(1) Efficacy:

For the efficacy in 123 efficacy-evaluable patients, the best overall response (BOR) in terms of Investigator-assessed CR+CRh rate was 33% (41/123) (See Section 8.1.2). However, no apparent correlation was identified between olutasidenib exposure at steady state and any efficacy endpoints.

(2) Safety:

For the overall safety in 153 safety-evaluable patients, a total of 46% (71/153) patients had TEAEs leading to dose interruption, 13% (20/153) had TEAEs leading to dose reduction, and 29% (45/153) had TEAEs leading to dose discontinuation.

At the proposed dosage in the pivotal cohort, the reported rates of differentiation syndrome as 14% (21/153) and QTc prolongation as 8% (13/153), respectively. These AEs are considered as class effect for the drug class. It is important to note that a positive trend of exposure-response correlation was identified for Grade 3+ PI-identified differentiation syndrome (Figure 1) and Grade 3+ hepatotoxicity (Figure 2). The incidence of differentiation syndrome and hepatotoxicity were managed by dosage interruption, modification, and discontinuation.

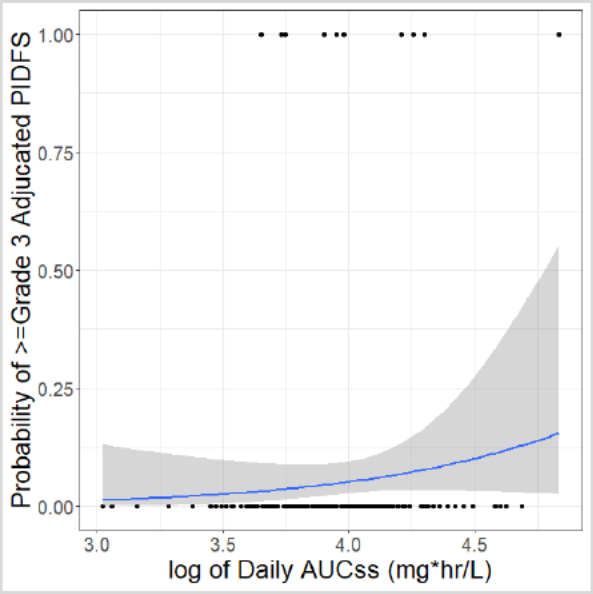
(3) PK/PD:

At the proposed dosage 150 mg BID in the pivotal cohort, the 150 mg BID dosage provided the highest olutasidenib exposure and maximal PD response, as shown in Figure 4 and Figure 5.

(4) Dosage for concomitant use with CYP3A inhibitors:

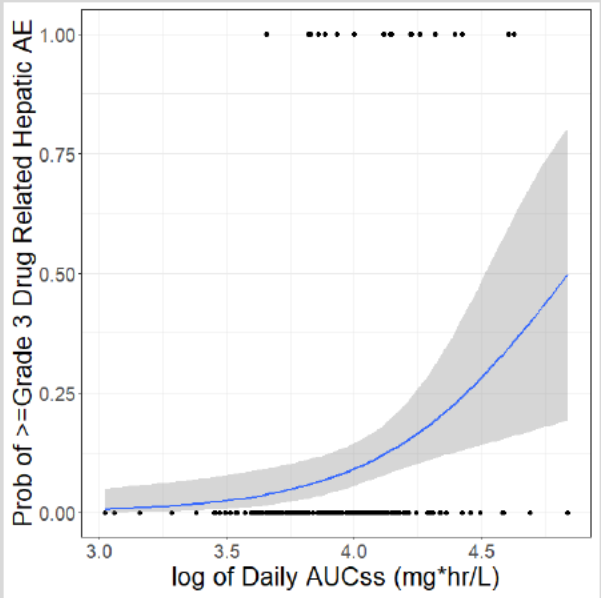
Based on dedicated DDI study, a strong CYP3A and P-gp inhibitor (itraconazole) did not change the PK of olutasidenib. Therefore, no dose adjustment is needed for patients on CYP3A inhibitors (e.g. many azole anti-fungal agents), which may be beneficial in the patient population for AML.

Figure 1. Relationship between olutasidenib AUC_{ss} and probability of Grade 3+ PI-identified differentiation syndrome occurrence for all patients taking olutasidenib monotherapy 150 mg BID in Study 2102-HEM-101.



Source: Reviewer's analysis.

Figure 2. Relationship between olutasidenib AUC_{ss} and probability of Grade 3+ hepatic AE occurrence for all patients taking olutasidenib monotherapy 150 mg BID in Study 2102-HEM-101.



Source: Reviewer's analysis.

6.2.2.2 Therapeutic Individualization

Data:
Refer to Section 6.2 Pharmacology and Clinical Pharmacokinetics, *Drug-Drug Interactions* and *Specific Populations*.

The Applicant's Position:

1. Olutasidenib exposure can be increased by high fat food intake, therefore it is recommended to take olutasidenib (b) (4) prior or 2 hours after a meal.
2. Co-administration of olutasidenib with a strong CYP3A4 inducer significantly reduces olutasidenib exposure. It is recommended to avoid co-administration with strong CYP3A4 inducers.
3. Olutasidenib may induce CYP3A4 and co-administration with sensitive CYP3A4 substrates is not recommended.

No therapeutic individualization is needed in the proposed indication based on intrinsic factors (body weight, age, gender, and hepatic or renal impairment). More information is in Section 6.3.2.

The FDA's Assessment:

(1) Food Intake Guidance:

FDA agrees with the Applicant that olutasidenib should be taken on an empty stomach, given the positive food effect increasing olutasidenib exposure based on the dedicated food effect study results. However, FDA disagrees with Applicant's proposal of taking olutasidenib (b) (4) *prior or 2 hours after meal*, given the lack of adequate assessment on the impact of food (b) (4) after a meal and the significant food effect (i.e., A high-fat high-calorie meal increased olutasidenib Cmax by 191% and $AUC_{0\text{-}inf}$ by 83%). FDA recommends taking olutasidenib **1 hour before or 2 hours after a meal,** per FDA guidance for industry: Food Effect Bioavailability and Fed Bioequivalence Studies, where an empty stomach is defined as *"1 hour before or 2 hours after a meal"*.

(2) Concomitant Medication Instruction

FDA disagrees with the Applicant to ONLY avoid co-administration with strong CYP3A4 inducers. Given the drug-interaction study with a strong CYP3A4 inducer (rifampin) substantially decreased olutasidenib AUC by 80%, the potential impact of a moderate CYP3A4 inducer on PK of olutasidenib could not be ruled out. Therefore, FDA recommends that both strong and moderate CYP3A4 inducer should be avoided for concomitant administration with olutasidenib. A post-marketing study should be conducted to adequately address the in vivo potential of moderate CYP3A4 inducer on PK of olutasidenib and inform the dosage recommendation for concomitant administration.

FDA agrees with the Applicant to avoid co-administration with sensitive CYP3A4 substrates, given the potential induction effect of olutasidenib. Postmarketing studies should be conducted to adequately address the in vivo potential of olutasidenib on PK of CYP1A2, 2B6, 2C8, 2C9,

2C19, 3A4, and OATP1B1 substrates.

(3) Dosage Recommendation for Hepatic Impairment

FDA agrees that no therapeutic individuation is needed in the proposed indication based on intrinsic factors, i.e., body weight, age, gender, and mild or moderate hepatic or renal impairment.

The assessment of dosage recommendation for patients with mild or moderate hepatic impairment (HI) was based on the population PK and exposure-response analysis. The followings are noted with regard to the PK and safety for patients with hepatic impairment:

a. Based on population PK assessment following NCI criteria, the olutasidenib exposure AUC_{ss} was generally comparable between patients with mild or moderate hepatic impairment and patients with normal hepatic function. Refer to Section 20.4.2.3 for detailed information.

b. Based on exposure-response analysis for safety (Figure 3), it is noted that patients with mild/moderate HI had higher probability of Grade 3+ PI-identified differentiation syndrome (PIIDS). In addition, based on the safety population for E-R analysis in all patients taking olutasidenib monotherapy 150 mg BID, the incidence rate of ≥ Grade 3 adjudicated PIIDS was 16.2% (6/37) in patients with mild or moderate HI (N=37) and 2.6% (4/155) in patients with normal hepatic function (N=155).

   It is noteworthy that differentiation syndrome (DS) is a class adverse reaction for IDH1 inhibitors. Dosage modification is recommended for all patients taking olutasidenib for management of DS during the olutasidenib treatment:
   - *If differentiation syndrome is suspected, withhold REZLIDHIA until signs and symptoms improve.*
   - *Administer systemic corticosteroids and initiate hemodynamic monitoring until symptom resolution and for a minimum of 3 days.*
   - *Resume REZLIDHIA at 150 mg twice daily after resolution of differentiation syndrome.*
   - *If a recurrence of differentiation syndrome is suspected, withhold REZLIDHIA and institute treatment per above guidance. After resolution of symptoms, REZLIDHIA may be resumed at a reduced dose of 150 mg once daily for a minimum of 7 days, after which it can be increased to 150 mg twice daily.*

c. Given that dosage modification for DS is recommended for overall patient population, and patients with mild/moderate HI (NCI criteria) had comparable PK with patients with normal hepatic function based on population PK assessment, no additional dosage modification is recommended for patients with mild/moderate HI. However, additional warning will also be included to caution patients with mild or moderate HI for increased

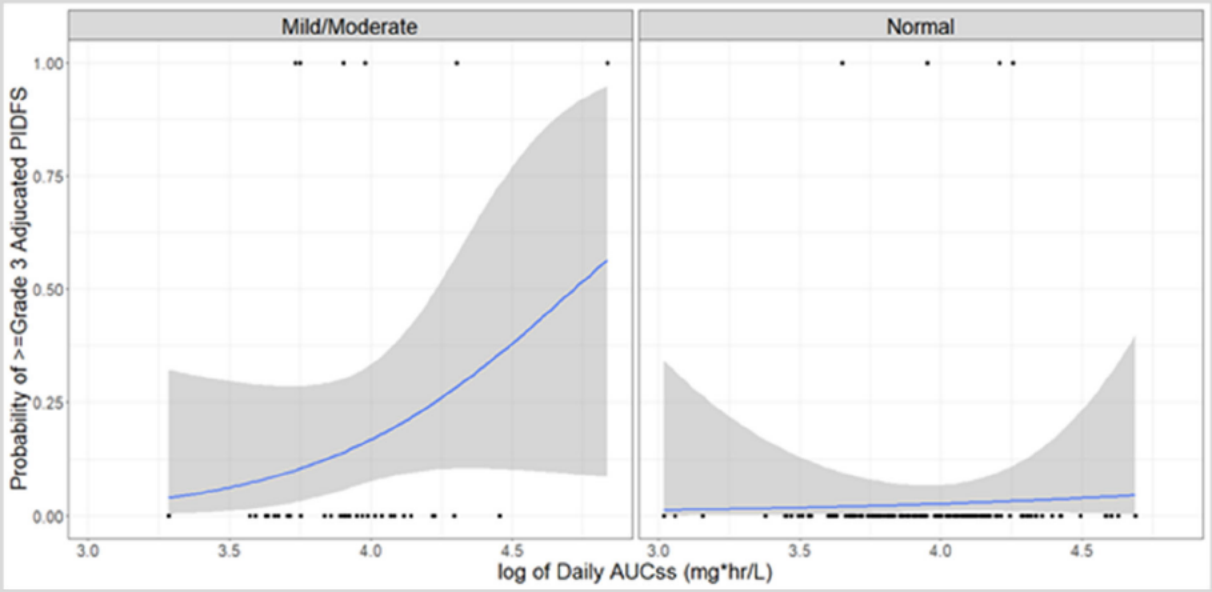
events of DS.

Based on the above assessments, FDA recommends the following with regard to assessment of hepatic impairment:

a. Dosage modification is recommended for general patient population in labeling Section 2.3 based on adverse reactions of differentiation syndrome. No additional dosage modification is recommended for patients with mild or moderate hepatic impairment (NCI criteria) based on PK. No dosage recommendation is established for patients with severe HI.

b. Add safety information to labeling Section 8.7 that patients with mild or moderate hepatic impairment should be closer monitored for events of differentiation syndrome.

Figure 3. Exposure-Response Relationship for Drug Related Adjudicated ≥ Grade 3 Principal Investigator Identified Differentiation Syndrome (PIDFS) in Patients with Olutasidenib 150 mg BID Monotherapy in Study 2102-HEM-101 stratified by hepatic functions (mild/moderate impairment versus normal function, NCI criteria).



Source: Reviewer's analysis.

(4) Exploratory Mutation Analyses and Response to Olutasidenib

The Applicant explored the impact of IDH1 R132 variants, IDH1 variant allele frequency (VAF), and co-mutated genes on the response to olutasidenib. Responses were seen across IDH1 R132 variants, with R132H being associated with the lowest CR + CRh rate. The distribution and frequency of co-mutated genes differed by R132 variant, with a higher frequency of co-

mutated NPM1 and FLT3 associated with IDH1 R132H. Response rates appeared to be lower in the subgroup of patients with co-mutations in Receptor Tyrosine Kinase (RTK) pathway genes, especially mutations in FLT3, regardless of IDH1variant. Additionally, based on limited data, lower baseline IDH1 VAF and VAF clearance post-baseline (defined as < 1% IDH1 VAF) were associated with CR/CRh responses. Variable responses according to R132 variant and co-mutated genes have been previously reported with IDH1 inhibitors. Collectively, these results support that both the IDH1 R132 variant and profile of co-mutated genes influence the response to olutasidenib. These findings could have implications for the design of future studies. Additional subject level data related to specific IDH1 variants and mutation analyses for other genes obtained under the trial protocol will be requested as part of a clinical PMR asking for long-term safety data.

6.2.2.3 Outstanding Issues

The Applicant's Position:
None.

The FDA's Assessment:

FDA assessed that there are outstanding issues related to adequacy of DDI assessment (Section 6.3.2.4). The Applicant is issued 1 PMR and 2 PMCs to assess the DDI potential of olutasidenib with moderate CYP3A4 inducers, substrates of CYP1A2, 2B6, 2C8, 2C9, 2C19, 3A4, and substrates of OATP1B1.

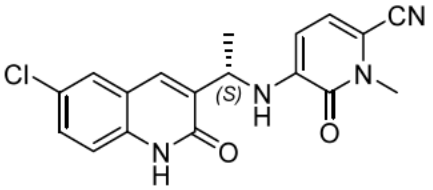
6.3 Comprehensive Clinical Pharmacology Review

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

Data:

Table 5: Highlights of Clinical Pharmacology for Olutasidenib

Pharmacology and Cardiac Safety	
Mechanism of action	Olutasidenib is a selective, small-molecule inhibitor of mutated IDH1. IDH mutation-specific inhibitors reduce aberrantly elevated levels of 2-HG, with accompanying in antitumor activity. Decrease in 2-HG production is expected to restore normal cellular differentiation and provide therapeutic benefit in IDH1-mutated cancers. In in vitro biochemical assays, olutasidenib suppressed 2-HG production in naturally occurring and genetically engineered cell lines expressing five different mutated IDH1 proteins (R132H, R132C, R132G, R132L, and R132S) with IC_{50} values ranging from 8 to 116 nM.
QT/QTc prolongation	At the recommended clinical dose of olutasidenib (150 mg twice daily), the mean (upper 90% confidence interval) increase in QTcF from baseline was 6.1 (9.3 msec). Olutasidenib does not cause clinically meaningful or large increases (i.e. ≥ 20 ms) in the QT interval.
General Information	

<table>
<tr><td>Chemical structure and molecular weight</td><td>Chemical structure of olutasidenib
 
Molecular weight of olutasidenib is 354.79 g/mol
The distribution coefficient Log D (at pH 7.4) = 4.04
One pKa was spectrophotometrically observed in the pH range 2.0-12.0: 11.63 ± 0.01</td></tr>
<tr><td>Solubility</td><td>Olutasidenib does not contain ionizable groups under physiological conditions; olutasidenib aqueous solubility is pH independent.
Fasted simulated intestinal fluid = 2.8 µg/mL
Fed simulated intestinal fluid= 19.1 µg/mL</td></tr>
<tr><td>Bioanalysis</td><td>A validated bioanalytical method using LC-MS/MS for the quantitation of olutasidenib in human plasma was used for clinical studies.</td></tr>
<tr><td>PK in healthy subjects vs patients</td><td>
<table>
<tr><th>Population</th><th>C_{max} (ng/mL)</th><th>AUC[c] (h*ng/mL)</th><th>CL/F (L/hr)</th></tr>
<tr><td>Patients with AML/MDS[a]</td><td>535.0 (58.7)</td><td>40680 (37.8)</td><td>3.3 (NA)</td></tr>
<tr><td>Healthy Subjects[b]</td><td>371.9 (34.3)</td><td>41600 (57.4)</td><td>4.1 (2.5)</td></tr>
</table>
[a] Study 2102-HEM-101, 150 mg BID olutasidenib, Cycle 2 Day 1, CL/F estimated from Population PK analysis
[b] Study 2102-HVS-104, 100 µCi 150 mg ^{14}C-olutasidenib
[c] AUC_{tau} for patients and AUC_{last} for healthy subjects
C_{max} and AUC are presented as GeoMean (GeoCV); Cl/F is arithmetic mean (SD)</td></tr>
<tr><td>Steady-state exposure at the proposed dosing regimen</td><td>Study 2102-HEM-101, Phase 2 Cohort 1, Cycle 2 Day 1, 150 mg BID:
C_{max} = 3136 (62) ng/mL; AUC_{tau} = 40680 (37.8) hr*ng/mL</td></tr>
<tr><td>Maximally Tolerated Dose (MTD) or Exposure</td><td>MTD for olutasidenib has not been determined (no DLT in Phase 1 of clinical study 2102-HEM-101).</td></tr>
<tr><td>Dose proportionality</td><td>Following a single dose and at steady-state, olutasidenib exposure increases were less than dose proportional in the 100 to 300 mg dose range.</td></tr>
<tr><td>Accumulation Ratio</td><td>For 150 mg BID at steady-state: C_{max} ~ 590 % and AUC ~ 400 %.</td></tr>
<tr><td>Steady-state PK variability</td><td>Study 2102-HEM-101, Phase 2 Cohort 1, Cycle 2 Day 1, 150 mg BID:
inter-subject variability (%CV) = 38% for AUC and 62% for C_{max}</td></tr>
<tr><td colspan="2">Absorption</td></tr>
<tr><td>Bioavailability</td><td>Olutasidenib oral capsule – absolute bioavailability (% F) has not been determined.</td></tr>
<tr><td>T_{max}</td><td>The median (range) T_{max} of olutasidenib is 4 hours (1 to 8 hours)</td></tr>
<tr><td>Food effect (fed/fasted)</td><td>Following administration of a single dose of olutasidenib in healthy subjects, a high-fat meal (approximately 800 to 1,000 calories, with approximately 50% of total caloric content of the meal from fat) increased olutasidenib C_{max} by 191% and AUC_{inf} by 83%.
<table>
<tr><th>Parameter</th><th>GMR (%)</th><th>90% Confidence Interval</th></tr>
<tr><td>AUC_{inf} (ng*hr/mL)</td><td>183.31</td><td>161.06 - 208.64</td></tr>
<tr><td>C_{max} (ng/mL)</td><td>291.00</td><td>252.61 - 335.23</td></tr>
</table></td></tr>
<tr><td colspan="2">Distribution</td></tr>
</table>

<table>
<tr><td>Volume of distribution</td><td>In healthy subjects, mean (SD) olutasidenib apparent volume of distribution (V/F) is 319 (89) L. In patients, based on population PK, V/F is approximately 201 L.</td></tr>
<tr><td>Plasma protein binding</td><td>Olutasidenib is 93% bound to human plasma proteins in vitro.</td></tr>
<tr><td>Blood to plasma ratio</td><td>Olutasidenib blood-to-plasma ratio ranges from 0.5 to 0.7.</td></tr>
<tr><td colspan="2">Elimination</td></tr>
<tr><td>Terminal elimination half-life</td><td>Mean (%CV) terminal elimination half-life of olutasidenib is 66.8 (34) hours.</td></tr>
<tr><td colspan="2">Metabolism</td></tr>
<tr><td>Fraction metabolized (% dose)</td><td>In a mass balance study, unchanged olutasidenib was the major circulating entity, accounting for approximately 92% of radioactivity in plasma.</td></tr>
<tr><td>Primary metabolic pathway(s)</td><td>Olutasidenib is metabolized primarily by CYP3A4 with minor contributions from CYP2C8, CYP2C9 and CYP2C19.</td></tr>
<tr><td colspan="2">Excretion</td></tr>
<tr><td>Primary excretion pathways</td><td>Based on the mass balance study, approximately 75% of olutasidenib was recovered in feces (35% unchanged) and 17% in the urine (1% unchanged).</td></tr>
<tr><td colspan="2">Drug Interaction Liability</td></tr>
<tr><td>Induction of metabolism</td><td>Olutasidenib may reduce exposure of concomitant medications that are sensitive substrates of CYP3A4, CYP2B6, CYP1A2, CYP2C8 and CYP2C9.</td></tr>
<tr><td>Inhibition of transporter systems</td><td>In vitro, olutasidenib is an inhibitor of P-gp, BCRP, OATP1B1, OATP1B3, OAT3, OCT2, MATE1 and MATE2K. Based on a mechanistic static DDI risk assessment, olutasidenib may impact exposure of concomitant medications that are sensitive OATP1B1 substrates.</td></tr>
<tr><td>Concomitant administration of strong CYP3A4/P-gp inhibitors or a strong CYP 3A4/P-gp inducers</td><td>No clinically meaningful change in olutasidenib exposure is observed with concomitant administration of a strong CYP3A4/P-gp inhibitor. A significant reduction in olutasidenib exposure is observed with concomitant administration of a strong CYP3A4/P-gp inducer.
<table>
<tr><th>Comparison</th><th>Parameter (Unit)</th><th>GMR %</th><th>90% CI</th></tr>
<tr><td rowspan="2">Itraconazole and Olutasidenib vs Olutasidenib alone</td><td>C_{max} (ng/mL)</td><td>81.58</td><td>(69.97, 95.11)</td></tr>
<tr><td>AUC_{inf} (h*ng/mL)</td><td>100.06</td><td>(85.41, 117.23)</td></tr>
<tr><td rowspan="2">Rifampin and Olutasidenib vs Olutasidenib alone</td><td>C_{max} (ng/mL)</td><td>56.68</td><td>(45.77, 70.20)</td></tr>
<tr><td>AUC_{inf} (h*ng/mL)</td><td>20.10</td><td>(16.37, 24.68)</td></tr>
</table></td></tr>
<tr><td colspan="2">Specific Populations</td></tr>
<tr><td>Mild or moderate hepatic impairment (HI)</td><td>Mild HI: Olutasidenib AUC_{inf} was 23% higher and C_{max} was 36% higher in the mild HI cohort compared to total matched healthy-control subjects. For unbound olutasidenib, $AUC_{inf,u}$ and $C_{max,u}$ were approximately 48%, and 34% higher, respectively.

Moderate HI: Olutasidenib AUC was 37% higher and C_{max} was 12% higher compared to total matched healthy-control subjects. $AUC_{inf,u}$, and $C_{max,u}$ were approximately 118%, and 42% higher, respectively.</td></tr>
</table>

AUC and C_{max} values are presented as GeoMean(GeoCV) unless otherwise indicated

The Applicant's Position:

The objective of the clinical pharmacology program was to describe the pharmacokinetics (PK) and pharmacodynamics (PD) of olutasidenib in subjects with AML, MDS, or advanced malignancies, subjects with mild and moderate hepatic impairment (HI), and in healthy subjects.

Factors that may affect clinical pharmacology were assessed prospectively through in vitro

studies, clinical studies, and by population PK modeling of the data from the primary study in subjects with AML or MDS (Study 2102-HEM-101). In vitro studies (using human biomaterials) that are pertinent to PK processes were conducted to provide fundamental information for clinical study design and data interpretation. These studies included evaluation of distribution, hepatic metabolism, and drug-drug interaction (DDI) potential with major enzymes and transporters. Clinical studies have been conducted in healthy volunteers to evaluate the effects of intrinsic factors (HI) and extrinsic factors (food effects) on olutasidenib PK. A drug-interaction study was also conducted to evaluate the effect of other drugs on olutasidenib PK. The population PK model was used to assess the potential sources of variability in olutasidenib PK and steady-state exposures in subjects with AML or MDS. Characterization of exposure-response relationships was also conducted using data from Study 2102-HEM-101. Exposure parameters were assessed versus parameters of patient efficacy and parameters of patient safety. Additionally, the probability of patients achieving the various efficacy endpoints and experiencing adverse events of interest were evaluated across quadrants of olutasidenib steady-state exposure.

A concentration-QTc analysis was conducted to characterize QTc prolongation risk using data from Study 2102-HEM-101 in subjects with AML.

Data from these studies and assessments were used to provide information on olutasidenib and guidance for using olutasidenib in the proposed USPI.

The FDA's Assessment:

FDA generally agrees with the Applicant that the clinical pharmacology properties of olutasidenib were adequately characterized, except for the following:

(1) **DDI Assessment:** FDA does not agree with the Applicant ant the DDI risk has been adequately assessed for olutasidenib. See Section 6.3.2.3 for more details.

(2) **QT Assessment:** The Applicant's QT assessment only covered olutasidenib exposure at the proposed dosage 150 mg BID at fasted condition. The QT assessment does not cover the increased in olutasidenib exposure when taken with food, while there were concentration-dependent effects in the in vitro study and in clinical studies. The following conclusion is included in the olutasidenib labeling for QT:

The largest mean increase in QTc interval was 6.2 msec (upper 90% confidence interval = 9.7 msec) in 33 patients with advanced hematologic malignancies with an IDH1 mutation following a single dose and multiple doses of the approved recommended olutasidenib dosage under fasted conditions. This increase in the QTc interval was concentration dependent.

Increased QT prolongation is expected with increased exposures of olutasidenib under a fed condition compared to that under fasting condition [see Clinical Pharmacology (12.3)]. The

clinical impact of this increase could not be determined because QTc intervals were not evaluated at higher olutasidenib exposures.

(3) **PK parameters:** The Applicant's original proposed accumulation ratio (AR) for AUC as 4.0 was mixed assessments of $AUC_{0\text{-}8h}$ and $AUC_{0\text{-}12h}$ based on Study 2102-HEM-101 Phase 2 Cohort 1. On September 9, 2022, the Applicant provided the following updates in response to FDA IR sent on September 2, 2022, where the AR values were estimated based on individual patient's $AUC_{0\text{-}8h}$ and C_{max} of C1D1 and C2D1, with and without dose modification (Table 6). Based on the Applicant's updated estimation, the mean values of AR were greater than the original estimation, i.e., 9.5 for AUC and 7.7 for C_{max} in all patients.

Table 6. Summary of accumulation ratio of 2102-HEM-101 Phase 2 Cohort 1.

Parameter	Statistics	Any Dose Modification		Overall
		Yes	No	
C_{max} Accumulation Ratio (AR)	N	13	73	86
	Arithmetic Mean	5.451	8.111	7.709
	CV%	86%	76%	78%
	Geometric Mean	3.429	6.441	5.855
	Geometric CV%	152%	76%	92%
$AUC_{0\text{-}8h}$ Accumulation Ratio (AR)	N	10	67	77
	Arithmetic Mean	6.868	9.857	9.469
	CV%	109%	73%	76%
	Geometric Mean	3.790	8.022	7.278
	Geometric CV%	183%	71%	90%

Source: Response to FDA RFI-ClinPharm -02 Sep 2022.

6.3.2 Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

Data:

Pharmacodynamic evaluations were performed in subjects with AML/MDS following a single-dose and multiple doses of olutasidenib (Study 2102-HEM-101). Consistent with the expected MOA of olutasidenib, 2-HG plasma concentrations in both Phase 1 and Phase 2 Cohort 1 were suppressed/reduced to near normal range for patients with AML and wild-type IDH1 (178 ng/mL; Janin, et al. 2014) at all dose levels tested, with 150 mg BID olutasidenib resulting in maximal 2-HG reduction (Figure 4).

By Cycle 2, the median 2-HG plasma concentration in Phase 2 Cohort 1 was 206.5 ng/mL (range: 44, 4902), and this PD response was sustained throughout treatment with olutasidenib 150 mg BID (Figure 5).

The 2-HG plasma concentrations were reduced by Cycle 2 in Phase 1 and by Cycle 2 and by Cycle 6 in Phase 2 Cohort 1 across all response categories (Figure 6). The lowest median levels were observed in CR/CRh responders and other responders.

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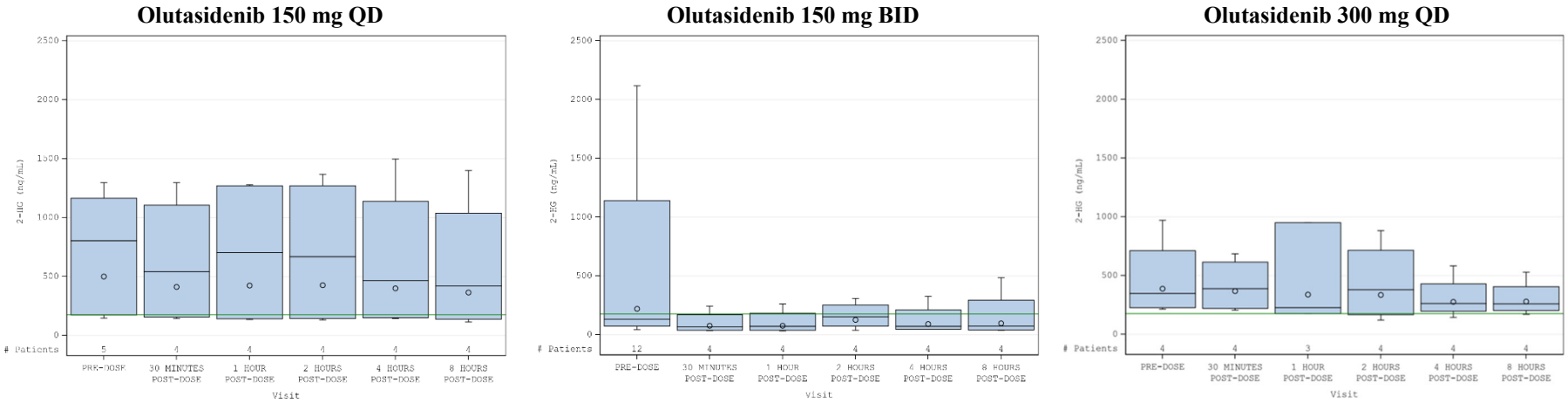
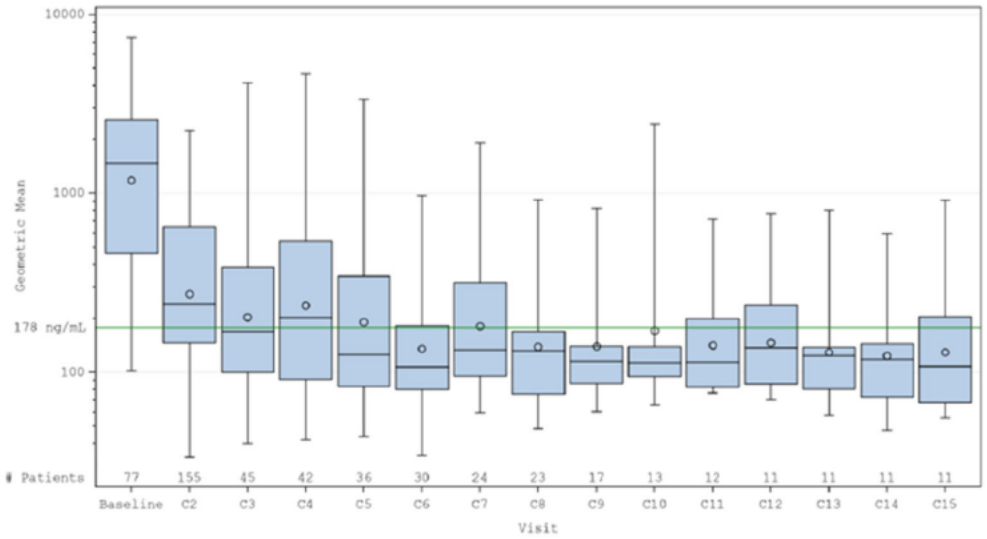
Figure 4: 2-HG (ng/mL) over Time by Olutasidenib Dose on Cycle 2 Day 1 (Pharmacodynamic Analysis Set)



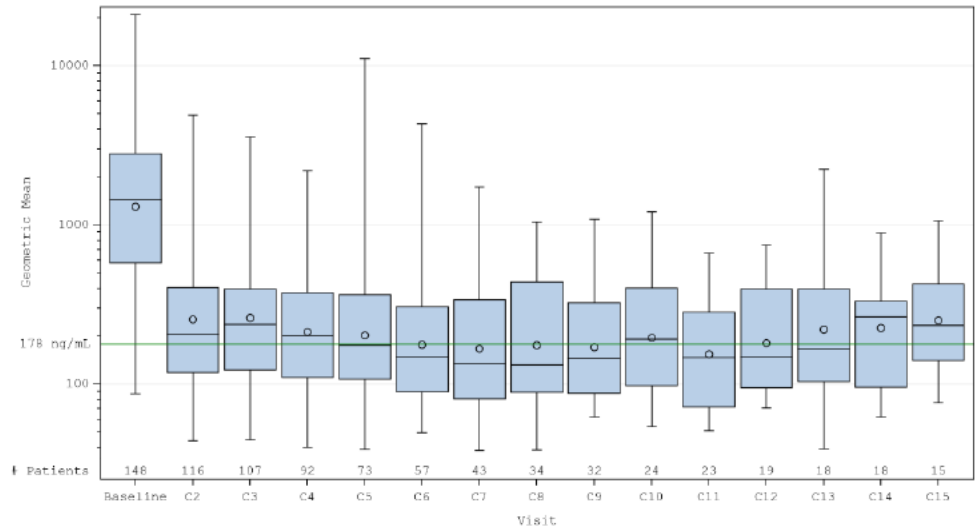
Source: Figure A20. Data Cutoff: 18 Jun 2020.
Abbreviations: 2-HG = 2 hydroxyglutarate; AML = acute myeloid leukemia; BID = twice daily; IDH = isocitrate dehydrogenase QD = once daily.
Note: The horizontal line inside the box represents the median; the symbol represents the mean. The lower and upper ends of the box represent the 25th and 75th percentiles, respectively. The whiskers extend to the minimum and maximum values for the group.
Note: The horizontal reference line at 178 ng/mL represents the normal level of 2-HG for AML patients with wild-type IDH.

Figure 5: 2-HG (ng/mL) over Time (PD Analysis Set)

Phase 1



Phase 2 Cohort 1



Abbreviations: 2-HG = 2-hydroxyglutarate; AML = acute myeloid leukemia; C = cycle; IDH1 = isocitrate dehydrogenase 1; PD = pharmacodynamic.

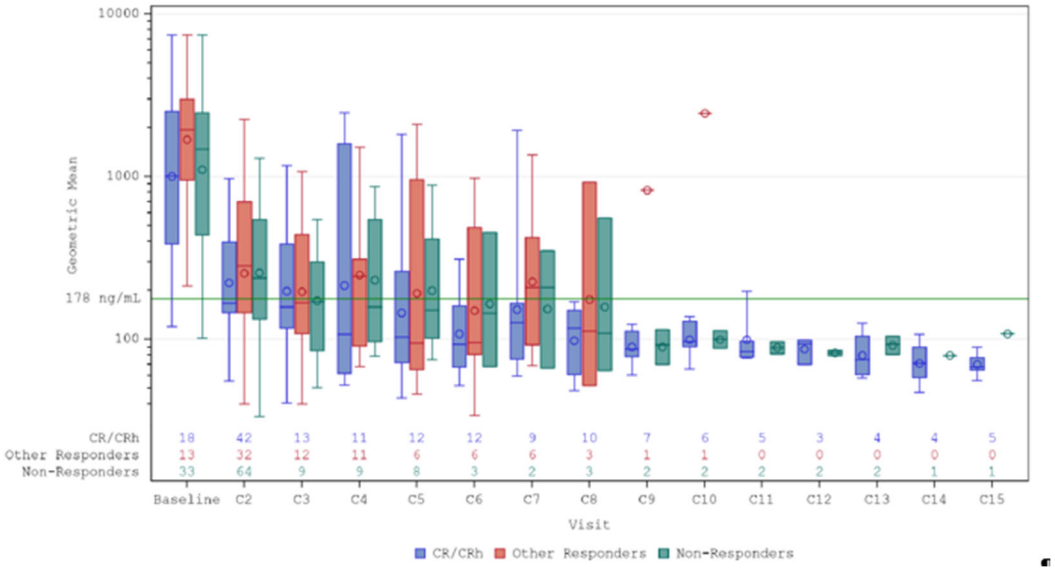
Note: The horizontal line inside each box represents the median; the symbol represents the mean. The lower and upper ends of the box represent the 25th and 75th percentiles, respectively. The whiskers extend to the minimum and maximum values for the group.

Note: The horizontal reference line at 178 ng/mL represents the normal level of 2-HG for AML patients with wild-type IDH1.

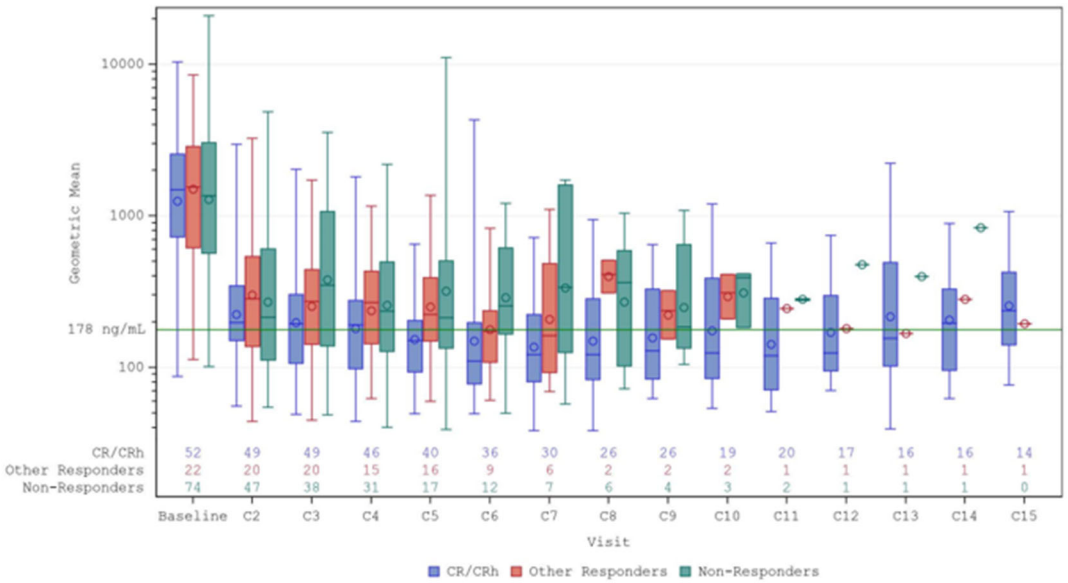
Sources: Study HEM-101 Phase 1 CSR Figure 14.2.10.2a. Study HEM-101 Phase 2 Cohort 1 CSR Figure 14.2.10.2d. Data Cutoff: 18 June 2020.

Figure 6: 2-HG (ng/mL) over Time by Response Category (PD Analysis Set)

Phase 1



Phase 2 Cohort 1



Abbreviations: 2-HG = 2-hydroxyglutarate; AML = acute myeloid leukemia; C = cycle; CR = complete remission; CRh = CR with partial hematologic recovery; IDH1 = isocitrate dehydrogenase 1; PD = pharmacodynamic.

Note: The horizontal line inside the box represents the median; the symbol represents the mean. The lower and upper ends of the box represent the 25th and 75th percentiles, respectively. The whiskers extend to the minimum and maximum values for the group.

Note: The horizontal reference line at 178 ng/mL represents the normal level of 2-HG for AML patients with wild-type IDH.

Sources: Study HEM-101 Phase 1 CSR Figure 14.2.10.3a. Study HEM-101 Phase 2 Cohort 1 CSR Figure 14.2.10.3b. Data Cutoff: 18 June 2020.

The Applicant's Position:
Yes. The results from Study 2102-HEM-101 provide evidence of effectiveness for olutasidenib 150 mg twice daily in adult R/R AML patients with *IDH1* mutations. PD data confirms MOA supporting the clinical response observed. Specifically, 2-HG plasma concentrations were suppressed/reduced to near normal range for patients with AML and wild-type IDH1 (178 ng/mL; Janin, et al. 2014) at all dose levels tested, with 150 mg BID olutasidenib resulting in maximal 2-HG reduction (Figure 5). Lowest median 2-HG levels were observed in CR/CRh responders and other responders (Figure 6).

The FDA's Assessment:

FDA generally agrees with the Applicant that the results from Study 2102-HEM-101 provide evidence of effectiveness for olutasidenib 150 mg twice daily in adult R/R AML patients with *IDH1* mutations.

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

Data:
Refer to Sections 6.2.2 and 6.3.2.1 for data supporting the dosing regimen of 150 mg BID for patients with R/R AML.

The Applicant's Position:
The proposed dose of olutasidenib is 150 mg, every 12 hours, at least 2 hours after a meal or at least (b) (4) prior to the next meal is appropriate for patients with R/R AML with IDH1 mutations. Dose holds and reductions are proposed for severe adverse events.

The FDA's Assessment:

FDA generally agrees with the Applicant that the proposed dosage of olutasidenib 150 mg twice daily in adult R/R AML patients with *IDH1* mutations is supported by the totality of safety, efficacy, PK and PD data in Study 2102-HEM-101 Phase 2 Cohort 1. The drug should be taken at an empty stomach, i.e., at least 1 hour before or 2 hours after a meal. Refer to Sections 6.2.2.1 and 6.2.2.2 for details.

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

Data:

In Study 2102-HVS-105, olutasidenib exposure was higher in subjects with hepatic impairment (HI) compared to those with normal hepatic function, however, the differences are not

anticipated to be clinically meaningful (based on exposure-safety analysis) Population pharmacokinetic analysis using the National Cancer Institute liver dysfunction categories (n=61 mild HI and n=7 moderate HI) also showed that mild or moderate hepatic impairment do not have clinically meaningful effects on olutasidenib pharmacokinetics.

It is concluded that no dosing adjustment is required in subjects with mild or moderate hepatic impairment. The pharmacokinetics and safety of olutasidenib in patients with severe hepatic impairment are unknown.

Based on the mass balance study, renal elimination plays a minor role in the overall elimination of olutasidenib, therefore a renal impairment (RI) study was not conducted. Renal function with creatinine clearance [CLcr] ≥24 mL/min as estimated by Cockcroft-Gault had no clinically meaningful effects on olutasidenib pharmacokinetics as assessed in the population PK model (n= 82 mild RI and n= 31 moderate RI with median [min,max] baseline creatinine clearance = 83.0 [24.0, 267] mL/min in study 2102-HEM-101). Olutasidenib pharmacokinetics in patients with CLcr <24 mL/min and patients on dialysis is unknown. It is concluded that no dosing adjustment is required in subjects with mild or moderate renal impairment.

Race was not evaluated as a potential covariate in the population PK model because data was missing for more than 20% of subjects. No dosage adjustments are recommended based on race.

Sex, age (median [min,max] = 70 [28, 90] years) and body weight (median [min,max] = 72 [36, 145] kg) were evaluated as a covariates in the population PK model and did not meaningfully impact exposure. No dosage adjustments are recommended based on sex, age or body weight.

The Applicant's Position:
No dose adjustments are required based on intrinsic factors (age, gender, body weight renal impairment, and hepatic impairment).

The FDA's Assessment:

FDA generally agrees with the Applicant that no dose adjustments are required based on intrinsic factors. However, safety information will be included in labeling Section 8.7 for the increased probability of differentiation syndrome for patients with mild or moderate hepatic impairment (NCI criteria). See Section 6.2.2.2 for details.

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

Data:
Following administration of 150 mg olutasidenib with a high fat meal (approximately 800 to 1,000 calories, with approximately 50% of total caloric content of the meal from fat), $AUC_{0\text{-}inf}$ was 83% higher and Cmax was 191% higher compared to fasted conditions. The 90% CIs for the GMRs were outside the 80.00% - 125.00% acceptance range and did not include 100%

indicating that there is a food effect for both peak and extent of exposure.

The effect of a strong CYP3A4 and P-gp inhibitor (itraconazole) and a strong CYP3A4/P-gp inducer (rifampin) on the PK of olutasidenib was evaluated in Study 2102-HVS-103.

Co-administration of olutasidenib with a strong CYP3A4/P-gp inhibitor did not significantly alter olutasidenib systemic exposure.

Co-administration of olutasidenib with a strong CYP3A4/P-gp inducer significantly reduced olutasidenib systemic exposure (C_{max} was approximately 43% lower and AUC was approximately 80% lower than olutasidenib alone).

In vitro data showed that olutasidenib induces CYP3A4, CYP2B6, CYP1A2, CYP2C8 and CYP2C9 and therefore may affect the pharmacokinetics of sensitive substrates of these enzymes.

The Applicant's Position:
Olutasidenib should be taken on an empty stomach ((b) (4) prior to or 2 hours after a meal).

Co-administration with strong CYP3A4 inducers should be avoided, as they may reduce efficacy of olutasidenib. Co-administration with sensitive CYP3A4 substrates is not recommended, as olutasidenib may reduce efficacy of these medications.

The FDA's Assessment:

FDA does not agree that the Applicant's assessments for food intake guidance or drug-drug interaction are adequate, with the following:

(1) Food intake guidance:
Given that a high fat meal increased olutasidenib $AUC_{0\text{-}inf}$ by 83% higher and C_{max} by 191% compared to fasted conditions, FDA agrees with the Applicant that olutasidenib should be taken on an empty stomach. However, FDA disagrees with Applicant's proposal of taking olutasidenib (b) (4) *prior or 2 hours after meal*, given the lack of adequate assessment on the impact of food (b) (4) after a meal. FDA recommends taking olutasidenib 1 hour before or 2 hours after a meal, per FDA guidance for industry: Food Effect Bioavailability and Fed Bioequivalence Studies, where an empty stomach is defined as *"1 hour before or 2 hours after a meal"*.

(2) Drug-drug interaction assessment:

a. Olutasidenib as a victim:

FDA does not agree that the assessment of CYP3A4 induction potential is adequate. Concomitant use with rifampin (a strong CYP3A4 inducer) significantly reduced olutasidenib systemic exposure by 43% for C_{max} and 80% for AUC, indicating that the impact of a moderate CYP3A4 inducer on PK of olutasidenib is not yet ruled out. Therefore, FDA recommends that both strong and moderate CYP3A4 inducer should be avoided for concomitant administration with olutasidenib. A PMC study should be conducted to adequately address the in vivo potential

of moderate CYP3A4 inducer on PK of olutasidenib and inform the dosage recommendation for concomitant administration.

FDA agrees that the assessment of CYP3A4 and P-gp inhibition potential is adequate. Based on the dedicated drug-drug interaction study, concomitant use with itraconazole (a strong CYP3A4 and P-gp inhibitor) does not affect olutasidenib AUC or C_{max}. Therefore, the risk of in vivo impact of a CYP3A4 or P-gp inhibitor on olutasidenib is ruled out.

Additionally, the in vivo auto-induction potential of CYP3A4 is also ruled out for olutasidenib. The projected accumulation ratio (AR) value for olutasidenib is expected to be about 8.5 (Equation: $1/[1-e^{-kel*tau}]$) by assuming linear stationary PK (terminal half-life 66 hours, BID dosing). Based on Applicant's response to FDA IR sent on September 2, 2022, the AR for AUC of olutasidenib was around 9 for patients without dosage modification in Cycle 1 (Table 6), indicating no/little auto induction existed for olutasidenib when taking at the proposed dosage 150 mg BID. Therefore, no further DDI assessment for auto-induction potential of olutasidenib is necessary.

FDA agrees with the Applicant that in vivo DDI study is not necessary for CYP2C8, 2C9, 1A2, and 2C19 inhibitor/inducer, given that olutasidenib is mainly metabolized by CYP3A4 (90%) in vitro with only minor contribution from CYP2C8, 2C9, 1A2 and 2C19 (Applicant's response to FDA IR sent on May 26, 2022). Since CYP2C8, 2C9, 1A2, and 2C19 only contributed up to 10% for olutasidenib in vitro metabolism, the clinical impact of these enzymes on PK of olutasidenib appears to be of low risk.

b. Olutasidenib as a perpetrator:

FDA does not agree that the lack of in vivo DDI study is acceptable with substrates of CYP1A2, 2B6, 2C8, 2C19, 3A4, or OATP1B1.

Based on in vitro assessment, olutasidenib is an inducer of CYP1A2, 2B6, 2C8, 2C19, and 3A4, and inhibitor of OATP1B1. The in vivo induction potential of olutasidenib on the CYP1A2, 2B6, 2C8, and 3A4 substrates and inhibition potential on OATP1B1 substrates have not been ruled out.

In addition, the potential of olutasidenib to induce CYP2C19 cannot be ruled out based on the hepatocyte induction study, especially when the response of the hepatocytes to the positive control rifampin was less than 2-fold and was less than the response to olutasidenib in most cases.

Therefore, a PMR study is needed the effect of olutasidenib on exposures of substrates of OATP1B1; a PMC study is needed the effect of olutasidenib on exposures of substrates of CYP1A2, 2B6, 2C8, 2C9, 2C19, 3A4.

FDA agrees with the Applicant to avoid co-administration with sensitive CYP3A4 substrates, given the potential induction effect of olutasidenib. The labeling restriction for concomitant use

with sensitive CYP3A4 substrates will be updated once the results of the post-marketing study are available for FDA review.

Primary Reviewer	Team Leader
Lili Pan, PhD	Xiling Jiang, PhD

7.0 Sources of Clinical Data

7.1 Table of Clinical Studies

Data:

Table 7: Listing of Clinical Trials Relevant to NDA 215814

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
2102-HEM-101	NCT02719574	Phase 1/2, multicenter, open-label, safety and efficacy study	Olutasidenib: 100 (with food), 150, 300 mg QD, or at 150 BID on Days 1 to 28 of each 28-day cycle For select cohorts: Azacitidine: 75 mg/m2/day IV on Days 1-7 of each cycle 28-day cycle until disease progression or unacceptable toxicity Cytarabine: 20 mg BID SC for 10 days every 28-day cycle	Phase 1 Primary: MTD, MED, DLTs, and the RP2D of olutasidenib as a single agent and in combination with azacitidine or cytarabine Secondary: PK and antileukemic or antimyelodysplastic activity of olutasidenib as a single agent and in combination with azacitidine or cytarabine Phase 2 Primary: antileukemic and antimyelodysplastic activity of olutasidenib as a single agent or in combination with azacitidine Secondary: safety, PK, and antileukemic or antimyelodysplastic activity of olutasidenib as a single agent and in combination with azacitidine	Continued treatment until disease progression/relapse, development of other unacceptable toxicity, confirmed pregnancy, undergoing an HSCT, death, or withdrawal of consent. Patients who participated in Phase 1 and 2 were followed for survival for up to 12 months and 36 months, respectively, after first dose or 28 days after last dose, whichever was longer.	Total: Dosed: 332 Olutasidenib single agent: 216 Olutasidenib + azacitidine: 115 Olutasidenib + cytarabine: 1 Ongoing: 86 Phase 2 Cohort 1[a] Dosed: 153 Ongoing: 43	AML and MDS patients with IDH1 mutations	57/ US, Australia, Canada, France, Germany, Italy, South Korea, Spain, and UK
		Studies to Support Safety						

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
2102-ONC-102	NCT03684811	Phase 1b/2, multicenter, multiple cohort safety and efficacy study	Olutasidenib: 150 mg BID on Days 1-28 of each 28-day cycle until documented disease progression or unacceptable toxicity For select cohorts: Azacitidine: 75 mg/m^2/day IV on Days 1-7 of each cycle 28-day cycle until disease progression or unacceptable toxicity Nivolumab: 240 mg IV infusion over 60 minutes every 2 weeks (Day 1 and 15 ± 2 days) Gemcitabine/Cisplatin: Cisplatin 25 mg/m^2 followed by gemcitabine 1000 mg/m^2 IV on Day 1 and Day 8 of every 28-day (±7 days) cycle for up to 6 cycles.	Phase 1b Primary: safety and tolerability of olutasidenib as monotherapy; confirm the dose to be further examined in expansion cohorts as monotherapy and combination therapy Secondary: PK and clinical activity of olutasidenib as single agent and in combination with other anti-cancer agents Phase 2 Primary: clinical activity of olutasidenib as a monotherapy or in combination with other anti-cancer agents Secondary: safety, PK, and antitumor activity of olutasidenib as single agent and in combination with other anti-cancer agents	Continued treatment until disease progression or unacceptable toxicity.	Dosed: 93 Olutasidenib single agent: 87 Olutasidenib + azacitidine: 6 Ongoing: 13	Advanced solid tumors and gliomas with IDH1 R132X mutations	27 / Australia, France, South Korea, Spain, UK, US
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
2102-HVS-103	N/A	Phase 1, single-center, single-dose, open-label, parallel group, DDI study	Cohort 1 Period 1: single oral dose of 150 mg olutasidenib Period 2: itraconazole 200 mg QD from Days 16 to 28; single oral dose of 150 mg olutasidenib on Day 21 Cohort 2 Period 1: single oral dose of 150 mg olutasidenib Period 2: rifampin 600 mg QD from Days 16 to 30; single oral dose of 150 mg olutasidenib on Day 23	Primary: effect of multiple oral doses of itraconazole and rifampin on PK of a single dose of olutasidenib Secondary: PK of olutasidenib with and without itraconazole; PK of olutasidenib with and without rifampin; and safety and tolerability	Cohort 1: 42 days(± 2); Cohort 2: 44 days(± 2)	Dosed/ Completed: 40	Healthy subjects	1/US
2102-HVS-104	N/A	Phase 1, single-center, single-dose, open-label, AME, and mass balance study	Single oral dose of 150 mg (~100 μCi) [^{14}C]-olutasidenib	Primary: AME, and mass balance of a single oral dose of 150 mg (~100 μCi) [^{14}C]-olutasidenib Secondary: safety and tolerability of a single oral dose of 150 mg (~100 μCi) [^{14}C]-olutasidenib	40 days	Dosed/ Completed: 6	Healthy male subjects	1/US

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
2102-HVS-105	N/A	Phase 1, single-center, single-dose, open-label, parallel group, HI study	Single oral dose of 150 mg olutasidenib	Primary: PK of olutasidenib in subjects with mild and moderate impaired hepatic function compared to matched healthy subjects Secondary: safety and tolerability of olutasidenib in subjects with mild and moderate impaired hepatic function	This was a single-dose study. The total duration of participation from screening to follow-up for each subject was approximately 56 days.	Dosed/ Completed: 25	Healthy subjects and subjects with mild and moderate HI	1/US
2102-HVS-106	N/A	Phase 1, single-center, single-dose, open-label, randomized, two treatment, two-period, two-sequence crossover study	Single oral dose of 150 mg olutasidenib	Primary: To assess the effect of food on the PK of a single dose of olutasidenib after a high-fat/high-calorie meal in healthy adult subjects Secondary: To determine the safety and tolerability of a single dose of olutasidenib with and without food in healthy adult subjects.	There were 2 periods of approximately 16 days each; washout phase was 21 days between olutasidenib dose in Period 1 and olutasidenib dose in Period 2.	Dosed/ Completed: 16	Healthy subjects	1/US

AME = absorption, metabolism, excretion; AZA = azacitidine; BID = twice daily; F = female; HI = hepatic impairment; IV = intravenous; M = male; NR = not reported; O = other; PK = pharmacokinetics; QD = once daily; SC = subcutaneous; UK = United Kingdom; US = United States

[a] Pivotal cohort of Study 2102-HEM-101. Includes patients with R/R AML who received olutasidenib as single agent.

The Applicant's Position:
The safety and efficacy of olutasidenib treatment in patients with relapsed/refractory AML with IDH1 mutations is demonstrated with data from Phase 2 Cohort 1 (pivotal cohort) of Study 2102-HEM-101. Additional supportive safety and efficacy data are provided from other cohorts within this study, including data from AML and MDS populations receiving multiple doses of olutasidenib as a single agent or in combination with hypomethylating agents, and the 2102-ONC-102 study in patients with solid tumors and gliomas.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment.

The FDA review was based on data from NDA 215814, relevant published literature, and relevant information in the public domain.

Study 2102-HEM-101 was used for the primary analysis of efficacy and safety. The applicant submitted a complete dataset for this study, using a data cut date of June 18, 2020, at the time of the initial NDA submission. The applicant submitted an updated data set for Study 2102-HEM-101, using a data cut date of June 18, 2021, at the time of the 90-day safety update (submitted to eCTD May 12, 2022). The updated data set from Study 2102-HEM-101 will form the basis for this clinical review.

At the time of the NDA submission, the applicant submitted complete datasets from 4 completed studies in healthy volunteers, as well as a dataset from the ongoing study of olutasidenib in patients with solid tumors (Table 7). Data from these studies were used to supplement the analysis of safety.

Of note, Studies 2102-HEM-101 and 2102-ONC-102 contain cohorts evaluating olutasidenib in combination with other antineoplastic agents (Table 7). Given that these cohorts evaluated combination regimens for which the applicant is not seeking an indication at this time, this data was considered minimally in the context of this review.

Summaries of data and statistical analyses by the reviewer were performed using JMP 16.0, SAS 9.4 (SAS Institute, Inc. Cary, NC). MedDRA Adverse Events Diagnostic Version 3.5 (MAED) (FDA, Silver Spring, MD) was used to look for safety signals. Study 2102-HEM-101 was open-label and did not include a comparator arm, and therefore the analyses of efficacy and safety are descriptive only. Where possible, confidence intervals are provided to assist in the interpretation of the efficacy data. For additional statistical methodologies, see Section 8.1.1.

8.0 Statistical and Clinical Evaluation

8.1 Review of Relevant Individual Trials Used to Support Efficacy

8.1.1 2102-HEM-101

Trial Design

The Applicant's Description:
Overall Trial Design
Study HEM-101 is an ongoing multicenter, Phase 1/2, open-label, dose-escalation, and expansion study to evaluate the safety, efficacy, PK, and PD of olutasidenib administered as a single agent and in combination with azacitidine or LDAC to patients with R/R AML or MDS with IDH1-R132 mutations. The study was comprised of 3 stages: a Phase 1 dose-escalation stage, a Phase 1 dose-expansion stage, and a Phase 2 stage (Figure 7).

The full study was conducted at 57 study centers, 47 of which enrolled Phase 2 Cohort 1 patients: 13 in the United States, 4 in Australia, 1 in Canada, 10 in France, 3 in Germany, 5 in Italy, 2 in the Republic of Korea, 5 in Spain, and 4 in the United Kingdom.

Although patients in the pivotal cohort (Cohort 1) contributing to the primary efficacy and safety evaluation were not all from the US, the foreign data is applicable to the safety and efficacy of the medicine for the purposes of NDA approval in the US. The primary endpoint was the rate of complete remission plus complete remission with partial hematological recovery (best overall response [BOR] of CR/CRh). This endpoint is widely used, and country-specific practices would not change the efficacy evaluation (Perl, et al. 2019; DiNardo, et al. 2018; Stein, et al. 2017; Roboz, et al. 2020; IDHIFA [enasidenib] Prescribing Information November 2020; Tibsovo [ivosidenib] Prescribing Information August 2021; FDA 2020; Cheson, et al. 2003; Cheson, et al. 2006). Furthermore, overall CR/CRh rate appeared to be consistent by region (North America, Europe, and Asia Pacific).

Phase 1 Dose-Escalation Stage and Dose-Expansion Stage:
Dose escalation was initiated using olutasidenib as a single agent in AML or MDS patients harboring an IDH1-R132 mutation, as determined by local mutation testing. This portion of the study utilized a 3+3 dose-escalation design to identify a MTD or MED. On the initial schedule (Schedule 1,), olutasidenib was given orally QD in continuous 28-day cycles. Doses of 100, 150 and 300 mg QD were tested. Based upon observed PK and clinical observations, the alternative schedule (Schedule 2, twice daily [BID]) of olutasidenib was initiated. During the course of dose escalation, a parallel-escalation arm was initiated for olutasidenib in combination with azacitidine (administered at the dose of 75 mg/m2 for 7 days intravenous [IV]/subcutaneous [SC] per every 28-day cycle) in patients with AML or MDS harboring an IDH1-R132 mutation. Doses of 150 mg QD and 150 mg BID were evaluated in combination with azacitidine. There were no dose-limiting toxicities (DLTs) observed at any dose, and an MTD was not determined.

Up to 14 additional patients were enrolled in up to two expansion cohorts each of olutasidenib 150 mg BID single agent or in combination with azacitidine in selected populations of patients with AML/MDS harboring IDH1-R132 mutations. These dose-expansion cohorts 1) further defined the safety profile of single-agent olutasidenib or the azacitidine combination and 2) provided an initial assessment of the clinical activity of olutasidenib.

Phase 2 Stage
Based on the totality of the safety, PK and PD data in the Phase 1 stage of the study, the 150 mg BID dose of olutasidenib was selected as the Recommended Phase 2 Dose (RP2D) for further evaluation in Phase 2, both as a single agent and in combination with azacitidine.

As of the data cutoff date of 18 Jun 2020, the Phase 2 stage of the study is ongoing. Specific populations of patients with AML/MDS harboring IDH1-R132 mutations were enrolled across eight cohorts to further characterize the safety and efficacy of olutasidenib 150 mg BID including:

Single-agent olutasidenib Cohorts:

- **Cohort 1: patients with R/R AML (Pivotal cohort to provide registrational data to support the proposed indication)**
- Cohort 2: patients with AML in morphologic complete remission or complete remission with incomplete hematologic recovery (CR/CRi) after prior therapy (± hematopoietic stem cell transplantation [HSCT]) with residual IDH1-R132 mutation (≥ 0.01%) detected in the bone marrow (testing performed at a local laboratory)
- Cohort 3: patients with R/R AML/MDS who have been previously treated with IDH1 inhibitor therapy including patients who were treated with olutasidenib on-study in another cohort and relapsed post-HSCT

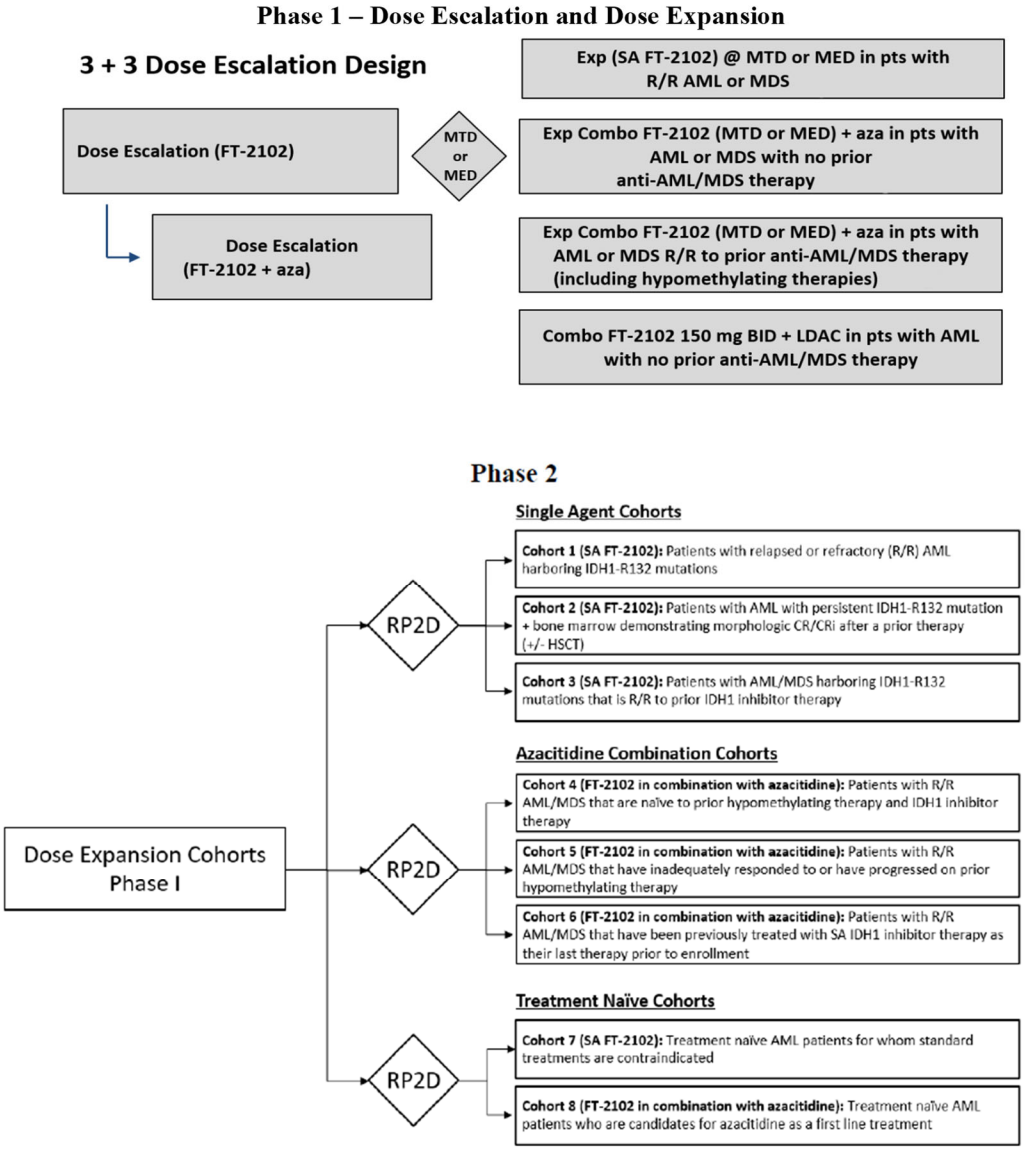
Azacitidine Combination Cohorts:

- Cohort 4: patients with R/R AML/MDS that is naïve to prior hypomethylating therapy and IDH1 inhibitor therapy
- Cohort 5: patients with R/R AML/MDS who have inadequately responded to or have progressed on prior hypomethylating therapy
- Cohort 6: patients with R/R AML/MDS who have been previously treated with IDH1 inhibitor therapy as their last therapy prior to study enrollment

Treatment Naïve Cohorts:

- Cohort 7 (single-agent olutasidenib): treatment naïve AML patients for whom standard treatments are contraindicated
- Cohort 8 (olutasidenib in combination with azacitidine): treatment naïve AML patients who are candidates for azacitidine as a first line treatment

Figure 7: Study 2102-HEM-101: Schematic



AML = acute myeloid leukemia; aza = azacitidine; BID = twice daily; combo = combination; Exp = expansion; HSCT = hematopoietic stem cell transplant; IDH = isocitrate dehydrogenase; LDAC = low-dose cytarabine; MDS = myelodysplastic syndrome; MED = maximum evaluated dose; MTD = maximum tolerated dose; pts = patients; RP2D = recommended Phase 2 dose; R/R = relapsed/refractory; SA = single-agent.

Patients enrolled in the Phase 1 dose-escalation/dose-expansion stages were followed for survival up to 12 months from Cycle 1 Day 1 (C1D1) or 28 days after administration of the last dose of study drug (whichever was longer). Patients enrolled in Phase 2 cohorts were followed for survival for up to 36 months from C1D1 or 28 days after administration of last study drug (whichever was longer).

Study Treatment

Study HEM-101 Phase 2 Cohort 1 was the planned pivotal cohort to provide registrational safety and efficacy data to support the use of olutasidenib in the treatment of patients with R/R AML. Phase 2 Cohort 1 included patients with R/R AML who received olutasidenib at the proposed dose of 150 mg BID, in continuous 28-day cycles (2 hours after food and 30 minutes prior to meal) until disease progression/relapse, unacceptable toxicity, HSCT, withdrawal of consent, or other withdrawal criteria were met. Dose holds and reductions (to 150mg QD) were allowed for adverse events including differentiation syndrome, hepatic effects and Grade 3 or higher treatment-related adverse events as specified in Table 8 and Table 9.

Table 8: Olutasidenib Recommended Dose Modifications for Adverse Events Unrelated to Liver Function Abnormalities

Severity of Adverse Events	**Dose Modifications for FT-2102** [c]	
	Non-Hematologic	**Hematologic**
Grade 1	Continue treatment at the same dose	Continue treatment at the same dose
Grade 2	Continue treatment at the same dose. If dose interruption is clinically indicated, resume dosing at same dose level after recovery to ≤ G1	Continue treatment at the same dose
Grade 3	Hold treatment until recovery to ≤ G1 or baseline, whichever is worse [a], then resume at the next lower dose level. Contact Medical Monitor if resumption of FT-2102 at full dose is clinically indicated.	Continue treatment at the same dose. If dose interruption is clinically indicated, resume dosing at same dose level after recovery to ≤ G2
Grade 4	Permanently discontinue treatment [b]	Hold treatment until recovery to ≤ G2 or baseline, whichever is worse, then resume at the next lower dose level. Contact Medical Monitor if resumption of FT-2102 at full dose is clinically indicated.

AE = adverse event.

[a] In the event of Grade 3 nausea, vomiting, diarrhea, or rash, the patient can continue at the same dose if the patient is responsive to treatment measures within 72 hr.

[b] A patient with a Grade 4 AE may resume treatment at the next lower dose level if the AE recovers to Grade 0-1 or baseline and if in the opinion of the Investigator and Sponsor, the patient can be monitored for recurrence of AE.

[c] Dose modification may be more or less conservative at the Investigator's discretion and after consultation with the medical monitor.

Table 9: Olutasidenib Recommended Dose Modifications for Liver Function Test Abnormalities

Laboratory Abnormality	Action to be Taken with olutasidenib
AST or ALT or total bilirubin is Grade 3	Hold olutasidenib
AST or ALT is > 3 times the ULN and patient has signs and symptoms of a hypersensitivity reaction not related to underlying disease [e.g., fatigue, nausea, vomiting, RUQ pain or tenderness, fever, rash and/or eosinophilia (>5%)]	Hold olutasidenib
For patient with elevated AST or ALT or total bilirubin at baseline: AST or ALT > 2 times baseline AND > 3.0 times ULN OR AST or ALT > 8.0 times ULN- whichever is lower- combined with total bilirubin > 2 times baseline AND > 2 times ULN	Hold olutasidenib
AST or ALT is > 3 times the ULN and the total bilirubin is > 2 times ULN and Alkaline phosphatase < 2 times ULN in the absence of a clear alternative explanation	Permanently discontinue olutasidenib
AST or ALT or total bilirubin is Grade 4	Permanently discontinue olutasidenib

ALT = alanine aminotransferase; AST = aspartate aminotransferase; RUQ = right upper quadrant; ULN = upper limit of normal.

Patients who discontinued for reasons other than disease progression/relapse or withdrawal of consent continued to be followed for response until progression/relapse occurred. Patients who discontinued for disease progression were followed for survival and subsequent therapy. Patients in who achieved an adequate response to study treatment and met other criteria required to undergo HSCT proceeded to HSCT after discontinuation of study treatment and were followed on study for disease evaluation and any new HSCT conditioning or other new antineoplastic therapies received until disease relapse, death, withdrawal of onset, loss to follow -up, or end of study.

Key Phase 2 Cohort 1 inclusion/exclusion criteria

Key inclusion criteria

- Pathologically proven acute myeloid leukemia (AML) (except acute promyelocytic leukemia [APL] with the t(15;17) translocation) as defined by WHO criteria which is relapsed or refractory to standard therapy and/or for which standard therapy is contraindicated or which has not adequately responded to standard therapy.
- Documented IDH1-R132 gene-mutated disease as evaluated by the site
- ECOG performance status 0-2
- Acceptable hepatic function defined as (a) Bilirubin ≤ 2 times ULN (≤ 3 times ULN in patients with Gilbert Syndrome) (b) Aspartate transaminase (AST, also referred to as SGOT), alanine transaminase (ALT, also referred to as SGPT) and alkaline phosphatase (ALP) ≤ 3 times ULN
- Acceptable kidney defined as serum creatinine ≤ 1.5 times ULN or calculated creatinine clearance ≥ 50 mL/min
- Baseline QTcF ≤ 450 msec; exception may be made for patients with bundle branch block with cardiology review

Key exclusion criteria

- Prior IDH1 targeted therapy
- Symptomatic central nervous system metastases or other tumor location (such as spinal cord compression, other compressive mass, uncontrolled painful lesion, bone fracture, etc.) necessitating an urgent therapeutic intervention, palliative care, surgery or radiation therapy
- Congestive heart failure (New York Heart Association Class III or IV) or unstable angina pectoris. Previous history of myocardial infarction within 1 year prior to study entry, uncontrolled hypertension or uncontrolled arrhythmias
- Active, uncontrolled bacterial, viral, or fungal infections, requiring systemic therapy

Study Assessments

The clinical activity of olutasidenib was evaluated by assessing response to treatment through evaluation of clinical findings and bone marrow/peripheral blood cell counts and morphology using the International Working Group (IWG) response criteria for AML (Cheson, et al. 2003), where applicable, and Stein, et al. 2017 (Table 10).

Per protocol, bone marrow was assessed for response at:

- Cycle 2 Day 1, if no peripheral blasts; otherwise, at Cycle 3 Day 1, regardless of peripheral blast count.
- At least every 2 cycles (4 to 8 weeks) until a morphologic CR was achieved (not just complete remission with incomplete blood count recovery [CRi] or morphologic leukemia-free state [MLFS]), then up to every 3 cycles (for duration of response assessment) for 12 cycles after CR achievement, then up to every 6 cycles thereafter.
- When progressive disease was suspected.

Peripheral blood samples were collected at Screening and at each timepoint that a bone marrow aspirate or biopsy was obtained. A complete schedule of all testing and procedures used to assess efficacy and safety is provided in Table 11.

Table 10: Response Assessment Criteria for AML

Category	Definition
Morphologic leukemia-free state (MLFS)	• Bone marrow blasts < 5% (in aspirate with spicules and 200 nucleated cells) • No blasts with Auer rods • No extramedullary disease

Category	Definition
Morphologic complete remission (CR)	• Bone marrow blasts < 5% (in aspirate with spicules and 200 nucleated cells) • No blasts with Auer rods • No extramedullary disease • Absolute neutrophil count (ANC) ≥ 1000/μL • Platelet count ≥ 100,000/μL • Transfusion independence
Cytogenetic CR (CRc)	CR with no residual cytogenetic abnormalities[a]
Molecular CR (CRm)	CR with undetectable *IDH1m* measurable residual disease (MRD)
CR with incomplete blood count recovery (CRi)	CR criteria except for ANC < 1000/μL or platelet count < 100,000/μL
CR with partial hematologic recovery (CRh)	Less than 5% bone marrow blasts and partial recovery of peripheral blood counts (platelet count > 50×10^9/L and ANC > 0.5×10^9/L)
Partial remission (PR)	Reduction of bone marrow blasts: • To a value between 5% to 25%, if baseline was ≥ 50% or • By 50% to a value > 5%, if baseline was between 5% to 49% Persistence of Auer rods, even if bone marrow blasts ≤ 5% Hematologic values consistent with a CR: ANC ≥ 1000/μL and platelets ≥ 100,000/μL.
Stable disease (SD)	Failure to achieve at least a PR but not meeting criteria for progressive disease. SD for a period of 8 weeks or more indicates clinical benefit (CB).
Recurrence, morphologic relapse	In patients who achieved CR, CRh, CRi, MLFS: • Reappearance of peripheral blasts, or • More than 5% bone marrow blasts (if no peripheral blasts, may repeat the bone marrow assessment to distinguish relapse from bone marrow regeneration) • Development of extramedullary disease
Disease progression	In patients with PR or SD: • For patients with 5% to 66% bone marrow blasts at nadir, a > 50% increase in bone marrow blast count percentage from the nadir and percentage is ≥ 20%; and • For patients with ≥ 67% bone marrow blasts at nadir, a doubling of the nadir absolute peripheral blood blast count with a final absolute peripheral blood blast count > 10×10^9/L • New extramedullary disease

Abbreviations: AML = acute myelogenous leukemia; IDH1m = isocitrate dehydrogenase 1 mutant.

a. Analysis by either conventional banded karyotyping or fluorescence in situ hybridization (FISH) was accepted.

Table 11: Schedule of Events

Study Procedures			Cycle 1									Cycle 2						Cycle 3		Cycle ≥ 4	End of Tx[a]	28-day Follow-up[b]	Survival Follow-up
Days	Pre-screening (Optional)	Screening (D–14 to D1)	D1	D2	D5 ± 1D	D8 ± 1D	D12 ± 2D	D15 ± 2D	D19 ± 2D	D22 ± 2D	D26 ± 2D	D1 ± 2D	D2 ± 2D	D4 ± 2D	D8 ± 2D	D15 ± 2D	D22 ± 2D	D1 ± 3D	D15 ± 2D	D1 ± 3D	± 7D	+ 7D	Q3M
Signed Informed Consent[c]		X[c]																					
Complete Medical History[d]		X																					
Concomitant Medications		X	X	X[e]		X		X		X		X				X		X		X	X	X	
Height and Weight[f]		X	X									X						X		X	X		
Vital Signs[g]		X	X			X		X		X		X						X		X	X		
ECOG PS		X	X									X						X		X	X		
Physical Examination		X	X			X[h]		X[h]		X[h]		X[h]				X[h]		X[h]		X[h]	X		
Serum or Urine Pregnancy[i]		X	X									X						X		X	X		
12-lead ECG[j]		X	X			X		X		X		X				X		X		X	X		
Holter Monitoring (Phase 2 only)[k]			X	X								X	X										
Clinical Serum Chemistries[l, m]		X	X		X[n]	X	X[n]	X	X[n]	X	X[n]	X			X[n]	X	X[n]	X	X[n]	X	X		
CBC with Differential and Platelet Count[m,o]		X	X		X[n]	X	X[n]	X	X[n]	X	X[n]	X			X[n]	X	X[n]	X	X[n]	X	X		
Coagulation Parameters[p]		X										X											
Bone Marrow Aspirate[q]		X										X						X		X	X		
Urinalysis[m,r]		X	X									X						X		X	X		

Study Procedures			Cycle 1									Cycle 2						Cycle 3		Cycle ≥ 4	End of	28-day	Survival
Days	Pre-screening (Optional)	Screening (D–14 to D1)	D1	D2	D5 ± 1D	D8 ± 1D	D12 ± 2D	D15 ± 2D	D19 ± 2D	D22 ± 2D	D26 ± 2D	D1 ± 2D	D2 ± 2D	D4 ± 2D	D8 ± 2D	D15 ± 2D	D22 ± 2D	D1 ± 3D	D15 ± 2D	D1 ± 3D	Tx[a] ± 7D	Follow-up[b] + 7D	Follow-up Q3M
AE Monitoring		Continuous																				X	
PK (Peripheral Blood)[s]			X	X		X		X		X		X[t]	X	X		X		X		X			
PD (Peripheral Blood)[u]	X	X	X	X		X		X		X		X	X	X		X		X		X			
EQ-5D-5L (Phase 2 only)		X[w]										X						X		X	X		
Study Drug Diary[x]			X									X						X		X			
Study Drug Admin[y,z,aa]			Drug will be given in accordance with the dosing schedules for olutasidenib, azacitidine, and LDAC																				
Survival[bb]																							X

Abbreviations: Admin = administration; AE = adverse event; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C1D1 = Cycle 1 Day 1; C2D1 = Cycle 2 Day 1; Ca = calcium; CBC = complete blood count; Cl = chloride; ECG = electrocardiogram; ECOG PS = Eastern Cooperative Oncology Group performance status; FSH = follicle-stimulating hormone; K = potassium; LDAC = low dose cytarabine; LDH = lactate dehydrogenase; LH = luteinizing hormone; MDS = myelodysplastic syndrome; Mg = magnesium; Na = sodium; PD = pharmacodynamic; PK = pharmacokinetic; Tx = treatment.

NOTE: All assessments were to be conducted predose unless specified otherwise.

Beginning with Cycle 5, scheduled assessments were performed every 2 cycles.

[a] End of Treatment visit were to be conducted within 7 days of the decision to discontinue treatment. End of Treatment assessments did not need to be repeated if they were completed within the previous 2 weeks (4 weeks for bone marrow assessments).

[b] 28-day Follow-up visit to be conducted within 28 days (+ 7 days) of last dose for AE follow-up and to capture initiation of new therapies (concomitant medications).

[c] Informed consent was to be completed prior to the initiation of any study-specific procedures or assessments. The informed consent process may have been completed prior to the Screening Period (ie, before Day -14) (see Appendix 16.1.1 Protocol Section 6.1.2).

[d] Included complete surgical and cardiac history and complete leukemia or MDS medical history. Complete leukemia or MDS medical history included applicable treatment history, as well as cytogenetic risk categorization at diagnosis by NCCN or ELN guidelines.

[e] Only required in patients enrolled in Phase 1 and patients in Phase 2 participating in Holter monitoring.

[f] Height at Screening only.

[g] Included temperature, blood pressure, pulse rate, and respiratory rate. Prior to dosing on Days 1, 8, 15, and 22 (Cycle 1); Cycle 2 predose on Days 1 and 15 and Cycle 3 and beyond predose on Day 1.

[h] Symptom-directed physical examination due to specific findings or abnormalities.

[i] Was to be performed on all female patients of childbearing potential and within 72 hr of dosing (Day 1 only of every cycle). At Screening, women who were aged 55 and under, not surgically sterile, and amenorrheic must have had LH, FSH, and estradiol measurements within the postmenopausal range for the institution, to be considered of nonchildbearing potential. A serum pregnancy test was required at Screening; serum or urine pregnancy tests were allowed for post-Screening visits.

[j] Phase 2: Electrocardiograms were to be performed in triplicate (within a 10-minute period) predose on C1D1 and C2D1, and at all study visits where indicated. All electrocardiograms were to be performed in a supine position.

[k] 24-hour 12-lead continuous Holter measurements were to be collected on C1D1 and C2D1 for patients at all centers in the US and select centers ex-US. The Holter measurements should run from approximately 1 hour before dosing until 24 hours (the next day). Patients were to remain supine for 10-15 minutes before and 5 minutes after ECG collection.

[l] Clinical serum chemistries included Na, K, Cl, bicarbonate, Mg, Ca, BUN, creatinine, AST, ALT, ALP, albumin, total bilirubin, direct bilirubin (collected only if total bilirubin is abnormal), LDH, glucose, amylase, lipase, uric acid, and thyroid function test (TFT) panel, which includes thyroid-stimulating hormone, free T3, and T4. In addition to the other chemistry panels, TFT panel is to be completed at Screening, C1D1, C2D1, and C3D1, then as clinically indicated.

[m] May have been performed from 48 hr (Cycle 2) or 72 hr (Cycle 3 and 4) prior to Day 1 of a cycle (see Appendix 16.1.1 Protocol Section 6.1).

[n] Clinical serum chemistries and CBC with differential and platelet count only at these study visits. May have been performed through local laboratory testing.

[o] Included hemoglobin, hematocrit, platelets, and white blood cell count with differential.

[p] Included prothrombin time and partial thromboplastin time.

[q] Bone marrow aspirate for response assessment as described in Appendix 16.1.1 Protocol Section 4.3. The laboratory manual provided details of sample collection timing. Local *IDH* confirmation may have occurred > 28 days prior.
C3D1 was to be done on any patient who did not undergo a C2D1 bone marrow aspirate or biopsy.
Patients who discontinued study treatment for reasons other than treatment failure and had not withdrawn consent from overall study participation, should have continued to be followed for disease response assessments until the time of disease progression/relapse or the initiation of a new treatment regimen. Patients who had stopped olutasidenib treatment for HSCT should have continued to be followed until disease progression/relapse. This information was to be documented on the appropriate eCRF page

[r] Urinalysis parameters included specific gravity, pH, total protein, protein, glucose, ketones, and blood. Microscopic examinations were to be performed as clinically indicated. For Cycle ≥ 3 and End of Study visit, urinalysis was to be performed if clinically indicated.

[s] Blood samples were collected for measurement of plasma concentrations of olutasidenib. Blood samples were collected relative to olutasidenib administration as described in Appendix 16.1.1 Protocol Section 6.4.

[t] A 72-hour wash-out post C2D1 dosing was requested from all patients participating in the dose-expansion stage. After the C2D1 olutasidenib AM dose, patients were asked to refrain from taking olutasidenib until the AM of C2D4. PK samples were collected on C2D2 and C2D4 (not required in Phase 2).

[u] Blood samples were collected for PD biomarker analysis for single agent olutasidenib. Blood was collected relative to olutasidenib administration as described in Appendix 16.1.1 Protocol Section 6.5.

[v] Optional pre-screening blood sample for 2-HG level detection and *IDH1* mutation testing (in 2-HG abnormal).

[w] EQ-5D-5L survey may have been completed anytime during screening prior to C1D1 dose.

[x] Study drug diary should have been distributed by the site to the patient at each clinic visit and collected at the next clinic visit.

[y] Single agent (olutasidenib): Olutasidenib was given in accordance with dosing schedule × 28 days out of 28 days. On C1D1 only a single dose of olutasidenib was taken.

[z] Combination agent (olutasidenib + azacitidine): azacitidine was administered via subcutaneous injection or intravenous infusion in combination with oral olutasidenib for 7 days, and then azacitidine was stopped for 21 days; a 48-hr dose interruption of the azacitidine for weekends or holidays was allowed. On C1D1 and C2D1, azacitidine was to be administered immediately prior to olutasidenib (to enable consistent PK assessments). On all other days and cycles when olutasidenib and azacitidine are co-administered, it was recommended to dose olutasidenib prior to azacitidine.

[aa] Combination olutasidenib + cytarabine: cytarabine was administered at a dose of 20 mg BID subcutaneously (SC) for 10 days every 28-day cycle

[bb] After a patient discontinued study treatment and completed their last study treatment visit, the study site may have contacted the patient approximately every 3 months to collect survival data and data pertaining to any other alternative anti-neoplastic therapy the patients began for up to 36 months for the Phase 2 part of the study. Patients who discontinued for reasons other than disease progression or who withdrew consent continued to be followed for response until progression occurred.

Concomitant medications
No other investigational medicinal products were allowed during the study. Concomitant medication(s) known to cause Torsades de Pointes (TdP) initiated less than the duration required to reach steady-state plasma concentration (approximately five half-lives) before the first dose of study drug were prohibited (medications used as needed were exempt from this exclusion). No concomitant anticancer therapy with the exception of hydroxyurea or CNS prophylaxis were allowed during this study.

Concomitant medications were permitted at the Investigator's discretion according to standard practice during the treatment period, except as noted above. Necessary supportive measures for optimal medical care were given throughout the study. Patients who enrolled in the study with leukocytosis at baseline or developed leukocytosis after initiation of therapy were allowed to receive hydroxyurea. Suggested guidelines for administering hydroxyurea are as follows:

- For white blood cell (WBC) count of 10 to 50 × 10^9/L hydroxyurea 500 mg four times a day should have been considered
- For WBC count > 50 × 10^9/L hydroxyurea 1000 mg four times a day should have been considered
- Hydroxyurea should have been tapered/discontinued when WBC count < 10 × 10^9/L

Patients who enrolled in the study and required CNS prophylaxis due to prior CNS involvement and remained asymptomatic may have received intrathecal chemotherapy at the discretion of the investigator. Patients may have received premedication for nausea and/or vomiting and antimicrobial treatment or prophylaxis at the discretion of the investigator.

The FDA's Assessment:
The FDA agrees with the applicant's description of the trial design. The FDA would like to comment that the dose modifications for hepatotoxicity will be slightly different in the USPI compared to what was listed in the protocol for ease of understanding.

Study Endpoints

The Applicant's Description:

The primary efficacy endpoint for Phase 2 Cohort 1 is the rate of CR+CRh based on the best overall response. CR/CRh is an accepted binary efficacy endpoint used commonly for AML as described in the recently published FDA Draft Guidance on AML and was agreed by the Agency to be adequate to demonstrate clinical benefit for a full approval in R/R AML in patients with IDH1 mutations at a Type C meeting (2018) prior to study start and again at the pre-NDA meeting (2021).

Secondary Efficacy Endpoints indicating additional evidence of clinical benefit, including complete remission with incomplete blood count recovery [CRi], morphologic leukemia-free state [MLFS], overall response rate [ORR], time to response [TTR], duration of response [DOR], EFS, and OS are also accepted measures of efficacy employed in AML clinical trials. Data from

these endpoints, as well as transfusion independence, are presented in support of the primary endpoint.

The FDA's Assessment:
FDA agrees with the Applicant's description of the study endpoints.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The SAP was amended 3 times as described in Table 13. As described in Section 3.2, feedback from the Agency was incorporated into the SAP at two instances prior to finalization. SAP v4 was finalized prior to the database lock for the pre-specified second interim analysis of the pivotal cohort, in which pre-planned efficacy criteria were met.

The following analysis sets were defined for the evaluation of efficacy and safety endpoints:

Full Analysis Set (FAS): all patients who received at least one dose of olutasidenib. This analysis set was used for efficacy analyses. For Phase 2 Cohort 1, the FAS was the same as the safety analysis set (SAS).

Efficacy Evaluable (EE) Analysis Set: all patients in Phase 2 Cohort 1 (the pivotal cohort) with IDH1-R132 mutations confirmed by central laboratory who received the first dose of olutasidenib at least 6 months before the analysis cutoff date (18 Jun 2020). This analysis set is the primary set for Phase 2 Cohort 1 efficacy evaluation.

Per protocol (PP) Analysis Set: a subset of patients in the EE Analysis Set, excluding patients who have protocol violations that could impact the evaluation of the efficacy of olutasidenib.

Safety Analysis Set (SAS): all patients who received at least one dose of study drug. All safety analyses are based on the Safety Set unless otherwise specified.

The number of patients planned for Phase 2 Cohort 1 was based on a group sequential design with one futility interim analysis at the time of ~33% of patients and one efficacy interim analysis at the time of ~67% of patients completing the first response assessments. If the study did not stop early for efficacy or futility, a total of 173 evaluable patients was needed to provide 90% power on a 1 sided 2.5% significance level. Given that to be included in the EE population a patient must have the IDH1-R132 mutation per the central test, approximately 190 patients were planned to be enrolled into this cohort to account for the possibility of discordance between the central and local tests.

For the first planned interim analysis of Phase 2 Cohort 1, futility was assessed. A review of the patient response data when 33% of the patients were evaluable for response was conducted (12 Feb 2019). If $\leq 6/58$ responses were observed (or unadjusted p-value ≥ 0.88), the trial may have stopped early for futility. The medical monitor reviewed and confirmed response data. The response rate exceeded the futility threshold and the study proceeded.

Analysis of data for 173 Phase 2 Cohort 1 patients at the second Interim Analysis (IA2) provides 90% power to test the null hypothesis that the true complete response rate (CR + CRh) was 15% or less versus the one-sided alternative hypothesis that the true complete response rate was greater than 15%, with a 2.5% significance level using a one-sided exact test for a binomial proportion, assuming the true response rate was 25%. The null hypothesis rate of 15% is approximately the complete response rate for azacitidine in this population (Willekens, et al. 2021); if the true complete response rate for olutasidenib were significantly greater than 15%, it would be evidence of clinically significant activity in this population.

The CR/CRh reference rate (the null hypothesis of 15%) is based on historical data in similar populations of patients with R/R AML. In large, Phase 3 studies of high-dose cytarabine or the Investigator's choice (e.g., hypomethylating agents (HMAs), multi-agent chemotherapy, cytarabine, hydroxyurea, or supportive care) in primary refractory AML or AML that has relapsed after one 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). Further, a large international multicenter retrospective study of the effectiveness of HMAs in R/R AML enrolled 655 patients from 12 centers who received azacitidine (57%) or decitabine (43%) (Stahl, et al. 2018). Median age at diagnosis was 65 years (range, 16-92). In total, 70% of patients had been diagnosed with de novo AML. Of the 30% who had secondary AML, 27% had therapy-related AML. The median number of prior therapies was 1 (range, 1-7); 26% had received 2 prior lines of therapy, and 18% had received 3 prior lines. Prior allogeneic HSCT was performed in 19% of patients. Among all patients, only 2% harbored a good-risk karyotype, whereas 40% had a poor-risk karyotype. Of the 655 patients studied, 365 (56%) had relapsed and 290 (44%) had refractory AML. Best response to HMAs was complete remission (CR; 11%) or CRi (5.3%). By the end of the study, 87% of the patients had died. Given that CRi in this study included CRh and non CRh responders and the CR rates of 12-16% reported in the large Phase 3 studies, the 15% CR/CRh rule out rate for Phase 2 Cohort 1 in the current study was selected for a background benchmark rate for a targeted non-intensive therapy in this population.

Alpha is controlled for the primary analysis within each Phase 2 cohort. Corrections for multiple comparisons are not applied for the secondary or exploratory endpoints.

Planned subgroup and sensitivity analyses

Patients who respond and stop olutasidenib to undergo HSCT were to continue to be followed until relapse. Duration of response endpoints (DRC/CRh, DCR, DOR) for these patients encompasses time between HSCT and relapse, death, or any new antileukemia therapy. For patients with no report of relapse by the end of the follow-up data collection, duration of response (DCR/CRh, DCR, DOR) will be censored as per Table 12.

Table 12: Censoring Rules

Case	Censoring Rule
Patient has no post baseline assessments and no date of death recorded	Censor at date of first dose

Case	Censoring Rule
Patient did not die or experience PD or relapse*	Censor at date of last adequate response assessment (any response assessment that is not "Not Evaluable" or "Not Done")
Patient in Phase 1 started on single agent therapy, but switched to combination therapy	Censor at date of last adequate response assessment prior to the combination therapy

*For patients who discontinue FT-2102 treatment to receive HSCT and remain on study to be followed until documented disease relapse, confirmation of relapse is not required in this situation, and a single occurrence of relapse will be considered as documented "confirmed" relapse in analyses of response.

A sensitivity analysis was conducted for duration of response of Phase 2, Cohort 1 patients, which analyzes duration of response as described above. An additional sensitivity analysis will be performed on DCR/CRh, DCR, and DOR in which HSCT will be handled as the end of response. Since this study was ongoing during the COVID-19 pandemic, a sensitivity analysis will be performed on OS, DCR, DCR/CRh, and DOR in which patients who have died due to COVID-19 will be censored to assess the effect that COVID-19 had on time to event endpoints.

For Phase 2 Cohort 1, a sensitivity analysis will be performed on the CR/CRh rate in which Atkinson and Brown confidence intervals will be calculated

The following sensitivity analyses of DCR/CRh will be performed with censoring rule variations in patients:

- Patients who undergo HSCT will be censored at the last adequate assessment prior to HSCT
- Patients who discontinued study treatment due to undocumented progression will be considered as events at the date of last dose
- Patients with subsequent anti-cancer therapies prior to an event date will be considered to be censored the day before the start of the anti-cancer therapy.

The following subgroup analyses will be performed:

- CR/CRh rate, ORR, DCR/CRh – For AML patients in the EE analysis set: AML type (primary or secondary), disease state (relapsed/refractory or treatment naive), AML cytogenetic risk classification, IDH1 mutation type , IDH1 mutation confirmed by central lab, age group, sex, region, race, baseline ECOG PS, prior HSCT for AML, prior HMA, prior IDH1 therapy, and prior FT-2102 therapy.
- OS, EFS – For AML patients in the FAS analysis set: AML type (primary or secondary), disease state (relapsed/refractory or treatment naive), AML cytogenetic risk classification, IDH1 mutation type, IDH1 mutation confirmed by central lab, age group, sex, region, race, baseline ECOG PS, prior HSCT for AML, prior HMA, prior IDH1 therapy, and prior FT-2102 therapy.

Table 13: Summary of Key SAP Amendments

SAP Version	Version Date	Information on SAP Update
1	03-Jun-2019	Original
2	11-Mar-2020	Numerous revisions based on regulatory agency interactions. Clarify language, describe imputation of missing data, clarify exposure calculations, edit algorithm for AESI differentiation syndrome, edit transfusion independence analysis, edit censoring rules for time to event endpoints
3	22-May-2020	This version of the SAP was updated in response to FDA Statistical Comments provided by the Agency on 28 Apr 2020. Add detail on alpha and beta spend for Phase 2 cohort 1 interim analyses, add sensitivity analysis for the effect of COVID-19 on time to event endpoints. Revise description of AESI analysis.
4	9-Sep-2020	Add detail about missing data imputation for QOL assessment. Update definition of BOR. Updates to DS analysis details. Add sensitivity analysis for efficacy.
Post-hoc	N/A	A list of hepatobiliary preferred terms was evaluated in addition to the hepatic SMQ defined in the SAP. Hepatic effects for all patients in the HEM-101 study are presented in a standalone report. The SAP specifies that TI will be summarized by Platelet Independence, RBC Independence, and "Both" (patients who were dependent on both platelets and RBC and became independent of both). The analysis added a fourth category, "Any," where patients could be dependent on any type of transfusion (platelet, RBC, or both) prior to baseline, and must be independent of all post baseline to qualify as independent in this category.

The FDA's Assessment:

In general, FDA agrees with the Applicant's description of the SAP of the Study 2102-HEM-101. The applicant is using CR+CRh as a palliative endpoint. This approach was used previously with FDA-approved targeted inhibitors, (e.g., ivosidenib, enasidenib, gilteritinib). Achievement of durable CR+CRh with transfusion independence was observed in these settings, often in the presence of continued low level residual disease. It is noted that the investigators set a relatively low bar by ruling out a CR+CRh rate of only 15%. The ultimate benefit will need to be weighed carefully against the observed safety profile.

Of note, the Applicant defined duration of response as the time from the date of the first response to the date of the relapse, death, or start of anti-cancer therapy. Patients who do not relapse are censored at the date of last response assessment. FDA recommended start of anti-cancer therapy be removed as an event, consistent with the recommendations in the FDA guidance *Acute Myeloid Leukemia: Developing Drugs and Biological Products for Treatment.* The Applicant accepted FDA's recommendation to exclude "start of anti-cancer therapy" as an event, and therefore, changed the definition to "Duration of response is defined as the time from the date of the first response to the date of the relapse or death. Patients who did not relapse were censored at the date of last response assessment."

Protocol Amendments

The Applicant's Description:

As of the cutoff date for this NDA, the original protocol (30 November 2015) was amended five times. Changes that had a major impact on the conduct of the study are summarized in Table 14.

Table 14: Substantive Changes to the Study Protocol with a Major Impact on Conduct of the Study

Protocol Version/ Amendment	Amendment Final	Summary of Significant Changes
Version 1 Original	30 November 2015	Not applicable
Version 2 Amendment 1	30 March 2017	• Modification of the primary objective to add the determination of maximum evaluated doses (MEDs, Phase 1) • Addition of dose expansion language, including the addition of proposed dose-expansion cohorts • Addition of response assessment language and response criteria derived from the International Working Group (IWG) response criteria for AML (2003) and MDS (2015), where applicable • Addition of olutasidenib dose modification language for the dose-escalation stage and for adverse events • Clarification of sample size considerations. • Additional PK and pharmacodynamic sample collection time points were added
Version 3 Amendment 2	20 October 2017	• Added language for the interim analysis. An interim futility analysis was performed for the Phase 2 Cohort 1, and interim analyses are performed in the Phase 2 cohorts that use two-stage designs after the first stage has been completed • Addition of a Phase 2 study component designed to evaluate the antileukemic and antimyelodysplastic activity of olutasidenib • Addition of a Phase 1 combination cohort of cytarabine and olutasidenib with modification of the objectives and study endpoints to include the new cohort. • Modification of the exploratory objectives and study endpoints to add the determination of the frequency of cancer-associated mutations and to add PK/PD and clinical response in each cohort (Phase 1 and Phase 2) and to add the evaluation of health-related quality of life (QOL) assessments (Phase 2). • Modification and expansion of the planned sample size to specify that approximately 110 patients may have been enrolled in the dose-escalation and dose-expansion stages (Phase 1) and that approximately 290 patients may have been enrolled in the 6 proposed Phase 2 cohorts. • Clarification and modification of inclusion and exclusion criteria, including disease definition and cohort-specific requirements for inclusion, a requirement for Phase 2 Cohorts 1-6 (SA and combination) to have pre-treatment formalin-fixed paraffin-embedded bone marrow aspirate or biopsy available for retrospective central confirmation of *IDH1-R132* mutation. Additionally, for Phase 1 SA Dose-escalation/Dose-expansion Cohorts and Phase 2 Cohorts 1, 2, 4 and 5 only, an exclusion criterion was added excluding patients who have been treated with an IDH1-targeted therapy • Addition of treatment considerations for rapid myeloid proliferation, presenting as leukocytosis. In the absence of differentiation syndrome, and unless clinically indicated, leukocytosis does not require dose interruption and should be managed by hydroxyurea per protocol • Addition of Phase 2 cohorts sample size considerations

Protocol Version/ Amendment	Amendment Final	Summary of Significant Changes
Version 4 Amendment 3	16 May 2018	• Specification of the single-agent Recommended Phase 2 dose Refinement of the Phase 1 secondary endpoint to include complete response with partial hematologic recovery • Refinement of the Phase 2 primary endpoints to: 1) for all cohorts except Cohort 2, define Complete Response as determined by the investigator per disease-specific criteria; and 2) for Cohort 2 only, assess event-free survival • Updates to study, phase, and cohort sample sizes and expansion of corresponding language. The updated planned sample size for Phase 2 is that approximately 320 patients may be enrolled in the 6 proposed Phase 2 cohorts. • Addition of new statistical methodology sections, including identification of study analysis populations and expansion of statistical analysis language, to provide new and more detailed sample size by study phase and methodology information for the study.
Version 5 Amendment 4	25 January 2019	• Modification of the primary endpoint for all Phase 2 cohorts except Cohort 2 to clarify that the Complete Response rate is based on the best overall response (BOR) and that for Cohort 2, the primary endpoint is the 4-month relapse free survival (RFS) rate • Added 2 new Phase 2 cohorts (treatment naïve single agent and combination cohorts) with applicable modifications to inclusion/exclusion criteria, planned total sample size and statistical methodology. • Addition of language detailing the follow-up of patients who undergo hematopoietic stem cell transplant (HSCT). • Definition of analysis populations was edited to align with previous regulatory precedent in this indication.
Version 6 Amendment 5	27 January 2020	• Descriptions and Inclusion Criteria for Phase 2 Cohorts 3 and 6 updated to only allow subjects with prior olutasidenib • A new precautions section was added to provide detail on patient monitoring and actions for adverse events potentially associated with hepatic injury that have been designated as Adverse Events of Special Interest (AESI) • A new table was added to provide recommended olutasidenib dose modifications for patients with liver function test abnormalities

The FDA's Assessment:

FDA agrees with the applicant's assessment.

Study Results

Compliance with Good Clinical Practices

Data:
The following investigator site audits were conducted by the Applicant to evaluate the study conduct and compliance with the ICH E6 Guideline for Good Clinical Practice, and applicable regulations and local laws.

Table 15: Audits conducted at Investigator sites

Auditee(s)	Audit Date
Jorge Cortes, MD (Site 002) The University of Texas MD Anderson Cancer Center Department of Leukemia, Unit 428 1515 Holcombe Boulevard Houston, TX 77030	15-17 January 2019
Justin Watts, MD (Site 009) University of Miami Fox Building 1550 NW 10th Avenue Miami, FL 33136	09-11 October 2019
Prof. Stephane De Botton (Site 331) Institute de Cancerologie Gustave Roussy DITEP/Medical Oncology Department 114 Rue Edouard Vaillant Villejuif Cedex 94805 France	02-03 December 2019

The Applicant's Position:
All studies were conducted in accordance with Good Clinical Practices, the Declaration of Helsinki, relevant FDA guidelines, and applicable national regulations, as per the Code of Federal Regulations, Title 21 (21 CFR 320.25).

The FDA's Assessment:
FDA agrees with the applicant's assessment. See also Section 4.1 regarding FDA's OSI inspection results.

Financial Disclosure

Data:
For covered pivotal Study 2102-HEM-101, all investigators provided financial disclosure information and none of the investigators had positive disclosable financial interests, see Appendix 19.2.

The Applicant's Position:
The Applicant has not entered into any financial arrangement with clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). Each clinical investigator was required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) and did not disclose any such interests. None of the investigators was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

The FDA's Assessment:
FDA agrees with the applicant's assessment.

Patient Disposition

Data:
Table 16 presents the disposition data for the 153 patients enrolled in the pivotal Phase 2 Cohort 1 as of the data cut for the second IA. Median treatment duration for these 153 patients was 142 days (range: 3, 795).

Table 16: Patient Disposition for Phase 2 Cohort 1 (All Enrolled Patients)

Disposition	Phase 2 Cohort 1 Olutasidenib 150 mg BID (N = 153) n (%)
Patients Enrolled[a]	153 (100)
Ongoing on Treatment	43 (28)
Discontinued Treatment	110 (72)
Primary Reason for Discontinuation of Treatment	
Protocol-Defined Disease Progression	47 (31)
Adverse Event	22 (14)
Death	15 (10)
Transplant	13 (8)
Investigator Decision	5 (3)
Permanent Withdrawal of Consent	5 (3)
Other	2 (1)
Patient Non-Compliance / Protocol Violation	1 (1)
Number of Patients Discontinued from Study	81 (53)

Includes patients who signed informed consent and were not screen failures.
Note: The number of patients N for each column, and the denominator for all percentages, is the number of patients in the Safety Analysis Set.

The Applicant's Position:
As of 18 June 2020, 43 patients (28%) were ongoing on treatment, and 110 (72%) had discontinued study treatment in the pivotal Phase 2 cohort 1 portion of the study. The most common reasons for permanent discontinuation of study treatment were disease progression (31%), AE (14%), death (10%), and transplant (8%). Of the 110 patients who discontinued treatment, 58 patients died in follow-up, 23 patients were lost to follow-up/withdrew, and 29 patients were still ongoing in the study as of data cutoff and being followed for survival.

The FDA's Assessment:
The FDA performed an analysis of patient disposition from the pivotal cohort based on the 90-day safety update. As of June 18th, 2021, 21 patients (14%) were continuing on treatment, while 132 patients (86%) had discontinued study treatment. The most common reasons for treatment discontinuation were progressive disease (47%), adverse event (20%), death (11%), and HSCT (12%). Of the 132 patients who discontinued treatment, 101 patients died in follow-up and 12 patients were still ongoing in the study as of data cut-off and being followed for survival and safety. The efficacy data are provided based on Phase 2 Cohort 1 as of 18 Jun 2021 in 147 patients (updated from 123 in original NDA) with centrally confirmed IDH1-R132–mutated R/R AML who were treated with olutasidenib 150 mg BID and received their first dose at least 6 months before the 18 Jun 2021 data cutoff date (EE Analysis Set). Also, see Section 8.1.1 and

Table 17. Table 18 shows the number of patients included in each analysis set for each data cut. Of note, the applicant did not collect data on patients that were screened and determined not to be eligible for the trial.

Table 17: Analysis Sets for Phase II Cohort 1 by Data Cut

	Original Data Cut (18 Jun 2020)	90-Day Safety Update Data Cut (18 Jun 2021)
Enrolled	153	153
Safety analysis population	153	153
Efficacy evaluable (EE) analysis population	123	147

Source: FDA analysis

Table 18: Patient Disposition of Phase II Cohort 1 (90-Day Safety Update)

Disposition	**Phase 2 Cohort 1 Olutasidenib 150mg BID (N=153) N (%)**
Number Treated	153
Number Continuing On-Treatment	21 (14)
Number Discontinued	132 (86)
Progressive Disease	62 (47)
Adverse Event	26 (20)
Death	14 (11)
HSCT	15 (12)
Physician Decision	7 (5)
Patient Decision	7 (5)
Other	4 (3)
Protocol Deviation	1 (1)

Source: FDA analysis

For the fourteen patients that were listed as "death" for discontinuation reason, the FDA adjudicated that five of those patients died from disease progression, six patients died from underlying AML (infection, bleeding complications), and two patients had death not otherwise specified (found deceased by family members).

Currently, forty-two patients (42) remain on study, with reasons for study discontinuations being similar to reasons for treatment discontinuation. Of the forty-two patients that remain on study, eleven (11) patients have started new anti-cancer therapy and are being followed for survival and safety follow-up.

Table 19: Patient Study Disposition of Phase II Cohort 1 (90-Day Safety Update)

Disposition	**Phase 2 Cohort 1 Olutasidenib 150mg BID (N=153) N (%)**
Number Treated	153
Number Continuing On-Study	42 (27)
Number Discontinued	111 (73)
Progressive Disease	53 (48)
Adverse Event	24 (22)
Death	14 (13)
HSCT Transplant	6 (5)
Physician Decision	6 (5)
Patient Decision	5 (5)
Other	2 (2)
Protocol Deviation	1 (1)

Source: FDA Analysis

Protocol Violations/Deviations

Data:

Table 20: Phase 2 Cohort 1 Summary of Confirmed Major Protocol Deviations (Safety Analysis Set)

Deviation Category	Phase 2 Cohort 1 Olutasidenib 150 mg BID (N = 153) n (%) [events]
Major Deviations – All	10 (7) [12]
Informed Consent[a]	3 (2) [3]
Safety Reporting[b]	2 (1) [2]
Inclusion/Exclusion[c]	2 (1) [2]
Other Deviation[d]	2 (1) [3]
Study Intervention[e]	1 (1) [1]
Trial Procedures[f]	1 (1) [1]
Major Deviations – COVID-19 Related	0

Abbreviations: BID = twice daily; ICF = informed consent form; SAE = serious adverse event.

[a] One patient was given the incorrect ICF version to sign; two patients' signatures for ICF version 3 were not reported.

[a] For two patients, the SAE was not reported within 24 hours.

[b] One patient enrolled with an *IDH2* mutation; one patient initiated a drug known to cause Torsades de Pointes for a duration less than required to reach steady-state plasma concentration (approximately five half-lives) before the first dose of olutasidenib.

[c] One patient initially signed the wrong version of the ICF; one patient was treated with a non-authorized medication.

[d] One patient should have had dose held due to adverse event, but the site did not hold the dose.

[e] One patient was seen by investigator before the Investigator's training log was completed.

Note: Patients are only counted once in each category.

The Applicant's Position:

The study was well conducted without any violations significantly impacting the data integrity or the safety or rights of patients. A total of 10 patients (7%) had a total of 12 confirmed major protocol deviations. The most common major protocol deviations were related to informed consent procedures (3 patients [2%]). There were no major deviations related to COVID-19 in the Phase 2 Cohort 1 SAS up to the cutoff date of 18 June 2020.

A total of 27 (18%) patients had a total of 70 confirmed minor deviations that were COVID-19 related, including a total of 68 deviations of trial procedures. There was one deviation informed consent related to COVID-19. The most common deviations were missed or altered visits due to COVID 19, changes to how medications were provided to patients due to COVID-19 and missed or delayed assessments. None of these minor deviations are believed to have had an effect on the overall conclusions related to safety or efficacy.

The FDA's Assessment:

The FDA agrees with the applicant's assessment.

Table of Demographic Characteristics

Data:

Table 21: Demographic Characteristics (Full Analysis Set and Efficacy Evaluable Analysis Set, Study HEM-101 Phase 2 Cohort 1)

Demographic Parameter	Full Analysis Set Olutasidenib 150 mg BID (N = 153)	Efficacy Evaluable Set Olutasidenib 150 mg BID (N = 123)
Sex at Birth, n (%)		
Female	74 (48)	60 (49)
Male	79 (52)	63 (51)
Age at Time of Consent (years)		
Mean (StdDev)	68.7 (10.43)	68.5 (10.48)
Median	71.0	71.0
Min, Max	32, 89	32, 87
Age Categories (years)		
< 65	37 (24)	32 (26)
65 to < 75	68 (44)	50 (41)
≥ 75	48 (31)	41 (33)
Race, n (%)		
White	71 (46)	55 (45)
Not Reported[a]	56 (37)	45 (37)
Other	16 (10)	14 (11)
Asian	5 (3)	4 (3)
Black or African American	5 (3)	5 (4)
Ethnicity, n (%)		
Hispanic or Latino	8 (5)	7 (6)
Not Hispanic or Latino	70 (46)	54 (44)
Not Reported	75 (49)	62 (50)

Source: Study HEM-101 Phase 2 Cohort 1 CSR Table 14.1.2.1b, Table 14.1.2.2, A46. Data cutoff date: 18 June 2020.

Abbreviations: BID = twice daily; StdDev = standard deviation.

[a] Sites in the European Union did not report race or ethnicity.

The Applicant's Position:

The demographic characteristics were representative of patients in the studies that were used to develop the null hypothesis, as well as those enrolled in the study which led to the approval of another commercially available IDH1 inhibitor for R/R AML.

In the EE Analysis Set, the 123 treated patients included 63 (51%) men and 60 (49%) women;

median age was 71 years and ranged from 32 to 87 years. The majority (74%) of patients in the EE Analysis Set were ≥ 65 years, including 33% of patients ≥ 75 years, which is representative of the AML patient population. Race was not reported for 37% of patients per local regulatory requirements; the remaining patients were White (45%), Other (11%), Black/African American (4%), or Asian (3%).

The FDA's Assessment:
The FDA performed an evaluation of the demographics in patients enrolled in study 2102-HEM-101.

Table 22: Demographic Characteristics of 2102-HEM-101* Full Analysis Set

Demographic Parameter	2102-HEM-101 (N=332)			
	Olutasidenib Cohort 1 EE Population (N=147)	Total Olutasidenib Single Agent (N=216)	Olutasidenib + Aza (N=115)	Total (N=332)*
Sex at Birth, n (%)				
Female	73 (50)	104 (48)	53 (46)	157 (47)
Male	74 (50)	112 (52)	62 (54)	175 (53)
Age (years)				
Median	71	71	70	71
Min, Max	32, 87	32, 90	28, 88	28, 90
Age Categories (years)				
<65	37 (25)	49 (23)	38 (33)	87 (26)
65-<75	65 (44)	98 (45)	45 (39)	143 (43)
≥75	45 (31)	69 (32)	32 (28)	102 (31)
Race, n (%)				
White	67 (46)	114 (53)	72 (63)	187 (56)
Asian	5 (3)	7 (3)	3 (3)	10 (3)
Black	5 (3)	10 (5)	5 (4)	15 (5)
Other	16 (11)	17 (8)	4 (4)	21 (6)
Not Reported	54 (37)	68 (32)	31 (27)	99 (30)

Source: FDA analysis
**Please note there is one patient that received olutasidenib + LDAC that is not included in the demographics table*

The FDA agrees that the median age of patients enrolled on study 2102-HEM-101 was reflective of the AML population in general. However, there was underrepresentation of minority patients (although a significant number of patients did not have their race reported) in this study, which may not be entirely reflective of the general AML population.

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

Data:

Demographic and Disease Characteristics	Olutasidenib (150 mg BID) N=123
ECOG PS, n (%)	
0	35 (28)
1	66 (54)
2	20 (16)
3	0 (0)
IDH1 Mutation, n (%)[1]	
R132C	68 (55)
R132H	30 (24)
R132G	11 (9)
R132S	10 (8)
R132L	4 (3)
Type of AML, n (%)	
De novo AML	78 (63)
Secondary AML	45 (37)
Cytogenetic Risk Status[2], n (%)	
Favorable	6 (5)
Intermediate	90 (73)
Poor	19 (15)
Unknown	8 (7)
Relapse Type	
Relapsed AML	82 (67)
Refractory AML	41 (33)
AML Relapsed/Refractory Patient Category, n (%)[3]	
Primary Refractory	38 (31)
Untreated Relapse[4]	69 (56)
Refractory Relapse[4]	16 (13)
Relapse Number[3]	
0	38 (31)
1	74 (60)
2	8 (7)
>3	3 (2)
Prior Stem Cell Transplantation for AML, n (%)	13 (11)
Transfusion Dependent at Baseline[5], n (%)	71 (58)
Number of Prior Anticancer Regimens, n (%)	
1	43 (35)
2	37 (30)
≥3	43 (35)
Median Number of Prior Therapies (Min, Max)	2 (1,7)
Number of Prior Venetoclax, n (%)	10 (8)
	48 (39)

Number of Prior HMA, n (%)	

[1] Using centralIDH1 assay testing results
[2] Cytogenetic risk categorization was investigator reported by NCCN or ELN guideline
[3] Patients are classified per FDA AML Developing Drugs and Biological Products for Treatment Draft Guidance definitions based on manual review of patient's prior therapies and determination of relapse number
[4] May be first or subsequent relapse
[5] Transfusion-Dependent at Baseline is defined as receiving a transfusion within 8 weeks prior to first dose of olutasidenib or noting transfusion dependence prior to coming on study

The Applicant's Position:
The baseline disease characteristics were representative of patients in the studies that were used to develop the null hypothesis, as well as those enrolled in the study which led to the approval of another commercially available IDH1 inhibitor for R/R AML.

Most patients (82%) had an ECOG PS of 0 or 1 and 16 (20%) patients had baseline ECOG PS of 2. Approximately one-third of patients (37%) had secondary AML, and most patients (88%) were classified as intermediate or poor cytogenetic risk. The most common R132 mutations were R132C and R132H in 55% and 24% of patients, respectively. Co-mutations were reported for the majority of patients including 61% of patients with one to three baseline co mutations and 14-15% with four to seven co mutations at baseline thereby indicating a patient population with molecularly diverse AML.

All patients had received prior anti-cancer therapies with a median of two prior regimens, and 21% of patients had received four or more prior regimens. Disease state was refractory for 33% of patients and was relapsed for 67%. Prior HSCT was reported for 11% of patients. The most common prior anti-neoplastic therapies included cytarabine (71%) and idarubicin (42%). Prior HMAs included azacitidine (33%) and decitabine (10%).

The FDA's Assessment:
The FDA performed an evaluation of the disease characteristics for patients enrolled in Cohort 1 of study 2102-HEM-101 for the 147 patients with confirmed IDH1 mutation.

Table 23: Disease Characteristics of Efficacy Evaluable Population for Phase 2 Cohort 1 (90-Day Safety Update)

Disease Characteristics	**Olutasidenib 150mg BID (N=147)**
Screening ECOG	
0	47 (31)
1	79 (52)
2	24 (16)
Type of AML	
Primary	97 (66)
Secondary	50 (34)

Relapsed/Refractory Category	
Primary Refractory	46 (31)
Refractory Relapse	20 (14)
Untreated Relapse	81 (55)
Cytogenetics	
Favorable	6 (4)
Intermediate	107 (73)
Poor	25 (17)
Unknown	9 (6)
IDH1 Mutation Type	
R132C	85 (58)
R132H	35 (24)
R132G	12 (8)
R132S	11 (7)
R132L	4 (3)
Prior Stem Cell Transplant	17 (12)
Transfusion Dependent at Baseline	86 (59)
Median Number of Prior Therapies (Min, Max)	2 (1,7)

Source: FDA analysis

The majority of patients had an ECOG of 0-1 (>80%), which again, may not be truly representative of the general AML population. Over 80% of patients enrolled had intermediate or poor-risk cytogenetics with 34% of patients having secondary AML. Seventeen (12%) of patients had received a prior HSCT. The most frequent IDH1 mutation was R132C and R132H, which is consistent with what is seen in the general population of patients with IDH1-mutated AML.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment Compliance

Treatment compliance, defined as the total dose taken of the total dose prescribed, was high with a median of 100% (range: 89% to 106%). A summary of dose intensity <80% by cycle is provided in Table 24 and dosing data are provided in Table 25.

Table 24: Summary of the Number of Subjects with Dose Intensity <80% by Cycle (Safety Analysis Set)

Cycle	Phase 2 Cohort 1 Olutasidenib 150 mg BID (N = 153)	
	Number of Subjects	Dose Intensity <80%
1	153	26 (17)
2	133	30 (23)
3	117	25 (21)
4	105	25 (24)
5	89	23 (26)
6	71	26 (37)
7	48	13 (27)
8	41	11 (27)
9	37	9 (24)
10	32	10 (31)
11	25	10 (40)
12	22	6 (27)
>12	21	9 (43)

Source: Study HEM-101 Phase 2 Cohort 1 CSR Table A48. Data cutoff date: 18 June 2020.

Table 25: Extent of Exposure to Olutasidenib (Safety Analysis Set, Phase 2 Cohort 1)

Extent of Exposure	Phase 2 Cohort 1 Olutasidenib 150 mg BID (N = 153)
Treatment Duration (Days)[a]	
Patients Discontinued Treatment, n (%)	110 (72)
Patients Censored (on Treatment), n (%)	43 (28)
Median	142.0
95% CI for Median	(112.0, 165.0)
25th percentile	64.0
75th percentile	290.0
Min, Max	3+, 795+
Cycles of Treatment Received[b]	
N	153
Mean (StdDev)	6.6 (6.03)
Median	5.0
Min, Max	1+, 29+
Doses Received	
N	153
Mean (StdDev)	328.4 (330.84)
Median	248.0
Min, Max	5, 1552
Total Doses Received, mg	
N	153
Mean (StdDev)	46391.2 (45813.51)
Median	34,050.0
Min, Max	750, 203850

Extent of Exposure	Phase 2 Cohort 1 Olutasidenib 150 mg BID (N = 153)
Treatment Compliance[c], %	
N	153
Mean (StdDev)	99.6 (1.38)
Median	100.0
Min, Max	89, 106

Source: Table 14.2.11.1b. Data cutoff date: 18 June 2020
Abbreviations: BID = twice daily; CI = confidence interval; Max = maximum; Min = minimum; StdDev = standard deviation.
Treatment duration is calculated as Date of Last Dose – Date of First Dose + 1. Median and quartiles are calculated using Kaplan-Meier method. Confidence interval for median is calculated using the Brookmeyer-Crowley method. Minimum and maximum are actual values rather than estimates.
For Phase 2 patients, the number of cycles of treatment received is calculated as duration of treatment in days divided by 28.
Treatment compliance is calculated as Total dose taken divided by Total dose prescribed × 100.

Concomitant Medications

All 153 patients in Phase 2 Cohort 1 received at least 1 concomitant medication. The most frequently used medications (≥ 20% of patients) are typical of those used by the population under study and included paracetamol (50%); hydroxycarbamide (46%); piperacillin/tazobactam (31%); potassium chloride (29%); allopurinol (29%); acyclovir (27%); levofloxacin (25%); dexamethasone and posaconazole (24% each); furosemide (23%); amoxicillin-clavulanic acid (22%); and sulfamethoxazole/trimethoprim and valaciclovir hydrochloride (20% each).

The Applicant's Position:

Treatment compliance was well maintained with mean and median of 99.6% and 100% respectively. Concomitant medication use was representative of an AML patient population.

The FDA's Assessment:

FDA notes that per the Applicant's assessment of dose intensity per treatment cycle, between 17% and 40% of patients did not receive > 80% dose intensity per cycle. This indicates that full doses may not be tolerated by a considerable proportion of patients (roughly a quarter of patients by cycle over time). Although cross-trial comparisons are difficult to interpret, dose intensity < 80% per cycle was much lower at ≤ 10% with the other IDH1 inhibitor ivosidenib. Drugs are generally considered tolerable if ≥ 80% of patients are able to tolerate ≥ 80% of the planned doses each cycle. Olutasidenib only achieved this goal only during cycle 1.

FDA agrees with the applicant's assessment regarding concomitant medications. In the updated safety report, 132 patients (86%) of patients in the full analysis set had discontinued treatment, with 21 (14%) of patients remaining on study. The median number of weeks on treatment and cycles received was 33.52 and 6, respectively. Please see table below:

Table 26: Extent of Exposure to Olutasidenib in the Full Analysis Set

Extent of Exposure	Phase 2 Cohort 1 Olutasidenib 150 mg BID (N=153)
Treatment Duration (weeks)	
Patients Discontinued Treatment, n (%)	132 (86%)
Patients on Treatment, n (%)	21 (14%)
Median	20.29
25th Percentile	9.07
75th Percentile	38.9
Min, Max	0, 149
Number of Cycles Received	
Patients Receiving Treatment	153
Mean	9
Median	6
Min, Max	1,38

Source: FDA analysis

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:
The primary efficacy endpoint in the Phase 2 Cohort 1 of Study HEM-101 is the CR/CRh rate, the proportion of patients who achieve a BOR of CR or CRh. As of 18 Jun 2020, the CR/CRh rate in Phase 2 Cohort 1 patients in the EE Analysis Set was 33% (Clopper-Pearson 95% CI: 25.1, 42.4). With the null hypothesis of 15% based on similar patient populations with R/R AML, success criteria for the primary efficacy endpoint for Phase 2 Cohort 1 was met. The CR/CRh rate of 33% was clinically meaningful, and the lower bound of the 95% CI was statistically significantly > 15%. The lower bound of the more conservative Atkinson-Brown 95% CI (22.7%, 33.6%), which corrects for a two-stage design, also exceeds 15%, demonstrating the robustness of the estimate. Thirty-seven of the 41 patients who achieved CR or CRh had best responses of CR for an overall CR rate of 30% (95% CI: 22.1, 39.0); notably, the lower bound of the 95% CI for this analysis also was > 15%.

The Applicant's Position:

The CR/CRh rate was consistent across Phase 2 Cohort 1 Analysis Sets, with the lower bounds of the 95% CI all > 15%.

The FDA's Assessment:
The Applicant submitted the 90-day safety update data on 05/12/2022, 07/01/2022, and 10/11/2022 (SN0017, SN0028 & SN0048); the SN028 submission updated the response result of one case from the SN0017 submission after FDA's adjudication and the SN0048 submission corrected errors in the ADSL dataset of the SN0028 submission. Table 27, Table 28, and Table

29 present the results of the selected efficacy endpoints by FDA using datasets ADSL (SDN 48), ADRS (SDN 28), and ADTTE (SDN 28) submitted to eCTD.

The full analysis set remained 153 enrolled patients. The efficacy evaluable set (EE Analysis Set) was updated from 123 in original NDA to 147 patients with centrally confirmed IDH1-R132–mutated R/R AML who were treated with olutasidenib 150 mg BID and received their first dose at least 6 months before the 18 Jun 2021 data cutoff date based on Phase 2 Cohort 1 as of 18 Jun 2021.

Table 27: Response Rates in Patients with Relapsed or Refractory AML (Study 2102-HEM-101) in the EE Analysis Set

Endpoint	REZLIDHIA (150 mg twice daily) N=147
CR+CRh[1] n (%)	51 (35)
95% CI	(27, 43)
Median DOCR+CRh[2] (months)	25.9
95% CI	(13.5, NR)
CR[1] n (%)	47 (32)
95% CI	(25, 40)
Median DOCR[2] (months)	28.1
95% CI	(13.8, NR)
CRh[1] n (%)	4 (2.7)
95% CI	(0.7, 6.8)
Observed DOCRh[2] (months)	1.8, 5.6, 13.5, 28.5+

Source: FDA analysis

CI: confidence interval; NR = not reached

[1] CR (complete remission) was defined as <5% blasts in the bone marrow, no blasts with Auer rods, no extramedullary disease, and full recovery of peripheral blood counts (platelets >100,000/microliter and absolute neutrophil counts [ANC] >1,000/microliter); CRh (complete remission with partial hematologic recovery) was defined as < 5% blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets > 50,000/microliter and ANC > 500/microliter).

[2] DOCR (duration of CR), DOCRh (duration of CRh), and DOCR+CRh (duration of CR+CRh) was defined as time since first response of CR, CRh or CR/CRh, respectively, to relapse or death, whichever is earlier. + indicates censored observation.

Table 28: Time to Response and Median Follow-up in Patients with Relapsed or Refractory AML (Study 2102-HEM-101) in the EE Analysis Set

Endpoint	REZLIDHIA (150 mg twice daily) N=147
Time to CR (months) **median** **min, max**	 2.8 0.9, 7.4
Time to CR+CRh (months) **median** **min, max** **Median follow up (months)** **95% CI** **min, max**	 1.9 0.9, 5.6 10.2 (7.7, 13.0) (0.2, 38.1)

Source: FDA analysis

Table 29: Transfusion Independence by Response in Patients with Relapsed or Refractory AML (Study 2102-HEM-101) in the EE Analysis Set

Baseline Transfusion Status	56-Day Independent N (%)
CR + CRh (N=51) **Dependent (N=18)** **Independent (N=34)**	 16 (89) 32 (94)
Total (N=147) **Dependent (N=86)** **Independent (N=61)**	 29 (34) 39 (64)

Source: FDA analysis

From the results, the review team concluded that:

Study 2102-HEM-101 demonstrated a CR+CRh rate of 35% (95% CI: 27%, 43%) with median duration of CR+CRh of 25.9 months (95% CI: 13.5, NR). These results passed the efficacy

criteria that, "if the true complete response rate for olutasidenib were significantly greater than 15%, it would be evidence of clinically significant activity in this population."

In addition, Study 2102-HEM-101 showed 1) similar CR+CRh time to response (median 1.9 months; range, 0.9 to 5.6 months) compared to ivosidenib (median 2 months; range, 0.9 to 5.6 months; data source: ivosidenib USPI); 2) similar transfusion independence (34% TD->TI and 64% TI->TI) compared to ivosidenib (37% TD->TI and 59% TI->TI; data source: ivosidenib USPI).

Data Quality and Integrity

The Applicant's Position:
No data integrity concerns were reported during study conduct or site audits.

The FDA's Assessment:
FDA agrees with the applicant's assessment.

Efficacy Results – Secondary and other relevant endpoints

Data:

Best overall response rate (BOR) and Overall response rate (ORR) data are presented in Table 30.

Table 30: Best Overall Response and Overall Response Rate (Efficacy Evaluable Analysis Set, Phase 2 Cohort 1)

Response, n (%)	**Olutasidenib (150 mg BID) N=123**
Overall Response Rate (PR or better), n (%)	57 (46)
95% CI[a]	(37.3, 55.6)
Best Overall Response[b]	
CR	37 (30)
CRh	4 (3)
CRi	14 (11)
MLFS	1 (1)
PR	1 (1)
SD	40 (33)
Progressive Disease	8 (7)
Not Evaluable/Not Done	18 (15)

Source: Table 14.2.1.1. Data cutoff date: 18 June 2020
Abbreviations: AML = acute myeloid leukemia; BID = twice daily; CB = clinical benefit; CI = confidence interval; CR = complete remission; CRh = CR with partial hematologic recovery; CRi = CR with incomplete recovery; MLFS = morphologic leukemia-free state; PR = partial remission; RD = resistant disease; SD = stable disease.

Clopper-Pearson 95% CIs are calculated based on binomial distribution.

[a] Best overall response for AML is defined as the best response on study. Assessment of response at a visit is presented in order from highest to lowest, and each patient is counted once in the highest category achieved on study

Time to CR/CRh (TTCR/CRh), time to complete response (TTCR), and time to response (TTR)

Time to CR/CRh

In the Phase 2 Cohort 1 EE Analysis Set, for the 41 patients who achieved a BOR of CR/CRh the median time to response was 1.90 months (range: 0.9, 5.6). Regardless of analysis set, the median time to CR/CRh for patients who achieved CR/CRh was < 2 months, and all responders had achieved CR/CRh by approximately 6 months. Similarly, the median time to CR was 1.90 months (range: 0.9, 5.6 months) and the median time to first overall response for the 57 patients who achieved response (PR or better) was 1.90 months (range: 0.9, 10.2 months)

Duration of CR/CRh (DCR/CRh), duration of complete remission (DCR), and duration of overall response (DOR)

Duration of CR/CRh

Table 31: Duration of CR/CRh (Efficacy Evaluable Analysis Set, Phase 2 Cohort 1)

Duration of CR/CRh (Months)	**Olutasidenib (150 mg BID) N=123**
Patients with CR/CRh, n	41
Patients with Event, n (%)	14 (34)
Patients Censored, n (%)	27 (66)
Median	NE
95% CI for Median	(10.60, NE)
25th percentile	7.40
75th percentile	NE
Min, Max[a]	0.0+, 25.0+
KM estimated % of patients with duration of CR/CRh of at least	
6 months (95% CI)	81 (64, 90)
12 months (95% CI)	61 (41, 77)
18 months (95% CI)	51 (29, 69)

Source: Table 14.2.2.1. Data cutoff date: 18 June 2020

Abbreviations: BID = twice daily; CI = confidence interval; CR = complete remission; CRc = cytogenetic CR; CRh = CR with partial hematologic recovery; CRm = molecular CR; EE = Efficacy Evaluable; HSCT = hematopoietic stem-cell transplantation; KM = Kaplan-Meier; min = minimum; max = maximum; NE = not estimable.

Note: CR includes CR, CRc, and CRm.

Note: Denominator for percentages is the number of patients with CR/CRh in the EE Analysis Set.

Note: Median and quartiles are calculated using KM method. The CI for the median is calculated using the Brookmeyer-Crowley method. Minimum and maximum are actual values rather than estimates.

Note: Duration of response is defined as the time from the date of the first response to the date of the relapse, death, or start of anti-cancer therapy. Patients who do not relapse are censored at the date of last response assessment.

Note: Duration of response was only collected post HSCT for patients who consented to Protocol Amendment 4 or later.

[a] The maximum duration is censored

Four sensitivity analyses were performed for the duration of CR/CRh as shown in Table 32. The first three were prespecified, and the fourth was performed post hoc.

1) Alternate HSCT Patient Censoring: Patients who had undergone HSCT were censored at the last adequate assessment prior to HSCT.
2) Alternate Censoring of Undocumented Progression: Patients who discontinued study treatment due to undocumented progression were counted as patients with an event at the date of last dose.
3) Alternate Censoring of Subsequent Anti-cancer Therapies: Patients with subsequent anti-cancer therapies prior to an event date were considered censored the day before the start of the anti-cancer therapy.
4) HSCT Event: Patients who had HSCT prior to progression ended their duration of response at the last adequate response assessment prior to HSCT, and HSCT was considered a patient event.

The median duration has not been reached for the first three separate sensitivity analyses, but the lower bounds of the 95% CI for the median were all ≥ 10.6 months (the lower bound of the 95% CI for the median in the primary analysis) (Table 32). When HSCT was considered to be an event in the time-to-event analysis, the KM-estimated median duration of CR/CRh was 13.8 months, with the lower bound of the 95% CI at 5.6 months and the upper bound not reached.

Table 32: Sensitivity Analyses for Duration of CR/CRh (Efficacy Evaluable Analysis Set, Study HEM-101 Phase 2 Cohort 1)

Duration of CR/CRh (Months)	Alternate HSCT Patient Censoring [a]	Alternate Censoring of Undocumented Progression [b]	Alternate Censoring of Subsequent Anti-cancer Therapies [c]	HSCT as a Patient Event[d]
Patients with Event, n (%)	11 (27)	14 (34)	9 (22)	20 (49)
Patients Censored, n (%)	30 (73)	27 (66)	32 (78)	21 (51)
Median	NE	NE	NE	13.8
95% CI for Median	(11.70, NE)	(10.60, NE)	(14.80, NE)	(5.62, NE)
25th percentile	7.40	7.40	13.80	3.88
75th percentile	NE	NE	NE	NE
Min, Max	0.0+, 25.0+	0.0+, 25.0+	0.0+, 25.0+	0.1+, 25.0+

Source: Study HEM-101 Phase 2 Cohort 1 CSR Table 14.2.2.8, Table 14.2.2.9, Table 14.2.2.10, Table A01. Data cutoff date: 18 June 2020; extracted 19 October 2020.

Abbreviations: CI = confidence interval; CR = complete remission; CRh = CR with partial hematologic recovery; EE = Efficacy Evaluable; max = maximum; min = minimum; HSCT = hematopoietic stem cell transplant; NE = not estimable.

Note: Denominator for percentages is 41, the number of patients with CR/CRh in the EE Analysis Set.

Note: Median and quartiles are calculated using the Kaplan-Meier method. The CI for the for median is calculated using the Brookmeyer-Crowley method. Minimum and maximum are actual values rather than estimates.

Note: Duration of response is defined as the time from the date of the first response to the date of the relapse, death, or start of anti-cancer therapy. Patients who did not relapse were censored at the date of last response assessment.

For this sensitivity analysis, an additional censoring rule was applied: Patients who had HSCT prior to progression were censored at the last adequate response assessment prior to HSCT.

For this sensitivity analysis, an additional censoring rule was applied: Patients who discontinued study treatment due to undocumented progression were considered as having an event at the date of last dose.

For this sensitivity analysis, patients receiving anti-cancer therapy were censored on the day before the start of their new anti-cancer therapy.

For this sensitivity analysis, HSCT was considered as a patient event. Patients who had HSCT prior to progression ended their duration of response at the last adequate response assessment prior to HSCT.

Data from other secondary endpoints follows:

Table 33: Duration of Complete Response (Efficacy Evaluable Analysis Set, Phase 2 Cohort 1)

Duration of Complete Response (CRm, CRc, or CR) (Months)	Olutasidenib (150 mg BID) N=123
Patients with Event, n (%)	12 (32)
Patients Censored, n (%)	25 (68)
Median	NE
95% CI for Median	(9.70, NE)
25th percentile	8.20
75th percentile	NE
Min, Max	0.0+, 20.3+
KM estimated % of patients with duration of complete response at least	
6 months (95% CI)	85 (67,93)
12 months (95% CI)	64 (43,79)
18 months (95% CI)	51 (28,70)

Source: Table 14.2.2.1. Data cutoff date: 18 June 2020

Abbreviations: BID = twice daily; CI = confidence interval; CR = complete remission; CRc = cytogenetic CR; CRm = molecular CR; EE = Efficacy Evaluable; HSCT = hematopoietic stem cell transplant; KM = Kaplan-Meier; max = maximum; min = minimum; NE = not evaluated.

Note: Denominator for percentages is the number of patients with response in each cohort in the analysis set.

Note: Median and quartiles are calculated using Kaplan-Meier method. The CI for the median is calculated using the Brookmeyer-Crowley method. Minimum and maximum are actual values rather than estimates.

Note: Duration of response is defined as the time from the date of the first response to the date of the relapse, death, or start of anti-cancer therapy. Patients who do not relapse are censored at the date of last response assessment.

Note: Duration of response was only collected post HSCT for patients who consented to Protocol Amendment 4 or later.

Table 34: Duration of Overall Response (Efficacy Evaluable Analysis Set, Phase 2 Cohort 1)

Duration of Overall Response (PR or better) (Months)	Olutasidenib (150 mg BID) N=123
Patients with Overall Response (PR or better)	57
Patients with Event, n (%)	26 (46)
Patients Censored, n (%)	31 (54))
Median	11.70
95% CI for Median	(7.40, NE)
25th percentile	5.60
75th percentile	NE
Min, Max	0.0+, 25.0+
KM estimated % of patients with duration of response of at least	
6 months (95% CI)	65 (51,77)
12 months (95% CI)	48 (32,62)
18 months (95% CI)	40 (24,56)

Source: Table 14.2.2.1. Data cutoff date: 18 June 2020
Abbreviations: BID = twice daily; CI = confidence interval; EE = Efficacy Evaluable; HSCT = hematopoietic stem cell transplant; KM = Kaplan-Meier; min = minimum; max = maximum; NE = not estimable; PR = partial response.
Note: Denominator for percentages is the number of patients with response in each cohort in the analysis set.
Note: Median and quartiles are calculated using KM method. The CI for the median is calculated using the Brookmeyer-Crowley method. Minimum and maximum are actual values rather than estimates.
Note: Duration of response is defined as the time from the date of the first response to the date of the relapse, death, or start of anti-cancer therapy. Patients who do not relapse are censored at the date of last response assessment.
Note: Duration of response was only collected post HSCT for patients who consented to Protocol Amendment 4 or later.

Table 35: Analysis of Event-Free Survival (Full Analysis Set, Phase 2, Cohort 1)

Event-Free Survival[a]	Phase 2 Cohort 1 Olutasidenib 150 mg BID (N = 153)
Patients with event, n (%)	95 (62)
Patients without event (censored), n (%)	58 (38)
Median	4.90
95% CI for Median	(4.20, 7.70)
25th percentile	1.90
75th percentile	14.30
Min, Max	0.0+, 25.9+
EFS Probability, % (95% CI)[b]	
3 Months	67 (58, 74)
6 Months	46 (37, 54)
9 Months	34 (25, 42)
12 Months	28 (20, 37)
24 Months	20 (13, 29)

Source: Table 14.2.5.1b. Data cutoff date: 18 June 2020
Abbreviations: BID = twice daily; CI = confidence interval; max = maximum; min = minimum.
Note: Denominator for percentages is the number of patients with response in each cohort in the analysis set.
Note: Event-free Survival (EFS) is defined as the time between first dose of study drug and disease progression, relapse, death from any cause, treatment failure, or start of other (non-protocol study drug) new antileukemia therapy, whichever occurs first.
Median and quartiles are calculated using Kaplan-Meier method. The CI for the median is calculated using the Brookmeyer-Crowley method. Minimum and maximum are actual values rather than estimates.

[a] Survival probability and CI are calculated based on Kaplan-Meier product-limit method and Greenwood's formulae.

Table 36: Overall Survival (Full Analysis Set, Phase 2 Cohort 1)

Overall Survival,[a] Months	**Phase 2 Cohort 1 Olutasidenib 150 mg BID (N = 153)**
Patients (%) with event	73 (48)
Patients (%) without event (censored)	80 (52)
Median	10.50
95% CI for Median	(7.70, 15.50)
25th percentile	3.80
75th percentile	NE
Min, Max	0.2, 25.9
OS Probability, % (95% CI)[b]	
3 Months	79 (72, 85)
6 Months	64 (55, 71)
9 Months	54 (45, 63)
12 Months	46 (36, 55)
24 Months	33 (22, 45)

Source: Table 14.2.4.1b. Data cutoff date: 18 June 2020
Abbreviations: BID = twice daily; CI = confidence interval; KM = Kaplan-Meier; max = maximum; min = minimum NE = not estimable; OS = overall survival.
Note: Denominator for percentages is the number of patients in each cohort in the analysis set.
Note: Overall survival (OS) is defined as the time from the date of the first dose until death from any cause.
Median and quartiles are calculated using KM method. The CI for the median is calculated using the Brookmeyer-Crowley method. Minimum and maximum are actual values rather than estimates.

[a] Survival probability and CI are calculated based on KM product-limit method and Greenwood's formulae.

Table 37: Transfusion Independence for at Least One ≥ 56 Day Time Period by Best Response Category (Efficacy Evaluable Analysis Set, Phase 2 Cohort 1)

Best Overall Response	Baseline Transfusion[a]	Post-Baseline Transfusion[b]		
		Dependent n (%)	56-Day Independent n (%)	Not Evaluated n (%)
Platelets				
CR (N = 37)	Dependent (N = 5)	0	5 (100)	0
	Independent (N = 32)	0	32 (100)	0
CRh (N = 4)	Dependent (N = 2)	0	2 (100)	0
	Independent (N = 2)	0	2 (100)	0
Other Responders[c] (N = 16)	Dependent (N = 9)	4 (44)	5 (56)	0
	Independent (N = 7)	1 (14)	5 (71)	1 (14)
Non-Responders (N = 66)	Dependent (N = 42)	14 (33)	10 (24)	18 (43)
	Independent (N = 24)	8 (33)	8 (33)	8 (33)
Overall (N = 123)	Dependent (N = 58)	18 (31)	22 (38)	18 (31)
	Independent (N = 65)	9 (14)	47 (72)	9 (14)
Red Blood Cells				
CR (N = 37)	Dependent (N = 10)	2 (20)	8 (80)	0
	Independent (N = 27)	2 (7)	25 (93)	0
CRh (N = 4)	Dependent (N = 2)	0	2 (100)	0
	Independent (N = 2)	0	2 (100)	0
Other Responders[c] (N = 16)	Dependent (N = 12)	6 (50)	6 (50)	0
	Independent (N = 4)	1 (25)	2 (50)	1 (25)
Non-Responders (N = 66)	Dependent (N = 44)	17 (39)	8 (18)	19 (43)
	Independent (N = 22)	9 (41)	6 (27)	7 (32)
Overall (N = 123)	Dependent (N = 68)	25 (37)	24 (35)	19 (28)
	Independent (N = 55)	12 (22)	35 (64)	8 (15)
Both Red Blood Cells and Platelet Transfusion				
CR (N = 37)	Dependent (N = 5)	0	5 (100)	0
	Independent (N = 32)	4 (13)	28 (88)	0
CRh (N = 4)	Dependent (N = 2)	0	2 (100)	0
	Independent (N = 2)	0	2 (100)	0
Other Responders[c] (N = 16)	Dependent (N = 9)	6 (67)	3 (33)	0
	Independent (N = 7)	3 (43)	3 (43)	1 (14)
Non-Responders (N = 66)	Dependent (N = 39)	15 (38)	7 (18)	17 (44)
	Independent (N = 27)	14 (52)	4 (15)	9 (33)
Overall (N = 123)	Dependent (N = 55)	21 (38)	17 (31)	17 (31)
	Independent (N = 68)	21 (31)	37 (54)	10 (15)
Any Red Blood Cell and/or Platelet Transfusion				
CR (N = 37)	Dependent (N = 10)	2 (20)	8 (80)	0
	Independent (N = 27)	2 (7)	25 (93)	0
CRh (N = 4)	Dependent (N = 2)	0	2 (100)	0
	Independent (N = 2)	0	2 (100)	0
Other Responders[c] (N = 16)	Dependent (N = 12)	8 (67)	4 (33)	0
	Independent (N = 4)	1 (25)	2 (50)	1 (25)
Non-Responders (N = 66)	Dependent (N = 47)	20 (43)	7 (15)	20 (43)
	Independent (N = 19)	9 (47)	4 (21)	6 (32)

Best Overall Response	Baseline Transfusion[a]	Post-Baseline Transfusion[b]		
		Dependent n (%)	56-Day Independent n (%)	Not Evaluated n (%)
Overall (N = 123)	Dependent (N = 71)	30 (42)	21 (30)	20 (28)
	Independent (N = 52)	12 (23)	33 (63)	7 (13)

Source: 2102-HEM-101 CSR Table 14.2.6.3. Data cutoff date: 18 June 2020
Abbreviations: CR = complete remission; CRh = CR with partial hematologic recovery; CRi = CR with incomplete recovery; eCRF = electronic Case Report Form; MLFS = morphologic leukemia-free state; PR = partial remission.
Transfusion-dependent at Baseline is defined as receiving a transfusion within 8 weeks prior to first dose of olutasidenib or noting transfusion dependence prior to coming on study per eCRF.

[a] The denominator is the number of patients who achieved the best overall response in the same response category.
[b] Includes patients who achieved best overall response of CRi, MLFS, or PR.

The Applicant's Position:

Secondary efficacy endpoints support the primary endpoint with regards to overall clinical benefit. The median duration of CR/CRh with olutasidenib has not yet been reached, with a lower bound on the 95% CI of 10.6 months. In the current study, the KM estimate of patients remaining in remission at 12 months was 61% (95% CI: 41, 77). Sensitivity analyses of the duration of CR/CRh were consistent with the primary analysis and confirmed the results. This represents a potential key differentiator in the comparative efficacy of these therapies.

The ORR was 46% (57/123 patients) and included the 41 (33%) patients who achieved CR/CRh, 14 (11%) patients who achieved CRi, and one patient each (1%) who achieved MLFS and PR. The median duration was 11.70 months (95% CI: 7.40 months, NE) with similar results observed in the FAS and the PP analysis sets. Furthermore, the median OS of 10.50 months in this pivotal cohort well exceeds the median OS data reported in historical studies. Conversion to transfusion independence, another recognized indicator of clinical benefit (FDA 2020), was achieved in 21/71 (30%) patients who were dependent on RBC and/or platelet transfusions at baseline.

Additionally, 14 of the 123 patients (11%) discontinued treatment and underwent HSCT, further suggesting the salvage potential of olutasidenib treatment as a bridge to the only currently available therapy with curative potential.

The FDA's Assessment:

See FDA conclusions under Section **Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)**. In summary, durable CR/CRh with associated achievement of transfusion independence would represent a clinically meaningful outcome in a population of patients with R/R AML treated without curative intent in the setting of therapies that do not have significant associated toxicities, (e.g., myelosuppression). Note, however, that FDA cannot confirm the

Sponsor's assertion that olutasidenib is an appropriate bridge to a potentially curative HSCT.

Also, Table 38 below is an update of Table 36 using the 90-day safety update data.

Table 38: Overall Survival (Full Analysis Set, Phase 2 Cohort 1) with data cut of 18 June 2021

Overall Survival, Months	**Phase 2 Cohort 1 Olutasidenib 150 mg BID (N = 153)**
Patients (%) with event	101 (66)
Patients (%) without event (censored)	52 (34)
Median	11.60
95% CI for Median	(8.90, 15.50)
25th percentile	3.90
75th percentile	32.70
Min, Max	0.2, 37.8
OS Probability, % (95% CI)	
3 Months	79 (72, 85)
6 Months	65 (57, 72)
9 Months	57 (49, 65)
12 Months	50 (41, 57)
24 Months	28 (20, 36)

Source: FDA Analysis

Dose/Dose Response

Data:
Data presented in 6.2.2.1 and 6.2.2.2. There were 28 patients with R/R AML treated in the dose escalation portion of Study 2102-HEM-101, 16 of which were treated with olutasidenib alone. The doses evaluated included 100 mg QD with food, 150 mg QD, 300 mg QD, and 150 mg BID. Pharmacodynamic data are presented for 2-HG reduction by dose is presented in Section 6.3.2.1 and results of the primary endpoint by dose are presented in Table 39.

A dose response relationship is not apparent likely due to the small sample size and limited dose ranges evaluated.

Table 39: Primary Outcome (CR/CRh) in the Proposed Indicated Population in 2102-HEM-101 Dose Escalation

Response Assessment	Single Agent Olutasidenib				
	100 mg QD (n=1)	150 mg QD (n=5)	150 mg BID (n=7)	300 mg QD (n=3)	Total (n=16)
CR/CRh Rate					
n (%)	0	2 (40)	1 (14)	1 (33)	4 (25)
95% CI[2]	NE	(5.3, 85.3)	(1.4, 57.9)	(0.8, 90.6)	(7.3, 52.4)
p-value[3]	NE	0.1648	0.6794	0.3859	0.2101

Source: 2102-HEM-101 CSR Table A49. Data cutoff date: 18 June 2020

In an exposure-response assessment with 324 patients, there was also no observed relationship between exposure and the probability of achieving a clinical response, exposure effects on the incidence of response were minimal for each of the efficacy endpoints, with p-value of 0.306 (Section 19.4.2.2).

The Applicant's Position:

The dose escalation portion of Study HEM-101 evaluated dosing regimens of 150 mg QD, 300 mg QD, 100 mg QD (with food), and 150 mg BID on Days 1 to 28 of each 28-day cycle. Olutasidenib 150 mg BID resulted in the highest olutasidenib exposure at steady-state and was determined to be a well-tolerated dose. Consistent with the expected MOA of olutasidenib, 2 HG plasma concentrations were suppressed with all doses tested. By predose Cycle 2, the median 2-HG plasma concentration for the olutasidenib 150 mg BID dose was near normal range for AML patients with wild-type IDH. This response was sustained throughout treatment. Therefore, olutasidenib 150 mg BID was identified as the maximum evaluated dose from the dose-escalation stage to be evaluated in dose-expansion cohorts.

The safety, PK and PD profile reported in patients treated with the olutasidenib 150 mg BID dose in the expansion cohorts was consistent with the profile of patients treated in the dose escalation.

Olutasidenib 150 mg BID was shown to provide clinically meaningful and durable efficacy and a manageable safety profile that was characteristic of symptoms or conditions frequently experienced by patients undergoing treatment for AML.

The FDA's Assessment:
FDA agrees with the Applicant's assessment. Please see section 6.2.2.1 for further commentary on dose and dose response.

Durability of Response

Data:
Data are presented in Section 0, Efficacy Results – Secondary and other relevant endpoints.

The Applicant's Position:

The CR/CRh responses were durable; while the median duration of CR/CRh has not yet been reached, 71% and 29% of patients were estimated to remain in remission at 6 and 12 months, respectively, with a maximum duration of 25.0+ months. In a sensitivity analysis where patients with HSCT prior to progression were considered to have an event at the last adequate assessment prior to HSCT, the median duration of CR/CRh was 13.8 months (95% CI: 5.62, NE).

The FDA's Assessment:

See FDA conclusions under Section Efficacy Results – Primary Endpoint (Including Sensitivity Analyses). The median DOR for CR/CRh was 25.9 months (95% CI: 13.5, NR) after taking FDA's recommendation to change the definition of DOR by excluding "start of anti-cancer therapy" as an event. In general, durable CR/CRh with associated achievement of transfusion independence would represent a clinically meaningful outcome.

Persistence of Effect

The Applicant's Position:

Data were not analyzed to evaluate persistence of effect.

The FDA's Assessment:

FDA agrees with the applicant's assessment.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

Figure 8: EQ-5D-5L Quality of Life by Dimension and Responder Status (Study HEM-101 Phase 2 Cohort 1, Efficacy Analysis Set)

Mobility Domain:

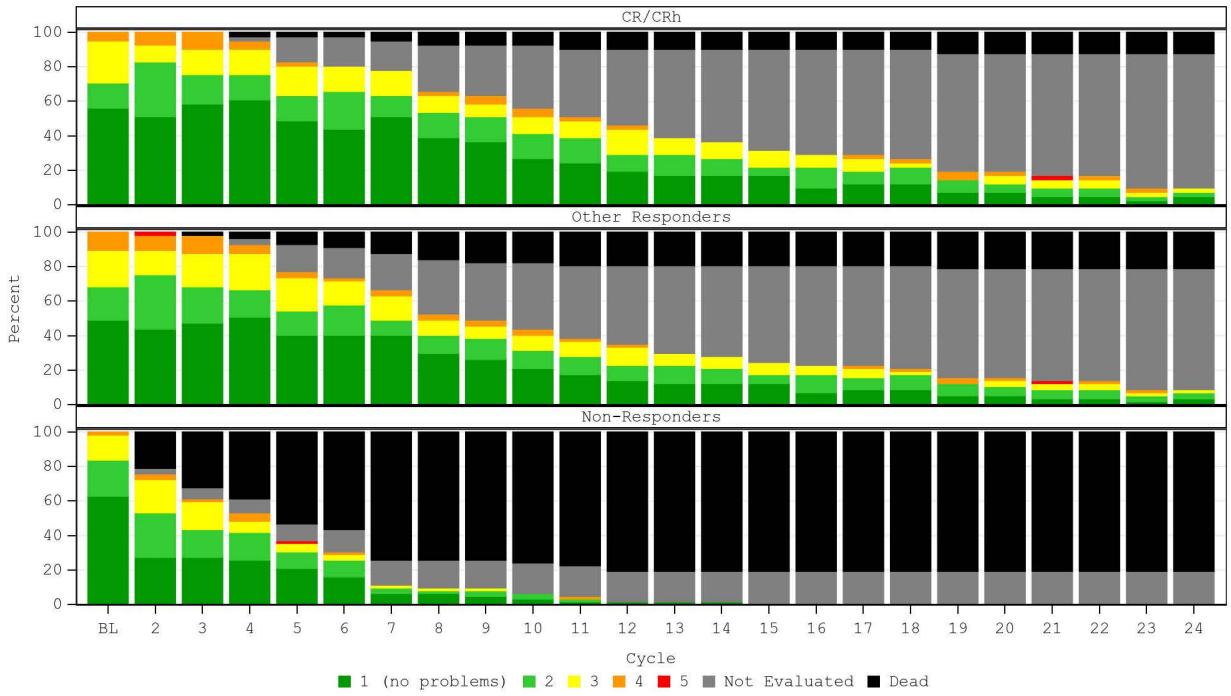
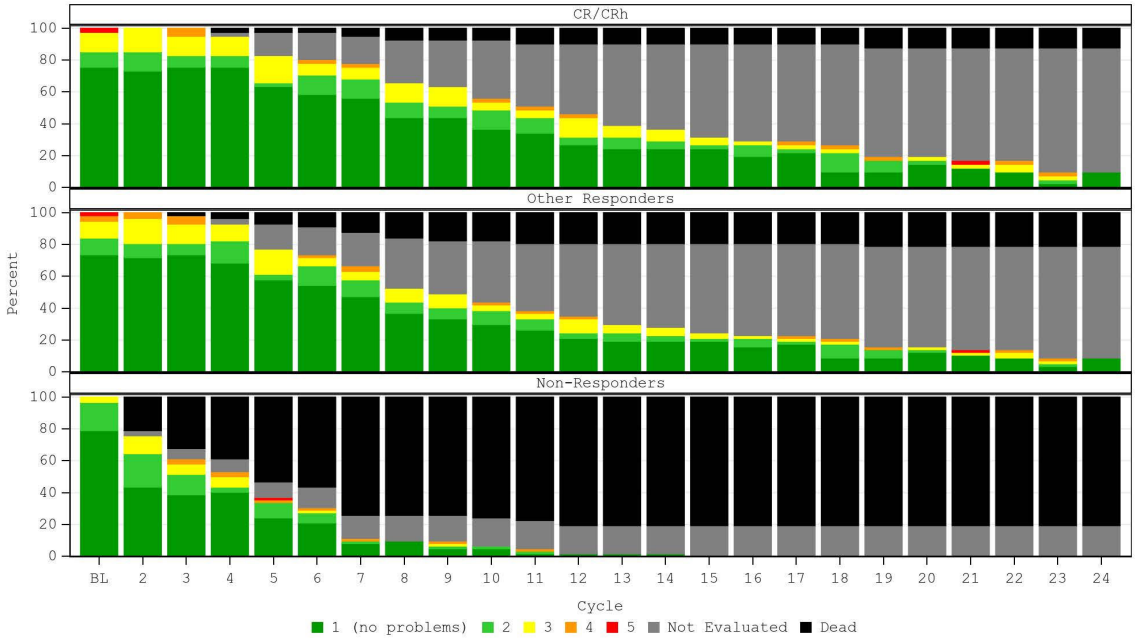


Figure 4: EQ-5D-5L Quality of Life by Dimension and Responder Status (Study HEM-101 Phase 2 Cohort 1, Efficacy Analysis Set; continued)

Self-Care Domain:



Usual Activities Domain:

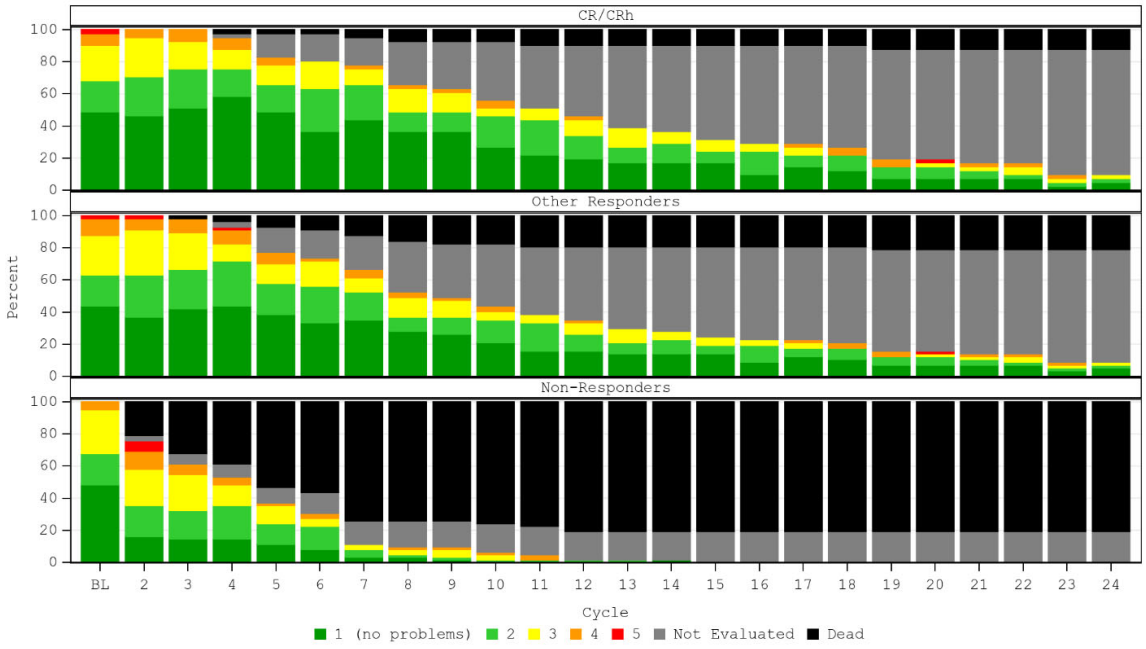
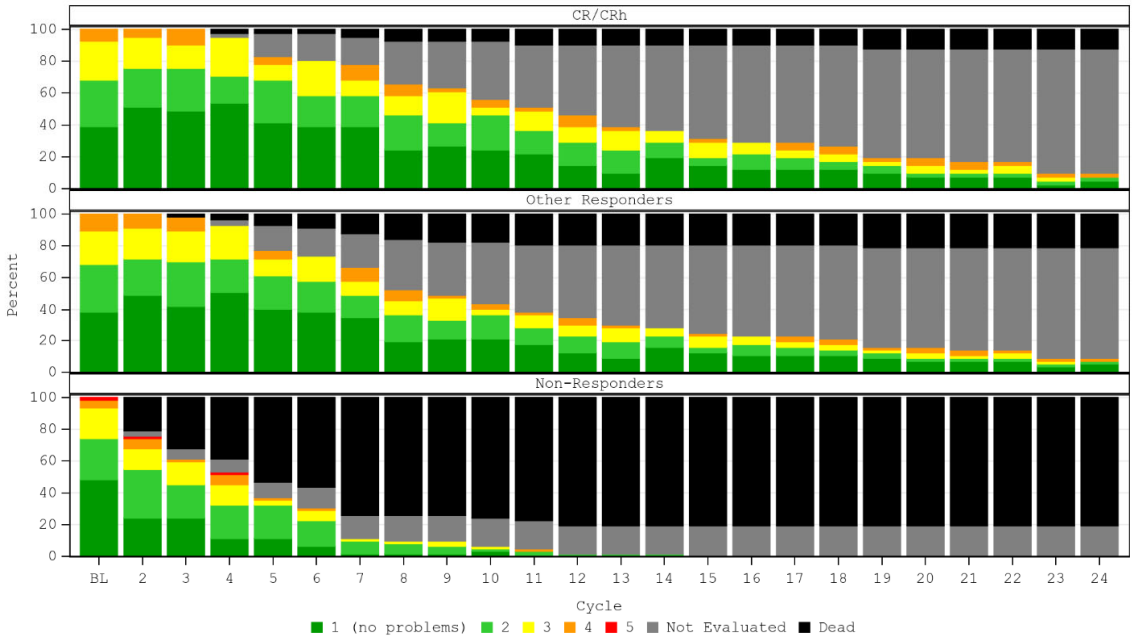
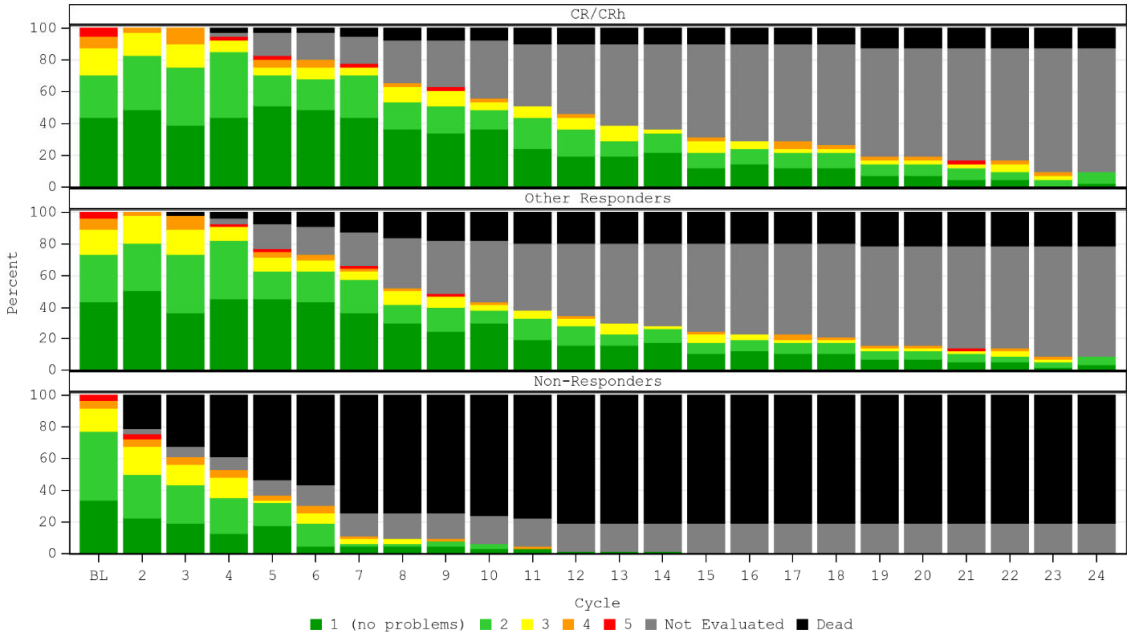


Figure 4: EQ-5D-5L Quality of Life by Dimension and Responder Status (Study HEM-101 Phase 2 Cohort 1, Efficacy Analysis Set; continued)

Pain/Discomfort Domain:



Anxiety/Depression Domain:



Source: Figure 14.2.8.5. Data cutoff date: 18 June 2020.
Abbreviations: CR = complete remission; CRh = CR with partial hematologic recovery.

The Applicant's Position:
The relative percentage of patients reporting each level for the five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) are similar for the CR/CRh and other responders and better than non-responders. Data suggest that remaining on treatment was associated with maintenance of QOL without an observed negative impact on QOL measures, regardless of response status.

The FDA's Assessment:
FDA notes that the analyses of COA (PRO) endpoints from a single cohort are exploratory in nature. Measurements of COA (PRO) in single-arm, open-label studies are difficult to interpret due to lack of a comparator group and potential bias due to knowledge of treatment assignment.

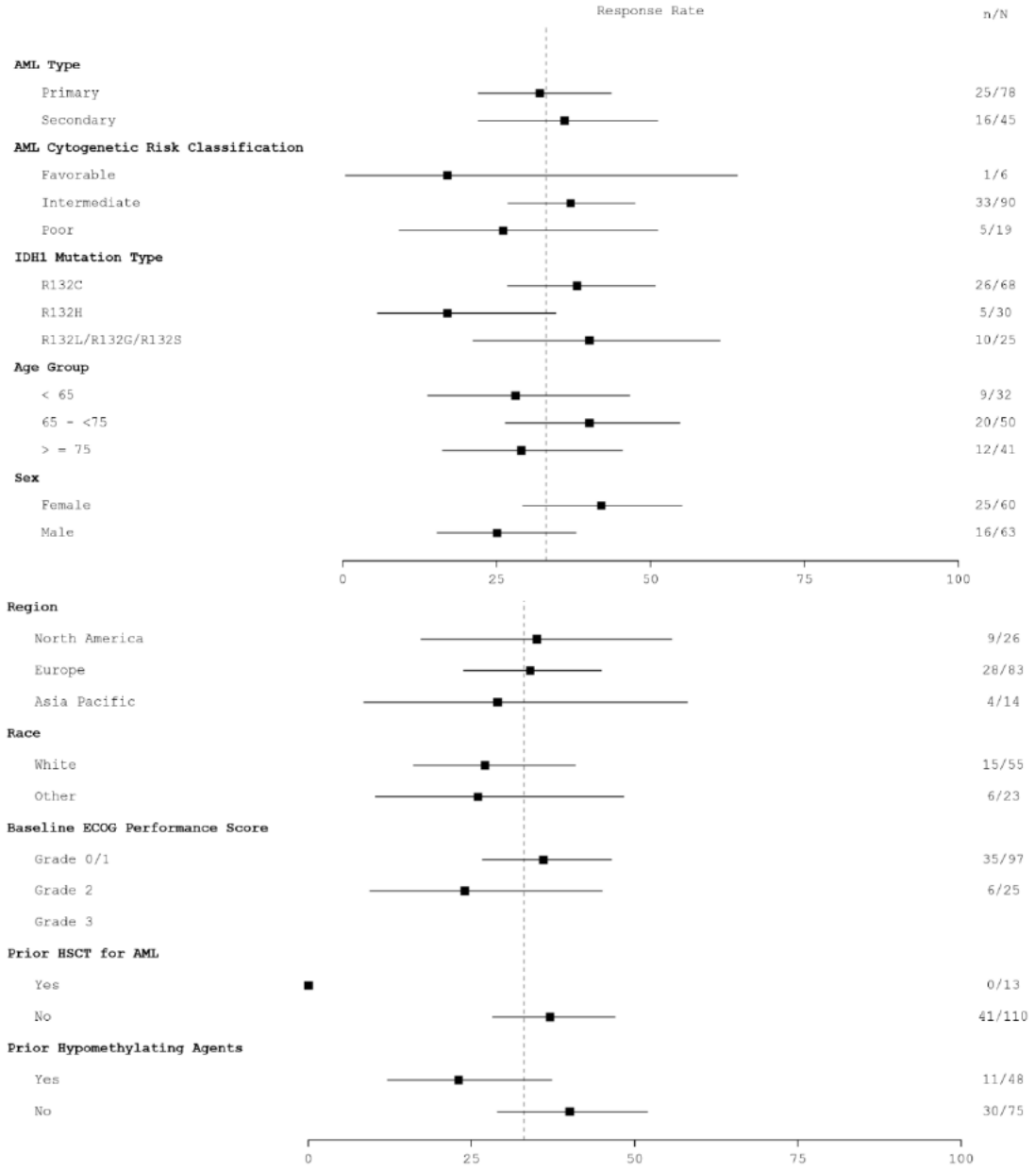
Additional Analyses Conducted on the Individual Trial

Data:

Forest plots of CR/CRh rate by subgroup in the EE Analysis Set of Phase 2 Cohort 1 are presented in Figure 9.

Subgroup analyses of CR/CRh rate (Figure 9) and ORR (Figure 10) were conducted for the Phase 2 Cohort 1 EE Analysis Set, by AML type, cytogenetic risk classification, *IDH1* mutation type, age group, sex, region, race, baseline ECOG PS, prior HSCT status, and prior hypomethylating agent status. An ad hoc analysis was performed for a subset of 12 patients in Phase 2 Cohort 1 who had prior venetoclax therapy. Although the sample size is small, the CR/CRh rate was 33% (4 of 12 patients; 95% CI: 9.9, 65.1), demonstrating that the efficacy achieved after prior venetoclax is similar to the overall Phase 2 Cohort 1 EE population.

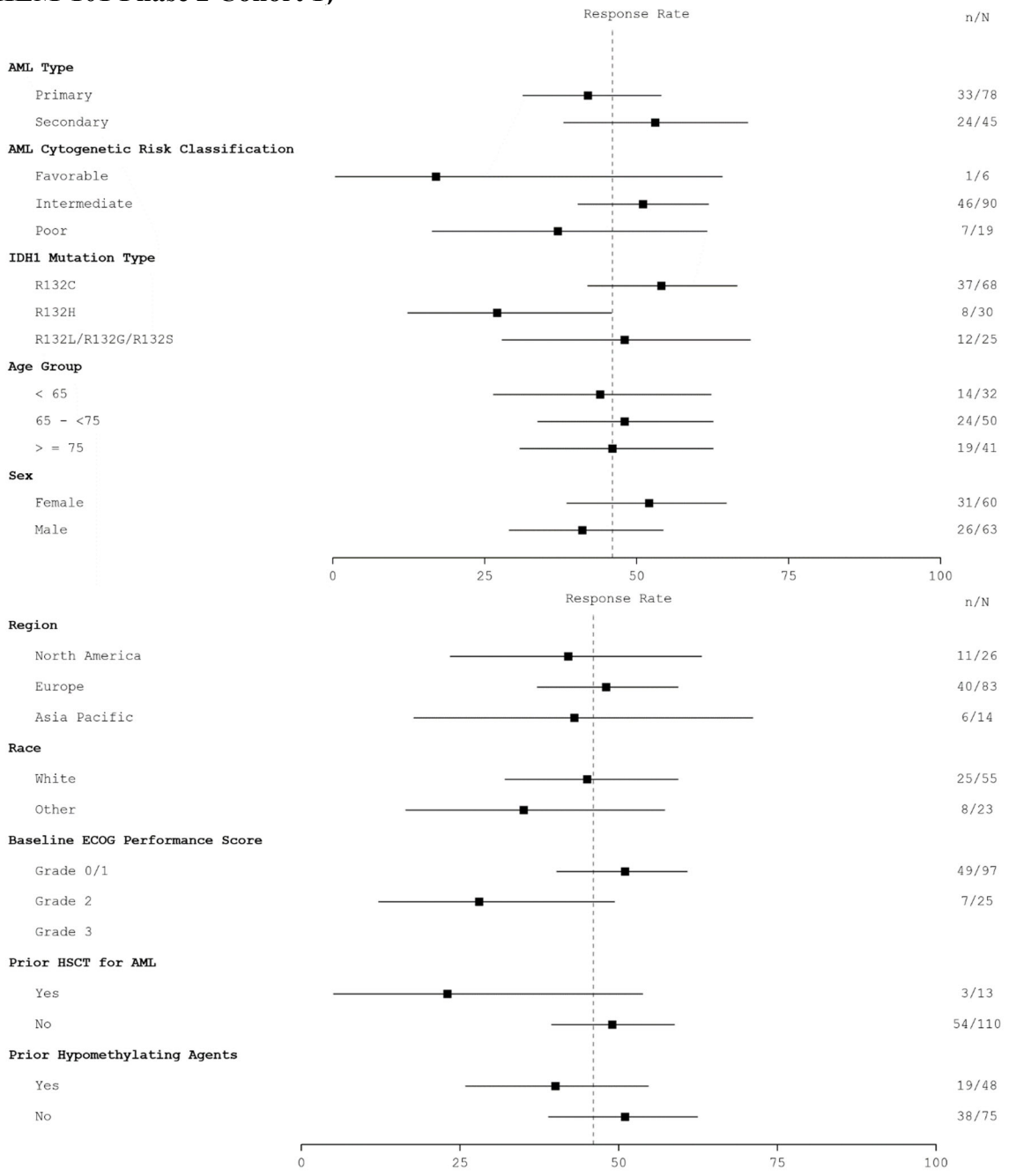
Figure 9: Forest Plot of CR/CRh Rate (Efficacy Evaluable Analysis Set, Study HEM-101 Phase 2 Cohort 1)



Source: Study HEM-101 Phase 2 Cohort 1 CSR Figure 14.2.1.7. Data cutoff date: 18 June 2020.
Abbreviations: AML = acute myeloid leukemia; CR = complete remission; CRh = CR with partial hematologic recovery; ECOG = Eastern Cooperative Oncology Group; EE = Efficacy Evaluable; HSCT = hematopoietic stem cell transplant; IDH = isocitrate dehydrogenase.

Note: The dotted reference line in the plot represents the CR/CRh rate for the EE Analysis Set overall (33%).

Figure 10: Forest Plot of Overall Response Rate (Efficacy Evaluable Analysis Set, Study HEM-101 Phase 2 Cohort 1)



Source: Study HEM-101 Phase 2 Cohort 1 CSR Figure 14.2.1.8. Data cutoff date: 18 June 2020.
Abbreviations: AML = acute myeloid leukemia; ECOG = Eastern Cooperative Oncology Group; EE = Efficacy Evaluable; HSCT = hematopoietic stem cell transplant; IDH1 = isocitrate dehydrogenase 1.
Note: The dotted reference line in the plot represents the response rate for the EE Analysis Set (46%) overall.

High-level Efficacy Results for Phase 2 Cohorts 2-8

In other Phase 2 R/R AML FAS cohorts, olutasidenib demonstrated meaningful clinical activity when administered in combination with AZA. Among R/R AML patients naïve to prior HMA and IDH1 inhibitor therapy (Cohort 4), the ORR and CR/CRh rates were 68% and 47%, respectively, with a median CR/CRh duration which was not met and a lower limit of the 95% CI for the median of 8.3 months. Among R/R AML patients who had inadequate responses or progressed on prior HMA therapy (Cohort 5) or who had previous IDH1 inhibitor treatment (Cohort 6), the ORR (62% and 53%, respectively) and CR/CRh rates (38% and 29%, respectively) indicate encouraging salvage activity with olutasidenib when administered in combination with AZA after treatment failure with HMA or IDH inhibitor therapy alone. In a small cohort of 4 AML patients R/R to prior IDH1 inhibitor therapy (Cohort 3), there were no responses observed. It is important to note that three of these patients were primary refractory to the prior IDH1 inhibitor therapy and the other patient's best response on IDH1 inhibitor therapy was PR. Investigators had the option to assign patients R/R to prior IDH1 inhibitor therapy to either Cohort 3 (SA olutasidenib) or Cohort 6 (olutasidenib in combination with AZA); these two patient groups should not be assumed to have similar baseline characteristics.

Additional evidence of olutasidenib's clinical activity was observed in the Phase 2 cohorts that enrolled patients with treatment-naïve (TN) AML who were treated with SA olutasidenib (Cohort 7) and olutasidenib in combination with AZA (Cohort 8). In Cohort 7, the ORR and CR/CRh rates were 50% and 20%, respectively, among TN AML patients treated with SA olutasidenib. In Cohort 8, the ORR and CR/CRh rates were 64% and 36% among TN AML patients treated with olutasidenib in combination with AZA. While the median DCR/CRh was not yet evaluable in either cohort, these responses indicate encouraging therapeutic potential in these patients who were not eligible to receive standard intensive frontline chemotherapy regimens.

In Phase 2 Cohort 2, patients with AML in morphologic CR/CRi after prior therapy (± HSCT) with measurable residual disease (MRD) received SA olutasidenib. The primary endpoint for this group is the 4-month relapse-free survival (RFS) rate, which is defined as the time between the date of first dose until relapse or death from any cause, whichever occurred first. A total of 12 patients (67%) without an RFS event were censored at the 4-month visit. The median RFS interval for Phase 2 Cohort 2 was 15.70 months (95% CI: 9.10, NE). The estimated RFS at 3, 6, 9, and 12 months was 89%, 89%, 81%, and 73%, respectively. Overall, these additional efficacy data support olutasidenib's potential to achieve meaningful clinical responses in AML patients with IDH1 mutations in various stages of treatment, as well as future potential to combine with AZA.

High-level Efficacy Results in MDS Patients Treated with the Recommended Dose of Olutasidenib in Phase 1 (Dose Escalation and Dose Expansion) of Study 2102-HEM-101

Table 40 provides efficacy results in patients with MDS treated with the recommended dose of olutasidenib during dose escalation and expansion (as monotherapy and in combination with azacitidine).

Table 40: Best Overall Response and Overall Response Rate as Assessed by Investigator – MDS: Olutasidenib 150 mg BID

Response Assessment Category - MDS	Olutasidenib 150 mg BID (n=3)	Olutasidenib 150 mg BID + Azacitidine (n=7)
Best Overall Response[1]		
Complete Remission (CR)	1 (33)	6 (86)
Marrow CR	1 (33)	0 (0)
Partial Remission (PR)	0 (0)	0 (0)
Clinical Benefit	0 (0)	0 (0)
Stable Disease	0 (0)	1 (14)
Disease Progression	0 (0)	0 (0)
Not Evaluable	0 (0)	0 (0)
Not Done	1 (33)	0 (0)
Overall Response Rate (PR or better)		
n (%)	2 (67)	6 (86)
95% CI[2]	(9.4, 99.2)	(42.1, 99.6)
Complete Response Rate (CR)		

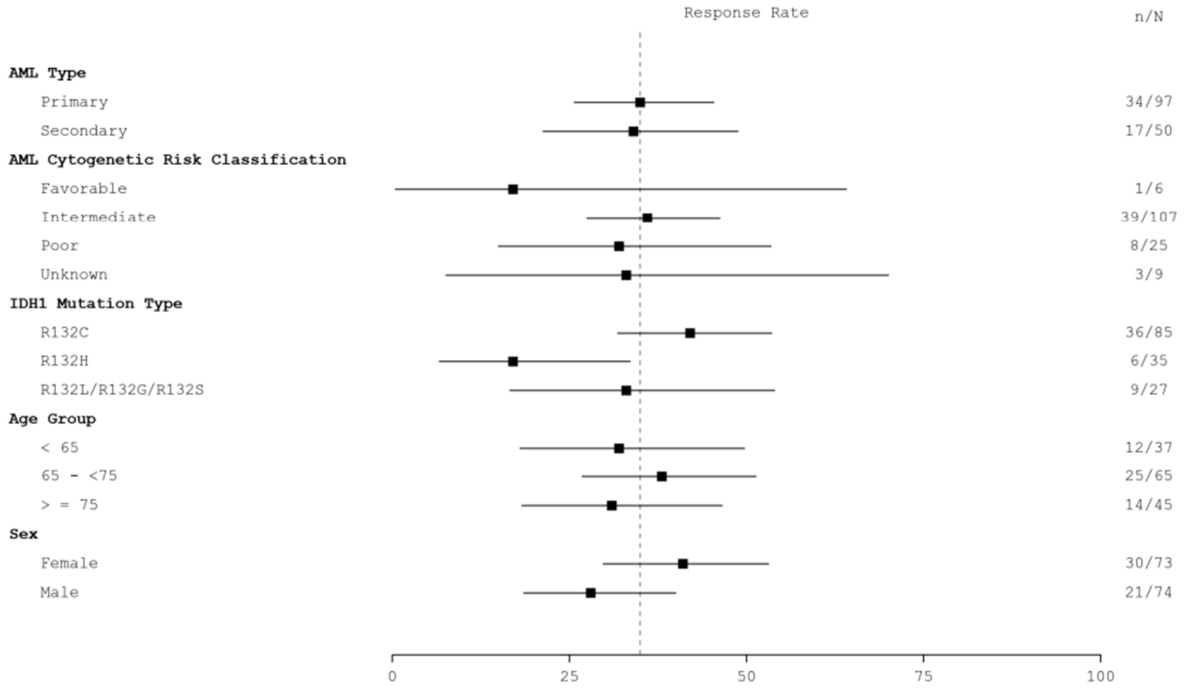
n (%)	1 (33)	6 (86)
95% CI[2]	(0.8, 90.6)	(42.1, 99.6)

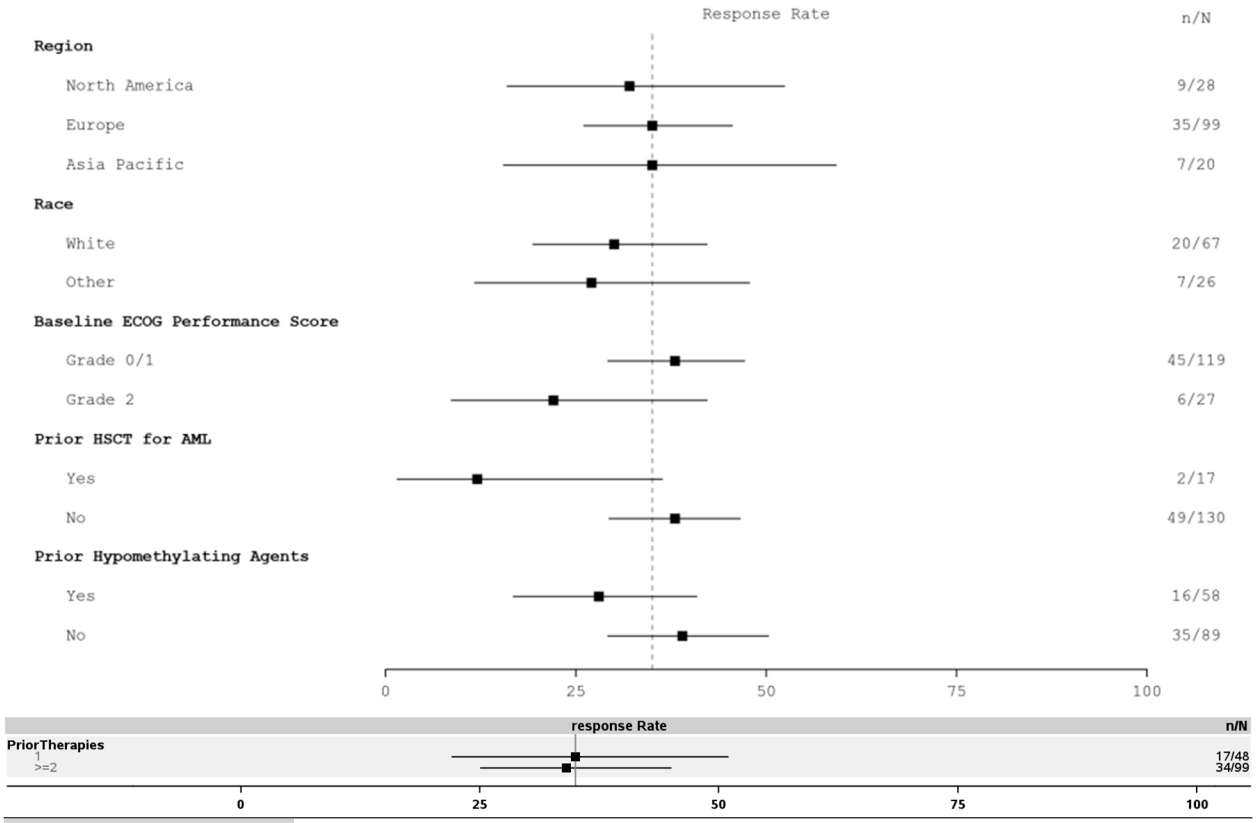
Source: Study HEM-101 Phase 2 Cohort 1 CSR Table 14.2.1.6a. Data cutoff date: 18 June 2020.
MDS = myelodysplastic syndrome; BID = twice daily; CI = confidence interval
[1] Best overall response for MDS is defined as the best response assessed by the investigator on study. Investigator assessment of response at a visit is presented in order from highest to lowest, and each patient is counted once in the highest category achieved on study.
[2] Clopper-Pearson 95% confidence intervals are calculated based on binomial distribution.

The Applicant's Position:
Sensitivity analyses of the duration of CR/CRh were consistent with the primary analysis and confirmed the results.

The FDA's Assessment:
FDA agrees with the applicant's assessment. We note that the data presented on Cohorts 2-8 is purely exploratory at this time. In addition, below Figure 11 presents updated forest plot of Figure 9 using the 90-day safety data (18 June 2021).

Figure 11: Forest Plot of CR/CRh Rate (Efficacy Evaluable Analysis Set, Study HEM 101 Phase 2 Cohort 1), 90-Day Safety Update





Source: FDA Analysis

As seen in the Figures above, results were generally consistent amongst the different baseline demographic and disease characteristics. However, the R132H mutation stood out as having a notably lower CR+CRh rate. This is also consistent with the data previously observed with ivosidenib (Ivosidenib multi-discipline review/summary, 2018). Thus, recommend adding a footnote to the efficacy results in Section 14 of the label to indicate a lower CR+CRh rate for this subpopulation.

8.1.2 Integrated Review of Effectiveness

The FDA's Assessment:
See the Integrated Assessment of Effectiveness below.

8.1.3 Assessment of Efficacy Across Trials

Primary Endpoints

The Applicant's Position:
Not applicable.

The FDA's Assessment:
FDA agrees as there was a single efficacy trial submitted to support the proposed indication.

Secondary and Other Endpoints

The Applicant's Position:
Not applicable.

The FDA's Assessment:
FDA agrees.

Subpopulations

The Applicant's Position:
Not applicable.

The FDA's Assessment:
FDA agrees.

Additional Efficacy Considerations

The FDA's Assessment:
FDA agrees.

8.1.4 Integrated Assessment of Effectiveness

The Applicant's Position:
Per the recently published FDA Draft Guidance on AML (FDA 2020), CR/CRh is an accepted binary efficacy endpoint used commonly for studies evaluating AML treatment and was the primary endpoint supporting approval for Tibsovo in a patient population with similar demographics and baseline disease characteristics. Both CR and CRh are associated with clinical benefit through disease control and establishment of hematopoiesis that reduces the risk of infection and bleeding and CR/CRh was agreed at a type C meeting and pre-NDA meeting as an

acceptable endpoint for an indication in this type of population. In the pivotal HEM-101 Phase 2 Cohort 1, the CR/CRh rate of 33% was statistically significantly greater than the reference rate of 15% based on historical data in similar populations of patients with R/R AML and met the primary endpoint and the early stopping criteria for this cohort. The CR/CRh rate of 33% is similar to the rate that supported approval of Tibsovo. The median duration of CR/CRh with olutasidenib was not reached with a lower bound on the 95% CI of 10.6 months. Additional supportive data include an ORR and median OR duration of 46% and 11.7 months as well as a median OS of 10.5 months. While the single arm study design limits direct comparison with other available therapies for R/R AML, the poor response rates with salvage therapies and overall prognosis of R/R AML is well described in numerous publications. The totality of efficacy data provide additional supportive evidence of a clinically meaningful and durable improvement in disease control with olutasidenib in a disease which remains difficult to treat in the relapsed and refractory setting despite recent advances in the understanding of leukemogenesis and the availability of novel therapies.

The FDA's Assessment:
In summary, the effectiveness of olutasidenib 150mg BID for treatment of patients with relapsed/refractory (R/R) AML harboring an IDH1 mutation is established by the CR + CRh rate, the durability of response, and supportive findings of transfusion independence. Given the relatively short median time to follow-up for patients, there is insufficient evidence to support long-term benefit and safety at this time. However, given the short-term safety profile appears to be tolerable, the effectiveness would be meaningful for patients seeking short-term relief from their R/R AML.

9.0 Review of Safety

The Applicant's Position:
The primary safety data in the proposed indication of R/R AML are derived from the ongoing Phase 1/2 Study 2102-HEM-101 conducted in patients with hematologic malignancies. Safety analyses were primarily performed using the Safety Analysis Set (SAS), defined as all patients who received at least one dose of olutasidenib, which included 153 patients in the pivotal Phase 2 Cohort 1.

Safety data in the integrated summary of safety were analyzed for a total of 332 patients with AML and MDS, including 216 who received single-agent olutasidenib, 115 who received olutasidenib in combination with azacitidine, and one who received olutasidenib in combination

with LDAC. Among these 332 patients, safety data are available from 179 patients with R/R AML who received single-agent olutasidenib, including the 153 patients in the pivotal Phase 2 Cohort 1. Supportive safety data from ongoing Study 2102-ONC-102 in 93 patients with glioma and other solid tumors available as of 03 Dec 2020 are included in the integrated safety analyses. A total of 512 patients, healthy volunteers, and subjects with hepatic impairment have been exposed to at least one dose of olutasidenib.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

9.1.1 Safety Review Approach

The Applicant's Position:
Demographic, baseline disease characteristics, and prior anti-cancer therapies were summarized for the Full Analysis Set (FAS). Because all enrolled patients received one dose of olutasidenib, the FAS is identical to the SAS for these analyses. Safety laboratory values, vital sign measurements, and ECG readings were summarized by visit. Change from baseline values were presented along with by visit summaries. Shifts in laboratory grades, as well as shifts in QT interval corrected using Fridericia's formula (QTcF), were tabulated. Assessment of changes in liver function tests (LFTs) were conducted. Abnormal safety assessments were flagged and separately presented.

Adverse events of hepatic dysfunction and QTc prolongation were identified as adverse events of special interest (AESIs). Differentiation syndrome (DS) was also identified as an AESI due to the observed effect of other drugs in the class.

The number of patients with an Investigator-reported AE of DS were summarized. In addition, a Sponsor assessment of candidate DS cases was conducted as per Montesinos, et al. 2009, using the methodology outlined in Norsworthy, et al. 2020. Candidate cases of DS were summarized based on AE and applicable clinical data and whether there was concomitant leukocytosis as recorded by leukocyte results from the laboratory data set or an AE of increased WBC count. The AE PTs and applicable clinical data findings were summarized into categories representing possible symptoms of DS and tabulated by the number of patients experiencing an event in the category in the first 90 and 180 days post-first dose. The specific methods of identifying candidate cases are fully described in Study HEM-101-SAP. Briefly, each candidate DS case was evaluated by trained hematologists/oncologists who reviewed available clinical information from each case and determined if, in their medical judgment, the spectrum of symptoms was consistent with possible DS. Candidate cases for which one or more of the events was an SAE were adjudicated by an independent committee of hematologists/oncologists.

To assess the potential hepatic effects of olutasidenib, Forma conducted an in-depth evaluation of data related to events of hepatic effects across the clinical program. This includes analysis of liver-related AEs based on both MedDRA individual PTs and specific grouped terms based on medical review and the nature of the observed effects with olutasidenib; laboratory data analyses to review changes in LFTs over time; assessment of potential Hy's law cases using evaluation of drug-induced serious hepatotoxicity (eDISH) plots; and a summarization of findings from the external expert in liver disease.
The AESI of QTc prolongation was defined by the MedDRA PT of ECG QT prolonged. Categorical analyses of the maximum post-baseline QTcF intervals and increases from baseline QTcF were also conducted. In addition, a 24-hour 12-lead continuous monitoring was performed on a subset of patients.

The FDA's Assessment:
FDA agrees with the Applicant's approach. The original dataset from study 2102-HEM-101, used a cutoff date of June 18th, 2020. The applicant then submitted an updated safety data set using a data cutoff date of June 18th, 2021 (submitted May 12th, 2022, SDN#17). The updated data set will form the basis of the safety review. Review of that demonstrated no significant differences in the amount of adverse events, AEs resulting in death, dose reductions or interruptions, or drug discontinuation due to AEs. Please be aware that because the FDA's analysis is based on the 90-day safety update, the numbers vary slightly between what the Sponsor has stated and the FDA analysis.

9.1.2 Review of the Safety Database

Overall Exposure

Data:

Table 41: Extent of Exposure to Olutasidenib (Safety Analysis Set)

Parameter n (%)	Hematologic Malignancies (Study 2102-HEM-101)				Solid Tumor (Study 2102-ONC-102) Total (N=93)	Overall (N=425)	HV data (N=87)
	R/R AML Olutasidenib Single Agent (N=179)	Olutasidenib Single Agent (N=216)	Olutasidenib + Azacitidine (N=115)	Total (N=332)			
Duration of Exposure (weeks)[a]							
N	179	216	115	332	93	425	87
Mean (SD)	24.2 (26.70)	26.9 (28.81)	29.0 (29.26)	27.6 (28.90)	23.0 (26.09)	26.6 (28.35)	2.04 (1.46)
Median	17.9	18.6	18.9	18.8	8.0	17.6	3.0
Min, Max	0, 200	0, 200	0, 136	0, 200	0, 101	0, 200	01, 3.3

Parameter n (%)	Hematologic Malignancies (Study 2102-HEM-101)				Solid Tumor (Study 2102-ONC-102) Total (N=93)	Overall (N=425)	HV data (N=87)
	R/R AML Olutasidenib Single Agent (N=179)	Olutasidenib Single Agent (N=216)	Olutasidenib + Azacitidine (N=115)	Total (N=332)			
Number of patients with exposure for at least, n (%)							
1 day	179 (100)	216 (100)	115 (100)	332 (100)	93 (100)	425 (100)	87 (100)
2 months	124 (69.3)	151 (69.9)	96 (83.5)	248 (74.7)	54 (58.1)	302 (71.1)	0 (0)
4 months	92 (51.4)	117 (54.2)	73 (63.5)	191 (57.5)	35 (37.6)	226 (53.2)	0 (0)
6 months	51 (28.5)	72 (33.3)	50 (43.5)	122 (36.7)	26 (28.0)	148 (34.8)	0 (0)
9 months	31 (17.3)	48 (22.2)	34 (29.6)	82 (24.7)	21 (22.6)	103 (24.2)	0 (0)
12 months	22 (12.3)	35 (16.2)	25 (21.7)	60 (18.1)	17 (18.3)	77 (18.1)	0 (0)
18 months	12 (6.7)	17 (7.9)	10 (8.7)	27 (8.1)	7 (7.5)	34 (8.0)	0 (0)

Source: ISS Table 1.5.1.1 and Table 1.5.1.2; ad hoc Table 1
AML = acute myeloid leukemia; BID = twice daily; R/R = relapsed/refractory; SD = standard deviation
Note: In Study 2102-HEM-101, one patient received 150 mg BID of olutasidenib with cytarabine and is included in the total column for that study and the overall column.
[a] Duration of exposure (weeks) = (date of last dose – date of first dose + 1)/7.

Table 42: Patients Treated with Different Planned Total Daily Doses of Olutasidenib by Safety Population

Planned total daily dose	Hematologic Malignancies (Study 2102-HEM-101)				Solid Tumor (Study 2102-ONC-102) Total (N=93*)	Overall (N=425)	HV (N=87)
	R/R AML Olutasidenib Single Agent (N=179)	Olutasidenib Single Agent (N=216)	Olutasidenib + Azacitidine (N=115)	Total (N=332)			
100 mg QD	1 (1)	3 (1)	0	3 (1)	0	3 (1)	0
150 mg QD	5 (3)	8 (4)	7 (6)	15 (5)	0	15 (4)	87 (100)
300 mg QD	3 (2)	4 (2)	0	4 (1)	0	4 (1)	0
150 mg BID	170 (95)	201 (93)	108 (94)	310 (93)	93 (100)	403 (95)	0

*6 patients received olutasidenib 150 mg BID in combination with azacitidine
Source: ISS ad hoc Table 2

Table 43: Extent of Exposure to Olutasidenib by Duration of Time (Safety Analysis Set, Phase 2 Cohort 1)

Number of patients with exposure for at least, n (%)	
1 day	153 (100)
2 months	115 (75)
4 months	80 (52)
6 months	42 (27)
9 months	28 (18)
12 months	18 (12)
18 months	10 (7)

Source: CSR HEM-101 Phase 2 Cohort 1 Listing 16.2.5.1. Data cutoff date: 18 Jun 2020.

The Applicant's Position:

A total of 512 patients, healthy volunteers, and subjects with hepatic impairment have been exposed to at least one dose of olutasidenib. 425 patients with hematologic malignancies and solid tumors were treated with at least one dose of olutasidenib, including 303 patients who received olutasidenib monotherapy, 121 patients who received olutasidenib in combination with azacitidine and 1 patient who received olutasidenib in combination with cytarabine. The median exposure duration for the total patient population (n=425) was 17.6 weeks (range: <1 to 200 weeks) with 148 (35%) patients having been exposed to olutasidenib for ≥ 6 months and 77 (18%) patients for ≥ 12 months. (Table 41).

As of the data cut-off, within Study 2102-HEM-101, 179 patients with R/R AML were treated with single agent olutasidenib with a median exposure of 17.9 weeks (range: <1 to 200 weeks) with 51 (28.5%) of patients having been exposed to olutasidenib for ≥ 6 months. In pivotal Phase 2 Cohort 1, as shown in Table 25, the median treatment duration was 142.0 days (range: 3 to 795 days). The mean (StdDev) cycles of treatment and doses received were 6.6 (6.03) cycles and 328.4 (330.84) doses, respectively. 43 patients (28%) were exposed for at least 6 months and 19 patients (12%) exposed for at least 1 year. In addition, 87 healthy volunteers and subjects with hepatic impairment were also exposed to olutasidenib. The overall exposure as of the data cut-off is adequate to support characterization of the olutasidenib safety profile and determine the benefit risk ratio for patients.

The FDA's Assessment:
FDA agrees with the Applicant's assessment. FDA performed an assessment of exposure of patients in Cohort 1 of study 2101-HEM-101 depicted in the Table 44 below:

Table 44: Pivotal Cohort (Cohort 1) Treatment Exposure Using Data from the 90-Day Safety Update

Treatment Duration (Months)	Phase 2 Cohort 1 (N=153)	Single Agent Olutasidenib* (N=216)
Mean (SD)	7.7 (8.6)	8.3 (9.9)
Median (Range)	4.7 (0-34)	4.7 (0-57)

0-3 months	54 (35)	81 (38)
3-6 months	47 (31)	58 (27)
6-9 months	14 (9)	16 (7)
9-12 months	6 (4)	10 (5)
>12 months	32 (21)	51 (24)

**Patients enrolled in study 2102-HEME-101 only*
Source: FDA Analysis

Please note that these numbers reflect the data from the 90-day safety update. For patients in Cohort 1, the median duration of treatment was 4.7 months. 52 patients (35%) received treatment for at least 6 months and 32 patients (21%) received treatment for at least 12 months. The median duration of treatment and percentage of patients receiving treatment for at least 6 months is similar to what was seen with ivosidenib in the R/R AML setting (Ivosidenib multi-discipline review/summary, 2018).

Relevant characteristics of the safety population:

Data:

Table 21 describes the demographic characteristics of the efficacy and safety populations in Phase 2 Cohort 1 and Table 45 below describes the demographic characteristics of the ISS populations and for the pooled healthy volunteers.

Table 45: Demographics by Study and Therapy

Demographic Parameter	2102-HEM-101 (n=332)			2102-ONC-102 (n=93)			Overall (n=425)	Healthy Volunteers (n=87)
	Olutasidenib Single Agent (n=216)	Olutasidenib + AZA (n=115)	Total (n=332)	Olutasidenib Single Agent (n=87)	Olutasidenib + AZA (n=6)	Total (n=93)		
Sex at Birth, n (%)								
Female	104 (48)	53 (46)	157 (47)	42 (48)	2 (33)	44 (47)	201 (47)	65 (75)
Male	112 (52)	62 (54)	175 (53)	45 (52)	4 (67)	49 (53)	224 (53)	22 (25)
Age at Time of Consent (years)								
Mean (StdDev)	69.0 (10.5)	66.3 (12.3)	68.1 (11.2)	53.5 (12.6)	42.0 (7.2)	52.7 (12.6)	64.7 (13.2)	43 (14)
Median	71	70	71	53	43	51	68	41
Min, Max	32, 90	28, 88	28, 90	23, 81	29, 49	23, 81	23, 90	20, 70
Age Categories (years)								
< 65	49 (23)	38 (33)	87 (26)	71 (82)	6 (100)	77 (83)	164 (39)	85 (98)
65 to < 75	98 (45)	45 (39)	143 (43)	12 (14)	0	12 (13)	155 (27)	2 (2)
≥ 75	69 (32)	32 (28)	102 (31)	4 (5)	0	4 (4)	106 (25)	0
Race, n (%)								
White	114 (53)	72 (63)	187 (56)	65 (75)	6 (100)	71 (76)	258 (61)	49 (56)
Not Reported[a]	68 (32)	31 (27)	99 (30)	15 (17)	0	15 (16)	114 (27)	1 (1)
Other	17 (8)	4 (4)	21 (6)	1 (1)	0	1 (1)	22 (5)	3 (3)
Asian	7 (3)	3 (3)	10 (3)	5 (6)	0	5 (6)	15 (4)	3 (3)
Black or African American	10 (5)	5 (4)	15 (5)	1 (1)	0	1 (1)	16 (4)	30 (35)
Ethnicity, n (%)								
Hispanic or Latino	14 (7)	7 (6)	21 (6)	6 (7)	1 (17)	7 (8)	28 (7)	18 (21)
Not Hispanic or Latino	112 (52)	76 (66)	188 (57)	62 (71)	5 (83)	67 (72)	255 (60)	69 (79)
Not Reported	90 (42)	32 (28)	123 (37)	19 (22)	0	19 (20)	142 (33)	0

Source: ISS Table 1.2.1.1 and ISS Ad hoc Table 3. Data cutoff date: 18 Jun 2020.
[a] Sites in the European Union did not report race or ethnicity.

The Applicant's Position:
The demographic profiles of the pivotal Phase 2 Cohort 1 safety (FAS/SAS) and efficacy (EE) analysis sets are similar. There was a balanced distribution of males (52%) and females (48%). Most patients (76%) were ≥ 65 years and median age across the 153 patients was 71.0 years (range: 32 to 89 years) which is representative of a population of patients with R/R AML.

The FDA's Assessment:
The demographics and baseline characteristics for study 2102-HEM-101 are presented in the table below:

Table 46: Demographics and Baseline Characteristics for Safety Populations of Study 2102-HEM-101

Demographic Parameter	2102-HEM-101 (N=332)			
	Phase 2, Cohort 1 (N=153)	Olutasidenib Single Agent (N=216)	Olutasidenib + Aza (N=115)	Total (N=332)
Sex at Birth, n (%)				
Female	74 (48)	104 (48)	53 (46)	157 (47)
Male	79 (52)	112 (52)	62 (54)	175 (53)
Age (years)				
Mean (SD)	68.7 (10.4)	69.0 (10.5)	66.3 (12.3)	68.1 (11.2)
Median	71	71	70	71
Min, Max	32,89	32, 90	28, 88	28, 90
Age Categories (years)				
<65	37 (24)	49 (23)	38 (33)	87 (26)
65-75	68 (44)	98 (45)	45 (39)	143 (43)
≥75	48 (31)	69 (32)	32 (28)	102 (31)
Race, n (%)				
White	71 (46)	114 (53)	72 (63)	187 (56)
Asian	5 (3)	7 (3)	3 (3)	10 (3)
Black	5 (3)	10 (5)	5 (4)	15 (5)
Other	16 (10)	17 (8)	4 (4)	21 (6)
Not Reported	56 (37)	68 (32)	31 (27)	99 (30)
Baseline CrCl				
≥90 mL/min	61 (40)	81 (38)	52 (45)	133 (40)
60 -89 mL/min	69 (45)	97 (45)	43 (37)	141 (42)
30-59 mL/min	23 (15)	36 (17)	20 (17)	56 (17)
≤30 mL/min	0	2 (0)	0	2 (0)

Source: FDA Analysis

The FDA agrees that the median age of patients enrolled on study 2102-HEM-101 was reflective of the AML population in general. However, all the patients had an ECOG status of 0-2 (over >80% had an ECOG of 0 or 1), most patients did not have renal dysfunction, and there was underrepresentation of minority patients (although a significant number of patients did not have their race reported). Thus, the patient population of study 2102-HEM-101 may not truly be representative of the general older or comorbid AML population in the United States.

Adequacy of the safety database:

The Applicant's Position:
The integrated safety analysis plan and safety database were discussed with the Agency at the 2020 ISS Type C meeting and 2021 pre-NDA meeting respectively. FDA input from both meetings was incorporated. In the 2018 Type C meeting, FDA communicated that with a minimum of 6 months of follow-up from the start of treatment for at least 115 patients at the proposed dose and schedule, safety data from approximately 200 patients total may be sufficient to support an NDA submission. These expectations were met as this application includes 153 patients in Phase 2 Cohort 1 treated with olutasidenib 150 mg BID with 123 having follow-up for at least 6 months. The application also includes safety data from a total of 512 subjects, 425 patients with AML, MDS, gliomas and other solid tumors. In addition, 148, 77 and 34 patients received olutasidenib for 6 months, 12 months, and 18 months, respectively.

The FDA's Assessment:
FDA agrees with the Applicant's assessment. Data is lacking, however, regarding long-term toxicities of olutasidenib, since the majority of patients with R/R AML have a short life expectancy. The demographics of the patients in the safety database (Table 46) are representative of typical patients with AML that participate on clinical trials.

9.1.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:
There is no available data regarding data integrity issues or submission quality.

The Applicant's Position:

No concerns have been identified in the quality and integrity of the submitted datasets and individual case narratives.

There were no major protocol deviations related to the COVID-19. The CSR for the pivotal cohort documents measures taken due to COVID-19:

- Patients were seen remotely via telehealth instead of in-clinic visits
- Safety laboratory analyses were performed at a local laboratory near the patient's home (laboratory normal ranges were provided as needed)
- Study diaries and treatment were shipped to the patients' home; shipping was done in accordance with site/country regulations
- Due to possible disruption of control measures at study sites as a result of the pandemic coronavirus disease 2019 (COVID-19), alternative secure methods for delivery of study drug directly to study patients may have been utilized for some patients. In all cases, if this occurred, existing regulatory requirements for maintaining study drug accountability were followed and documented.

There were not enough COVID-19 cases to warrant sensitivity analyses as outlined in the SAP.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

Categorization of Adverse Event

The Applicant's Position:

Adverse events and severe adverse events were defined according to ICH E2A guidelines. Treatment-emergent Adverse Events (AEs) are recorded from the time of first dose through 28 days after the last dose of study drug, and serious adverse events from the time of informed consent to 28 days after the last dose of study drug. AEs are coded using MedDRA version 19.1, with verbatim terms coded by System Organ Class (SOC) and Preferred Term (PT). AE causality was provided by the investigator and AE severity was graded by the investigator via the NCI CTCAE version 4.03. AEs were tabulated and summarized as incidences per patient. Sponsor coding conventions were applied during the creation of analysis datasets.

As of protocol version 6, adverse events potentially associated with liver injury have been identified as AESI and include all events of Grade 2 or higher elevations in ALT, AST, or total bilirubin in patients with normal LFTs at baseline and any hepatic adverse event, e.g., acute hepatitis, cholestatic hepatitis, cholestasis, or hepatic insufficiency. Procedures for reporting AESIs are described in the protocol.

The FDA's Assessment:
FDA agrees with the Applicant's assessment. Terms that referred directly to relapse, persistence

of disease, or progression of AML were excluded from FDA's analyses. TEAEs were summarized by maximum grade per patient.

FDA compared the verbatim adverse event term with the coded MedDRA PT for all adverse events reported on Study 2102-HEM-101 and did not identify any irregularities. FDA grouped some related PTs for all analyses. A listing of the grouped terms can be found in Section 20.5. SMQ analysis was also performed using MAED, an no additional safety signals were identified beyond those discussed below.

Routine Clinical Tests

The Applicant's Position:

All protocol-required laboratory assessments were conducted in accordance with the laboratory manual and the Schedule of Assessments outlined in Table 11.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

9.1.4 Safety Results

Deaths

Data:

Table 47: Deaths by Safety Pool

Population / Treatment	On or within 28 days of last dose of olutasidenib	> 28 days after last dose of olutasidenib
2102-HEM-101		
R/R AML Olutasidenib Single Agent (n=179)	52 (39)	37 (21)
Olutasidenib Single Agent (n=216)	58 (24)	41 (19)
Olutasidenib + azacitidine (n=115)	24 (21)	21 (18)
Total (n=332)	82 (25)	63 (19)
2102-ONC-102		
Olutasidenib Single Agent (n=87)	10 (12)	32 (27)
Olutasidenib + azacitidine (n=6)	0	0
Total (n=93)	10 (11)	32 (34)
Overall patients (n=425)	92 (22)	95 (22)
Healthy volunteers (N=87)	0	0

Source: ISS Ad hoc Table 4

As of 18 June 2020, 73 (48%) patients in Phase 2 Cohort 1 had died from any cause. Forty-five (29%) patients died on treatment defined as death that occurred after the start of olutasidenib through 28 days after the last dose of olutasidenib. A summary of TEAEs leading to on-treatment death reported in Phase 2 Cohort 1 is presented in Table 49.

Table 48: Safety Analysis Set, Phase 2 Cohort 1 – Deaths

Category	Olutasidenib 150 mg BID (N=153) n (%)
Total deaths	73 (48%)
30-day mortality	13 (18)
60-day mortality	24 (33)
On-treatment deaths	45 (29)
Adverse reaction	1 (1)
Direct effect of active AML	41 (91)
Intercurrent event	3 (5)

Source: Source: CSR HEM-101 Phase 2 Cohort 1 Table 14.3.2.2. Data cutoff date: 18 Jun 2020; adhocdd

The majority of on-treatment deaths were related to progression of AML or its complications. Treatment-emergent AEs leading to death that occurred in more than one patient were disease progression (14%), pneumonia (2%), and cerebral hemorrhage, death not otherwise specified (NOS), respiratory failure, and sepsis (1% each).

Table 49: Treatment-Emergent Adverse Events Leading to Death by MedDRA System Organ Class and Preferred Term (Safety Analysis Set, Phase 2 Cohort 1)

System Organ Class Preferred Term	Olutasidenib 150 mg BID (N=153) n (%)
Patients with any TEAEs leading to death	***45* (29)**
General disorders and administration site conditions	**23 (15)**
Disease progression	21 (14)
Death[a]	2 (1)
Multiple organ dysfunction syndrome	1 (1)
Infections and infestations	**7 (5)**
Pneumonia	3 (2)
Sepsis	2 (1)
Pneumonia fungal	1 (1)
Septic shock	1 (1)
Respiratory, thoracic, and mediastinal disorders	**5 (3)**
Respiratory failure	2 (1)
Acute respiratory distress syndrome	1 (1)
Differentiation syndrome[b]	1 (1)
Pleural effusion	1 (1)

System Organ Class Preferred Term	Olutasidenib 150 mg BID (N=153) n (%)
Nervous system disorders	**3 (2)**
Cerebral haemorrhage	2 (1)
Haemorrhage intracranial	1 (1)
Cardiac disorders	**2 (1)**
Atrioventricular block	1 (1)
Cardiac failure congestive	1 (1)
Blood and lymphatic system disorders	**1 (1)**
Febrile neutropenia	1 (1)
Gastrointestinal disorders	**1 (1)**
Gastrointestinal haemorrhage	1 (1)
Injury, poisoning, and procedural complications	**1 (1)**
Subdural haematoma	1 (1)
Renal and urinary disorders	**1 (1)**
Acute kidney injury	1 (1)
Vascular disorders	**1 (1)**
Aortic stenosis	1 (1)

Source: CSR HEM-101 Phase 2 Cohort 1 Table 14.3.1.10b. Data cutoff date: 18 Jun 2020.
BID = twice daily; MedDRA = Medical Dictionary of Regulatory Activities; PT = preferred term; TEAE = treatment-emergent adverse event
[a] Verbatim term: Death (unknown cause); narratives for these are provided in Module 5.3.5.1.
[a] Acute promyelocytic leukaemia differentiation syndrome is the MedDRA, version 19.1 PT.

Two fatal TEAEs were assessed as treatment related by the Investigator: one event of disease progression and one event of DS.

The Applicant's Position:
R/R AML is a high acuity disease with a high fatality rate and on-treatment deaths were expected in this study population. TEAEs leading to on-treatment death were reported in 45 (29%) of 153 patients treated with olutasidenib in Phase 2 Cohort 1, the majority of which were related to progression of AML or its complications. TEAEs leading to death in more than one patient were disease progression (21 patients, 14%), pneumonia (3 patients, 2%), and cerebral hemorrhage death NOS, respiratory failure, and sepsis (2 patients each, 1%).

The FDA's Assessment:
In general, the FDA agrees with the Applicant's attribution of deaths. For the purposes of this review, the FDA focused on the evaluation of deaths in patients with R/R AML in Cohort 1. In the 90-day safety update, there were 101 total deaths, but the number of on-treatment deaths remained the same at 45. The following table lists the most frequent causes of on-treatment deaths in the pivotal cohort:

Table 50: On Treatment Deaths due to TEAEs in ≥2 Patients at Time of 90-Day Safety Update

Preferred Term	Phase 2 Cohort 1 Olutasidenib 150mg BID (N=153)
Patients with Any TEAEs Leading to Death	45 (29)
Disease Progression	27 (60)
Intracranial Hemorrhage*	5 (3)
Death NOS	2 (1)
Cardiac Disorder	2 (1)
Differentiation Syndrome	2 (1)

Grouped Term (Please see Section 20.5)
Source: FDA Analysis

FDA noted an error in the Applicant's calculation of 30-day and 60-day mortality in Table 48 above. There were 13/153 (8%), not 18%, deaths in the first 30 days and 24/153 (16%), not 33%, deaths in the first 60 days. The corrected incidences are included in the Table below, which reflects deaths at the time of the 90-day safety update. These early mortality rates are comparable to those seen with the currently approved IDH1-inhibitor ivosidenib (Ivosidenib multi-discipline review/summary, 2018).

Table 51: Phase 2, Cohort 1 - Deaths at Time of 90-Day Safety Update

Category	Olutasidenib 150mg BID (N=153) N (%)
Total Deaths	101 (66)
30-day Mortality	13 (8)
60-day Mortality	24 (16)
On-treatment Deaths*	**45 (29)**
Disease Progression	27 (60)
Complication of AML	10 (22)
Death NOS	2 (4)
Intracranial Hemorrhage	2 (4)
Cardiac Disorder	2 (4)
Adverse Reaction	2 (4)

Deaths on or within 28 days of last olutasidenib dose
Source: FDA Analysis

The dataset provided by the sponsor identified disease progression as cause of death of 21 of the 45 on-treatment deaths (47%). However, they reported complications of AML as the underlying cause of death in 40 (89%) of patients.

FDA reviewed individual patient narratives for on-treatment deaths and deaths due to disease progression from Cohort 1. The narratives were well-written and easy to follow. The FDA considered the root cause of death to be the underlying AML when supported by stable or worsening of disease in the marrow or peripheral blood by count or flow cytometry, imaging report, or description of other objective evidence. The FDA adjudicated 27 of the on-treatment deaths were due to AML disease progression and 10 deaths were due to complications from AML in patients from Cohort 1. There were two fatal treatment-emergent adverse reactions of differentiation syndrome, one of which was acknowledged by the Applicant above. FDA adjudicated a second death being due to differentiation syndrome. The patient was a 68-year old man that started treatment with olutasidenib on (b) (6). On (b) (6), he experienced Grade 2 differentiation syndrome and passed away the same day from respiratory failure. As data is limited for this patient, the FDA assesses his death to be due to complications from differentiation syndrome. The two deaths NOS occurred in an 83-year old woman and a 54-year old man, respectively. Both patients passed away during the night and were found by family members the following morning. The 54-year old patient had recently experienced disease progression on day 127 (was subsequently taken off treatment) and passed away on day 133. It is not conclusive that he died from disease progression, however, the FDA considers his death an intercurrent event given his recent disease progression.

Please note, that the two deaths due to intracranial hemorrhage were due to an undiagnosed brain aneurysm that ruptured and a traumatic fall that led to grade 5 subdural hematoma (intercurrent event). The deaths due to cardiac disorders were due to preexisting congestive heart failure and severe aortic stenosis that may have been exacerbated by the patient's underlying AML. Thus, both of these deaths are considered intercurrent events.

Serious Adverse Events

Data:

Table 52 presents serious TEAEs reported in ≥ 5% of patients in Phase 2 Cohort 1. Serious TEAEs were reported in 102 (67%) patients. The most commonly reported SAEs (≥ 5% of patients) were disease progression (23 patients, 15%), febrile neutropenia (22 patients, 14%), pneumonia (13 patients, 8%), and differentiation syndrome (13 patients, 8%).

A total of 32 (21%) patients had serious TEAEs reported that were considered related to olutasidenib by the Investigator. Treatment-related serious TEAEs reported in two or more patients included DS (13 patients, 8%), hepatic enzyme increased (4 patients, 3%), and WBC count increased (3 patients, 2%).

Table 50: Serious Adverse Events Reported in ≥ 5% of Patients by MedDRA Preferred Term (Safety Analysis Set, Phase 2 Cohort 1)

Preferred Term	Phase 2 Cohort 1 Olutasidenib 150 mg BID (N = 153) n (%)
Patients with Any Serious TEAEs	102 (67)
Disease progression	23 (15)
Febrile neutropenia	22 (14)
Pneumonia	13 (8)
Differentiation syndrome[a]	13 (8)

Source: Table 14.3.1.6b Data cutoff date: 18 June 2020
Abbreviations: BID = twice daily; MedDRA = Medical Dictionary of Regulatory Activities; TEAE = treatment-emergent adverse event.
Note: Adverse events are coded using the MedDRA dictionary, Version 19.1. A TEAE is an AE that emerges during treatment, having been absent pretreatment, or worsens relative to the pretreatment state.
Acute promyelocytic leukaemia differentiation syndrome is the MedDRA Version. 19.1 preferred term.

Across the 2102-HEM-101 and 2102-ONC-102 studies, SAEs were reported in 260 (61%) of the 425 patients, including 222 (67%) of 332 patients with hematologic malignancies and 38 (41%) of 93 patients with solid tumors. The most common types of SAEs were infections reported in 106 (25%) of all 425 patients nearly all of which were reported among patients with hematologic malignancies (104 patients, 31%) compared to patients with solid tumors (2 patients, 2%).

Disease progression was the most common SAE overall and in both study populations, reported in 63 (15%) of the 425 patients, including 43 (13%) of 332 patients with hematologic malignancies and 20 (22%) of 93 patients with solid tumors. Other SAEs reported in > 5% of the overall population were febrile neutropenia, pneumonia, and DS; these events were reported only among patients with hematologic malignancies with incidence in this group of 16%, 10%, and 7%, respectively.

No notable differences in the incidence of common SAEs were observed among patients with hematologic malignancies who received single agent and combination treatment with olutasidenib, either the overall rate (64% and 71%, respectively) or across individual preferred terms.

There were no SAEs reported in healthy volunteers.

The Applicant's Position:
R/R AML is a serious, life threatening disease and the incidence of SAEs (67%) is expected in this study population. The most commonly reported SAEs (≥ 5% of patients) were disease progression (23 patients, 15%), febrile neutropenia (22 patients, 14%), pneumonia (13 patients, 8%), and differentiation syndrome (13 patients, 8%). Differentiation syndrome is potentially life-threatening condition and known class effect of IDH inhibitors requiring early recognition and intervention often requiring a hospitalized setting. The other most frequently reported SAEs,

disease progression, febrile neutropenia, and pneumonia, are considered to be related to the underlying disease.

The FDA's Assessment:
FDA performed an independent assessment of SAEs in Study 2102-HEM-101.

Table 51: List of Common SAEs (≥5%), Phase 2, Cohort 1 and Single-Agent Olutasidenib at Time of 90-Day Safety Update

Grouped Term	Phase 2 Cohort 1 Olutasidenib 150mg BID (N=153)	Single Agent Olutasidentib (N=216)
Febrile Neutropenia*	26 (17)	37 (17)
Pneumonia*	19 (12)	24 (11)
Sepsis*	15 (10)	19 (9)
Differentiation Syndrome	14 (9)	18 (8)
Transaminitis*	9 (6)	11 (5)
Intracranial Hemorrhage*	7 (5)	10 (5)
Leukocytosis	6 (4)	13 (6)

Grouped Term (Please see Appendix 20.5)
Source: FDA Analysis

In general, the FDA agrees with the Applicant's assessment of the number of SAEs. FDA has calculated higher rates of febrile neutropenia and pneumonia due to using grouped terms and FDA's evaluation based on the 90-day safety update. In addition, the FDA noted higher rates of sepsis, transaminitis, and intracranial hemorrhage when using grouped terms. As febrile neutropenia, pneumonia and sepsis are all expected complications of AML, and olutasidenib has not been shown to be myelosuppressive (see laboratory data below), they will not be included in the USPI. On review of the cases of intracranial hemorrhage, the patients were thrombocytopenic due to their disease or had an undiagnosed ruptured aneurysm and were not the result of treatment with olutasidenib. Thus, intracranial hemorrhage will not be added to the USPI. Therefore, only differentiation syndrome and transaminitis were considered to be SAEs as a result of treatment with olutasidenib and have been added to the USPI.

Overall, in study 2102-HEM-101, the most common SAE reported was infections in 151/332 patients (45%). Of note, there were no significant differences in SAEs between patients that received single-agent olutasidenib or combination therapy with azacitidine.

Reviewer Comments: The most common SAEs reflect common complications for patients with AML, with the exception of differentiation syndrome, leukocytosis, and hepatotoxicity. Because

this was a single-arm study, these three SAEs are presumed to be at least possibly related to treatment with olutasidenib.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

Adverse events leading to discontinuation of study treatment were reported in 45 (29%) patients in Phase 2 Cohort 1, the most common of which included disease progression in 20 (13%) patients, and pneumonia, febrile neutropenia, and differentiation syndrome in 3 (2%) patients each. All other events leading to discontinuation of study treatment were reported in 1 or 2 patient each (Table 54). Most TEAEs leading to treatment discontinuation were assessed as not related to olutasidenib. Treatment-related TEAEs resulting in discontinuation of olutasidenib occurring in more than one patient included differentiation syndrome (3 patients, 2%), LFT abnormal (2 patients, 1%), and LFT increased (2 patients, 1%). Bone marrow failure, disease progression, biliary tract disorder, cholangitis, hepatic enzyme increased, WBC count increased, and tumor lysis syndrome each led to treatment discontinuation in one patient.

Table 52: Adverse Events Leading to Olutasidenib Treatment Discontinuation by MedDRA Preferred Term (Safety Analysis Set, Phase 2 Cohort 1)

Preferred Term	Phase 2 Cohort 1 Olutasidenib 150 mg BID (N = 153) n (%)
Patients with Any TEAEs Leading to Discontinuation of Study Treatment	45 (29)
Disease progression	20 (13)
Pneumonia	3 (2)
Febrile neutropenia	3 (2)
Differentiation syndrome[a]	3 (2)
Haemorrhage intracranial	2 (1)
Liver function test abnormal	2 (1)
Liver function test increased	2 (1)
Respiratory failure	2 (1)
Bone marrow failure	1 (1)
Atrioventricular block	1 (1)
Death	1 (1)
Multiple organ dysfunction syndrome	1 (1)
Biliary tract disorder	1 (1)
Cholangitis	1 (1)
Hepatic enzyme increased	1 (1)
Lipase increased	1 (1)
Neutrophil count decreased[b]	1 (1)
Red blood cell count decreased[c]	1 (1)
White blood cell count increased[d]	1 (1)

Preferred Term	Phase 2 Cohort 1 Olutasidenib 150 mg BID (N = 153) n (%)
Tumour lysis syndrome	1 (1)
Seizure	1 (1)
Delirium	1 (1)

Source: Table 14.3.1.8b Data cutoff date: 18 June 2020
Abbreviations: BID = twice daily; MedDRA = Medical Dictionary of Regulatory Activities; TEAE = treatment-emergent adverse event.
Note: Adverse events are coded using the MedDRA dictionary, Version 19.1. A TEAE is an AE that emerges during treatment, having been absent pretreatment, or worsens relative to the pretreatment state.
Acute promyelocytic leukaemia differentiation syndrome is the MedDRA Version. 19.1 preferred term.
[a] Includes preferred terms of neutrophil count decreased and neutropenia.
[b] Includes preferred terms of red blood cell count decreased and anemia.
[c] Includes preferred terms of white blood cell count increased and leukocytosis.

The Applicant's Position:
Olutasidenib was well-tolerated in R/R AML treated in pivotal Phase 2 Cohort 1 with an AE profile which was manageable through dose modifications and supportive care. The majority of patients who experienced AEs leading to treatment discontinuation had AEs which were assessed as not related to olutasidenib and included disease progression (13%), pneumonia and febrile neutropenia (2% each). Of the 21 patients with AEs of Differentiation syndrome (DS), only 3 patients discontinued treatment, indicating that DS is manageable with early recognition and appropriate medical management.

The FDA's Assessment:
The FDA analysis of TEAEs leading to treatment discontinuation in Cohort 1 are depicted in the table below:

Table 53: Adverse Events Leading to Olutasidenib Treatment Discontinuation by Preferred Term (Safety Analysis Set, Phase 2 Cohort 1) >2 Patients

Preferred Term	Phase 2 Cohort 1 Olutasidenib 150mg BID (N=153)
Patients with Any TEAEs Leading to Discontinuation	28 (18)
Transaminitis*	5 (3)
Differentiation Syndrome	5 (3)
Febrile Neutropenia*	3 (2)
Pneumonia*	3 (2)
Intracranial Hemorrhage*	2 (1)
Gallbladder Disorders*	2 (1)

Grouped Term (Please see Appendix 20.5)

Source: FDA Analysis

Overall, there were 28 patients that had a TEAE that led to treatment discontinuation. Twelve patients (8%) had an adverse reaction (AR) leading to olutasidenib discontinuation, with the most common being transaminitis, differentiation syndrome, and gallbladder disorders. Febrile neutropenia, infections, and bleeding complications, are frequent adverse events seen in patients with AML and are considered unrelated to olutasidenib given lack of evidence that olutasidenib is myelosuppressive. Hepatobiliary events are a unique toxicity seen with olutasidenib (please see section 8.2.5.1 for further analysis of hepatic effects with olutasidenib) and not necessarily complications seen in patients with AML. Likewise, differentiation syndrome is an established complication of IDH inhibitors. Thus, these ARs have been added to the USPI.

Dose Interruption/Reduction Due to Adverse Effects

Data:
Dose Reduction

Treatment-emergent AEs leading to dose reduction were reported in 20 (13%) patients in Phase 2 Cohort 1 (Table 56). The TEAEs leading to dose reduction in more than one patient were ALT increased (3 patients, 2%), AST increased (2 patients, 1%), asthenia (2 patients, 1%), DS (2 patients, 1%), and GGT increased (2 patients, 1%). All other events leading to dose reduction occurred in only one patient each (Table 56).

Treatment-related TEAEs resulting in a dose reduction in more than one patient included ALT increased (3 patients, 2%), asthenia (2 patients, 1%), AST increased (2 patients, 1%), and GGT increased (2 patients, 1%). All other treatment-related TEAEs resulting in a dose reduction were in one patient each.

Table 54: Adverse Events Leading to Olutasidenib Dose Reduction by MedDRA Preferred Term in >1 Patient (Safety Analysis Set, Phase 2 Cohort 1)

Preferred Term	Phase 2 Cohort 1 Olutasidenib 150 mg BID (N = 153) n (%)
Patients with Any TEAEs Leading to Olutasidenib Dose Reduction	20 (13)
Alanine aminotransferase increased	3 (2)
Aspartate aminotransferase increased	2 (1)
Asthenia	2 (1)
Differentiation syndrome[a]	2 (1)
Gamma-glutamyltransferase increased	2 (1)

Source: Table 14.3.1.13b Data cutoff date: 18 June 2020
Abbreviations: BID = twice daily; MedDRA = Medical Dictionary of Regulatory Activities; TEAE = treatment-emergent adverse event.

Note: Adverse events are coded using the MedDRA dictionary, Version 19.1. A TEAE is an AE that emerges during treatment, having been absent pretreatment, or worsens relative to the pretreatment state.
Acute promyelocytic leukaemia differentiation syndrome is the MedDRA Version. 19.1 preferred term.
[a] Includes preferred terms of neutrophil count decreased and neutropenia.

Dose Hold

Table 57 presents the TEAEs that led to dose hold in 2% or more of patients in the Phase 2 Cohort 1 SAS.

Table 55: Adverse Events Leading to Olutasidenib Dose Hold in ≥ 2% of Patients Overall by MedDRA Preferred Term (Safety Analysis Set, Phase 2 Cohort 1)

Preferred Term	Phase 2 Cohort 1 Olutasidenib 150 mg BID (N = 153) n (%)
Patients with Any TEAEs Leading to a Dose Hold	71 (46)
Febrile neutropenia	7 (5)
Alanine aminotransferase increased	6 (4)
Gamma-glutamyltransferase increased	5 (3)
Hepatic enzyme increased	5 (3)
White blood cell count increased[a]	5 (3)
Neutrophil count decreased[b]	5 (3)
Aspartate aminotransferase increased	4 (3)
Lipase increased	3 (2)
Pyrexia	3 (2)
Disease progression	3 (2)
Vomiting	3 (2)

Source: Table 14.3.1.15b Data cutoff date: 18 June 2020
Abbreviations: BID = twice daily; MedDRA = Medical Dictionary of Regulatory Activities; TEAE = treatment-emergent adverse event.
Note: Adverse events are coded using the MedDRA dictionary, Version 19.1. A TEAE is an AE that emerges during treatment, having been absent pretreatment, or worsens relative to the pretreatment state.
Includes preferred terms of white blood cell count increased and leukocytosis.
[a] Includes preferred terms of neutrophil count decreased and neutropenia.

The Applicant's Position:
Guidance for dose hold and dose reduction was provided in the protocol. Febrile neutropenia was the most common AE leading to dose hold but was assessed as treatment related in only 1 patient. AEs leading to dose reduction were less frequent. Dose hold and reduction were important for managing hepatic effects AESIs and minimizing treatment discontinuations due to these AEs as further described in Section 8.2.5.1.

The FDA's Assessment:
FDA performed an analysis of TEAEs leading to treatment reduction and interruption using data

from the 90-day safety update. The TEAEs are summarized in the tables below:

Table 56: Adverse Events Leading to Olutasidenib Dose Reduction by Preferred Terms in ≥2 Patients (Safety Analysis Set, Phase 2 Cohort 1) 90-Day Safety Update

Grouped Term	Phase 2 Cohort 1 Olutasidenib 150mg BID (N=153)
Patients with Any TEAEs Leading to Dose Reduction	24 (16)
Transaminitis*	9 (6)
Differentiation Syndrome	2 (1)
Fatigue*	2 (1)

Source: FDA Analysis

Overall, 24/153 (16%) patients had a TEAE that led to dose reduction. However, of those twenty-four patients that had a dose reduction, seventeen (11%) were due to an adverse reaction. This included: transaminitis (9 patients), differentiation syndrome (2 patients), fatigue/asthenia (2 patients), rash (1 patient), decreased appetite (1 patient), vomiting (1 patient), and mucositis (1 patient). As mentioned earlier in this review, hepatobiliary adverse reactions are a unique toxicity and thus, has been added to the USPI. None of the other adverse reactions will be added to the USPI given the low incidences leading to a dose reduction.

Table 57: Adverse Events Leading to Olutasidenib Dose Hold in ≥ 2% of Patients Overall by Preferred Terms (Safety Analysis Set, Phase 2 Cohort 1) 90-Day Safety Update

Grouped Term	Phase 2 Cohort 1 Olutasidenib 150mg BID (N=153)
Patients with any TEAEs Leading to a Dose Hold	77 (50)
Transaminitis *	16 (10)
Differentiation Syndrome	11 (7)
Febrile Neutropenia	8 (5)
Gallbladder Disorders*	5 (3)
Leukocytosis	5 (3)
Neutropenia	5 (3)
Mucositis *	4 (3)
Lipase Increase	3 (2)
Pyrexia	3 (2)
Vomiting	3 (2)

**=Grouped Term*

Source: FDA Analysis

Approximately half the patients treated in the pivotal cohort needed a dose interruption (77 patients, 50%), with 49 patients having an adverse reaction (32%) leading to dose interruption. The most frequent adverse reactions that led to dose interruption were: transaminitis, differentiation syndrome, gallbladder disorders, leukocytosis and mucositis. For the purposes of labeling, only transaminitis and differentiation syndrome will be added to the label given the incidence is greater than 5%.

Significant Adverse Events

Data:

Table 58: Grade 3 or 4 Adverse Events Reported in ≥ 5% of Patients Overall by MedDRA System Organ Class and Preferred Term (Safety Analysis Set, Phase 2 Cohort 1)

System Organ Class Preferred Term	Olutasidenib 150 mg BID (N=153) n (%)
Patients with any Grade 3 or 4 TEAEs	***116 (76)***
Investigations	**67 (44)**
Red blood cell count decreased[a]	29 (19)
Platelet count decreased[a]	24 (16)
Neutrophil count decreased[a]	20 (13)
White blood cell count increased[a]	14 (9)
Infections and infestations	**46 (30)**
Pneumonia	12 (8)
Blood and lymphatic system disorders	**37 (24)**
Febrile neutropenia	31 (20)
Respiratory, thoracic, and mediastinal disorders	**25 (16)**
Differentiation syndrome[b]	12 (8)
Metabolism and nutrition disorders	**21 (14)**
Hypokalaemia	8 (5)
Vascular disorders	**10 (7)**
Hypertension	7 (5)

Source: CSR HEM-101 Phase 2 Cohort 1 Table 14.3.1.4b. Data cutoff date: 18 Jun 2020.

BID = twice daily; MedDRA = Medical Dictionary of Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event

[a] Includes PTs using sponsor coding conventions.

[b] Acute promyelocytic leukemia differentiation syndrome is the MedDRA, version 19.1 PT.

The Applicant's Position:
The most common Grade 3 or Grade 4 events were primarily related to myelosuppression and included febrile neutropenia (20%), decreased RBC count (19%), decreased platelet count (16%), and decreased neutrophil count (13%) which are expected in patients with R/R AML.

The FDA's Assessment:
FDA performed an independent assessment of Grade 3 or 4 AEs using data from the 90-day safety update.

Table 59: List of Grade 3 or 4 AEs in ≥5% of Patients by MedDRA System Organ Class (Phase 2, Cohort 1) 90-Day Safety Update

System Organ Class Preferred Term	Olutasidenib 150 mg BID (N=153) n (%)
Patients with any Grade 3 or 4 TEAEs	129 (84)
Investigations	
Red Blood Cell Decreased	31 (20)
Platelet Count Decreased	25 (16)
Neutrophil Count Decreased	20 (13)
Transaminitis*	18 (12)
White Blood Cell Count Increased	14 (9)
Infections and Infestations	
Pneumonia*	15 (10)
Infection*	15 (10)
Sepsis*	12 (8)
Blood and Lymphatic Disorders	
Febrile Neutropenia*	33 (22)
Differentiation Syndrome	13 (9)
Metabolism and Nutrition Disorders	
Hypokalemia	9 (6)
Vascular Disorders	
Hypertension	7 (5)

Grouped Term
Source: FDA Analysis

Based on the 90-day safety update, the most frequent causes of Grade 3 or 4 TEAEs remained relatively consistent. In general, the most common causes of Grade 3 or 4 AEs reflect common consequences of patients with R/R AML. However, transaminitis, leukocytosis, differentiation syndrome, and hypertension were the most common AEs at least be possibly related to treatment with olutasidenib. Hypokalemia also occurred but was better captured in the laboratory data (see below).

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Table 60: Common Adverse Events (≥ 10%) by MedDRA Preferred Term (Safety Analysis Set, Phase 2 Cohort 1)

Preferred Term	Olutasidenib 150 mg BID (N=153)
Patients with any TEAEs	***153 (100)***
Nausea	58 (38)
Constipation	38 (25)
White blood cell count increased[a]	38 (25)
Red blood cell count decreased[a]	37 (24)
Pyrexia	35 (23)
Febrile neutropenia	33 (22)
Fatigue	32 (21)
Diarrhoea	29 (19)
Platelet count decreased[a]	28 (18)
Dyspnoea	28 (18)
Hypokalaemia	28 (18)
Vomiting	26 (17)
Decreased appetite	24 (16)
Asthenia	23 (15)
Disease progression	23 (15)
Differentiation syndrome[b]	21 (14)
Cough	21 (14)
Neutrophil count decreased[a]	20 (13)
Oedema peripheral	20 (13)
Pneumonia	19 (12)
Epistaxis	17 (11)
Back pain	16 (10)
Hypertension	16 (10)
Alanine aminotransferase increased	15 (10)
Headache	15 (10)

Source: CSR HEM-101 Phase 2 Cohort 1 Table 14.3.1.18b. Data cutoff date: 18 Jun 2020.

AE = adverse event; BID = twice daily; MedDRA = Medical Dictionary of Regulatory Activities; PT = preferred term; TEAE = treatment-emergent adverse event

[b] Includes PTs using sponsor coding conventions

[c] Acute promyelocytic leukemia differentiation syndrome is the MedDRA, version 19.1 PT.

Table 61: Common Adverse Events (≥ 10%) by Preferred Term by Study, Dose and Therapy (ISS)

Preferred Term n (%)	Hematologic Malignancies (Study 2102-HEM-101)							Solid Tumor (Study 2102-ONC-102 (n=93)	Pooled HV (n=87)
	Olutasidenib Single Agent (n=216)					Olutasidenib + Azacitidine (n=115)	Overall (n=332)		
	100 mg QD (n=3)	150 mg QD (n=8)	300 mg QD (n=4)	150 mg BID (n=201)	Total (n=216)				
Patients with at least one TEAE	3 (100)	8 (100)	4 (100)	199 (99)	214 (99)	114 (99)	329 (99)	90 (97)	28 (32)
Febrile neutropenia	2 (67)	2 (25)	0	41 (20)	45 (21)	24 (21)	69 (21)	0	0
Constipation	1 (33)	2 (25)	0	47 (23)	50 (23)	54 (47)	104 (31)	29 (31)	2 (2)
Diarrhea	1 (33)	1 (13)	0	36 (18)	38 (18)	39 (34)	78 (24)	20 (22)	1 (1)
Nausea	1 (33)	5 (63)	2 (50)	73 (36)	81 (38)	63 (55)	145 (44)	52 (56)	2 (2)
Vomiting	1 (33)	4 (50)	0	32 (16)	37 (17)	38 (33)	75 (23)	17 (18)	0
Asthenia	0	1 (13)	0	26 (13)	27 (13)	22 (19)	49 (15)	13 (14)	0
Fatigue	1	5 (63)	1 (25)	45 (22)	52 (24)	35 (30)	87 (26)	34 (37)	1 (1)
Edema peripheral	0	1 (13)	0	27 (13)	28 (13)	19 (17)	48 (15)	4 (4)	0
Pyrexia	1 (33)	4 (50)	2 (50)	42 (21)	49 (23)	24 (21)	73 (22)	3 (3)	0
Pneumonia	1 (33)	3 (38)	1 (25)	23 (11)	28 (13)	18 (16)	46 (14)	0	0
Neutrophil count decreased	0	3 (38)	0	26 (13)	29 (13)	34 (30)	64 (19)	8 (9)	0
Platelet count decreased	1 (33)	2 (25)	2 (50)	37 (18)	42 (19)	43 (37)	85 (26)	11 (12)	0
Red blood cell count decreased	0	1 (13)	1 (25)	47 (23)	49 (23)	28 (24)	77 (23)	12 (13)	0
White blood cell count increased	0	4 (50)	0	43 (21)	47 (22)	26 (23)	73 (22)	0	0
Alanine aminotransferase increased	0	0	0	21 (10)	21 (10)	10 (9)	32 (10)	36 (39)	0
Aspartate aminotransferase increased	0	1 (13)	0	19 (10)	20 (9)	8 (7)	29 (9)	33 (36)	0
Blood alkaline phosphatase increased	0	1 (13)	0	11 (6)	12 (6)	10 (9)	23 (7)	26 (28)	0
Decreased appetite	0	3 (38)	1 (25)	30 (15)	34 (16)	23 (20)	57 (17)	25 (27)	0

Hypokalemia	1 (33)	3 (38)	1 (25)	34 (17)	39 (18)	30 (26)	69 (21)	7 (8)	0
Back pain	0	0	1 (25)	22 (11)	23 (11)	10 (9)	33 (10)	3 (3)	3 (3)
Differentiation syndrome	0	0	1 (25)	26 (13)	27 (13)	12 (10)	39 (12)	0	0
Dizziness	1 (33)	2 (25)	1 (25)	15 (8)	19 (9)	18 (16)	37 (11)	9 (10)	5 (6)
Headache	1 (33)	3 (38)	1 (25)	21 (10)	26 (12)	26 (23)	52 (16)	14 (15)	4 (5)
Insomnia	2 (67)	0	0	18 (9)	20 (9)	13 (11)	33 (10)	11 (12)	2 (2)
Cough	0	2 (25)	0	30 (15)	32 (15)	27 (24)	59 (18)	14 (15)	1 (1)
Dyspnea	0	3 (38)	0	36 (18)	39 (18)	20 (17)	59 (18)	12 (13)	0
Epistaxis	1 (33)	1 (13)	1 (25)	20 (10)	23 (11)	14 (12)	37 (11)	3 (3)	0
Hypertension	0	2 (25)	0	20 (10)	22 (10)	19 (17)	41 (12)	10 (11)	0

Source: ISS Table 2.2.1.1; ISS Ad hoc Table 5; ISS Ad hoc Table 7

Table 62: Adverse Reactions Reported in ≥10% (Any Grade) or ≥5% (Grade ≥3) of Patients with Relapsed or Refractory AML

	Olutasidenib 150 mg BID (N=153)	
Body System Adverse Reaction	**All Grades n (%)**	**Grade ≥3 n (%)**
Gastrointestinal Disorders		
Nausea	58 (38)	0 (0)
Constipation	38 (25)	0 (0)
Diarrhea	29 (19)	2 (1)
Vomiting	26 (17)	1 (1)
Abdominal pain[1]	25 (16)	1 (1)
Stomatitis[2]	20 (13)	2 (1)
General Disorders and Administration Site Conditions		
Fatigue[3]	52 (34)	3 (2)
Edema[4]	23 (15)	3 (2)
Investigations		
White blood cell count increased	38 (25)	14 (9)
Platelet count decreased	28 (18)	24 (16)
Metabolism and Nutrition Disorders		
Decreased appetite	24 (16)	3 (2)
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal pain[5]	31 (20)	2 (1)
Nervous System Disorders		
Headache	15 (10)	0 (0)
Respiratory, Thoracic and Mediastinal Disorders		
Dyspnea[6]	31 (20)	6 (4)
Differentiation syndrome[7]	21 (14)	13 (8)
Cough	21 (14)	0 (0)
Skin and subcutaneous tissue disorders		
Rash[8]	18 (12)	1 (1)
Vascular Disorders		
Hypertension	16 (10)	7 (5)

[1] Abdominal pain grouped term includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness

[2] Stomatitis grouped term includes stomatitis, tongue ulceration, gingivitis ulcerative, mouth ulceration

[3] Fatigue grouped term includes asthenia and fatigue

[4] Edema grouped term includes face edema, generalized edema and peripheral edema

[5] Musculoskeletal pain grouped term includes back pain, bone pain, arthralgia, musculoskeletal chest pain, musculoskeletal pain, neck pain

[6] Dyspnea grouped term includes dyspnea, dyspnea exertional, respiratory distress

[7] Also referred to as acute promyelocytic leukemia differentiation syndrome

[8] Rash grouped term includes rash, rash erythematous, rash macular, rash maculo-papular, dermatitis exfoliative

The Applicant's Position:
Olutasidenib 150 mg BID showed a safety profile primarily reflecting symptoms or conditions frequently experienced by patients undergoing treatment for AML as well as manageable adverse reactions such as differentiation syndrome and hepatic effects. The adverse effects reported in Phase 2 Cohort 1 were predictable and readily recognized, which can be monitored and successfully managed by physicians through dose modifications and standard supportive therapy. The most common TEAEs, including treatment-related and severe events, were those that are frequently reported among patients with advanced hematologic malignancies. Common GI events (nausea, constipation) are known side effects of medications such as antimicrobial agents and pain medications, which are often prescribed to manage AML complications. Myelosuppression (decreased RBC and WBC count, febrile neutropenia) and associated constitutional symptoms (fatigue, pyrexia) are expected in this patient population. The observed AESIs of DS and hepatic effects in patients who received single agent olutasidenib in Phase 2 Cohort 1 were managed with dose holds and dose reductions, when needed. As with other IDH1 and IDH2 inhibitors, DS is a significant, potentially life threatening risk with olutasidenib treatment, for which early recognition and intervention with steroids and management of concomitant leukocytosis, if present, is warranted for optimal outcomes. Hepatic effects TEAEs, when reported, were mostly characterized by reversible, asymptomatic transaminase elevations and alkaline phosphatase elevations with or without elevations in total bilirubin initially observed at routine visits.

The FDA's Assessment:

The FDA performed an independent analysis of the most common AEs TEAEs reported in patients in study 2101-HEM-101. All patients in study 2102-HEM-101 experienced a TEAE. The most common TEAEs for patients Cohort 1 are summarized in Table 65 below:

Table 63: Most Common TEAEs (≥ 10%) in Phase 2 Cohort 1, 90 Day Safety Update

Preferred Term	Olutasidenib 150mg BID (N=153)
Patients with any TEAEs	**153 (100)**
Fatigue*	55 (36)
Nausea	58 (38)
Arthralgia*	43 (28)
Constipation	40 (26)
Red Blood Cell Count Decreased	40 (26)
Dyspnea*	37 (24)
Pyrexia	36 (24)
White Blood Cell Count Increased	36 (24)
Mucositis	35 (23)
Febrile Neutropenia	33 (22)

Diarrhea	30 (20)
Hypokalemia	30 (20)
Platelet Count Decreased	30 (20)
Transaminitis	31 (20)
Vomiting	26 (17)
Cough	24 (16)
Decreased Appetite	24 (16)
Differentiation Syndrome	22 (14)
Peripheral Edema	22 (14)
Pneumonia	20 (13)
Epistaxis	18 (12)
Headache	19 (12)
Hypertension	16 (10)

Grouped Term
Source: FDA Analysis

There were some TEAEs that were expected for patients with AML that are receiving treatment for their malignancy (e.g., RBC decreased, febrile neutropenia, platelet count decreased, pneumonia, and epistaxis). Fatigue, decreased appetite, GI toxicities and arthralgia were frequent and were also seen with ivosidenib, another IDH1 inhibitor, indicating that this may be a specific class effect of IDH1 inhibitors. Dyspnea, pyrexia, cough, and edema were also common and could be seen in association with DS. Of note, the incidence of DS of 14% was per investigators. See below for more information on FDA adjudication of DS. WBC increased (leukocytosis) is another TEAE that was frequently seen with olutasidenib but occurring at slightly lower rates than what was seen with ivosidenib in patients with R/R AML (TIBSOVO USPI). Of note, the laboratory AEs in the Table above (aside from leukocytosis) were conveyed with the common laboratory abnormalities in the label instead of with the adverse reaction data.

In addition, the FDA evaluated the most frequent TEAEs across different dose levels in study 2102-HEM-101.

Table 64: Selected TEAEs by Dose Level on Study 2102-HEM-101 90-Day Safety Update

Preferred Term	**Olutasidenib Single Agent (N=216)**				
	100mg QD (N=3)	**150mg QD (N=8)**	**300mg QD (N=4)**	**150mg BID (N=201)**	**Total (N=216)**
Patients with at least one TEAE	**3 (100)**	**8 (100)**	**4 (100)**	**201 (100)**	**216 (100)**
Febrile Neutropenia	2 (67)	2 (25)	0	41 (20)	45 (21)
Nausea	1 (33)	5 (63)	2 (50)	74 (37)	82 (38)
Constipation	1 (33)	2 (25)	0	49 (24)	52 (24)
Diarrhea	1 (33)	1 (13)	0	39 (19)	41 (19)

Differentiation Syndrome	0	0	1 (25)	29 (14)	30 (14)
Transaminitis*	0	2 (25)	0	42 (21)	44 (20)
Gallbladder Disorders*	0	0	0	19 (9)	19 (9)
Fatigue	1 (33)	5 (63)	1 (25)	51 (25)	58 (27)
Platelet Count Decreased	1 (33)	2 (25)	2 (50)	40 (20)	45 (21)
RBC Count Decreased	0	1 (13)	1 (25)	51 (25)	53 (25)

Grouped Term
Source: FDA Analysis

Reviewer Comments: Given the limited number of patients that received dosing other than 150mg BID, it's difficult to make definitive conclusions about safety across dosing cohorts. However, based on the limited data there does not appear to be increased toxicity with the 150mg BID dose compared to others.

The following table lists common adverse reactions seen in patients in Cohort 1.

Table 65: Adverse Reactions Reported in ≥10% (Any Grade) or ≥5% (Grade ≥3) of Patients in Cohort 1

	Olutasidenib 150mg BID (N=153)	
Gastrointestinal Disorders	**All Grades n (%)**	**Grades 3-4 n (%)**
Nausea	57 (38)	0 (0)
Constipation	39 (26)	0 (0)
Mucositis*	35 (23)	5 (3)
Diarrhea	31 (20)	2 (1)
Abdominal Pain*	28 (18)	1 (1)
Vomiting	25 (16)	1 (1)
General Disorders and Administration Site Conditions		
Fatigue/malaise*	55 (36)	2 (1)
Pyrexia	36 (24)	1 (1)
Edema*	27 (18)	4 (3)
Metabolism and Nutrition Disorders		
Decreased Appetite	25 (16)	3 (2)
Blood System and Lymphatic System Disorders		
Leukocytosis	38 (25)	14 (9)
Differentiation Syndrome	25 (16)	13 (8)
Musculoskeletal and Connective Tissue Disorders		

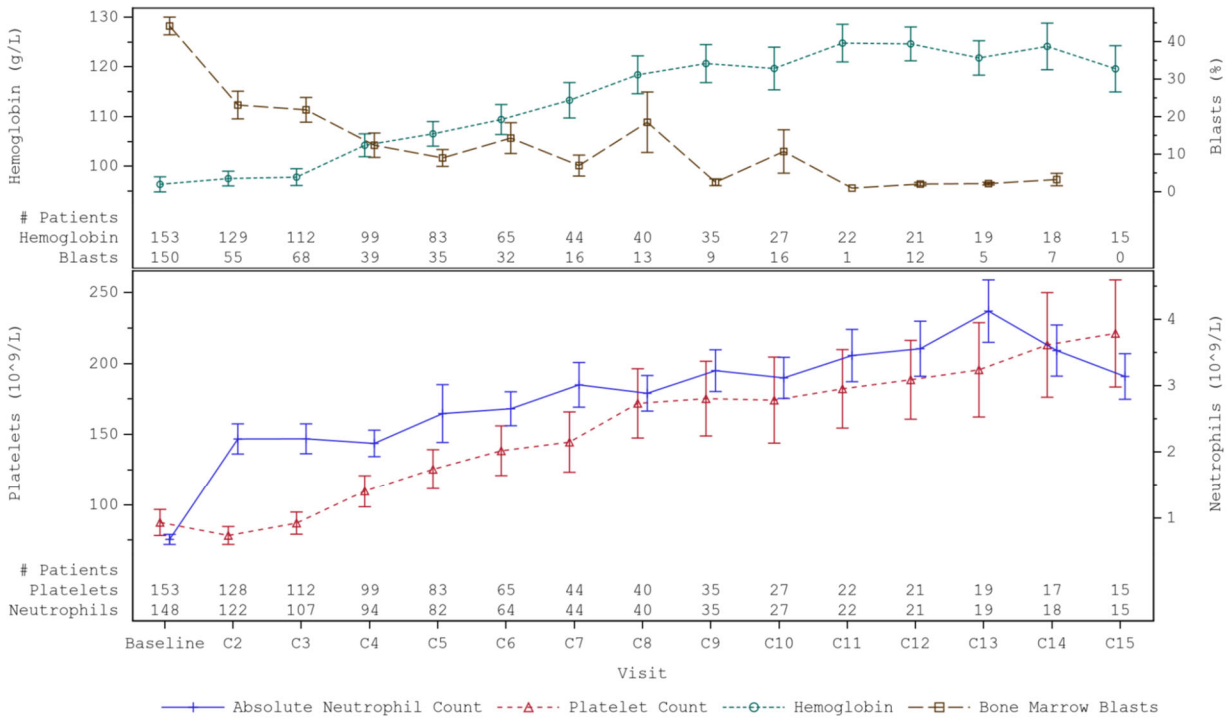
Arthralgia*	43 (28)	4 (3)
Respiratory, Thoracic, and Mediastinal Disorders		
Dyspnea*	37 (24)	8 (5)
Cough*	26 (17)	1 (1)
Nervous System Disorders		
Headache	19 (13)	0 (0)
Vascular Disorders		
Hypertension*	16 (10)	7 (5)
Skin and Subcutaneous Tissue Disorders		
Rash*	36 (24)	2 (1)
Investigations		
Transaminitis*	31 (20)	18 (12)

=Grouped Term
Source: FDA Analysis

Laboratory Findings

Data:

Figure 12: Mean (+/- SE) ANC, Platelet Count, Hemoglobin, and Bone Marrow Blasts: Full Analysis Set, Phase 2 Cohort 1



Source: CSR HEM-101 Phase 2 Cohort 1 Figure 14.2.7.3a. Data cutoff date: 18 Jun 2020.

Table 66: Summary of Shifts in Laboratory Parameters from Baseline to Worst CTCAE Grade (Safety Analysis Set, Phase 2 Cohort 1)

Laboratory abnormalities		Olutasidenib 150 mg BID (N=153) n (%)						
	Sample size	Baseline Grade				All Grade Shift	On-treatment shift to Grade 3/4	
		Grade 0/1	Grade 2	Grade 3	Grade 4		Grade 3	Grade 4
	Hematology							
Hemoglobin - decrease	152	61 (40)	64 (42)	27 (18)	0 (0)	85 (56)	60 (39)	0 (0)
Neutrophils – decrease	147	18 (12)	12 (8)	31 (21)	86 (59)	43 (29)	9 (6)	32 (22)
Platelets – decrease	150	56 (37)	21 (14)	36 (24)	37 (25)	91 (61)	17 (11)	54 (36)
WBC - increase	152	152 (100)	0 (0)	0 (0)	0 (0)	2 (1)	2 (1)	0 (0)
WBC – decrease	152	55 (36)	22 (14)	39 (26)	36 (24)	65 (43)	25 (16)	28 (18)
	Chemistry							
Creatinine	153	153 (100)	0 (0)	0 (0)	0 (0)	65 (42)	3 (2)	0 (0)
ALT increase	151	151 (100)	0 (0)	0 (0)	0 (0)	63 (42)	17 (11)	2 (1)
AST increase	151	151 (100)	0 (0)	0 (0)	0 (0)	65 (43)	10 (7)	2 (1)
Total bilirubin increase	151	150 (99)	1 (1)	0 (0)	0 (0)	42 (28)	4 (3)	0 (0)
ALP increase	150	148 (99)	2 (1)	0 (0)	0 (0)	60 (40)	9 (6)	0 (0)
Potassium decrease	151	149 (99)	0 (0)	2 (1)	0 (0)	65 (43)	8 (5)	5 (3)
Sodium decrease	151	150 (99)	0 (0)	1 (1)	0 (0)	61 (40)	10 (7)	1 (1)
Uric acid increase	150	149 (99)	0 (0)	0 (0)	1 (1)	36 (24)	0 (0)	5 (3)
Lipase increase	144	143 (99)	1 (1)	0 (0)	0 (0)	31 (22)	11 (8)	1 (1)

Source: CSR HEM-101 Phase 2 Cohort 1 Table 14.3.7.1b, Table 14.3.6.1b., Table 14.3.6.2b, Table A35. Data cutoff date: 18 Jun 2020.

The Applicant's Position:

The incidence of baseline Grade 3 and 4 hematological parameters and on treatment shifts to Grade 3 or 4 values is expected for the RR AML patient population evaluated in Phase 2 Cohort 1. The most common Grade 3 or 4 chemistry shifts occurred for ALT (19 [12%]), AST (12 [8%]). As of protocol version 6, on-treatment increases of Grade 2 or higher elevations in ALT, AST, or total bilirubin in patients were reported as AESIs which are further described in Section

8.2.5.1.

The FDA's Assessment:
The FDA performed an independent assessment of the most common laboratory abnormalities for patients enrolled in Cohort 1 depicted in the table below:

Table 67: Common Laboratory Abnormalities Phase 2 Cohort 1, 90-Day Safety Update

	Olutasidenib 150mg BID (N=153)	
Parameter	**All Grades (%)**	**Grades 3-4 (%)**
Platelets Decreased	62	47
Lymphocytes Decreased	62	38
Hemoglobin Decreased	57	41
Aspartate Aminotransferase Increase	47	10
Alanine aminotransferase increased	46	13
Potassium decreased	46	9
Sodium decreased	42	7
Alkaline Phosphatase Increased	42	7
Creatinine Increased	38	2
Neutrophils Decreased	30	29
Lymphocytes Increased	26	3
Bilirubin Increased	26	2
Uric Acid Increased	25	3
Lipase Increased	24	8

Source: FDA Analysis

Reviewer Comments: Hematological abnormalities are expected in patients with AML receiving treatment. Platelets dipped following the first cycle of treatment and improved during subsequent cycles. Although decreases in hemoglobin were seen in preclinical toxicology studies with olutasidenib, this did not appear to be seen clinically in the population overall. Preclinical toxicology studies showed increases in platelet counts, so it is unlikely that the initial dip in platelet counts was related to olutasidenib. In regards to hepatotoxicity, almost half the patients treated experienced AST, ALT elevations, and alkaline phosphatase increase, but most were Grades 1-2. Several factors can contribute to LFT abnormalities in patients with AML, but because this was a single-arm trial, attribution to olutasidenib cannot be excluded.

Vital Signs

Data:
All clinically significant abnormal findings associated with vital signs were to be reported as

TEAEs. The most common TEAEs (≥ 5% of patients) associated with vital signs abnormalities were pyrexia (35 patients, 23%), hypertension (16 patients, 10%), and hypotension (9 patients, 6%).

Table 68: Incidence of Abnormal Post-baseline Vital Signs

Parameter	Olutasidenib 150 mg BID (N=153) n (%)
SBP ≧160 mmHg	39 (26)
SBP <90 mmHg	9 (6)
DBP ≧100 mmHg	9 (6)
Heart Rate <50 bpm	3 (2)
Heart Rate >120 bpm	10 (7)
Temperature ≧38ºC	23 (15)

Source: CSR HEM-101 Phase 2 Cohort 1 Table A50. Data cutoff date: 18 Jun 2020.

The Applicant's Position:
Across the studies, there were no clinically meaningful trends from baseline or differences between treatment arms in patient weight, blood pressure (including diastolic and systolic values), heart rate, or body temperature. For the patients with TEAEs of hypertension, no action was taken with olutasidenib (e.g. dose reduction or discontinuation).

The FDA's Assessment:
The FDA agrees with the applicant's assessment. Pyrexia is a common AE seen in patients with AML. However, pyrexia may be associated with DS in patients treated with IDH inhibitors, and thus, should be included in the USPI. Sixteen patients (10%) experienced an AE of hypertension, with seven patients (5%) experiencing Grade 3-4 hypertension. As this is an unexpected AE, hypertension will be listed in the label for olutasidenib.

Electrocardiograms (ECGs)

Data:

The overall incidence of Investigator-reported TEAEs of ECG QT prolonged is summarized for Phase 2 Cohort 1 in Table 71. Treatment-emergent AEs of ECG QT prolonged were uncommon in the study, reported in 13 patients (8%) overall. Most events were Grade 1 or Grade 2 in severity that resolved without requiring modifications to olutasidenib dosing. No Grade 4 or Grade 5 events were reported; only one patient had a Grade 3 event that was assessed as unrelated to treatment.

No AEs of ECG QT prolonged led to olutasidenib dose reduction or discontinuation (CSR HEM-101 Phase 2 Cohort 1 Listing 16.2.7.1). Olutasidenib dose was held for two patients, one of whom had history of atrial flutter, atrial fibrillation, and had ongoing hypertension and obesity and presented with a Grade 3 event that was considered serious and unrelated to olutasidenib (Patient (b) (6)). Although dosing was held for this patient, olutasidenib treatment resumed and was ongoing as of the data cutoff date with no further events of QT prolongation.

Table 69: Summary of Electrocardiogram QT Prolonged as Reported by the Investigator (Phase 2 Cohort 1 Safety Analysis Set)

Electrocardiogram QT Prolonged	Olutasidenib 150 mg BID (N=153) n (%)
Any TEAE	13 (8)
Any Grade 3 TEAE	1 (1)
Any treatment-related TEAE	5 (3)
Any treatment-related Grade 3 or 4 TEAE	0
Any serious TEAEs	1 (1)
Any treatment-related serious TEAEs	0
Any TEAE leading to study drug discontinuation	0
Any TEAE leading to dose modifications	2 (1)
Any TEAE leading to dose reduction	0
Any treatment-related TEAE leading to dose reduction	0
Any TEAE leading to dose hold	2 (1)
Any treatment-related TEAE leading to dose hold	2 (1)
Any TEAE leading to death	0

Source: CSR HEM-101 Phase 2 Cohort 1 Table 14.3.1.2b, Table 14.3.1.3b, Table 14.3.1.4b, Table 14.3.1.5b, Table 14.3.1.6b, Table 14.3.1.8b, Table 14.3.1.9b, Table 14.3.1.10b, Table 14.3.1.11b, Table 14.3.1.12b, Table 14.3.1.13b, Table 14.3.1.14b, Table 14.3.1.15b, Table 14.3.1.16b, Table 14.3.1.20b. Data cutoff date: 18 Jun 2020.

BID = twice daily; TEAE = treatment-emergent adverse event

The FDA's Assessment:

The FDA generally agrees with the applicant's assessment of QTc prolongation. In the updated 90-day safety report, twelve (12) patients in Cohort 1 experienced an AE of QTc prolongation. One patient had a grade 3 QTc prolongation and two patients had their dose temporarily held due to QTc prolongation. There were no grade 4 or 5 QTc prolongations.

For patients receiving single-agent olutasidenib in study 2102-HEM-101, 13 patients had a

TEAE of QTc prolongation, with no additional cases of dose interruption, reduction, or withdrawal.

Table 70: TEAEs of Electrocardiogram QT Prolonged Study 2102-HEM-101, 90-Day Safety Update

Electrocardiogram QT Prolonged	Olutasidenib 150mg BID Phase 2, Cohort 1 (N=153)	Single-Agent Olutasidenib (N=216)
Any TEAE	12 (8)	13 (6)
Any Grade 3 or 4 TEAE	1 (1)	1 (1)
Serious TEAEs	1 (1)	1 (1)
Any TEAE leading to study drug discontinuation	0	0
Any TEAE leading to dose reduction	0	0
Any TEAE leading to dose interruption	2 (1)	2 (1)
Any TEAE leading to death	0	0

Source: FDA Analysis

Reviewer comments: Given the occurrence of QTc prolongation on the clinical trial at an incidence of 8%, this risk should be communicated in the USPI under the Table in Section 6. See also review of ECG data in the Section below.

QT

Data:

Shift Analysis of Maximum Post-Baseline QTcF Changes

Categorical analyses of ECG data showed six patients (4%) with shifts of QTcF to ≥ 500 msec and 10 patients (7%) with a change from baseline of > 60 msec (Table 73). Of these, only one patient (Patient (b) (6)) reported a TEAE of ECG QT prolonged.

Table 71: Categorical Analysis of Maximum Post-Baseline Absolute QTcF and Shift from Baseline QTcF (Safety Analysis Set, Phase 2 Cohort 1)

Baseline Value	Maximum Post-Baseline Value					
	≤ 450 msec n (%)	> 450 to ≤ 480 msec n (%)	> 480 to ≤ 500 msec n (%)	> 500 msec n (%)	> 30 to ≤ 60 msec CFB n (%)	> 60 msec CFB n (%)
≤ 450 msec	93 (61)	37 (24)	5 (3)	3 (2)	34 (22)	10 (7)
> 450 to ≤ 480 msec	0	5 (3)	5 (3)	1 (1)	4 (3)	0
> 480 to ≤ 500 msec	0	0	1 (1)	2 (1)	1 (1)	0
> 500 msec	0	0	0	0	0	0
Total	93 (61)	42 (28)	11 (7)	6 (4)	39 (26)	10 (7)

Source: CSR HEM-101 Phase 2 Cohort 1 Table 14.3.8.2b. Data cutoff date: 18 Jun 2020.

BID = twice daily; CFB = change from baseline; ECG = electrocardiogram; QTcF = heart rate-corrected QT interval using Fridericia's method

Note: Baseline for QTcF was defined as the average of the last three QTcF measurements taken prior to first dose of study treatment. Percentages are based on the number of patients in the cohort (N=152) who have both a baseline value and a post-baseline value. When selecting the visit with the maximum post-baseline value, the value for a given nominal timepoint was the average of the triplicate ECG parameter at that visit.

Holter Monitoring Substudy

A 24-hour Holter monitoring substudy was conducted in 33 single agent-treated patients (150 mg BID following a single dose at steady state). Electrocardiograms were collected digitally in triplicate on Day 1 of Cycle 1 and Cycle 2 at 45, 30, and 15 minutes predose, and 0.5, 1, 2, 4, 8, and 24 hours post dose. Electrocardiograms were sent for a treatment-blinded, high-resolution measurement of the cardiac intervals and morphological assessment by a central cardiologist blinded to the study treatment. A brief summary of the results is described below; the full analysis results of this substudy are presented in a separate Cardiac Safety Report.

Olutasidenib did not show effects on heart rate, AV conduction as measured by the PR interval, or cardiac depolarization as measured by the QRS duration. There were no new clinically relevant morphological changes demonstrating a signal of concern.

There also was no evidence of a large effect of olutasidenib (>20 msec) on cardiac repolarization as evidenced by the results of the primary analysis (concentration-QTc modeling) and secondary analyses (time matched and categorical outlier analyses).

Based on the concentration-QTc analysis (Table 74), the upper bound of the two-sided 90% confidence interval of the predicted mean ΔQTcF was less than 10 msec at the observed steady-state geometric mean of the maximum olutasidenib concentration (C_{max}) for 150 mg BID (C_{max} 3487 ng/mL) and a ΔQTcF with 90% upper confidence bound exceeding 20 ms can be excluded

up to an estimated olutasidenib plasma concentration of ~6800 ng/mL. Overall, data from this substudy confirmed no large or clinical relevant effect on QTcF at the exposures anticipated with the clinical dose of 150 mg BID.

Table 72: Predicted QTcF Effect Based on Concentration-QTc Analysis

Treatment	Visit	Geometric mean C_{max} of olutasidenib (ng/mL)	ΔQTcF estimate (ms) (90% CI)
150 mg BID	Cycle 1 Day 1	655.5	2.10 (0.08, 4.13)
	Cycle 2 Day 1	3014.5	6.10 (2.85, 9.34)
10 ms Threshold	.	3260	6.51 (3.02, 10.00)
20 ms Threshold	.	6775	12.46 (4.92, 20.00)

The Applicant's Position:

In the cardiac safety substudy, olutasidenib had no clear effects on heart rate, PR and QRS interval duration, or ECG morphology, and no clinically relevant effect on cardiac repolarization (ie, change in corrected QT interval by Fridericia formula [ΔQTcF] > 20 msec) as evidenced by the results of the primary analysis (concentration-QTc modeling) and secondary analyses (time-matched and categorical outlier analyses).

Based on the concentration-QTc analysis, the predicted mean (upper 90% confidence interval) increase in QTcF from baseline (ΔQTcF) was 6.1 msec (9.3 msec) at the geometric mean Cmax for 150 mg BID at steady-state, confirming that olutasidenib does not prolong QTc to any clinically relevant extent. No large changes in QTc interval (>20 ms) are expected at the recommended dose.

The FDA's Assessment:

In the ECG sub-study (N=33), one patient experienced a QTcF greater than 500 msec. There were two patients that experienced PR greater than 200 msec with an increase in ΔPR >25%, three patients experienced HR greater than 100 bpm with an increase in ΔHR >25%, and one patient experienced QRS greater than 100 ms with an increase in ΔQRS >25%. Please see table below for analysis of QTc prolongation in the ECG sub-study:

Table 73: QTc Prolongation ECG Substudy of 2102-HEM-101

Treatment	Total (N)		≤450msec		450 -480 msec		480-500msec		>500msec	
	#Patients	#Obs	#Patients	#Obs	#Patients	#Obs	#Patients	#Obs	#Patients	#Obs

150mg Olutasidenib BID	**33**	**450**	**25**	**391**	**6**	**53**	**1**	**5**	**1**	**1**

Source: FDA Analysis

In the pivotal cohort, there were four (4) patients that had an EKG shift >500msec. The majority of the patients (89%) did not experience a QTc prolongation >480 msec. Please see table below for EKG shifts for patients enrolled on the pivotal cohort:

Table 74: Categorical Analysis of Maximum Post-Baseline Absolute QTcF and Shift from Baseline QTcF (90 Day Safety Update)

Baseline Value	Maximum Post-Baseline Value				Change from Baseline	
	≤450 msec N (%)	>450 to≤480 msec N (%)	>480 to ≤500 msec N (%)	>500 msec N (%)	> 30 to ≤ 60 msec N (%)	> 60 msec N (%)
≤ 450 msec	88 (58)	41 (27)	8 (5)	0	48 (32)	6 (4)
> 450 to ≤ 480 msec	1 (1)	6 (4)	2 (1)	1 (1)	2 (1)	0
> 480 to ≤ 500 msec	0	0	2 (1)	3 (2)	1 (1)	0
≥500 mcsec	0	0	0	0	0	0
Total	89 (58)	47 (31)	12 (8)	4 (3)	51 (34)	6 (4)

Source: FDA Analysis

Reviewer Comments: Please note that there was one patient who did not have a post-baseline EKG and the following table only has results for 152 patients. Although QTc prolongation was an adverse event of special interest, olutasidenib appears to have less cardiac effects than the FDA-approved IDH1 inhibitor ivosidenib (Tibsovo USPI). Nonetheless, the risk of QTc interval prolongation should be communicated in Section 6 of the label.

Immunogenicity

The Applicant's Position:
Not applicable as this was not assessed or expected.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

9.1.5 Analysis of Submission-Specific Safety Issues

8.2.5.1 Hepatic Effects

Data:

The incidence of selected hepatic effects TEAEs is summarized for Phase 2 Cohort 1 in Table 77. Overall, 33 (22%) of the 153 patients in Phase 2 Cohort 1 reported any hepatic effects TEAEs. By PT coded using MedDRA version 23.0, the most frequent selected hepatic effects TEAEs of any grade included increased ALT (10%), increased AST (8%), increased GGT (5%), increased hepatic enzyme (5%), and increased blood bilirubin (4%) (ISS Table 2.23.4).

Grade 3 or Grade 4 selected hepatic effects TEAEs were reported in 19 (12%) of the 153 patients; most of these events (15 of 19 [79%]) were assessed as treatment related. Serious hepatic effects TEAEs were reported in 10 (7%) patients, all of which were considered related to treatment. No selected hepatic effects TEAE led to acute liver failure.

Dose holds due to hepatic effects TEAEs were reported in 15 (10%) patients and dose reductions in 6 (4%) patients. Hepatic effects TEAEs leading to discontinuation were uncommon, reported in 7 (5%) of 153 patients in Phase 2 Cohort 1. The Hepatic Effects Summary includes more detail on the number of patients that were able to stay on study with or without dose hold, dose reduction or rechallenge.

Most patients experienced hepatic effects TEAEs within the first two cycles of treatment with a median time to first event onset of 29 days (range: 2 to 197 days) (ISS Table 2.27.3). The median number of events per patient was 2 (95% confidence interval: 1, 5). These events resolved quickly with a median time to resolution of 8 days (range: 1 to 315 days). As of data cutoff, 17 events were ongoing (censored).

Table 75: Summary of Selected Hepatobiliary Adverse Event Incidence (Phase 2 Cohort 1 Safety Analysis Set)

Selected Hepatobiliary Adverse Events	Olutasidenib 150 mg BID (N=153) n (%)
Any TEAE	33 (22)
Any Grade 3 or 4 TEAE	19 (12)
Any treatment-related TEAE	22 (14)
Any treatment-related Grade 3 or 4 TEAE	15 (10)
Any serious TEAEs	10 (7)
Any treatment-related serious TEAEs	10 (7)
Any TEAE leading to study drug discontinuation	7 (5)
Any TEAE leading to dose reduction	6 (4)
Any TEAE leading to dose hold	15 (10)
Any treatment-related TEAE leading to dose hold	13 (9)

Selected Hepatobiliary Adverse Events	Olutasidenib 150 mg BID (N=153) n (%)
Any TEAE leading to death	0

Source: ISS Table 2.22.4. Data cutoff date: 18 Jun 2020.

BID = twice daily; TEAE = treatment-emergent adverse event

Note: Adverse events are coded using MedDRA, version 23.0.

A review of hepatic effects TEAEs and hepatic function laboratory data among 425 patients with hematologic malignancies and solid tumors, including 179 patients in the target indication of R/R AML who received single-agent olutasidenib shows that the hepatic effects AESI reported during treatment with olutasidenib as a single-agent or in combination with azacitidine were mostly characterized by asymptomatic, low-grade transaminase elevations and alkaline phosphatase elevations with or without elevations in total bilirubin observed at routine visits. Elevations in bilirubin were uniformly associated with elevated alkaline phosphatase levels. In events assessed by an independent hepatologist as probably or highly likely due to DILI, a cholestatic-hepatocellular injury pattern was observed. There have been no reports of liver failure across the olutasidenib clinical program.

Most hepatic effects TEAEs occurred early with a median time to onset of any grade hepatic effects TEAE of 29.0 days and of Grade 3 or 4 events of 36.0 days, i.e., the median time to onset was within Cycles 1 or 2 of treatment. Most hepatic effects TEAEs resolved with or without dose modifications with a median duration of 8.0 days for events of any grade and of 9.0 days for Grade 3 or 4 TEAEs.

Among the 117 patients with a hepatic effects TEAE, 61 patients had TEAEs leading to a dose modification for these events, including 32 (10%) of the 332 patients with hematologic malignancies and 29 (31%) of the 93 patients with solid tumors; 44 of these 61 patients were rechallenged following resolution of the hepatic effects TEAE. Among the 44 patients who were rechallenged, 36 (82%) were able to continue on olutasidenib therapy with or without dose reduction. Overall, 18 patients withdrew from treatment due to hepatic effects TEAEs following either a first occurrence or a second occurrence following rechallenge. Overall, 56 of the 117 patients with hepatic effects TEAEs did not undergo dose modification for the event. Half of these patients (28 of 56, 50%) remained on study treatment without dose modification with resolution of the hepatic effects TEAE during continued treatment and 10 (18%) had resolution of the hepatic effects TEAE following a dose hold that was reported for another TEAE.

Assessment of Potential Hy's Law

Across 425 patients in Clinical Study 2102-HEM-101 and Clinical Study 2102-ONC-102, 19 (4%) had ALT and/or AST > 3 × ULN concurrent with total bilirubin > 2 × ULN (±7 days); 18 of the 19 patients had concurrent ALP > 2 × ULN and therefore did not met criteria for Hy's law (ISS Listing 1.6). One patient, Patient (b) (4) had ALT > 3 × ULN and total bilirubin > 2 × ULN within a 7-day period with ALP < 2 × ULN; however, the elevation in total bilirubin was concurrent with SAEs of seizure and acute kidney injury with the total bilirubin elevation recovering by the time the ALT elevation occurred 5 days later. The 19 patients included nine (3%) of the 332 patients with hematologic malignancies and 10 (11%) of the 93 patients with solid tumors. Brief descriptions of the elevations for each of these 19 patients are provided below.

Brief Narratives for Patients with Peak ALT or AST > 3 × ULN Concurrent with Total Bilirubin > 2 × ULN

Study HEM-101

Patient (b) (6), Newly-Diagnosed AML, Olutasidenib 150 mg BID in Combination with Azacitidine

Concurrent elevations in ALT > 3 × ULN and total bilirubin > 2 × ULN were reported on Days 115, 172 and 200 with maximum elevations in transaminase levels on Day 200 with ALT 4.9 × ULN; total bilirubin at that time was 3.3 × ULN and AST was 2.3 × ULN. All elevations on these days were concurrent with elevated ALP > 2 × ULN. **Hy's law criteria were not met**. The events did not lead to dose modifications. The patient was discontinued from study treatment on Day 229 due to progressive disease. At the last assessment on Day 235, ALT and total bilirubin were improving.

Patient (b) (6), Newly-Diagnosed MDS, Olutasidenib 150 mg BID in Combination with Azacitidine

Concurrent elevations in ALT (20.6 × ULN) and total bilirubin (2.6 × ULN) were reported on Day 27 with concomitant elevated ALP (5.7 × ULN); AST was not reported. **Hy's law criteria were not met**. The events did not lead to dose modifications. Liver enzymes improved with ALT and total bilirubin within the normal range on Day 64. The patient remained on treatment through Day 455 and was subsequently discontinued due to progressive disease.

Patient (b) (6), R/R AML, Single-agent Olutasidenib 150 mg BID

Concurrent elevations in ALT (12.6 × ULN), AST (8.5 × ULN), and total bilirubin (2.9 × ULN) were noted on Day 22 with an elevated ALP of 5 × ULN. Grade 2 blood bilirubin increased and Grade 4 increased liver function tests were reported at that time. **Hy's law criteria were not met**. Concurrent AEs of febrile neutropenia and Sweet's syndrome (acute febrile neutrophilic dermatosis), associated concomitant treatments and ongoing prophylactic antibiotics may have

been contributing factors. Treatment was held and subsequently withdrawn due to the elevation in LFTs with the patient receiving the last dose on Day 21. On Day 32 (11 days post treatment) total bilirubin and AST normalized and ALT was improving.

Patient (b) (6), R/R AML, Single-agent Olutasidenib 150 mg BID

On Day 96, the patient was hospitalized with a 3-day history of conjunctival jaundice, pruritus, asthenia, fever, and bilirubinemia. The patient denied abdominal pain. Concurrent elevations in ALT (4.4 × ULN) and total bilirubin (13.3 × ULN) were noted on Day 96 with an elevated ALP of 2.1 × ULN (per MedWatch report). **Hy's law criteria were not met**. Liver biopsy findings noted intralobular bile duct inflammatory infiltrate with intact lobule and sinusoidal structure suggesting a mixed cholestatic-hepatocellular injury pattern. Liver enzymes improved following olutasidenib treatment interruption; however, increases were noted following re-challenge at a reduced dose (Day 112, ALT: 3.2 × ULN and total bilirubin: 5.6 × ULN) and the patient was discontinued from treatment. Following olutasidenib discontinuation, LFTs were stable or improving as of the last available data.

Patient (b) (6), R/R AML, Single-agent Olutasidenib 150 mg BID

On Day 38, transaminase elevations were noted (ALT 9.0 × ULN; AST 4.5 × ULN) with bilirubin in the normal range. Olutasidenib dosing was held. On Day 42, concurrent elevations in ALT (9.7 × ULN) and total bilirubin (3.3 × ULN) were noted with an elevated ALP of 3.3 × ULN; AST was 2.1 × ULN. The patient was hospitalized at that time for Grade 3 hepatic enzyme increased. **Hy's law criteria were not met**. No definitive etiology was identified by liver magnetic resonance imaging or liver biopsy. Liver enzyme elevations initially improved with olutasidenib treatment hold; however, concurrent ALT 7.7 × ULN, AST 7.0 × ULN and total bilirubin 2.5 × ULN recurred on Day 77 after treatment resumed at a reduced dose; ALP was 3.8 × ULN and so again Hy's law criteria were not met. The patient was withdrawn from treatment at that time due to the elevations in hepatic enzymes (Day 77). Liver enzymes were improving as of the last assessment on Day 92.

Patient (b) (6), R/R AML, Single-agent Olutasidenib 150 mg BID

This patient had elevations in total bilirubin (2.4 × ULN) on Day 18 and in ALT (3.3 × ULN) on Day 23, i.e., within a 7-day window; AST was 1.7 × ULN on Day 18 and 1.3 × ULN on Day 23. However, the total bilirubin elevations were in the setting of multiple SAEs (acute kidney injury and seizure) with multiple other AEs (differentiation syndrome, diarrhea, hyperuricemia) and concurrent treatment with posaconazole (starting Day 8). The elevation in total bilirubin had resolved to within the normal range at the time of the ALT elevation. **Hy's law criteria were not met**. The patient discontinued treatment due to seizure on Day 18.

Patient (b) (6), AML in Complete Remission (minimal residual disease [MRD] positive), Olutasidenib 150 mg BID

Concurrent elevations in ALT (34.5 × ULN), AST (21.0 × ULN). and total bilirubin (2.7 × ULN) were reported on Day 26 with concomitant elevated ALP (3.5 × ULN). **Hy's law criteria were not met**. The patient was hospitalized with abdominal pain and Grade 3 acute hepatitis. The events resolved and the patient was discharged on Day 29. Following a dose hold, ALT, AST and total bilirubin recovered to normal range on Day 46 and olutasidenib was restarted at a reduced dose of 150 mg QD. Thereafter the patient had some fluctuations in ALT but none concurrent with elevations in total bilirubin > 2 × ULN. The patient continued on treatment through Day 284, at which time olutasidenib was discontinued due to physician's decision.

Patient (b) (6), R/R AML, Single-agent Olutasidenib 150 mg BID

Concurrent elevations in ALT (6 × ULN), AST (4.3 × ULN), and total bilirubin (2.6 × ULN) were reported on Day 84 with ALP 3.9 × ULN in the setting of a hemolyzed blood sample. **Hy's law criteria were not met**. The patient was ongoing on treatment as of the data cutoff.

Patient (b) (6), R/R AML, Single-agent Olutasidenib 150 mg BID

Concurrent elevations in ALT (48.9 × ULN), AST (32.2 × ULN), and total bilirubin (4 × ULN) were first detected on Day 26 with an elevated ALP (3.6 × ULN). The patient was hospitalized for Grade 3 cholangitis. **Hy's law criteria were not met**. Findings of a liver biopsy were suggestive of a cholangiolitic drug reaction. Olutasidenib was held and subsequently withdrawn due to the event with the last dose administered on Day 26. Synthetic liver function testing remained intact throughout the event, and ALT and total bilirubin had recovered to near normal range at the time of the last study assessment on Day 50.

Study ONC-102

Patient (b) (6), Intrahepatic Cholangiocarcinoma, Single-agent Olutasidenib 150 mg BID

Concurrent ALT (3.3 × ULN), AST (6.2 × ULN), and total bilirubin (2.7 × ULN) were reported on Day 36 with concurrent elevated ALP (9.4 × ULN). **Hy's law criteria were not met**. The patient had been withdrawn from olutasidenib treatment on Day 34 due to physician decision. Hepatic enzyme elevations were ongoing at the time of the patient's death 26 days post treatment due to gastrointestinal hemorrhage secondary to progressive IHCC.

Patient (b) (6), Chondrosarcoma, Single-agent Olutasidenib 150 mg BID

On Day 36, ALT was elevated to 3.4 × ULN with total bilirubin in the normal range and olutasidenib dosing was held; by Day 38, ALT (8.3 × ULN) and AST (6.0 × ULN) were further elevated with total bilirubin remaining in the normal range. Concurrent ALT (21.9 × ULN), AST (5.9 × ULN), and total bilirubin (2.1 × ULN) were reported on Day 42 with concurrent elevated ALP (2.9 × ULN). **Hy's law criteria were not met**. Olutasidenib was permanently withdrawn

due to TEAEs of ALT, blood bilirubin, and blood ALP increased. The LFTs were improving as of the last assessment on Day 62 with ALT 2.1 × ULN, AST 1.2 × ULN, and total bilirubin in the normal range.

Patient (b) (6), Glioma, Single-agent Olutasidenib 150 mg BID

On Day 40 the patient was hospitalized with Grade 4 acute hepatitis with fatigue and jaundice. He denied vomiting, pruritus, abdominal pain or altered mental status. In hospital, LFTs were elevated (ALT 1793 IU/L, AST 444 IU/L, total bilirubin 9.3 mg/dL; normal ranges not provided) (per MedWatch). International normalized ratio (INR) was 0.96 and viral testing was negative. Olutasidenib was withdrawn due to the event. On Day 45, concurrent ALT (29.4 × ULN), AST (10.8 × ULN), and total bilirubin (16.5 × ULN) were reported with concurrent elevated ALP (3.8 × ULN). **Hy's law criteria were not met**. The LFTs were improving by Day 49 and at the last assessment on Day 67 ALT was 2.3 × ULN and total bilirubin was 1.6 × ULN; AST was in the normal range.

Patient (b) (6), Glioma, Single-agent Olutasidenib 150 mg BID in Combination with Azacitidine

From Day 15 to Day 31, the patient was receiving acetaminophen 500 mg for treatment of right shoulder impingement. On Day 31, transaminase levels were elevated with ALT 27.4 × ULN and AST 11.7 × ULN; total bilirubin was in the normal range. The patient was asymptomatic and INR was 1.0. Grade 4 elevation in hepatic enzymes was reported as an SAE. Treatment was initially held for the LFT elevations and subsequently withdrawn. On Day 34 concurrent ALT (28.3 × ULN), AST (8.9 × ULN), and total bilirubin (2.3 × ULN) were reported with concurrent elevated ALP (4.1 × ULN). **Hy's law criteria were not met**. The LFTs improved off treatment and at the last assessment (Day 59), ALT was 1.5 × ULN and AST and total bilirubin were in the normal range.

Patient (b) (6), Intrahepatic Cholangiocarcinoma, Single-agent Olutasidenib 150 mg BID

Concurrent ALT (3.8 × ULN), AST (4.4 × ULN), and total bilirubin (7.1 × ULN) were reported on Day 43 with concurrent elevated ALP (4.1 × ULN). **Hy's law criteria were not met**. The patient was withdrawn from treatment at that time due to elevations in LFTs. Total bilirubin continued to increase with a maximum 9.8 × ULN on Day 50; transaminase levels were stable. At the last assessment on Day 57, LFTs remained elevated with ALT 3.0 × ULN, AST 3.6 × ULN and total bilirubin was 8.6 × ULN.

Patient (b) (6), Chondrosarcoma, Single-agent Olutasidenib 150 mg BID

Concurrent ALT (6.2 × ULN), AST (3.5 × ULN), and total bilirubin (3.8 × ULN) were reported on Day 29 with concurrent elevated ALP (3.8 × ULN). **Hy's law criteria were not met**. Olutasidenib was held from Day 27 to Day 56 and resumed at a reduced dose of 150 mg QD. Hepatic enzyme elevations recovered following olutasidenib dose interruption and did not recur

following treatment resumption with dose reduction to 150 mg QD. The patient discontinued olutasidenib due to progressive disease on Day 168.

Patient (b) (6), Glioma, Single-agent Olutasidenib 150 mg BID

On Day 31, the patient was hospitalized after developing intractable nausea and vomiting with weakness and malaise. Transaminase levels were marginally elevated (ALT 1.2 × ULN; AST 2.5 × ULN) and bilirubin was in the normal range. Olutasidenib was held due to these events and the patient was subsequently withdrawn on Day 33 due to disease progression. Ten days post treatment (Day 43), concurrent AST (5.2 × ULN) and total bilirubin (2.5 × ULN) were reported with concurrent elevated ALP (4.5 × ULN); ALT was 2.9 × ULN. **Hy's law criteria were not met**. The LFTs were in the normal range two weeks later (Day 56).

Patient (b) (6), Intrahepatic Cholangiocarcinoma, Single-agent Olutasidenib 150 mg BID

This patient experienced Grade 2 rash on Day 19 which worsened to Grade 3 and the following day and olutasidenib dosing was held; treatment was subsequently discontinued without restarting due to disease progression. Eight days post treatment on Day 27 in the setting of disease progression, AST was elevated to 4.2 × ULN. On Day 48, 29 days after the last dose of olutasidenib, the patient was hospitalized for clinical deterioration due to progression of her underlying IHCC. Concurrent AST (4.4 × ULN) and total bilirubin (5.5 × ULN) were reported at that time in the setting of disease progression with concurrent elevated ALP (6.5 × ULN); ALT was 1.7 × ULN. **Hy's law criteria were not met**.

Patient (b) (6), Intrahepatic Cholangiocarcinoma, Single-agent Olutasidenib 150 mg BID

Transaminase levels were initially elevated on Day 28 with ALT 8.1 × ULN and AST 5.8 × ULN; total bilirubin was in the normal range. Treatment with olutasidenib was held for the transaminase elevations. One week later on Day 35, concurrent ALT (7.3 × ULN), AST (3.1 × ULN) and total bilirubin (6.6 × ULN) with concurrent ALP of 3.7 × ULN. **Hy's law criteria were not met**. On Day 42, olutasidenib was permanently withdrawn due to progressive disease. Total bilirubin increased further and was 8.8 × ULN with ALT 3.6 × ULN and AST 1.9 × ULN on Day 42; ALP was also elevated (4.2 × ULN).

Patient (b) (6), Chondrosarcoma, Single-agent Olutasidenib 150 mg BID

Concurrent elevations in ALT and AST > 3 × ULN and total bilirubin > 2 × ULN were reported on Days 22, 24 and 26 with maximum elevations on Day 24 with ALT 16.4 × ULN, AST 11.7 × ULN and total bilirubin 4.8 × ULN. All elevations on these days were concurrent with concomitant elevated ALP > 2 × ULN. **Hy's law criteria were not met**. Olutasidenib was held from Day 22 to Day 39 and then resumed at a reduced dose of 150 mg QD. Liver function tests then improved during the interruption. The patient was withdrawn from olutasidenib treatment on Day 51 due to disease progression.

In addition, in the overall clinical program of 425 patients, an independent hepatologist found 33 probable and 8 highly likely DILI cases using the Rocky, Seef et al. 2010 classification.

The Applicant's Position:
The observed AESI of hepatic effects in patients who received olutasidenib in Phase 2 Cohort 1 was managed with dose holds and dose reductions, when needed. Hepatic effects TEAEs, when reported, were mostly characterized by reversible, asymptomatic, transaminase elevations and alkaline phosphatase elevations with or without elevations in total bilirubin initially observed at routine visits. The events assessed by an independent hepatologist as probable or highly likely due to DILI had a mixed cholestatic-hepatocellular injury pattern without evidence of liver failure. Many of the patients with hepatic effect TEAE continued on treatment without dose modification; among those who underwent dose modification, many were able to remain on treatment with olutasidenib with or without dose reduction.

The FDA's Assessment:

The FDA did an independent analysis of hepatobiliary events for Cohort 1 summarized in the table below:

Selected Hepatobiliary Events	**Olutasidenib 150mg BID (N=153) N (%)**
Any TEAE	43 (28)
Any Grade 3 or 4 TEAE	25 (16)
Serious TEAEs	11 (7)
Any TEAE leading to study drug discontinuation	7 (5)
Any TEAE leading to dose reduction	10 (7)
Any TEAE leading to dose interruption	22 (14)
Any TEAE leading to death	0

Source: FDA Analysis

The median time to onset of hepatoxicity for patients in Cohort 1 (defined as presenting with transaminitis with or without elevated bilirubin) was 1.2 months (range: 2 days to 17.5 months) after first dose of olutasidenib. The median time to resolution was 12 days (range: 1 day to 17 months).

Specifically, the most frequent hepatobiliary TEAE reported was transaminitis, which is a grouped term that encompasses several AE terms with similar clinical meaning. The transaminitis grouped term includes the following AE terms: alanine aminotransferase increased, aspartate aminotransferase increased, hepatic enzyme increased, hypertransaminasaemia, liver function test abnormal, liver function test increased, transaminases increased, hepatitis acute, and

blood alkaline phosphatase increased. Thirty-one (89%) of the hepatobiliary TEAEs were due to transaminitis. There were no events of Hy's Law in Cohort 1.

In regards to biliary events, these included AEs of blood bilirubin increase, biliary colic, biliary tract disorder, cholangitis, and cholestasis. Two patients had olutasidenib treatment discontinued due to a biliary AE (cholangitis and biliary tract disorder).
Most of the hepatobiliary TEAEs were reversible with dose interruption, however seven patients (5%) had olutasidenib therapy discontinued due to a hepatobiliary TEAE.

The FDA also evaluated the rates of hepatobiliary events in all patients enrolled in study 2102-HEM-101. Among the 335 patients treated with single-agent olutasidenib or in combination with LDAC or azacitidine, 30% (99 patients) experienced a hepatobiliary TEAE, with one fatal event in the combination cohort.

Table 76: Hepatobiliary TEAEs on Study 2102-HEM-101, 90-Day Safety Update

Selected Hepatobiliary Events	Olutasidenib Single-Agent (N=216)	Olutasidenib Combination (N=119)	Total (N=335)
Any TEAE	63 (29)	36 (30)	99 (30)
Any Grade 3 or 4 TEAE	35 (16)	12 (10)	47 (14)
Serious TEAEs	14 (6)	5 (4)	19 (6)
Any TEAE leading to study drug discontinuation	8 (4)	5 (4)	13 (4)
Any TEAE leading to dose reduction	15 (7)	3 (3)	18 (5)
Any TEAE leading to dose interruption	28 (13)	10 (8)	38 (11)
Any TEAE leading to death	0	1 (1)	1 (0)

Source: FDA Analysis

The rates of hepatobiliary events were comparable between patients that received single-agent olutasidenib versus those that received combination therapy with olutasidenib. Finally, the FDA conducted an evaluation of hepatobiliary events for patients that received olutasidenib in Study 2101-ONC-102 depicted in the table below:

Table 77: Hepatobiliary TEAEs on Study 2102-ONC-102

Selected Hepatobiliary Events	2101-ONC-101 (N=93)
Any TEAE	57(61)
Any Grade 3 or 4 TEAE	33 (35)
Serious TEAEs	6 (6)
Any TEAE leading to study drug discontinuation	7 (8)

Any TEAE leading to dose reduction	7 (8)
Any TEAE leading to dose interruption	27 (29)
Any TEAE leading to death	0

Source: FDA Analysis

The dose of olutasidenib in study 2102-ONC-102 ranged from 150mg-300mg daily. The rates of hepatobiliary events were higher in the oncology trial, but there were no hepatobiliary AEs that led to death. It should be noted that some patients in 2102-ONC-102 received combination therapy with gemcitabine, cisplatin, and nivolumab which may have affected the rates of hepatobiliary TEAEs (gemcitabine and nivolumab can hepatic events). Finally, the FDA also reviewed AEs from the healthy volunteer dataset and there were no hepatobiliary events reported.

Reviewer Comments: Most of the hepatobiliary events seen in in patients treated with olutasidenib were elevations in LFTs. Please note, that these tables include both hepatoxicity and gallbladder disorders (ie, cholangitis, cholelithiasis) and numbers vary slightly from what is listed in the USPI.
The FDA would like to comment more on the event of "biliary tract disorder" and the fatal hepatobiliary event. First, the event of "biliary tract disorder" was seen in a 72-year old woman that experienced grade 4 ALT and AST elevation and grade 2 alkaline phosphatase and bilirubin increase on day 26. She underwent a liver biopsy (Day 29) that was diagnosed as cholangiolitic drug reaction. Olutasidenib was not restarted after the event.
Second, the one fatal hepatobililary event occurred in a 78-year old woman with newly-diagnosed AML that received combination therapy with olutasidenib and azacitidine. On day 26, she developed grade 4 ALT and AST elevation. Hepatitis serology and testing for autoimmune hepatitis was negative. She underwent a liver biopsy on day 38 that revealed a severe cholestatic pattern of injury caused by drug induced liver injury. She eventually passed away from complications related to her drug-induced liver injury on day 49. Although this death did not occur in the pivotal cohort, this fatal event of hepatotoxicity will be listed in the USPI.

8.2.5.2 Differentiation Syndrome (DS)

Data:

Similar to other IDH1 and IDH2 inhibitors, DS is a significant, potentially life-threatening risk with olutasidenib treatment, for which early recognition and intervention with steroids and management of concomitant leukocytosis, if present, is warranted.

Two types of summaries were conducted to assess the incidence of DS: 1) based on TEAEs of MedDRA preferred term DS as reported by the Investigator, and 2) based on a review of

candidate cases per Montesinos, et al. 2009, using the methodology outlined in Norsworthy, et al. 2020.

Investigator-Reported Treatment-Emergent Adverse Events of Differentiation Syndrome

A summary of DS TEAEs as reported by the Investigator is presented in Table 80. A total of 21 patients (14%) experienced DS TEAEs, all of which were assessed by the Investigator as treatment related. Of these, 12 patients (8%) experienced Grade 3 or Grade 4 DS TEAEs. Olutasidenib dose modifications due to a DS TEAE were reported: 12 patients had their doses held, two patients had their doses reduced, and three patients had olutasidenib permanently withdrawn. Of the patients with dose holds, nine patients resumed treatment with olutasidenib.

Seven patients with DS events also had TEAEs of increased WBC count reported concurrently or near the time of the DS AEs (within 7 days of DS TEAE start date). Of note, all seven patients had WBC < 15×10^9 at baseline.

One patient, a 70-year-old male (Patient (b) (6)) with refractory AML experienced Grade 5 DS (CSR HEM-101 Phase 2 Cohort 1 Listing 16.2.7.1).

Most patients experienced DS TEAEs within the first two cycles of treatment with median time to first DS event of 11 days (range: 1 to 135 days) and median duration of 12 days (range: 1 to 56 days) (CSR HEM-101 Phase 2 Cohort 1 Listing 16.2.7.2). Most DS TEAEs were treated with dexamethasone (intravenous [IV] or oral). Other medications that were used to manage DS events included oral hydroxycarbamide, oral furosemide for edema due to DS, IV methylprednisolone, oral corticosteroid NOS, oral mercaptopurine, and IV antibiotics (CSR HEM-101 Phase 2 Cohort 1 Listing 16.2.4.9).

Table 78: Summary of Differentiation Syndrome as Reported by the Investigator (Safety Analysis Set, Phase 2 Cohort 1)

Differentiation Syndrome	Olutasidenib 150 mg BID (N=153) n (%)
Any TEAE	21 (14)
Any Grade 3 or 4 TEAE	12 (8)
Any treatment-related TEAE	21 (14)
Any treatment-related Grade 3 or 4 TEAE	12 (8)
Any serious TEAEs	13 (8)
Any treatment-related serious TEAEs	13 (8)
Any TEAE leading to study drug discontinuation	3 (2)
Any TEAE leading to dose modifications	13 (8)

Differentiation Syndrome	Olutasidenib 150 mg BID (N=153) n (%)
Any TEAE leading to dose reduction	2 (1)
Any treatment-related TEAE leading to dose reduction	2 (1)
Any TEAE leading to dose hold	12 (8)
Any treatment-related TEAE leading to dose hold	12 (8)
Any TEAE leading to death	1 (1)

Source: CSR HEM-101 Phase 2 Cohort 1 Table 14.3.1.2b, Table 14.3.1.3b, Table 14.3.1.4b, Table 14.3.1.5b, Table 14.3.1.6b, Table 14.3.1.8b, Table 14.3.1.9b, Table 14.3.1.10b, Table 14.3.1.11b, Table 14.3.1.12b, Table 14.3.1.13b, Table 14.3.1.14b, Table 14.3.1.15b, Table 14.3.1.16b, Table 14.3.1.19b. Data cutoff date: 18 Jun 2020.

BID = twice daily; TEAE = treatment-emergent adverse event

Adjudicated Cases of Differentiation Syndrome

An assessment of candidate cases of potential DS was conducted using the methodology outlined in Norsworthy, et al. 2020, and included DS TEAEs as reported by Investigators. All candidate cases identified through this process were adjudicated

A summary of candidate DS cases within 90 days of the first olutasidenib dose that underwent adjudication in Phase 2 Cohort 1 is presented in Table 81. Sixteen patients (10%) had cases adjudicated as possible or probable DS, 5 (31%) of whom had multiple episodes and half had cases assessed as severe. Eleven (69%) of the 16 patients had concomitant leukocytosis, defined as having an AE of leukocytosis, hyperleukocytosis, or increased WBC count or had leukocyte counts > 10×10^9/L within 7 days before or after a DS AESI. The median time to onset for a possible or probable DS was 12.5 days (range: 0 to 86 days).

Table 79: Summary of Candidate Cases of Differentiation Syndrome Within 90 Days of First Dose that Underwent Adjudication (Safety Analysis Set, Phase 2 Cohort 1)

Parameter	Olutasidenib 150 mg BID (N=153) n (%)
Total Investigator Reported DS Cases (any time)	21 (14)
Total Candidate DS Cases within 90 days Adjudicated[a]	
Patients with DS TEAE per Investigator	20 (13)
Patients with TEAEs per DS Algorithm	40 (26)
Category Met in DS Algorithm[b]	
Fever	29 (19)

Parameter	Olutasidenib 150 mg BID (N=153) n (%)
Kidney injury	22 (14)
Dyspnoea	20 (13)
Pulmonary infiltrates	13 (8)
Weight gain	8 (5)
Hypotension	5 (3)
Adjudication Results	
Possible/probable DS cases	16 (10)
Cases unlikely to be DS	35 (23)
Not enough information	3 (2)
Characteristics of Possible/Probable DS Cases	
Severity	
Severe	8 (50)
Moderate	7 (44)
Multiple episodes	5 (31)
Concomitant leukocytosis	11 (69)
Time to onset (days)	
n	16
Median	12.5
25^{th}, 75^{th} percentile	7.0, 21.0
Minimum, Maximum	0, 86

Source: CSR HEM-101 Phase 2 Cohort 1 Table 14.3.1.22b. Data cutoff date: 18 Jun 2020.

AESI = adverse event of special interest; BID = twice daily; DS = differentiation syndrome; TEAE = treatment-emergent adverse event

[a] Candidate cases of DS were reviewed by an Adjudication Committee. Patients were considered candidate cases if they had Investigator-reported DS or two DS AESIs from different categories within 7 days of each other.

[b] Patients may counted in more than one category.

The Applicant's Position:

In the clinical trial of patients with relapsed or refractory AML, differentiation syndrome was reported by the Investigators in 14% (21/153) of patients treated at any time and determined to be possible or probable case of differentiation syndrome by the adjudicators in 10% (16/153) of patients within the first 90 days of olutasidenib treatment. The observed event of DS in patients who received olutasidenib in Phase 2 Cohort 1 was managed with dose holds and dose reductions, when needed. As with other IDH1 and IDH2 inhibitors, DS is a significant, potentially life threatening risk with olutasidenib treatment, for which early recognition and

intervention with steroids and management of concomitant leukocytosis, if present, is warranted for optimal outcomes.

The FDA's Assessment:
FDA performed an independent analysis of potential DS cases using the Montesinos approach as previously described (Norsworthy et al, 2020). Using the algorithm on the 90-day safety update datasets, we identified potential DS cases in 67/153 (44%) patients. FDA reviewed narratives from all 67 patients and twenty-five patients (16%) were considered to at least possibly have differentiation syndrome. There were twenty-two investigator reported cases of DS and an additional three (3) cases of DS adjudicated by the FDA. The three additional cases of DS are summarized below:

1. Patient ID# (b) (6): A 76-year old woman started treatment with olutasidenib 150mg BID on (b) (6). On day 13, she was hospitalized with neutropenic fever (Grade 3), hypoxia (grade 3), and rising WBC (0.9 → 3.7). She also had grade 3 back pain. Due to concern for DS she was treated with dexamethasone and then a steroid taper and diuresis and symptoms improved.
2. Patient ID# (b) (6): A 74-year old man started treatment with olutasidenib 150mg BID on (b) (6). On day 49, he was admitted to the hospital for failure to thrive, with subjective fevers, increased dyspnea, cough, and weight loss. A CXR was negative. He was treated for presumed DS with hydroxyurea (WBC went from 3.3 x 10^9/L → 7.2 x 10^9/L) and dexamethasone and was discharged from the hospital on day 53. Olutasidenib was held from days 49-53 and restarted at the same dose on day 54.
3. Patient ID# (b) (6): A 61-year old lady started treatment with olutasidenib 150mg BID on (b) (6). On day 18, he was admitted to the ICU with fevers, respiratory distress, and leukocytosis (WBC=90, baseline= 7.7). Infectious work-up was negative (including bronchoscopy). He was treated with hydroxyurea and dexamethasone and the event was considered resolved on day 34. Olutasidenib was held on days 18-28, and restarted at a lower dose of 100mg BID on day 29.

The following table lists the twenty-five patients to have at least possibly had an AE of DS and the severity:

Table 80: FDA Analysis of Differentiation Syndrome Cases

Patient ID#	Day of Onset	Severity*	Resumed Olutasidenib	Fatal
(b) (6)	10	Moderate	N	N
	11	Moderate	Y	N

(b) (6)				
	17	Moderate	Y	N
	1	Moderate	Y	N
	2	Moderate	Y	N
	20	Moderate	Y	N
	45	Moderate	Y	N
	135	Moderate	Y	N
	8	Moderate	Y	N
	18	Moderate	N	N
	6	Moderate	Y	N
	4	Moderate	Y	N
	8	Severe	N	Y
	7	Moderate	N	N
	3	Moderate	Y	N
	30	Moderate	Y	N
	15	Moderate	Y	N
	Unknown	Moderate	Y	N
	29	Moderate	Y	N
	4	Unknown	N	Y
	13	Moderate	Y	N
	49	Moderate	Y	N
	18	Moderate	Y	N
	41	Moderate	Y	N
	561	Unknown	N	N

**Based on Montensinos Criteria*
Source: FDA Analysis

The additional case of DS assessed by the sponsor at the time of the 90-day safety update was

patient ID# (b) (6), who experienced DS 561 days from their first dose of olutasidenib. There were two (2) fatal cases of DS, and six (6) patients did not resume treatment with olutasidenib after their diagnosis of DS. The majority of the cases occurred within the first month of treatment, but there was one case that occurred 561 days (18 months) after the first day of treatment. In the case of the patient that experienced DS 18 months after treatment initiation, data is limited to provide additional information on his clinical course. The time course of differentiation syndrome will be characterized in Section 5.1 of the USPI.

Overall, in study 2101-HEM-101, forty-two (13%) patients had an investigator-reported AE of differentiation syndrome (30 single agent and 12 in the combination cohort), with twenty-two being Grade 3 or 4. The only fatal events of differentiation syndrome were in the pivotal cohort.

Reviewer Comments: Differentiation syndrome is a known adverse event seen with IDH1/2 inhibitors. The rates of DS with olutasidenib are similar to what has been seen with other IDH1/2 inhibitors. In regards to efficacy, of the 25 patients that experienced DS in the pivotal cohort, four patients achieved a CR and one patient achieved a CRi. There does not appear to be a predictive effect of having DS on response.

8.2.5.3 QTc Prolongation

Data:
Refer to section 8.2.4 for data on TEAEs of ECG prolonged, shift analysis of maximum post-baseline QTcF changes and results from a holter substudy.

The Applicant's Position:
The risk of clinically significant olutasidenib-associated QTc prolongation was low, as demonstrated in the Holter monitoring QTc substudy.

The FDA's Assessment:
The FDA agrees with the Applicant's assessment. Only 8% of patients had a QTc prolongation, with only 1 patient having Grade 3 or higher QTc prolongation (there was no Grade 4 or Grade 5 AEs).

9.1.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:
Not applicable.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

9.1.7 Safety Analyses by Demographic Subgroups

Data:

Subgroup analyses of TEAEs in Studies 2102-HEM-101 were conducted by (< 65 years and ≥ 65 years), sex, race, ECOG PS (PS 0/1 and PS 2).

Age

Among the 216 patients in Study 2102-HEM-101 treated with single agent olutasidenib, there were 49 patients < 65 years and 167 patients ≥ 65 years. Compared to patients< 65 years, in patients ≥ 65 years there was a higher overall incidence (> 10% difference) in Serious TEAEs (67.1% verse 55.1%), TEAEs leading to dose hold (49.1 % verses 38.8%). There were no meaningful differences in AEs leading to treatment discontinuation (28.7% verse 22.4% or TEAEs leading to death (28.1% versus 30.6%). The only TEAEs which occurred at a higher incidence (>10%) in patients ≥ 65 years compared to patients< 65 years included RBC decreased (25.7% versus 12.2%) and hypertension (12.6% versus 2%).

Sex

Among the 216 patients in Study 2102-HEM-101 treated with single agent olutasidenib, there were 112 male patients and 104 female patients. Higher overall incidences (> 10% difference) were noted for Grade 3 or 4 TEAEs (female 81.7%; male 71.4%) and TEAEs leading to dose hold (female 52.9% versus 41.1%). There were no meaningful differences in AEs leading to treatment discontinuation (female 7.7%; males 5.4%) or TEAEs leading to death (female 26.9%; male 30.4%). The only TEAEs which occurred at a higher incidence (>10%) in female patients compared to male patients febrile neutropenia (28.8% versus 13.4%) and hypokalemia (26% versus 10.7%).

Race

Among the 216 patients in Study 2102-HEM-101 with race reported and treated with single agent olutasidenib, there were 114 white patients and 34 non-white patients. Higher overall incidences (> 10% difference) were noted for SAEs (non-white 79.4%; white 63.2%), TEAEs leading to treatment discontinuation (non-white 47.1%; white 21.9%), TEAEs leading to dose hold (non-white 61.8%; white 46.5%) and TEAEs resulting on death (non-white 41.2%; white 25.4%.) TEAEs which occurred at a higher incidence (>10%) in non-white patients compared to white patients included constipation (35.3% versus 21.9%), WBC increase (29.4% versus 19.3%), hypokalemia (29.4% versus 16.7%) and pneumonia (23.5% versus 13.2%). The only TEAE which occurred at a higher incidence (>10%) in white patients compared to non-white patients was platelet count decreased (17.5% versus 2.9%).

ECOG PS

Among the 216 patients in Study 2102-HEM-101 treated with single agent olutasidenib, there were 175 patients with ECOG PS 0 or 1 and 40 patients with ECOG PS 2. Higher overall incidences (> 10% difference) were noted for SAEs (ECOG 2 85%; ECOG 0/1 59.4%), TEAEs leading to treatment discontinuation (ECOG 2 50% ; ECOG 0/1 21.7%), TEAEs leading to dose hold (non-white 61.8%; white 46.5%) and TEAEs resulting on death (ECOG 2 60%; ECOG 0/1 21.1%.) TEAEs which occurred at a higher incidence (>10%) in ECOG 2 patients compared to ECOG 0/1 patients included hypokalemia (30% versus 15.4%) and disease progression (30% versus 8.6%). TEAEs which occurred at a higher incidence (>10%) in ECOG 0/1 patients compared to ECOG 2 patients included platelet count decreased (21.7% versus 10%), RBC decreased (25.1% versus 12.5%), and headache (14.3% versus 2.5%).

The Applicant's Position:
In the integrated summary of safety (ISS), overall AE summaries and incidences were presented according to age (< 65 years and ≥ 65 years), sex, race, ECOG PS (PS 0/1 and PS 2). Differences between ECOG PS categories were expected with specific AE profile differences representative of time on treatment. While the safety profile was generally comparable across demographic subgroups of patients with hematological malignancies treated with single agent olutasidenib, there were some minor differences noted which were not considered clinically significant and would merit the subgroup-specific dosing or monitoring guidance.

The FDA's Assessment:
The FDA conducted an independent analysis across sub-groups for age and sex. The FDA did not do a sub-group analysis for race given the low-number of minority patients enrolled. FDA agrees with the applicant's assessment that the TEAEs that occurred at a greater than ≥10% frequency in patients <65 versus ≥65 was red blood cell decreased (13.5% vs 30.4%) and hypertension (2.7% vs 13.0%). In addition, the FDA adjudicated TEAEs rates of transaminitis* to be higher in patients ≥65 versus patients <65 (23.5% vs 10.8%). In regards to sex, the FDA agrees with the applicant's assessment of higher TEAEs rates of febrile neutropenia (29.7% vs 16.5%) and hypokalemia (28.4% vs 11.4%) in women versus men.
In addition, the FDA adjudicated that arthralgia* (36.5% vs 20.3%) and mucositis* (29.7% vs 16.8%) were seen at higher rates in women versus men. Additionally, rates of dyspnea* were higher in men versus women (29.1% vs 18.9%).

=grouped term See Section 20.5

9.1.8 Specific Safety Studies/Clinical Trials

Data:

As olutasidenib undergoes hepatic metabolism, the effect of HI on the exposure of olutasidenib was explored in Child Pugh A (mild impairment; Child-Pugh score of 5 to 6) and Child-Pugh B

(moderate impairment; Child-Pugh score of 7 to 9) subjects as compared with matched healthy volunteers following a single 150 mg dose of olutasidenib (Study 2102-HVS-105).

In subjects with HI, olutasidenib $AUC_{0\text{-}inf}$ was approximately 23% higher in the mild HI cohort and approximately 37% higher in the moderate HI cohort compared to total matched healthy control subjects. C_{max} was approximately 36% higher in the mild HI cohort and 12% higher in the moderate HI cohort compared to total matched healthy-control subjects.

Olutasidenib plasma protein binding (as measured by mean fraction unbound; converted to %) was similar across cohorts with varying degrees of hepatic function (2.22%, 2.56%, 2.30%, and 3.57% for mild HI, moderate HI, total HI, and total matched healthy-control subjects, respectively. For the mild HI cohort compared to the total matched healthy-control group, $AUC_{0\text{-}infu}$ and C_{maxu} for unbound olutasidenib were approximately 48%, and 34% higher, respectively. For the moderate HI cohort compared to the matched healthy-control subjects, $AUC_{0\text{-}infu}$, and C_{maxu} were approximately 118%, and 42% higher, respectively. These results should be interpreted with caution given the limited number of subjects with estimable unbound olutasidenib PK profiles (3 mild HI, 1 moderate HI, and 1 matched healthy-control) as well as the high variability observed.

The Applicant's Position:

Olutasidenib exposure was higher in subjects with HI compared to those with normal hepatic function, however, the differences are not anticipated to be clinically meaningful. It is concluded that no dosing adjustment is required in subjects with mild or moderate HI. There was no dedicated QT study or dedicated study in patients with renal impairment.

The FDA's Assessment:
FDA agrees with the applicant's assessment. Please see section 6.2.2.2 for the FDA's assessment of olutasidenib dosing in patients with hepatic impairment.

9.1.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development
The Applicant's Position:
Carcinogenicity studies have not been conducted with olutasidenib.

A tabulation of only the secondary primary neoplasms in the neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC in the integrated safety populations and in Phase 2 Cohort 1 is presented below in Table 83. The incidence of secondary primary neoplasms in the overall population is 4 patients (0.9%) with the following cancers: basal cell carcinoma (1 patient), cervix carcinoma stage 0 (1 pt) and squamous cell carcinoma of the skin (2 patients). In the pivotal cohort safety analysis set, there were no secondary primary neoplasms.

Table 81: Incidence of secondary primary neoplasms in the neoplasms benign, malignant and unspecified (incl cysts and polyps) SOC

System Organ Class Preferred Term n (%)	2102-HEM-101 (n=332)			2102-ONC-102 (n=93)			Overall (n=425)	Phase 2 Cohort 1 (n=153)
	Olutasidenib Single Agent (n=216)	Olutasidenib + AZA (n=115)	Total (n=332)	Olutasidenib Single Agent (n=87)	Olutasidenib + AZA (n=6)	Total (n=93)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	31 (14.4)	17 (14.8)	48 (14.5)	4 (4.6)	0	4 (4.3)	52 (12.2)	2 (1)
Basal cell carcinoma	1 (0.5)	0	1 (0.3)	0	0	0	1 (0.2)	0
Cervix carcinoma stage 0	0	1 (0.9)	1 (0.3)	0	0	0	1 (0.2)	0
Squamous cell carcinoma of the skin	1 (0.5)	1 (0.9)	2 (0.6)	0	0	0	2 (0.5)	0

Source: ISS Table 2.2.1.1 and CSR HEM-101 Phase 2 Cohort 1 Table 14.3.1.2b. Data cutoff date: 18 Jun 2020.

The FDA's Assessment:
In the updated safety report, 10 (2.4%) patients had a secondary primary neoplasm (all in study 2102-HEM-101). The following is the breakdown of secondary primary neoplasms: four patients with basal cell carcinoma, four patients with squamous cell carcinoma, and 1 patient with stage 0 cervical carcinoma. 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.

Human Reproduction and Pregnancy
The Applicant's Position:
Based on findings in animal studies, olutasidenib was not teratogenic or embryocidal when administered during the period of organogenesis to rats at doses up to 12 times the exposure at the recommended human daily dose or to rabbits at the same exposure at the recommended human daily dose. The risk in pregnancy is unknown. No cases of pregnancy have been reported in the clinical experience with olutasidenib. There are no studies to assess the presence or absence of olutasidenib in human milk, the effects on the breastfed infant, or the effects on milk production.

The FDA's Assessment:
See FDA's assessment in Section 5.5.4.

Pediatrics and Assessment of Effects on Growth
The Applicant's Position:
Not applicable as no pediatric study has started to date.

The FDA's Assessment:
FDA agrees with the applicant's assessment.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
Data:
Overdose

Three events of overdose were reported for R/R AML patients receiving olutasidenib 150 mg BID in the pivotal cohort. Two patients receiving SA olutasidenib 150 mg BID took a dose of 300 mg instead of 150 mg for a total daily dose of 450 mg. One patient receiving SA olutasidenib 150 mg BID took a total daily dose of 600 mg on one day. There were no reported clinical sequalae.

Based on data across the clinical development program, no clinical sequelae from higher-than-directed dosing of olutasidenib has been reported to date.

Drug Abuse

No potential for drug abuse or drug dependence has been observed for olutasidenib across the clinical development program. Review of nervous system disorder TEAEs did not reveal any clinically relevant concerns with the most common events being mild to moderate headache, dizziness and dysgeusia.

Withdrawal and Rebound
No safety signal has been identified after abrupt discontinuation of olutasidenib treatment, nor has a withdrawal syndrome associated with olutasidenib treatment cessation been observed.

The Applicant's Position:

The FDA's Assessment:
FDA agrees with the applicant's assessment.

9.1.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience
The Applicant's Position:
Olutasidenib has not been approved for commercial use in any country/region world-wide.

The FDA's Assessment:
FDA agrees with the applicant's assessment.

Expectations on Safety in the Postmarket Setting
Data:

The Applicant's Position:

The safety profile of olutasidenib is acceptable and manageable for the intended patient population. Overall, the AE profile for olutasidenib is characteristic of those symptoms or conditions frequently experienced by patients undergoing treatment for AML or the underlying disease itself and are expected, readily recognized, and managed by the physicians who care for these patients through dose modifications and standard of care measures.

The risk of DS and its management are described in Section 5 Warnings and Precautions of the proposed labeling.

The risk of hepatic effects and their management is described in Section 5 Warnings and Precautions of the proposed labeling. The hepatic effects observed in the overall olutasidenib clinical program were mostly characterized by reversible, asymptomatic, transaminase elevations and alkaline phosphatase elevations with or without elevations in total bilirubin which are readily monitorable.

The prescribing information also includes drug interaction and dosage and administration recommendations.

The FDA's Assessment:
The safety profile in the post-market setting is expected to be similar to that observed on the clinical trials. It is possible that there will be more cases of severe hepatotoxicity and rare adverse reactions such as QT interval prolongation. Long-term safety of olutasidenib will be monitored in the post-market setting and safety and efficacy will be evaluated in pediatric patients (currently no pediatric patients have been exposed to olutasidenib).

9.1.11 Integrated Assessment of Safety

The Applicant's Position:

The ISS presents safety data from a total of 512 subjects and patients across 6 clinical studies, including three Phase 1 studies in healthy adults, one Phase 1 study in adults with mild or moderate HI, and two Phase 1/2 studies conducted in patients with hematologic malignancies and solid tumors harboring an IDH1 mutation.

The primary safety data in the proposed indication of R/R AML are derived from the ongoing Phase 1/2 Study 2102-HEM-101 conducted in patients with hematologic malignancies. As patient participation in this study is ongoing, an interim data cut was made based on a data cutoff of 18 Jun 2020. As of this date, safety data were analyzed for a total of 332 patients with AML and MDS, including 216 who received single-agent olutasidenib, 115 who received olutasidenib in combination with azacitidine, and one who received olutasidenib in combination with LDAC. Among these 332 patients, safety data are available from 179 patients with R/R AML who received single-agent olutasidenib, including the 153 patients in the pivotal Phase 2 Cohort 1. Supportive safety data from ongoing Study 2102-ONC-102 in 93 patients with glioma and other solid tumors available as of 03 Dec 2020 are included in the integrated safety analyses.

In total, safety data evaluating multiple-dose administration of olutasidenib are available from 425 patients who had been exposed to olutasidenib at the time of the interim data cuts of Studies 2102-HEM-101 and 2102-ONC-102, with 148 patients having received olutasidenib for at least 6 months.

Overall, the AE profile for single-agent olutasidenib, as well as the incidences of SAEs, are characteristic of those symptoms or conditions frequently experienced by patients undergoing treatment for hematologic malignancies or solid tumors or the underlying disease itself and are

expected, readily recognized, and managed by the physicians who care for these patients through dose modifications and standard-of-care measures.

Across all 425 patients, the most commonly reported TEAEs were nausea (46%), constipation (31%), fatigue (29%), diarrhea (23%), vomiting (22%), platelet count decreased (23%), and RBC count decreased (21%). Similar to the overall population, the most common TEAEs among the 179 patients with R/R AML who received single-agent olutasidenib were nausea (38%), constipation (25%), WBC count decreased (25%), fatigue and RBC count decreased (24%), pyrexia and febrile neutropenia (23%). Differences in the incidence of common TEAEs between patients with hematologic malignancies and those with solid tumors were observed and appeared to be primarily related to the disease under study.

Most (77%) of the 425 patients experienced at least one Grade 3 or 4 TEAE, primarily platelet count decreased (18%), neutrophil count decreased (15%), febrile neutropenia (15%), and RBC count decreased (14%). Consistent with the disease under study, the most common Grade 3 or 4 TEAEs for the 179 patients with R/R AML who received single-agent olutasidenib were cytopenias and infection, including febrile neutropenia (22%), RBC count decreased (20%), platelet count decreased (16%), neutrophil count decreased (12%), and pneumonia and WBC count decreased (each, 9%). Not unexpectedly given the known safety profile of azacitidine which includes a warning for cytopenias, the incidence of Grade 3 or 4 TEAEs was higher among patients who received combination therapy with azacitidine (88%) compared to those who received single-agent olutasidenib (76%). Among patient with solid tumors, the Grade 3 or 4 incidence of ALT increased was notably higher compared to patients with hematologic malignancies (23% vs 4%).

Grade 5 TEAEs were reported in 95 (22%) of the 425 patients. The majority of these events were attributed to the patient's underlying malignancy or disease complications. In 3 patients, the TEAEs leading to death were reported as treatment-related by the investigators, including disease progression (Patient (b) (6)), DS (Patient (b) (6)), and elevation in LFTs concurrent with sepsis and progression of AML (Patient (b) (6)).

Across the 425 patients, 260 (61%) experienced at least one SAE. Disease progression was the most common SAE overall (15% of patients) and in both study populations (13% of patients with hematologic malignancies and 22% of patients with solid tumors). Other commonly reported SAEs among patients with R/R AML were febrile neutropenia (16%), pneumonia (10%), and DS (8%).

Dose modification guidance, including interruptions, reductions, or withdrawals, was provided in the protocols for patients experiencing specific hematologic and non-hematologic toxicities, including LFT abnormalities. Most TEAEs that led to dose modifications were managed by dose holds (49% of the 425 patients); TEAEs leading to dose reductions were reported in 13% of patients. Consistent with protocol requirements, most TEAEs leading to olutasidenib dose

interruptions and dose reductions were laboratory abnormality TEAEs in the SOC of Investigations, primarily ALT increased, AST increased, and DS. Overall, 24% of patients had TEAEs which led to olutasidenib withdrawal, most commonly disease progression (9% of patients).

Similar to other IDH1 and IDH2 inhibitors, DS is a significant, potentially life-threatening risk with olutasidenib treatment, for which early recognition and intervention with steroids and management of concomitant leukocytosis, if present, is warranted for optimal outcomes. Among patients with hematologic malignancies, DS was reported as a TEAE by investigators in 39 (12%) of 332 patients with a similar incidence in patients who received single-agent olutasidenib (13% of 216 patients) and those who received combination therapy with azacitidine (10% of 115 patients). Treatment was held for DS in 27 (8%) of the 332 patients and dose reductions were instituted in five (2%). The dose modification measures were effective for most patients with only three patients (<1%) discontinuing olutasidenib due to a DS TEAE. As noted above, one patient experienced a fatal TEAE of DS.

Based on adjudication of potential candidate cases of DS, including TEAEs and other associated symptoms using the methodology outlined in Norsworthy, et al. 2020, 35 (11%) of patients with hematologic malignancies who received olutasidenib as a single agent or in combination with azacitidine had cases adjudicated as possible/probable DS; in 18 patients (6%), the case was assessed as severe. The incidence was similar among the 216 patients who received single-agent olutasidenib (11%) and for the 166 patients with R/R AML who received singe-agent olutasidenib at a dose of 150 mg BID (11%). Most of the patients with possible/probable candidate cases of DS had concurrent leukocytosis. Median time to onset of possible/probable DS cases in patients with R/R AML who received singe-agent olutasidenib at a dose of 150 mg BID was 12.5 days.

Review of the data across 425 patients shows that the hepatic effects AESI reported during treatment with olutasidenib as a single-agent or in combination with azacitidine were mostly characterized by reversible, asymptomatic, low-grade transaminase elevations and alkaline phosphatase elevations with or without elevations in total bilirubin initially observed at routine visits. Elevations in bilirubin were uniformly associated with elevated alkaline phosphatase levels. In events assessed by a consulting hepatologist, (b) (4), as probably or highly likely due to drug induced liver injury, a cholestatic-hepatocellular injury pattern was observed. For many of these events, patients were receiving other medications known to cause hepatotoxicity. There have been no reports of liver failure across the olutasidenib clinical program.

Based on review of TEAEs and the results of an analysis of the relationship between olutasidenib concentration and ECG QTc, olutasidenib was not associated with clinically significant QTc prolongation across the clinical program. Review of ECG findings in individual patients indicated that the observed increases in QTcF were often confounded by baseline bundle branch

block, cardiopulmonary disease history, as well as the concomitant use of medications identified as having potential to independently prolong the QTc interval, specifically azoles and fluoroquinolones which are commonly used as supportive care in AML patients. In the cardiac safety substudy, olutasidenib had no clear effects on heart rate, PR and QRS interval duration, or ECG morphology, and no clinically relevant effect on cardiac repolarization (ie, change in corrected QT interval by Fridericia formula [ΔQTcF] > 20 msec) as evidenced by the results of the primary analysis (concentration-QTc modeling) and secondary analyses (time-matched and categorical outlier analyses).

Based on the concentration-QTc analysis,the predicted mean (upper 90% confidence interval) increase in QTcF from baseline (ΔQTcF) was 6.1 msec (9.3 msec) at the geometric mean C_{max} for 150 mg BID at steady-state, confirming that olutasidenib does not prolong QTc to any clinically relevant extent. No large changes in QTc interval (>20 ms) are expected at the recommended dose.

Overall, the olutasidenib safety profile has been well characterized across 425 patients with malignancies, including 179 patients with R/R AML. Routine risk minimization activities are considered sufficient to manage the safety concerns with olutasidenib and physicians can be adequately informed of potential risks of treatment through appropriate monitoring as described in the product label.

The FDA's Assessment:
The safety of olutasidenib was evaluated in detail in the 425 patients that have had at least one dose of olutasidenib, including 153 patients with R/R AML that have received single-agent olutasidenib. The median duration of treatment for patients for patients with R/R AML that received single-agent olutasidenib was 4.7 months. The 30-day and 60-day mortality rates were 8% (13/153) and 16% (24/153), respectively.

Three adverse reactions warrant close attention:

1. Hepatobiliary toxicity: Some patients treated with olutasidenib developed hepatotoxicity, with elevations in ALT, AST, alkaline phosphatase, with or without elevations in total bilirubin. Hepatotoxicity occurred as early as 1 day and up to 17.5 months after initiation of olutasidenib. After careful review of the data, the incidence of hepatotoxicity was 23%, with 13% being Grade 3 or higher. The majority of incidences of hepatotoxicity resolved with dose interruption with only 3% of patients discontinuing treatment due hepatoxicity.
   A small proportion of patients experienced biliary events including cholangitis, cholestasis, biliary colic, and biliary tract disorder. Overall, six patients (4%) had biliary adverse event. Most of the events occurred with concomitant LFT derangement and were not isolated events.

Reviewer Comments: As there were no fatal events of hepatotoxicity in patients with R/R AML that received single-agent olutasidenib, this will not be listed as a black box warning in the PI. However, given that 20% of patients experienced an event of hepatotoxicity, it will be listed in the warning and precautions section in the PI. In addition, given that gallbladder disorders were not infrequent in this population, it will also be listed in section 6 of the PI.

2. Differentiation Syndrome: Twenty-five patients treated with olutasidenib developed differentiation syndrome. The most frequently reported symptoms and signs included: leukocytosis (65%), fever (44%), pulmonary infiltrates/congestion (40%), dyspnea (32%), and hypoxia (24%). Differentiation syndrome occurred as early as 1 day and up to 18 months of treatment initiation with olutasidenib. Most of the cases of DS were manageable with dose interruption of olutasidenib and supportive treatment with steroids, hydroxyurea, with or without diuretics. Nineteen (76%) patients resumed treatment with olutasidenib, suggesting that differentiation is manageable and non-fatal in most patients.

   Reviewer Comments: As there were two cases of fatal DS in patients with R/R AML treated with olutasidenib, this adverse reaction warrants a black box warning in the PI.

3. Leukocytosis: Thirty-eight patients (25%) experienced leukocytosis, with fourteen patients (9%) having a Grade 3 or 4 event. Leukocytosis was primarily managed with hydroxyurea. Only five patients (3%) required dose interruption due to leukocytosis. There were no dose reductions or dose withdrawals due to leukocytosis.

The most common adverse reactions were (≥20%) were: nausea, fatigue/malaise, arthralgia, constipation, leukocytosis, rash, dyspnea, mucositis, diarrhea and transaminitis. Serious adverse reactions were reported in 25% of patients, with the most frequent (≥5%) serious adverse reactions being: differentiation syndrome and transaminitis.

Overall, 49/153 (32%) experienced an adverse reaction that led to treatment interruption. The most common adverse reactions that led to treatment discontinuation were transaminitis (10%), differentiation syndrome (7%), gallbladder disorders (3%), and leukocytosis (3%). Sixteen patients (11%), had an adverse reaction that led to dose reduction, with the most common causes being due to transaminitis (6%) and differentiation syndrome (1%). Finally, twelve patients (8%) experienced an adverse reaction that led to permanent discontinuation of olutasidenib. The most common adverse reactions that led to treatment discontinuation were transaminitis (3%), differentiation syndrome (3%), and gallbladder disorders (1%).

Reviewer Comments: Although transaminitis and differentiation syndrome can be life-threatening and potentially fatal, there were few treatment discontinuations due to these causes. In addition, there were only two fatal treatment-emergent adverse reactions (differentiation

syndrome) suggesting that olutasidenib 150mg BID is tolerable in patients with R/R AML.

SUMMARY AND CONCLUSIONS

9.2 Statistical Issues

The FDA's Assessment:

The submitted clinical data from study 2102-HEM-101 demonstrated:

1) a CR+CRh rate of 35% (95% CI: 27%, 43%) with median duration of CR+CRh of 25.9 months (95% CI: 13.5, NR). The results from the interim analysis passed the pre-specified efficacy criterion of the lower boundary of the response rate for olutasidenib greater than 15%.
2) similar CR+CRh time to response (median 1.9 months; range, 0.9 to 5.6 months) and transfusion independence (34% TD->TI and 64% TI->TI) compared to the FDA approved IDH1 inhibitor ivosidenib (data source: ivosidenib USPI).

Of note, FDA recommended start of anti-cancer therapy be removed as an event from the Applicant's original definition of DOR. The Applicant accepted FDA's recommendation and changed the definition to "Duration of response is defined as the time from the date of the first response to the date of the relapse or death. Patients who did not relapse were censored at the date of last response assessment."

9.3 Conclusions and Recommendations

The FDA's Assessment:

The efficacy of olutasidenib was established on the basis of durable CR + CRh rate, and the rate of conversion of transfusion-dependence to transfusion-independence in study 2102-HEM-101 (please refer to Statistical comments above). The median duration of treatment at this time is relatively short at 4.7 months, so long-term benefits are unknown. However, short-term benefits are meaningful for patients seeking improved quality of life. Olutasidenib was well-tolerated with only a few patients discontinuing treatment due to an adverse reaction. Serious risks, such as differentiation syndrome and hepatotoxicity, can be appropriately managed with labeling. In light of the immediate clinical benefit and relatively tolerability, the review team recommends regular approval of olutasidenib for patients with R/R AML with a susceptible IDH1 mutation as detected by an FDA-approved test.

Haiyan Chen, PhD
Primary Statistical Reviewer

Jonathon Vallejo, PhD
Statistical Team Leader

Ashley Woods, MD
Primary Clinical Reviewer

Kelly Norsworthy, MD
Clinical Team Leader

10.0 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:
This application was not presented to the Oncologic Drug Advisory Committee or any other external consultants.

11.0 Pediatrics

The Applicant's Position:

On 20 December 2019, FDA confirmed agreement with the initial Pediatric Study Plan which was submitted to IND 127313 on 25 November 2019 (SN 0201).

The FDA's Assessment:

There is currently no data regarding the use of olutasidenib in the pediatric population.

The Applicant submitted an amended iPSP on June 29th, 2022, to evaluate olutasidenib in pediatric patients with low-grade gliomas. On September 7th, 2022, FDA submitted written responses to the amended iPSP to the applicant. On October 24th, 2022, the Applicant submitted an agreed-upon iPSP. However, FDA decided to administratively close the amended iPSP because the marketing application was already filed. Per the 2020 FDA guidance entitled "Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended, "Once the FDA accepts for filing an application or supplemental application, it is not necessary to submit amendments to the iPSP because changes to the plan for pediatric development can be negotiated during the review cycle as appropriate." Instead, the proposed changes to their pediatric development program were considered by the review team during the application review cycle and informed our issuance of a post-marketing requirement for a pediatric clinical trial.

12.0 Labeling Recommendations

The table below summarizes changes to the proposed United States Prescribing Information (USPI) and Medication Guide (MG) made by FDA. See the final approved USPI and MG for REZLIDHIA (olutasidenib) accompanying the approval letter for more information.

Data:

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Highlights of Prescribing Information	Included a boxed warning for differentiation syndrome	FDA agreed with some modifications to add more direct language. Per 21 CFR 201.57(d)(8) the Highlights of Prescribing Information should be no longer than ½ page; a waiver for this requirement is acceptable.
1 Indications and Usage	Included adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation	FDA agreed but added the phrase "as detected by an FDA-approved test" to the end of the indication statement.
2.1 Patient Selection	Included patients selected based on the presence of IDH1 mutations in blood or bone marrow	FDA agreed.
2.2 Recommended Dosage	Included a recommended dosage of 150 mg twice daily (b) (4) prior to or 2 hours after a meal until disease progression or unacceptable toxicity	FDA edited the instructions to at least 1 hour before or 2 hours after a meal and made some additional edits for clarity and added recommendations for how to handle vomited doses.
2.3 Monitoring and Dose Modifications for Toxicities	Included monitoring of blood counts, and blood chemistries including liver function tests prior to initiation of REZLIDHIA and frequently during treatment	FDA generally agreed with some modifications, including the addition of dosage modifications for noninfectious leukocytosis.
3 Dosage Forms and Strengths	Included oral dosage form of 150 mg opaque white capsule imprinted with "OLU 150"	FDA agreed.
4 Contraindications	N/A	N/A
5 Warning and Precautions	Included W&P for differentiation syndrome and hepatic effects	FDA changed the title of the (b) (4) W&P to Hepatotoxicity to better describe

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

		this adverse reaction. FDA modified language in the W&P to provide more direct statements and to align with current labeling practice.
6 Adverse Reactions	Included safety information from 153 adults with R/R AML who received 150 mg twice daily	FDA modified this section based on current labeling practice including adding information about dose reductions due to adverse reactions, modifying the adverse reactions and laboratory abnormalities tables to include an all-grades column and a grade 3 to 4 column, as well as reordering the list in the table to be in descending order by SOC and then within SOC. FDA also recommended shortening the list of individual terms used in a grouped term in the footnote section of the adverse reaction table to avoid long lists of near synonyms by using one footnote: "Includes multiple similar adverse reaction terms." for some terms, while including all the composite terms for other more clinically significant/unusual adverse reactions.
7 Drug Interactions	7.1 Included recommendations for strong CYP3A4 inducers 7.2 Included recommendation against co-administration of REZLIDHIA with medications that are sensitive substrates of CYP3A4 enzymes	FDA generally agreed but modified this section to align with current labeling practice and updated section 7.1 to include that concomitant use of Rezlidhia with a moderate CYP3A inducer may reduce Rezlidhia efficacy.
8 Use in Specific Population	Included information about use in pregnancy, lactation, pediatric, geriatric, renal impairment, and hepatic impairment	FDA revised sections 8.1 and 8.2 to align with PLLR recommendations, including information about duration not to breastfeed during and after treatment with Rezlidhia based on its half-life (5 x T1/2). FDA modified section 8.5 to note that compared to patients younger than 65 years, the rate of hypertension and hepatotoxicity was higher in those over 65 years.

		FDA modified section 8.6 (renal impairment) to align with current labeling practice. FDA modified section 8.7 (hepatic impairment) to align with current labeling practice and to add cautionary language about the increased probability of differentiation syndrome and grade 3 or higher hepatotoxicity in patients with mild or moderate hepatic impairment.
11 Description	Included chemical name, structure, formula, weight, solubility, form and dosage, and inactive ingredients.	FDA generally agreed but modified the product name to match the established pharmaceutical class as in the Highlights and recommended adding a description of the drug substance appearance. FDA also revised the description section to fully describe the capsule shell and black printing ink as they were not complete.
12 Clinical Pharmacology	Included mechanism of action, pharmacodynamics, and pharmacokinetics	In section 12.1, FDA added text to define susceptible IDH1 mutation and removed language that was promotional in nature. In section 12.2, any pharmacodynamic claims of a promotional nature were removed. Exposure-response data added to reflect an increased risk of differentiation syndrome and grade 3 or higher hepatotoxicity with increased olutasidenib exposure. QT study results added. In section 12.3, revisions made to align with recommendations in the *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* guidance and to align with current labeling practice.
13 Nonclinical Toxicology	Included carcinogenesis, mutagenesis, and impairment of fertility	Section 13.2 Animal Toxicology and/or Pharmacology added to describe phototoxicity in vitro and

		in vivo in a pigmented rat study.
14 Clinical Studies	Included efficacy data from the pivotal cohort of an open-label basket clinical trial in 123 adults with relapsed or refractory AML with a centrally confirmed IDH1 mutation	FDA modified this section to remove (b) (4) [redacted] FDA edited further to align with current labeling practice for presenting the results of a single arm study for AML.

The Applicant's Position:
This NDA reflects the first submission of labeling; therefore, there are no changes to identify.

The FDA's Assessment:
FDA revised the USPI as described in the table above. The MG was updated to align with changes made to the USPI.

13.0 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:
REMS is not required.

14.0 Postmarketing Requirements and Commitment

The FDA's Assessment:

The following PMR's/PMCs will be issued to the sponsor:

1. PMR #1: Conduct a study to further characterize the incidence and severity of differentiation syndrome, hepatotoxicity, and other serious toxicities that may develop with longer term use of olutasidenib, in patients with relapsed or refractory acute myeloid leukemia (AML). This data may come from Study 2102-HEM-101. Include data from approximately 179 patients with relapsed or refractory AML that received olutasidenib as monotherapy. Patients should be followed for 3 years. Data should include exploratory subgroup analyses and corresponding subject level data that includes cytogenetics, specific IDH1 mutations, and mutation analyses for other genes as obtained under the study protocol.
2. PMR #2: Conduct a clinical trial to determine the appropriate dose of olutasidenib, and to assess safety, tolerability, pharmacokinetics, and pharmacodynamics of olutasidenib, in pediatric patients ages ≥12 to < 18 years with IDH1-mutated gliomas. Patients should be followed for at least 12 months (52 weeks). Include at least 6 patients ≥12 to < 18 years old.
3. PMR #3: Conduct a clinical drug interaction study to evaluate the effect of repeated doses of olutasidenib on the pharmacokinetics of substrates of OATP1B1. Assess the magnitude of increased drug exposure and determine appropriate dosage recommendations when olutasidenib is administered concomitantly with OATP1B1 substrates. Design and conduct the study in accordance with the FDA Guidance for Industry titled, "Clinical Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."
4. PMC #1: Conduct a clinical drug interaction study to evaluate the effect of repeated doses of a moderate CYP3A inducer on the pharmacokinetics of olutasidenib to assess the magnitude of decreased drug exposure and determine appropriate dosage recommendations when olutasidenib is administered concomitantly with moderate CYP3A inducers. Design and conduct the study in accordance with the FDA Guidance for Industry titled, "Clinical Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions."
5. PMC #2: Conduct a clinical drug interaction study to evaluate the effect of repeated doses of olutasidenib on the pharmacokinetics of substrates of CYP1A2, 2B6, 2C8, 2C9, 2C19, and 3A. Assess the magnitude of decreased drug exposures to determine appropriate dosage recommendations when olutasidenib is administered concomitantly with CYP substrates. Design and conduct the study in accordance with the FDA Guidance for Industry titled, "Clinical Drug Interaction Studies —Cytochrome P450 Enzyme- and

Transporter-Mediated Drug Interactions."

15.0 Division Director (DHOT) (NME ONLY)

Haleh Saber, PhD

16.0 Division Director (OCP)

Brian Booth, PhD

17.0 Division Director (OB)

Mark Levenson, PhD

18.0 Division Director (Clinical)

R. Angelo de Claro, MD

19.0 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

Marc Theoret, MD

20.0 Appendices

20.1 References

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20.2 Financial Disclosure

The Applicant's Position:

In compliance with 21 CFR 54, the Applicant provided FDA Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators).

As agreed with FDA in the 13 May 2021 pre-NDA meeting, for BIMO planning, datasets and other associated information requested in the BIMO guidances will be provided for the 2102-HEM-101 Phase 2 Cohort 1 only (pivotal cohort providing primary safety and efficacy for the NDA). Accordingly, the listing of clinical investigators provided is for those who contributed to enrollment into Phase 2 Cohort 1.

The Applicant has not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). Each listed clinical investigator was required to disclose if they had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b). No clinical investigators participating in [redacted] (b) (4) disclosed any such interests nor were any the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

The FDA's Assessment:
The FDA agrees with the Applicant's assessment but notes that Study [redacted] (b) (4) (a study of an unrelated product) was incorrectly referenced instead of Study 2102-HEM-101.

Covered Clinical Study (Name and/or Number):* 2102-HEM-101

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from

		Applicant)
Total number of investigators identified: 47		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
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: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
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) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

20.3 Nonclinical Pharmacology/Toxicology

The Applicant's Position:

- Olutasidenib is a potent and selective inhibitor of mutated IDH1, but not wild type IDH1 or mutated IDH2.
- Olutasidenib displays little or no off-target activity against a broad panel of other receptors and kinases.

- Olutasidenib is highly protein-bound, does not have a high affinity for red blood cells, and can cross the blood:brain barrier.
- There is no indication of human-specific metabolites. In plasma collected from human patients after multiple oral doses of olutasidenib after BID dosing at 150 mg/kg/day, unchanged parent compound was the predominant drug-related component. No detected metabolite approached or exceeded the 10% TDRE threshold specified by the FDA and ICH.
- Based on static mechanistic models for predicting DDIs, the potential for olutasidenib to cause CYP induction mediated clinical DDIs with coadministered sensitive substrates of CYP3A4, 1A2, 2B6, 2C8, and 2C9 cannot be discounted.
- Based on static mechanistic models for predicting DDIs, the potential for olutasidenib to cause reversible CYP inhibition-mediated DDIs with coadministered sensitive substrates is deemed low for the isoforms tested.
- While BCRP and P-gp gut-mediated PK interactions with coadministered substrates of P-gp or BCRP cannot be discounted, low olutasidenib solubility in simulated intestinal fluid may mitigate this risk.
- Olutasidenib is described as a potential clinically relevant inhibitor of OATP1B1.
- The risk of olutasidenib-mediated interactions with OAT3 and OAT2 is low.
- Comparisons between the AUC values observed in the toxicology studies and those in the pivotal clinical study show that the safety margins range between 1- and 12-fold for unbound olutasidenib.
- Olutasidenib did not demonstrate any potential for genotoxicity or embryofetal toxicity.
- Olutasidenib demonstrated a potential for phototoxicity in the nonclinical studies; however, a potential for phototoxicity has not been identified in clinical trials in patients.
- Liver and GI effects noted in rats and/or monkeys have also been noted in the clinic. However, the QTc interval prolongation effects noted in monkeys did not translate to clinically relevant QTc interval prolongation, and the thyroid effect noted in rats was secondary to altered hepatic function and has not been observed in the clinic.
- Taken together, the results of the nonclinical studies support the registration of olutasidenib for the treatment of patients with relapsed or refractory AML with mutations in the IDH1 gene.

The FDA's Assessment:

See Section 5 for FDA pharmacology/toxicology review and position. Of note, the FDA review identified that olutasidenib did demonstrate embryo-fetal toxicity which resulted in embryo-fetal death and altered fetal growth when administered to pregnant rats and rabbits during the period of organogenesis at exposures up to 10 times and 0.7 times, respectively, the human exposure at the recommended daily dose.

20.4 OCP Appendices (Technical documents supporting OCP recommendations)

20.4.1 Summary of Bioanalytical Method Validation and Performance

The FDA's Assessment:

A bioanalytical method was developed to determine olutasidenib concentration in the biological samples collected in clinical studies. The method was fully validated at (b) (4) for use in the following clinical studies: 2102-HEM-101, 2102-ONC-102, 2102-HVS-103, 2102-HVS-105 and 2102-HVS-106 and was partially validated at (b) (4) for use in the hAME study (2102-HVS-104) to support bioanalysis of radioactive material in the study.

Table 84 and Table 85 below listed the bioanalytical reports describing the individual method performance for all clinical studies. Overall, the method and performance are reasonable.

Table 82. Summary method performance of a bioanalytical method to measure FT-2102 in human plasma (K_2EDTA)

Bioanalytical method validation report name, amendments, and hyperlinks	**Validation of an LC-MS/MS Method for the Analysis of FT-2102.1 in Human Plasma (K_2EDTA)** Report # CD-0013-RB-BV-RPT-01 Long-Term Stability Evaluations for FT-2102.1 in Stock Solutions and in Human Plasma (K_2EDTA) by LC-MS/MS Analysis Report # CD-0014-RB-BL-RPT-01	
Method description	An analytical method for quantification of olutasidenib (FT-2102) and stable, isotopically labeled FT-2102 internal standard in human plasma (K_2EDTA) using protein precipitation extraction and analysis using liquid chromatography tandem mass spectrometry (LC-MS/MS).	
Materials used for calibration curve & concentration	Human plasma K_2EDTA	
Validated assay range	10.0 – 5000 ng/mL	
Material used for QCs & concentration	Human plasma K_2EDTA	
Minimum required dilutions (MRDs)	Not applicable	
Source & lot of reagents (LBA)	Not applicable	
Regression model & weighting	Linear, $1/x^2$	
Validation parameters	**Method validation summary**	**FDA Acceptability**

Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	8	Yes
	Cumulative accuracy (%bias) from LLOQ to ULOQ Olutasidenib (FT-2102)	-7.8 to 2.0 %	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ Olutasidenib (FT-2102)	≤ 4.9%	Yes
QCs performance during accuracy & precision	**Cumulative accuracy (%bias) in QCs** QCs: Inter-batch: Intra-batch:	-3.7 to 1.0% -5.1 to 5.0%	Yes
	Inter-batch %CV QCs:	≤ 7.1%	Yes
	Total Error (TE) QCs:	Not applicable	N/A
Selectivity & matrix effect	Matrix Effects: Six total lots tested. Range of observed bias: -9.3 to -1.0%.		Yes
Interference & specificity	Six total replicates tested (double blanks and control blanks). No interference observed at the retention time of FT-2102.		Yes
Hemolysis effect	One lot tested. Range of observed bias: 1.3 to 1.6%.		Yes
Lipemic effect	One lot tested. Range of observed bias: 0.8 to 3.0%.		Yes
Dilution linearity & hook effect	Highest concentration tested: 25000 ng/mL Dilution factor: 50 Range of observed bias: 0.0% Hook effect: not applicable		Yes
Bench-top/process stability	FT-2102 in K_2EDTA whole blood (room temperature for 2 hours): % difference (3750 ng/mL) = 0.0% FT-2102 in K_2EDTA plasma (room temperature for 28 hours): % difference for QC-Low (30.0 ng/mL) = -3.7 and QC-High (3750 ng/mL) = -4.3%.		Yes
Freeze-Thaw stability	4 cycles of -80°C/room temperature: % difference QC-Low (30.0 ng/mL) =-1.3 and QC-High (3750 ng/mL) = -0.3%. 4 cycles of -20°C/room temperature: % difference QC-Low (30.0 ng/mL) = -1.0 and QC-High (3750 ng/mL) = -4.3%.		Yes

Long-term storage	Long-term stability of FT-2102 in human plasma (K_2EDTA) has been established for 384 days at -80°C and 379 days at -20°C.	Yes
Parallelism	Not applicable	
Carry over	% analyte (FT-2102) carry over: < 11.7% % internal standard carry over: 0.0%	Yes
Method performance in study: 2102-HEM-101 LC-MS/MS Analysis of FT-2102 and Azacytidine in Human Plasma (K2EDTA) in Support of FORMA Therapeutics, Inc. Study Number 2102-HEM-101; Report No. CD-0011-RB-BS-RPT-01		
Assay passing rate	(including incurred sample reanalysis (ISR))	
Standard curve performance	• Cumulative bias range: -1.6 to 1.0% • Cumulative precision: ≤ 4.1% CV	Yes
QC performance	• Cumulative bias range: -4.4 to 0.3% • Cumulative precision: ≤ 6.9% CV • TE: Not applicable	Yes
Method reproducibility	Incurred sample reanalysis was performed in 10% of study samples and the results for over two-thirds of the study samples that were selected for reanalysis were acceptable (within ±20.0% difference between the original and reanalysis values).	Yes
Study sample analysis/ stability	All study samples were analyzed within the established stability period (384 days at -80°C).	
Method performance in study 2102-ONC-102 LC-MS/MS Analysis of FT-2102 in Human Plasma (K2EDTA) and Cerebrospinal Fluid in Support of FORMA Therapeutics, Inc. Study Number 2102-ONC-102; Report No. CD-0039-RB-BS-RPT-01		
Assay passing rate	(including incurred sample reanalysis (ISR)) 100%	Yes
Standard curve performance	• Cumulative bias range: -1.5 to 2.0% • Cumulative precision: ≤ 4.2% CV	Yes
QC performance	• Cumulative bias range: -3.2 to 10.0% • Cumulative precision: ≤ 59.4% CV (QC-Low; 2 QCs did not meet acceptance criteria and were not removed from summary statistics). ≤9.3% For QC-Mid, High and Dil • TE: Not applicable	Yes
Method reproducibility	Incurred sample reanalysis was performed in 10% of study samples and the results for over two-thirds of the study samples that were selected for reanalysis were acceptable (within ±20.0% difference between the original and reanalysis values).	Yes
Study sample analysis/ stability	All study samples were analyzed within the established stability period (384 days at -80°C).	
Method performance in study 2102-HVS-103 LC-MS/MS Analysis of FT-2102 in Human Plasma (K_2EDTA) in Support of FORMA Therapeutics, Inc. Study Number 2102-HVS-103; Report No. CD-0040-RB-BS-RPT-01		

Assay passing rate	(including incurred sample reanalysis (ISR))	100%
Standard curve performance	• Cumulative bias range: -2.6 to 1.6% • Cumulative precision: ≤ 4.8% CV	Yes
QC performance	• Cumulative bias range: -3.0 to -0.5% • Cumulative precision: ≤ 4.4% CV • TE: Not applicable	Yes
Method reproducibility	Incurred sample reanalysis was performed in 10% of study samples and 100% of samples met the pre-specified criteria	Yes
Study sample analysis/ stability	Longest duration of study sample storage: 85 Days at -80°C. Long-term stability coverage: 384 Days at -80°C	
Method performance in study 2102-HVS-104 Bioanalytical Sample Analysis Report in Support of the Study Entitled, "An Open-Label, Single-Dose Study to Assess the Absorption, Metabolism, Excretion, and Mass Balance of FT-2102 in Healthy Adult Male Subjects"; Report No. RPT05008		
Assay passing rate	(including incurred sample reanalysis (ISR)) 100%	Yes
Standard curve performance	• Cumulative bias range: -2.6 to 6.0% • Cumulative precision: ≤ 7.35% CV	Yes
QC performance	• Cumulative bias range: -2.67 to 4.40% • Cumulative precision: ≤ 3.73% CV • TE: Not applicable	Yes
Method reproducibility	Incurred sample reanalysis was performed in 12% of study samples and 100 % of samples met the pre-specified criteria	Yes
Study sample analysis/ stability	The longest actual sample storage time prior to analysis is 44 days at -80°C. Long-term stability coverage: 384 Days at -80°C	
Method performance in study 2102-HVS-105 LC-MS/MS Analysis of FT-2102 in Human Plasma (K2EDTA) in Support of FORMA Therapeutics, Inc. Study Number 2102-HVS-105; Report No. CD-0060-RB-BS-RPT-01		
Assay passing rate	(including incurred sample reanalysis (ISR)) 81.8%	Yes
Standard curve performance	• Cumulative bias range: -3.0 to 3.0% • Cumulative precision: ≤ 4.5% CV	Yes
QC performance	• Cumulative bias range: 0.8 to 5.0% • Cumulative precision: ≤ 16.8% CV (QC-Low), ≤6.8% (QC-Mid and High) • TE: Not applicable	Yes
Method reproducibility	Incurred sample reanalysis was performed in 10% of study samples and the results for over two-thirds of the study samples that were selected for reanalysis were acceptable (within ±20.0% difference between the original and reanalysis values).	Yes
Study sample analysis/ stability	All samples were analyzed within the established the long-term stability matrix (384 Days at -80°C).	
Method performance in study 2102-HVS-106 LC-MS/MS Analysis of FT-2102 in Human Plasma (K2EDTA) in Support of Forma Therapeutics, Inc Study Number 2102-HVS-106; Report No. CD-0061-RB-BS-RPT-01		
Assay passing rate	(including incurred sample reanalysis (ISR))	Yes

	90.0%	
Standard curve performance	• Cumulative bias range: -6.0 to 5.2% • Cumulative precision: ≤ 5.8% CV	Yes
QC performance	• Cumulative bias range: -9.2 to 4.3% • Cumulative precision: ≤ 5.9% CV • TE: Not applicable	Yes
Method reproducibility	Incurred sample reanalysis was performed in 10% of study samples and the results for over two-thirds of the study samples that were selected for reanalysis were acceptable (within ±20.0% difference between the original and reanalysis values).	Yes
Study sample analysis/ stability	All study samples were analyzed within the established stability period (384 days at -80°C).	

Table 83. Summary of method modification(s) and cross-validation results

Bioanalytical method validation report name and hyperlink	Method Validation of an LC-MS/MS Assay for the Determination of FT-2102.1 in K2EDTA Human Plasma; Report # RPT05001		
Changes in method	No changes in the method. This was due to a bioanalytical facility change.		
New validated assay range if any	10.0 to 5000 ng/mL		
Validation parameters	**Cross-validation performance**		**FDA Acceptability**
Standard calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	-2.00 to 3.20%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 11.3%	Yes
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 4 QCs	0.53 to 5.67%	Yes
	Inter-batch %CV	≤ 7.92%	Yes
	Percent total error (TE)	NA	**N/A**
Cross-validation	Not applicable		
List other parameters	Dilution integrity (50-fold) % Bias: Assay selectivity (6 lots). No interference observed at the retention time of FT-2102.	-0.4%	Yes

20.4.2 Population PK Analysis

Population PK analysis was performed on 4517 observations from 324 subjects for Study 2102-HEM-101 and 796 observations from 25 subjects for Study 2102-HVS-105. The number of samples below the quantitation limit (BLQ) after the administration of the first dose ("post-treatment BLQ") were 122 (2.60%) and 30 (3.6%) in studies 2102-HEM-101and 2102-HVS-105 respectively. BLQ samples were excluded from the analysis. Data from 2 subjects were all BLQ and therefore were not modeled.

20.4.2.1 Executive Summary

The FDA's Assessment:

Two-compartmental model with 1st-order absorption constant rate and 1st-order elimination constant rate captured the PopPK data and there was no clinically meaningful covariate identified in patients. PK data of only 1 of 3 Phase 1 clinical studies in health volunteers were included in the original population PK analysis. In addition, NCI classification for hepatic impairment had been mis-applied using baseline ALT instead of AST. Upon FDA information request, the applicant included all 3 Phase 1 studies in the PPK analysis where NCI hepatic impairment was correctly classified using baseline AST. The Applicant's updated PPK modeling analysis is generally acceptable.

Overall, the clearance in AML patients (mean ± SD of 3.15 ± 1.19, n=326) was about 2.5 times that in healthy volunteers (1.21 ± 0.17, n=81). Female patients' CL was 86% of males. There was no large impact on CL observed for the other covariates, including body weight, hepatic impairment, and renal impairment.

20.4.2.2 PPK Assessment Summary

The Applicant's Position:

The baseline demographics of the continuous covariates and categorical covariates evaluated in the population PK analysis are shown in Table 86-Table 88 respectively.

The estimate for apparent clearance (CL/F) was 3.25 L/h, volume of distribution (V_2/F) of the central compartment was 201 L, volume of distribution (V_3/F) of the peripheral compartment was 4613 L, and absorption rate (KA) was 6.282 1/h.

A 2-compartment model with first-order elimination adequately described olutasidenib plasma concentration data, and the PK parameters were precisely estimated. The covariates included were body weight on V_2/F, sex on CL/F and V_2/F and study on CL/F V_2/F and KA.

Diagnostic plots for the final PK model are presented in Figure 16: Goodness-of-Fit Plots for the Final Population PK Model

and Figure 17 and model parameters are shown in Table 88.

A forest plot analysis was performed (Figure 20) to visually evaluate the impact of covariate effects on exposure. A large difference in exposure was observed between studies likely due to study design differences, however a large impact on exposure was not observed for other covariates, including body weight and sex.

General Information		
Objectives of PPK Analysis		• Characterize Olutasidenib's PK profile • Identify the impact of subject characteristics (i.e., covariates) on systemic (i.e., plasma) exposure to olutasidenib • Predict individual exposures for the Exposure-Response assessment
Studies Included		2102-HEM-101 and 2102-HVS-105
Dose(s) Included		100 mg QD with food, 150 mg QD, 300 mg QD, 150 mg BID and single dose of 150 mg
Population Included		*Healthy and ITT*
Population Characteristics (Table 86 and Table 87)	General	2102-HEM-101: Age median (range): 70.0 (28.0, 90.0) yr, 76% subj >=65 yr, 31% subj >=75 yr) Weight median (range): 72.0 (36.3, 145) kg n (XX%) male: 169 (52.2%) n (XX%) in each race: White 183 (56.5%), Black/African-American 14 (4.3%), Asian 9 (2.8%), Other 20 (6.2%, Missing 98 (30.2%) 2102-HVS-105: Age median (range): 61.0 (38.0, 70.0) yr, *8% subj >=65 yr, 4% subj >=75 yr)* Weight median (range): 77.1 (52.6, 135) kg n (XX%) male: 17 (68.0%) n (XX%) in each race: White 16 (64.0%), Black/African-American 5 (20.0%), Asian 1 (4.0%), American Indian/Alaskan Native 1 (4.0%), Multiple 2 (8.0%)
	Organ Impairment	*Hepatic (NCI): n (%) in each category* 2102-HEM-101: Normal: 262 (80.9%) Mild: 59 (18.2%) Moderate: 3 (0.9%)

		2102-HVS-105: Normal: 19 (76.0%) Mild: 2 (8.0%) Moderate: 4 (16.0%) *Renal:* 2102-HEM-101: Estimated GFR (mL/min/1.73 m^2) Median (range)= 86.2 (27.9, 137)
	Pediatrics (if any)	None
No. of Patients, PK Samples, and BLQ		*Specify n (%) of pre-/post-dose BLQ* 4517 observations from 324 subjects for Study 2102-HEM-101 796 observations from 25 subjects for Study 2102-HVS-105 BLQ samples: 122 (2.60%) in 2102-HEM-101 and 30 (3.6%) in 2102-HVS-105
Sampling Schedule	Rich Sampling	2102-HVS-105: Predose, at 1, 1.5, 2, 2.75, 3.5, 4.25, 5, 5.75, 6.5, 7.25, 8, 10, 12, 24, 36, 48, 60, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408, and 432 hours post-dose.
	In ITT Population	2102-HEM-101: Cycle 1 Day 1: Predose, 0.5, 1, 2, 4 and 8 hours post-dose Cycle 1 Days 2, 8, 15 and 22: Predose Cycle 2 Day 1: Predose, 0.5, 1, 2, 4 and 8, 24, 72 hours post-dose Cycle 2 Day 15: Predose Cycle 3 and 4, Day 1: Predose
Covariates Evaluated	Static	Table 86 and Table 87
	Time-varying	N/A

Final Model	**Summary**	**Acceptability [FDA's comments]**
Software and Version	Dataset preparation: SAS (Version 9.4). Data exploration and visualization: R (Version 3.6.3 or higher) Nonlinear mixed-effects modeling software: NONMEM®; version 7.4.4), a software package for nonlinear mixed-effects analysis (ICON, Hanover, MD, US), was used for population PK and simulation to derive exposure measure for subsequent E-R analyses.	Acceptable.

	Population PK model evaluation and E-R analyses: R (version 3.6.3 or higher).	
Model Structure	2-compartment oral model with first order elimination	Acceptable.
Model Parameter Estimates	Table 88	Acceptable.
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	Table 88	Acceptable.
BLQ for Parameter Accuracy	BLQ values were kept in the analysis dataset and flagged accordingly. Fewer than 3% of the data were BLQ; therefore, imputation methods, such as the M3 likelihood imputation, were not performed.	Acceptable.
GOF, VPC	Figure 16: Goodness-of-Fit Plots for the Final Population PK Model and Figure 17	Acceptable.
Significant Covariates and Clinical Relevance	Figure 20	See Figure 20 and related text.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.3 PK	No population-PK language was proposed in Section 12.3 of the USPI.	Acceptable.

Table 84: Summary of Continuous Covariates in the Population PK Dataset

	2102-HEM-101 (N=324)	2102-HVS-105 (N=25)	Overall (N=349)
Age (years)			
Mean (SD)	67.9 (11.3)	58.4 (6.87)	67.2 (11.3)
Median [Min, Max]	70.0 (28.0, 90.0)	61.0 [38.0, 70.0]	70.0 [28.0, 90.0]
Baseline body weight (kg)			
Mean (SD)	73.8 (17.1)	84.9 (22.2)	74.6 (17.7)
Median [Min, Max]	72.0 [36.3, 145]	77.1 [52.6, 135]	72.6 [36.3, 145]
Baseline lean body weight (kg)			
Mean (SD)	52.6 (9.81)	58.8 (12.9)	53.0 (10.2)
Median [Min, Max]	53.6 [30.5, 88.3]	57.7 [35.1, 87.6]	53.7 [30.5, 88.3]
Baseline body surface area (m^2)			
Mean (SD)	1.82 (0.223)	1.97 (0.293)	1.83 (0.231)
Median [Min, Max]	1.82 [1.23, 2.59]	1.92 [1.45, 2.64]	1.83 [1.23, 2.64]

Table 84: Summary of Continuous Covariates in the Population PK Dataset

	2102-HEM-101 (N=324)	2102-HVS-105 (N=25)	Overall (N=349)
Baseline body mass index (kg/m^2)			
Mean (SD)	26.3 (6.48)	28.4 (4.95)	26.4 (6.40)
Median [Min, Max]	25.0 [16.0, 91.9]	27.5 [20.0, 39.6]	25.3 [16.0, 91.9]
Baseline alanine aminotransferase (U/L)			
Mean (SD)	25.2 (19.5)	27.7 (16.4)	25.4 (19.3)
Median [Min, Max]	20.0 [4.00, 159]	22.0 [6.00, 69.0]	20.0 [4.00, 159]
Baseline aspartate aminotransferase (U/L)			
Mean (SD)	24.3 (13.5)	30.2 (18.1)	24.7 (13.9)
Median [Min, Max]	20.0 [5.00, 138]	23.0 [12.0, 79.0]	21.0 [5.00, 138]
Baseline alkaline phosphatase (U/L)			
Mean (SD)	99.6 (50.7)	81.9 (54.8)	98.3 (51.1)
Median [Min, Max]	86.0 [26.4, 482]	71.0 [38.0, 326]	85.0 [26.4, 482]
Missing	1 (0.3%)	0 (0%)	1 (0.3%)
Baseline bilirubin (mg/dL)			
Mean (SD)	0.601 (0.309)	0.772 (0.583)	0.613 (0.338)
Median [Min, Max]	0.526 [0.117, 2.28]	0.500 [0.300, 2.20]	0.526 [0.117, 2.28]
Baseline estimated GFR (mL/min/1.73 m^2)			
Mean (SD)	84.0 (19.8)	91.9 (17.0)	84.5 (19.7)
Median [Min, Max]	86.2 [27.9, 137]	92.4 [59.3, 133]	86.5 [27.9, 137]
Baseline creatinine clearance (mL/min)			
Mean (SD)	89.0 (36.1)	112 (40.8)	90.7 (36.9)
Median [Min, Max]	83.0 [24.0, 267]	104 [64.8, 224]	83.0 [24.0, 267]

Abbreviations: BLQ=below the lower limit of quantitation; No.=number; PK=pharmacokinetic
Source: Report FORM-PMX-FT2102-2633, Table 12

Table 85: Summary of Categorical Covariates in the Population PK Dataset

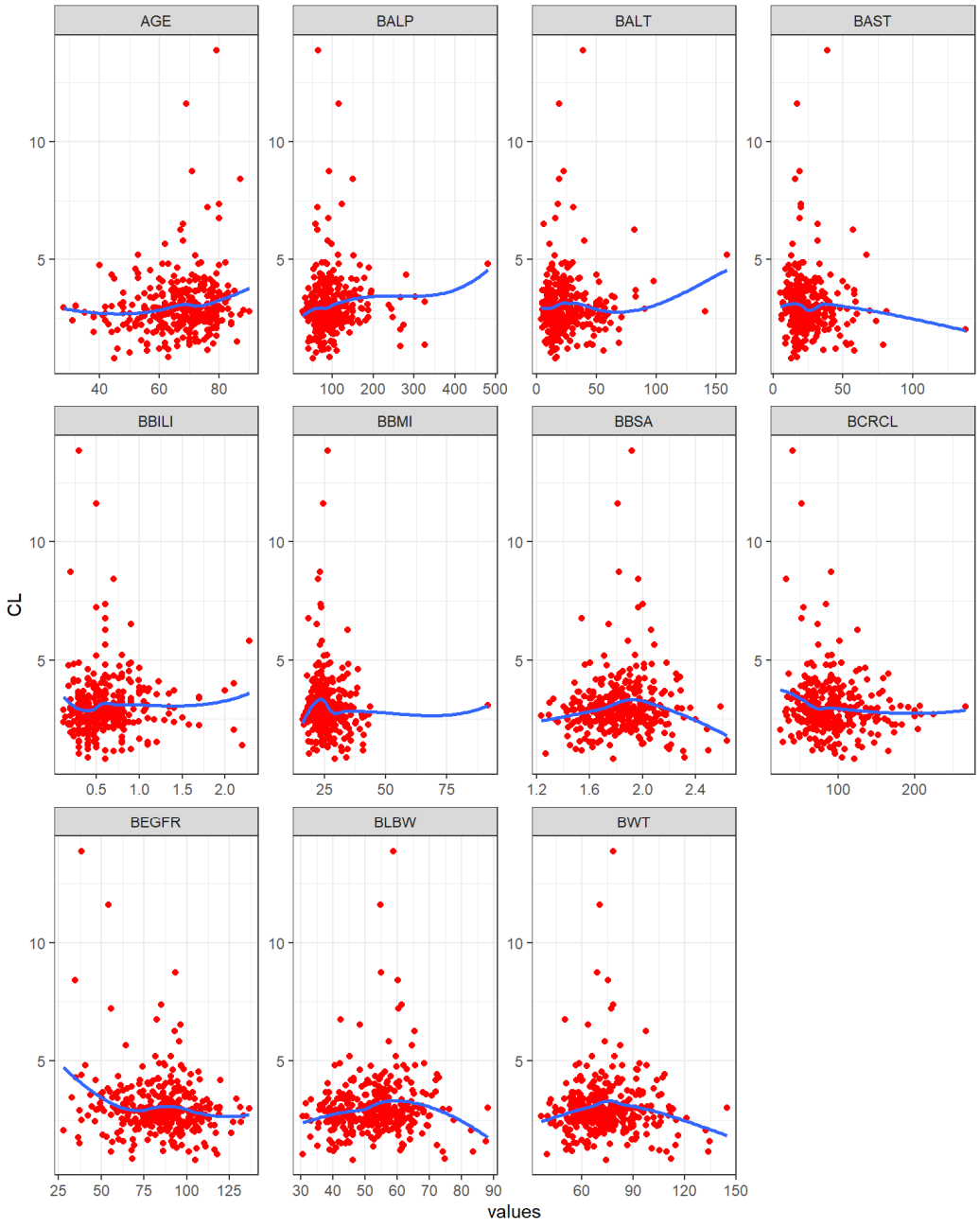
	2102-HEM-101 (N=324)	2102-HVS-105 (N=25)	Overall (N=349)
Sex, N (%)			
Male	169 (52.2%)	17 (68.0%)	186 (53.3%)
Female	155 (47.8%)	8 (32.0%)	163 (46.7%)
Race, N (%)			

Table 85: Summary of Categorical Covariates in the Population PK Dataset

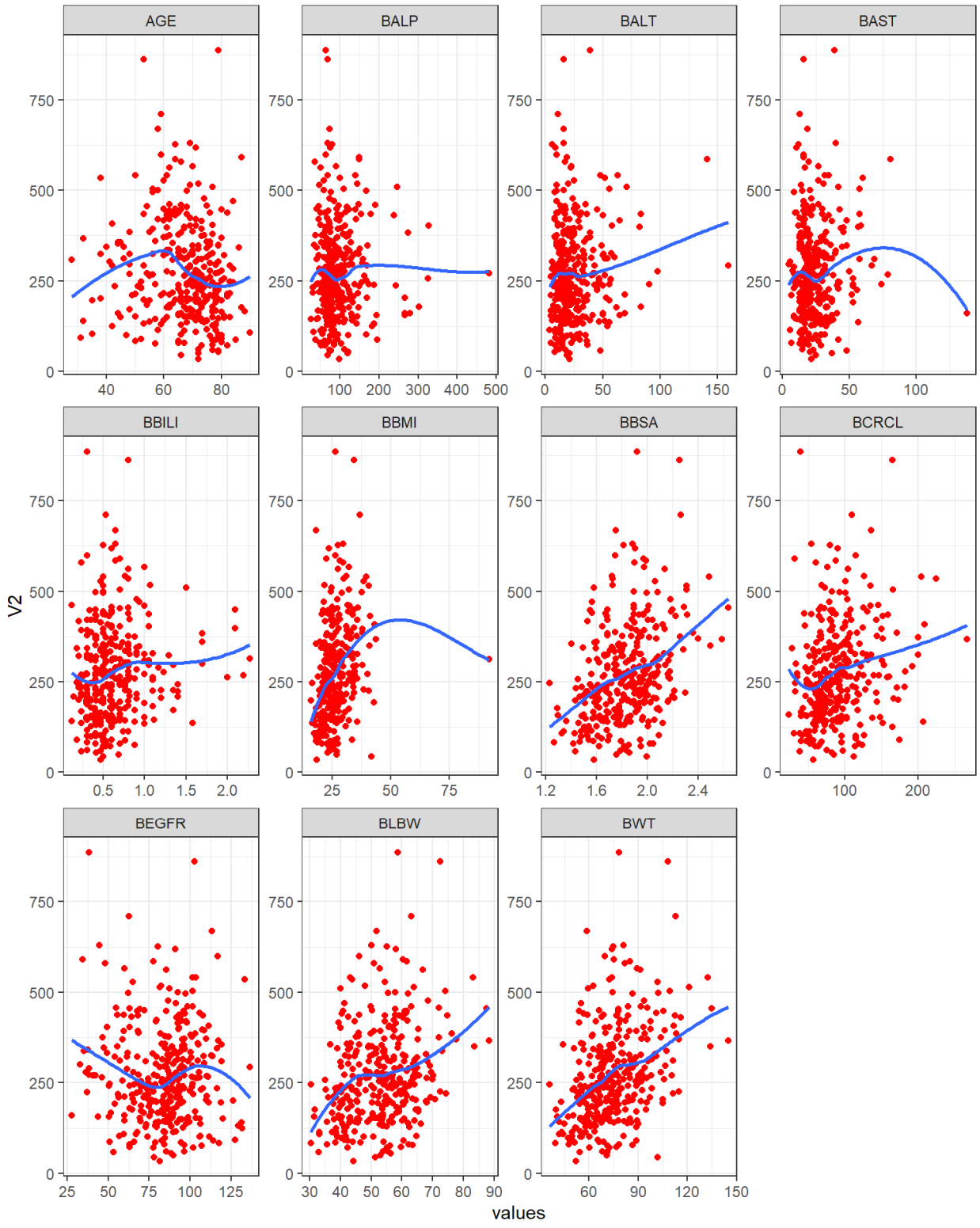
	2102-HEM-101 (N=324)	2102-HVS-105 (N=25)	Overall (N=349)
White	183 (56.5%)	16 (64.0%)	199 (57.0%)
Black or African American	14 (4.3%)	5 (20.0%)	19 (5.4%)
Asian	9 (2.8%)	1 (4.0%)	10 (2.9%)
American Indian/Alaskan Native	0 (0%)	1 (4.0%)	1 (0.3%)
Multiple	0 (0%)	2 (8.0%)	2 (0.6%)
Other	20 (6.2%)	0 (0%)	20 (5.7%)
Missing	98 (30.2%)	0 (0%)	98 (28.1%)
Baseline ECOG score, N (%)			
0	109 (33.6%)	0 (0%)	109 (31.2%)
1	159 (49.1%)	0 (0%)	159 (45.6%)
2	55 (17.0%)	0 (0%)	55 (15.8%)
3	1 (0.3%)	0 (0%)	1 (0.3%)
Missing	0 (0%)	25 (100%)	25 (7.2%)
Hepatic Impairment, N (%)			
Normal	262 (80.9%)	19 (76.0%)	281 (80.5%)
Mild	59 (18.2%)	2 (8.0%)	61 (17.5%)
Moderate	3 (0.9%)	4 (16.0%)	7 (2.0%)
Combination Drug, N (%)			
monotherapy	208 (64.2%)	25 (100%)	233 (66.8%)
combination with azacitidine	115 (35.5%)	0 (0%)	115 (33.0%)
combination with LDAC	1 (0.3%)	0 (0%)	1 (0.3%)

Abbreviations: ECOG=Eastern Cooperative Oncology Group; LDAC=low-dose cytarabine; N=number of subjects with available information; PK=pharmacokinetic
Source: Report FORM-PMX-FT2102-2633, Table 13

Figure 13: Scatter Plots of Individual η Estimates Versus Continuous Covariates for the Base Model



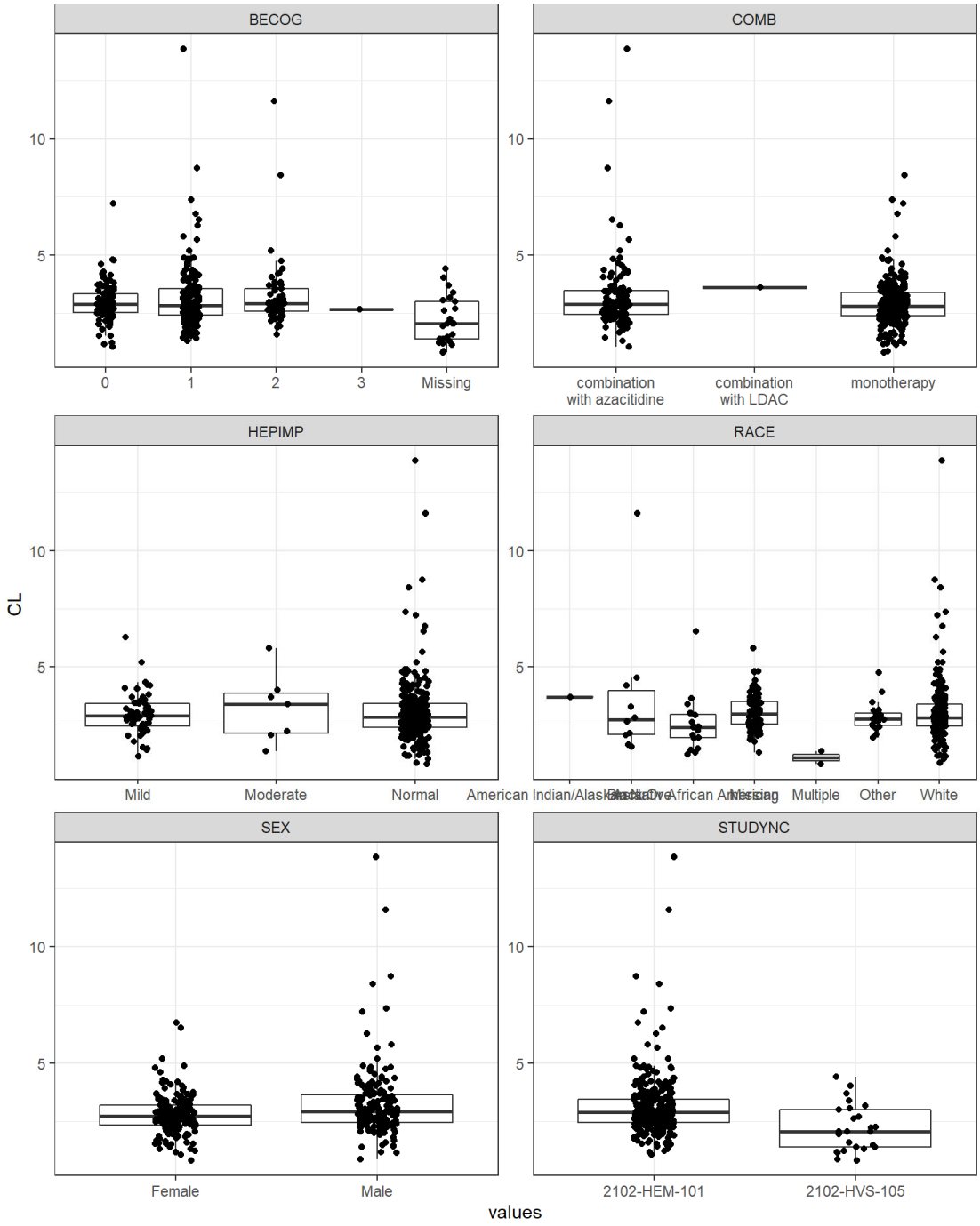
Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.



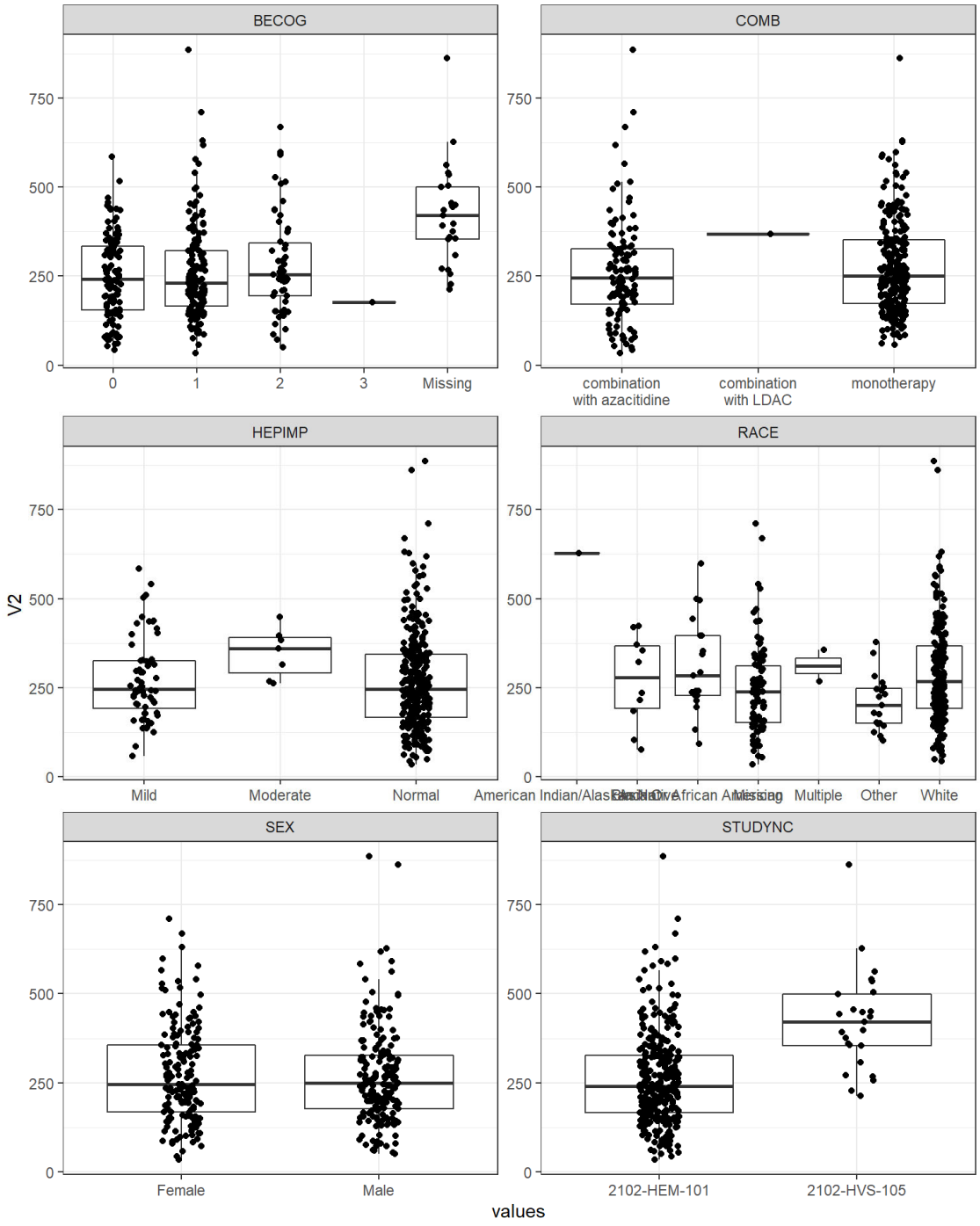
Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Source: Report FORM-PMX-FT2102-2633, Figure 35
Abbreviations: BALT=baseline alanine aminotransaminase; BAST=baseline aspartate aminotransaminase; BALP=baseline alkaline phosphatase; BBILI=baseline total bilirubin; BBMI=baseline body mass index; BBSA=baseline body surface area; BCRCL=creatinine clearance; BEGFR=baseline estimated glomerular filtration rate; BLBW=baseline lean body weight; BWT=baseline body weight; CL = apparent clearance; KA=first-order absorption rate constant; Q=apparent intercompartmental clearance; V2=apparent volume of distribution of the central compartment; V3=apparent volume of distribution of the peripheral compartment; ; PK=pharmacokinetic

Figure 14: Box Plots of Individual η Estimates Versus Categorical Covariates for the Base Model



Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.



Source: Report FORM-PMX-FT2102-2633, Figure 36

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Abbreviations: BECOG=baseline Eastern Cooperative Oncology Group score; COMB=combination drug administration; HEPIMP=hepatic impairment; CL = apparent clearance; KA=first-order absorption rate constant; Q=apparent intercompartmental clearance; STUDYNC = Study name; V2=apparent volume of distribution of the central compartment; V3=apparent volume of distribution of the peripheral compartment; ; PK=pharmacokinetic; PK=pharmacokinetic

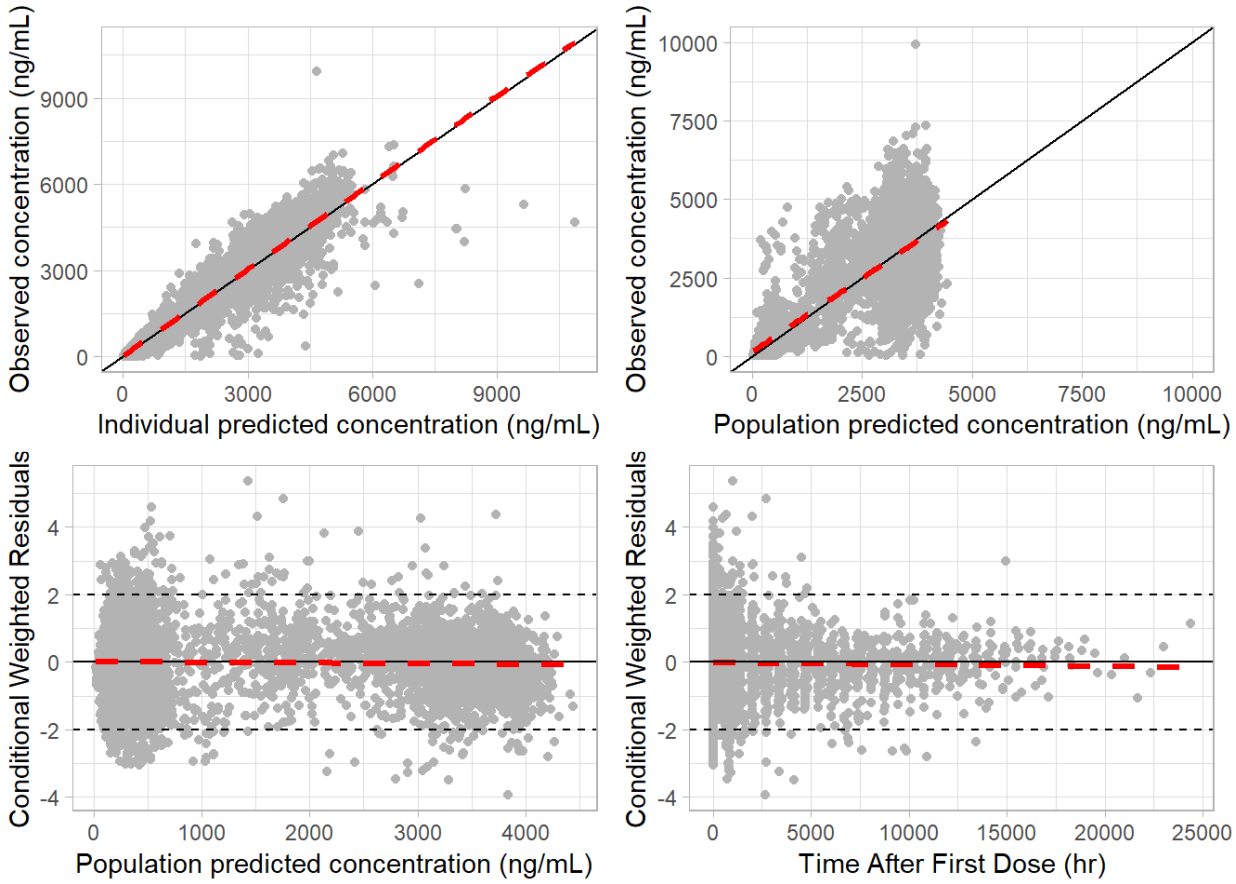
Table 86: Final Population PK Model Parameter Estimates

Parameters	Estimates	%RSE	Bootstrap Median [95% CI]	
CL/F (L/h)	3.25	4.7	3.22 [2.82, 3.47]	
V_2/F (L)	201	5.5	200 [180, 225]	
KA (1/h)	0.282	7.2	0.277 [0.245, 0.317]	
Q/F (L/h)	0.528	21.4	0.541 [0.327, 0.859]	
V_3/F (L)	4613	20.5	4667 [2301, 13133]	
Proportional error (%)	0.265	9.8	0.253 [0.227, 0.278]	
Additive error (ng/mL)	40.7	60.7	51.6 [34.3, 74.2]	
Sex on CL/F	-0.164	26.4	-0.157 [-0.248, -0.0797]	
Study on CL/F	-0.479	14.9	-0.507 [-0.686, -0.297]	
Body weight on V_2/F	1.23	11.8	1.25 [0.94, 1.49]	
Sex on V_2/F	0.293	32.7	0.296 [0.112, 0.469]	
Study on V_2/F	0.657	16.1	0.668 [0.421, 1.02]	
Study on KA	0.693	37.3	0.734 [0.101, 1.67]	
Random effects	**Estimates (SD)**	**%RSE**	**Bootstrap Median [95% CI]**	**Shrinkage (%)**
CL/F (L/h)	0.15	13	0.143 [0.0791, 0.188]	21.4
V_2/F (L)	0.264	14.9	0.259 [0.182, 0.346]	15.7
KA (1/h)	0.66	10.7	0.652 [0.517, 0.796]	21.6
Q/F (L/h)	1.54	25.2	1.54 [0.907, 2.52]	38.3
V_3/F (L)	1.09	36.8	1.01 [0.204, 2.32]	72.9

Abbreviations: CI=confidence interval; CL/F=apparent clearance; CV=coefficient of variation; KA=first-order absorption rate constant; Q/F=apparent intercompartmental clearance; RSE=relative standard error; V_2/F=apparent volume of distribution of the central compartment; V_3/F=apparent volume of distribution of the peripheral compartment; CI = confidence interval

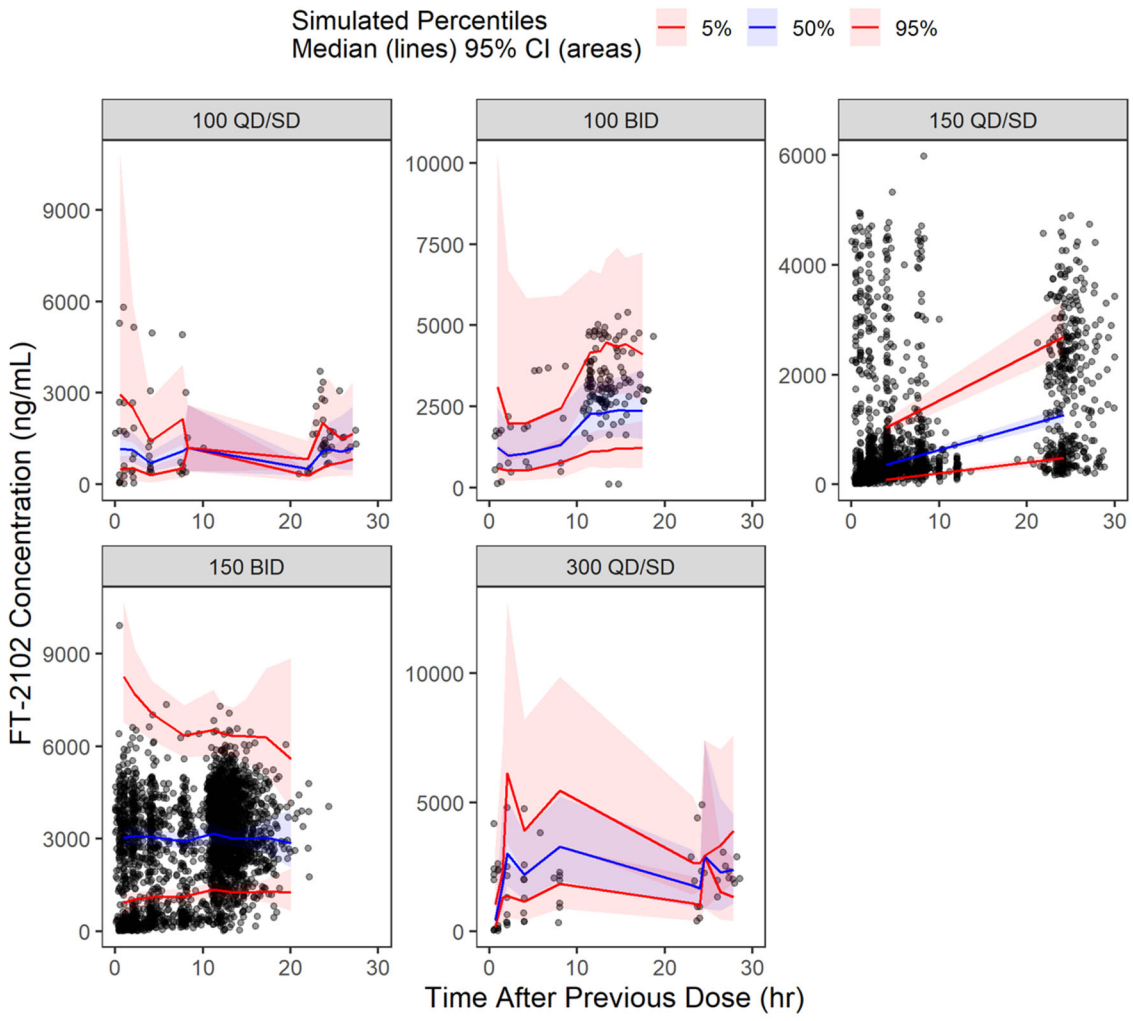
Source: Report FORM-PMX-FT2102-2633, Table 26

Figure 15: Goodness-of-Fit Plots for the Final Population PK Model



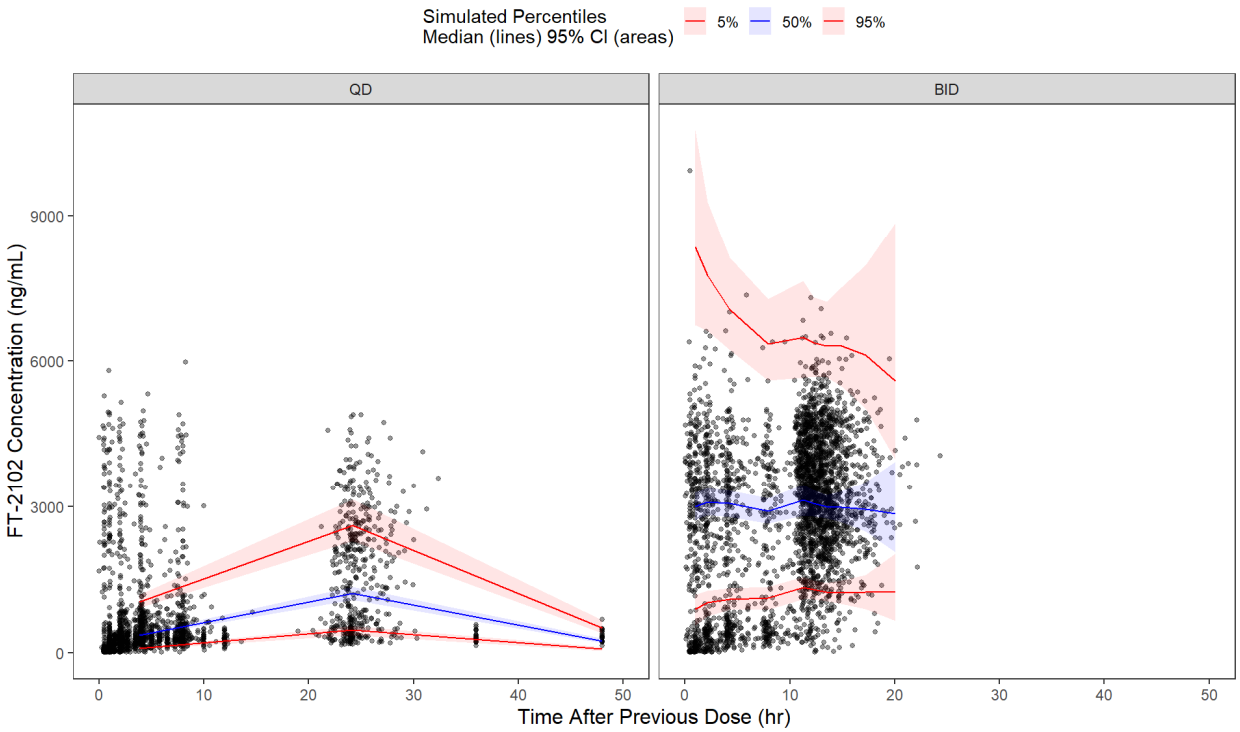
Notes: Dots are individual data points, and dashed red lines are regression lines. In the 2 plots in the upper row, solid black lines are lines of identity. In the 2 plots in the lower row, dashed black lines show the boundaries of the CWRES ± 2 interval.
Abbreviations: CWRES=conditional weighted residuals; GOF=goodness-of-fit
Source: Report FORM-PMX-FT2102-2633, Figure 10

Figure 16: VPC of Final Population PK Model, Stratified by Dose



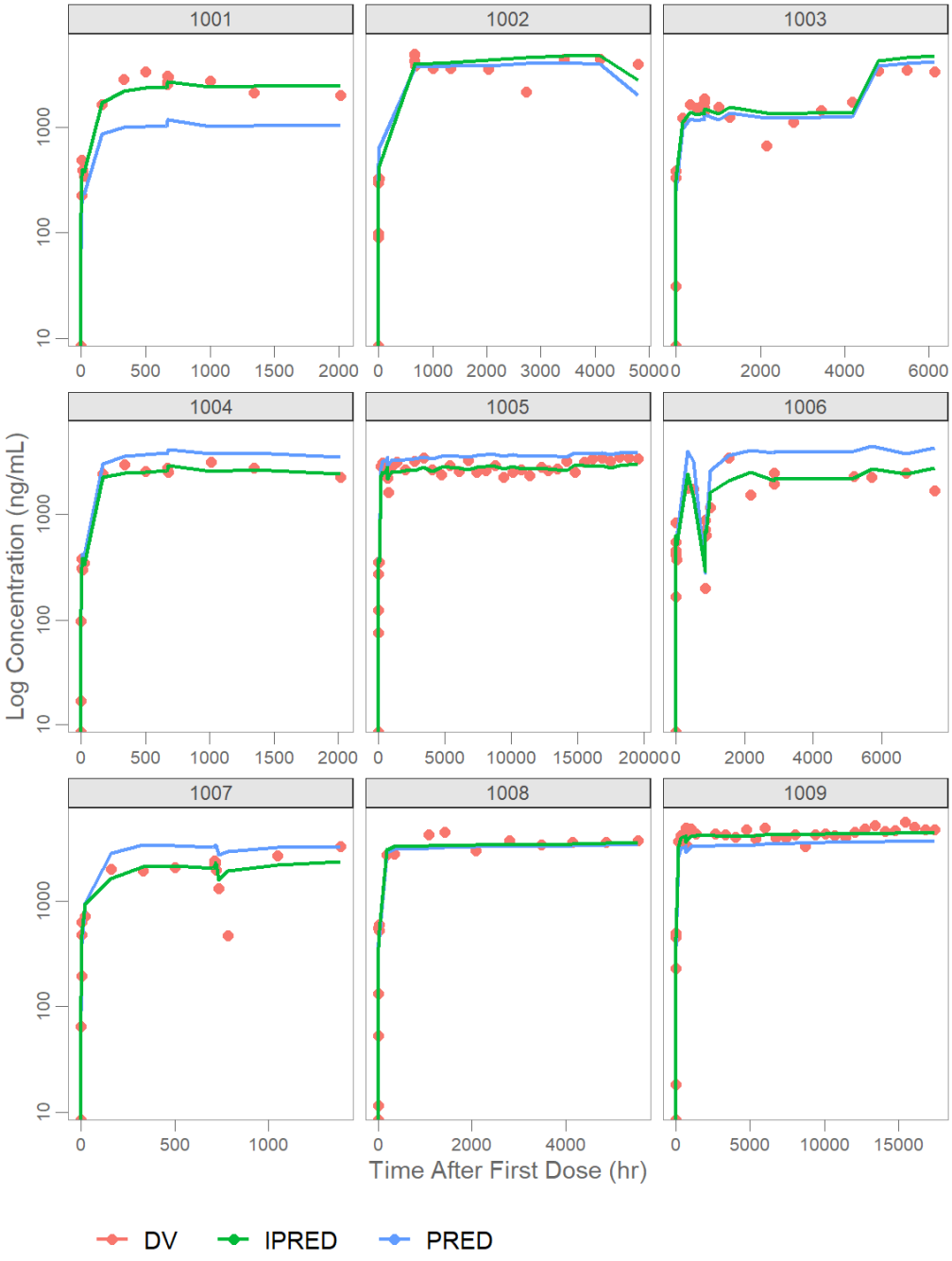
Source: VPC by Dose_15 March 2022; data on file

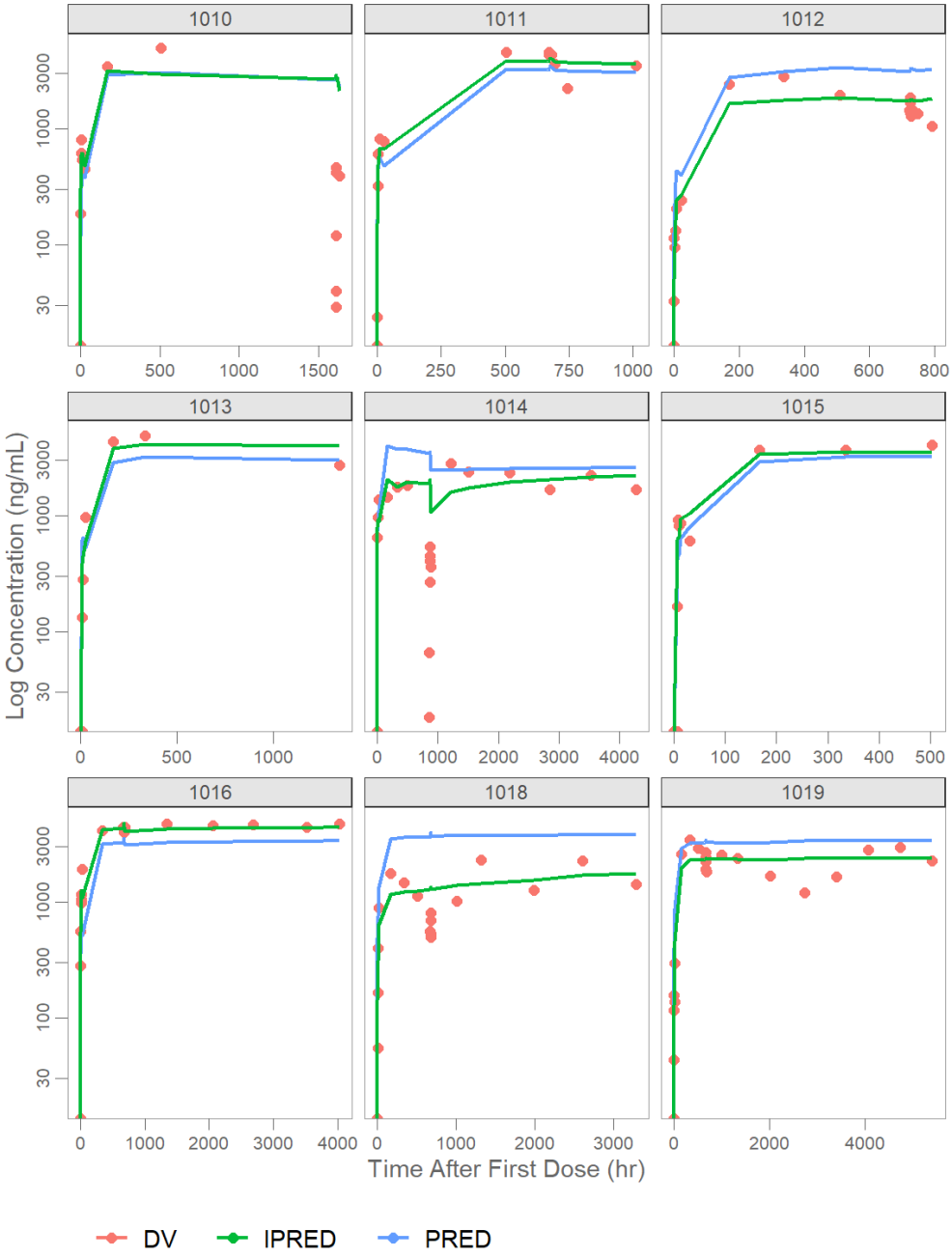
Figure 17: VPC Stratified by Dosing Frequency



Source: Report FORM-PMX-FT2102-2633, Figure 12
Abbreviations: CI=confidence interval; VPC=visual predicative check

Figure 18: Individual Concentration-Time Profiles Based on the Final Population PK Model for Representative Subjects (Log scale)

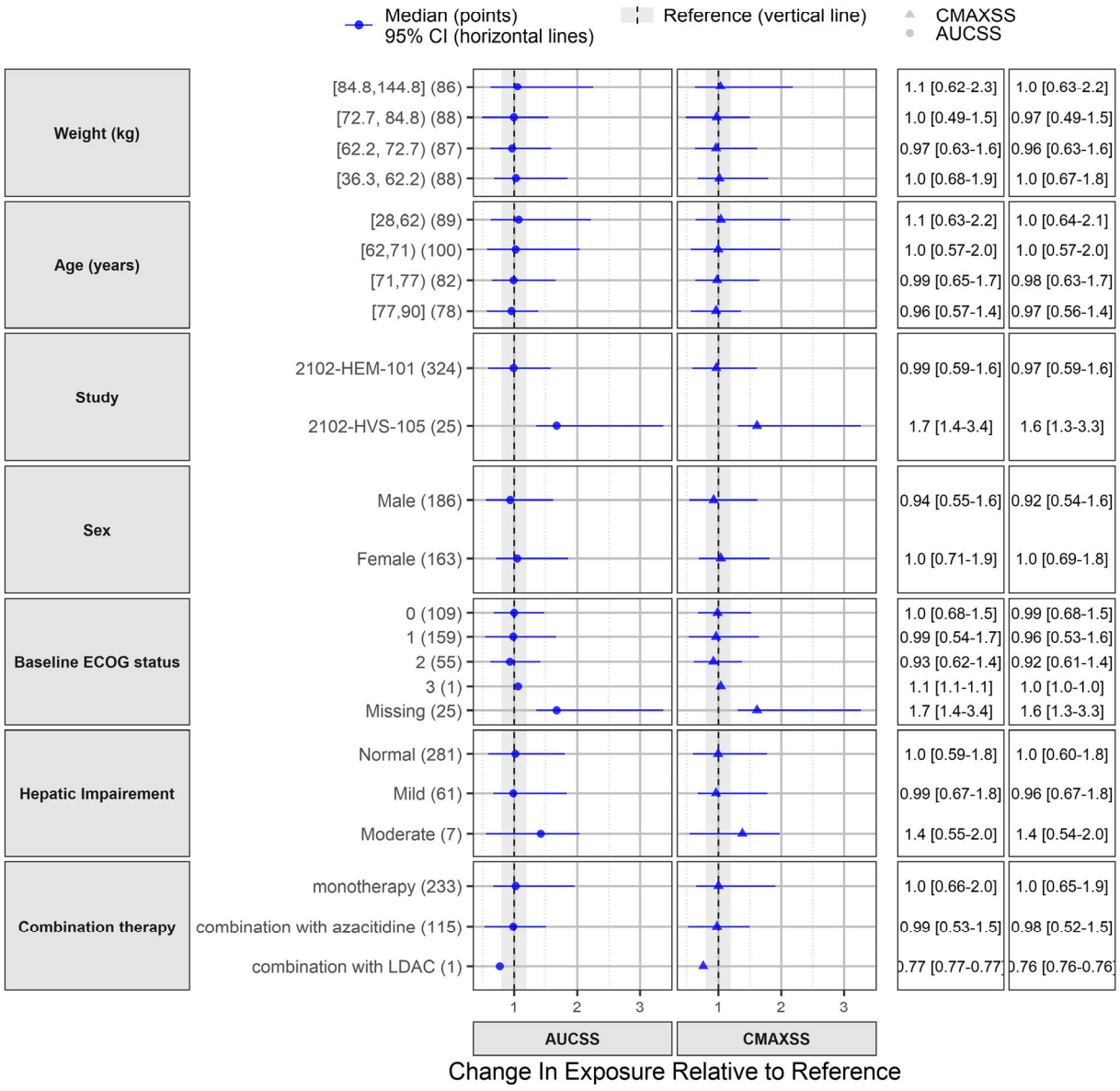




Source: Report FORM-PMX-FT2102-2633, Figure 38
Notes: Filled circles represent observed data. Green and blue lines represent individual and population predictions, respectively. Subject IDs are in panels above each plot.

Abbreviations: DV=observed concentration; IPRED=individual predicted concentration; PRED=population predicted concentration

Figure 19: Covariate Effects Plot for Olutasidenib



Notes: Panels to the right of the plots indicate reference-normalized median and 90% CI for AUC and CMAX, respectively. Gray shaded area indicates clinically relevant limits, 20% above or below the reference individual.

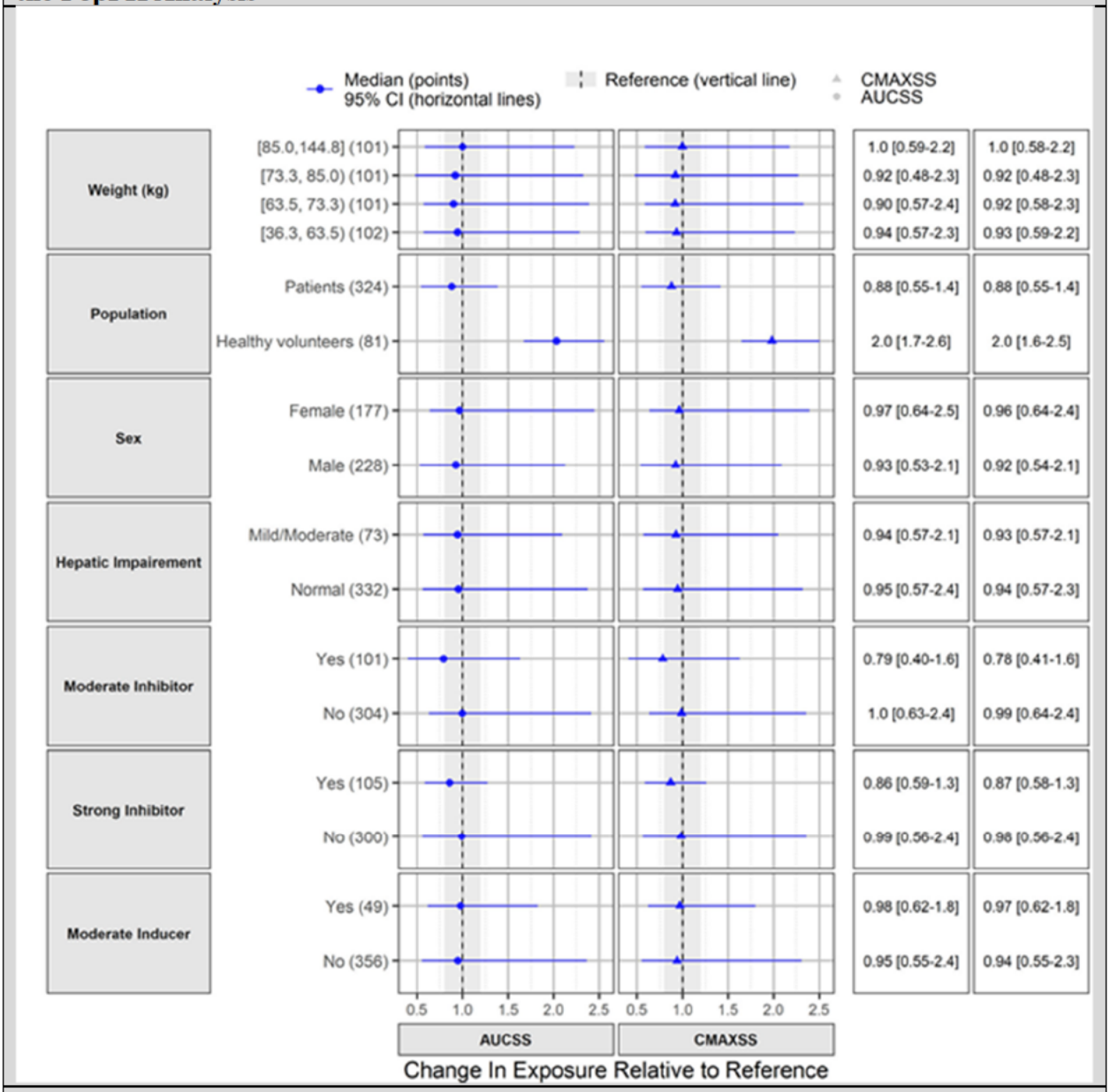
Notes: Reference is male, white, 78 years old, with body weight of 78 kg, with no hepatic impairment BECOG status of 0, receiving 150 mg BID of FT-2102.
Abbreviations: AUC=area under the serum concentration-time curve; BECOG=baseline Eastern Cooperative Oncology Group score; BID = twice daily; CI=confidence interval; CMAX=maximum observed serum concentration; LDAC=low-dose cytarabine
Source: Report FORM-PMX-FT2102-2633, Figure 13

The FDA's Assessment:

Upon FDA information request, the applicant updated the population pharmacokinetics analysis by including another two Phase 1 studies (2102-HVS-103 and 2102-HVS-106/fasted) and the results demonstrated that:

- Both AUCss and Cmax ss in healthy volunteers are two times that of AML patients (Figure 21).
- Post-hoc analysis of CL from the updated PopPK output suggested a gender effect (with mean±sd 3.19±0.93 L/h for male and 2.74±0.80 L/h for female, $p<0.05$) in patients (Figure 22).
- There was no large impact on CL observed for the other covariates, including body weight, hepatic impairment, and renal impairment.

Figure 20. Covariate Effects Plot for Olutasidenib After Studies 103 and 106 Included in the PopPK Analysis



Source: Applicant's Sep2022 PopPK Analysis in Response to FDA Information Request

Figure 21. Covariate Effect in AML Patients Based on Post-hoc Analysis of the Output of Applicant's Sep2022 PopPK Analysis

```
glm(formula = d$CL ~ d$SEX + d$AGE + d$BWT + d$RACE + d$RENIMP +
    d$HEPIMP + d$BALT + d$BASTULN + d$BALB + d$BALP + d$BSCR +
    d$BBILI + d$BBILIULN + d$BCRCL + d$BEGFR + d$BECOG)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-1.5728  -0.5498  -0.0624   0.3878   3.9071

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept)  4.064e+00  3.348e+00   1.214   0.2263
d$SEX       -5.300e-01  2.517e-01  -2.105   0.0366 *
d$AGE       -4.201e-03  1.346e-02  -0.312   0.7553
d$BWT       -7.030e-03  9.446e-03  -0.744   0.4576
d$RACE      -1.118e-03  1.334e-03  -0.838   0.4032
d$RENIMP     1.433e-02  1.755e-01   0.082   0.9350
d$HEPIMP    -1.886e-01  2.143e-01  -0.880   0.3797
d$BALT      -2.468e-03  4.350e-03  -0.567   0.5710
d$BASTULN    1.704e-03  1.199e-02   0.142   0.8872
d$BALB      -1.273e-02  1.206e-02  -1.056   0.2925
d$BALP       2.788e-03  1.586e-03   1.759   0.0802 .
d$BSCR      -3.166e-01  1.083e+00  -0.292   0.7703
d$BBILI      4.240e-01  2.321e-01   1.827   0.0693 .
d$BBILIULN   1.021e+00  5.242e-01   1.947   0.0529 .
d$BCRCL     -4.002e-05  5.832e-03  -0.007   0.9945
d$BEGFR     -4.110e-03  1.540e-02  -0.267   0.7898
d$BECOG      2.878e-02  9.931e-02   0.290   0.7723
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

Source: FDA Reviewer's Analysis.

Notably, applicant's analyses, as presented in Figure 20 and Figure 23, are misleading for gender effect on exposure due to inappropriately included health volunteers in the 95% confidence calculation which inflated the actual variability of CL in patients.

20.4.2.3 PPK Review Issues

The Applicant's original population PK analysis described above was not adequate. As the original Applicant's PPK analysis included only one of the 3 Phase 1 studies in health volunteers, and the hepatic impairment (HI) NCI classification was based on baseline ALT instead of AST. Upon reviewer's request, the applicant updated the analysis by including 2 additional Phase 1 studies (2102-HVS-103 and 2102-HVS-106/fasted) and corrected HI NCI classification. All covariates in the previous model were retained. One additional covariate (moderate CYP3A4 inhibitor on CL/F) was found significant. Steady-state exposure boxplots by sex and hepatic function/sex also showed

no trends and differences between males and females in relation to hepatic function. Hepatic impairment covariate using NCI definition was not a significant covariate, however, it was included in the final model based on the FDA's request. Consistent with the previous analysis, the forest plot showed higher exposure in healthy volunteers compared to patients. There was no large impact on exposure observed for the other covariates, including body weight, sex, hepatic impairment, and use of moderate CYP3A4 inducers or strong CYP 3A4 inhibitors. The effect of moderate CYP3A4 inhibitors was borderline, with exposure being slightly lower than the reference.

20.4.2.4 Reviewer's Independent Analysis

The Applicant's updated population PK model is generally acceptable and no independent PopPK analysis was conducted by the FDA. Post-hoc analysis suggested that females have 16% higher exposure than males and patients' exposure is about 50% of healthy volunteers. There is no other covariate identified for olutasidenib exposure.

For exposure-response analysis, CL values from the output of applicant's run201.ctl associated with NONMEM dataset "FT2102-poppk-withconmed-TTE-09SEP2022-scm.csv" were used.

20.4.3 Exposure-Response Analysis

The E-R analysis dataset included 324 subjects from Study 2102-HEM-101 and post hoc exposure estimates are available for all subjects (Table 89). Table 90 and Table 91 provide a summary of continuous and categorical covariates included in the E-R dataset. Subject covariates summarized by C_{avg} quartile confirm that covariates were generally equally distributed across the exposure range (Table 92).

The relationship between olutasidenib exposure (steady-state C_{avgss}, C_{maxss}, and C_{minss}) and the probability of experiencing a clinical response or a safety endpoint (AE) was evaluated using univariate logistic regression analysis. Due to the high correlation among C_{avgss}, C_{maxss}, and C_{minss}, each exposure metric was tested separately against each efficacy endpoint using univariate logistic regression. The exposure metric that produced the lowest AIC and was selected as the exposure measure for the E-R analysis. Due to the high correlation among the body size covariates, the combination of each body size covariate with the appropriate exposure metric was tested separately for each endpoint. The body size covariate that produced the lowest AIC and was selected as the covariate for the E-R analysis. For categorical covariates, only the covariate for which each category had at least 5 events was included to the full model.

Table 87: Summary of Simulated FT-2102 Exposure at Steady State

Exposure (Unit)	No. of Subjects	Mean (SD)	Median [Min, Max]
100 mg FT-2102/BID			
AUC_{ss} (h•ng/mL)	17	40457.1 (9661.69)	39200 [28879, 64197]
C_{avgss} (ng/mL)	17	3371.4 (805.14)	3267 [2407, 5350]
C_{maxss} (ng/mL)	17	3480 (822.48)	3453 [2525, 5514]
C_{minss} (ng/mL)	17	3227.4 (794.87)	3212 [2223, 5122]
100 mg FT-2102/QD			
AUC_{ss} (h•ng/mL)	7	45456.4 (16006.52)	44883 [28370, 69516]
C_{avgss} (ng/mL)	7	1894 (666.94)	1870 [1182, 2896]
C_{maxss} (ng/mL)	7	2054.3 (683.72)	1971 [1334, 3022]
C_{minss} (ng/mL)	7	1694.9 (654.33)	1740 [987, 2732]
150 mg FT-2102/BID			
AUC_{ss} (h•ng/mL)	243	51179.9 (15247.02)	51286 [10857, 142110]
C_{avgss} (ng/mL)	243	4265 (1270.58)	4274 [905, 11842]
C_{maxss} (ng/mL)	243	4384.9 (1290.84)	4391 [925, 11998]
C_{minss} (ng/mL)	243	4108 (1262.97)	4123 [875, 11684]
150 mg FT-2102/QD			
AUC_{ss} (h•ng/mL)	54	62551.3 (20352.09)	57269 [37594, 125912]
C_{avgss} (ng/mL)	54	2606.3 (848)	2386 [1566, 5246]
C_{maxss} (ng/mL)	54	2775.8 (876.34)	2574 [1632, 5353]
C_{minss} (ng/mL)	54	2366.9 (860.57)	2206 [1342, 5107]
300 mg FT-2102/QD			
AUC_{ss} (h•ng/mL)	3	100507.7 (46324.67)	75333 [72222, 153969]
C_{avgss} (ng/mL)	3	4187.8 (1930.19)	3139 [3009, 6415]
C_{maxss} (ng/mL)	3	4380.7 (1867.74)	3331 [3274, 6537]
C_{minss} (ng/mL)	3	3902.5 (2043.21)	2925 [2531, 6251]
Overall			
AUC_{ss} (h•ng/mL)	324	52845.6 (17692)	51607 [10857, 153969]
C_{avgss} (ng/mL)	324	3889.7 (1368.79)	3845 [905, 11842]
C_{maxss} (ng/mL)	324	4018.8 (1377.48)	3980 [925, 11998]
C_{minss} (ng/mL)	324	3717.6 (1379.5)	3705 [875, 11684]

Abbreviations: AUC_{ss}=area under the plasma concentration-time curve at steady state; BID = twice daily; C_{avgss}=average plasma concentration at steady state; C_{maxss}=maximum plasma concentration at steady state; C_{minss}=minimum plasma concentration at steady state; Max=maximum; Min=minimum; No.=number; QD = once daily; SD=standard deviation

Source: Report FORM-PMX-FT2102-2633, Table 27

Table 88: Summary of Continuous Covariates in E-R Dataset

Covariate	Mean (SD)	Median [Min, Max]	Missing N (%)
Age (years)	67.9 (11.3)	70.0 [28.0, 90.0]	0 (0%)
Body weight (kg)	73.8 (17.1)	72.0 [36.3, 145]	0 (0%)
Lean body weight (kg)	52.6 (9.81)	53.6 [30.5, 88.3]	0 (0%)
Body surface area (m^2)	1.82 (0.223)	1.82 [1.23, 2.59]	0 (0%)
Body mass index (kg/m^2)	26.3 (6.48)	25.0 [16.0, 91.9]	0 (0%)

Note: Numeric columns formatted as mean (SD) and median [range].
Abbreviations: E-R=exposure-response; Max=maximum; Min=minimum; N=number of subjects with available information; SD=standard deviation
Source: Report FORM-PMX-FT2102-2633, Table 21

Table 89 Summary of Categorical Covariates in the E-R Dataset

Covariate	Value	N=324 n (%)
Sex	Male	169 (52.2%)
	Female	155 (47.8%)
Race	Caucasian	183 (56.5%)
	Black or African American	14 (4.3%)
	Asian	9 (2.8%)
	Other	20 (6.2%)
	Missing	98 (30.2%)
Baseline ECOG status	0	109 (33.6%)
	1	159 (49.1%)
	2	55 (17.0%)
	3	1 (0.3%)
Combination drug	Monotherapy	208 (64.2%)
	Combination with azacytidine	115 (35.5%)
	Combination with LDAC	1 (0.3%)
Number of prior anti-cancer regimens	1	81 (25.0%)
	2	87 (26.9%)
	3	48 (14.8%)
	4	40 (12.3%)
	5	12 (3.7%)

Covariate	Value	N=324 n (%)
	6	9 (2.8%)
	7	1 (0.3%)
	9	1 (0.3%)
	Missing	45 (13.9%)
Prior transplantation	No	324 (100%)
	Yes	0 (0%)
AML cytogenetic risk classification	Favorable	9 (2.8%)
	Intermediate	192 (59.3%)
	Poor	55 (17.0%)
	Unknown	43 (13.3%)
	Missing	25 (7.7%)
MDS disease state	Newly diagnosed	7 (2.2%)
	Relapsed/refractory	15 (4.6%)
	Missing	302 (93.2%)
Analysis disease status	Relapsed/refractory	258 (79.6%)
	Treatment naive	48 (14.8%)
	Missing	18 (5.6%)
Prior history of MDS	No	248 (76.5%)
	Yes	76 (23.5%)

Abbreviations: AML=acute myeloid leukemia; ECOG=Eastern Cooperative Oncology Group; E-R=exposure-response; LDAC=low-dose cytarabine; MDS=myelodysplastic syndrome; N=total number of subjects; n=number of subjects with available information
Source: Report FORM-PMX-FT2102-2633, Table 22

Table 90: Covariate Distribution Over C_{avgss} Quartiles for all Subjects Included in the Exposure-Response Analysis

C_{avgss} Quartile	Covariate								
Sex	Male	Female							
Q1	48	33							
Q2	45	36							
Q3	41	40							
Q4	35	46							
Race	Unknown	White	Black	Asian	Other				
Q1	24	43	3	2	9				
Q2	32	42	3	2	2				
Q3	18	52	2	3	6				

Q4	24	46	6	2	3				
Combination drug	Monotherapy	Azacitidine	LDAC						
Q1	45	36	0						
Q2	56	24	1						
Q3	55	26	0						
Q4	52	29	0						
Disease type	Missing	Relapsed/ refractory	Naïve						
Q1	3	60	18						
Q2	5	67	9						
Q3	5	63	13						
Q4	3	68	8						
Baseline ECOG score	0	1	2	3					
Q1	22	46	13	0					
Q2	29	36	16	0					
Q3	32	34	14	1					
Q4	26	43	12	0					
Number of prior anticancer regimens	Missing	1	2	3	4	5	6	7	9
Q1	17	19	17	10	11	3	3	0	1
Q2	9	21	23	9	11	3	4	1	0
Q3	11	18	21	15	10	5	1	0	0
Q4	8	23	26	14	8	1	1	0	0
Prior transplantation	No								
Q1	81								
Q2	81								
Q3	81								
Q4	81								
Cytogenetic risk	Missing	Favorable	Intermediate	Poor	Unknown				
Q1	11	2	46	14	8				
Q2	5	3	50	12	11				
Q3	6	1	46	15	13				
Q4	3	3	50	14	11				
MDS disease state	Missing	Newly	Replased/refractory						
Q1	71	3	7						
Q2	77	1	3						
Q3	76	2	3						
Q4	78	1	2						
Prior history of MDS	No	Yes							

Q1	63	18							
Q2	63	18							
Q3	59	22							
Q4	63	18							
Age (year)	(27.9,63]	(63,70]	(70,76]	(76,90.1]					
Q1	19	23	18	21					
Q2	19	21	19	22					
Q3	20	19	23	19					
Q4	26	17	22	16					
Baseline BMI (kg/m2)	(15.9,22.4]	(22.4,25]	(25,28.7]	(28.7,92]					
Q1	19	31	13	18					
Q2	24	23	20	14					
Q3	18	15	23	25					
Q4	22	13	22	24					
Baseline BSA (m2)	(1.23,1.67]	(1.67,1.82]	(1.82,1.97]	(1.97,2.59]					
Q1	17	20	25	19					
Q2	16	26	21	18					
Q3	25	14	20	22					
Q4	23	21	16	21					
Baseline body weight (kg)	(36.2,61.9]	(61.9,72]	(72,84]	(84,145]					
Q1	19	23	22	17					
Q2	20	27	16	18					
Q3	22	14	23	22					
Q4	20	20	17	24					
Baseline lean body weight (kg)	(30.4,44.6]	(44.6,53.6]	(53.6,59.3]	(59.3,88.4]					
Q1	17	22	19	23					
Q2	17	18	28	18					
Q3	26	14	18	23					
Q4	21	27	16	17					

Source: Covariate distribution vs exposure quartiles; data on file

20.4.3.1 E-R (efficacy) Executive Summary

The FDA's Assessment:

FDA exploratory univariate analysis of major efficacy endpoints (ORR, CBR, and CR/CRH) suggested that the exposure-efficacy relationship was slightly positive in patients with normal liver function but flat or negative in patients with mild/moderate hepatic impairment. This analysis could be considered exploratory given majority of data was associated with one olutasidenib dose level, 150 mg BID.

20.4.3.2 E-R (efficacy) Assessment Summary

The Applicant's Position:

The number (% occurrence) of subjects with CR/CRh was 117 (36%) (Table 93). The response rate appeared to be generally similar across exposure quartiles, however, the highest incidence of CR/CRh occurred at the highest quartile of exposure (Table 94). Evaluation of exposure distributions for responders and non-responders for CR/CRh confirmed that exposure ranges were similar for responders and non-responders (Figure 23).

The relationship between olutasidenib exposure (steady-state C_{avgss}, C_{maxss}, and C_{minss}) and the probability of experiencing a clinical response (CR/CRh) was evaluated using univariate logistic regression analysis. There was no observed relationship between exposure and the probability of achieving a clinical response, exposure effects on the incidence of response were minimal for each of the efficacy endpoints, with p-value of 0.306 (Figure 24).

Final model parameter estimates for a multivariate logistic regression analysis with selected covariates performed for CR/CRh are presented in Table 95. Model predicted occurrence of CR/CRh and 95% CI across exposure quantiles at steady state are presented in Table 96.

General Information		
Goal of ER analysis		To characterize the relationship between olutasidenib exposure and efficacy endpoints.
Study Included		2102-HEM-101
Endpoint		Primary: CR/CRh Secondary: CBR, ORR
No. of Patients (total, and with individual PK)		324
Population Characteristics (Table 90 and Table 91)	General	2102-HEM-101: Age median (range): 70.0 (28.0, 90.0) yr Weight median (range): 72.0 (36.3, 145) kg n (XX%) male: 169 (52.2%) n (XX%) in each race: White 183 (56.5%), Black/African-American 14 (4.3%), Asian 9 (2.8%), Other 20 (6.2%, Missing 98 (30.2%)
	Pediatrics (if any)	None
Dose(s) Included		100 mg, 150 mg, 300 mg QD and 150 mg BID
Exposure Metrics Explored (range)		Due to the high correlation among C_{avgss}, C_{maxss}, and C_{minss}, each exposure was tested separately against each efficacy endpoint using univariate logistic regression. The exposure metric that produced the lowest AIC was selected for the E-R analysis.
Covariates Evaluated		Table 90 and Table 91

Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	Exploratory univariate logistic regression analysis. Only the efficacy endpoints with p-value <0.05 in the exploratory analysis were included in the formal E-R analysis (multivariate logistic regression using selected covariates).	The updated E-R analysis on efficacy was acceptable.
Model Parameter Estimates	Table 95	The updated E-R analysis on efficacy was acceptable.
Model Evaluation	VPC	
Covariates and Clinical Relevance	Baseline BMI, ECOG Score 1 and 2	Not clinically relevant
Simulation for Specific Population	N/A	The updated E-R analysis on efficacy was acceptable.
Visualization of E-R relationships	Figure 23 *and* Table 96	The updated E-R analysis on efficacy was acceptable.
Overall Clinical Relevance for ER		N/A
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	No exposure efficacy language was proposed in Section 12.2 of the USPI.	Acceptable

Table 91: Summary of Primary Efficacy Endpoint Observations (N=324)

Efficacy Endpoint	Number of Observations (n) (%)	Occurrence (%)
CR/CRh	324 (100)	117 (36)

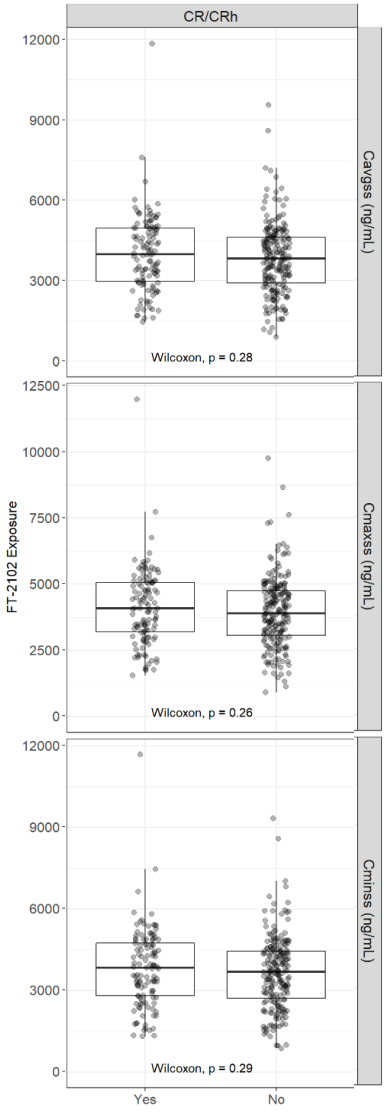
Abbreviations: AE=adverse event; CR=complete remission; CRh=complete response with partial hematologic recovery; N=number of subjects; n=number of subjects with available endpoint information
Source: Report FORM-PMX-FT2102-2633, Table 18

Table 92: Summary of Primary Efficacy Endpoint Observations [Occurrence (%)] by Exposure Quartile

	Occurrence (%)			
Efficacy Endpoint	**Q1 (N=81)**	**Q2 (N=81)**	**Q3 (N=81)**	**Q4 (N=81)**
C_{avgss} range (ng/mL)	**(894,2.95e+03]**	**(2.95e+03,3.84e+03]**	**(3.84e+03,4.75e+03]**	**(4.75e+03,1.19e+04]**
CR/CRh	28 (35)	27 (33)	26 (32)	36 (44)
C_{maxss} range (ng/mL)	**(914,3.07e+03]**	**(3.07e+03,3.98e+03]**	**(3.98e+03,4.86e+03]**	**(4.86e+03,1.2e+04]**
CR/CRh	29 (36)	27 (33)	25 (31)	36 (44)
C_{minss} range (ng/mL)	**(1.19e+03,3.52e+03]**	**(3.52e+03,4.51e+03]**	**(4.51e+03,5.34e+03]**	**(5.34e+03,1.16e+04]**
CR/CRh	28 (35)	28 (35)	25 (31)	36 (44)

Abbreviations: AE=adverse event; C_{avgss}=average plasma concentration at steady state; C_{maxss}=maximum plasma concentration at steady state; C_{minss}=minimum plasma concentration at steady state; CR=complete remission; CRh=complete response with partial hematologic recovery; N=number of subjects; Q=quantile
Source: Report FORM-PMX-FT2102-2633, Table 19

Figure 22: Distribution of Steady-State Exposure Versus CR/CRh



Source: Report FORM-PMX-FT2102-2633, Figure 56

Table 93: Final Model Parameter Estimates – CR/CRh

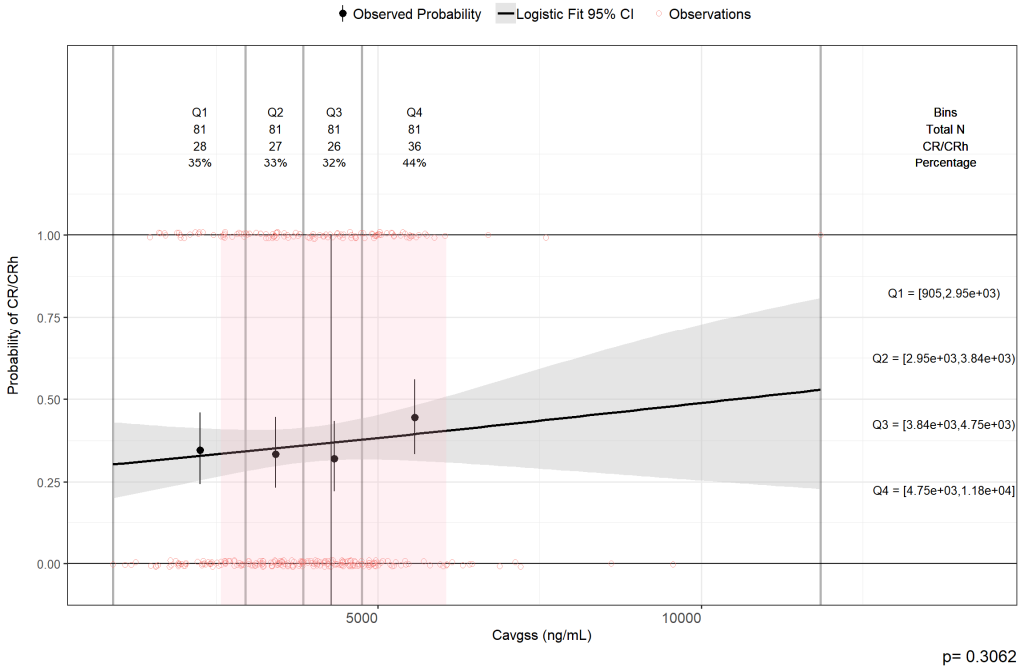
Parameter	Estimate	RSE%	p-Value	Odds Ratio (95% CI)
(Intercept)	-2.0e+00	34.1%	0.0035	
C_{maxss} (ng/mL)	5.2e-05	166.5%	0.5479	1.0001 (0.99988, 1.0002)
Baseline BMI (kg/m2)	5.7e-02	37.8%	0.0082	1.0589 (1.017, 1.1063)

Baseline ECOG: Score1	-2.6e-01	100.2%	0.3191	0.77375 (0.4667, 1.2824)
Baseline ECOG: Score2	-1.4e+00	29%	0.0005	0.23653 (0.099119, 0.51608)

Abbreviations: BMI=body mass index; CI=confidence interval; C_{maxss}=maximum plasma concentration at steady state; CR=complete remission; CRh=complete response with partial hematologic recovery; ECOG= Eastern Cooperative Oncology Group; RSE=relative standard error

Source: Report FORM-PMX-FT2102-2633, Table 42

Figure 23: Relationship Between Steady-State Exposures and Probability of CR/CRh



Notes: The independent variables were divided into 4 equally sized rank-ordered groups. Black points and error bars represent the observed proportions and 95% CIs for each exposure group (plotted at the mean exposure within each exposure group), respectively. The black curve represents the prediction of the univariate logistic regression model, and the gray shaded region represents the 95% CI of the prediction. Percentages in the upper part of the graph represent the proportion of subjects in each exposure group who experienced AE. The black vertical solid black line represents the median of the predicted exposure at steady state for subjects who took FT-2102 150 mg BID, and the pink shaded region represents 90% CI of the predicted exposure at steady state for subjects who took FT-2102 150 mg BID.

Abbreviations: BID=twice daily; C_{avgss}=average plasma concentration at steady state; CI=confidence interval; C_{maxss}=maximum plasma concentration at steady state; C_{minss}=minimum plasma concentration at steady state; CR=complete remission; CRh=complete response with partial hematologic recovery; N=number of subjects; p=p-value of logistic regression model slope; Q=quantile

Source: Report FORM-PMX-FT2102-2633, Figure 27

Table 94: Model Predicted Occurrence of CR/CRh across Exposure Quantile at Steady State

Binary Efficacy Endpoint	Model-Predicted Incidence (95% CI)		
	P10	P50	P90
C_{avgss} (ng/mL)			
CR/CRh	0.066 (0.037, 0.114)	0.11 (0.08, 0.151)	0.175 (0.122, 0.244)
C_{maxss} (ng/mL)			
CR/CRh	0.066 (0.037, 0.115)	0.111 (0.08, 0.151)	0.174 (0.122, 0.243)
C_{minss} (ng/mL)			
CR/CRh	0.065 (0.036, 0.112)	0.111 (0.08, 0.152)	0.172 (0.121, 0.238)

Abbreviations: C_{avgss}=average plasma concentration at steady state; CI=confidence interval; C_{maxss}=maximum plasma concentration at steady state; C_{minss}=minimum plasma concentration at steady state; CR=complete remission; CRh=complete response with partial hematologic recovery; P10=10th quantile; P50=50th quantile; P90=90th quantile

Source: Report FORM-PMX-FT2102-2633, Table 50

20.4.3.3 E-R (safety) Executive Summary

The FDA's Assessment:

FDA exploratory univariate analysis suggested a positive exposure-response relationship for ≥ Grade 3 adjudicated PI identified differentiation syndrome (DIFATRG3) and treatment emergent ≥ Grade 3 hepatoxicity. For DIFATRG3, the rate was 16.2% (6/37) for patients with mild/moderate hepatic impairment vs 2.6% (4/155) for patients with normal liver function.

20.4.3.4 E-R (safety) Assessment Summary

The Applicant's Position:

The number (% occurrence) of subjects with observed AE incidence are presented in Table 97 and AE incidences stratified by Cavgss quartile are in Table 98. AE incidence appeared to be similar across exposure quartiles for all safety endpoints, except for a trend for differentiation syndrome endpoints and an inverse trend for hepatic AE endpoints.

The relationship between olutasidenib exposure (steady-state C_{avg}, C_{max}, and C_{min}) and the probability of experiencing AEs was evaluated using univariate logistic regression analysis. Final model parameter estimates are presented in Table 99.

Increased exposure was correlated with the increased probability of PI-identified differentiation syndrome and drug-related PI-identified differentiation syndromebut was not correlated with severe (grade 3 or higher) cases of PI-reported differentiation syndrome.

There was an inverse relationship between exposure and all hepatic AE endpoints. Hepatic AE at any grade, Grade 3+ hepatic AE, and drug-related hepatic AE were less likely to occur as exposure at steady state increased; the reason for this negative correlation is unknown. There was no apparent correlation between the FT-2102 exposure at steady state and the other safety endpoints. The relationship between Cavgss and probability of an AE occurrence with a linear logistic regression fit is shown in Figure 25. The model predicted AE incidence and 95% CI across exposure quantiles are provided in Table 100.

General Information			
Goal of ER analysis		To conduct a safety E-R analysis to identify predictors of selected safety events.	
Study Included		2102-HEM-101	
Population Included		R/R AML and MDS	
Endpoint		*Major common AE/SAE, AE of interest*	
No. of Patients (total, and with individual PK)		324	
Population Characteristics (Table 90 and Table 91)	General	2102-HEM-101: Age median (range): 70.0 (28.0, 90.0) yr, *74% subj >=65 yr, 31% subj >=75 yr)* Weight median (range): 72.0 (36.3, 145) kg n (XX%) male: 169 (52.2%) n (XX%) in each race: White 183 (56.5%), Black/African-American 14 (4.3%), Asian 9 (2.8%), Other 20 (6.2%, Missing 98 (30.2%)	
	Organ impairment	*Hepatic (NCI): n (%) in each category* 2102-HEM-101: Normal: 262 (80.9%) Mild: 59 (18.2%) Moderate: 3 (0.9%)	
	Pediatrics (if any)	-None	
	Geriatrics (if any)	*74% subj >=65 yr, 31% subj >=75 yr)*	
Dose(s) Included		100 mg, 150 mg, 300 mg QD and 150 mg BID	
Exposure Metrics Explored (range)		See Table 89 for simulated steady-state exposures. Due to the high correlation among C_{avgss}, C_{maxss}, and C_{minss}, each exposure was tested separately against each AE occurrence using univariate logistic regression. The exposure metric that produced the lowest AIC was selected for the E-R analysis.	
Covariates Evaluated			
Final Model Parameters		**Summary**	**Acceptability**

		[FDA's comments]
Model Structure	Exploratory univariate logistic regression analysis. Safety endpoints with p-value <0.05 in the exploratory analysis were included in the formal E-R analysis (multivariate logistic regression using selected covariates).	The updated E-R analysis on safety was acceptable.
Model Parameter Estimates	Table 99	The updated E-R analysis on safety was acceptable.
Model Evaluation	VPC	The updated E-R analysis on safety was acceptable.
Covariates and Clinical Relevance		N/A
Simulation for Specific Population	NA	N/A
Visualization of E-R relationships	Figure 24 and Table 100	The updated E-R analysis on safety was acceptable.
Overall Clinical Relevance for ER	Increased exposure was correlated with the increased probability of PI-identified differentiation syndrome and drug-related PI-identified differentiation syndrome but was not correlated with severe (grade 3 or higher) cases of PI-reported differentiation syndrome. Black box warning for differentiation syndrome is included in the USPI.	Hepatic AE is also correlated with exposure when ER analyses were conducted upon corrected exposure in response to FDA information request.
Labeling Language	**Description**	**Acceptability [FDA's comments]**
12.2 Pharmacodynamics	No exposure safety language was proposed in Section 12.2 of the USPI.	Increased olutasidenib exposure was correlated with the increased probability of differentiation syndrome and Grade ≥ 3 hepatotoxicity in patients with AML following the approved

		recommended olutasidenib dosage.

Table 95: Summary of Safety Endpoint Observations (N=324)

Safety Endpoint	AE Occurrence (%)
Differentiation syndrome (Adjudicated)	38 (11.73)
Differentiation syndrome (PI-identified)	39 (12.04)
Differentiation syndrome_drug-related (Adjudicated)	26 (8.02)
Differentiation syndrome _drug-related (PI-identified)	37 (11.42)
Differentiation syndrome _grade3 (Adjudicated)	31 (9.57)
Differentiation syndrome _grade3 (PI-identified)	22 (6.79)
Differentiation syndrome _grade3_drug-related (Adjudicated)	18 (5.56)
Differentiation syndrome _grade3_drug-related (PI-identified)	22 (6.79)
Hepatic AE	70 (21.6)
Hepatic AE_drug-related	43 (13.27)
Hepatic AE_drug-related_grade3	27 (8.33)
Hepatic AE_grade3	36 (11.11)
Leukocytosis	54 (16.67)
Leukocytosis_drug-related	21 (6.48)
Leukocytosis_grade3	26 (8.02)
Leukocytosis_grade3_drug-related	10 (3.09)
Liver function abnormality	77 (23.77)
Lymphopenia	11 (3.4)
Lymphopenia_drug-related	4 (1.23)
Lymphopenia_grade3	5 (1.54)
Lymphopenia_grade3_drug-related	2 (0.62)
Nausea	142 (43.83)
Nausea_drug-related	83 (25.62)
Nausea_grade3	5 (1.54)
Nausea_grade3_drug-related	2 (0.62)

Safety Endpoint	AE Occurrence (%)
Neutropenia	127 (39.2)
Neutropenia_drug-related	35 (10.8)
Neutropenia_grade3	118 (36.42)
Neutropenia_grade3_drug-related	34 (10.49)
Thrombocytopenia	73 (22.53)
Thrombocytopenia_drug-related	17 (5.25)
Thrombocytopenia_grade3	52 (16.05)
Thrombocytopenia_grade3_drug-related	14 (4.32)

Abbreviations: AE=adverse event; N=number of subjects with available information; PI=principal investigator
Source: Report FORM-PMX-FT2102-2633, Table 14

Table 96: Summary of Safety Endpoint Observations [AE Occurrence (%)] by Cavgss Quartile

	FT-2102 C_{avgss} Quartile			
Safety Endpoint	**Q1 (N=81)**	**Q2 (N=81)**	**Q3 (N=81)**	**Q4 (N=81)**
C_{avgss} range (ng/mL)	**(894,2.95e+03]**	**(2.95e+03,3.84e+03]**	**(3.84e+03,4.75e+03]**	**(4.75e+03,1.19e+04]**
Differentiation syndrome (Adjudicated)	9 (11.11)	10 (12.35)	7 (8.64)	12 (14.81)
Differentiation syndrome (PI-identified)	7 (8.64)	8 (9.88)	9 (11.11)	15 (18.52)
Differentiation_ syndrome drug-related (Adjudicated)	6 (7.41)	6 (7.41)	4 (4.94)	10 (12.35)
Differentiation syndrome _drug-related (PI-identified)	7 (8.64)	7 (8.64)	8 (9.88)	15 (18.52)
Differentiation syndrome _grade3 (Adjudicated)	9 (11.11)	9 (11.11)	5 (6.17)	8 (9.88)
Differentiation syndrome _grade3 (PI-identified)	6 (7.41)	6 (7.41)	4 (4.94)	6 (7.41)
Differentiation syndrome _grade3_drug-related (Adjudicated)	5 (6.17)	5 (6.17)	3 (3.7)	5 (6.17)
Differentiation syndrome _grade3_drug-related (PI-identified)	6 (7.41)	6 (7.41)	4 (4.94)	6 (7.41)

	FT-2102 C_{avgss} Quartile			
Safety Endpoint	**Q1 (N=81)**	**Q2 (N=81)**	**Q3 (N=81)**	**Q4 (N=81)**
C_{avgss} range (ng/mL)	**(894,2.95e+03]**	**(2.95e+03,3.84e+03]**	**(3.84e+03,4.75e+03]**	**(4.75e+03,1.19e+04]**
Hepatic AE	25 (30.86)	22 (27.16)	11 (13.58)	12 (14.81)
Hepatic AE_drug-related	17 (20.99)	12 (14.81)	9 (11.11)	5 (6.17)
Hepatic AE_drug-related_grade3	14 (17.28)	8 (9.88)	2 (2.47)	3 (3.7)
Hepatic AE_grade3	18 (22.22)	10 (12.35)	3 (3.7)	5 (6.17)
Leukocytosis	16 (19.75)	9 (11.11)	14 (17.28)	15 (18.52)
Leukocytosis_drug-related	9 (11.11)	4 (4.94)	4 (4.94)	4 (4.94)
Leukocytosis_grade3	9 (11.11)	3 (3.7)	8 (9.88)	6 (7.41)
Leukocytosis_grade3_drug-related	5 (6.17)	1 (1.23)	2 (2.47)	2 (2.47)
Liver function abnormality	24 (29.63)	24 (29.63)	13 (16.05)	16 (19.75)
Lymphopenia	4 (4.94)	4 (4.94)	0 (0)	3 (3.7)
Lymphopenia_drug-related	3 (3.7)	1 (1.23)	0 (0)	0 (0)
Lymphopenia_grade3	2 (2.47)	2 (2.47)	0 (0)	1 (1.23)
Lymphopenia_grade3_drug-related	2 (2.47)	0 (0)	0 (0)	0 (0)
Nausea	45 (55.56)	33 (40.74)	34 (41.98)	30 (37.04)
Nausea_drug-related	20 (24.69)	25 (30.86)	24 (29.63)	14 (17.28)
Nausea_grade3	3 (3.7)	1 (1.23)	0 (0)	1 (1.23)
Nausea_grade3_drug-related	0 (0)	1 (1.23)	0 (0)	1 (1.23)
Neutropenia	36 (44.44)	35 (43.21)	21 (25.93)	35 (43.21)
Neutropenia_drug-related	13 (16.05)	6 (7.41)	5 (6.17)	11 (13.58)
Neutropenia_grade3	35 (43.21)	31 (38.27)	20 (24.69)	32 (39.51)
Neutropenia_grade3_drug-related	12 (14.81)	6 (7.41)	5 (6.17)	11 (13.58)
Thrombocytopenia	18 (22.22)	20 (24.69)	17 (20.99)	18 (22.22)
Thrombocytopenia_drug-related	6 (7.41)	1 (1.23)	5 (6.17)	5 (6.17)
Thrombocytopenia_grade3	10 (12.35)	15 (18.52)	13 (16.05)	14 (17.28)
Thrombocytopenia_grade3_drug-related	4 (4.94)	1 (1.23)	5 (6.17)	4 (4.94)

Abbreviations: AE=adverse event; C_{avgss}=average plasma concentration at steady state; N=number of subjects with available information; PI=principal investigator; Q=quantile
Source: Report FORM-PMX-FT2102-2633, Table 15

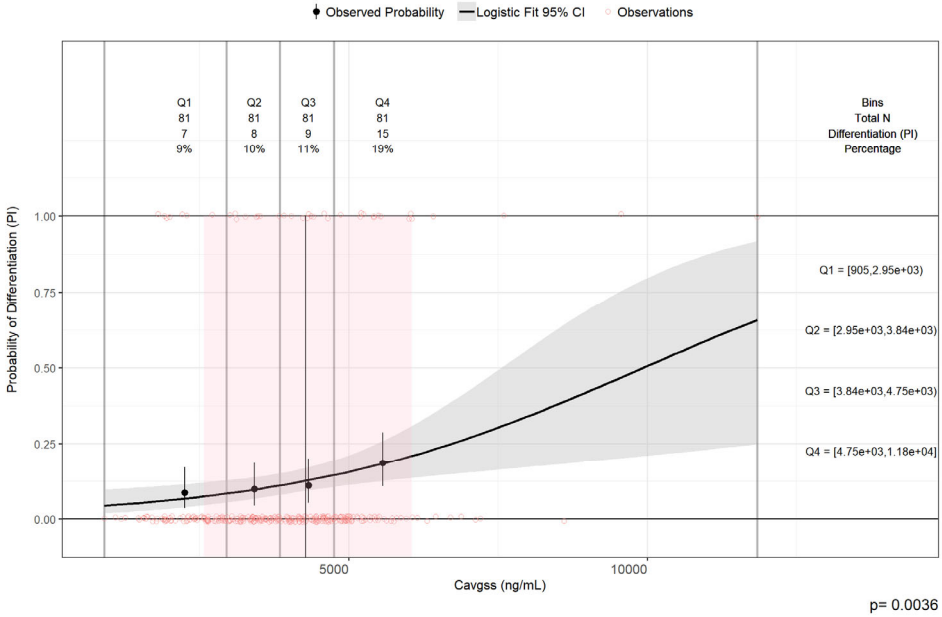
Table 97: Final Model Parameter Estimates – Safety

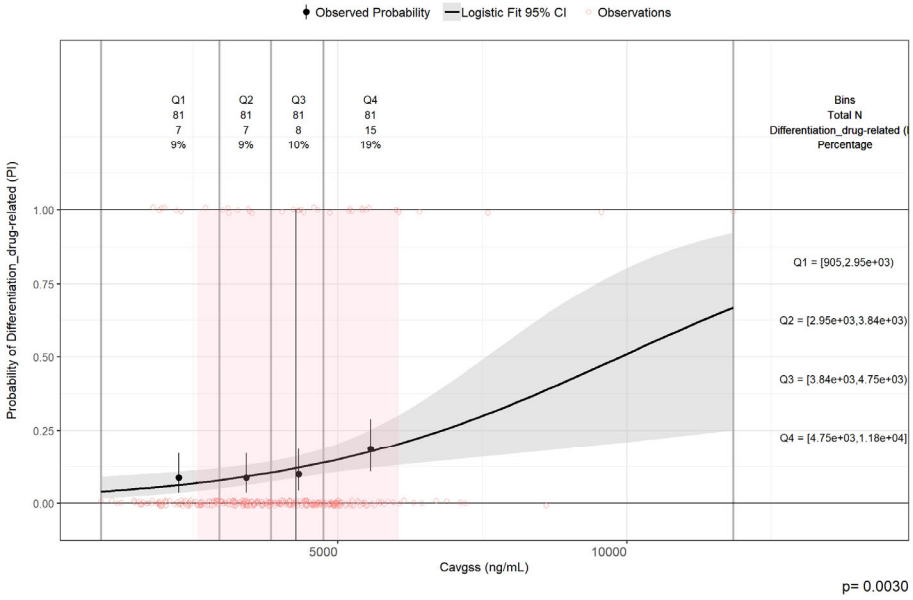
Differentiation Syndrome (PI-Identified)				
Parameter	**Estimate**	**RSE%**	**p-Value**	**Odds Ratio (95% CI)**
(Intercept)	-3.36000	15.5%	<0.0001	
C_{minss} (ng/mL)	0.00035	33.8%	0.0031	1.0003 (1.0001, 1.0006)
Drug-Related Differentiation Syndrome (PI-Identified)				
(Intercept)	-3.47000	15.4%	<0.0001	
C_{minss} (ng/mL)	0.00036	33.3%	0.0027	1.0004 (1.0001, 1.0006)
Hepatic AE				
(Intercept)	-2.29000	47.2%	0.034	
C_{maxss} (ng/mL)	-0.00027	41.3%	0.015	0.99973 (0.99951, 0.99994)
Age (year)	0.02950	47.2%	0.034	1.0299 (1.0034, 1.0598)
Hepatic AE (≥ Grade 3)				
(Intercept)	-1.14000	47.7%	0.0365	
C_{minss} (ng/mL)	-0.00044	34.3%	0.0036	0.99956 (0.99925, 0.99985)
Sex: Female	1.04000	36.8%	0.0065	2.8338 (1.365, 6.19)
Drug-Related Hepatic AE (≥ Grade 3)				
(Intercept)	-1.49000	44%	0.0230	
C_{avgss} (ng/mL)	-0.00044	39.3%	0.0108	0.99956 (0.9992, 0.99989)
	Sex: Female	37.3%	0.0071	3.3352 (1.4359, 8.4657)

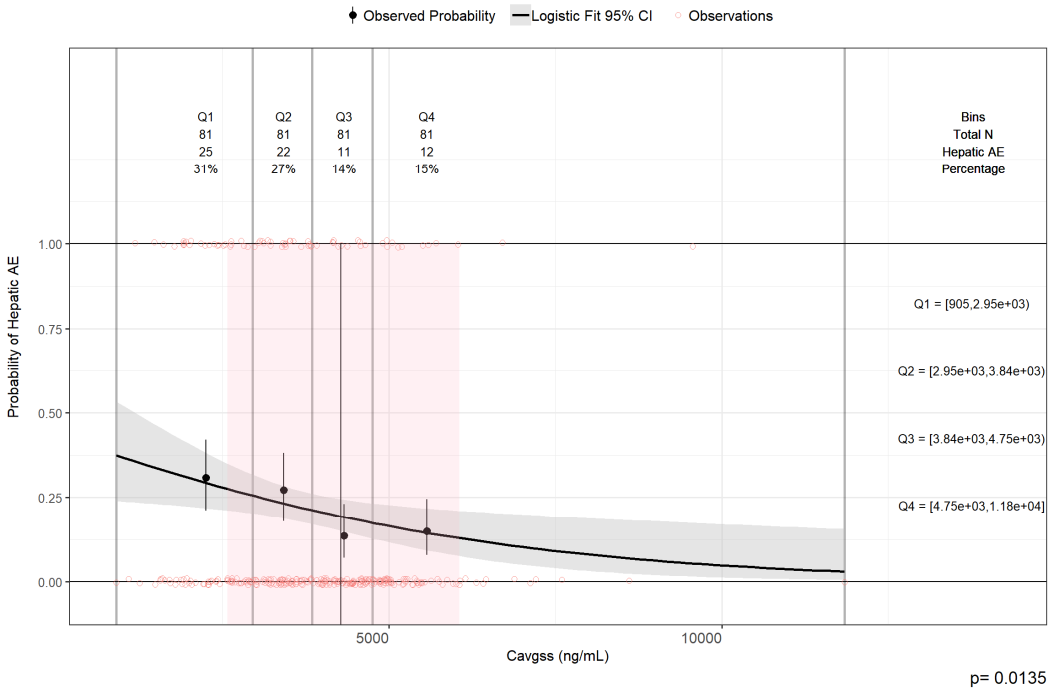
Abbreviations: CI=confidence intervals; C_{avgss}=average plasma concentration at steady state; C_{minss}=minimum plasma concentration at steady state; C_{maxss}=maximum plasma concentration at steady state; PI=principal investigator; RSE=relative standard error

Source: Report FORM-PMX-FT2102-2633, Table 31, Table 33, Table 35, Table 37

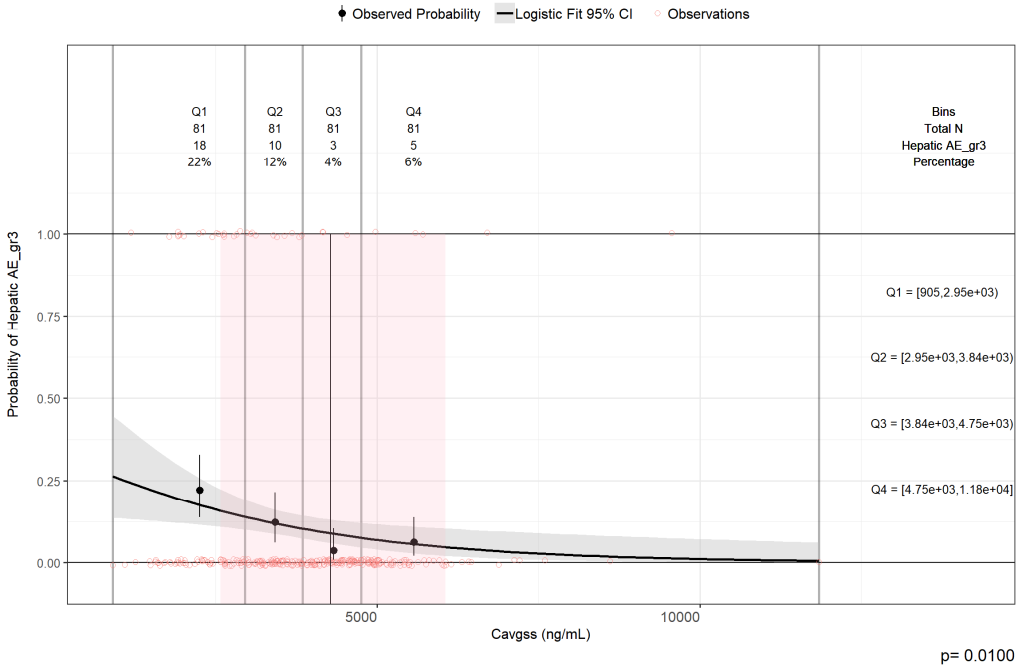
Figure 24: Relationship Between C_{avg} at Steady State and Probability of an AE Occurrence





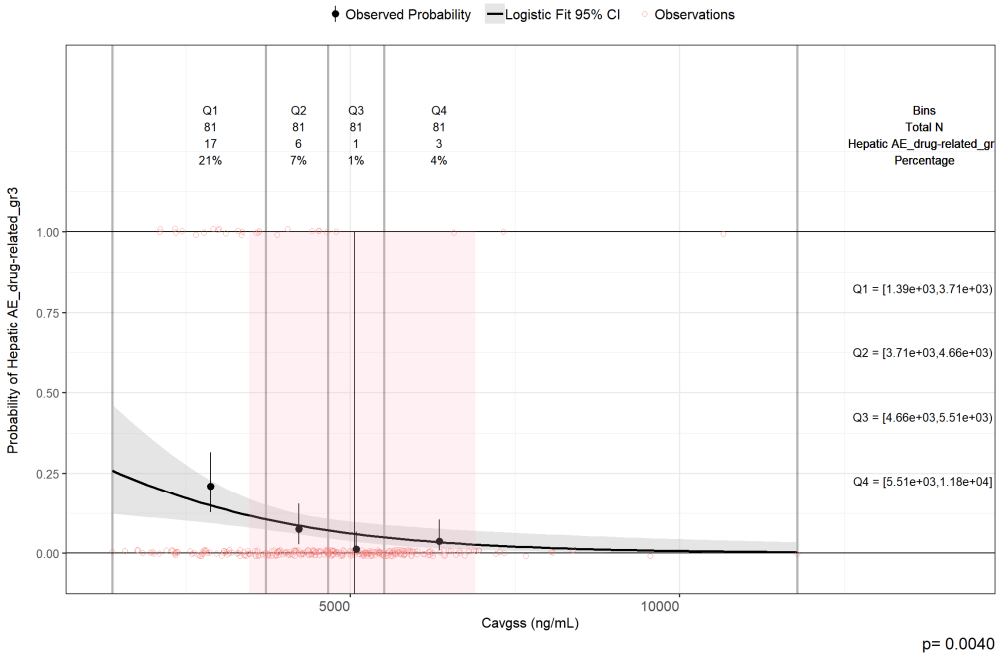


p= 0.0135



p= 0.0100

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.



Notes: The independent variables were divided into 4 equally sized rank-ordered groups. Black points and error bars represent the observed proportions and 95% CIs for each exposure group (plotted at the mean exposure within each exposure group), respectively. The black curve represents the prediction of the univariate logistic regression model, and the gray shaded region represents the 95% CI of the prediction. Percentages in the upper part of the graph represent the proportion of subjects in each exposure group who experienced AE. The black vertical solid black line represents the median of the predicted exposure at steady state for subjects who took FT-2102 150 mg BID, and the pink shaded region represents 90% CI of the predicted exposure at steady state for subjects who took FT-2102 150 mg BID.

Abbreviations: AE=adverse event; BID=twice daily; C_{avgss}=average plasma concentration at steady state; CI=confidence interval; C_{maxss}=maximum plasma concentration at steady state; C_{minss}=minimum plasma concentration at steady state; N=number of subjects; gr3=Grade 3+; p=p-value of logistic regression model slope; Q=quantile

Source: Report FORM-PMX-FT2102-2633, Figure 16, Figure, 17, Figure 18, Figure 19, Figure 20

Table 98: Model Predicted AE Occurrence across Exposure Quantile at Steady State

AE	Model-Predicted Incidence (95% CI)		
	P10	P50	P90
C_{avgss} (ng/mL)			
Differentiation (Adjudicated)	0.093 (0.055, 0.152)	0.115 (0.084, 0.155)	0.14 (0.094, 0.204)
Differentiation (PI)	0.066 (0.037, 0.114)	0.11 (0.08, 0.151)	0.175 (0.122, 0.244)
Differentiation_drug-related (Adjudicated)	0.058 (0.03, 0.107)	0.077 (0.053, 0.113)	0.102 (0.063, 0.159)

Differentiation_drug-related (PI)	0.06 (0.033, 0.107)	0.104 (0.074, 0.144)	0.168 (0.117, 0.236)
Differentiation_drug-related_gr3 (Adjudicated)	0.047 (0.022, 0.098)	0.055 (0.035, 0.086)	0.063 (0.034, 0.114)
Differentiation_drug-related_gr3 (PI)	0.064 (0.033, 0.121)	0.068 (0.045, 0.101)	0.072 (0.04, 0.126)
Differentiation_gr3 (Adjudicated)	0.087 (0.05, 0.149)	0.095 (0.068, 0.132)	0.103 (0.064, 0.163)
Differentiation_gr3 (PI)	0.064 (0.033, 0.121)	0.068 (0.045, 0.101)	0.072 (0.04, 0.126)
Hepatic AE	0.297 (0.219, 0.389)	0.212 (0.17, 0.261)	0.149 (0.099, 0.219)
Hepatic AE_drug-related	0.184 (0.122, 0.269)	0.129 (0.096, 0.171)	0.091 (0.053, 0.151)
Hepatic AE_drug-related_gr3	0.135 (0.082, 0.215)	0.077 (0.052, 0.114)	0.045 (0.021, 0.092)
Hepatic AE_gr3	0.179 (0.117, 0.265)	0.103 (0.074, 0.143)	0.059 (0.031, 0.111)
Leukocytosis	0.145 (0.095, 0.214)	0.165 (0.129, 0.21)	0.187 (0.132, 0.257)
Leukocytosis_drug-related	0.07 (0.036, 0.132)	0.065 (0.043, 0.097)	0.06 (0.031, 0.113)
Leukocytosis_drug-related_gr3	0.04 (0.016, 0.098)	0.03 (0.016, 0.056)	0.023 (0.008, 0.066)
Leukocytosis_gr3	0.082 (0.045, 0.144)	0.08 (0.055, 0.115)	0.079 (0.045, 0.136)
Liver test abnormality	0.278 (0.205, 0.366)	0.237 (0.194, 0.287)	0.203 (0.144, 0.278)
Lymphopenia	0.037 (0.014, 0.089)	0.034 (0.019, 0.06)	0.032 (0.013, 0.077)
Lymphopenia_drug-related	0.034 (0.012, 0.09)	0.005 (0.001, 0.03)	0.001 (0, 0.023)
Lymphopenia_drug-related_gr3	0.017 (0.004, 0.068)	0.003 (0, 0.031)	0 (0, 0.042)
Lymphopenia_gr3	0.026 (0.008, 0.082)	0.014 (0.005, 0.036)	0.008 (0.001, 0.045)
Nausea	0.493 (0.406, 0.581)	0.439 (0.386, 0.494)	0.39 (0.313, 0.473)
Nausea_drug-related	0.277 (0.205, 0.363)	0.256 (0.212, 0.307)	0.238 (0.175, 0.314)
Nausea_drug-related_gr3	0.005 (0, 0.044)	0.006 (0.001, 0.025)	0.008 (0.001, 0.042)
Nausea_gr3	0.033 (0.011, 0.091)	0.012 (0.004, 0.035)	0.004 (0.001, 0.036)
Neutropenia	0.412 (0.329, 0.5)	0.392 (0.341, 0.447)	0.374 (0.299, 0.456)
Neutropenia_drug-related	0.134 (0.083, 0.21)	0.107 (0.078, 0.146)	0.086 (0.05, 0.145)
Neutropenia_drug-related_gr3	0.126 (0.076, 0.2)	0.104 (0.075, 0.143)	0.087 (0.051, 0.147)
Neutropenia_gr3	0.399 (0.316, 0.488)	0.365 (0.314, 0.419)	0.333 (0.261, 0.415)
Thrombocytopenia	0.197 (0.138, 0.272)	0.224 (0.181, 0.273)	0.251 (0.188, 0.328)
Thrombocytopenia_drug-related	0.054 (0.026, 0.111)	0.052 (0.033, 0.083)	0.051 (0.025, 0.101)
Thrombocytopenia_drug-related_gr3	0.042 (0.018, 0.094)	0.043 (0.026, 0.072)	0.044 (0.021, 0.092)

Thrombocytopenia_gr3	0.125 (0.08, 0.19)	0.157 (0.121, 0.202)	0.194 (0.138, 0.264)
C_{maxss} (ng/mL)			
Differentiation (Adjudicated)	0.093 (0.056, 0.153)	0.115 (0.085, 0.155)	0.139 (0.093, 0.204)
Differentiation (PI)	0.066 (0.037, 0.115)	0.111 (0.08, 0.151)	0.174 (0.122, 0.243)
Differentiation_drug-related (Adjudicated)	0.058 (0.03, 0.107)	0.078 (0.053, 0.113)	0.102 (0.063, 0.159)
Differentiation_drug-related (PI)	0.061 (0.034, 0.107)	0.104 (0.075, 0.144)	0.168 (0.116, 0.236)
Differentiation_drug-related_gr3 (Adjudicated)	0.048 (0.022, 0.098)	0.055 (0.035, 0.086)	0.063 (0.034, 0.114)
Differentiation_drug-related_gr3 (PI)	0.065 (0.033, 0.122)	0.068 (0.045, 0.101)	0.071 (0.039, 0.125)
Differentiation_gr3 (Adjudicated)	0.088 (0.05, 0.15)	0.095 (0.068, 0.133)	0.102 (0.063, 0.163)
Differentiation_gr3 (PI)	0.065 (0.033, 0.122)	0.068 (0.045, 0.101)	0.071 (0.039, 0.125)
Hepatic AE	0.301 (0.222, 0.394)	0.211 (0.169, 0.26)	0.147 (0.097, 0.216)
Hepatic AE_drug-related	0.187 (0.124, 0.272)	0.129 (0.096, 0.171)	0.09 (0.052, 0.15)
Hepatic AE_drug-related_gr3	0.135 (0.082, 0.216)	0.077 (0.052, 0.113)	0.045 (0.021, 0.092)
Hepatic AE_gr3	0.18 (0.117, 0.266)	0.103 (0.074, 0.143)	0.06 (0.031, 0.112)
Leukocytosis	0.145 (0.095, 0.214)	0.165 (0.129, 0.21)	0.187 (0.132, 0.258)
Leukocytosis_drug-related	0.071 (0.037, 0.133)	0.065 (0.043, 0.097)	0.059 (0.031, 0.113)
Leukocytosis_drug-related_gr3	0.04 (0.016, 0.098)	0.03 (0.016, 0.056)	0.023 (0.008, 0.067)
Leukocytosis_gr3	0.082 (0.045, 0.146)	0.08 (0.055, 0.115)	0.078 (0.044, 0.135)
Liver test abnormality	0.281 (0.207, 0.37)	0.237 (0.194, 0.287)	0.2 (0.142, 0.275)
Lymphopenia	0.034 (0.013, 0.084)	0.034 (0.019, 0.06)	0.034 (0.014, 0.08)
Lymphopenia_drug-related	0.034 (0.012, 0.091)	0.005 (0.001, 0.03)	0.001 (0, 0.023)
Lymphopenia_drug-related_gr3	0.017 (0.004, 0.069)	0.003 (0, 0.03)	0.001 (0, 0.042)
Lymphopenia_gr3	0.027 (0.008, 0.084)	0.014 (0.005, 0.036)	0.008 (0.001, 0.045)
Nausea	0.492 (0.405, 0.58)	0.439 (0.386, 0.494)	0.391 (0.313, 0.474)
Nausea_drug-related	0.275 (0.203, 0.361)	0.256 (0.212, 0.307)	0.24 (0.176, 0.317)
Nausea_drug-related_gr3	0.005 (0, 0.045)	0.006 (0.001, 0.024)	0.007 (0.001, 0.043)
Nausea_gr3	0.033 (0.012, 0.093)	0.012 (0.004, 0.035)	0.004 (0.001, 0.035)
Neutropenia	0.413 (0.33, 0.502)	0.392 (0.341, 0.447)	0.373 (0.298, 0.455)
Neutropenia_drug-related	0.133 (0.082, 0.209)	0.107 (0.078, 0.146)	0.087 (0.05, 0.147)
Neutropenia_drug-related_gr3	0.125 (0.075, 0.199)	0.104 (0.075, 0.143)	0.088 (0.051, 0.148)

Neutropenia_gr3	0.4 (0.317, 0.49)	0.365 (0.314, 0.418)	0.333 (0.26, 0.414)
Thrombocytopenia	0.197 (0.138, 0.273)	0.224 (0.182, 0.273)	0.251 (0.188, 0.327)
Thrombocytopenia_drug-related	0.055 (0.026, 0.113)	0.052 (0.033, 0.083)	0.05 (0.024, 0.101)
Thrombocytopenia_drug-related_gr3	0.043 (0.019, 0.096)	0.043 (0.026, 0.072)	0.043 (0.02, 0.092)
Thrombocytopenia_gr3	0.125 (0.08, 0.189)	0.157 (0.121, 0.202)	0.194 (0.138, 0.265)
C_{minss} (ng/mL)			
Differentiation (Adjudicated)	0.091 (0.054, 0.15)	0.115 (0.085, 0.155)	0.14 (0.095, 0.202)
Differentiation (PI)	0.065 (0.036, 0.112)	0.111 (0.08, 0.152)	0.172 (0.121, 0.238)
Differentiation_drug-related (Adjudicated)	0.057 (0.03, 0.107)	0.078 (0.053, 0.113)	0.1 (0.063, 0.155)
Differentiation_drug-related (PI)	0.059 (0.033, 0.106)	0.105 (0.075, 0.145)	0.165 (0.115, 0.23)
Differentiation_drug-related_gr3 (Adjudicated)	0.047 (0.022, 0.097)	0.055 (0.035, 0.086)	0.063 (0.034, 0.112)
Differentiation_drug-related_gr3 (PI)	0.063 (0.032, 0.119)	0.068 (0.045, 0.101)	0.072 (0.041, 0.125)
Differentiation_gr3 (Adjudicated)	0.087 (0.049, 0.148)	0.095 (0.068, 0.133)	0.103 (0.065, 0.161)
Differentiation_gr3 (PI)	0.063 (0.032, 0.119)	0.068 (0.045, 0.101)	0.072 (0.041, 0.125)
Hepatic AE	0.292 (0.215, 0.383)	0.211 (0.169, 0.26)	0.156 (0.106, 0.225)
Hepatic AE_drug-related	0.182 (0.12, 0.266)	0.129 (0.096, 0.171)	0.095 (0.057, 0.154)
Hepatic AE_drug-related_gr3	0.135 (0.082, 0.215)	0.076 (0.051, 0.113)	0.046 (0.022, 0.093)
Hepatic AE_gr3	0.18 (0.117, 0.266)	0.102 (0.072, 0.142)	0.061 (0.033, 0.112)
Leukocytosis	0.145 (0.095, 0.214)	0.166 (0.129, 0.21)	0.185 (0.132, 0.254)
Leukocytosis_drug-related	0.07 (0.036, 0.131)	0.065 (0.043, 0.097)	0.061 (0.032, 0.112)
Leukocytosis_drug-related_gr3	0.041 (0.016, 0.099)	0.03 (0.016, 0.056)	0.023 (0.008, 0.064)
Leukocytosis_gr3	0.081 (0.044, 0.143)	0.08 (0.055, 0.115)	0.08 (0.046, 0.135)
Liver test abnormality	0.274 (0.201, 0.361)	0.237 (0.193, 0.286)	0.208 (0.15, 0.281)
Lymphopenia	0.04 (0.016, 0.095)	0.034 (0.019, 0.06)	0.029 (0.011, 0.072)
Lymphopenia_drug-related	0.034 (0.012, 0.091)	0.005 (0.001, 0.03)	0.001 (0, 0.023)
Lymphopenia_drug-related_gr3	0.017 (0.004, 0.068)	0.002 (0, 0.033)	0 (0, 0.044)
Lymphopenia_gr3	0.026 (0.008, 0.083)	0.014 (0.005, 0.036)	0.008 (0.001, 0.044)
Nausea	0.494 (0.406, 0.582)	0.438 (0.385, 0.493)	0.392 (0.317, 0.472)

Nausea_drug-related	0.28 (0.207, 0.366)	0.256 (0.211, 0.306)	0.237 (0.176, 0.311)
Nausea_drug-related_gr3	0.004 (0, 0.042)	0.006 (0.001, 0.025)	0.008 (0.001, 0.039)
Nausea_gr3	0.032 (0.011, 0.091)	0.012 (0.004, 0.035)	0.005 (0.001, 0.036)
Neutropenia	0.41 (0.327, 0.498)	0.392 (0.34, 0.446)	0.377 (0.304, 0.456)
Neutropenia_drug-related	0.136 (0.084, 0.213)	0.106 (0.077, 0.145)	0.086 (0.05, 0.143)
Neutropenia_drug-related_gr3	0.127 (0.078, 0.202)	0.104 (0.075, 0.142)	0.087 (0.051, 0.144)
Neutropenia_gr3	0.397 (0.314, 0.486)	0.364 (0.313, 0.418)	0.337 (0.266, 0.416)
Thrombocytopenia	0.196 (0.137, 0.272)	0.224 (0.182, 0.273)	0.251 (0.189, 0.324)
Thrombocytopenia_drug-related	0.053 (0.025, 0.108)	0.052 (0.033, 0.083)	0.052 (0.027, 0.101)
Thrombocytopenia_drug-related_gr3	0.041 (0.017, 0.091)	0.043 (0.026, 0.072)	0.045 (0.022, 0.092)
Thrombocytopenia_gr3	0.125 (0.08, 0.19)	0.158 (0.122, 0.202)	0.191 (0.138, 0.259)

Abbreviations: AE=adverse event; C_{avgss}=average plasma concentration at steady state; CI=confidence interval; C_{maxss}=maximum plasma concentration at steady state; C_{minss}=minimum plasma concentration at steady state; P10=10th quantile; P50=50th quantile; P90=90th quantile
Source: Report FORM-PMX-FT2102-2633, Table 48

The FDA's Assessment: Plots 3-5 of Figure 25 and numbers in Table 100 were incorrect due to incorrect exposure values for some patients. Upon FDA request, the applicant corrected the plots and numbers but not updated in this document. Please see Reviewer's Independent Analysis for more information about the correct exposure response plots of efficacy and safety endpoints, particularly, the ER result for hepatoxicity.

20.4.3.5 E-R Review Issues

Applicant's exposure-response analyses were unacceptable due to incorrect CAVGSS calculation using 150 mg QD dose (apparently based on the last dosage of the individual in the trial) for some patients who administered 150 mg BID regimen during most of the treatment period, particularly for the patients who transitioned to 150 mg QD from 150 mg BID due to safety issues. FDA issued an IR requesting the applicant to correct all efficacy and safety endpoints based on correct exposure. The Applicant's updated analysis results were consistent with FDA Reviewer's independent analysis. See below for details.

20.4.3.6 Reviewer's Independent Analysis

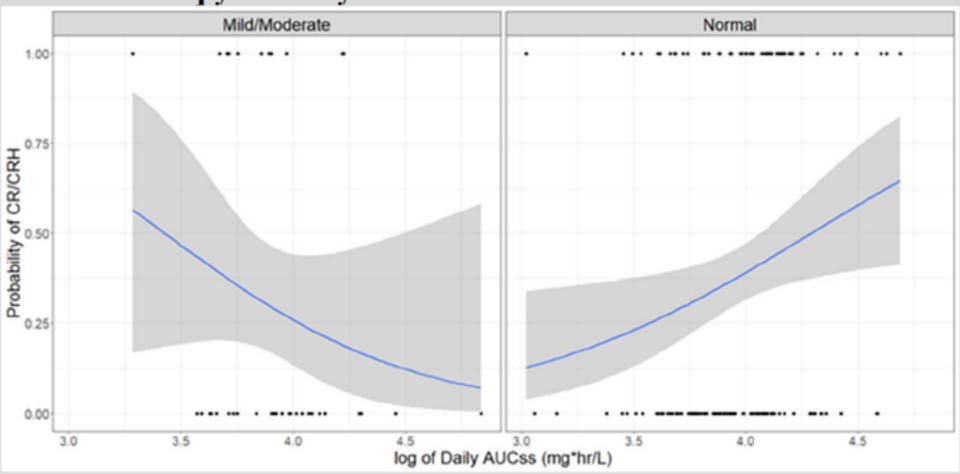
Objectives: To explore exposure-response relationship for major efficacy and safety endpoints based on updated population pharmacokinetics.

Method: For patients on 150 mg BID olutasidenib monotherapy only, exposure was generated for each individual patient based on 300 mg daily dose and CL value from applicant's run201.ctl associated with NONMEM dataset "FT2102-poppk-withconmed-TTE-09SEP2022-scm.csv". Safety and efficacy data were from "er.xpt".

Results: The exploratory univariate analysis results of exposure-response relationship of major efficacy endpoints are shown in Figure 26 for CRH, Figure 27 for ORR, and Figure 28 for CBR in patients with olutasidenib BID monotherapy.

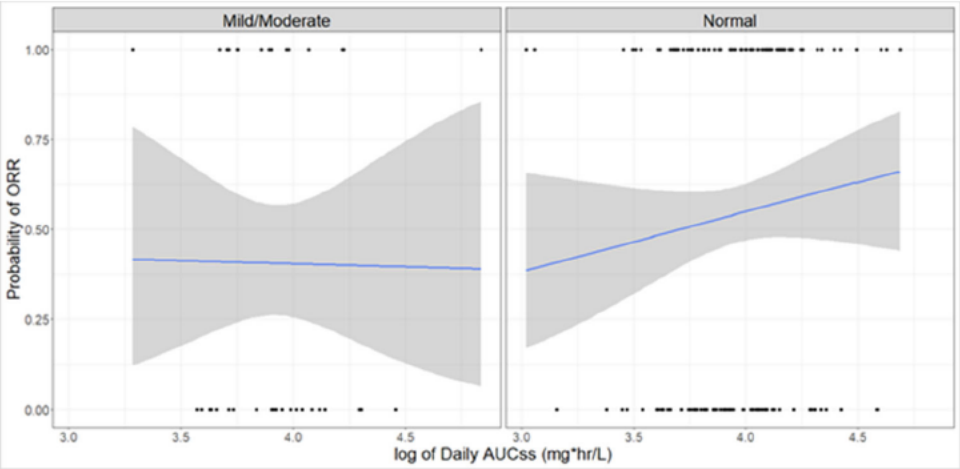
Additional exploratory analysis also showed that, in general, the exposure-efficacy relationship was slightly positive in patients with normal liver function but flat or negative in patients with mild/moderate hepatic impairment.

Figure 25: Exposure-Response Relationship for CR/CRH in Patients with Olutasidenib 150 mg BID Monotherapy of Study 101



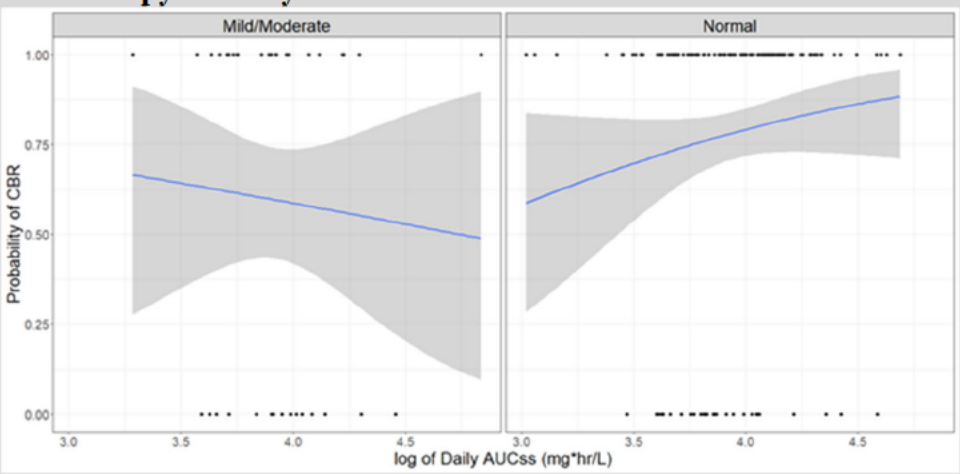
Source: FDA Reviewer's Analysis

Figure 26: Exposure-Response Relationship for ORR in Patients with Olutasidenib 150 mg BID Monotherapy of Study 101



Source: FDA Reviewer's Analysis

Figure 27: Exposure-Response Relationship for CBR in Patients with Olutasidenib 150 mg BID Monotherapy of Study 101



Source: FDA Reviewer's Analysis

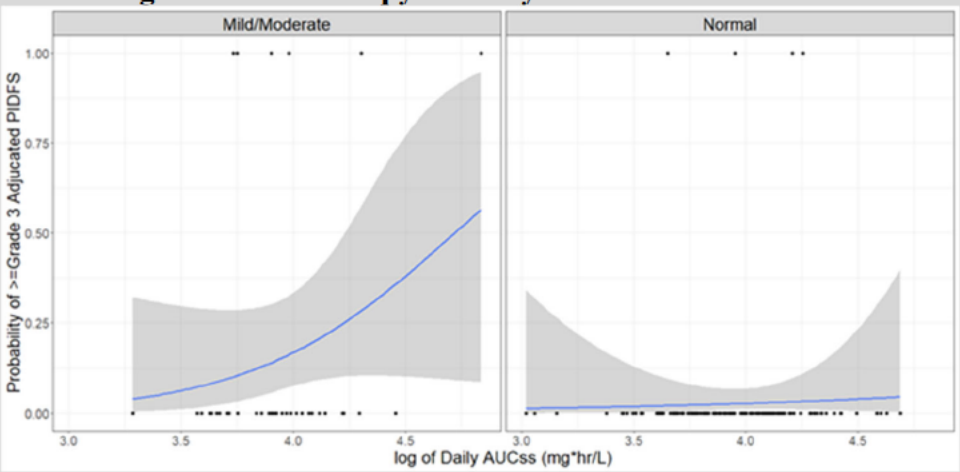
The exploratory univariate analysis results of exposure-response relationship of major safety endpoints showed that:

- A positive exposure-response relationship for ≥ Grade 3 adjudicated PI identified differentiation syndrome (DIFATRG3, Figure 1 in Section 6) and treatment emergent ≥ Grade 3 hepatoxicity in general patient population (Figure 2 in Section 6).

- In Figure 29, DIFATRG3 rate was 16.2% (6/37) for patients with mild/moderate hepatic impairment vs 2.6% (4/155) for patients with normal liver function.

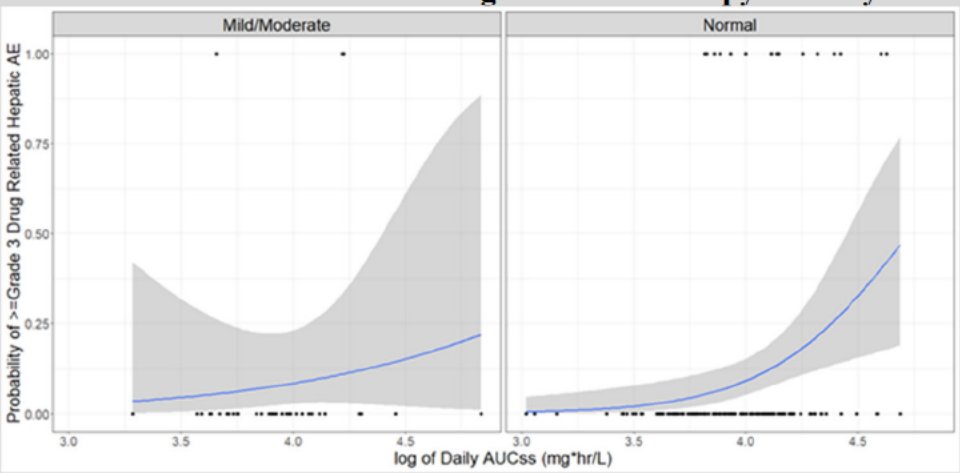
- In Figure 30, the AE rate was 8.1% (3/37) for patients with mild/moderate hepatic impairment vs 10.3% (16/155) for patients with normal liver function.

Figure 28: Exposure-Response Relationship for Drug Related Adjudicated ≥ Grade 3 Principal Investigator Identified Differentiation Syndrome (PIDFS) in Patients with Olutasidenib 150 mg BID Monotherapy of Study 101



Source: FDA Reviewer's Analysis

Figure 29: Exposure-Response Relationship for Treatment Emergent ≥ Grade 3 Hepatic Toxicity in Patients with Olutasidenib 150 mg BID Monotherapy of Study 101



Source: FDA Reviewer's Analysis

20.4.3.7 Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

E-R analyses support the recommended dose of 150 mg twice daily.

Although efficacy (CR/CRh) is not significantly associated with increased olutasidenib exposure

at steady state, the highest incidence of CR/CRh occurred at the highest quartile of exposure.

Although PI-identified differentiation syndrome and drug-related differentiation syndrome are significantly associated with increased olutasidenib exposure, specifically in the highest quartile of exposure, it was not significantly associated with severe (grade 3 or higher) cases of PI-reported differentiation syndrome. This risk is monitorable and manageable with dose interruption or dose reduction. Finally, there was no apparent correlation between the olutasidenib exposure at steady state and the other safety endpoints.

The FDA's Assessment:

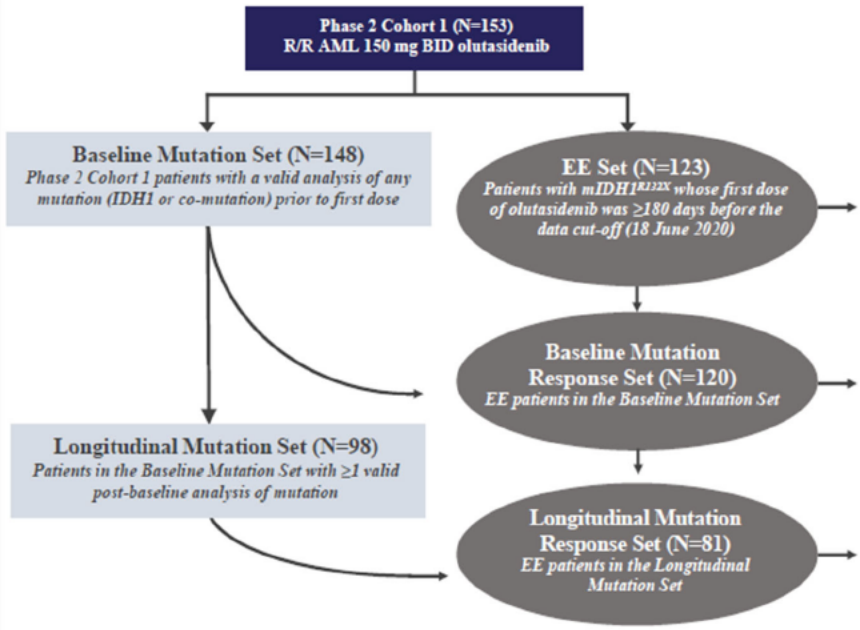
See Section 20.4.3.6 for reviewer's E-R analysis about efficacy and safety. Overall, we agree the recommended dose of 150 mg BID is a clinically acceptable dose.

20.4.4 Exploratory Mutation Analysis

The FDA's Assessment:

Overview, Response Definitions, and Analysis Sets:
Different datasets (**Figure 31**) were used by the Applicant to conduct subgroup analyses of response by IDH1 R132 variant (R132C/H/L/G/S), IDH1 VAF, and co-mutated genes. The clinical data cutoff for these analyses was 18 June 2020. Of the datasets presented in **Figure 31**, the Baseline Mutation Best Response Set (N=120) was used for the analyses shown in Table **101**, Table **102**, Table **103**, Table **104** and **Figure 32**. Three patients included in the primary efficacy population were excluded from this set. Patients who achieved a complete remission (CR) or complete remission with partial hematologic recovery (CRh) were considered Responders.

Figure 30: Analysis Sets and Best Overall Response to Treatment with Olutasidenib



AML: acute myelogenous leukemia; BID: twice daily; CR/CRh: complete remission/complete remission with incomplete hematologic recovery; CRi: complete remission with incomplete hematologic recovery; EE: efficacy evaluable; IDH1: isocitrate dehydrogenase 1; MLFS: morphologic leukemia-free state; PR: partial remission

Source: Applicant's Figure 1, Mutational Analysis Report.

IDH1 Variant and Response:

Whole blood or blood pellets collected at screening and analyzed by either digital polymerase chain reaction (ddPCR) or NGS were used for the analyses. If a given sample was analyzed by both methods, data from next generation sequencing (NGS) were used.

Responses were seen across IDH1 R132 variants, with lowest CR/CRh rates observed in the subgroup of patients with R132H (
Table 101).

Table 99: CR/CRh Rate by IDH1 R132 Variant (Baseline Mutation Response Set, N=120)

IDH1 R132 Variant	Number of Patients	CR/CRh, N (%)
Total	*120*	*40 (33.3)*
R132C	66	25 (37.9)
R132G	11	4 (36.4)
R132H	29	5 (17.2)
R132L	3	2 (66.7)
R132S	10	4 (40.0)
R132C & R132L	1	0

Source: Adapted from Applicant's Table 6, Mutational Analysis Report.

Co-Mutation Analyses:

Co-mutations were assessed by NGS using a 74-gene custom myeloid panel. Mutations were detected in each gene based on the sequence coverage and the sensitivity limit of the NGS assay (1% VAF). If several mutations were detected in a gene, the mutations were aggregated, and the gene was considered co-mutated. All mutations were reported regardless of known pathogenicity. Single nucleotide polymorphisms were not reported (FDA Information request 8/29/2022). Genes were grouped in functional categories by the Applicant as follows:

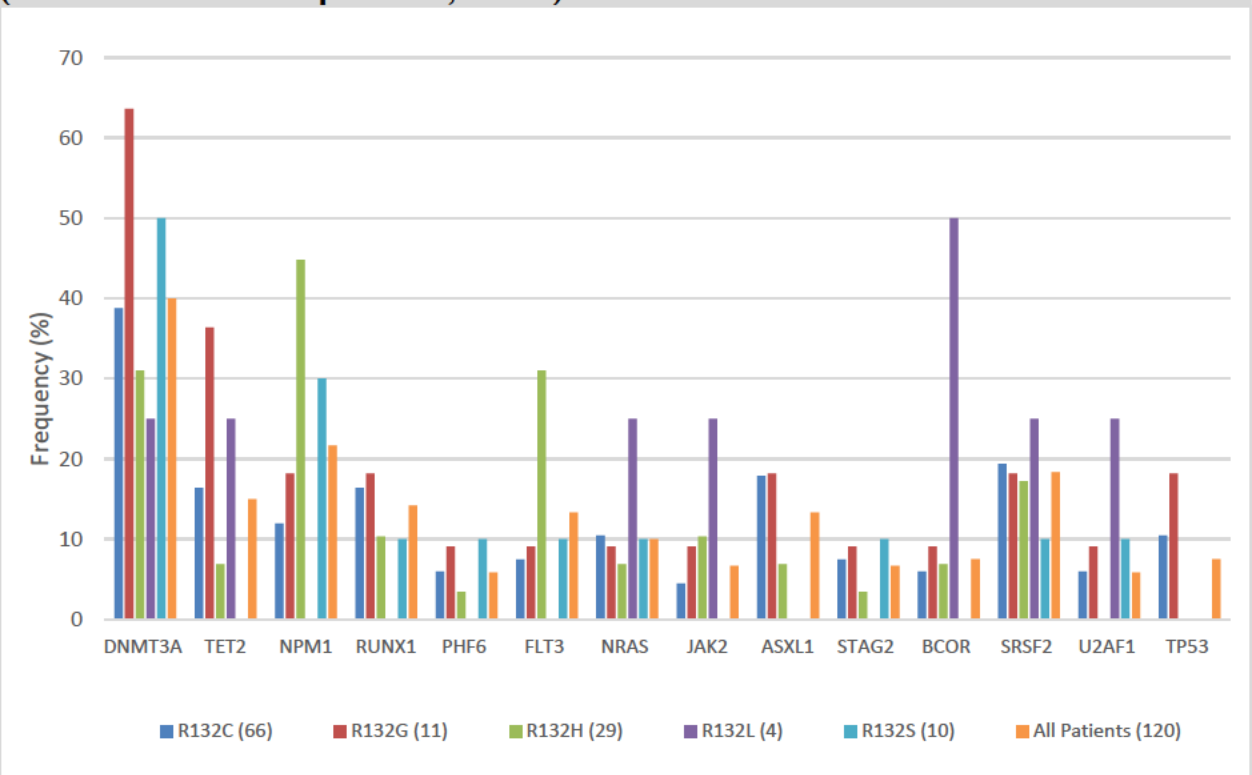
- RTK Pathway (CALR, CBL, CSF3R, EPOR, ETNK1, FLT3, JAK, JAK2, KIT, KRAS, MPL, NF1, NRAS, PTPN11, SETBP1, SH2B3)
- Chromatin (ASXL1, ASXL2, BCOR, STAG2, BCORL1, EED, SUZ12, EZH2, EP300, SMC1A, SMC3)
- Differentiation (CEBPA, CREBBP, CUX1, ETV6, GATA2, NFE-2, NPM1, PHF6, RUNX1, WT1)
- Epigenetics (DNMT3A, TET2)
- Splicing (ATRX, PRPF8, SRSF2, U2AF1, SF3B1, ZRSR2)
- Other (ATM, CHEK2, MYC, PPM1D, TP53)

Profile of co-mutated genes: The most common co-mutated genes identified in samples of patients included in the Baseline Mutation Best Response Set (N=120) were DNMT3A (43%), NPM1 (23%), SRSF2 (19%), TET2 (15%), RUNX1 (14%), ASXL1 (13%), FLT3 (12%), and NRAS (10%). Similar results were observed for the Baseline Mutation set (N=148).

The frequency and spectrum of co-mutated genes varied by R132 variant (**Figure 32**). FLT3 and NPM1 co-mutated genes appear to be preferentially associated with R132H (FLT3 31% in R132H vs. 8% in non-R132H; NPM1 48% in R132H vs. 16% in non-R132H). Different co-mutation patterns and prognosis by R132 variant have been previously described with IDH1

inhibitors (Falini et al, 2019), suggesting R132 variants, despite affecting the same hotspot in IDH1, might have differential functional consequences.

Figure 31: Baseline Co-Mutated Genes (>5% of Patients) Overall and by IDH1 Variant (Baseline Mutation Response Set, N=120)



Source: Reviewer exploratory analysis based on ADVF dataset; Patients may be counted more than once, as most patients had more than one co-mutated gene identified.

Co-mutated genes and response: Of the 74-gene panel used in this analysis, most patients (58%) had 1-3 mutated genes identified, no mutations were identified in 15% of patients, and 27% had ≥4 mutated genes. Patients who achieved a best response of CR/CRh were more likely to have fewer (≤ 3) baseline co-mutated genes compared with those who did not achieve CR/CRh (Table 102). The Applicant also reported a positive correlation between higher number of baseline co-mutations (co-mutated genes) and higher baseline blast count.

No CR/CRh responses were observed in patients with co-mutated FLT3 regardless of R132 variant. The Applicant argues that the lower response rate in the R132H subgroup is likely explained by higher frequency of FLT3 co-mutations (9/29, 31%) (Table 103). Additionally, it appears that patients with mutated NRAS and PTPN11 (also in the RTK pathway category) had

lower rates of CR/CRh compared with patients with co-mutated genes in the Epigenetics, Chromatin, or Splicing pathway categories (Table 104).

Table 100: CR/CRh Rate by Number of Co-Mutated Genes (Baseline Mutation Response Set, N=120)

Number of Co-Mutated Genes	Number of Patients	CR/CRh, N (%)
0	18	7 (38.9)
1-3	70	29 (41.4)
4-10	32	4 (12.5)

Source: Adapted from Applicant's Table 5, Mutational Analysis Report.

Table 101: CR/CRh Rate by Selected Co-Mutated Genes (Baseline Mutation Response Set, N=120)

Co-Mutated Genes	Number of Patients	CR/CRh, N (%)
IDH1 R132H (N=29)		
FLT3	9	0
NPM1	14	2 (14.2)
Both FLT3 and NPM1	8	0
Neither FLT3 nor NPM1	14	3 (21.4)
Total	*29*	*5 (17.2)*
IDH1 Non-R132H (N=91)		
FLT3	5	0
NPM1	14	2(13.3)
Both FLT3 and NPM1	4	0
Neither FLT3 nor NPM1	73	33 (45.2)
Total	*91*	*35 (38.5)*

Source: Modified from Applicant's Table 7, Mutational Analysis Report. Patients may have more counted more than once for single NPM1 and FLT3 gene analyses.

Table 102: CR/CRh Rate by Co-Mutated Gene and Pathway (Baseline Mutation Best Response Set, N=120)

Gene Category/Co-Mutated Gene(s)	Number of Patients	CR/CRh, N (%)
Epigenetics	61	23 (37.7)
DNMT3A	51	19 (37.3)
TET2	18	8 (44.4)
Differentiation	54	9 (16.7)
NPM1	28	4 (14.3)
RUNX1	17	2 (11.8)
RTK Pathway	48	8 (16.7)
FLT3	14	0
NRAS	12	1 (8.3)
Chromatin	37	10 (27.0)
ASXL1	16	6 (37.5)
Splicing	37	11 (29.7)
SRSF2	23	9 (39.1)

Source: Applicant's Table 8, Mutational Analysis Report.

Response to Treatment by IDH1 Variant Allele Frequency

DNA for mutational analyses was extracted from peripheral whole blood and plasma. IDH1 variant frequencies were determined using ddPCR (limit of sensitivity of 0.1%) or NGS. The Applicant reported that 19% of patients within the longitudinal Mutation Set (N=98, **Figure 31**) achieved VAF clearance (defined as < 1% IDH1 VAF) across IDH1 R132 variants.

In the Baseline Mutation Response Set (N=120), baseline IDH1 VAF ranged from 0.2% to 52%. Patients who achieved CR/CRh (responders) had lower mean baseline IDH1 VAF (median=12.5; mean=17.6 (95% CI; 13.2-23.4)) compared to non-responders (median=29; mean=27.6 (95% CI; 23.8-31.3)). Responders were also more likely to have IDH1 VAF clearance compared to non-responders (28% (11/39) vs 7% (3/42)). It should be noted, however, that these analyses may be limited in utility since the number of patients with longitudinal samples available for analysis decreased after Cycle 2.

20.5 Additional Safety Analyses Conducted by FDA

The FDA's Assessment:
The following table lists grouped terms created by the FDA:

Preferred Term(s)	Grouped Term
Rash, Rash maculo-papular, Rash papular, Rash pruritic, Dermatitis acneiform, Dermatitis atopic, Eczema, Erythema, Dermatitis exfoliative, Papule, Psoriasis, Rosacea, Skin lesion, Toxic skin eruption, Urticaria, dermo-hypodermitis, eczema nummular, Genital erythema, Graft versus host disease in skin, Rash macular, Rash postular, Macule, Stasis dermatitis	Rash
Flank pain, Muscle spasms, Muscle tightness, Muscle twitching, Muscular weakness, Musculoskeletal chest pain, Musculoskeletal discomfort, Musculoskeletal pain, Musculoskeletal stiffness, Myalgia,	Myalgia
Gingival hypertrophy, Gingival oedema, Gingivitis, Gingivitis ulcerative, Oesophagitis, Oral disorder, Colitis, Mouth ulceration, Mucosal Dryness, Mucosal Inflammation, Stomatitis, Tongue ulceration, Oral pain, Oropharyngia, Oropharyngeal pain, Pharyngitis, Proctalgia, Proctitis, Colitis ischaemic, Colitis microscopic, Vocal cord inflammation	Mucositis
Hypertension, Blood pressure increased	Hypertension
Asthenia, Fatigue, Malaise	Fatigue/malaise
Fluid overload, Oedema, Oedema peripheral, Face oedema, Generalised oedema, Eyelid oedema, Hypervolaemia, Ascites, Eye Oedema, Oedema genital, Peripheral swelling	Edema
Acute pulmonary oedema, Dyspnoea, Dyspnoea exertional, Hypoxia, Acute respiratory failure, Tachypnoea, Respiratory failure, Oxygen saturation decreased, Acute Respiratory Distress Syndrome, Dyspnoea paroxysmal nocturnal, Orthopnoea, Respiratory distress	Dyspnea
Acute kidney injury, blood creatinine increased, Renal failure, Renal impairment	Renal insufficiency
Cough, Productive cough, Upper-airway cough syndrome	Cough
Arthralgia, Back pain, Bone pain, Cancer pain, Neck pain, Arthritis, Pain in extremity, Joint Effusion, Joint Injury, Joint range of motion decreased, Joint swelling	Arthralgia
Arrhythmia, Atrial fibrillation, Atrial flutter, Atrial tachycardia, Atrioventricular block, Atrioventricular block first degree, Bradycardia, Sinus bradycardia, Sinus tachycardia, Extrasystoles, Supraventricular tachycardia, Tachycardia, Right Bundle Branch Block, Ventricular extrasystoles, Ventricular tachycardia, Heart rate increased	Arrhythmia
Abdominal Discomfort, Abdominal Distension, Abdominal Pain, Abdominal Pain Lower, Abdominal Pain Upper, Abdominal Rigidity, Abdominal Tenderness, Gastrointestinal pain	Abdominal Pain
Alanine Aminotransferase Increased, Aspartate aminotransferase increased, Hepatic enzyme increased, Hypertransaminasaemia, Liver function test abnormal, Liver function test increased, Transaminases increased, Hepatitis acute, Blood alkaline phosphatase increased	Transaminitis
Cholangitis, Cholecystitis, Cholelithiasis, Cholestasis, Gallbladder perforation, Biliary colic, Biliary tract disorder, blood bilirubin increased	Gallbladder Disorders
Haemorrhage intracranial, Subdural haematoma, Cerebral Hemorrhage Haemorrhagic stroke, Subarachnoid haemorrhage, Subdural haemorrhage	Intracranial Hemorrhage
Febrile Neutropenia, Febrile bone marrow aplasia	Febrile Neutropenia
Pneumonia legionella, Pneumonia pseudomonal, Pneumonia mycoplasmal, Pneumonia, Lower respiratory tract infection, Lung disorder, Lung infection, Bronchitis, Bronchopneumopathy, Pneumonia klebsiella, Pneumonia pneumococcal, Pneumonia pseudomonal, Respiratory tract infection	Pneumonia

NDA 215814				

Signatures (delete discipline if not part of review)

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Moran Choe	OOD/DHOT	Section: 5	Select one: ☑ Authored ☐ Approved
	Signature: Moran Choe -S Digitally signed by Moran Choe -S Date: 2022.11.22 08:59:35 -05'00'			
Nonclinical Team Leader	Brenda Gehrke	OOD/DHOT	Section:5	Select one: ☐ Authored ☑ Approved
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Nonclinical Team Deputy Division Director (NME Only)	Haleh Saber	OOD/DHOT	Section: 5	Select one: ☐ Authored ☑ Approved
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Clinical Reviewer	Ashley Woods	OOD/DHM1	Sections: 2, 3, 7, 8, 9, 10, 11, 12, and 13	**Select one:** ☑ Authored ☐ Approved
	Signature: Ashley C. Woods -S Digitally signed by Ashley C. Woods -S Date: 2022.11.23 10:35:27 -05'00'			
Clinical Team Leader	Kelly Norsworthy	OOD/DHM1	Sections: 1, 2, 3, 7, 8, 9, 10, 11, 12, and 13	**Select one:** ☐ Authored ☑ Approved
	Signature: Kelly Norsworthy -S Digitally signed by Kelly Norsworthy -S Date: 2022.11.23 11:10:24 -05'00'			
Statistical Reviewer	Haiyan Chen	OB/DBIX	Sections: 7 and 8	**Select one:** ☑ Authored ☐ Approved
	Signature: Haiyan Chen -S Digitally signed by Haiyan Chen -S Date: 2022.11.22 14:12:12 -05'00'			
Statistical Team Leader	Jonathon Vallejo	OB/DBIX	Sections: 7 and 8	**Select one:** ☐ Authored ☑ Approved
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Cross-Disciplinary Team Leader (CDTL)	Kelly Norsworthy	OOD/DHM1	Sections: All	**Select one:** ☐ Authored ☑ Approved
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Division Director (Clinical)	R. Angelo de Claro	OOD/DHM1	Sections: All	**Select one:** ☐ Authored ☑ Approved
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Division Director (OB) (NME only)	Mark Levenson	OB/DBIX	Sections: 7 and 8	**Select one:** ☐ Authored ☑ Approved

(NME only)	**Signature:** Mark S. Levenson -S Digitally signed by Mark S. Levenson -S Date: 2022.11.23 10:10:38 -05'00'			
Office Director or signatory (NME only)	Marc Theoret	OCE	Sections: All	**Select one:** ☐ Authored ☑ Approved
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DHOT: Division of Hematology, Oncology, Toxicology				
OCP: Office of Clinical Pharmacology				
DPM: Division of Pharmacometrics				
DTPM: Division of Translational and Precision Medicine (DTPM)				
DCPI: Division of Cancer Pharmacology I				
OB: Office of Biostatistics				
DBIX: Division of Biometrics IX				
DHM1: Division of Hematologic Malignancies 1				
OCE: Oncology Center of Excellence				

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MARC R THEORET
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My signature indicates that I have considered the FDA assessments and recommendations included in this Review in determining the regulatory action.