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RESEARCH**

APPLICATION NUMBER:

217779Orig1s000

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 “Data” and “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	NME NDA
Application Number(s)	NDA 217779
Priority or Standard	Standard
Submit Date(s)	June 16, 2023
Received Date(s)	June 16, 2023
PDUFA Goal Date	June 16, 2024
Division/Office	Division of Hematologic Malignancies I Office of Oncologic Diseases
Review Completion Date	May 24, 2024
Established Name	Imetelstat
(Proposed) Trade Name	RYTELO
Pharmacologic Class	Telomerase inhibitor
Code name	GRN163L, JNJ-63935937
Applicant	Geron Corporation
Formulation(s)	Lyophilized powder for intravenous injection
Dosing Regimen	7.1 mg/kg imetelstat (equivalent to 7.5 mg/kg imetelstat sodium) by intravenous infusion over 2 hours every 4 weeks
Applicant Proposed Indication(s)/Population(s)	For the treatment of transfusion-dependent anemia in adult patients with low- to intermediate-1 risk myelodysplastic syndromes (MDS) who have failed to respond or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESA)
Recommendation on Regulatory Action	Regular approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of adult patients with low- to intermediate-1 risk myelodysplastic syndromes (MDS) with transfusion-dependent anemia requiring 4 or more red blood cell units over 8 weeks who have not responded to or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESA)

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Version date: June 2022 (ALL NDA/ BLA reviews)

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NDA/BLA Multi-disciplinary Review and Evaluation NDA 217779
RYTELO, imetelstat

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OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRM=Division of Risk Management

Version date: June 2022 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Glossary

AC	Advisory committee
ADA	Anti-drug antibodies
ADME	Absorption, distribution, metabolism, excretion
ADR	Adverse drug reaction
AE	Adverse event
AEI	Adverse events of interest
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC _{0-∞}	Area under the plasma concentration versus time curve from Time 0 to infinity
BLA	Biologics license application
BM	Bone marrow
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
CFU	Colony-forming units
CI	Confidence interval
CL	Clearance
C _{max}	Peak plasma concentration
CMH	Cochran-Mantel-Haenszel
CML	Chronic myeloid leukemia
CNS	Central nervous system
COI	Concepts of interest
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
COVID-19	Coronavirus Disease 2019
CR	Complete remission
CrCL	Creatinine clearance
CRF	Case report form

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CRO	Contract research organization
CRT	Clinical review template
CSR	Clinical study report
CSS	Controlled Substance Staff
CTCAE	Common terminology criteria for adverse event
CV%	Coefficient of variation
CYP	Cytochrome P450
DEC-C	Decitabine and cedazuridine
Del(5q)	Deletion of the long arm of chromosome 5
DMC	Data monitoring committee
DMF	Drug master file
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eCTD	Electronic Common Technical Document
EDC	Electronic data capture
EFD	Embryo-fetal development
EPO	Erythropoietin
EOI	End of infusion
E-R	Exposure-response
ESA	Erythropoiesis-stimulating agents
ET	Essential thrombocythemia
ETASU	Elements to assure safe use
EU	European Union
FACIT	Functional Assessment of Chronic Illness Therapy
FACT-An	Functional Assessment of Cancer Therapy – Anemia-Related Effects
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
GGT	Gamma-glutamyl transferase
GLP	Good laboratory practice
GRMP	Good review management practice
HEC	Hepatic Expert Committee
hERG	Human ether-a-go-go-related gene
HgB	Hemoglobin
HI-E	Hematologic improvement-erythroid
HMA	Hypomethylating agent
HPC	Hematopoietic progenitor cell
HPLC	High performance liquid chromatography

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HR	Hazard Ratio
HSC	Hematopoietic stem cell
HSCT	Hematopoietic stem cell transplant
HTB	High transfusion burden
hTERT	Human telomerase reverse transcriptase
IC ₅₀	Half maximal inhibitory concentration
ICH	International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IND	Investigational New Drug Application
Int-1	Intermediate-1
Int-2	Intermediate-2
IP	Intraperitoneal(ly)
iPSP	Initial pediatric study plan
IPSS	International Prognostic Scoring System
IRC	Independent Review Committee
IRR	Infusion-related reaction
ISE	Integrated summary of effectiveness
ISS	Integrated summary of safety
ITT	Intent to treat
IV	Intravenous
IWG	International Working Group
JMML	Juvenile myelomonocytic leukemia
LFT	Liver function test
LR	Lower-risk
LS	Least squares
LSC	Leukemia stem cell
LTB	Low transfusion burden
MATE	Multidrug and toxin extrusion protein
mCR	Molecular complete remission
MDS	Myelodysplastic syndromes
MDS-RS ⁺	MDS with ringed sideroblasts
MDS-RS ⁻	MDS without ringed sideroblasts
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
mITT	Modified intent to treat
MK	Megakaryocyte
MM	Mismatched control
MPN	Myeloproliferative neoplasms
MS	Mass spectrometry
NCI	National Cancer Institute
NDA	New Drug Application

NE	Non-estimable
NME	New molecular entity
NOAEL	No-observed-adverse-effect level
OATP	Organic anion transporting polypeptide
OCS	Office of Computational Science
ODN	Oligonucleotide
ODWG	Organ Dysfunction Working Group
OPQ	Office of Pharmaceutical Quality
OS	Overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PFS	Progression free survival
PD	Pharmacodynamic(s)
PDX	Patient sample-derived xenograft
p-gp	P-glycoprotein
PI	Prescribing information
PK	Pharmacokinetic(s)
PMC	Postmarketing commitment
PMR	Postmarketing requirement
popPK	Population PK
PP	Per protocol
PPI	Patient package insert
PR	Partial remission
PREA	Pediatric Research Equity Act
PRO	Patient reported outcome
PS	Performance Status
PSUR	Periodic Safety Update report
PV	Polycythemia vera
PY	Patient-years
q2w	Once every 2 weeks
q3w	One every 3 weeks
q4w	One every 4 weeks
QoL	Quality of life
QUALMS	Quality of Life in Myelodysplasia Scale
qw	Once weekly
RBC	Red blood cells
REMS	Risk evaluation and mitigation strategy
ROW	Rest of World
RSE	Relative standard errors
SAE	Serious adverse event

SAP	Statistical analysis plan
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	Standard deviation
SGE	Special government employee
SOC	Standard of care
TA	Telomerase activity
TEAE	Treatment emergent adverse event
TGI	Significant tumor growth inhibition
TI	Transfusion independence
TIW	Three times a week
TK	Toxicokinetic
TL	Telomere length
T _{max}	Time to peak plasma concentration
UGT	Uridine diphospho-glucuronate-glucuronosyltransferase
HLM	Human liver microsomes
ULN	Upper limit of normal
USPI	US Prescribing Information
UV	Ultra-violet
VAF	Variant allele frequency
WHO	World Health Organization
WRO	Written Response Only

1 Executive Summary

1.1. Product Introduction

Drug Established Name:	Imetelstat
Trade Name:	Rytelo
Dosage Forms:	Lyophilized powder (47 mg, 188 mg) for intravenous injection
Chemical Class:	Small molecule, oligonucleotide
Therapeutic Class:	Enzyme inhibitor
Mechanism of Action:	Inhibitor of human telomerase

Imetelstat is a covalently-lipidated 13-mer oligonucleotide that binds to the template region of the RNA component of human telomerase (hTR), inhibits telomerase enzymatic activity and prevents telomere binding. Shorter telomere length and high telomerase activity have been reported in lower-risk myelodysplastic syndrome (MDS), suggesting that telomerase may be a relevant therapeutic target for this population.

Imetelstat is being developed for the treatment of anemia in patients with lower-risk MDS and has also been investigated in patients with other hematologic malignancies, including myelofibrosis, and solid tumors. The Applicant submits a New Drug Application (NDA) with results from a randomized phase 3 study 63935937MDS3001 (IMerge, MDS3001) to support the indication “for the treatment of adult patients with low- to intermediate-1 risk myelodysplastic syndromes (MDS) with transfusion-dependent anemia requiring 4 or more red blood cell units over 8 weeks who have not responded to or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESA)” based on an analysis of 8-week red blood cell transfusion independence (RBC-TI). Imetelstat is administered at 7.1 mg/kg (equivalent to imetelstat sodium 7.5 mg/kg) once every 4 weeks by intravenous infusion over 2 hours.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial Evidence of Effectiveness (SEE) was established with one adequate and well-controlled clinical investigation and confirmatory evidence.

Information submitted by the Applicant provides substantial evidence for the effectiveness of imetelstat for the treatment of low- to intermediate-1 risk MDS with transfusion dependent anemia requiring 4 or more red blood cell units over 8 weeks after loss of response to ESA treatment. The efficacy of imetelstat has been established primarily on the results of a single randomized, placebo-controlled, multicenter, blinded trial in (Study MDS3001, IMerge).

Support of the efficacy of imetelstat for this indication was provided from the phase 2 part of MDS3001 which preceded phase 3.

In the phase 3 part of MDS3001, patients were randomized (2:1) to receive either imetelstat (N=118) or placebo (N=59). Results of the trial demonstrated that imetelstat increases 8-week and 24-week RBC transfusion independence (RBC-TI) in this population. The primary endpoint was the rate of 8-week RBC-TI demonstrated at 39.8% (95% CI: 30.9, 49.3) with imetelstat treatment versus 15.0% (95% CI: 7.1, 26.6) with placebo treatment ($p < 0.001$) and the rate of 24-week RBC-TI was 28.0% (95% CI: 20.1, 37.0) with imetelstat treatment versus 3.3% (95% CI: 0.4, 11.5) with placebo treatment ($p = < 0.001$).

However, a statistically significant treatment effect was not observed on other secondary endpoints reflective of a disease-modifying effect, including erythroid response (HI-E) per International Working Group (IWG) 2006 criteria, complete remission or partial remission (CR or PR), and overall survival (OS). In addition, the patient-reported outcomes collected in the Phase 3 study did not reflect an improvement in fatigue or other anemia-related symptoms.

Despite the lack of improvement in efficacy endpoints other than RBC-TI, the demonstration of improvement in 8- and 24-week RBC-TI was determined to outweigh the risks of treatment with imetelstat, and the review team recommends regular approval.

Labeling will describe the primary endpoint of ≥ 8 -week RBC-TI and the key secondary endpoint of ≥ 24 -week RBC-TI. Median follow up time was similar between arms (19.5 months with imetelstat versus 17.5 months with placebo) and will also be reported in labeling.

Supportive information was provided from the phase 2 part of MDS3001. The population enrolled in phase 2 was similar but included patients with more prior therapies and allowed prior treatment with lenalidomide and hypomethylating agents (HMAs). Fifty-seven (57) patients were enrolled and the 8-week RBC-TI in this population was 36.8% (95% CI: 24.5, 50.7) for all subjects in the Phase 2 study, which is generally consistent with the 8-week RBC-TI rate observed in the Phase 3 study.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

MDS is a heterogeneous disorder arising from clonal expansion of a hematopoietic progenitor. This leads to bone marrow dysplasia, ineffective hematopoiesis, and a risk of transformation to AML. Patients with MDS are broadly classified into lower risk and higher risk disease categories based on several factors that impact survival. The median survival is reported to be 5.7 years for low risk and 3.5 years for intermediate-1 risk, with some patients surviving up to 1 to 2 decades. Anemia is the most common manifestation of MDS leading to fatigue, decreased quality of life, and the need for red blood cell transfusion. Initial treatment for anemia due to MDS is typically erythropoiesis-stimulating agents (ESAs) and few treatments are available for patients who lose response to ESAs.

Study MDS3001-Phase 3 was a randomized, placebo-controlled, multicenter, blinded trial in patients with low- to intermediate-1 risk MDS with transfusion dependent anemia requiring 4 or more red blood cell units over 8 weeks who have failed to respond to, lost response to, or are ineligible for ESA treatment. Patients were treated with imetelstat 7.1 mg/kg IV every 4 weeks, given as a 2-hour infusion, or a matching placebo. The primary endpoint was 8-week RBC transfusion independence. Patients were randomized (2:1) to receive either imetelstat (N=118) or placebo (N=59).

The primary efficacy trial, Study MDS3001-Part 2 (Phase 3), met its primary endpoint of 8-week RBC-TI (39.8% imetelstat versus 15.0% placebo; $p < 0.001$) in addition to the key secondary endpoint of 24-week RBC-TI (28.0% imetelstat versus 3.3% placebo; $p < 0.001$). Although the median duration of RBC-TI was only 5.0 weeks (95% CI 4.0, 7.7) for imetelstat versus 3.9 weeks (95% CI 3.6, 4.0) for placebo in all subjects, the median duration of RBC-TI in 8-week RBC-TI responders was 51.6 weeks (95% CI 26.9, 83.9) for imetelstat versus 13.3 weeks (95% CI 8.0, 24.9) for placebo, indicating that a subset of patients has a clinically meaningful duration of benefit.

However, there was no evidence of a statistically significant treatment effect on the key secondary endpoint of HI-E per IWG 2006 criteria, or on other secondary endpoints reflective of a disease-modifying effect such as CR/PR or OS. Additionally, the patient-reported outcomes collected in the Phase 3 study did not reflect an improvement in fatigue or other anemia-related symptoms. There were also residual

uncertainties regarding the impact of imetelstat on overall medical resource utilization and the applicability of the trial results to the US population.

There are concerns regarding the safety profile, given the high rate of cytopenias including grade 3-4 neutropenia (71% with imetelstat versus 7% with placebo) and thrombocytopenia (65% with imetelstat versus 8% with placebo) observed with imetelstat. Subjects treated with imetelstat also required more interventions for cytopenias, such as myeloid growth factors and platelet transfusions, compared to patients receiving placebo. Thirty-five percent of patients required myeloid growth factor at least once during treatment in the imetelstat arm compared to 2 patients in the placebo arm. Most of those patients required multiple administrations of myeloid growth factor. Eighteen percent of patients on the imetelstat arm required at least one platelet transfusion during treatment, with patients requiring platelet transfusions in up to 10 separate episodes. Despite the increased use of growth factor support for patients who experienced neutropenia in the imetelstat arm, a higher rate of infection was observed in patients who received imetelstat (all grade infections 42% with imetelstat versus 34% with placebo). Similarly, patients receiving imetelstat experienced more hemorrhagic events (all grade hemorrhage 21% with imetelstat versus 12% with placebo). However, the rates of Grade 3-4 infections and hemorrhage were notably similar between the imetelstat and placebo arms.

Given residual uncertainties regarding the benefit-risk profile of imetelstat, FDA held an Oncologic Drugs Advisory Committee (ODAC) meeting on 14 March 2024. The ODAC voted that the potential benefits of imetelstat outweigh the risks. Given this, in addition to the high unmet need for the proposed patient population, FDA has concluded that the benefits of imetelstat outweigh the risks for the treatment of adult patients with low- to intermediate-1 risk MDS with transfusion-dependent anemia requiring 4 or more red blood cell units over 8 weeks who have not responded to or have lost response to or are ineligible for ESA.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	- MDS is a chronic condition with no curative treatment options except hematopoietic stem cell transplant (HSCT) - Lower-risk MDS (LR-MDS) has a long life expectancy and treatment is typically aimed at reducing symptom burden - Transfusion burden due to anemia is a common complication of lower risk MDS and can lead to lower quality of life, iron overload, and other issues	There is an urgent need for new therapeutic options for patients with MDS, including both treatment for the underlying disease and for amelioration of symptoms.
Current Treatment Options	- Typical frontline therapy for transfusion-dependent anemia due to LR-MDS includes erythropoiesis stimulating agents (ESAs). - Luspatercept is another option for frontline therapy and was recently FDA approved for use in this setting; it is also indicated for use after ESA failure in patients with anemia due to MDS with ringed sideroblasts (MDS-RS) or myelodysplastic/myeloproliferative neoplasms with ringed sideroblasts and thrombocytosis (MDS/MPN-RS-T). - Lenalidomide is approved for the treatment of transfusion-dependent anemia in the subset of patients with LR-MDS with deletion 5q (del5q) and is sometimes used off-label in patients without del5q. - Hypomethylating agents such as azacitidine, decitabine, and decitabine-cedazuridine, are additional therapeutic options, though often reserved for the treatment of high-risk MDS or refractory LR-MDS in clinical practice.	The current treatment options for treating anemia in the context of MDS after ESA failure are inadequate and further options are needed.
Benefit	Study MDS3001-Part 2 (Phase 3) was an international, multi-center, double-blind, randomized (2:1), placebo-controlled trial comparing imetelstat (n=118) vs placebo (n=60) in patients with transfusion-dependent anemia (requiring at least 4 RBC units/8 weeks at baseline)	Imetelstat demonstrated superiority over placebo in Study MDS3001-Part 2 (Phase 3) on the primary endpoint of 8-week RBC-TI and the key secondary endpoint of 24-week RBC-TI. A subset of patients had a clinically meaningful

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	due to IPSS low- or intermediate-1 risk MDS who have failed to respond, or have lost response to, or are ineligible for ESA. • In the ITT analysis of 8-week RBC-TI, the primary endpoint, the rate difference was 24.8% (95% CI 9.9, 36.9). • In the ITT analysis of 24-week RBC-TI, a key secondary endpoint, the rate difference was 24.6% (95% CI 12.6, 34.2). • The median duration of response was 51.6 weeks (95% CI 26.9, 83.9) for 8-week RBC-TI responders, suggesting a clinically meaningful duration of benefit for a subset of patients. However, the median duration of response was only 5.0 weeks (95% CI 4.0, 7.7) when considering all subjects treated with imetelstat. • Analyses of 8-week RBC-TI over subgroups showed a consistent treatment effect favoring imetelstat over placebo in most subgroups tested. The rate was higher with placebo in the subgroup of patients with prior luspatercept use but the number of patients in this subgroup was too few to draw conclusions. The treatment effect was marginal for subjects with lower transfusion burden at baseline (defined as 4-7 RBC units in 16 weeks in at least 2 transfusion episodes). • There was no major difference between arms with regard to the secondary endpoints of HI-E per IWG 2006 criteria, CR/PR, or OS. • Patient-reported outcomes were exploratory and not controlled for multiplicity. That said, there was no major difference between arms with regard to the PRO endpoint of interest, the proportion of patients who experienced deterioration of fatigue.	duration of RBC-TI benefit. However, the HI-E, CR/PR, and OS results are not supportive of a disease-modifying treatment effect. The patient-reported outcomes were exploratory but are also not supportive of a treatment effect.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	- Imetelstat was associated with a higher risk of Grade 3+ AEs, SAEs, and AEs leading to treatment modification. However, the rate of fatal AEs is similar to placebo. - Imetelstat was associated with a high risk of cytopenias with resultant need for intervention and increased risk of all grade infection and hemorrhage. However, the rates of Grade 3-4 infection and hemorrhage were similar to placebo. - Infusion-related reactions occurred in 8% of patients with MDS treated with imetelstat; Grade 3-4 infusion-related reactions occurred in 1.7%. - Imetelstat was associated with a higher risk of fractures, arthralgias/myalgias, and bone pain. - Although patient-reported deterioration in fatigue for at least 2 consecutive fatigue assessments (as measured by FACIT-Fatigue) was similar between arms, investigator-reported all grade fatigue was slightly higher in the imetelstat arm. - A QT assessment has not been completed. - Lower dosages of imetelstat have not been evaluated in patients with LR-MDS. - Serious toxicities were mitigated in the clinical trials by use of premedications, frequent monitoring for known toxicities, and dose modifications.	Imetelstat has increased toxicities compared to placebo, including cytopenias and tolerability issues. However, the rates of Grade 3-4 infection and hemorrhage with imetelstat are similar to placebo, suggesting that serious consequences of cytopenias are able to be mitigated. Per the Oncology Drug Advisory Committee discussion on 14 March 2024, the safety profile of imetelstat is acceptable for patients with transfusion-dependent anemia due to LR-MDS. Further characterizations of safety, optimal dosage, pharmacokinetics, and effects on QT are needed. A patient medication guide is required to inform and educate patients of the risks of thrombocytopenia and neutropenia and when to seek immediate medical attention. Labeling should include warnings for the serious risks of thrombocytopenia, neutropenia, infusion-related reactions, and embryofetal toxicity, and instructions for monitoring and dose 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
	☒	Clinical outcome assessment (COA) data, such as	
	☒	Patient reported outcome (PRO)	Section 8.1.1, Pivotal Study in Support of Efficacy of Imetelstat – Study MDS3001
	☐	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.		

X

Lori Ehrlich, MD, PhD
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Myelodysplastic syndromes (MDS) are serious and life threatening and are characterized by ineffective hemopoiesis, which manifests in abnormal dysplastic cell morphology in one or more hematopoietic cell lines and the development of peripheral cytopenias ([Foran and Shammo, 2012](#); [Adès, 2014](#); [Bejar and Steensma, 2014](#)). Myelodysplastic syndromes are one of the most common hematologic malignancies in older people, with a median age at diagnosis of over 70 years old and less than 10% of patients being younger than 50 years old ([Neukirchen, 2011](#); [Fenaux, 2021](#)). Lower-risk (LR) MDS are characterized by the presence of bone marrow (BM) dysplasia, low BM blast percentage, low number and depth of cytopenia(s), and a variety of karyotypic and molecular abnormalities ([Carraway and Saygin, 2020](#)). While LR MDS patients generally have a lower risk of progression to acute myeloid leukemia (AML) and an overall better prognosis, there are certain features in LR MDS that could result in higher-risk disease, including presence and number of cytopenias and certain mutations ([DeZern and Dalton, 2022](#)), as well as short telomeres and high telomerase activity ([Mittelman, 2010](#)). Median survival in LR MDS ranges from 32.0 months to 56.1 months ([Zeidan, 2019](#)). Infection is the most common cause of death in LR MDS, representing more than one-third of all disease-related deaths; leukemic transformation and (mostly intracranial or gastrointestinal) bleeding complications are the cause of death in approximately 15% and 13% of LR MDS patients, respectively ([Zeidan, 2019](#)).

Approximately 40% of LR MDS patients develop anemia and become transfusion dependent, which together with lower hemoglobin (Hgb) levels have a significant negative correlation with survival and are associated with an increased likelihood of progression to AML ([Malcovati, 2005](#); [Platzbecker, 2012](#); [Hellstrom-Lindberg and van de Loosdrecht, 2013](#); [Zeidan, 2013](#); [Adès, 2014](#); [Fenaux, 2021](#)). Patients with chronic transfusion dependent anemia are highly symptomatic and suffer from exhaustive fatigue, shortness of breath and palpitations resulting in an impaired quality of life (QoL) and most importantly, shortened overall survival (OS). Over time patients develop end organ dysfunction not only due to chronic anemia but also because of iron overload from numerous and frequent transfusions ([Singhal, 2017](#); [Germing, 2019](#); [de Swart, 2020](#); [Platzbecker, 2021](#)). In addition, long-term red blood cell (RBC) transfusion dependence has other clinical and economic consequences, including a potentially negative impact on health related QoL, iron overload and its associated end organ complications, higher risk of cardiovascular complications, and increased risk of infections ([Platzbecker, 2021](#); [Volpe, 2022](#)). Furthermore, a higher rate of RBC transfusion has been shown to correlate significantly

with decreased progression free survival (PFS) and OS and achieving transfusion independence (TI) with treatment has been significantly associated with prolonged OS in multiple studies and a meta-analysis (De Witte, 2020; Braga Lemos, 2021; Santini, 2022). Therefore, achieving TI for LR MDS patients represents an important clinical benefit that can have a substantial impact on day-to-day functioning and longer-term clinical outcomes such as improved survival rates and lower risk of disease progression.

The FDA's Assessment:

Myelodysplastic syndromes (MDS) are a heterogeneous group of disorders characterized by anemia, ineffective erythropoiesis, dysplastic changes in hematologic cells, and varying degrees of neutropenia and thrombocytopenia. It is a rare disease, with an incidence in the United States of 3.8 per 100,000 estimated for 2019. It is more common in men and is more common in older patients, with an incidence of 13.0 in people aged 65-74 and 39.7 for people aged 75 and older. Some ethnic variation is observed, with the highest incidence in non-Hispanic Whites at 4.2, lowest incidence in Asians at 2.4, and intermediate risk for Blacks, Hispanic/Latinos, and American Indian/Alaskan Natives (SEER Cancer Statistics Explorer Network, SEER*Explorer, updated June 8, 2023, accessed August 16, 2023).

Various systems for characterizing the risk of MDS have been proposed. One commonly used system is the International Prognosis Scoring System (IPSS) (Greenberg 1997), updated to the Revised International Prognosis Scoring System (IPSS-R) in 2012 (Greenberg 2012) and then to the Molecular International Prognosis Scoring System (IPSS-M) in 2022 (Bernard 2022). The IPSS utilizes bone marrow blast percentage, karyotype, and number of cytopenias to divide MDS into four risk categories (low, intermediate-1, intermediate-2, and high). The IPSS-R takes each cell line (red blood cells, platelets, and neutrophils) into account separately and uses five prognostic categories from very low to very high risk. The IPSS-M incorporates molecular features to divide MDS into 6 risk categories (very low, low, moderate low, moderate high, high, very high risk). Historically, patients with IPSS low and intermediate or IPSS-R very low, low, and intermediate risk have been considered to be lower risk, although patients with IPSS-R intermediate risk may be considered higher risk depending on their blast count and other variables.

Patients with MDS have a variable prognosis, but are at increased risk of infection, bleeding, and complications of anemia. In addition, MDS may transform into acute myeloid leukemia (AML). AML that occurs as transformation from MDS is resistant to therapy and has a poorer prognosis than de novo AML. Patients with IPSS low and intermediate-1 disease have a median survival of 5.7 and 3.5 years, respectively (Greenberg 1997). The risk of transformation to AML is low for patients with IPSS low MDS and is about 6% per year for patients with intermediate-1 MDS. Similarly, patients with IPSS-R very low, low, and intermediate risk MDS have a median survival of 8.8, 5.3, and 3.0 years, respectively. Twenty-five percent of patients with IPSS-R low

and intermediate disease will transform to AML in 10.8 and 3.2 years, respectively (Greenberg 2012).

Patients with MDS often require red blood cell (RBC) or platelet transfusion due to the anemia that is associated with MDS. As noted above, the requirement for RBC transfusion has a deleterious effect on patient survival and quality of life (QOL) (Fenaux 2021). Patients who require RBC transfusions to treat or ameliorate MDS risk iron overload, require frequent clinic visits for monitoring and transfusion, and may not have complete resolution of symptoms associated with anemia. However, it is not clear that improving anemia or reducing transfusion burden is associated with an improved survival or quality of life. A meta-analysis of QOL evaluations in patients with MDS treated for anemia found no clear relationship between QOL and treatment of anemia (Mo 2023). Specific issues regarding issues surrounding various methods of reducing transfusion burden with specific agents will be discussed below.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

The number of approved therapies for all risk categories of MDS is limited, and not all agents have been shown to be highly efficacious or improve survival. The proposed indication for imetelstat is transfusion-dependent anemia in adult patients with low- to intermediate-1 risk MDS who have failed to respond or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESA).

Currently there are no approved treatments that are inclusive of this patient population, who as a result have an unanswered and high unmet need as outlined in [Applicant Table 1](#).

Applicant Table 1: Current Treatments for LR MDS

Therapies for LR MDS ^a	RS- and RS+	Non del(5q)	IPSS low/Int-1
Luspatercept	No (only RS+)	Yes	Yes
Lenalidomide	Yes	No	Yes
HMA (including DEC-C ^b)	Yes	Yes	No ^b

DEC-C = decitabine and cedazuridine; HMA = hypomethylating agent; Int-1 = intermediate-1; IPSS = International Prognostic Scoring system; LR MDS = lower-risk MDS; RS+/- = with or without ring sideroblasts.

^a Differential treatment patterns across the US population by race, ethnicity, sex or age have not been identified to date.

^b DEC-C is approved in patients with IPSS intermediate- 1 MDS; however, it is not recommended in LR MDS unless following azacitidine or decitabine failure.

Currently available treatments for LR MDS include:

- Erythropoiesis-stimulating agents have been well established as first-line treatment of anemia in LR MDS. However, patients with LR MDS without del(5q) who have failed ESA treatment or do not respond or have short response to ESAs are at a higher risk of transformation to AML and poorer survival [median 36.7 vs. 54.3 months in patients with longer response to ESA; (Kelaidi, 2013).
- Lenalidomide is approved as a treatment of transfusion-dependent anemia due to LR MDS associated with del(5q). The del(5q) mutation is observed in 10% to 15% of patients with MDS. Lenalidomide is not currently approved to treat MDS patients who are non-del(5q). The sub-set of transfusion dependent patients with non-del(5q) MDS who are treated with lenalidomide do not respond or have TI of short duration.
- Hypomethylating agents have been used in LR MDS patients, but they are primarily used in patients with higher risk MDS. In LR MDS, they have not been shown to modify the natural history of the disease or prolong OS in patients with LR MDS (Garcia-Manero, 2014; Wan and Han, 2021). Given the limited benefit observed in LR MDS, hypomethylating agents (HMA) are generally not recommended as standard of care for this patient population (NCCN, 2022). Although decitabine and cedazuridine (DEC-C) is approved in the US for treatment of MDS with intermediate-1 risk, the National Comprehensive Cancer Network recommends DEC-C for treating higher-risk patients as an alternative to azacitidine or decitabine or as a bridge to HSCT (NCCN, 2022).
- Luspatercept is approved for the treatment of anemia failing and ESA and requiring ≥ 2 RBC units over 8 weeks in MDS-RS⁺ patients. The 8-week TI rate is 38% with median duration of response of 30.6 weeks (Fenaux, 2020). However, benefit was shown mostly in patients with a lower transfusion burden and coupled with the restriction to MDS-RS⁺ patients, which are less likely to progress to AML compared with the larger pool of MDS-RS⁻ patients, this leaves a large proportion of the transfusion-dependent LR MDS patients still underserved.

In summary, to date, there is no therapy for the treatment of transfusion dependent anemia in LR MDS who have failed to respond or have lost response or are ineligible to ESA that has shown sustained and durable activity in a broad patient population that alleviates the core signs and symptoms of transfusion dependency in a continuous manner.

The FDA's Assessment:

There are few treatment options available for patients with MDS. Approved treatments for MDS are limited to hypomethylating agents (decitabine, azacitidine, decitabine-cedazuridine) and lenalidomide for patients with del 5q. Luspatercept was recently approved for treatment of anemia in ESA-naïve patients with IPSS-R very low- to intermediate-risk MDS who may require regular RBC transfusions. Luspatercept was also previously approved for the treatment of anemia failing an ESA and requiring 2 or more RBC units over 8 weeks in adults with very low-

to intermediate-risk MDS with ringed sideroblasts or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis. ESA are often used for treatment of anemia in MDS but are not approved for use in MDS and do not treat the underlying disease.

The only potentially curative option is hematopoietic stem cell transplantation (HSCT). However, HSCT has been associated with lower survival in patients with lower risk MDS and is not recommended for patients with lower risk disease (Koreth 2013; Cutler 2004).

The hypomethylating agents (HMAs) azacitidine and decitabine are approved for use in MDS. The approval for azacitidine does not specify IPSS or IPSS-R score (Vidaza USPI). Decitabine and oral decitabine/cedazuridine are approved for use in MDS with the following French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high risk IPSS groups (Dacogen USPI and Inqovi USPI). In practice, use of HMAs is frequently restricted to higher risk MDS. However, one study examining the use of azacitidine in patients with IPSS low or intermediate-1 risk disease who were transfusion dependent and ESA resistant showed hematologic improvement and increased transfusion independence in patients who received azacitidine compared to best supportive care (Sanchez-Garcia 2018). Studies using decitabine in lower risk MDS have demonstrated better response rates compared to supportive care but have mixed results concerning survival and event-free survival (Ye 2021).

Anemia is a major symptom for patients with MDS and may worsen concurrent medical issues such as arterial vascular disease. As noted above, transfusion dependence is a poor prognostic sign for patients with MDS. However, it is not clear that achieving transfusion independence with treatment leads to improved survival or quality of life (Garcia-Manero 2023). One retrospective study suggested longer overall survival in patients with lower risk MDS treated with ESAs (Park2008). However, a prospective trial comparing ESA to supportive care found no statistically significant overall survival benefit (Greenberg 2009). Treatment with oral azacitidine (Garcia-Manero2021) has been associated with a higher risk of death early in treatment and luspatercept (Clinical Review for luspatercept BLA, Original-2, 2019) has been associated with a higher risk of progression to AML and second primary malignancies. Treatment of patients with 5q- MDS was associated with a higher rate of transfusion independence compared to placebo, but no significant increase in survival or decrease in risk of transformation to AML were reported (Fenaux 2011). As noted above, one study of azacitidine in lower risk disease showed higher rates of TI compared to supportive care only. However, this trial did not demonstrate any change in leukemia-free survival (Sanchez-Garcia 2018).

Trials reporting quality of life (QOL) outcomes in patients with lower risk MDS with transfusion dependence treated with a variety of agents have not consistently shown improvement in QOL

outcomes. Some studies (Sanchez-Garcia 2018; Santini 2016; Greenberg 2009) have shown no or minimal improvement in quality of life among patients on active treatment in clinical trials, although it should be noted that patients who respond may have improved QOL by some measures (Santini 2016; Greenberg 2009). Analysis of QOL data in patients treated with luspatercept showed a decrease in QOL (Clinical Review for luspatercept BLA, Original-2, 2019).

Trials using a variety of agents to treat MDS or anemia in MDS have not consistently demonstrated that a decrease in transfusion dependence results in better outcomes for patients overall. Thus, it cannot be assumed that decreased transfusion burden or TI will result in either a survival benefit or improved quality of life. Transfusion independence must be supported by evidence of improvement in clinical outcomes to ensure that the patient is benefiting from treatment.

3 Regulatory Background

3.1.U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Imetelstat is not currently registered or approved in the US or other regions, but is in development for low- and intermediate-1 (Int-1) risk MDS and intermediate-2 (Int-2) and high-risk myelofibrosis (MF) in the US under Investigational New Drug Application (IND) 147072 and IND 072072, respectively. Imetelstat was granted Orphan Drug Designation for the treatment of MDS in 2015, as well as Fast Track Designation for MDS in 2017. Geron currently has two ongoing Phase 3 studies, one in MDS and the other in MF, (b) (4)

During the course of development of imetelstat for treatment of transfusion dependent MDS, Food and Drug Administration (FDA) provided advice to the Applicant in 4 formal interactions, including two type C meetings (2016 and 2017) to agree on the study design of MDS3001, a Type C meeting (2016) to discuss aspects of the chemistry, manufacturing, and controls development plan, and a Type C meeting (2016) to agree the nonclinical program was sufficient to support registration. In addition, an amended initial pediatric study plan (iPSP) has been agreed with the Agency (letter dated 14 March 2023).

Consistent with FDA Guidance *Naming of Drug Products Containing Salt Drug Substances* (June 2015), doses of imetelstat are expressed as milligrams of the active moiety in the Clinical Pharmacology [Section 6](#), Clinical [Sections 7](#) and [8](#), and related Appendix materials in [Section 19.4](#). With regard to the Nonclinical Pharmacology/Toxicology [Section 5](#), study drug doses are

expressed as milligrams of imetelstat sodium (the active substance), a salt of imetelstat, with the exception of [Sections 5.5.2](#) and [5.5.4](#) where study drug doses are expressed as the active moiety since data discussed in those sections related to genotoxicity, fertility and embryo-fetal developmental toxicity are included in the proposed product label. To convert a quantity of imetelstat salt to the equivalent quantity of imetelstat, a factor of 0.9416 based on relative molar mass of the free acid form (4610 g/mol) to the sodium salt (4896 g/mol; $4610/4896 = 0.9416$) is applied (ie, 1 mg imetelstat sodium = 0.9416 mg imetelstat).

The FDA's Assessment:

Imetelstat is not currently registered or approved in the U.S. or other regions. However, an application for marketing approval has been submitted to the EMA.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

A summary of key interactions with the FDA regarding imetelstat development and MDS3001, the pivotal study for this New Drug Application (NDA) is provided in [Applicant Table 2](#).

Applicant Table 2: Summary of Key Interactions With the FDA Regarding Imetelstat Development and the Pivotal Study MDS3001

Date	Milestone and Details
11 May 2005	Original IND 072072 for imetelstat (GRN163L), a telomerase enzyme inhibitor intended for use in patients with advanced hematological and solid tumor malignancies activated.
23 December 2015	Orphan Drug Designation (#15-5014) granted for the treatment of patients with MDS
27 April 2016	Type C meeting to obtain agreement with the Agency regarding whether proposed study design, endpoints, dose, and statistical analysis for Part 2 of Study 63935937MDS3001 are acceptable and would support registration.
27 April 2016	Type C meeting to obtain agreement with Agency regarding the selection of starting materials in synthesis of drug substance and proposed strategy for calculation of the assay in the drug substance specifications.
11 May 2016	Type C Meeting Written Response Only (WRO) regarding whether the nonclinical development program for imetelstat in the intermediate-2 risk/high risk MF and low risk/intermediate risk MDS indications is adequate and would support registration.
15 June 2017	End of Phase 2 Type C Meeting WRO regarding agreement on continuation of Part 2 MDS3001 and protocol modifications to support registration.
27 October 2017	Fast Track Designation granted for MDS that is not associated with the del(5q) cytogenetic abnormality and who are refractory or resistant to treatment with an ESA.

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Date	Milestone and Details
25 July 2022	Type C meeting WRO to obtain Agency feedback on the content and format of the chemistry, manufacturing and controls, nonclinical, clinical pharmacology, and clinical sections of the NDA.
09 December 2022	Rolling Review of NDA granted.
27 January 2023	NDA Rolling Submission 1 submitted (SN 0001)
02 March 2023	Pre-NDA Type B meeting to discuss the suitability of the submission of a NDA for the treatment of adult patients with low to intermediate-1 risk MDS who are transfusion-dependent and have failed to respond or have lost response or are ineligible for ESA.

The FDA's Assessment:

The key regulatory history for imetelstat is as follows:

- On April 8, 2005, the original IND 072072 for imetelstat was submitted, intended for use in patients with advanced hematological and solid tumor malignancies. The IND was deemed safe to proceed on May 11, 2005.
- On December 23, 2015, imetelstat was granted orphan drug designation for the treatment of patients with MDS.
- On October 27, 2017, imetelstat was granted fast track designation for the treatment of adult patients with transfusion-dependent anemia due to low or intermediate-1 risk MDS that is not associated with the del5q abnormality and who are refractory or resistant to treatment with an ESA.
- On June 16, 2023, the Applicant submitted NDA 217779 for imetelstat, the subject of this review.

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

4.1. Office of Scientific Investigations (OSI)

Study MDS3001 was conducted at 19 centers in the US and 93 centers outside the US. OSI conducted inspections at 3 clinical sites: ES10002, IT10002, and US10021. Sites ES10002 and IT10002 enrolled the highest number of subjects overall and had a high number of protocol deviations. Site US10021 enrolled the highest number of subjects domestically, reported no SAEs and had a complaint made against the investigator. The classification for the inspection of the 3 clinical sites was no action indicated. The OSI Reviewer concluded that the data as audited were considered reliable for review of the application.

4.2. Product Quality

The following information is summarized from the Product Quality Assessment.

Imetelstat sodium is a sodium salt of a 13-mer oligonucleotide N3'→P5' thio-phosphoramidate conjugated with a lipid palmitoyl group attached to the 5' terminus through an aminoglycerol linker. The structure of imetelstat sodium includes thiophosphoramidate linkages, with sulfurization of the native phosphodiester, and replacement of the 3'-oxygen to provide a 3'-amino group.

The applicant provided sufficient information to assure the identity, strength, purity, and quality of the proposed drug product. All associated manufacturing, testing, packaging facilities were deemed acceptable. The Applicant claimed a categorical exclusion from the requirement for an environment assessment, and the claim was accepted under 21 CFR 25.31(b).

The Product Quality team recommended approval of the NDA with PMCs for batch acceptance criteria and annual reports on batch and stability data to tighten specification limits for product related substances.

4.3. Clinical Microbiology

Microbiology review was completed and included in the Product Quality assessment aid. The microbiology review was adequate.

4.4. Devices and Companion Diagnostic Issues

Not applicable. No devices or companion diagnostics were required for approval.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Imetelstat is a 13-mer thio-phosphoramidate oligonucleotide telomerase inhibitor indicated for the treatment of adult patients with low- to intermediate 1 risk myelodysplastic syndromes (MDS) with transfusion-dependent anemia requiring 4 or more red blood cell units over 8 weeks who have not responded to or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESA). It binds to the template region of the RNA component of human telomerase (hTR), which lies in the catalytic site of human telomerase reverse transcriptase (hTERT), resulting in competitive inhibition of hTERT enzymatic activity. The nonclinical development program for imetelstat included various in vitro and in vivo studies to evaluate the pharmacology, pharmacokinetics, general toxicology, reproductive and developmental effects, and the genotoxic potential of imetelstat.

In vitro studies have shown that imetelstat inhibited telomerase activity in the HT-3 human cervical carcinoma cell line in a concentration-dependent manner with an IC_{50} of 0.056 μ M. The in vivo activity of imetelstat was assessed using multiple mouse models. A single or repeated administration of imetelstat in mice resulted in telomerase inhibition in the liver tissues collected for activity analysis. The anti-tumor activity of imetelstat was evaluated in the OVCAR-5 human ovarian cancer xenograft model. The animals were administered imetelstat intraperitoneally (IP) at 15 or 30 mg/kg three times per week (TIW) for 50 days. The results showed tumor growth inhibition with an average reduction in tumor volume of 34% and 53%, respectively, at 15 and 30 mg/kg. No xenograft studies were conducted in MDS cells lines, and this was described by the Applicant as being due to the lack of MDS specific cell lines and mouse xenograft models.

In the safety pharmacology study conducted in monkeys (Study No. GS04-072), 4 male animals were assigned to a single treatment group. The animals were treated with vehicle control, 5 mg/kg, 10 mg/kg, and 15 mg/kg of imetelstat from Days 1-28 via IV infusion. Each animal received a dose of vehicle control on Day 1 and increasing doses of imetelstat on Days 2, 9, 21 and 28. There were no test article-related changes observed in the cardiovascular, central nervous or respiratory systems. Consistent with these findings, the electrocardiogram (ECG) assessments evaluated in the 9-month toxicology study in monkeys were considered normal and no test article-related changes were observed.

The plasma exposures of imetelstat increased in a dose-dependent manner in mice without showing a sex-difference. In monkeys, increases in plasma exposure were slightly greater than

dose proportional and higher exposures in male compared to female monkeys were observed. Distribution studies demonstrated high (> 90%) plasma protein binding of imetelstat across species (human, monkey, rat, and mouse). The highest concentration of imetelstat was seen in the liver and kidney, followed by the bone marrow and spleen. An excretion study in rats showed that the primary route of elimination was urine with approximately 62% to 82% of the dose recovered by 168 hours post-dose.

Repeat-dose studies in mice and monkeys were conducted to assess the general toxicology of imetelstat. The drug was dosed for 6 months in rats and 9 months in monkeys via IV administration, which is consistent with the intended clinical route of administration. Overall, adverse findings included activation of the alternative complement pathway, thrombocytopenia, altered coagulation, and toxicities in the liver and kidney. In the 6-month mouse study, imetelstat was administered at dose levels of 5, 15, or 20 mg/kg by IV bolus injection twice a week (BIW) with an 8-week recovery period. A total of 16 mortalities occurred including 4 animals in the control group. The cause of the deaths was either considered unrelated to imetelstat or could not be determined. Local reaction of tail discoloration was noted at the injection site, which correlated with microscopic observations of necrosis/inflammation and vascular/perivascular fibrosis. Decreased RBC parameters and extramedullary hematopoiesis in the spleen were observed. Increased liver, kidney and spleen weights were also noted. Microscopic findings in the liver consisted of increases in inflammatory foci and Kupffer cells, and/or histiocytic aggregates. In the 9-month monkey study, imetelstat was administered at doses of 5, 10, or 15 mg/kg via 2-hour IV infusion once weekly with an 8-week recovery period. There was no imetelstat-related mortality. Imetelstat-related findings included decreases in RBC parameters and platelet counts, and erythroid hyperplasia evident based on the evaluation of bone marrow smears. Prolongation of activated partial thromboplastin time (aPTT) and activation of alternative complement pathways (Bb, C5a) were observed. Increased liver and kidney weights correlated with microscopic changes in the kidney (glomerulosclerosis, tubular hemorrhage, and protein casts) and liver (capsular telangiectasis and brown pigment deposition in Kupffer cells). Other toxicities occurred in the uterus (endometrium atrophy), brain (mononuclear cell infiltration in the choroid plexus) and spleen (enlarged).

In a pivotal embryo-fetal development (EFD) study in mice, imetelstat was administered to pregnant mice via slow-bolus IV injection on gestation day (GD) 6, 9, and 12 at doses of 4.7, 14.1 or 28.2 mg/kg (equivalent to 0, 5, 15 or 30 mg/kg imetelstat sodium). In a dose range-finding (DRF) study in mice, increased rates of post-implantation loss and early resorptions were observed at the high dose of 28.2 mg/kg (equivalent to 30 mg/kg imetelstat sodium). The exposure (based on AUC) at 28.2 mg/kg was 2.5 times the human exposure at the recommended clinical dose of 7.1 mg/kg. In a pivotal EFD study in rabbits, imetelstat was administered to pregnant rabbits by 2-hour IV infusion on GD 6 and 13, at doses of 4.7, 14.1 or

28.2 mg/kg (equivalent to 5, 15 or 30 mg/kg imetelstat sodium). Increased rates of post-implantation loss and early resorptions that resulted in a decreased number of viable fetuses and litter size per animal, and decreased uterine weight were observed at ≥ 14.1 mg/kg. The high dose of 28.2 mg/kg was maternally toxic due to mortality. The mid dose of 14.1 mg/kg had exposure that was 9.3 times the exposure at the recommended clinical dose based on the AUC values.

In genetic toxicity studies, imetelstat 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 mouse bone marrow micronucleus assay. The highest dose tested in the in vivo mouse assay was the maximum-tolerated dose (103.6 mg/kg) of imetelstat.

The need for carcinogenicity studies depends on the life expectancy of the patients for the proposed indications. Based on the literature provided by the Applicant and discussion with the clinical team, the life expectancy for patients with lower risk MDS (defined variously, but usually as low or intermediate-1 risk disease by IPSS) and ESA failure or transfusion dependency is > 5 years and carcinogenicity risk assessment is warranted for the intended patient population. To address the carcinogenicity risk assessment of imetelstat, there will be separate Post Marketing Requirements (PMRs) for carcinogenicity assessments in the mouse and rat species.

With regard to the label, the proposed established pharmacological class (EPC) for imetelstat is “oligonucleotide telomerase inhibitor”. The structural information of the drug (oligonucleotide) has been added to the EPC to better describe the drug class. Additionally, a Warning and Precaution for Embryo-Fetal Toxicity has been added based on the findings in the EFD toxicity studies and the need for contraception. The recommendation for the duration of contraception of 1 week follows the recommendations described in the FDA guidance *Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations*.

This NDA is approvable from a pharmacology/toxicology perspective.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

Imetelstat is a New Molecular Entity (NME) and there are no referenced NDAs, Biologics Licence Applications (BLAs), or Drug Master Files (DMFs) related to nonclinical pharmacology or toxicology data for imetelstat.

5.3. Pharmacology

5.3.1. Primary pharmacology

The Applicant's Position:

Telomerase is highly expressed and activated in most cancers and neoplastic progenitor cells while generally undetectable in normal somatic cells, making it a rational target for cancer therapy (Harley, 2008). Imetelstat is a first in class telomerase inhibitor that specifically targets malignant cells that are characterized by the abnormal elevation of telomerase activity (TA). The primary pharmacology of imetelstat has been evaluated in various cancer cell lines in vitro, and in malignant hematopoietic stem/progenitor cells (HPCs/HSCs) and leukemia stem cells (LSCs) from primary patient samples ex vivo. These studies demonstrate that imetelstat inhibits TA in a dose-dependent manner, leading to loss of a cancer cell's ability to maintain telomere length, and resulting in inhibition of cell proliferation, reduction in colony formation and induction of apoptosis/senescence (Herbert 2005, Shammass 2008, Brennan 2010, Mosoyan 2017, Wang 2018, Baerlocher 2019). In addition, imetelstat has shown anti-tumor activity in vivo in xenograft models of relevant myeloid malignancies (Study PRE-14-004, Bruedigam 2014, Ma 2017, Wang 2018).

Due to the lack of MDS specific cell lines and mouse xenograft models and given the increased expression of telomerase across most cancer types, particularly myeloid malignancies that are closely related to MDS, nonclinical data were generated in models of other tumor types that are relevant to demonstrate imetelstat's mechanism of action and antitumor activity.

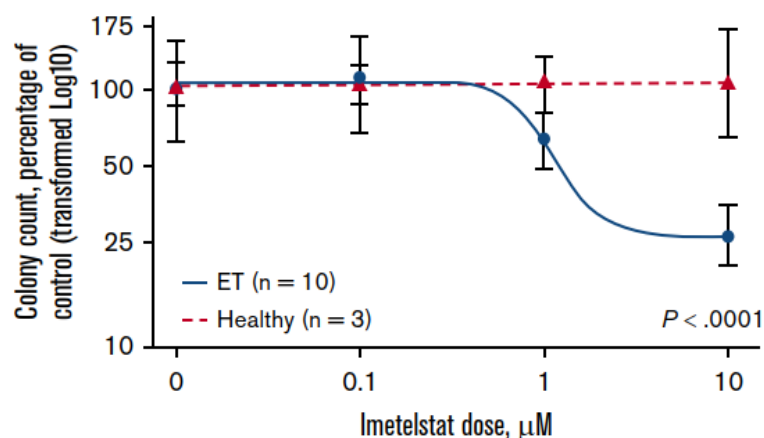
Dose-dependent inhibition of TA by imetelstat was demonstrated in vitro in multiple cancer cell lines of different tumor types treated with 0.1–10 μM of imetelstat in vitro for 24 hours to evaluate TA level by Telomerase Repeated Amplification Protocol. The half maximal inhibitory concentration (IC_{50}) values ranged from 0.15 to 1.35 μM (Herbert, 2005). These data confirm the mechanism-of-action based pharmacodynamic activity of imetelstat in vitro, at clinically achievable concentrations.

The relationship of plasma concentration, TA inhibition and antitumor efficacy was evaluated across in vivo mouse models to understand the optimal pharmacodynamic (PD) effect of imetelstat needed for anti-tumor efficacy. The IP administration of 30 mg/kg imetelstat TIW resulted in plasma concentrations of the drug in mice (71.5 $\mu\text{g/mL}$; Study P0006-2010) comparable to clinically achievable exposures (peak plasma concentration [C_{max}] of 89.2 $\mu\text{g/mL}$ in MDS patients), and resulted in $\geq 50\%$ inhibition of TA in tumor and surrogate tissues (Studies GS03-047 and GS03-034), leading to significant tumor growth inhibition (TGI) (53%) in xenograft models (Study 4D Protocol 0017-2009). The effects on TGI were usually seen after 3 to 4 weeks of treatment on a TIW schedule at a minimum dose of 15 mg/kg in nude mice. These results

suggest that $\geq 50\%$ inhibition of TA is the mechanism-of-action-based optimal PD effect of imetelstat needed for anti-tumor efficacy, and that the imetelstat exposure levels required to achieve such pharmacodynamic activity are achievable in patients.

Myelodysplastic Syndromes are a myeloid malignancy characterized by clonal myeloproliferation arising from malignant HSCs/HPCs with a high level of TA (Briatore, 2009). The anti-malignant HSCs/HPCs and LSCs activity of imetelstat was evaluated using models of other relevant myeloid malignancies including essential thrombocythemia (ET), MF, chronic myeloid leukemia (CML) and AML. Imetelstat at clinically relevant concentrations demonstrated selective activity on growth inhibition and cell death/apoptosis induction in HSCs/HPCs or LSCs in primary samples from ET (Applicant Figure 1) (Baerlocher, 2019), MF (Mosoyan, 2017; Wang, 2018), CML (Ma, 2017) and AML (Study PRE-14-003) patients *ex vivo*, while it had minimal effects on normal HSCs/HPCs.

Applicant Figure 1: Differential Effects of Imetelstat on Megakaryocytes Growth

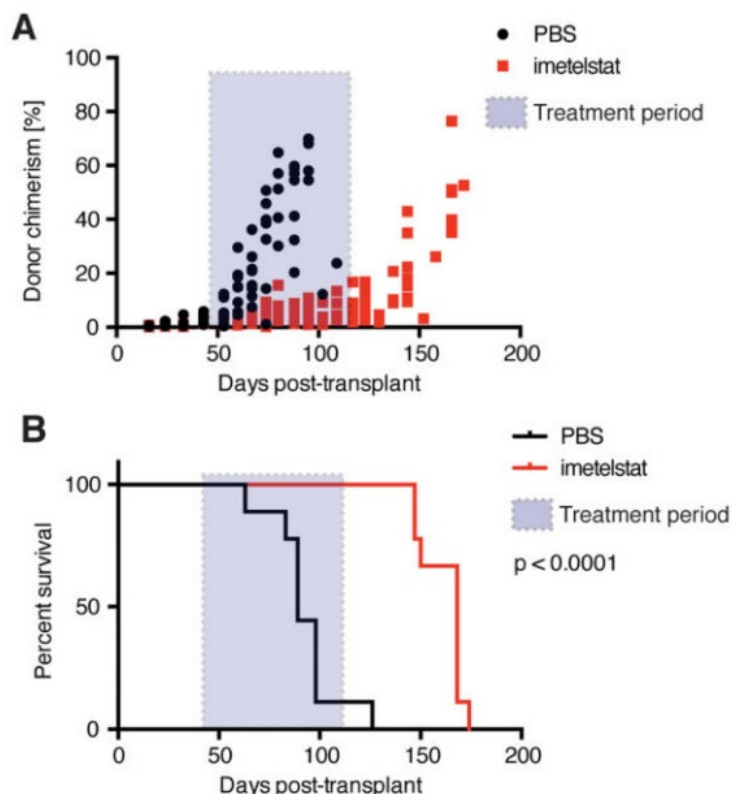


Dose-response analysis of colony-forming units (CFU) of megakaryocytes (MK) growth from mononuclear cells of ET patients compared with that of healthy individuals at different clinically relevant concentrations of imetelstat (Baerlocher, 2019).

In vivo anti-tumor activity of imetelstat was also evaluated using models of myeloid malignancies, including AML, CML or MF patient sample-derived xenograft (PDX) models. As an example, in one study NSGS immunodeficient mice were injected with primary AML cells isolated from adult patients, and then treated with 15 mg/kg of imetelstat, intraperitoneally (IP), three times a week (TIW). Imetelstat caused significant inhibition of AML engraftment and outgrowth, leading to prolonged OS compared to vehicle control (Applicant Figure 2) (Bruedigam, 2014). Additionally, study PRE-14-004 showed that imetelstat significantly reduced the LSC population in the bone marrow of the pediatric AML PDX mice and inhibited self-renewal capacity of LSC by significantly delaying engraftment in mice and improving

survival in the secondary transplantation. Similar results with imetelstat treatment were also observed in CML and MF PDX models (Ma, 2017; Wang, 2018).

Applicant Figure 2: Effects of Imetelstat on Human Acute Myeloid Leukemia Stem Cells Function and Survival in Primary Acute Myeloid Leukemia xenografts



A) Donor chimerism (hCD45%); B) survival analysis of tertiary human MLL-AF9 AML patient (AML X):NSGS transplants treated with telomerase inhibitor imetelstat or vehicle control. N = 9; two independent experiments. Statistical differences in survival were calculated by Mantel-Cox test. Adapted from (Bruedigam, 2014).

Collectively, these nonclinical data provide evidence that imetelstat reduces/eliminates the malignant HSCs/HPCs and LSCs in vitro/ex vivo and in vivo in models of myeloid malignancies. This is particularly relevant to the proposed indicated MDS patient population, as malignant HSCs are the disease-initiating cells in MDS (Pang, 2013), and malignant HPCs have a reduced ability to differentiate, thus leading to cytopenias, particularly anemia, due to ineffective hematopoiesis (Foran and Shammo, 2012). Elimination of such malignant HPCs may facilitate restoration of normal hematopoiesis in these patients.

The FDA's Assessment:

The FDA generally concurs with the Applicant's statements. Only the pharmacology studies conducted by the Applicant or data for which the Applicant has the right of reference are used in this review to support the NDA. Additional details and clarifications regarding the studies are provided in the review below.

An in vitro study has shown that imetelstat inhibited telomerase activity in the HT-3 human cervical carcinoma cell line in a concentration-dependent manner with an IC_{50} of 0.056 μ M (Study No. GR12-023). A study using mouse passaged pediatric AML patient-derived xenograft (PDX) lines were conducted to assess the effect of imetelstat on leukemia stem cells (Study No. PRE-14-003). The cells were treated ex vivo with imetelstat or mismatch oligonucleotide at final concentrations of 0, 1, 2.5, 5, 10, or 20 μ M for 48 or 96 hours. The results showed that imetelstat increased the cell death compared to the mismatch oligonucleotide.

In an in vivo study, repeated doses of imetelstat were administered IP at 6.15, 18.45, 36.9, or 55.35 mg/kg TIW for a total of 5 or 9 doses in non-tumor-bearing NOD.scid mice (Study No. GS03-047). Liver tissues were collected for telomerase inhibition analysis. The results showed $\geq 50\%$ of telomerase inhibition in all groups that received 9 doses of imetelstat. In the groups that received 5 doses of imetelstat, doses at ≥ 18.45 mg/kg resulted in $\geq 50\%$ of telomerase inhibition. A single IV administration of imetelstat (36.9 mg/kg) in BALB/c mice resulted in $\geq 50\%$ telomerase inhibition in liver tissue at 24 hours post-dose and persisted up to 168 hours post-dose (Study no. GS03-034).

The effect of imetelstat was evaluated in the OVCAR-5 human ovarian cancer subcutaneous (SC) xenograft model in Hsd nu/nu mice (Study No. 4D Protocol 0017-2009). The animals were administered imetelstat IP at 15 or 30 mg/kg TIW for 50 days. The results showed tumor growth inhibition with an average reduction in tumor volume of 34% and 53%, respectively, at 15 and 30 mg/kg.

5.3.2. Secondary Pharmacology

The Applicant's Position:

Due to self-renewal capacity, a fraction of human normal HPCs express telomerase to support proliferative capability for replacing mature blood cells continuously throughout life (Hohaus, 1997). Although TA is tightly regulated during hematopoiesis, presence of TA in normal HPCs indicates a potential mechanism of action to explain clinical adverse events observed with imetelstat, such as thrombocytopenia. Studies GRN01 and GRN05 evaluated the effect of imetelstat on normal HPCs using in vitro colony forming assays and showed that imetelstat at 3.75, 7.5 and 15 μ M only impacts colony formation of normal megakaryocytic progenitors (CFU-MK) but not normal erythroid or myeloid progenitors. Furthermore, published results indicated

that imetelstat selectively suppressed spontaneous growth of malignant CFU-MK from patients with ET in a dose-dependent manner, while having no effect on clonogenicity of normal MK progenitors ([Applicant Figure 1](#)) ([Baerlocher, 2019](#)).

Using an *ex vivo* megakaryopoiesis system, Mosoyan 2017 showed that imetelstat affected normal megakaryopoiesis solely by delaying MK precursor maturation, and such effect was reversible upon drug withdrawal ([Mosoyan, 2017](#)). This may account for one of the potential mechanisms of imetelstat-induced, reversible thrombocytopenia in patients. In contrast, imetelstat has more global effects on several stages along the hierarchy of malignant megakaryopoiesis, including selectively decreasing clonogenicity, preventing MK maturation and reducing the secretion of fibrogenic factors. These data provide potential mechanisms by which imetelstat exerts its inhibitory effects on malignant MK.

The FDA's Assessment:

The FDA generally concurs with the Applicant's statements. Only the pharmacology studies that the Applicant conducted or has the right of reference are used in this review to support the NDA.

The effects of imetelstat on human erythroid, myeloid and megakaryocyte (MK) progenitor proliferation were evaluated by in vitro colony forming assays (Study No. GRN01). Normal human bone marrow cells were cultured and treated with 0, 0.9, 1.875, 3.75, 7.5 or 15 μ M of imetelstat. Colony formation of erythroid, myeloid, and multipotential progenitors were assessed after 14 days and clonogenic progenitors of the megakaryocytic were assessed after 10-12 days. Imetelstat did not inhibit erythroid or myeloid colony number (although colony morphology was compromised at 15 μ M), but significantly inhibited the number of MK colony growth at $\geq 3.75 \mu$ M.

A study was conducted to further investigate the effect of imetelstat on MK colony growth using the same method and imetelstat concentrations as described above (Study No. GRN05). Treatment with $\geq 7.5 \mu$ M imetelstat resulted in an increase in the number of small MK colonies (each containing 2-20 cells), representing more mature MK progenitor cells and a decrease in the number of large MK colonies (each contains > 50 cells), which resemble the progeny of the most primitive MK progenitor cells with a high proliferative potential.

5.3.3. Safety Pharmacology

The Applicant's Position:

The safety pharmacology of imetelstat was evaluated in vitro and in vivo ([Applicant Table 3](#)).

Applicant Table 3: Cardiovascular Safety Pharmacology Studies Evaluating Imetelstat

Type of Study (GLP Compliance)	Species/ Strain (Gender, No. per group)	Method of Administration	Dose or Concentration	Noteworthy Findings	Study Number (eCTD Location)
Effects on hERG potassium channels (Non-GLP)	HEK293 cells expressing hERG (NA)	In vitro	10 and 50 μ M (~50 and 250 μ g/mL)	The IC ₅₀ was not determined as imetelstat did not inhibit the hERG channel at 10 or 50 μ M (approximately 50 or 250 μ g/mL), while the positive control cisapride inhibited hERG current by 79.5% at 90 nM.	007-TOX-2007 (4.2.1.3)
Effects on hERG potassium channels (GLP)	HEK293 cells expressing hERG (NA)	In vitro	125, 250 and 750 μ g/mL (~25, 50 and 150 μ M)	The IC ₅₀ was not determined as Imetelstat did not inhibit hERG channel up to 750 μ g/mL tested. The mean inhibition was 5.9%, -6.1% and -3.6% at concentration of 125, 250 and 750 μ g/mL (or approximately 25, 50, or 150 μ M), respectively, compared to 9.3% for the vehicle control article. The IC ₅₀ for positive control cisapride was 11.5 nM.	PRE-14-002 (4.2.1.3)
Effects on cardiovascular CNS and respiratory systems (GLP)	Cynomolgus Monkeys (4 males per Group)	IV infusion	5, 10, 15 mg/kg	No treatment-related clinical signs or changes observed in mean arterial pressure, heart rate, , respiratory rate, body temperature, ECG, neurological condition, blood gas parameters or chemistry and hematology parameters up to the highest dose tested (15 mg/kg) in telemetered monkeys.	GS04-072 (4.2.1.3)

Abbreviations: GLP = good laboratory practice; hERG = human ether-a-go-go-related gene; HEK =human embryonic kidney; μ M = micromolar; IV = Intravenous; NA = not applicable; IC₅₀ = concentration resulting in 50% inhibition; CNS = central nervous system; ECG = electrocardiogram.

Results from two in vitro studies (007-TOX-2007 and PRE-14-002) to evaluate imetelstat effects on the human ether-a-go-go-related gene (hERG) ion channel were consistent in demonstrating that the IC₅₀ was not determined since there was no inhibition effect of imetelstat on hERG currents at concentrations up to 750 mg/mL, which results in a safety margin for imetelstat at least > 140 x higher than the human free plasma concentration at C_{max} (~5.35 μ g/mL) based on population PK (popPK) predicted C_{max} of 89.2 μ g/mL for the MDS population following a 7.1 mg/kg dose (equivalent to 7.5 mg/kg imetelstat sodium) and fraction unbound of 0.06 (human plasma protein binding of 94%). In these studies, slight increases in hERG current were observed at 50, 250 and 750 μ g/mL of imetelstat. The agonist effect was not dose dependent,

and it may not be clinically relevant as it occurred at a concentration > 46 x higher than free plasma concentrations of imetelstat predicted in MDS patients.

In the safety pharmacology study in telemetered cynomolgus monkeys (Study GS04-072), no significant changes in mean arterial pressure, heart rate, respiratory rate, body temperature, electrocardiographic activity, or blood gas parameters were observed up to the highest dose tested (15 mg/kg) at imetelstat plasma concentration levels > 2.6 x higher than imetelstat C_{max} in subjects with MDS. Consistent with these findings, there were no imetelstat-related changes observed in electrocardiography, blood pressure, and respiratory rate at dose levels up to 15 mg/kg/week in the chronic toxicity study in monkeys (002-TOX-2008).

Overall, imetelstat is considered to have very low likelihood of presenting any safety risk for the cardiovascular, central nervous system (CNS) and respiratory systems.

The FDA's Assessment:

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

In the safety pharmacology study in cynomolgus monkeys (Study No. GS04-072), 4 male monkeys were assigned to a single treatment group. The animals were treated with vehicle control, 5 mg/kg, 10 mg/kg, and 15 mg/kg of imetelstat from Days 1- 28 via IV infusion. Each animal received a dose of vehicle control on Day 1 and increasing doses of imetelstat on Days 2, 9, 21 and 28. The results showed that single IV doses of imetelstat up to 15 mg/kg were well tolerated by cynomolgus monkeys, with no treatment-related clinical signs or changes in mean arterial pressure, heart rate, body temperature, ECG, neurological condition, blood gas parameters or chemistry and hematology parameters. Consistent with these findings, the ECG assessments evaluated in the 9-month toxicology study in monkeys were considered qualitatively and quantitatively normal and no test article-related changes were observed.

5.4. ADME/PK

The Applicant's Position:

Single Dose Pharmacokinetics

Imetelstat is administered as an intravenous (IV) infusion, so absorption is not necessary for the drug to reach systemic circulation. In the chronic toxicology studies in mice and monkeys (Studies 003-TOX-2008 and 002-TOX-2008, respectively) and embryo-fetal developmental (EFD) toxicity studies in mice and rabbits (Studies 006-TOX-2008 and 007-TOX-2008, respectively), imetelstat was quantified in the plasma of animals using a validated competitive nucleic acid hybridization enzyme-linked immunosorbent assay. In these studies, imetelstat plasma

exposures on Day 1 increased in a dose-dependent manner under the administered dosing schedules (i.e., 5 to 20 mg/kg). In mice, exposure levels increased in a linear manner, without any significant differences in values measured in male and female mice. In rabbits and monkeys, increases in plasma exposure to imetelstat (C_{max} and area under the plasma concentration-time curve from time 0 to infinity [$AUC_{0-\infty}$] values) were greater than dose proportional, suggesting a possible nonlinear clearance mechanism in those species. In addition, in the chronic toxicology study in monkeys, systemic exposure to imetelstat ($AUC_{0-\infty}$) was higher for male than for female monkeys at all dose levels (by approximately 1.2- to 1.4-fold on Day 1; however, statistical analysis of these differences was not conducted). Across species, the time to peak plasma concentration (T_{max}) levels occurred at the first sampling timepoint at 0.08 hours following dosing, and the plasma $t_{1/2}$ of imetelstat on Day 1 ranged from a few hours (approximately 2 to 6 hours) in mice to up to 13.2 hours in monkeys, which suggests an interspecies difference in clearance, possibly due to differences in metabolic rate.

Distribution

Distribution studies demonstrated that in vitro plasma protein binding of imetelstat was high (> 90%) across species (human, monkey, rat, and mouse) and was independent of test concentration (from 10 to 100 μ M) (Study GP05-007). Tissue distribution after IV administration of [^{35} S]-imetelstat to rats of 1 and 5 mg/kg was wide, with the highest concentrations of radioactivity seen in the liver and kidney, followed by bone marrow and spleen (Studies (b) (4)-493005 and GS03-020). In addition, a xenograft mouse study using a human OVCAR-5 cell line designed to evaluate distribution of imetelstat to tumor and bone marrow demonstrated rapid distribution of imetelstat into those tissues (Study P0006-2010).

Metabolism and Excretion

Imetelstat is likely metabolized into smaller fragments by nucleases in tissues and the component fragments (metabolites) eliminated in the urine as the primary route (Gaus, 1997; Griffey, 1997; Crooke, 2000; Geary, 2001; Yu, 2007; Geary, 2009). Following IV administration of [^{35} S]-imetelstat to rats at 1 and 5 mg/kg, approximately 62% to 82% of the dose was recovered in the urine by 168 hours post-dose and the fecal recovery accounted for approximately 12% to 21% of the dose (Studies (b) (4)-493005 and GS03-020). In a separate study ((b) (4)-493007, (b) (4)-493007 Supplemental), the results of high performance liquid chromatography (HPLC) with ultra-violet (UV), radiometric and mass spectrometry (MS) detection indicated that intact imetelstat was not detected in urine.

Pharmacokinetic Drug Interactions

The assessment of imetelstat inhibition of transporters, and inhibition and induction of drug metabolizing enzymes, has been performed in vitro using human biomaterials and those studies are summarized in Section 6.3.2.4 below. In an in vivo study, imetelstat did not affect the

pharmacokinetics (PK) of a known Cytochrome P450 (CYP) 2C8 (CYP2C8) substrate in the rat following IV co-administration (Study ^{(b) (4)}-493006).

A summary of key absorption, distribution, metabolism, excretion (ADME)/PK characteristics most relevant to interpretation of pharmacology/toxicology information is provided in

[Applicant Table 4.](#)

Applicant Table 4: Summary of Key Imetelstat ADME/PK Characteristics

Absorption/Pharmacokinetics						
Treatment Day 1 toxicokinetic (TK) data from toxicology studies (Imetelstat dissolved in sterile 0.9% sodium chloride and administered as a slow IV bolus injection in mice, or a 2-h IV infusion in rabbits and monkeys.)						
A 6-month intravenous toxicity study in mice with an 8-week recovery period (Study 003-TOX-2008; eCTD 4.2.3.2; GLP; N = 2/sex/group/timepoint)	Single-dose plasma PK of imetelstat after IV administration in CD-1 mice					
	Dose (mg/kg)	Sex	t _{max} (h)	C _{max} (µg/mL)	AUC _{0-∞} (µg.h/mL)	
	5	Female	0.083	93.6	80.8	
		Male	0.083	97.5	142.2	
	15	Female	0.083	267.6	354.4	
		Male	0.083	323.9	510.3	
	20	Female	0.083	414.0	697.4	
		Male	0.083	453.0	807.7	
	AUC _{0-∞} = area under the plasma concentration-time curve from 0 to infinity; C _{max} = peak plasma concentration; t _{max} = time to peak plasma concentration.					
	An Intravenous Developmental Toxicity Study in Mice (Study 006-TOX-2008; eCTD 4.2.3.5.2; GLP; N = 3 females/group/timepoint)	Single-dose plasma PK of imetelstat after IV administration in CD-1 mice				
Dose (mg/kg)		t _{max} (h)	C _{max} (µg/mL)	AUC _{0-∞} (µg.h/mL)	t _{1/2} (h)	
5		0.08	156.7	179.1	1.87	
15		0.08	386.6	589.6	5.94	
30		0.08	1054	1927	2.74	
AUC _{0-∞} = area under the plasma concentration-time curve from 0 to infinity; C _{max} = peak plasma concentration; t _{1/2} = terminal half-life; t _{max} = time to peak plasma concentration.						
An Intravenous Developmental Toxicity Study in Rabbits (Study 007-TOX-2008; eCTD 4.2.3.5.2; GLP; N = 3 females/group)	Single-dose PK of imetelstat after IV administration in New Zealand White rabbits					
	Dose (mg/kg)	t _{max} (h) ^a	C _{max} (µg/mL)	AUC _{0-∞} (µg.h/mL)	t _{1/2} (h)	CL (mL/h/kg)
	5	0.083	155.6 ± 23.3	450.2 ± 71.6	1.66 ± 0.24	11.3 ± 1.67
	15	0.083	733.9 ± 22.5	5381 ± 117.3	5.08 ± 0.24	2.79 ± 0.06
	30	0.083	1679 ± 348.9	15365 ± 3161	7.48 ± 1.39	2.02 ± 0.46
	AUC _{0-∞} = area under the plasma concentration-time curve from 0 to infinity; CL = clearance; C _{max} = peak plasma concentration; t _{1/2} = terminal half-life; T _{max} = time to peak plasma concentration. Data expressed as group mean ± standard deviation (SD). ^a T _{max} determined at the first blood sampling time point of 0.083 hours (5 minutes) post-infusion.					
A 9-month Toxicity Study of Imetelstat in Cynomolgus Monkeys Followed	Single-dose PK of imetelstat after IV administration in Cynomolgus monkeys					
	Dose (mg/kg)	Sex	t _{max} (h) ^a	C _{max} (µg/mL)	AUC _{0-∞} (µg.h/mL)	t _{1/2} (h)
	5	Female	0.083	65.7 ± 10.2	276.4 ± 48.9	5.24 ± 0.42

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 TRADENAME, imetelstat

by a 14-week Recovery Period (Study 002-TOX-2008; eCTD 4.2.3.2; GLP; N = 3 to 5/sex/group)		Male	0.083	69.6 ± 3.67	336.6 ± 22.2	13.2 ± 0.72			
	10	Female	0.083	155.4 ± 30.0	860.7 ± 124.2	11.3 ± 0.55			
		Male	0.083	199.8 ± 27.3	1188 ± 228.2	10.3 ± 0.09			
	15	Female	0.083	338.7 ± 57.4	2478 ± 506.2	9.41 ± 0.79			
		Male	0.083	294.0 ± 94.5	3294 ± 1427	9.46 ± 1.41			
	AUC _{0-∞} = area under the plasma concentration-time curve from 0 to infinity; C _{max} = peak plasma concentration; t _{1/2} = terminal half-life; t _{max} = time to peak plasma concentration. Data expressed as group mean ± SD. ^a T _{max} determined at the first blood sampling time point of 0.083 hours (5 minutes) post-infusion.								
Distribution									
A Single-Dose Intravenous Pharmacokinetic and Tissue Distribution Study of [³⁵ S]-Imetelstat In Rats (Study (b)(4)-493005; eCTD 4.2.2.3; GLP; N = 3 males/group/timepoint)	Single-dose tissue distribution of imetelstat, formulated in normal saline after IV administration in Sprague Dawley rats								
	Sample	Target/Actual Dose (mg/kg)							
		1 / 0.86				5 / 3.72			
	C _{max} (µg/g) ^a	t _{max} (h)	AUC ₀₋₁₆₈ (µg.h/g) ^a	t _{1/2} (h)	C _{max} (µg/g) ^a	t _{max} (h)	AUC ₀₋₁₆₈ (µg.h/g) ^a	t _{1/2} (h)	
	Plasma	17.1	0.083	15.7	87	72.0	0.083	107	88
	Liver	9.79	6	824	50	44.1	6	3916	68
	Kidneys	12.8	6	1320	98	38.0	6	4087	89
	Heart	0.25	6	21.0	63	1.40	6	127	70
	Lung	0.25	6	22.0	71	1.31	6	114	62
	Spleen	5.32	24	459	58	21.6	6	2249	105
	Pancreas	0.25	6	21.0	88	1.57	24	131	60
	Adrenal Glands	1.84	6	142	63	6.91	24	656	63
	Adipose tissue	0.04	6	2.6	102	0.21	6	15.3	NA
	Brain	0.04	24	3.0	58	0.19	6	10.5	70
	Mesenteric lymph nodes	0.51	24	46.4	55	4.98	24	417	61
	Bone	1.33	6	110	69	6.32	6	557	68
	Bone Marrow	6.27	6	628	64	25.1	24	2705	97
	Muscle	0.07	6	4.9	82	0.31	6	23.4	80
	Stomach	0.16	24	13.3	54	0.55	6	55.9	NA
	Small Intestine	0.29	24	25.7	62	1.54	24	139	67
	Large Intestine	0.28	6	22.9	58	1.34	6	121	65
	Thymus	0.07	6	5.8	78	0.54	6	58.3	NA
	Thyroid	0.19	6	15.4	149	1.24	24	112	NA

Version date: June 2022 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

	<table><tr><td>Pituitary</td><td>0.43</td><td>6</td><td>12.8</td><td>32</td><td>2.44</td><td>6</td><td>91.5</td><td>52</td></tr><tr><td>Salivary Glands</td><td>1.03</td><td>6</td><td>33.0</td><td>50</td><td>3.08</td><td>6</td><td>137</td><td>50</td></tr><tr><td>Skin</td><td>0.29</td><td>24</td><td>19.0</td><td>47</td><td>1.15</td><td>6</td><td>87.0</td><td>76</td></tr><tr><td>Eyes</td><td>0.15</td><td>6</td><td>6.0</td><td>92</td><td>0.62</td><td>6</td><td>37.0</td><td>62</td></tr><tr><td>Epididymis</td><td>0.21</td><td>6</td><td>17.0</td><td>120</td><td>0.88</td><td>24</td><td>101</td><td>121</td></tr><tr><td>Testes</td><td>0.29</td><td>24</td><td>37.9</td><td>108</td><td>2.51</td><td>24</td><td>261</td><td>115</td></tr><tr><td>Prostate</td><td>0.11</td><td>6</td><td>7.90</td><td>59</td><td>0.61</td><td>6</td><td>45.6</td><td>83</td></tr></table> AUC₀₋₁₆₈ = area under the plasma concentration-time curve from 0 to 168 hours; C_{max} = peak plasma concentration; t_{1/2} = terminal half-life; t_{max} = time to peak plasma concentration. Post-dose Sampling Times (h): 0.083, 0.25, 0.5, 1, 3, 6, 12, 24, 48, 96, and 168. ^a Data reflect imetelstat equivalents.	Pituitary	0.43	6	12.8	32	2.44	6	91.5	52	Salivary Glands	1.03	6	33.0	50	3.08	6	137	50	Skin	0.29	24	19.0	47	1.15	6	87.0	76	Eyes	0.15	6	6.0	92	0.62	6	37.0	62	Epididymis	0.21	6	17.0	120	0.88	24	101	121	Testes	0.29	24	37.9	108	2.51	24	261	115	Prostate	0.11	6	7.90	59	0.61	6	45.6	83
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Plasma Protein Binding Studies by Equilibrium Dialysis (Study GP05-007; eCTD 4.2.2.3; non-GLP)	Plasma protein binding of [³⁵S]-Imetelstat using mouse, rat, monkey and human plasma <table><tr><td></td><td colspan="3">Plasma Protein Binding (Mean %) ^a</td></tr><tr><td>[Imetelstat]</td><td>10 μM</td><td>30 μM</td><td>100 μM</td></tr><tr><td>Mouse</td><td>94.1</td><td>93.1</td><td>93.2</td></tr><tr><td>Rat</td><td>93.6</td><td>92.8</td><td>92.7</td></tr><tr><td>Monkey</td><td>94.4</td><td>93.6</td><td>93.4</td></tr><tr><td>Human</td><td>94.4</td><td>93.7</td><td>93.6</td></tr></table> ^a Calculated based on imetelstat equivalents.		Plasma Protein Binding (Mean %) ^a			[Imetelstat]	10 μM	30 μM	100 μM	Mouse	94.1	93.1	93.2	Rat	93.6	92.8	92.7	Monkey	94.4	93.6	93.4	Human	94.4	93.7	93.6																																							
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No standalone metabolism studies with imetelstat were performed.																																																																
Excretion																																																																
A Single-Dose Intravenous Pharmacokinetic and Tissue Distribution Study of [³⁵ S]-Imetelstat In Rats (Study ^(b) ₍₄₎ -493005; eCTD 4.2.2.3; GLP; N = 5 males/group/ timepoint)	Urinary and fecal excretion of imetelstat formulated in normal saline after IV administration in Sprague Dawley rats <table><tr><th rowspan="2">Target/Actual Dose (mg/kg)</th><th rowspan="2">Post-dosing Time (h)</th><th colspan="2">Mean Radioactivity Excretion (% of administered dose)</th></tr><tr><th>Urine ^a</th><th>Feces</th></tr><tr><td rowspan="5">1 / 0.86</td><td>0-12</td><td>20.45</td><td>0.08</td></tr><tr><td>12-24</td><td>10.58</td><td>2.57</td></tr><tr><td>24-96</td><td>33.84</td><td>6.52</td></tr><tr><td>96-168</td><td>16.43</td><td>2.99</td></tr><tr><td>0-168 (Total)</td><td>81.29</td><td>12.16</td></tr><tr><td rowspan="5">5 / 3.72</td><td>0-12</td><td>18.74</td><td>0.17</td></tr><tr><td>12-24</td><td>9.73</td><td>1.84</td></tr><tr><td>24-96</td><td>33.79</td><td>6.87</td></tr><tr><td>96-168</td><td>16.31</td><td>2.67</td></tr><tr><td>0-168 (Total)</td><td>78.58</td><td>11.55</td></tr></table> ^a Data includes urine and cage rinse. Data reflect imetelstat equivalents.	Target/Actual Dose (mg/kg)	Post-dosing Time (h)	Mean Radioactivity Excretion (% of administered dose)		Urine ^a	Feces	1 / 0.86	0-12	20.45	0.08	12-24	10.58	2.57	24-96	33.84	6.52	96-168	16.43	2.99	0-168 (Total)	81.29	12.16	5 / 3.72	0-12	18.74	0.17	12-24	9.73	1.84	24-96	33.79	6.87	96-168	16.31	2.67	0-168 (Total)	78.58	11.55																									
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A Single-Dose Intravenous Pharmacokinetic and Tissue Distribution Study of [³⁵ S]-GRN140719 in Rats (Study GS03-020; eCTD 4.2.2.5; GLP; N = 5 males/group/ timepoint)	Excretion of imetelstat formulated after IV administration in Sprague Dawley rats					
	Target/Actual Dose (mg/kg)	Mean Radioactivity Excretion Balance: 0-168 h (% Dose)				
		Urine	Feces	Cage Wash	Carcass	Total Recovery^a
	1 / 0.87 ^b	81.60	17.95	1.05	0.52	111.9
	5 / 3.5	61.66	20.83	0.89	0.69	96.9
^a Sum of cage wash, tissues, gastrointestinal tract contents, urine, feces, and carcass.						
^b Animal No. 31453 was not included in Group 1 data due to apparent mis-dosing (Total Recovery < 55%).						
Data reflect imetelstat equivalents.						
Summary PK parameters from pharmacokinetic studies.						
Refer to above Absorption/PK subsection of this table for Treatment Day 1 TK data from toxicology studies, and to Sections 5.5.1 and 5.5.4 below for repeat-dose TK data from toxicology studies.						
Tabulation of any exposure margins used in proposed labeling.						
Estimated Margin to Effect Values for Maternal and Developmental Toxicities Observed in Mice and Rabbits						
	Toxicity Type	Dose (mg/kg)	AUC_{0-∞}^a (µg.h/mL)	Margin to Effect (AUC at Toxic Dose in Animal/AUC in Humans^b)		
Mouse	Maternal Toxicity	N/A	N/A	N/A		
	Embryo-Lethality	30	1374.32	2.5 x		
Rabbit	Maternal Toxicity	15	5226.6	9.4 x		
	Embryo-Lethality	30	10636.7	19.2 x		

AUC_{0-∞} = area under the plasma concentration versus time curve from Time 0 to infinity.

^a Data represent mean exposure level values in females on Day 12 in mice and on Day 13 in rabbits.

^b Value for AUC_{0-∞} at the intended clinical dose equals 554 µg.h/mL based on popPK predictions for the MDS population (imetelstat sodium 7.1 mg/kg, 2-h IV infusion).

The FDA's Assessment:

The FDA generally concurs with the Applicant's assessment. The Applicant stated that the margin for the embryo-lethality effect for the mouse is 2.5 times the human exposure at the recommended clinical dose. The embryo-lethality was observed in the DRF study in female mice (Study No. 004-TOX-2008) with an AUC_{0-last} value of 342.9 hr•µg/mL at 30 mg/kg on Day 12. This results in a margin of approximately 0.6 times the human exposure at the recommended clinical dose; however, the Applicant stated that the TK samples from the DRF study were only collected at 5 minutes and 1-hour post-dose in that study, thus reflecting a truncated PK profile. As such, the AUC value of 1374.32 µg.h/mL from the 28.2 mg/kg group in the definitive EFD study in mice (Study 006-TOX-2008) was used in the safety margin calculation. The values from the TK data in the general toxicology study in mice also showed similar exposure values as in the definitive EFD study in mice, supporting the use of the exposure values from the definitive EFD study for the margin.

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:

A comprehensive program of nonclinical toxicology studies was conducted with imetelstat that fulfilled all relevant International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for the development of a drug to treat a life-threatening condition, including guidelines S9, S1A, and S4 ([ICH S1A, 1995](#); [ICH S4, 1998](#); [ICH S9, 2009](#)). In addition, the imetelstat development program is consistent with the industry standards for the development of oligonucleotide (ODN) drugs ([Berman, 2014](#); [Cavagnaro, 2014](#)). Pivotal studies were conducted according to Good Laboratory Practice (GLP) (Organisation for Economic Cooperation and Development Principles of GLP).

The mouse and monkey were used for the single- and repeat-dose toxicity studies, and mouse and rabbit were used for the EFD toxicity studies. These species were selected based on sequence homology to the template region of the RNA component of human telomerase and expected relevant pharmacologic action of imetelstat across species, from human to monkey to rabbit to rodent, as well as species-specific sensitivities to known ODN class effects.

The general toxicities observed in rodents and/or non-rodents with imetelstat dosing were cytopenias (most notably thrombocytopenia), complement activation, and coagulation abnormalities. Complement activation and coagulation abnormalities were related to the plasma concentration of imetelstat and reflect the well-characterized toxicity profile of the related phosphorothioate ODN class. Such effects were most pronounced in the initial toxicity studies that tested very high doses of imetelstat ranging from 5 to 1230 mg/kg in mice and from 5 to 130 mg/kg in monkeys (by bolus IV injection and IV infusion) and demonstrated that the high IV doses (ie, ≥ 73.8 mg/kg) produced excessive imetelstat exposures that were poorly tolerated. As demonstrated in the 9-month toxicity study in monkeys (002-TOX-2008), the degree and potential adverse sequelae of complement activation and coagulation abnormalities can be mitigated by administering imetelstat over a 2-hour IV infusion, even at doses (15 mg/kg/week) that produced exposures (C_{max}) in animals that are 6-7 x higher than the C_{max} in MDS patients at the proposed clinical dose. Mild to moderate decreases in platelet counts were seen at 10 and 15 mg/kg/week doses in the 9-month toxicity study in monkeys.

Additional imetelstat toxicities observed in the chronic pivotal toxicity studies, ie, the 6-month study in mice (003-TOX-2008) and the 9-month study in monkeys, included microscopic findings in the liver and kidney (described in [Applicant Table 5](#) and [Applicant Table 6](#) below). Importantly, there were no degenerative changes or alterations in clinical pathology parameters indicative of hepatic dysfunction or injury (ie, no substantial elevations in serum

transaminases, bilirubin, or alkaline phosphatase), nor were there any remarkable changes in parameters of kidney function.

The toxicity studies most relevant to the intended clinical use of imetelstat based on duration of treatment in both species, as well as the mode of administration employed (ie, 2-hour IV infusion in monkeys), are the chronic pivotal toxicity studies in mice and monkeys. Findings from these studies are summarized in detail in the tabulated summaries below in [Applicant Table 5](#) and [Applicant Table 6](#).

Applicant Table 5: Tabulated Summary of Data from Chronic Pivotal Toxicology Study of Imetelstat in Mice

Study title / study number / electronic Common Technical Document (eCTD) location: GRN163L – A 6-month intravenous toxicity study in mice with an 8-week recovery period / 003-TOX-2008 / 4.2.3.2	
Key Drug-related Adverse Findings	
• Discoloration at the injection site (tail vein), with dose-dependent severity at ≥ 5 mg/kg/day, which correlated with microscopic observations of necrosis/inflammation and vascular/perivascular fibrosis at the injection site of the 20 mg/kg animals. • Mild decreases in RBC parameters (hematocrit, Hgb, and RBC counts) observed at ≥ 15 mg/kg in both sexes, and these findings correlated with extramedullary hematopoiesis in the spleen at 20 mg/kg and increased spleen weights (at all dose levels). • Changes in organ weights included increases in liver weights at ≥ 15 mg/kg in both sexes and increased kidney weights in males at 20 mg/kg. • Microscopic findings in the liver consisted of increases in mixed inflammatory foci and increases in the number of Kupffer cells (hyperplasia of this cell type) and/or histiocytic aggregates containing brown and/or blue pigment in the liver. • Most systemic effects showed evidence of recovery after the 8-week treatment-free period. Increases in spleen weight at ≥ 5 mg/kg and in liver weight at 20 mg/kg in males were considered to be partially reversible. • No-observed-adverse-effect level (NOAEL) for systemic toxicity: 20 mg/kg NOAEL for local (tail vein injection site) toxicity: 5 mg/kg	
GLP compliance: Yes	
Methods	
Dose and frequency of dosing:	0, 5, 15 or 20 mg/kg for 6 months + 8 weeks recovery; twice a week dosing.
Method of administration:	IV bolus injection
Formulation/Vehicle:	0.9% sodium chloride
Species/Strain:	Mouse/CD-1
Number/Sex/Group:	12 (main study; terminal sacrifice at Day 182), 12 (recovery; terminal sacrifice at Day 238)
Age:	13 weeks
Satellite groups:	TK evaluation (36 /sex/group)
Deviation from study protocol affecting interpretation of results:	No

Observations and Results:

Dose (mg/kg)	0 (Control)		5		15		20	
	M	F	M	F	M	F	M	F
Main Study								
TK: AUC _{0-∞} (µg.h/mL)								
Day 1	NA	NA	142.2	80.8	510.3	354.4	807.7	697.4
Day 91	NA	NA	148.9	155.6	791.7	499.4	960.9	683.8
Day 182	NA	NA	144.3	166.5	724.0	485.7	29.2	925.5
C _{max} (µg/mL)								
Day 1	NA	NA	97.5	93.6	323.9	267.6	453.0	414.0
Day 91	NA	NA	102.3	83.1	503.9	308.3	465.6	343.3
Day 182	NA	NA	55.6	98.6	272.7	147.3	250.3	311.1
Noteworthy Findings:								
Body Weight	No significant changes observed							
Food Consumption (g/animal/day) W1 – W26 (Δ%)	6.0 – 5.2 (-13.3%)	6.2 – 5.4 (-12.9%)	6.3 – 5.1 (-19.0%)	5.8 – 4.6* (-20.7%)	6.0 – 5.0 (-16.7%)	6.2 – 4.5* (-27.4%)	6.3 -4.9 (-22.2%)	6.2 – 5.0* (-19.4%)
Clinical Observations	NC	NC	Injection site: tail discoloration increased with dose, including scabs, edema, erythema, black and dry tail, at ≥ 15 mg/kg.					
Ophthalmoscopy	No test article-related changes observed							
Hematology								
RBC (10 ⁶ /µL)	9.11	9.05	9.01	9.19	8.68	↓8.35*	↓8.52*	↓8.33*
Hg (g/dL)	14.2	14.1	13.5	14.4	↓13.2**	↓12.8*	↓12.9**	↓13.2*
Hematocrit (%)	45.2	43.7	↓42.7*	45.2	↓42.0**	40.8	↓41.8**	42.0
Reticulocytes (10 ⁹ /µL)	301.4	455.8	285.0	316.5	278.2	286.7	347.9	↓260.0*
Serum Chemistry								
AST (U/L)	58	69	78	73	65	74	66	↑96*
Globulin (g/dL)	2.4	2.0	2.4	2.1	2.5	↓2.3*	2.5	↓2.3*
Albumin/Globulin Ratio	1.2	1.5	1.1	↓1.4*	1.1	↓1.3**	1.2	↓1.3**
Urinalysis	No test article-related changes observed							
Organ Weights (organ to body weight %)								
Liver	4.81	4.41	4.93	4.41	↑5.49 **	↑5.06 *	↑5.39 **	↑5.50 **
Spleen	0.20	0.33	↑0.28 *	0.33	↑0.34 **	↑0.45 **	↑0.37 **	↑0.49 **
Prostate	0.08	NA	0.11	NA	↑0.12*	NA	0.11	NA
Unscheduled Deaths	2	2	1	2	4	0	4	1
Cause of Death								
Tail necrosis	0	0	0	0	0	0	2	0

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Dose (mg/kg)	0 (Control)		5		15		20	
	M	F	M	F	M	F	M	F
Cardiopulmonary thrombosis	0	0	0	0	0	0	1	0
Accidental trauma	0	1	0	0	1	0	0	0
Procedure related	1	0	0	2	0	0	0	0
Cervical skin necrosis	0	0	0	0	2	0	0	0
Undetermined	1	1	1	0	1	0	1	1
	Deaths were evenly distributed among study groups, including the control group. There was no apparent relationship between these deaths and imetelstat treatment.							
Gross Pathology (incidence)								
Injection site								
Discolored	1	1	1	2	4	5	4	5
Scab	1	1	1	1	2	4	3	2
Missing	0	0	1	0	1	2	5	4
Kidneys								
Enlarged	0	0	0	0	3	0	2	0
Discolored	0	1	0	1	2	2	2	1
Liver								
Discolored	1	2	4	2	6	0	3	2
Enlarged	0	0	0	0	1	1	1	1
Ovaries								
Cyst	NA	4	NA	5	NA	7	NA	6
Uterus								
Distended	NA	6	NA	6	NA	5	NA	8
Spleen								
Enlarged	0	0	0	0	0	2	2	3
Histopathology (Incidence)								
Tail (Injection Site)								
Necrosis	1	4	NT	NT	NT	NT	5	10
Thrombus	0	0					3	6
Inflammatory cell infiltrate	2	4					3	5
Vascular/perivascular fibrosis	1	2					9	8
Heart								
Aortic valve/periaortic inflammation	0	0	NT	NT	NT	NT	0	2
Kidneys								
Basophilic tubules	2	2	NT	NT	NT	NT	2	0
Perivascular inflammatory cell-infiltrate	2	6	NT	NT	NT	NT	4	5
Tubules: Eosinophilic material	0	0					2	3

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Dose (mg/kg)	0 (Control)		5		15		20	
	M	F	M	F	M	F	M	F
Tubular vacuolation	0	0					1	0
Cortical scar(s)	0	0					2	0
Liver								
Increased Kupffer cells and/or histiocytic aggregates with brown/blue pigment	0	0	NT	NT	NT	NT	10	12
Increased mixed inflammatory cell foci with or without extramedullary hematopoiesis	0	0					6	6
Mononuclear cell foci	6	7					6	11
Increased glycogenic vacuolation	8	2					5	2
Spleen								
Increased extramedullary hematopoiesis	0	0	NT	NT	NT	NT	5	6
Ovaries								
Follicular cyst(s)	NA	1	NT	NT	NT	NT	NA	7
Recovery Evaluation								
Body Weight (g) W1 – W34 (Δ%)	38.2-47.3 (+23.8%)	27.2-35.2 (+29.4%)	39.6-47.3 (+19.4%)	27.8-33.5 (+20.5%)	38.4-46.4 (+20.8%)	28.4-33.5 (+18.0%)	39.1-45.3 (+15.9%)	27.8-31.4 (+12.9%)
Food Consumption (g/animal/day) W1 – W34 (Δ%)	6.0-4.5 (-25.0%)	6.2-6.1 (-1.6%)	6.3-5.1 (-19.0%)	5.8-5.1 (-12.1%)	6.0-4.8 (-20.0%)	6.2-5.9 (-4.8%)	6.3- 5.3** ↑(-15.9%)	6.2-6.1 (-1.6%)
Hematology	No significant changes observed							
Serum Chemistry								
Albumin/Globulin Ratio	1.2	1.4	1.1	1.3	1.1	1.4	1.2	↓1.2*
Organ Weights (organ to body weight %)								
Liver	4.86	4.58	4.96	4.84	5.13	4.99	↑5.50 **	4.80
Gross Pathology	No test article related macroscopic findings were observed in any recovery phase animals							
Histopathology (incidence)								
Tail (injection site)								
Necrosis	0	0	NT	NT	NT	NT	2	0
Thrombus	0	0					1	0

Dose (mg/kg)	0 (Control)		5		15		20	
	M	F	M	F	M	F	M	F
Inflammatory cell infiltrate	1	0					1	1
Vascular/perivascular fibrosis	8	3					8	10
Liver								
Increased Kupffer cells and/or histiocytic aggregates with brown/blue pigment	0	0	NT	NT	NT	NT	5	11
Increased mixed inflammatory cell foci with or without extramedullary hematopoiesis	0	0					2	3
Mononuclear cell foci	8	7					4	9
Increased glycogenic vacuolation	10	6					5	4

AST = aspartate aminotransferase; AUC0-∞ = area under the plasma concentration vs. time curve from Time 0 to infinity; Cmax = peak plasma concentration; F = females; Hg = hemoglobin; RBC = red blood cells; M = males; NA = not applicable; NC = no change; NT = not tested; TK = toxicokinetic; W = week.

* Statistically significant difference from control mean, P < .05.

** Statistically significant difference from control mean, P < .01.

Applicant Table 6: Tabulated Summary of Data from Chronic Pivotal Toxicology Study of Imetelstat in Cynomolgus Monkeys

Study title / study number / eCTD location: A 9-month Toxicity Study of GRN163L in Cynomolgus Monkeys Followed by an 14-week Recovery Period / 002-TOX-2008 / 4.2.3.2 Key Drug-related Adverse Findings - Mild decreases in RBC parameters at ≥ 5 mg/kg. - Evidence of erythroid hyperplasia at 15 mg/kg based on evaluation of bone marrow smears. - Platelet counts were highly variable but were mildly lower at 10 and 15 mg/kg. - Moderate prolongation of activated partial thromboplastin time (aPTT) acutely following dosing (when measured on Day 239). - Initial activation of complement that was immediate and driven by the alternative pathway (Bb). For longer-term treatment beyond 6 months, the Bb diminished but was still significantly high. Chronic treatment caused depletion of classical pathway activity (CH50), indicating consumption of complement factors stemming from activation. 10 and 15 mg/kg/week dose levels produced a biologically significant degree of complement activation, based on increases in C5a. During the recovery period, the values for all complement parameters remained only slightly elevated over baseline and showed reversal. - Increased liver and kidney weights, with microscopic correlates of mild to moderate changes in the kidney (mesangial thickening, glomerulonephritis/sclerosis, deposition in interstitium, renal tubular

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hemorrhage, protein casts, and regeneration) and in the liver (telangiectasis, brown pigment deposition in Kupffer cells).	
- Changes also noted in the uterus (atrophy of the endometrium), choroid plexus (minimal lymphoid follicle formation and mononuclear cellular infiltration), and general systemic arteritis, including at the injection site. - Most changes showed evidence of recovery after a 14-week drug-free period. Test article-related changes that persisted through the end of the recovery period in high-dose (15 mg/kg/) animals were generally diminished in severity and included increased kidney weights, decreased indices of red cell mass, enlarged spleen, discoloration of the liver and kidney, and microscopic changes in the kidneys, liver, and choroid plexus. - NOAEL: not determined; Highest Non-Severely Toxic Dose Level: 15 mg/kg	
GLP compliance: Yes	
Methods	
Dose and frequency of dosing:	0, 5, 10 or 15 mg/kg for 9 months + 14 weeks recovery; once a week dosing.
Method of administration:	2-h IV infusion
Formulation/Vehicle:	0.9% sodium chloride
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	3 (main study; terminal sacrifice at Day 267), 2 (recovery; terminal sacrifice at Day 365)
Age:	5 to 8 years
Satellite groups:	No
Deviation from study protocol affecting interpretation of results:	No

Observations and Results:

Dose (mg/kg)	0 (Control)		5		10		15	
	M	F	M	F	M	F	M	F
Main Study								
TK: AUC_{0-∞} (µg.h/mL)								
Day 1	NA	NA	337 ± 22	276 ± 49	1188 ± 228	861 ± 124	3294 ± 1427	2478 ± 506
Day 85	NA	NA	1001 ± 169	779 ± 381	3417 ± 1503	2398 ± 971	8297 ± 2301	6344 ± 2417
Day 176	NA	NA	1651 ± 243	824 ± 248	3924 ± 1067	2423 ± 833	12274 ± 2706	10111 ± 3505
Day 267	NA	NA	1748 ± 359	1061 ± 412	2611 ± 1551	2180 ± 156	11339 ± 3506	8056 ± 3115
C_{max} (µg/mL)								
Day 1	NA	NA	69.6 ± 3.7	65.7 ± 10.2	200 ± 27.3	155 ± 30.0	294 ± 94.4	339 ± 57.4
Day 85	NA	NA	140 ± 1.2	142 ± 41.6	339 ± 41.7	262 ± 33.7	556 ± 129	501 ± 101
Day 176	NA	NA	137 ± 34.6	121 ± 25.6	447 ± 30.4	452 ± 212	524 ± 186	573 ± 40.1
Day 267	NA	NA	127 ± 38.2	112 ± 29.9	206 ± 100	225 ± 22.7	612 ± 308	528 ± 194

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Dose (mg/kg)	0 (Control)		5		10		15	
	M	F	M	F	M	F	M	F
Noteworthy Findings:								
Body Weight (kg) D -1 – D266 (Δ%)	4.53 – 5.10 (+12.6%)	2.77 – 3.13 (+13.0%)	5.31 – 5.45 (+2.6%)	2.77 – 3.04 (+9.7%)	5.03 – 5.24 (+4.2%)	2.54 – 2.69 (+5.9%)	4.39 – 4.30 (-2.1%)	2.64 – 2.55 (-3.4%)
Food Consumption (qualitative)	No test article-related changes observed.							
Clinical Observations	No test article-related changes observed.				Increase in the occurrence and duration of soft or liquid stools in females.			
Ophthalmoscopy	No test article-related changes observed.							
Electrocardiography	No test article-related changes observed.							
Hematology (Day -7 – Day 267)								
RBC (10 ⁶ /μL)	6.6 – 6.7	6.1 – 6.2	5.8 – 4.7	6.0 – 5.6	6.4 – 5.1	6.7 – 5.9	6.2 – 4.6	6.2 – 4.5
Hg (g/dL)	12.0 – 12.2	11.2 – 11.2	11.3 – 9.7	10.9 – 10.5	11.6 – 9.9	11.5 – 10.9	11.7 – 9.3	10.8 – 8.6
Hematocrit (%)	41.8 – 43.0	39.2 – 40.2	37.6 – 32.1	37.9 – 37.5	39.9 – 34.6	40.8 – 39.5	40.2 – 32.9	37.6 – 31.2
Platelets (10 ³ /μL)	390 – 371	372 – 355	296 – 202	333 – 270	256 – 210	410- 275	433 – 247	434 – 314
Reticulocytes (10 ³ /μL)	64 – 30	54 – 26	71 – 28	48 – 31	65 – 50	55 – 34	76 – 98	40 – 87
Coagulation (Day -7 to Day 239)								
Prothrombin Time (s)	10.5 – 10.5	10.8 – 11.1	10.3 – 11.1	10.1 – 11.1	10.9 – 11.9	10.5 – 11.3	10.3 – 14.8	11.3 – 13.4
aPTT (s)	16.8 – 17.4	19.1 – 19.9	16.5 – 28.7	16.6 – 26.0	16.8 – 27.7	16.4 – 28.2	17.9 – 51.0	19.2 – 40.1
Serum Chemistry (Day -7 to Day 239)								
Albumin (g/dL)	4.3 – 4.2	4.0 – 3.9	4.2 – 3.6	4.3 – 4.0	4.2 – 3.5	4.4 – 4.1	4.1 – 3.1	4.1 – 2.7
Globulin (g/dL)	3.4 – 3.4	3.2 – 3.2	2.9 – 3.5	3.2 – 3.7	3.7 – 5.1	3.1 – 3.7	3.4 – 4.4	3.5 – 5.4
Albumin/Globulin Ratio	1.3 – 1.3	1.3 – 1.2	1.5 – 1.1	1.3 – 1.1	1.2 – 0.8	1.4 – 1.1	1.2 – 0.7	1.2 – 0.5
Blood Urea Nitrogen (mg/dL)	17 – 19	16 – 20	19 – 17	20 – 17	19 – 17	19 – 18	18 – 24	21 – 33
Urinalysis	No test article-related changes observed							
Complement Factor Analysis (Day 1 – Day 260)								
Bb (μg/mL) – Pre	100 – 261	100 – 302	100 – 481	100 – 321	100 – 275	100 – 447	100 – 539	100 – 564
10 Min	197 – 287	132 – 370	260 – 1710	147 – 811	2517-2252	520 – 1005	7977-3061	5449-2457
CH50 (U/mL) – Pre	100 – 86	100 – 84	100 – 69	100 – 96	100 – 110	100 – 107	100 – 114	100 – 56
10 Min	97 – 93	106 – 78	99 – 22	117 – 99	96 – 65	114 – 88	101 – 73	105 – 0
C5a (ng/mL) – Pre	100 – 99	100 – 99	100 – 98	100 – 120	100 – 118	100 – 126	100 – 134	100 – 131
10 Min	100 – 98	96 – 99	105 – 101	107 – 110	108 – 133	104 – 134	161 – 185	136 – 140
Bone Marrow Smear (Day 269)								
myeloid:erythroid ratio	1.3	1.6	1.1	1.1	1.0	0.9	0.5	1.0
Organ Weights (organ to body weight %)								
Kidneys	0.30	0.38	0.37	0.41	0.38	0.47	0.49	0.54
Liver	1.41	1.97	1.56	1.97	2.01	2.32	2.09	2.40

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Dose (mg/kg)	0 (Control)		5		10		15	
	M	F	M	F	M	F	M	F
Spleen	0.28	0.23	0.41	0.29	0.59	0.61	0.62	0.66
Thymus	0.04	0.10	0.05	0.10	0.03	0.08	0.04	0.03
Unscheduled Deaths	0	0	0	0	0	0	0	0
Gross Pathology Terminal Necropsy (Incidence)	Heart: hemo-rrhage (1) Spleen: enlarge-ment (1)	NC	Liver: discolora-tion (1) Spleen: enlarge-ment (1)	Lungs/ Bronchi: Nodule (1) Spleen: adhesion (1)	Liver: discolora-tion (1) enlarge-ment(1) Spleen: enlarge-ment (3)	Spleen: enlarge-ment (1)	Liver: discolora-tion (2) enlarge-ment(1) Spleen: enlarge-ment (3)	Colon: Retention (1) Kidneys: Dots (1) Spleen: enlarge-ment (2)
Histopathology (organ-specific test article-related findings)								
Kidney								
Glomerulosclero-sis	0	0	0	0	0	0	1	1
Hemorrhage, renal tubule	0	0	0	0	1	0	2	2
Protein casts in tubules	0	0	0	0	0	1	2	2
Brown pigment	1	0	0	0	0	0	0	0
Regenerating tubules	0	0	0	0	0	1	1	0
Liver								
Telangiectases	0	0	2	0	2	0	2	2
Brown pigment in Kupffer cells	0	0	3	1	1	1	2	2
Brain								
Lymphoid follicle formation	0	0	2	0	1	1	1	0
Uterus								
Endometrial atrophy	NA	0	NA	0	NA	0	NA	3
Recovery Evaluation								
Body Weight (kg) Day -1 – Day 371 (Δ%)	4.53–4.83 (+6.6%)	2.77–3.51 (+26.7%)	NT	NT	NT	NT	4.39–5.04 (+14.8%)	2.64–2.87 (+8.7%)
Clinical Observations	–	–	NT	NT	NT	NT	Previous findings resolved	
Hematology (Day -7 – Day 365)								
RBC (10 ⁶ /μL)	6.6 – 7.0	6.1 – 6.3	NT	NT	NT	NT	6.2 – 5.6	6.2 – 5.7
Hg (g/dL)	12.0-12.8	11.2 – 11.3	NT	NT	NT	NT	11.7 – 10.7	10.8 – 9.6

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Dose (mg/kg)	0 (Control)		5		10		15	
	M	F	M	F	M	F	M	F
Hematocrit (%)	41.8-45.5	39.2 – 41.3	NT	NT	NT	NT	40.2 – 37.0	37.6 – 34.8
Platelets (10 ³ /μL)	390-408	372 – 407	NT	NT	NT	NT	433 – 296	434 – 524
Coagulation (Day -7 – Day 365)								
aPTT (s)	16.8 – 17.7	19.1 – 20.3	NT	NT	NT	NT	17.9 – 20.9	19.2 – 20.4
Serum Chemistry								
Albumin/Globulin Ratio	1.3 – 1.3	1.3 – 1.0	NT	NT	NT	NT	1.2 – 0.7	1.2 – 0.7
Blood Urea Nitrogen (mg/dL)	17 – 20	16 – 17	NT	NT	NT	NT	18 – 29	21 – 63
Organ Weights (% of organ to body weight)								
Kidneys	0.32	0.34	NT	NT	NT	NT	0.51	0.66
Liver	1.67	1.90	NT	NT	NT	NT	1.54	2.68
Spleen	0.28	0.31	NT	NT	NT	NT	0.39	0.56
Gross Pathology	Test article-related changes still observed in the high-dose (15 mg/kg/week) animals: enlarged spleen, and discoloration of liver, kidney, heart (with no microscopic correlate).							
Histopathology (organ-specific test article-related findings)	Microscopic changes in the kidneys (glomerulosclerosis, hemorrhage and protein casts in renal tubules, regenerating tubules) and liver (brown pigment in Kupffer cells).							

aPTT = activated partial thromboplastin time; AUC_{0-∞} = area under the plasma concentration vs. time curve from Time 0 to infinity; C_{max} = peak plasma concentration; F = females; Hg: hemoglobin; RBC = red blood cells; M = males; NA = not applicable; NC = no change; NT = not tested; TK = toxicokinetic; W = week.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment for the general toxicology studies. The review below provides a summary for the 8-week repeat-dose studies in mice and monkeys conducted by the Applicant.

In the 8-week GLP repeat-dose toxicity study in mice with a 4-week recovery period (Study No. GS04-070), the animals were administered imetelstat at doses of 5, 15, or 30 mg/kg BIW via IV injection. There was a total of 20 early deaths or moribund sacrifices during the study, mainly occurring at the HD (30 mg/kg): 14 males and 2 females in the HD group, 1 male in the MD group (15 mg/kg), and 3 males in the LD (5 mg/kg) group. There were no clinical signs that preceded the deaths, and the cause of the deaths was not determined. Decreases in platelet and lymphocyte counts were observed at ≥15 mg/kg. Increased blood urea nitrogen (BUN) and decreased phosphorus levels were observed in males at ≥15 mg/kg. Increases in liver and

spleen weights were observed at ≥ 15 mg/kg, which correlated with microscopic findings in these organs. Notable microscopic findings included neutrophil infiltrate and increased extramedullary hematopoiesis in the spleen, extramedullary hematopoiesis in the liver, and minimal mineralization of myocytes in the heart of males. Additional findings of minimal to mild lymphoid atrophy in the spleen and thymus were also observed. An increase in the severity of hemorrhage at the injection sites in the tail veins of the mice was observed at ≥ 15 mg/kg. Imetelstat-related effects were reversible by the end of the recovery period.

The 8-week GLP repeat-dose study in monkeys with a 4-week recovery period evaluated imetelstat doses of vehicle control (2 groups for infusion rates), 5, 10, 15, and 20 mg/kg administered once weekly via IV infusion (vehicle control and 20 mg/kg groups were infused over 24 hours; the other vehicle control, 5, 10, and 15 mg/kg groups were infused over 6 hours; Study No. GS04-071). There was no unscheduled mortality in any of the treatment groups. A dose-dependent prolongation of aPTT was observed but moderated in the 20 mg/kg with 24-hour infusion group. Increases in plasma Bb indicative of activation of the alternative complement pathway were observed at ≥ 10 mg/kg. No effects on CH50 (total hemolytic complement) or C5a levels were noted. Increases in BUN and creatinine were noted at 20 mg/kg, reflecting an effect on renal function that correlated with increased kidney weight and proteinuria. Decreases in albumin and increases in globulin levels were noted at ≥ 15 mg/kg. Microscopic findings included mesangial thickening and glomerulonephritis in the kidney, cellular infiltration in the liver, mononuclear cell infiltration in the brain, and thickened catheter tip site. There was inflammation, thrombosis, proliferation, hemorrhage, and necrosis observed microscopically in the area of the infusion site. The changes in brain, kidney and tissues surrounding the IV catheter tip remained after a 4-week recovery period.

5.5.2. Genotoxicity

The Applicant's Position:

In a standard battery of genotoxicity studies (summarized in [Applicant Table 7](#)), imetelstat was not mutagenic in an in vitro bacterial mutagenicity assay (Ames test) or clastogenic in an in vitro chromosomal aberrations assay (using cultured human peripheral blood lymphocytes) or in a standard mouse in vivo micronucleus assay.

Applicant Table 7: Genotoxicity Studies Conducted with Imetelstat

Type of Study (GLP Compliance)	Test System	Dose/ Concentration	Results	Study Number (eCTD Location)

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In vitro bacterial reverse mutation assay (Ames test) (GLP)	<i>Salmonella typhimurium</i> (TA1535, TA1537, TA98 and TA100) and <i>E. coli</i> (WP2 uvrA) strains	100 to 5000 µg/plate, ± microsomal enzymes (S9) (3 days)	No genotoxic effects observed at imetelstat concentrations up to 5000 µg/plate	GS04-068 (4.2.3.3.1)
In vitro chromosomal aberrations (GLP)	Cultured human peripheral blood lymphocytes	33.9 to 5000 µg/mL (with and without metabolic activation; 3- or 22-hour treatment/harvest period)	No genotoxic effects observed at imetelstat concentrations up to 2450 µg/mL	GS04-066 (4.2.3.3.1)
In vivo micronucleus test (GLP)	Mouse/ CD-1	0, 25.9, 51.8 and 103.6 mg/kg (equivalent to 0, 27.5, 55 and 110 mg/kg imetelstat sodium) (single dose)	Imetelstat did not induce a biologically relevant increase in micronucleated polychromatic erythrocytes at IV dose levels up to 103.6 mg/kg (equivalent to 110 mg/kg imetelstat sodium), which was the maximum tolerated dose	GS04-067 (4.2.3.3.2)

The FDA's Assessment:

The FDA concurs with the Applicant's assessment. The review below provides additional information for the methods and data presented by the Applicant.

In the initial chromosomal aberration study, human peripheral blood lymphocytes were incubated with imetelstat at 33.9 – 5000 µg/mL for 3 hours with and without metabolic activation and harvested 22 hours after the initial treatment. Cells treated with concentrations up to 2450 µg/mL without metabolic activation and up to 1200 µg/mL with metabolic activation were analyzed for chromosomal aberrations. In the confirmatory assay, human peripheral blood lymphocytes were incubated with imetelstat at 37.5 – 2500 µg/mL without metabolic activation for 22 hours and 150 µg/mL – 2000 µg/mL with metabolic activation for 3 hours. Cells treated with concentrations up to 800 µg/mL without metabolic activation and up to 100 µg/mL with metabolic activation were analyzed for chromosomal aberrations. No statistically significant increases in cells with chromosomal aberrations, polyploidy, or endoreduplication were observed.

5.5.3. Carcinogenicity

The Applicant's Position:

In alignment with ICH S9 guidance, carcinogenicity studies have not been conducted with imetelstat based on its intended clinical use for treatment of transfusion-dependent anemic patients with MDS who have a limited life-expectancy.

The FDA's Assessment:

The FDA disagrees with the Applicant that no carcinogenicity risk assessment is warranted for the intended patient population, which includes patients with low-risk MDS. The need for carcinogenicity studies depends on the life expectancy of the patients for the proposed indications. FDA asked the Applicant to provide justification for not conducting carcinogenicity studies based on the life expectancy of low-risk MDS. Based on the literature provided by the Applicant and discussion with the clinical team, the life expectancy for patients with lower risk MDS (defined variously, but usually as low or intermediate-1 risk disease by IPSS) and ESA failure or transfusion dependency can be > 5 years and carcinogenicity risk assessment is warranted for the intended patient population. To address the carcinogenicity risk assessment of imetelstat, there will be separate Post Marketing Requirements (PMRs) for carcinogenicity assessments in the mouse and rat species.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

Fertility, Pre- and Post-Natal Development

Consistent with ICH S9 guidelines, standalone fertility, pre- and post-natal development studies were not conducted based on imetelstat's intended clinical use for treatment of transfusion-dependent anemic patients with MDS with limited life-expectancy. However, information from general chronic toxicology studies informed assessments of potential impairment of fertility. In the chronic toxicity study in monkeys where imetelstat was administered once weekly for 9 months, uterine endometrial atrophy was noted at the high dose of 14.1 mg/kg (equivalent to 15 mg/kg imetelstat sodium), reflecting a mean exposure (based on AUC) that is approximately 14.5-times the human exposure at the recommended clinical dose. This finding was reversible after a 14-week recovery period. There were no gross or histological changes for the male reproductive tissues noted at any dose tested, i.e., up 18.8 mg/kg (equivalent to 20 mg/kg imetelstat sodium) in the 6-month toxicity study in mice or 14.1 mg/kg (equivalent to 15 mg/kg imetelstat sodium) in the 9-month toxicity study in monkeys, reflecting mean exposures (based on AUC) that are 1.7-times and 20.5-times, respectively, the human exposure at the recommended clinical dose (Studies 003-TOX-2008 and 002-TOX-2008, respectively).

Embryo-Fetal Development

In EFD toxicity studies (refer to [Applicant Table 8](#) and [Applicant Table 9](#)), imetelstat was not teratogenic, and there was no evidence of any fetal external malformations in either species. Embryo-lethal effects were observed at 28.2 mg/kg (equivalent to 30 mg/kg imetelstat sodium) in both species, noted as increased post-implantation loss due to an increase in early resorptions, resulting in a decrease in viable fetuses and litter size per animal. These effects

were observed at a dose that produced exposures (based on AUC) that are approximately 2.5-times (mice) or 19.2-times (rabbits) the human exposure at the recommended clinical dose.

In mice, there were no maternal or developmental toxicities observed at the doses tested in the pivotal EFD study (up to 28.2 mg/kg/dose; Study 006-TOX-2008; [Applicant Table 8](#)). However, embryo-lethality was observed at 28.2 mg/kg/dose in the dose range-finding EFD study in mice (refer to [Applicant Table 9](#); Study 004-TOX-2008), and those results are taken into consideration in Sponsor's assessment of risk of embryo-lethality included in the proposed product label.

In the pivotal EFD study in rabbits (007-TOX-2008; [Applicant Table 8](#)), doses of 14.1 and 28.2 mg/kg (equivalent to 15 and 30 mg/kg imetelstat sodium) were considered to be maternally toxic based on a decrease in mean gestation body weight, such effects occurring at exposures that are 9.4- to 19.2 times, respectively, the human exposure at the recommended clinical dose.

Applicant Table 8: Pivotal Embryo-Fetal Developmental Toxicity Studies

Study title / study number / eCTD location: GRN163L: An Intravenous Developmental Toxicity Study in Mice / Study 006-TOX-2008 / eCTD 4.2.3.5.2	
Study type: Embryo-fetal developmental toxicity study	
Key Drug-related Adverse Findings	
• Imetelstat-related maternal or developmental effects were not observed at any dose level in this study. • No evidence of treatment-related teratogenic effects were observed at dose levels up to 28.2 mg/kg/dose (equivalent to 30 mg/kg/dose imetelstat sodium). • The NOAEL for maternal and developmental toxicities was determined at the high dose (28.2 mg/kg/dose) given the lack of toxicities.	
GLP compliance: Yes	

Methods	
Dose and frequency of dosing:	0, 4.7, 14.1 or 28.2 mg/kg (equivalent to 0, 5, 15 or 30 mg/kg imetelstat sodium), once per day on gestation days (GD) 6, 9 and 12.
Route of administration:	Slow bolus IV injection
Formulation/Vehicle:	0.9% sodium chloride
Species/Strain:	Mouse/CD-1
Number/Sex/Group:	30 females
Age:	10 weeks
Satellite groups:	TK evaluation (36 females/group)
Study design:	On GD 17, each surviving main study female was euthanized and immediately subjected to a cesarean section, followed by ovarian, uterine, fetal examination and maternal necropsy.

Observations and Results:

Version date: June 2022 (ALL NDA/ BLA reviews)

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

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Dose (mg/kg)	0 (Control)	4.7	14.1	28.2
TK:				
AUC _{0-∞} (µg.h/mL)				
Day 6	NA	179.05	589.59	1927.07
Day 12	NA	126.27	622.27	1374.32
C _{max} (µg/mL)				
Day 6	NA	156.69	386.63	1054.35
Day 12	NA	117.25	524.80	707.67
Dams (no. of animals)	30	30	30	30
No. Pregnant	29	29	26	30
No. Died or Sacrificed Moribund	2	1	0	0
No. Aborted or With Total Resorption of Litter	2	0	0	0
Clinical Observations	No test article-related changes observed.			
Necropsy Observations	No test article-related changes observed.			
Body Weight (g) GD 0 – GD17 (Δ%)	27.35 – 52.06 (+90.3%)	27.34 – 54.32 (+98.7%)	27.32 – 53.76 (+96.8%)	27.48 – 55.42* ↑ (+101.7%)
Mean No. Corpora Lutea	15.4	14.9	15.0	15.1
Mean No. Implantations	13.8	14.1	14.2	14.2
Mean % Pre-Implantation Loss	6.88	4.96	6.13	5.79
Litters:				
No. Litters Evaluated	25	28	26	30
Mean Litter Size	12.0	13.5	13.3	13.5
Mean No. Resorptions	1.8	0.6*	0.9	0.7*
No. of Litters With Dead Fetuses	0	0	0	0
Mean % Post-Implantation Loss	16.32	4.91*	6.27*	5.03*
Mean Fetal Body Weight (g)	1.02	0.99	0.98	0.99
Fetal Sex Ratios (% of males)	54.3	49.8	49.1	50.1
Fetal Examination:				
No. Fetuses Evaluated	322	377	345	405
Gross External and Visceral Anomalies	No treatment-related developmental toxicities were observed. Fetal evaluations did not reveal any statistically significant effects on fetal sex ratio, fetal weight, or increases in the litter incidence of malformations or variations in the treatment groups, as compared to the controls.			

Δ = variation; AUC_{0-∞} = area under the plasma concentration vs. time curve from Time 0 to infinity; C_{max} = peak plasma concentration; GD = gestation day; TK = toxicokinetics.

* Statistically significant difference from control mean, P < .05.

** Statistically significant difference from control mean, P < .01.

Study title / study number / eCTD location: GRN163L: An Intravenous Developmental Toxicity Study in Rabbits / Study 007-TOX-2008 / eCTD 4.2.3.5.2 Study type: Embryo-fetal developmental toxicity study Key Drug-related Adverse Findings The 14.1 and 28.2 mg/kg dose levels (equivalent to 15 and the 30 mg/kg imetelstat sodium dose levels) were considered maternally toxic based on the observation of red material in the pan/bedding

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 TRADENAME, imetelstat

(correlating with a statistically significant increase in the incidence of early resorptions), and mean gestation body weight loss. - Developmental toxicities observed included decreases in viable fetuses and litter size per animal, as well as increases in the incidence of early resorptions, rate of post-implantation loss, and decreased uterine weight at 28.2 mg/kg. - No evidence of treatment-related teratogenic effects was observed at dose levels up to 28.2 mg/kg. - The NOAEL for maternal and developmental toxicities was designated at 4.7 mg/kg (equivalent to 5 mg/kg imetelstat sodium). GLP compliance: Yes

<u>Methods</u>	
Dose and frequency of dosing:	0, 4.7, 14.1 or 28.2 mg/kg (equivalent to 0, 5, 15 or 30 mg/kg imetelstat sodium), once per day GD 6 and 13.
Route of administration:	2-hour IV infusion
Formulation/Vehicle:	0.9% sodium chloride
Species/Strain:	Rabbit/New Zealand White
Number/Sex/Group:	23 females
Age:	7 months
Satellite groups:	TK evaluation (3 females/group)
Study design:	On GD 29, each surviving main study female was euthanized and immediately subjected to a cesarean section, followed by ovarian, uterine, fetal examination and maternal necropsy.

Observations and Results:

Dose (mg/kg)	0 (Control)	4.7	14.1	28.2
TK (mean ± SD):				
AUC_{0-∞} (µg.h/mL)				
Day 6	NA	450.2 ± 71.6	5381 ± 117.3	15365 ± 3161
Day 13	NA	412.4 ± 126.4	5227 ± 1152	10637 ± 1214
C_{max} (µg/mL)				
Day 6	NA	155.6 ± 23.3	733.9 ± 22.5	1679 ± 348.9
Day 13	NA	124.2 ± 22.0	702.0 ± 150.5	1202 ± 110.6
Does (no. of animals)	23	23	23	23
No. Pregnant	21	22	23	22
No. Died or Sacrificed Moribund	0	0	0	1
No. Aborted or With Total Resorption of Litter	0	1	2	3
Clinical Observations				
Presence of red material in the pan/bedding ^a	0	1	1	6
Few/absent feces	0	8	3	5
Necropsy Observations	No test article-related changes observed.			
Body Weight (g) GD 0 – GD29 (Δ%)	3.27 – 3.70 (+13.1%)	3.31 – 3.75 (+13.3%)	3.33 – 3.69 (+10.8%)	3.32 – 3.60 (+8.4%)

Dose (mg/kg)	0 (Control)	4.7	14.1	28.2
Food Consumption (g/animal/day)	121.9	129.2	122.1	118.0
Mean No. Corpora Lutea	10.3	10.1	10.2	9.9
Mean No. Implantations	9.3	9.3	8.4	8.9
Mean % Pre-Implantation Loss	9.4	8.04	13.14	8.19
Litters:				
No. Litters Evaluated	21	21	21	18
No. Live Fetuses	190	186	173	↓ 137
Mean Litter Size	9.0	8.5	7.9	↓ 6.5**
Mean No. Resorptions	0.3	0.8	0.5	↑ 2.4*
No. of Litters With Dead Fetuses	0	0	0	0
Mean % Post-Implantation Loss	2.79	8.91	9.70	↑ 28.21
Mean Fetal Body Weight (g)	40.55	41.31	41.30	40.22
Fetal Sex Ratios (% of males)	50.6	55.6	50.8	56.6
Fetal Examination:				
Gross external, visceral and skeletal anomalies	The fetal (external, visceral and skeletal) examination for malformations and variations did not reveal statistically significant changes at the doses tested, as compared to control animals.			

Δ = variation; AUC_{0-∞} = area under the plasma concentration vs. time curve from Time 0 to infinity; C_{max} = peak plasma concentration; GD = gestation day; SD = standard deviation; TK = toxicokinetics.

* Statistically significant difference from control mean, P < .05.

** Statistically significant difference from control mean, P < .01.

^a Showed a close relationship to females with total litter loss.

Applicant Table 9: Non-pivotal Embryo-fetal Developmental Toxicity Studies

Species/ Strain	Method of Administration	Dosing Period	Doses (mg/kg)	No./ Group	Noteworthy Findings	Study Number (eCTD location)
Mouse/ CD-1	Slow bolus IV injection	DRF EFD – Once per day on GD 6, 9 and 12	0, 4.7, 9.4, 14.1 and 28.2 mg/kg (equivalent to 0, 5, 10, 15 and 30 mg/kg imetelstat sodium)	8 F; 15 F for TK	No adverse clinical findings, changes in gestation body weight, or gestation food consumption seen. An increase in the post-implantation loss observed at 28.2 mg/kg, which was primarily due to an increase in early resorptions. No evidence of any fetal external malformations following treatment with imetelstat at the dose levels tested. Based on these data, 0, 4.7, 14.1 and 28.2 mg/kg doses were selected for the definitive (pivotal) mouse developmental toxicity study.	004-TOX- 2008 (4.2.3.5.2)
Rabbit/ New	2 h IV infusion	DRF EFD	0, 4.7, 9.4, 14.1 and	6 F	A single high-dose (28.2 mg/kg/dose) female found dead on GD 17. For the	005-TOX- 2008

Species/ Strain	Method of Administration	Dosing Period	Doses (mg/kg)	No./ Group	Noteworthy Findings	Study Number (eCTD location)
Zealand White		study – Once per day on GD 6 and 13	28.2 mg/kg (equivalent to 0, 5, 10, 15 and 30 mg/kg imetelstat sodium)		other 28.2 mg/kg animals, a decrease in mean body weight change and food consumption was observed during the first days of dosing (GD 6-10), and the difference from the control group mean was statistically significant. An increase in post-implantation loss at 28.2 mg/kg was observed, which was primarily due to early resorptions. No evidence of any fetal malformations at the dose levels tested. Based on these data, 0, 4.7, 14.1, and 28.2 mg/kg doses were selected for the definitive (pivotal) rabbit developmental toxicity study.	(4.2.3.5.2)

DRF = dose-range finding; EFD = embryo-fetal development; F = females; GD = gestation day; IV = intravenous; TK = toxicokinetics.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's assessment for the embryo-fetal developmental (EFD) toxicity studies. Due to an unusually high incidence of post-implantation loss of 16% observed in the concurrent vehicle control group in the pivotal study compared to 3% observed in the DRF control group and 6.4% in the historical control data ((b) (4))

we reviewed both the DRF and pivotal EFD studies in mice. The doses and schedule of administration were identical for the two studies. Based on the response to the information request sent to the Applicant, the high mean post-implantation loss in the control group of the pivotal study was due to the unusually high post-implantation loss rate of 100% observed in two animals, which skewed the overall mean value. The re-calculated mean post-implantation loss was 8.7% without the outliers.

In the DRF EFD study in mice (Study No. 004-TOX-2008), dose levels of 4.7, 9.4, 14.1, or 28.2 mg/kg/dose (equivalent to 5, 10, 15, or 30 mg/kg/dose imetelstat sodium) were administered via a slow bolus IV injection on GD 6, 9 and 12. All animals survived to the scheduled euthanasia except for two animals, one in the control group and one in the low-dose group. There was a marked increase in the post-implantation loss at the HD level of 28.2 mg/kg (24% vs. 3% in the control). The effect was considered test-article related and was mainly due to an increase in early resorption of fetuses (2.7 per animal vs. 0.1 per animal in the control) in the HD group. No other imetelstat-related effects were observed in the uterine and ovarian examinations. These

data demonstrated embryo-lethality toxicity at 28.2 mg/kg in mice with an $AUC_{0-\infty}$ of 1374.32 $\mu\text{g}\cdot\text{h}/\text{mL}$, which is 2.5 times the human exposure at the recommended clinical dose (Refer to the FDA assessment in section 5.4 ADME/PK for the explanation on the AUC value and margin).

	Incidences (mice)				
Dose (mg/kg/dose)	0	4.7	9.4	14.1	28.2
Mean % Post-Implantation Loss	2.98	9.11	7.18	4.89	23.73
Early Mean No. Resorptions	0.1	1.3	0.8	0.6	2.7
No. Litter Size	13.3	12.6	12.0	12.3	10.4

Study No. 004-TOX-2008

After review of the DRF and pivotal studies in rabbits, the Agency concluded that the HD of 28.2 mg/kg is maternally toxic due to mortality (1 female in each of the DRF and pivotal studies). The mid-dose of 14.1 mg/kg resulted in increased pre- and post-implantation loss compared to the concurrent control. The mid-dose had an $AUC_{0-\text{last}}$ of 5227 $\mu\text{g}\cdot\text{h}/\text{mL}$, which is 9.3 times the human AUC at the recommended human dose (the safety margin was updated based on the updated clinical exposure value).

	Incidences (rabbits)				
Dose (mg/kg/dose)	0	4.7	9.4	14.1	28.2
Mean % Post-Implantation Loss	7.22	5.37	2.86	0	49.8
Early Mean No. Resorptions	0.5	0.5	0	0	3.3
No. Litter Size	8.3	7.5	10	9.4	5.0

Study No. 005-TOX-2008

5.5.5. Other Toxicology Studies

Impurity Qualification

The Applicant's Position:

Taking into consideration the recommendations of the ICH S9 guidance for anticancer products, no standalone studies with impurities were conducted. The qualified levels of specified impurities (ie, product related substances and impurities), and related safety margins in relation to the proposed specification limits, have been determined based on evaluation of the imetelstat lots used in the chronic toxicology studies.

The FDA's Assessment:

FDA considers body surface area (mg/m²) the appropriate approach to compare the levels of the impurities in the nonclinical and clinical oligonucleotide batches. The proposed limits for several impurities in the drug substance specification exceed the qualification levels based on batches from the monkey toxicology studies. Two different lots (Lots #GAI-06-029-S4-B1-5.7 and #MM040520) were both used in the studies and the impurity doses were calculated using the highest percentage for a given impurity across the two batches to reflect the highest level of a given specified impurity.

To qualify the impurities in imetelstat, the FDA considered multiple factors including the drug class (oligonucleotide), the nature of the impurities, the pharmacokinetics data, and the differences in dosing frequency between the animal studies and clinical trials. Based on the TK data from the 9-month toxicology study in monkeys showing an accumulation in the exposure (AUC) to imetelstat of 3-5-fold during the duration of the study, the impurities (being closely related to the API) are anticipated to also accumulate at the same or comparable levels. Given the accumulation together with the difference in the dosing frequency between animals and patients (higher frequency of dosing in animals), the FDA agrees that the impurities are qualified at the proposed specifications.

Immunotoxicity

The Applicant's Position:

A systematic assessment of the immunotoxicity potential of imetelstat in the 6-month mouse and 9-month monkey studies (003-TOX-2008 and 002-TOX-2008, respectively) indicated that there were no adverse effects, including no degenerative changes, on lymphatic organs such as the spleen, lymph nodes, and thymus suggestive of an immunotoxic response to imetelstat treatment. Additionally, there was no evidence of an immune suppression response in the chronic toxicity studies. Consistent with the expected ODN class effects ([Levin AA and Henry SP, 2008](#)), repeated dosing of imetelstat in general toxicity studies showed non-specific immune stimulation, including injection site inflammation correlated with systemic mononuclear cell infiltration in tissues, with mice showing greater sensitivity than monkeys.

The FDA's Assessment:

The FDA concurs.

Local Tolerance

The Applicant's Position:

Local tolerance to imetelstat administration at the injection site was evaluated in general toxicity studies in mice, rats, and monkeys. Injection site findings were largely limited to tail vein injection sites in mice and included vascular irritation, discoloration and microscopic observations of necrosis/inflammation and vascular/perivascular fibrosis. This injection site

pathology was likely attributable to extravasation of imetelstat from the very small tail veins which commonly occurs with IV bolus injections in rodent studies and is not considered clinically relevant.

The FDA's Assessment:

The FDA concurs.

Phototoxicity

The Applicant's Position:

An in vitro phototoxicity study of imetelstat in BALB/c 3T3 cells incubated for one hour at concentrations ranging from 68.1 to 1000 µg/mL, which utilized a neutral-red uptake endpoint that also reflects cytotoxicity, showed no effects, thereby confirming the absence of any potential for imetelstat to elicit phototoxicity (Study MB 10-19402.30).

The FDA's Assessment:

The FDA concurs.

X

X

Primary Reviewer

Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

Imetelstat sodium (i.e., imetelstat) is a 13-mer N3'→P5' thio-phosphoramidate oligonucleotide with a palmitoyl lipid covalently attached by an aminoglycerol linker to the 5' thio-phosphate of the first nucleotide. It has a complementary sequence to the RNA component of human telomerase reverse transcriptase (hTERT) that lies in the active or catalytic site of hTERT, resulting in competitive inhibition of hTERT and prevention of telomerase binding. Rather than modulating gene expression products, the imetelstat mechanism of action resembles classic active site inhibition.

The proposed indication for imetelstat is the treatment of transfusion-dependent anemia in adult patients with low- to intermediate-1 risk myelodysplastic syndromes (LR-MDS) who have failed to respond or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESAs). The proposed dosing regimen is 7.1 mg/kg imetelstat (equivalent to 7.5 mg/kg imetelstat sodium via the salt rule) as 2-hour infusion every four weeks.

The clinical pharmacology package includes data from nine clinical studies, pharmacometrics analyses, and an evaluation of immunogenicity. The pivotal trial is 63935937MDS3001 (MDS3001), a completed Phase 2/3 study in subjects with LR-MDS. The Phase 2 part was an open-label, single-arm trial and the Phase 3 (pivotal) part was a double-blind, randomized, placebo-controlled trial. The Applicant's pharmacometrics analyses include population PK (popPK) analyses and exposure-response (E-R) analyses for safety and efficacy using data from the monotherapy studies CP14A004, CP05-101, CP04-151, CP14B013, CP14B015, MYF2001, MDS3001. The immunogenicity analysis used data collected from two studies (Studies MYF2001 and MDS3001).

The clinical pharmacology review focused on 1) the acceptability of the proposed dosing regimen; 2) the effects of anti-drug antibodies (ADAs) on pharmacokinetics (PK), safety, and efficacy of imetelstat; 3) the drug-drug interaction (DDI) potential of imetelstat as an inhibitor of transporters; and 4) the effect of mutations in MDS-related genes on response to imetelstat.

Recommendations: The Office of Clinical Pharmacology has reviewed the information submitted in NDA 217779. This NDA is approvable from a clinical pharmacology perspective. However, an assessment on the risk/benefit profiles suggests the proposed dosing regimen

warrants further dose optimization. The key review issues with specific recommendations are summarized below in Table 10.

Table 10: Key Clinical Pharmacology Review Issues

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	The primary evidence of effectiveness is the superiority of imetelstat vs placebo in the achievement of 8-week red blood cell (RBC) transfusion independence (TI) from the pivotal study MDS3001 (See Section 8.1). Supportive evidence of effectiveness comes from the superiority in selected secondary endpoints including 24-week TI and the duration of TI, as well as the results of E-R analysis showing higher imetelstat average concentration (Cavg) associated with higher probability of achieving 8-week TI. However, the E-R analysis for efficacy has significant limitations because of the single dose level and the frequent dose modification in the study.
General dosing instructions	The proposed recommended dosing regimen is 7.1 mg/kg imetelstat as a two-hour infusion every four weeks. The proposed dosing regimen in the target LR-MDS patient population may not be optimized, and additional dose exploration will be required. Despite meeting the primary efficacy endpoint in Study MDS3001, only one dose level has been evaluated in the LR-MDS patient population, and data from the other submitted studies had issues that preclude confidence in an assessment of the dose-response relationships on the efficacy, safety, and pharmacodynamic endpoints. Additionally, higher rates of Grade 3/4 TEAEs, particularly thrombocytopenia and neutropenia, and higher rates of dose modifications, interruptions, and discontinuations were observed in the imetelstat treatment arm compared to the placebo arm. In addition, the E-R analysis for safety identified a positive relationship between the risks for Grade 3/4 thrombocytopenia and maximum plasma concentration (Cmax) in the first cycle, suggesting a potential to further optimize dosage selection in the proposed patient population.
Dosing in patient subgroups	1. No therapeutic individualization of imetelstat is needed based upon intrinsic factors such as age, sex, race (81% White, 4% Asian, 7% Black, 8% other/unknown), mild to moderate renal impairment (CrCL 30 to < 90 mL/min), mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin > 1x to 1.5x ULN and any AST), or moderate hepatic impairment (total bilirubin > 1.5x to 3x ULN and any AST). The PK of imetelstat has not been adequately characterized in patients with severe renal impairment (CrCL 15 and < 30 mL/min), end-stage renal

Review Issue	Recommendations and Comments
	disease, or severe hepatic impairment (total bilirubin > 3x ULN and any AST). 2. No dose adjustment is needed based on the presence of ADAs. The median time to the formation of ADAs was longer than the median time to the onset of 8-week TI or adverse events. 3. No dose adjustment is needed based on SF3B1 mutational status, as this was considered exploratory.
Drug-drug interactions	Imetelstat is an inhibitor of OATP1 and OATP1B3 based upon <i>in vitro</i> study data. However, there is low risk for clinically meaningful drug-drug interactions (DDIs) due to the short half-life and long dosing interval. The risks for clinically meaningful drug-drug interactions due to CYP450 enzymes are low.
Labeling	The proposed labelling recommendations are acceptable upon the Applicant's agreement to the FDA revisions to the draft label.

6.2. Summary of Clinical Pharmacology Assessment

The clinical pharmacology program for imetelstat consists of 9 completed clinical studies with imetelstat administered as a single agent or in combination with various systemic anticancer agents across a wide range of doses (0.4 to 11.0 mg/kg) and dose schedules (once weekly [qw], once every 2 weeks [q2w], one every 3 weeks [q3w], once every 4 weeks [q4w]). Population PK analysis using clinical PK data from 7 monotherapy studies with serial or sparse PK sampling were conducted to quantitatively describe the PK of imetelstat in subjects and to evaluate the effects of relevant covariates (e.g., demographics, laboratory baseline values, disease status) that may contribute to the variability in imetelstat exposure in individual subjects.

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data and Applicant's Position:

Clinical Pharmacokinetics: The PK of imetelstat were evaluated in patients with solid tumors and hematologic malignancies following intravenous administration. Imetelstat exposure (AUC) increases in a more than dose proportional manner over the 0.4 to 11.0 mg/kg dose range. In subjects with MDS receiving an intravenous infusion of imetelstat of 7.1 mg/kg over 2 hours, the geometric mean (coefficient of variation [CV%]) C_{max} in plasma was 89.2 µg/mL (27.2%) with peak concentrations observed at the end of the infusion. The AUC_{0-28} was 554 h*µg/mL (43.4%). Imetelstat does not accumulate between treatment cycles following every four-week dosing in patients with MDS. The geometric mean (CV%) apparent half-life for imetelstat in plasma is approximately 4.9 hours (45.4%) in patients with MDS following a 7.1 mg/kg dose.

Absorption: The drug product is administered intravenously; no food effect is expected. In subjects with MDS receiving an intravenous infusion of imetelstat 7.1 mg/kg over 2 hours, maximum imetelstat concentrations were reached by the end of infusion.

Distribution: The geometric mean (CV%) volume of distribution at steady state was 11.5 L (26.1%). Human plasma protein binding of imetelstat was greater than 94% in vitro at clinically relevant concentrations.

Elimination: The geometric mean (CV%) apparent half-life for imetelstat in plasma is approximately 4.9 hours (45.4%) in patients with MDS following a 7.1 mg/kg dose. Nonclinical studies demonstrated that urine is the primary route of elimination, with 62% to 82% recovery of radiolabeled imetelstat in urine and 12 to 21% recovery in feces after 1 week. Unchanged imetelstat is not detected in the urine of rats that were administered radiolabeled imetelstat.

The FDA's Assessment:

The FDA generally agrees with the Applicant's description of the clinical pharmacology properties of imetelstat. It is noted that the reporting of PK exposures (e.g., C_{max}, AUC) in this review is based on the mass concentration of the salt form, whereas the reporting of dosage is based on a conversion to the acid form. The reporting of PK exposures (based on updated popPK analysis; refer to Section 19.4.1) will be converted to molar concentration in the product label. This linear conversion does not impact the calculation of other PK parameters (e.g., T_{max}, T_{1/2}, etc.) or the exposure-response analyses.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data and Applicant's Position:

General Dosing

The proposed imetelstat dosing regimen is 7.1 mg/kg q4w via 2 hour IV infusion for treatment of patients with MDS. This is the same dosage as studied in the MDS3001 trial. Selection of this proposed dosing regimen is based on the the clinical efficacy and safety results from the pivotal Phase 3 study, MDS3001, and the supportive Phase 2 portion of MDS3001, along with results from exposure-response (E-R) analyses, clinical PK and target engagement, and supportive nonclinical data ([Section 6.3.2.2](#)).

The FDA's Assessment:

It is unclear whether the dosing regimen (7.1 mg/kg imetelstat as a two-hour infusion every four weeks) is optimized. Limited dose finding was conducted in the target population. In the

current dosing regimen, high rates of dose modifications, high rates of Grade 3+ thrombocytopenia and positive E-R relationships for Grade 3+ adverse events were observed. Refer to Section 6.3.2.2 for details of the reviewer's analysis.

6.2.2.2. Therapeutic Individualization

Data:

Data regarding the impact of intrinsic and extrinsic factors on imetelstat PK are described in Sections 6.3.2.3 and 6.3.2.4.

The Applicant's Position:

No therapeutic individualization is required for imetelstat based on intrinsic or extrinsic factors. No clinically relevant PK differences were seen for sex, age, race, mild to moderate hepatic impairment, or mild to moderate renal impairment. There is limited information on the effect of severe hepatic impairment, severe renal impairment, or end-stage renal disease on imetelstat PK ([Section 6.3.2.3](#)).

Body weight with theory-based allometric exponents was included as a covariate in the popPK analysis. Using body-weight-based dosing, there is limited exposure variation expected for subjects with low body weight (52 kg) or high body weight (107 kg) compared to a reference subject of 70 kg, supporting the use of the body-weight-based dosing approach for imetelstat ([Section 6.3.2.3](#)).

Dose adjustments for food-drug or drug-drug interactions extrinsic factors are not necessary for imetelstat ([Section 6.3.2.4](#)).

The FDA's Assessment:

The FDA agrees that no therapeutic individualization of imetelstat is needed based upon intrinsic factors from the popPK modeling results and the analysis on the mutational status of SF3B1. Refer to Section 6.2.2.3, Section 19.4.1, and Section 19.4.3.

6.2.2.3. Outstanding Issues

Data:

Not applicable.

The Applicant's Position:

Not applicable.

The FDA's Assessment:

The FDA does not agree. First, the submission of a QT assessment report is pending. Second, the clinical pharmacology review team cannot conclude that the dose of imetelstat in the target MDS patient population is optimized because only one dose has been evaluated, and after considering the safety data and high rates of dose modifications observed in patients treated with imetelstat in Study MDS3001. Additional dose finding/dosage optimization for the proposed indication will be considered.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data and Sponsor's Position:

An overview of the pharmacology, ADME properties, clinical PK, and immunogenicity of imetelstat is provided below.

Pharmacology	
Mechanism of Action	Imetelstat is a specific inhibitor of human telomerase that binds with high affinity to the template region of the RNA component of human telomerase and acts as a direct competitive inhibitor of telomerase enzymatic activity, which prevents telomere binding. Telomerase activity and human telomerase reverse transcriptase (hTERT) RNA expression are known to be significantly increased in MDS and malignant stem and progenitor cells. Imetelstat treatment leads to selective loss of such neoplastic cells' ability to maintain telomere length, resulting in inhibition of malignant cell proliferation and induction of apoptosis/senescence leading to the observed reduction of malignant clones (Section 5.3).
Pharmacodynamics	At the recommended dosage of 7.1 mg/kg administered as a 2 hours IV infusion q4w in patients with MDS, imetelstat reduced TA by $\geq 50\%$ from baseline in 60.0% (21/35) of participants compared to 37.5% (9/24) of participants in the placebo group during the first 2 cycles (Study MDS3001).
General Information and PK Properties	
Bioanalysis	Bioanalytical assays were developed and fully validated in compliance with appropriate GLP and have been used to measure plasma concentrations of imetelstat and to detect anti-drug antibodies (ADA) to imetelstat. Imetelstat plasma concentrations were determined using a hybridization enzyme-linked immunosorbent assay (lower limit of quantification of 0.367

	µg/mL to 0.588 µg/mL). ADA against imetelstat were assayed in a three-tiered approach: 1) a screening assay which detected anti-imetelstat antibodies; 2) a confirmatory competition assay to assess the specificity of initial positive screening results; and 3) a titration assay for confirmed positive results to obtain semi-quantitative results for titers of detected ADA.
Exposure and Variability	The geometric mean (CV%) C _{max} is 89.2 µg/mL (27.2%) and AUC _{0-28d} is 554 h*µg/mL (43.4%) for subjects with MDS receiving 7.1 mg/kg imetelstat, based on derived PK parameters from the popPK model (Study MDS3001).
Dose Proportionality	C _{max} and AUC _{0-24h} increased more than dose proportionally over the range of 0.4 to 11.0 mg/kg in subjects with solid tumors and hematologic malignancies (Study CP05-101 and CP14B015) and 19 to 226 mg/m ² in subjects with CLD (Study CP04-151).
Accumulation	No appreciable accumulation is observed in end of infusion (EOI) concentrations after multiple treatment cycles with q4w (Study MDS3001), q3w (MYF2001), or qw dosing frequency (Study CP14B015).
Absorption	
No absorption process is necessary for imetelstat to reach systemic circulation due to administration as an IV infusion.	
T _{max}	Observed near EOI for 2 h infusions in subjects with MDS (Study MDS3001).
Distribution	
Protein Binding	Imetelstat is 94% bound to human plasma proteins (Study GP05-007; Section 5.4).
Organ Distribution	Imetelstat rapidly distributes from plasma to tissue, with the highest concentrations in the liver and kidney followed by bone marrow and spleen (Study GS03-020, Study (b) (4)-493005; Section 5.4).
Volume of Distribution	The geometric mean (CV%) V _{ss} is 11.5 L (26.1%) for subjects with MDS receiving 7.1 mg/kg imetelstat, based on derived PK parameters from the popPK model (Study MDS3001).
Metabolism	
Primary pathway	Imetelstat is likely metabolized into smaller fragments by nucleases in tissues with component fragments excreted in urine (Gaus, 1997 ; Griffey, 1997 ; Crooke, 2000 ; Geary, 2001 ; Yu, 2007 ; Geary, 2009). Hepatic CYP enzymes are not expected to metabolize imetelstat (Geary, 2009 ; FDA, 2022).

Elimination and Excretion	
Half-life	The geometric mean (%CV) apparent $t_{1/2}$ is 4.9 h (45.5%) for subjects with MDS receiving 7.1 mg/kg, based on derived PK parameters from the popPK model (Study MDS3001).
Clearance	For subjects with MDS receiving 7.1 mg/kg imetelstat, clearance (CL) was estimated to be 0.97 L/h from the popPK analysis (Study MDS3001).
Excretion Pathways	Nonclinical studies demonstrated that urine is the primary route of elimination of radiolabeled imetelstat, with 62 to 82% recovery in urine and 12 to 21% recovery in feces by 168 h post-dose (Study (b) (4) -493005, Study GS03-020; Section 5.4). Unchanged imetelstat is not detected in urine of rats administered radiolabeled imetelstat (Study (b) (4) -493007; Section 5.4).
Dosing Considerations	
Intrinsic Factors	Based on popPK analysis, there are no clinically meaningful impacts of age, sex, race, mild or moderate hepatic impairment, or mild or moderate renal impairment on imetelstat PK (Section 6.3.2.3). Therefore, no dose adjustments are warranted for these intrinsic factors. Body weight with theory-based allometric exponents was included as a covariate on imetelstat in the popPK analysis supporting the use of body weight-based dosing for imetelstat (Section 6.3.2.3).
Extrinsic Factors	Imetelstat is not expected to be impacted by food-drug or victim-based drug-drug interactions (Section 6.3.2.4). Imetelstat was evaluated as a perpetrator of drug-drug interactions in vitro. Imetelstat does not induce CYP enzymes, inhibit CYP enzymes, or inhibit P-glycoprotein (P-gp). Imetelstat was found to inhibit the uridine diphospho-glucuronate-glucuronosyltransferase (UGT) 1A1 enzyme and organic anion transporting polypeptide (OATP) 1B1 and OATP1B3 transporters in vitro. Based on an integrated assessment of clinical PK characteristics and safety data, imetelstat is unlikely to cause clinically meaningful drug-drug interactions (Section 6.3.2.4). Therefore, no dose adjustments are warranted for food-drug or drug-drug interactions.
Proarrhythmic Potential	
hERG Inhibition	Imetelstat does not inhibit the hERG channel at concentrations up to 140x unbound C_{max} in subjects with MDS (Study PRE-14-002; Section 5.3.3).
Nonclinical QT Study	In a nonclinical safety pharmacology study in monkeys, there were no treatment-related clinical signs including effects on CNS, mean

	arterial pressure, heart rate, respiration rate, body temperature, electrocardiogram (ECG) activity, or blood gas parameters at imetelstat plasma concentrations $>2.6 \times C_{\max}$ in subjects with MDS (Study GS04-072; Section 5.3.3).
Clinical QT Study	A clinical ventricular repolarization/QTc substudy is ongoing in subjects with MDS under Study MDS3001. Analyses of ECG parameters and the relationship between imetelstat exposure and the QT/QTc interval will be conducted. Results will be provided upon completion of the study with an integrated risk assessment of nonclinical and clinical data to fully characterize the proarrhythmic potential of imetelstat.
Cardiac Safety	Based on review of clinical adverse events of ECG QT prolonged and associated cardiac events across imetelstat-monotherapy treated subjects with hematologic malignancies, no signal of cardiac toxicity with imetelstat treatment has been identified.
Immunogenicity	
Incidence	ADA against imetelstat developed at a generally low frequency in subjects with MDS (16.9%) and MF (20.6%) (Study MDS3001, Study MYF2001). No subjects had pre-existing immunogenicity to imetelstat that was boosted by treatment, and all ADA positive subjects exhibited a treatment-induced ADA response. The median time to onset of ADA was late in treatment at approximately 25 weeks in MF and 38 weeks in MDS (after 8 treatment cycles in each study), and the median peak titer of ADA for subjects with ADA positivity was low in both studies (median titer values of 30 for MDS and 60 for MF).
Clinical Impact	There was no discernable effect of ADA on imetelstat PK (Applicant Figure 47), safety, or efficacy. ADA do not impact the overall benefit/risk profile of imetelstat.

The FDA's Assessment:

The FDA generally agrees with the Applicant on the clinical pharmacology properties of imetelstat with caveats.

- No clinical ADME studies were conducted with imetelstat. The statement that “Imetelstat is likely metabolized into smaller fragments by nucleases” is supported by the available nonclinical data on imetelstat, no PK differences in the limited number of patients with severe renal impairment or hepatic impairment in the imetelstat clinical studies, and literature reports on drugs with similar molecular structures.
- The QT-study report is pending and remains subject to full review upon receipt.

- The use of telomerase activity (TA) as a biomarker for its effect on the treatment of transfusion dependent anemia may not be meaningful. The correlation between TA and TI have not been systemically evaluated throughout the development program. The Applicant claims that supportive evidence of effectiveness comes from $\geq 50\%$ telomerase activity inhibition being observed in 60% (21/35) of patients in the randomized treatment arm of Study MDS3001. However, this was also observed in 37.5% (9/24) of patients in the randomized placebo arm and not maintained in the Part 1 portion of Study MDS3001 (43% or 9/21). In addition, the median reduction in telomerase activity in the placebo group was similar to those reported in the Part 1 portion of Study MDS3001 or at the higher dose levels in the early phase studies in solid tumors. The use of TA data is therefore considered as exploratory and may not a meaningful biomarker to support dose selection for TI.
- Imetelstat is an inhibitor of OATP1B1 and OATP1B3, but does not present a high risk of clinically meaningful DDIs with substrates of these transporters due to the short half-life of imetelstat in conjunction with the once monthly dosing interval (refer to Section 6.3.2.4).

6.3.2. Clinical Pharmacology Questions

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

Data:

Exposure-response analyses for efficacy explored the relationship between the primary efficacy endpoint, proportion of subjects achieving ≥ 8 -week TI, and the key secondary endpoint, proportion of subjects achieving ≥ 24 -week TI, and imetelstat exposure. The analyses utilized efficacy data from the target population [non-del(5q) karyotype and without prior treatment with either hypomethylating agents or lenalidomide] in Phase 2 and Phase 3 of Study MDS3001 alone ([Section 19.4.2.2](#)).

In Study MDS3001, E-R analyses showed a statistically significant positive exposure-efficacy relationship between the proportion of subjects who met the primary efficacy endpoint of ≥ 8 -week TI and imetelstat average concentration up to the time of the event (C_{avg}) ([Applicant Figure 50](#)). In Study MDS3001, E-R analyses showed a statistically significant positive exposure-efficacy relationship between the proportion of subjects who met the key secondary efficacy endpoint of ≥ 24 -week TI and C_{avg} ([Applicant Figure 51](#)).

The Applicant's Position:

Based on totality of data, the Applicant believes the imetelstat clinical pharmacology program together with the efficacy results from Study MDS3001 provides sufficient evidence of effectiveness at the intended registration dosing regimen of 7.1 mg/kg q4w. The results from

exposure-efficacy analyses suggest that imetelstat doses (and accordingly C_{avg}) lower than 7.1 mg/kg q4w may result in reduced clinical efficacy.

The FDA's Assessment:

The clinical pharmacology analyses provided supportive evidence of effectiveness, but the analyses are associated with notable limitations.

- Despite meeting the primary efficacy endpoint in Study MDS3001, essentially only one dose level has been evaluated in the LR-MDS patient population. Limited dose finding in the target patient population from the pivotal study and frequent dose modifications introduces confounding factors that limited the interpretation of exposure-response analyses results on the efficacy endpoint. It is noted that, if the E-R relationship for efficacy could be further validated with additional clinical data, the Applicant could consider alternative dosages with lower doses (e.g., <7.1 mg/kg) and an alternative dosing frequency (e.g., more frequent than Q4W) to explore the possibility of maintaining clinical efficacy while reducing toxicity.
- The early phase studies used overall response as the clinical endpoint, and TA inhibition was used to support dose selection in the early clinical development, using data from mainly patients with myelofibrosis. Overall, this data was used to demonstrate that imetelstat doses lower than 7.1 mg/kg would not achieve sufficient telomerase activity inhibition for response. Changing efficacy endpoints from overall response in early phase studies to 8-week RBC TI in the pivotal study resulted in interpretability issues with dose selection from the early phase studies as a correlation between overall response and RBC TI has not been established.
- Hematology labs were not consistently collected in the early phase studies that evaluated multiple dosages in solid tumors, myelofibrosis, and other diseases, and a lack of time course data in hematology labs hinders analysis of a dose-response relationship at alternative dosages that are pertinent to MDS.

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

Data:

Justification of the 7.1 mg/kg q4w dosing regimen is supported by the observed clinical efficacy and safety results from the pivotal, randomized placebo-controlled Phase 3 study MDS3001, and the supportive MDS3001 Phase 2 study, the cumulative available data on imetelstat clinical PK and target engagement, and results from comprehensive E-R analyses, along with supportive nonclinical studies. The key rationale for the imetelstat dosing regimen in patients with LR MDS is as follows:

- Efficacy results from the Phase 3 of Study MDS3001 confirmed the treatment benefit of imetelstat demonstrating superiority of imetelstat 7.1 mg/kg q4w over placebo in the LR MDS population.
 - Clinical dose intensity analysis demonstrated that >75% of subjects received 7.1 mg/kg q4w at the time of onset of 8-week TI, and for subjects treated with imetelstat in the Phase 3 study, mean relative dose intensity was >95% and >93% in the period of time leading up to the achievement of 8-week TI and 24-week TI, respectively.
- Safety results from the Phase 3 of Study MDS3001 demonstrated a manageable safety profile that is consistent with Phase 2 and the imetelstat clinical program.
 - Dose intensity analyses showed that >90% mean relative dose intensity with respect to the 7.1 mg/kg q4w dosing regimen was achieved over the treatment period for all subjects, despite dose modifications which occurred as mandated per protocol.
 - While neutropenia and thrombocytopenia are frequent with imetelstat treatment, these cytopenias were largely based on changes in laboratory values and were transient, with the majority of subjects recovering within the 4-week dosing schedule. Of clinical importance, severe infections or bleeding occur at low rates that are similar to those in the placebo arm.
- E-R analyses from the Phase 3 of Study MDS3001 support the imetelstat 7.1 mg/kg q4w dose and dosing regimen.
 - Exposure-efficacy analysis demonstrated a statistically significant positive E-R relationship for 8-week TI rate and 24-week TI rate.
 - Exposure-safety analysis demonstrated no significant E-R relationship for Grade 3/4 neutropenia and a positive E-R relationship for Grade $\geq$ 3 thrombocytopenia (statistically significant for $C_{\max}$ and approaching significance for AUC).
 - Investigations of toxicity in identified subpopulations in MDS3001 Phase 2 and Phase 3 with potentially higher imetelstat exposure showed no clear trends between incidence of Grade $\geq$ 3 thrombocytopenia and increasing body weight quartiles or between sex. These analyses support that these subpopulations are not expected to be at increased risk of Grade 3/4 thrombocytopenia, and along with low rates of high-grade bleeding events in MDS patients in Study MDS3001, support the limited clinical impact of the characterized exposure-safety relationships.
 - E-R analyses showed no significant E-R relationship between subjects recovering from Grade 3/4 neutropenia or thrombocytopenia and imetelstat exposure in MDS3001 Phase 2 and Phase 3 with more subjects recovering within 4 weeks compared to 2 weeks, supporting the 4-week schedule.

- Finally, the popPK analysis incorporated body weight with theory-based allometric exponents as a covariate contributing to imetelstat PK variability, supporting the imetelstat body weight-based dosing approach.

The Applicant's Position:

The intended registration dosing regimen of 7.1 mg/kg q4w for imetelstat is appropriate for patients with LR MDS. This is supported by the clinical efficacy, safety, PK, and E-R relationships along with the supportive nonclinical data demonstrating a favorable benefit/risk profile in the LR MDS population.

The FDA's Assessment:

Given the high rates of grade 3 AEs and dose interruptions and modifications, it is unclear whether a lower dose or an alternative regimen may provide similar efficacy with reduced rates of AEs or dose modifications. Consequently, further dose optimization is warranted.

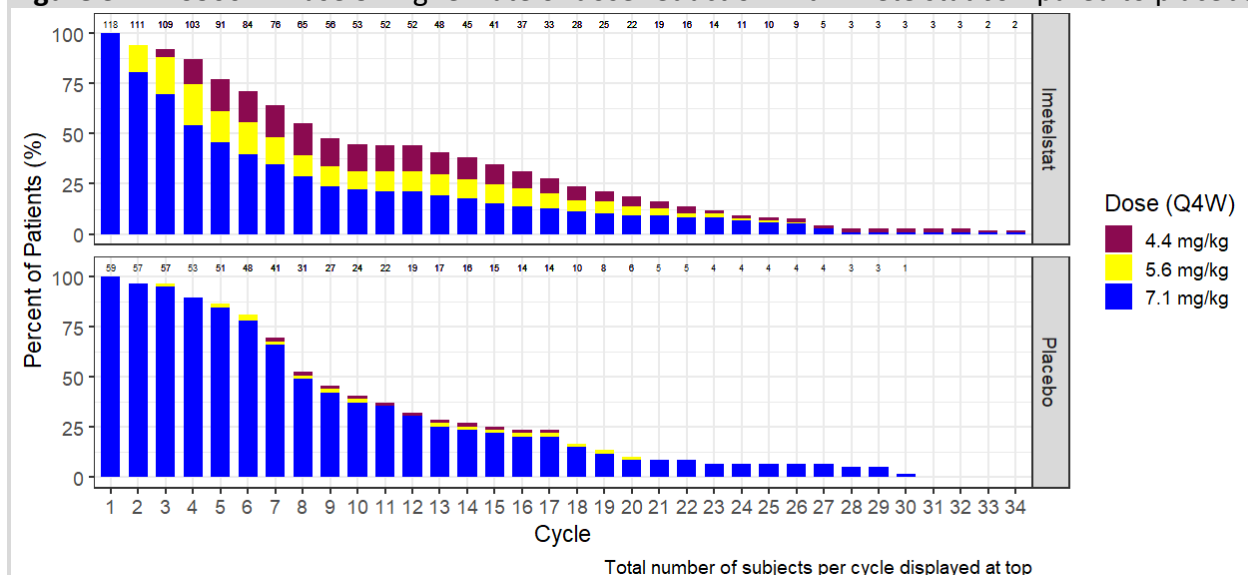
- There is limited dose exploration in patients with LR-MDS. While imetelstat doses of 0.4 mg/kg to 11.7 mg/kg, alone or in combination with other agents, and dosing schedules from weekly to every 4 weeks have been explored in a variety of indications throughout the drug development program, dosages lower than 7.1 mg/kg Q4W have not been explored in the context of MDS.
- There was a high rate of dose modifications with imetelstat compared to placebo in Study MDS3001, as shown in Table 11 and Figure 3 below. The reviewers noted that high rates of dose reduction and dose modification indicate safety and tolerability issues at the proposed dosing regimen, whereas dose intensity may not be a sensitive indicator for safety concerns (e.g., a treatment that results in rapid dose modification or a calculation using an early cutoff date can yield high dose intensity despite of high dose modification rate).

Table 11: MDS3001-Phase 3: High dose modification rate with imetelstat compared to placebo

	Imetelstat (N=118)	Placebo (N=59)
Dose delay by >3 days	73%	30.5%
Dose delay by >7 days	64%	22%
Dose reduction due to AE	49%	7%
Infusion interrupted, decreased rate, or aborted due to AE	6%	0
Discontinuation due to AE	14%	0

Source: FDA analysis using ADEX dataset; Data cutoff 13 October 2022

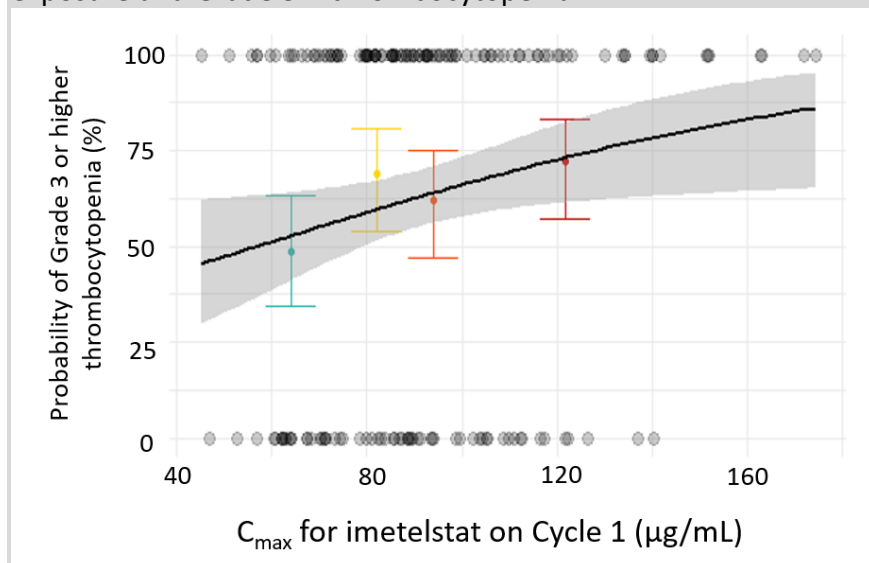
Figure 3: MDS3001-Phase 3: Higher rate of dose reduction with imetelstat compared to placebo



Source: FDA analysis using ADEX dataset; Data cutoff 13 October 2022

- There are high rates of Grade 3/4 TEAEs, particularly thrombocytopenia and neutropenia, in the imetelstat arm in Study MDS3011. The E-R analysis indicates that higher imetelstat Cycle 1 C_{max} is associated with higher incidence of Grade 3/4 thrombocytopenia in patients with LR-MDS patients (Figure 4). The positive E-R relationships for Grade 3/4 thrombocytopenia is also observed in the pooled analysis in pooled datasets including data from other studies. This relationship can also be verified through interventions, where 18% of patients receiving imetelstat required platelet transfusions on treatment (median: 1 transfusion, range: 1 to 10) compared to 3% of patients receiving placebo. This finding suggests that the starting dose and regimen of imetelstat are too high and may be further optimized.

Figure 4: MDS3001-Phase 3: Positive exposure-response relationship between imetelstat exposure and Grade 3-4 thrombocytopenia



Source: FDA analysis using ER_THR.csv dataset; Data cutoff 13 October 2022

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g., race, ethnicity, age, performance status, genetic subpopulations, etc.)?

Data:

Age

The popPK analysis included subjects ranging from 21 to 87 years (median 67 years). No effect of age was identified on imetelstat PK ([Section 19.4.1](#)).

Sex

PopPK analysis identified sex as a significant covariate on imetelstat CL with a limited effect on estimated C_{max} and AUC for females relative to males (increase of ≤30%) ([Section 19.4.1](#), [Applicant Figure 48](#)). Overall, the effect of sex on imetelstat exposure is not expected to be clinically relevant as the size of the effect is within the between-subject variability in imetelstat PK. Supportive of this, there is no evidence of increased toxicity (Grade 3/4 neutropenia or thrombocytopenia) in females in Study MDS3001 ([Section 19.4.2.4](#)).

Race

There was no effect of race on imetelstat PK identified in the popPK analysis, for which race was categorized as White/Caucasian versus all others (Black/African American, Asian, Other) based on the distribution of data (80.7% (342/424) of subjects were White; [Section 19.4.1](#)). The

observed distribution of race in the popPK dataset reflects the overall incidence of MDS, which is most prevalent in individuals who are white (Neukirchen, 2011; Ma, 2012; Visser, 2012).

Body Weight

Body weight with theory-based allometric exponents was included as a covariate on imetelstat V_c , CL, and transfer rate from the central to the peripheral compartment (K_{back}) in the popPK analysis, which included subjects ranging from 44 to 161 kg (median 75 kg). Using body-weight-based dosing, there is limited exposure variation expected for subjects with low body weight (52 kg) or high body weight (107 kg) compared to a reference subject of 70 kg (Section 19.4.1, Applicant Figure 48).

Hepatic Impairment

The effect of hepatic impairment on imetelstat PK was assessed in the popPK analysis using National Cancer Institute (NCI)- Organ Dysfunction Working Group (ODWG) hepatic function category, with categories assessed as normal function (N = 256), mild impairment (N = 119), combined moderate or severe impairment (N = 27, including N = 24 with moderate impairment and N = 3 with severe impairment), and missing (N = 22), based on the distribution of data. There was no evidence for differences in imetelstat CL across hepatic function categories (Section 19.4.1, Applicant Figure 45).

Renal Impairment

The effect of renal impairment on imetelstat PK was assessed in the popPK analysis using categorical renal function and continuous creatinine clearance (CrCL) as covariates. Renal function categories were assessed as normal function (N = 156), mild impairment (N = 147), and combined moderate or severe impairment (N = 121, including N = 115 moderate impairment and N = 6 severe impairment). There was no evidence for differences in imetelstat CL across renal function categories or across CrCL values (Section 19.4.1, Applicant Figure 46).

The Applicant's Position:

Given the totality of the data based on results from the imetelstat popPK analysis, together with subgroup analysis for the efficacy and safety, no dose adjustments are required for sex, age, race, mild to moderate hepatic impairment, or mild to moderate renal impairment. There is limited information on the effect of severe hepatic impairment, severe renal impairment, or end-stage renal disease on imetelstat PK. The use of the body-weight-based dosing approach for imetelstat is supported by available clinical data.

The FDA's Assessment:

The FDA agrees that no therapeutic individualization of imetelstat is needed based upon intrinsic factors from popPK modeling such as age, sex, race (81% White, 4% Asian, 7% Black, 8% other/unknown), mild to moderate renal impairment (CrCL 30 to < 90 mL/min), mild hepatic

impairment (total bilirubin $\leq$ ULN and AST $>$ ULN, or total bilirubin $>$ 1x to 1.5x ULN and any AST), or moderate hepatic impairment (total bilirubin $>$ 1.5x to 3x ULN and any AST). Dedicated PK studies have not been conducted in patients with severe renal impairment (CrCL $<$ 30 mL/min) or severe hepatic impairment (total bilirubin $>$ 3x ULN and any AST). However, 4 patients with severe hepatic impairment and 14 patients with severe renal impairment (creatinine clearance $>$ 20 mL/min) were included in the population PK analysis and the analysis does not suggest meaningful differences in PK exposure. Refer to Section 19.4.1.

In the patients with severe renal or hepatic impairment in Study MDS3001, the incidence rate of Grade 3/4 thrombocytopenia was not higher than those in the general population. Considering that imetelstat is not designed to target liver or kidney and is likely broken down into small fragments by nucleases, no additional PK studies in patients with severe renal or hepatic impairment are warranted.

Additionally, no dose adjustment is needed based on SF3B1 mutational status. Refer to Section 19.4.3 for details.

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

Data:

Food Effect

Imetelstat is not susceptible to food-drug interactions because it is administered via IV infusion.

Victim Drug-Drug Interactions

Imetelstat, like other ODNs, is likely metabolized into smaller fragments by nucleases in tissues and the component fragments are excreted in urine ([Section 5.4](#), ([Gaus, 1997](#); [Griffey, 1997](#); [Crooke, 2000](#); [Geary, 2001](#); [Yu, 2007](#); [Geary, 2009](#))). Hepatic CYP enzymes are not expected to metabolize ODNs, and modulation of drug transporters is not expected to impact PK of ODNs ([Geary, 2009](#); [FDA, 2022](#)).

Perpetrator Drug-Drug Interactions

CYP Induction: Imetelstat does not induce the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4 in vitro (Study 303-1160).

CYP Inhibition: Imetelstat causes little to no inhibition of CYP2C8, CYP1A2, CYP2B6, CYP2E1, CYP2C9, CYP2C19, CYP2D6, or CYP2C8 in hepatocytes (Study FK12087, Study FK11110).

Imetelstat does not cause time-dependent inhibition of CYP enzymes ([Kazmi, 2019](#)).

UGT Inhibition: Imetelstat inhibits UGT1A1 in human liver microsomes with a R value that exceeds the threshold for further evaluation (Study XT135035). However, this result is likely an artifact of the test system due to nonspecific effects in human liver microsomes (HLMs), as seen

for imetelstat with CYP enzymes in HLMs and as reported for other ODNs for enzyme inhibition assays in this test system (Kazmi, 2018).

Transporter Inhibition: Imetelstat does not inhibit P-gp in vitro (Study 18019). Imetelstat inhibits OATP1B1 and OATP1B3 with R values that exceed the threshold for further evaluation (Study XT138038). In vitro studies to assess whether imetelstat inhibits BCRP, BSEP, OAT1, OAT3, OCT1, OCT2, multidrug and toxin extrusion protein (MATE) 1, and MATE2-K are ongoing. Clinical Evaluations: Imetelstat is dosed infrequently (q4w) and rapidly cleared from plasma ($t_{1/2}$ of 4.9 hours), there are no clinically relevant elevations in the OATP1B1/OAT1P1B3 and UGT1A1 endogenous substrate bilirubin in imetelstat-treated subjects compared to placebo in MDS, and there is no indication of altered safety profiles when imetelstat is administered with concomitant substrates of OATP1B1/OATP1B3 (statins) or UGT1A1 (deferasirox) in subjects with MDS.

The Applicant's Position:

Consistent with other ODNs, imetelstat has limited risk of clinically relevant DDIs based on nonclinical data and an integrated assessment of PK characteristics and clinical data. Dose adjustments for food-drug, victim-based drug-drug interactions, or perpetrator-based drug-drug interactions are not necessary for imetelstat.

The results of the ongoing in vitro study to assess potential for imetelstat to inhibit additional drug transporters will be provided within 60 days of submission of the NDA.

The FDA's Assessment:

The FDA generally agrees with the Applicant that there is a low risk of clinically meaningful DDIs. The study report for XT228134 that evaluated in vitro BCRP, BSEP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1, and MATE2-K inhibition was submitted on 8/8/2023. The results indicate that imetelstat is an inhibitor of OATP1B1 and OATP1B3, with R values greater than the guidance recommended cutoff value of 1.1. However, the review team agrees that the short half-life of imetelstat in conjunction with the once monthly dosing interval would not produce meaningful DDIs with substrates of these transporters.

X

X

Primary Reviewer

Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

The efficacy of imetelstat for patients with LR MDS that is relapsed after, refractory to or ineligible for ESA therapy, is supported by the Phase 2/3 study, MDS3001, using the cutoff date of 13 October 2022, which is one year from the last patient randomized (primary analysis). This application summarizes the key efficacy results from the randomized, double-blind, placebo-controlled, Phase 3 Study MDS3001 (pivotal). Efficacy results from the Phase 2 open label portion of Study MDS3001, with a focus on the subset of subjects without the del(5q) cytogenetic abnormality and without prior treatment with either lenalidomide or HMAs (referred to as non-del(5q) and lenalidomide/HMA-naïve; N = 38), are also be provided as supportive evidence of efficacy where relevant.

The overall evaluation of safety summarized in the Summary of Clinical Safety (SCS), presents the safety from the MDS3001 Phase 3 study (Group A), and the combined Phase 2 and Phase 3 LR MDS population (Group B). An additional safety group (Group C), includes pooled data from 5 clinical studies of imetelstat as monotherapy in hematological malignancies, including 4 completed Phase 2 studies and the pivotal MDS3001-Phase 3 study for a total of 450 subjects, of which 391 were treated with imetelstat monotherapy and 59 were treated with placebo as outlined in [Applicant Table 41](#).

A listing of studies in support of efficacy and safety is provided in [Applicant Table 12](#).

Applicant Table 12: Studies Included in Pooled Safety Analyses for the Summary of Clinical Safety

Phase	Study ID	Protocol Title	Number of Centers	Subjects Enrolled (Planned/ Actual)	Subjects Treated with Imetelstat	Design/Control	Starting Dose and Schedule of Imetelstat ^d	Study Duration	Sex (M/F) Age (range) Race	Study Status
Controlled Studies										
2/3	MDS3001	A Study to Evaluate Imetelstat (GRN163L) in Transfusion-Dependent Subjects with IPSS Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS) that is Relapsed/ Refractory to Erythropoiesis-Stimulating Agent (ESA) Treatment	77	2:1 Imetelstat monotherapy: Placebo <u>Imetelstat</u> Planned: 115 Actual: 118 <u>Placebo</u> Planned: 55 Actual: 60	Imetelstat monotherapy: 118 Placebo: 59	Phase III, double blind, randomized, placebo-controlled, multicenter study of imetelstat or placebo in transfusion-dependent subjects with low or intermediate-1 risk MDS that is relapsed/refractory to ESA treatment	7.1 mg/kg IV every 4 weeks ^a	11Sep2019 to Primary analysis CCO = 13Oct2022	M: 111 F: 67 (39 to 87 yrs) White (80%)	Ongoing
Uncontrolled Studies										
2	MDS3001	A Study to Evaluate Imetelstat (GRN163L) in Transfusion-Dependent Subjects with IPSS Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS) that is Relapsed/ Refractory to Erythropoiesis-Stimulating Agent (ESA) Treatment	48	Planned: 55 Actual: 57	Imetelstat monotherapy : 57	Phase II, single arm open label, multicenter study of imetelstat in transfusion dependent subjects with low or intermediate-1 risk MDS that is relapsed/refractory to ESA treatment	7.1 mg/kg IV every 4 weeks ^a	11Dec2015 to Primary analysis CCO = 13Oct2022	M: 32 F: 25 (46 to 83 yrs) White (81%)	Ongoing

NDA/BLA Multi-disciplinary Review and Evaluation NDA 217779 imetelstat
 TRADENAME, imetelstat

Phase	Study ID	Protocol Title	Number of Centers	Subjects Enrolled (Planned/ Actual)	Subjects Treated with Imetelstat	Design/Control	Starting Dose and Schedule of Imetelstat ^d	Study Duration	Sex (M/F) Age (range) Race	Study Status
2	CP14B013	A Phase II Trial to Determine the Effect of Imetelstat (GRN163L) on Patients with Previously Treated Multiple Myeloma	2	Planned: 32 Actual: 13	Imetelstat monotherapy: 9 Imetelstat combination: 4 ^b	Phase II, open label study to determine the rate of improvement in response of subjects with previously treated multiple myeloma to imetelstat alone or in combination with lenalidomide maintenance therapy	7.1 mg/kg or 8.9 mg/kg over 2 hours on Days 1, 8 every 28 days	28Feb2011 to 04Sep2014	M: 5 F: 8 (40 to 68 yrs) White (62%) Black or African American (39%)	Completed CCO = 20Nov2014
2	CP14B015	A Phase II Trial to Evaluate the Activity of Imetelstat (GRN163L) in Patients with Essential Thrombocythemia or Polycythemia Vera who Require Cytoreduction and Have Failed or Are Intolerant to Previous Therapy, or who Refuse Standard Therapy	7	Planned: ~20 Enrolled: 21	Imetelstat monotherapy: 20	Phase II, open label study of single agent imetelstat in subjects with ET or PV who had failed or were intolerant to at least one prior therapy or who refuse standard therapy	7.1-8.9 mg/kg over 2 hours weekly or as needed based on hematologic response/toxicity ^c	14Jan2011 to 06Jan2015	M: 9 F: 11 (21 to 83 yrs) White (90%) Black or African American (10%)	Completed

Version date: June 2022 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

NDA/BLA Multi-disciplinary Review and Evaluation NDA 217779 imetelstat
 TRADENAME, imetelstat

Phase	Study ID	Protocol Title	Number of Centers	Subjects Enrolled (Planned/ Actual)	Subjects Treated with Imetelstat	Design/Control	Starting Dose and Schedule of Imetelstat ^d	Study Duration	Sex (M/F) Age (range) Race	Study Status
2	CP14B019 (formerly MC1285)	A Pilot Open-Label Study of the Efficacy and Safety of Imetelstat (GRN163L) in Myelofibrosis and other Myeloid Malignancies	1	Planned: up to 148 Actual: 80	Imetelstat monotherapy: 80	Phase II, open label, single center, Phase 2 multicohort study to evaluate imetelstat in myelofibrosis and other myeloid malignancy subjects including MDS	Starting dose and schedule: 7.1 or 8.9 mg/kg over 2 hours every 3 or 4 weeks; 8.9 mg/kg weekly allowed for Cycle 1 in Arm B.	29Oct2012 to 24May2018	M: 54 F: 26 (45 to 93 yrs) White (93%)	Completed
2	MYF2001	A Randomized, Single-Blind, Multicenter Phase 2 Study to Evaluate the Activity of 2 Dose Levels of Imetelstat in Subjects with Intermediate-2 or High-Risk Myelofibrosis (MF) Relapsed/Refractory to Janus Kinase (JAK) Inhibitor	115	Planned: 200 Actual: 107	Imetelstat monotherapy: 107	Phase II, open label, multicenter study to evaluate the safety and efficacy of imetelstat with two different dose levels for the treatment of MF who had been previously treated with a Janus Kinase (JAK) inhibitor	8.9 or 4.4 mg/kg IV every 3 weeks	28Aug2015 to 26Apr2018	M: 67 F: 40 (31 to 86 yrs) White (82%)	Completed

^a Dose in Study MDS3001 could be elevated to 8.9 mg/kg (free acid)^d prior to Amendment 2 (see MDS3001 CSR [Phase 3]/[Section 9.8.1](#)).

^b Combination therapy subjects from Study CP14B013 are not included in Safety analyses.

^c Dose in Study CP14B015 could be elevated to 11.0 mg/kg.(free acid)^d

^d In the clinical study reports (CSRs), study drug doses are expressed as milligrams of imetelstat sodium (the active substance), a salt of imetelstat. Doses in this table are shown for the active moiety (free acid). To convert a quantity of imetelstat salt to the equivalent quantity of imetelstat, a factor of 0.9416 based on relative molar mass of the free acid form (4610 g/mol) to the sodium salt (4896 g/mol; 4610/4896 = 0.9416) is applied (i.e., 1 mg imetelstat sodium = 0.9416 mg imetelstat).

CCO = clinical cutoff date; ET = essential thrombocythemia; F = female; GRN163L = imetelstat; IPSS = International Prognostic Scoring System; IV = intravenous; M = male; PV = polycythemia vera.

Version date: June 2022 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

The Applicant's Position:

The primary study supporting the evaluation of efficacy in this application is the MDS3001-Phase 3 study, which compared the efficacy of imetelstat at the 7.1 mg/kg q4w dose (equivalent to 7.5 mg/kg imetelstat-sodium) with placebo in terms of RBC TI and alleviation of anemia. The Phase 3 MDS3001 study is supported by the Phase 2 MDS3001 study and a high degree of consistency was observed for the efficacy and safety data across both studies. A detailed description of the results is provided in the sections below.

The FDA's Assessment:

FDA agrees with the Applicant's position that the primary study supporting the evaluation of efficacy in this application is the MDS3001-Phase 3 study. The MDS3001-Phase 2 study is considered supportive. Other studies that examine the use of imetelstat in conditions other than MDS and doses other than that used in MDS3001 are used as supportive data when assessing safety.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

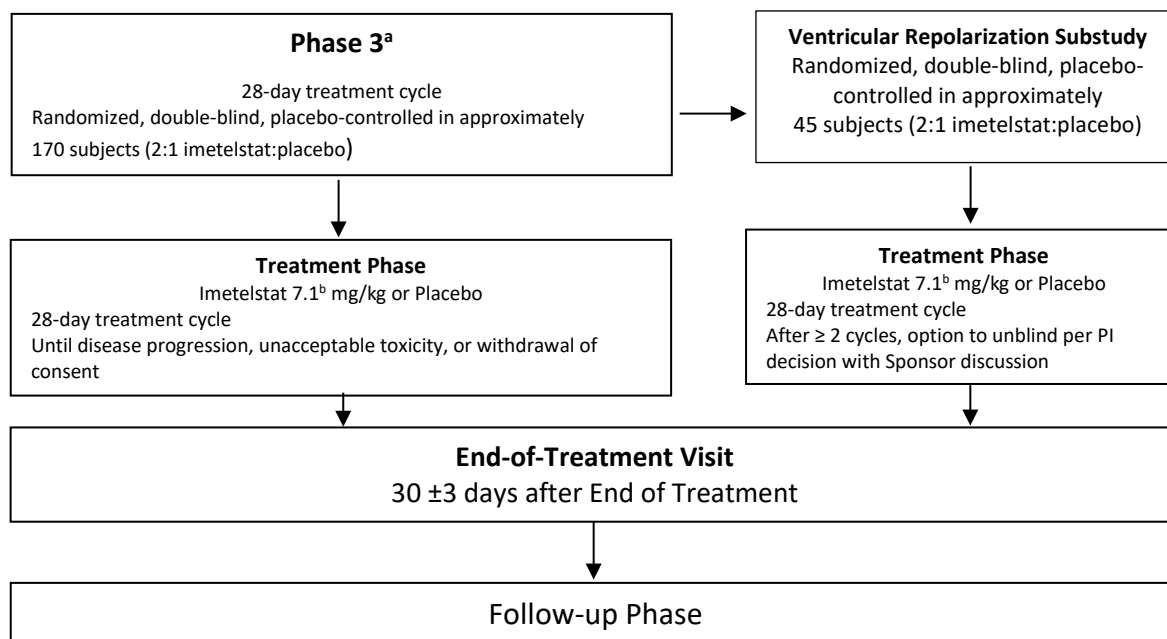
8.1.1. Pivotal Study in Support of Efficacy of Imetelstat – Study MDS3001

Trial Design

The Applicant's Description:

Study MDS3001 is a global 2-part, multicenter, Phase 2/3 study of imetelstat in transfusion-dependent subjects with International Prognostic Scoring System (IPSS) low or intermediate-1 risk MDS that is relapsed/refractory to or ineligible for ESA treatment. Part 2 (hereafter referred to as MDS3001-Phase 3 study) is a Phase 3 double-blind, randomized study to compare the efficacy of imetelstat with placebo ([Applicant Figure 5](#)) and provides the pivotal efficacy and safety data for this NDA submission. Part 1 (hereafter referred to as MDS3001-Phase 2 study) is a Phase 2, open-label, single-arm study to assess the efficacy and safety of imetelstat and provides strongly supportive data to Phase 3.

Applicant Figure 5: Schematic Overview of the Study



^a. Supportive care, including transfusions or myeloid growth factors, is to be administered as needed per investigator discretion and according to local standard practices.

^b. Dose based on active moiety (free acid), which is equivalent to 7.5 mg/kg imetelstat-sodium.

The primary objective of the Phase 3 study was to compare the efficacy, in terms of RBC TI, of imetelstat to placebo. Key secondary objectives included safety, time to and duration of RBC TI, ≥ 24 -week TI, and rate of hematologic improvement.

The choice of placebo as a comparator, randomized study design and primary endpoint for Phase 3 was discussed and agreed upon with FDA as outlined in [Section 3](#).

Choice of placebo control:

Blinded placebo-controlled study design provides the best opportunity for a rigorous demonstration of efficacy and safety, with the least potential for bias. At the time of study initiation there was no standard of care for transfusion-dependent LR-MDS patients who were relapsed or refractory to ESAs. The use of placebo control was also consistent with other ongoing Phase 3 studies at that time in subjects with LR MDS, including studies investigating the safety and efficacy of luspatercept, lenalidomide, and oral azacitidine. To ensure integrity of the blind, imetelstat and placebo were provided to the site in matching vials with blinded labels, had similar reconstitution characteristics, were administered IV in same way, and required premedication. Subjects in both treatment groups received supportive care in addition to study drug.

Randomization and stratification:

Randomization and stratification were used in the Phase 3 study to minimize bias in the assignment of subjects to treatment groups (per FDA guidance for studies where evidence of clinical benefit using symptom endpoints are assessed), to increase the likelihood that subject attributes (e.g., demographic and baseline characteristics) are evenly balanced across treatment groups, and to enhance the validity of statistical comparisons across treatment groups. The 2:1 randomization scheme was chosen to limit the number of subjects in the placebo group, to increase the likelihood of subjects receiving active treatment with imetelstat, and to study the safety of imetelstat in a larger cohort.

Choice of Efficacy Endpoints

The primary endpoint was achievement of ≥ 8 -week TI and achieving ≥ 24 -week TI was a key secondary endpoint. Transfusion independence is a relevant measure of efficacy in LR MDS as it targets the most common symptom of the disease (transfusion-dependent anemia) and as such indicates clinical benefit in this patient group. The use of TI as a primary endpoint was discussed and agreed with FDA during Type C meeting in 2017 (see [Section 3](#)) and in accordance with feedback from FDA, comprehensive transfusion history for patients was collected pre-study (up to 16 weeks) to establish baseline transfusion burden and actively assessed and documented in the electronic Case Report Form (eCRF) at every study visit. In addition, intense data monitoring at the clinical sites was implemented to ensure the rigor of the data, and the process for

handling missing data was prespecified in the MDS3001 statistical analysis plan (SAP) which was submitted to FDA. Transfusion independence has also formed the basis of approval for other products in similar lower risk MDS disease settings.

Achievement of hematologic improvement-erythroid (HI-E), including reduction in transfusion burden, and cytogenetic response are established endpoints in LR MDS per International Working Group (IWG) response criteria. Decrease of mutation burden and improvement in measures of fatigue by Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue questionnaire may be considered additional measures of efficacy in LR MDS.

Safety assessments for the MDS3001 Phase 2 and Phase 3 studies include incidence, intensity, and type of adverse events (AEs), vital signs measurements, clinical laboratory values, ECG changes, and deaths, all of which are standard endpoints for evaluating the safety of new treatments.

Trial Location

Study MDS3001 was conducted globally in 17 countries in North America, European Union (EU) and Rest of World (ROW).

Dose Selection

In the clinical study reports (CSRs), study drug doses are expressed as milligrams of imetelstat sodium (the active substance), a salt of imetelstat. To convert a quantity of imetelstat salt to the equivalent quantity of imetelstat, a factor of 0.9416 based on relative molar mass of the free acid form (4610 g/mol) to the sodium salt (4896 g/mol; $4610/4896 = 0.9416$) is applied (ie, 1 mg imetelstat sodium = 0.9416 mg imetelstat).

Data from nonclinical, PK, pharmacodynamic, and clinical studies across the imetelstat clinical program were utilized to inform the MDS dosing schedule.

In the Phase 2 pilot study of imetelstat in MF and other myeloid malignancies (Study CP14B019), subjects with MDS or MDS/ myeloproliferative neoplasms (MPN) overlap received a starting imetelstat dose of 7.1 mg/kg imetelstat (equivalent to 7.5 mg/kg imetelstat-sodium) every 4 weeks. Subsequent doses were adjusted based on investigator assessment of toxicity and clinical response, resulting in individualized regimens that included 5.6 mg/kg imetelstat (equivalent to 6.0 mg/kg imetelstat-sodium), 7.1 mg/kg and 8.9 mg/kg imetelstat (equivalent to 9.4 mg/kg imetelstat-sodium) every 4 weeks. Prolonged thrombocytopenia or neutropenia were not observed in the MDS cohort.

In addition, the PK/pharmacodynamic relationship across the imetelstat clinical program suggested that a dose of 7.1 mg/kg provides optimal target engagement. In the Phase 2 study MYF2001 in MF, PK exposure was correlated with pharmacodynamic effect, so that a higher

percentage of subjects in the highest exposure quartile for imetelstat achieved optimal pharmacodynamic effect ($\geq 50\%$ reduction in TA or hTERT) compared to subjects in the lower exposure quartiles, indicating exposure-dependent on-target activity of imetelstat. In that study, $\geq 50\%$ reduction in TA or hTERT by imetelstat correlated with clinical benefits, including OS (Mascarenhas, 2021).

The estimated TA change at median C_{max} of 7.1 mg/kg in Study MDS3001 Phase 2 was similar to that obtained in the 8.9 mg/kg dose arm of Study MYF2001, indicating optimal target engagement.

This was consistent with the observed clinical benefit/risk profile in study MYF2001 and the Phase 2 study MDS3001, where data showed that greatest benefit, including TI, was achieved during treatment with 7.1 mg/kg before any dose modifications or dose escalation. The safety profile was acceptable and manageable and the observed Grade 3/4 cytopenias were reversible to Grade 2 or less within 4 weeks.

Based on the available data, the proposed starting dose of 7.1mg/kg imetelstat every 4 weeks in the Phase 3 MDS3001 study was discussed and agreed with FDA as part of the Type C meeting in June 2017 and subsequent interactions.

Treatment Assignment

Subjects were randomly assigned 2:1 to receive either imetelstat or placebo. Randomization was based on a computer-generated randomization schedule prepared before the study by or under the supervision of the Sponsor. Randomization was stratified by prior RBC transfusion burden (≤ 6 or > 6 units RBC) and by IPSS risk group (low versus intermediate-1). Prior RBC transfusion burden is defined as the maximum number of RBC units transfused over an 8-week period during the 16 weeks prior to randomization. Pre-transfusion Hb should have been ≤ 9.0 g/dL to count toward the 4 units total unless there was a clinical rationale for transfusing at a higher Hb level.

Blinding

Geron personnel with direct management of the study sites (with the exception of Geron Clinical Drug Supply Management and Geron Pharmacovigilance Team), the Geron and contract research organization (CRO) study teams, the Investigator, the study site personnel, and the subject remained blinded to each patient's treatment. The investigator was not provided with randomization codes. The codes were maintained within the Interactive Web Response System, which had the functionality to allow the investigator to break the blind for an individual subject. Data that had the potential to unblind the treatment assignment (ie, study drug plasma concentrations) were handled with special care to ensure that the integrity of the blind was maintained and the potential for bias minimized. To that end, imetelstat and placebo were

provided to the site in matching vials with blinded labels, had similar reconstitution characteristics, were administered IV in same way and both required pre-medication.

Dose Modifications

Study drug dose delay or reduction for Grade 3 or Grade 4 toxicities observed at the time of the planned dose of the next cycle was instituted as needed, as described below. These instructions were not applicable when toxicities occurred mid-cycle and subsequently resolved to Grade < 3 by the time of the next planned dose. Imetelstat could have been held for up to 28 days from the expected start date of the scheduled cycle; a hold > 28 days had to be reviewed and approved by the Sponsor.

The starting dose was 7.1mg/kg of imetelstat (equivalent to 7.5 mg/kg of imetelstat sodium) IV every 4 weeks. Subjects were allowed 2 dose reductions to 5.6mg/kg (equivalent to 6.0 mg/kg imetelstat sodium) q4w and 4.4mg/kg (equivalent to 4.7 mg/kg imetelstat sodium) q4w. All dose modifications were recorded in the Dosage Administration eCRF.

Premedication

All subjects who received an infusion of study drug had to be premedicated with an antihistamine (diphenhydramine 25 to 50 mg or equivalent) and a corticosteroid (hydrocortisone 100 to 200 mg or equivalent), either IV or orally. Premedications were administered per local standard of care approximately 1 hour prior to study drug infusion. If per investigator's discretion premedication(s) was/were contraindicated for a subject, modifications were to be reviewed and approved by the Sponsor's medical monitor. It was recommended that subjects be monitored for at least 1 hour after the infusion was completed.

Concomitant Medications

Subjects received supportive care as clinically indicated. This included blood product support (transfusions and use of myeloid growth factors [eg, granulocyte-colony stimulating factor], to be administered as needed per investigator discretion and according to local standard practices), iron chelation therapy, anti-diarrheals, anti-emetics, analgesics, antibiotic treatment, and treatment of other medical conditions.

The following medications were prohibited during the study: ESA therapy, chemotherapy (anti-cancer/hypomethylating agents) including any anti-MDS therapy, immunomodulatory drugs (eg, lenalidomide), immunotherapy, experimental therapy, and radiotherapy. Systemic use of corticosteroids in excess of prednisone 20 mg/day or its equivalent for more than 10 days was prohibited unless reviewed and approved by the Sponsor's medical monitor. Long-term, chronic use of corticosteroids at any dose was also to be reviewed and approved by the Sponsor's medical monitor. Corticosteroids used as premedication were permitted.

Procedures and Evaluations

The Phase 3 study consisted of 3 phases: a Screening Phase of up to 28 days during which subject eligibility was reviewed and approved by the Sponsor prior to randomization; a

Treatment Phase that extended from Cycle 1 Day (D) 1 until disease progression or unacceptable toxicity, or withdrawal of consent; and a Post-treatment Follow-up Phase which continues until death, loss to follow-up, withdrawal of consent, or the End of the Study (whichever occurs first). The End of the Study is defined as 2 years after the randomization of the last subject in the main Phase 3 study or anytime the Sponsor terminates the study, whichever comes first. In addition, subjects are continuing in survival follow-up as part of an extension phase, until 5 years from the first dose of imetelstat or after 3 years of post-treatment follow-up (MDS3001 Protocol Amendment 8, Section 9.1.6).

Efficacy was evaluated by the proportion of subjects achieving RBC TI lasting at least any consecutive 8-week and 24-week period, starting from Study Day 1 until subsequent anti-cancer therapy, if any. Study Day 1 for Phase 3 was defined as the day of randomization. Efficacy evaluation also included time to the 8-week or 24-week RBC TI, duration of RBC TI, rate of HI-E per modified IWG 2006 and revised IWG 2018, rates of CR, PR, or mCR per modified IWG 2006, OS, PFS, time to progression to AML, amount and relative change in units of RBC transfusions, rate of myeloid growth factors usage, and medical resource utilization. Exploratory efficacy variables included measurements of telomere length (TL), TA and hTERT, cytogenetic and mutation status, and PROs. Pharmacokinetic parameters and immunogenicity of imetelstat were also assessed.

Safety was evaluated by analysis of the incidence, intensity, and type of treatment-emergent adverse events (TEAEs), vital signs measurements, clinical laboratory values, ECGs, and deaths.

For the Phase 3 study an Independent Review Committee (IRC) was established to adjudicate investigator-assessed disease response (CR, PR, mCR, or cytogenetic response) and response (CR, PR, mCR, or cytogenetic response) for subjects with > 5% baseline bone marrow blasts and/ or cytogenetic abnormalities at baseline based on the central pathology reviewer's assessment. The IRC assessed response based on the modified IWG Response Criteria 2006 for MDS ([Cheson, 2006](#)).

The FDA's Assessment:

To support the marketing application for imetelstat for the proposed indication, the Applicant submitted the results of Study 63935937MDS3001 (MDS3001, IMerge). The study was comprised of two parts. Part 1 was a single-arm, open-label, Phase 2 trial. Part 2 was a randomized, double-blind, placebo-controlled, Phase 3 trial. The results of Phase 3 provide the primary basis for the Applicant's claim of efficacy for imetelstat, with the results of Phase 2 considered supportive. The study design is detailed by the Applicant above.

In Phase 3, a total of 178 eligible subjects were randomized in a 2:1 ratio to receive either imetelstat or placebo. Randomization was stratified by prior RBC transfusion burden (≤ 6 or > 6

units RBC over an 8-week period during the 16 weeks prior to randomization) and by IPSS risk group (low risk versus intermediate-1 risk).

The primary endpoint was 8-week RBC transfusion independence (RBC-TI), defined as the proportion of subjects without any RBC transfusion during any consecutive 8 weeks starting from Study Day 1 until subsequent anti-cancer therapy, if any. If subsequent anti-cancer therapy was not reported, the end date of a transfusion-independent interval was determined by either an RBC transfusion or the last transfusion follow-up status date. The study was designed to have 88% power to detect a 22.5% difference in 8-week RBC-TI (30% versus 7.5%) between imetelstat and placebo with a 2-sided alpha of 0.05. Notably, there was no specific hemoglobin threshold for transfusion pre-specified in the protocol. Supportive care, including transfusions and myeloid growth factors, could be administered as needed per investigator discretion and according to local standard practices.

Per statistical analysis plan (SAP), the secondary endpoints included in the hypothesis testing with overall Type I error rate 0.05 (2-sided): 24-week RBC TI, Rate of HI-E per modified IWG 2006, progression-free survival (PFS), overall survival (OS). Other secondary endpoints included duration of 8-week RBC-TI; rates of complete remission (CR), partial remission (PR), or marrow complete remission (mCR); time to AML progression; rate and duration of myeloid growth factor usage; and medical resource utilization. Exploratory endpoints included changes in mutational burden and patient reported outcomes, among others.

Clinical Reviewer comment:

The choice of placebo control as a comparator, randomized study design, and primary endpoint for Phase 3 was discussed with the FDA prior to trial initiation as noted by the Applicant above. However, it should be noted that the FDA advised the Applicant that randomization to imetelstat versus physician's choice would be ideal, though a blinded placebo-controlled study offers the least potential for introducing bias. Additionally, the choice of 8-week RBC-TI as a primary endpoint was indeed discussed during a Type C meeting in 2016 (not 2017 as stated above). However, the FDA noted at the time that whether a positive result for this endpoint is supportive of registration will depend on the risk-benefit analysis at the time of review and that if the safety profile outweighs durable duration of TI, this would not be viewed favorably.

Furthermore, it should be noted that the FDA does not consider HI-E, cytogenetic response, or decrease of mutation burden to be established measures of efficacy in lower-risk MDS at this time. There is also inadequate evidence of content validity for the FACIT-Fatigue questionnaire to support regulatory decision-making at this time.

Eligibility Criteria

The Applicant's Description:

Key inclusion criteria:

- Myelodysplastic syndromes according to World Health Organization (WHO) 2008 criteria
- IPSS low- or intermediate-1 risk MDS
- Red blood cell transfusion dependent defined as requiring at least 4 RBC units transfused over an 8-week period during the 16 weeks prior to Cycle 1 Day 1 (Phase 2) or Randomization (Phase 3); pre-transfusion Hgb should be $\leq 9.0\text{g/dL}$ to count toward the 4 units total
- Relapsed/refractory to ESA treatment, as defined by meeting any one of the criteria below:
 - Received at least 8 weeks of treatment with a minimum weekly dose of epoetin alfa 40,000 U, epoetin beta 30,000 U, or darbepoetin alfa 150 μg (or equivalent agent/dose), without having achieved a Hgb rise $\geq 1.5\text{ g/dL}$ or decreased RBC transfusion requirement by at least 4 units over 8 weeks
 - Transfusion dependence or reduction in Hgb by $\geq 1.5\text{ g/dL}$ after hematologic improvement, in the absence of another explanation
 - Endogenous serum erythropoietin (EPO) level $>500\text{ mU/mL}$
- Hematology lab test values within the following limits:
 - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/\text{L}$ independent of growth factor support
 - Platelets $\geq 75 \times 10^9/\text{L}$ independent of platelet transfusion
- Biochemical laboratory test values must be within the following limits:
 - Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) ≤ 2.5 times the upper limit of normal (ULN)
 - Serum creatinine $\leq 2.0 \times \text{ULN}$
 - Total bilirubin $\leq 3 \times \text{ULN}$ and direct bilirubin $\leq 2 \times \text{ULN}$ (unless due to Gilbert's syndrome, ineffective erythropoiesis due to MDS, or hemolysis due to RBC transfusion)

Key exclusion criteria:

- Prior treatment with a hypomethylating agent (eg, azacitidine, decitabine), lenalidomide, thalidomide, or other thalidomide analogues (Phase 3 specific)
- Subject with del(5q) karyotype (Phase 3 specific)
- Subject with MDS/MPN overlap syndrome
- Subject had received an experimental or investigational drug or had used an invasive investigational medical device within 30 days prior to randomization or was currently enrolled in an investigational study

The FDA's Assessment:

Eligible patients were adults with the following key disease-related eligibility requirements, as noted by the Applicant above:

- Diagnosis of MDS according to the World Health Organization (WHO) 2016 criteria
- Low or intermediate-1 risk by IPSS
- RBC transfusion dependent, defined as requiring at least 4 RBC units transfused over an 8-week period during the 16 weeks prior to randomization; pre-transfusion Hgb was required to be ≤ 9.0 g/dL to count towards the 4 units total
- Relapsed or refractory to ESA treatment, or erythropoietin level > 500 mU/mL
- Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$ /L independent of growth factor support
- Platelets $\geq 75 \times 10^9$ /L independent of platelet transfusion

During the course of the Phase 2 study, when 32 subjects had been enrolled, the Applicant observed better 8-week RBC-TI responses in the subgroup of subjects without del5q and without prior treatment with a hypomethylating agent (e.g., azacitidine or decitabine) or lenalidomide, when compared to all subjects. The following “target population” was thus defined, and eligibility requirements added accordingly, for the remainder of the Phase 2 study and the entirety of the Phase 3 study:

- No del5q karyotype
- No prior treatment with a hypomethylating agent (HMA) or lenalidomide

Study Endpoints

The Applicant's Description:

Applicant Table 13: Efficacy Endpoints and Analyses for Study MDS3001-Phase 3

Endpoint	Description	Analysis Set	Statistical Analysis
Primary Efficacy Endpoints			

Endpoint	Description	Analysis Set	Statistical Analysis
8-week RBC TI Rate	The proportion of subjects without any RBC transfusion during any consecutive 8 weeks starting from Day 1 ^a	ITT	Summarized as frequency and percentage with 95% 2-sided exact Clopper-Pearson CIs. Difference in TI and its 95% CI were presented using Wilson Score method (Newcombe, 1998). The comparison was based on a stratified CMH test adjusting for the following baseline covariates used for stratified randomization: 1. prior RBC transfusion burden (≤ 6 or > 6 units RBC) 2. IPSS risk group (low- or intermediate-1 risk) Sensitivity analyses were conducted as described in the Study MDS3001 SAP.
Key Secondary Efficacy Endpoints ^b			
24-week RBC TI Rate	The proportion of subjects without any RBC transfusion during any consecutive 24 weeks starting from Day 1 ^a	ITT	Summarized as frequency and percentage with 95% 2-sided exact Clopper-Pearson CI. Difference in TI and its 95% CI were presented using Wilson Score method. Treatment comparison made using stratified CMH test adjusting for the stratification factors
Duration of RBC TI	The first day of the longest RBC TI period to the date of the first RBC transfusion after the TI period starts	ITT 8-week (24-week) TI Responder	The distributions were compared using a stratified log-rank test. The KM method was used to estimate the distribution for each treatment. The treatment effect (hazard ratio) and 2-sided 95% CIs were estimated using a stratified Cox regression model with treatment as the sole explanatory variable.

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Endpoint	Description	Analysis Set	Statistical Analysis
Amount and relative change in RBC transfusions	Amount of RBC transfusions per 8-week (16-week) is defined as the total number of RBC transfusion units in a given 8-week (16-week) interval during study. Relative change in RBC transfusions = (amount of RBC transfusions–prior RBC transfusion burden) / prior RBC transfusion burden multiply by 100%.	ITT	Summarized descriptively by treatment by time point
Rate of hematologic improvement (HI-E, HI-P, and HI-N) ^d	The proportion of subjects who achieve HI-E, HI-P, or HI-N ^c	ITT	Summarized as frequency and percentage with 95% 2-sided exact Clopper-Pearson CI. Difference in TI and its 95% CI were presented using Wilson Score method. Treatment comparison made using stratified CMH test adjusting for the stratification factors
Time to 8-week RBC TI	The time from Day 1 to the first day of the first 8-week RBC TI period.	ITT 8-week TI Responder	Summarized descriptively
Time to 24-week RBC TI	The time from Day 1 to the first day of the first 24-week RBC TI period.	ITT 24-week TI Responder	Summarized descriptively
Rates of CR, PR, or mCR	The proportion of subjects who achieve CR, PR or mCR per modified IWG 2006 (Cheson, 2006).	ITT	Summarized as frequency and percentage with 95% 2-sided exact Clopper-Pearson CI.
OS	The time from Day 1 to death from any cause. Survival time of living subjects was censored on the last date a subject was known to be alive or lost to follow-up.	ITT	The distributions were compared using a stratified log-rank test. The KM method was used to estimate the distribution for each treatment. The treatment effect (hazard ratio) and 2-sided 95% CIs were estimated using a stratified Cox regression model with treatment as the sole explanatory variable.

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Endpoint	Description	Analysis Set	Statistical Analysis
PFS	The time from Day 1 to the first date of disease progression or death from any cause, whichever occurred first.	ITT	The distributions were compared using a stratified log-rank test. The KM method was used to estimate the distribution for each treatment. The treatment effect (hazard ratio) and 2-sided 95% CIs were estimated using a stratified Cox regression model with treatment as the sole explanatory variable.
Time to progression to AML	The time from Day 1 to the date of AML diagnosis.	ITT	The KM method was used to estimate the distribution for each treatment.
Rate of myeloid growth factors usage	The proportion of subjects who received any myeloid growth factors starting from Day 1.	ITT	Summarized descriptively by treatment group. Duration of myeloid growth factor administered starting from Day 1 was also summarized.
Exploratory Efficacy and Biomarker Endpoints			
FACIT-Fatigue	Proportion of subjects who experienced a decrease of ≥ 3 points for ≥ 2 consecutive non-missing cycles.	PRO	Summarized descriptively by treatment group. A sensitivity analyses was done by replicating the analysis with the ITT population and with alternate definitions of meaningful deterioration.
Cytogenetic status	Status at baseline and change from baseline over time.	Biomarker Analysis Set	Biomarker measures and the change from baseline were listed, tabulated, and plotted where appropriate. Subjects were grouped by treatment, biomarker subgroups, and clinical response. Correlation of baseline or changes of biomarkers with clinical parameters were analyzed by appropriate statistical methods.
TA, hTERT, and TL	Status at baseline and change from baseline over time (TL at baseline only).		
Mutation status	Status at baseline and change from baseline over time including at the time of suspected response (CR, PR, HI-E [Hb], or progressive disease).		

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AML = acute myeloid leukemia; CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CR = complete remission; FACIT = Functional Assessment of Chronic Illness Therapy; Hb = hemoglobin; HI-E = hematologic improvement-erythroid; HI-N = hematologic improvement-neutrophil; HI-P = hematologic improvement-platelet; hTERT = human telomerase reverse transcriptase; IPSS = International Prognostic Scoring System; ITT = intent-to-treat; IWG = International Working Group; KM = Kaplan-Meier; mCR = marrow complete remission; N/A=not applicable; OS = overall survival; PFS = progression-free survival; PR = partial remission; PRO = patient-reported outcome; RBC = red blood cell; TA = telomerase activity; TI = transfusion independence; TL = telomere length

^a Day 1 was defined as the day of randomization for subjects enrolled in Phase 3.

^b The ≥ 24 -week RBC TI and rate of HI-E per modified IWG 2006 (Cheson, 2006) were considered the most important secondary endpoints, and thus were used as gate keepers and tested at the α level sequentially. The ≥ 24 -week RBC TI was the first gate keeper and rate of HI-E per modified IWG 2006 (Cheson, 2006) was the second gate keeper.

^c According to modified IWG 2006 response criteria (Cheson, 2006), HI-E was defined as a Hb increase of ≥ 1.5 g/dL above pretreatment and lasts ≥ 8 weeks or reduction of ≥ 4 units of RBC transfusion units/8 weeks compared with the prior RBC transfusion burden. According to revised 2018 IWG criteria (Platzbecker, 2019), HI-E is defined using a 16-week interval. HI-P was defined as absolute increase in platelet count of $\geq 30 \times 10^9/L$ for subjects starting with $> 20 \times 10^9/L$ platelets or increase from $< 20 \times 10^9/L$ to $> 20 \times 10^9/L$ and by $\geq 100\%$ lasts ≥ 8 weeks. HI-N was defined as $\geq 100\%$ increase in neutrophil count and an absolute increase $> 0.5 \times 10^9/L$ lasts ≥ 8 weeks.

^d Due to protocol inclusion criteria of ANC $1.5 \times 10^9/L$, no subjects could be considered eligible for HI-N response. Note that in order to be considered TI, a subject must have completed continuous transfusion assessment throughout the observation period during which his or her TI was determined.

The FDA's Assessment:

FDA agrees with the description of the primary endpoint for Study MDS3001-Phase 3 listed by the Applicant above. Per SAP, the secondary endpoints included in the hypothesis testing with overall Type I error rate 0.05 (2-sided): 24-week RBC TI, Rate of HI-E per modified IWG 2006, PFS, OS. All other endpoints not included in the hypothesis testing with overall Type I error rate 0.05 (2-sided) are considered exploratory. Additionally, exploratory endpoints included not only patient-reported outcomes (PROs) per the FACIT-Fatigue questionnaire, but additional PRO measures using the QUALMS, FACT-An, EQ-5D-5L, and PGIC questionnaires.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The statistical analysis plan was agreed upon with FDA and version 2.0 was finalized before the conduct of the prespecified primary analysis of the pivotal MDS3001-Phase 3 study, at which time the Sponsor was unblinded to treatment randomization assignment.

The primary hypothesis of this study is that the imetelstat will significantly improve the rate of RBC TI as compared to placebo in transfusion-dependent subjects with low or intermediate-1 risk MDS that is relapsed or refractory to ESA treatment. The hypothesis was tested using a stratified Cochran-Mantel-Haenszel (CMH) test adjusting for the stratification factors at a 2-sided significant level of 0.05. Efficacy data were compared between the imetelstat and placebo groups based on the Intent-to-Treat (ITT) population.

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Power and Sample Size

On the basis of historical data, 8-week RBC TI rate was expected to be approximately 7.5% in patients with low or intermediate-1 risk MDS without any active treatment (Raza, 2008; Santini, 2014). The 8-week RBC TI rate with imetelstat treatment was expected to be approximately 30% based on preliminary data from a cohort of 9 subjects in Study CP14B019 (Tefferi, 2016). Approximately 170 subjects were initially planned to be randomized in a 2:1 ratio to receive either imetelstat or placebo. Using a 2:1 ratio randomization and a 2-group continuity corrected Chi square test with 0.05 (2 sided) significance level, 150 subjects were needed to achieve a power of approximately 88% to detect the difference between an RBC TI rate of 30% in the imetelstat group and an RBC TI rate of 7.5% in the placebo group. After correction for a 10% drop-out rate, a total of approximately 170 subjects (115 in imetelstat group and 55 in placebo group) were planned.

Efficacy Analysis

Statistical methods for the primary and the key secondary endpoints are outlined in Applicant Table 13.

Safety Analysis

All safety summaries and analyses were based on the Safety Analysis Set, which included all subjects who received at least 1 dose of study drug. Safety variables were tabulated by descriptive statistics. Adverse events that had missing causality (after data querying) were assumed to be related to study drug. Protocol-defined adverse events of interest (AEI) included liver function abnormalities based on laboratory data and hepatic AEs. All hepatic AEs based on Medical Dictionary of Regulatory Activities (MedDRA)-defined search criteria and liver function test (LFT) abnormalities were reviewed by an independent Hepatic Expert Committee (HEC) that consisted of 3 hepatologists, at least quarterly, and as needed. Bleeding events, infections, and infusion-related reaction (IRR) events were also analyzed as other selected AEs. After the start of the Coronavirus Disease 2019 (COVID-19) pandemic in March 2020, events related to COVID-19 were also monitored as AEs.

Biomarker Analysis

Statistical methods for biomarker data are outlined in Applicant Table 13.

PRO Analysis

Details of the PRO analyses are provided in the clinical study report (CSR) MDS3001-Phase 3 Section 9.7.1.6 and the PRO SAP (CSR MDS3001-Phase 3 Appendix 16.1.9) and were previously communicated to FDA in a complete response (submitted 18 February 2022) to an information request raised by the Agency (IND 147027, Serial No. 0059). The main PRO objective was to explore the hypothesis that, while they are on treatment, subjects treated with imetelstat are not more likely to experience a meaningful deterioration in fatigue, as measured by the FACIT-

Fatigue score, than subjects treated with placebo, regardless of their transfusion-dependence status. The proportion of subjects who experienced an episode of meaningful deterioration in fatigue was calculated in the PRO population for each treatment group. Sensitivity analyses were conducted to investigate the impact of missing PRO assessments and robustness of the results on the main PRO objective. The proportion of subjects who experienced a meaningful improvement in fatigue was also explored. Sustained and meaningful deterioration/improvement in fatigue was defined as ≥ 3 -point decrease/increase on the FACIT-Fatigue Scale for ≥ 2 consecutive non-missing treatment cycles.

Missing or Partial Data

No imputations for missing data were made for the primary and secondary efficacy endpoints. In order to be considered transfusion independent, a subject must have completed continuous transfusion assessments throughout the qualifying observation period where his/her TI was determined. An apparent transfusion-free period with 1 or more missing transfusion assessments was not considered a qualifying 8-week or 24-week TI period. Subjects with no qualifying observation periods were considered non-responders.

In general, imputation of partial missing dates was made for AE onset date, AE resolution date, date of death, start and end dates of concomitant therapy, and date of initial diagnosis. Imputation rules for partial dates are described in Section 4.2.3 of the SAP

Multiplicity Testing

For Phase 3, a sequential gate-keeping procedure and Hochberg procedure (Hochberg, 1988) was implemented to ensure that the overall Type I error rate for the secondary endpoints was controlled. The ≥ 24 -week RBC TI and rate of HI-E per modified IWG 2006 (Cheson, 2006) were considered the most important secondary endpoints, and thus were used as gate keepers and tested at the α level sequentially. Let α be the critical type I error rate 0.05 (2-sided). The 24-week RBC TI was the first gate keeper and rate of HI-E per modified IWG 2006 (Cheson, 2006) was the second gate keeper. If the nominal P value was $< \alpha$ for the 24-week RBC TI, then the rate of HI-E was tested next at the α level. If the nominal P value was $< \alpha$ for rate of HI-E as well, the remaining selected secondary hypotheses (PFS and OS) were tested using a Hochberg procedure.

Interim and Final Analysis

The primary efficacy analysis was planned at 12 months after the last subject was randomized in the main part of Phase 3 study, and the final analysis will be performed at the End of the Study defined as 24 months after randomization of the last subject in the main part of Phase 3 study or anytime the sponsor terminated the study, whichever came first. No interim analysis was planned.

Planned Subgroup Analysis

Subgroup analyses were performed to assess the consistency and robustness of the treatment benefit, mainly for the rate of RBC TI and the rate of HI-E. CMH tests between the 2 treatment groups within each subgroup were calculated for Phase 3. Results were displayed in forest plots. Subgroups investigated included demographic factors, and baseline characteristics. Subgroup analyses were also performed for selected safety parameters.

SAP Amendments

Amendments to the SAP are summarized in Applicant Table 14.

Applicant Table 14: SAP Version History

Version No.	Effective Date	Summary of Change(s)
1.0	09OCT2020	Original SAP
2.0	15SEP2022	1. Modified the Ventricular Repolarization (QTc) substudy in Part 2 to separate it from the main study per Protocol Amendment 7. 2. Removed PRO measures from secondary endpoints and sequential hypothesis testing per discussion with FDA. Consider PROs as exploratory endpoints that will be descriptively summarized. 3. Clarified Part 1 refers to Phase 2 part and Part 3 refers to Phase 3 part of the study throughout the document. 4. Clarified that the primary efficacy analysis is planned 12 months (and no longer 15 months) after the last subject is randomized in the main study of Part 2 per Protocol Amendment 7.

The FDA's Assessment:

FDA agrees with the Applicant's description of the statistical power, sample size, missing data, multiplicity, interim and final analysis, and SAP amendments. See *Efficacy Results – Secondary or exploratory COA (PRO) endpoints* section for comments on the secondary and exploratory endpoints and their analyses. No overall Type I error rate-controlled subgroup analyses were prespecified in SAP. Therefore, subgroup analyses conducted by FDA did not include hypothesis testing and did not include stratification factors due to small sample sizes and/or events in some subgroups.

Regarding the change in PRO hypothesis testing, the following was provided by the Applicant in the information request response under IND 147027, Seq. 0059 (received on 18 February 2022):

“Based on a systematic approach to update the PRO measurement strategy in the MDS3001 study, Geron plans to change the positioning of the PRO endpoint for the MDS3001 study by reclassifying it from a secondary to an exploratory endpoint.

The stepwise approach to update the PRO measurement strategy for the MDS3001 study started with the identification of the core concepts of interest (COI) to measure in the specific context of use (COU) of the MDS3001 study. These COIs were established from the review of published qualitative literature and patient blogs describing the experience of LR MDS. A comprehensive conceptual model of the experience of patients with LR MDS was created from this research, covering symptoms (fatigue, gastrointestinal, systemic, cardio-respiratory, pain and neuropathy, and transfusion-specific), physical functioning (mobility, activities of daily living, work/school impact, and sleep/rest) and psychosocial functioning (emotional well-being, and social/leisure). Three expert MDS clinicians reviewed the conceptual model and endorsed fatigue, cardio- respiratory, and systemic symptoms as the most pertinent and relevant symptoms to patients, and acknowledged that symptom burden, especially fatigue, can lead to physical and psychosocial impacts. Subsequently, an item-to-concept mapping was performed considering all items of the PRO measures collected in the MDS3001 study. Tentative item sets from the Functional Assessment of Cancer Therapy-Anemia (FACT-An) and Quality of Life in Myelodysplasia Scale (QUALMS) were identified to assess each COI. The evaluation of the psychometric performances of these item sets using available data from a blinded interim data cut of the MDS3001 study provided supportive evidence for the use of the FACIT-Fatigue score to measure fatigue in this COU, but the psychometric performance of the item sets tested for the measurement of the other COIs (especially physical functioning and shortness of breath) were deemed not strong enough to warrant their use as secondary endpoints of the study.

Geron considered that the benefit of imetelstat in terms of transfusion burden reduction and independence would not be at the cost of less controlled core symptoms of LR MDS. Based on the findings of the PRO measurement strategy described above, the assessment of fatigue using the FACIT-Fatigue score would be the COI measured for symptom control, however, the sample size of the study does not provide sufficient power to demonstrate the absence of deterioration of fatigue in imetelstat versus placebo treated patients in this COU.

For these reasons, Geron does not plan to use the MDS3001 study to formally demonstrate the benefit of imetelstat compared with placebo in terms of PRO endpoint and the PRO data will not be used for the specification of secondary endpoints of the study. Instead, the PRO data will be included as exploratory endpoints, with descriptive analyses to document the change in PRO scores targeting the COIs over the course of the study.”

Protocol Amendments

The Applicant's Description:

The original protocol, dated 29 July 2015, was amended 8 times. Phase 3 of the study started enrolling under Amendment 3.

Amendment 1 was completed on 31 May 2016 with the following important changes following consultation with Health Authorities:

- The definitions of “prior RBC transfusion burden” and “transfusion dependent” were revised to include the 16 weeks (changed from 12 weeks) prior to study entry. RBC transfusion history collection period was increased to 16 weeks before study entry (changed from 12 weeks).
- Inclusion criterion no. 13 was added. Subjects with the del(5q) karyotype were eligible if they had failed treatment with lenalidomide.
- The requirement was added that total bilirubin must be $\leq 3 \times \text{ULN}$. Requirement for direct bilirubin was changed from $\leq 1.5 \times \text{ULN}$ to $\leq 2 \times \text{ULN}$. Subjects with elevated bilirubin due to Gilbert's syndrome could be eligible to participate in the study.
- The independent Data Monitoring Committee's (DMC) involvement in the study was extended to Phase 2.

Amendment 2 was completed on 31 August 2017 following an analysis of Part 1, Week-24 data, with the following important changes:

- Beginning with this amendment, enrolled subjects were to have non-del(5q) LR-MDS and no prior treatment with either a HMA or lenalidomide. Exclusion criteria were revised to exclude prior use of HMAs and lenalidomide, and to specify the minimum allowable interval following prior use of an ESA or any chemotherapy, immunomodulatory, or immunosuppressive therapy. Subjects with the del(5q) karyotype were excluded from the study.
- Individuals previously diagnosed with IPSS intermediate-2 or high risk MDS were excluded from the study. Subjects with MDS/MPN overlap syndrome were excluded.
- Enrollment in Part 1 was expanded to include approximately 22 additional subjects in the target population meeting the revised entry criteria. Total enrollment in Part 1 (initial cohort plus expanded cohort) was to increase from up to 30 subjects to approximately 55 subjects.
- Dose escalation to 9.4 mg/kg and dose re-escalation following dose reduction was no longer permitted. Clarification added that subjects whose dose was previously escalated (before Amendment 2) could continue at the 9.4 mg/kg dose.

Amendment 3 was completed on 18 April 2019, with the following important changes:

- Sponsor changed from Janssen Research & Development to Geron Corporation.

- The planned primary efficacy analysis was to be performed at 15 months (and no longer 12 months) after the last subject was randomized in the Phase 3 part (note that this was changed back to 12 months via Amendment 7).

Amendment 4 was completed on 23 March 2020, with the following important changes in consideration of the COVID-19 pandemic:

- Guidelines for the management of subjects who had confirmed COVID-19 infection, had clinical signs and symptoms consistent with COVID-19 infection, or had been exposed to a person with confirmed COVID-19 infection. A subsection was added to the protocol to include dose modification guidance regarding COVID-19 for subjects on treatment. Text was added to elucidate COVID-19 screening procedures and enrollment decisions as they pertained to COVID-19, and to elucidate monitoring, follow-up and reporting of clinical signs and symptoms of COVID-19 infection.

Amendment 5 was completed on 29 June 2020, to clarify eligibility criteria/assessments and study procedures pertaining to the Phase 3 study. This amendment also further clarified considerations regarding the COVID-19 pandemic, including the provision for remote monitoring of study sites. The following important changes were made:

- Added text to establish an IRC to adjudicate investigator-assessed disease response (CR, PR, mCR, or cytogenetic response) based on the modified IWG 2006 criteria. Responsibilities, authorities, and procedures were detailed in a separate charter

Amendment 6 was completed on 01 April 2021, with the following important changes:

- The dose modification criteria for LFT elevations and hepatic AEs were changed. Modifications were made to Table 9 that decreased the number of times the dose could be reduced due to Grade 3 or 4 ALT, AST, or bilirubin elevations, and Grade 3 or 4 hepatic AEs before discontinuing treatment. Modification and stopping criteria were added for Grade 2 ALT or AST with concomitant Grade 2 bilirubin elevations. Guidance was provided on investigations into possible causes of LFT elevations and hepatic AEs and subsequent monitoring.
- ALT or AST > 3.0 x ULN with Bilirubin > 2.0 x ULN was added as an AEI.

Amendment 7 was completed on 02 September 2021, with the following important changes:

- The planned primary efficacy and safety analysis from the main MDS3001 study was returned to 12 months (this was changed from 12 months to 15 months via Amendment 3) after the last subject is randomized in the Phase 3 study, as sufficient follow-up information would be collected by that time to determine the benefit/risk of imetelstat in low risk, transfusion dependent MDS subjects.
- Guidance regarding the disruptions due to the COVID-19 pandemic was modified to recommend that study sites follow local standard of care and local recommendations for quarantine, vaccination and/or potential dosing delays. Guidance was provided for beginning/resuming study treatment after a positive COVID-19 test or infection based on updated knowledge and guidance.

- Modifications to the Ventricular Repolarization sub-study were made to include adjustments to eligibility criteria, time and events table, schedule of ECG and PK assessments, and unblinding activities.

Amendment 8 was completed on 13 Dec 2022.

The primary reason for this amendment was to add an Extension Phase to evaluate long-term safety, OS, and disease progression including progression to AML, until 5 years from the first dose of imetelstat or after 3 years of post-treatment follow-up. This amendment was in effect after the cutoff date for the primary analysis, and therefore does not apply to this CSR.

The FDA's Assessment:

FDA agrees that the protocol was amended as noted above.

Additional clarification on IRC establishment is provided below.

Per Amendment 5, "Added text to establish an Independent Review Committee (IRC) to adjudicate investigator-assessed disease response (CR, PR, mCR, or cytogenetic response) based on the modified IWG 2006 criteria." Per CSR, "In the Phase 3 study, bone marrow assessments were performed centrally at baseline and during disease evaluation visits. In addition, a baseline bone marrow blast of > 5% based on modified IWG 2006 criteria was used as a cutoff for assessment of CR, PR, and mCR, and all potential responses were adjudicated by the Independent Review Committee (IRC) for Phase 3."

8.1.2. Study Results

Compliance with Good Clinical Practices

Data:

MDS3001 study was conducted in compliance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice (GCP) regulations, ethical principles from the Declaration of Helsinki and applicable country and/or local statutes. The original protocol and protocol amendments were approved by an independent Institutional Review Board /Ethics Committee associated with each study center. Signed informed consent was obtained from all participants prior to enrollment in the study.

The Applicant's position:

The MDS3001 study was conducted in compliance with GCP regulations.

The FDA's Assessment:

FDA agrees that the study appears to have been conducted in compliance with GCP regulations.

Financial Disclosure

Data:

Financial disclosure information was collected from all investigators participating in the pivotal MDS3001 study and adequately disclosed. Additional details are provided in [Section 19.2](#) of this Assessment Aid.

The Applicant's Position:

Geron certifies that 1) the company has not entered into any financial arrangement whereby the value of compensation to the investigator could be affected by the outcome of the study; 2) no listed investigator disclosed a proprietary interest in the product or a significant equity holding in Geron; and 3) no listed investigator was the recipient of significant payments of other sorts. The integrity of the MDS3001 study data was not affected by financial interests of the investigators.

The FDA's Assessment:

Seventeen investigators on the study did not submit a financial disclosure form, however these were investigators who either did not assist on the study, did not have any patients in the study, or were from sites which never enrolled any patients. Financial disclosure information was submitted from all other investigators and there were no reportable financial disclosures per the Applicant.

Patient Disposition

Data:

See below.

The Applicant's Position:

A total of 178 subjects were enrolled in the study at 77 sites across 17 countries. All 178 subjects were included in the ITT population, 118 of which were randomized to receive imetelstat and 60 subjects were randomized to receive placebo. In total, 177 subjects were treated (118 subjects received imetelstat and 59 subjects received placebo) and are included in the safety population. At the time of the clinical cutoff (13 October 2022), 63 (35.4%) subjects discontinued from the study; 42 (35.6%) subjects in the imetelstat group and 21 (35.0%) subjects in the placebo group.

At the cutoff date, 27 (22.9%) subjects in the imetelstat group and 14 (23.7%) subjects in the placebo group were still receiving study treatment and 91 (77.1%) and 45 (76.3%) subjects, respectively, had discontinued treatment.

The FDA's Assessment:

FDA agrees with the patient disposition information summarized by the Applicant, aside from the percent of patients who discontinued treatment in the placebo group (45/60 = 75%). Some additional results are listed below.

Table 15 shows treatment discontinuation summary. Figure 6 shows time on treatment.

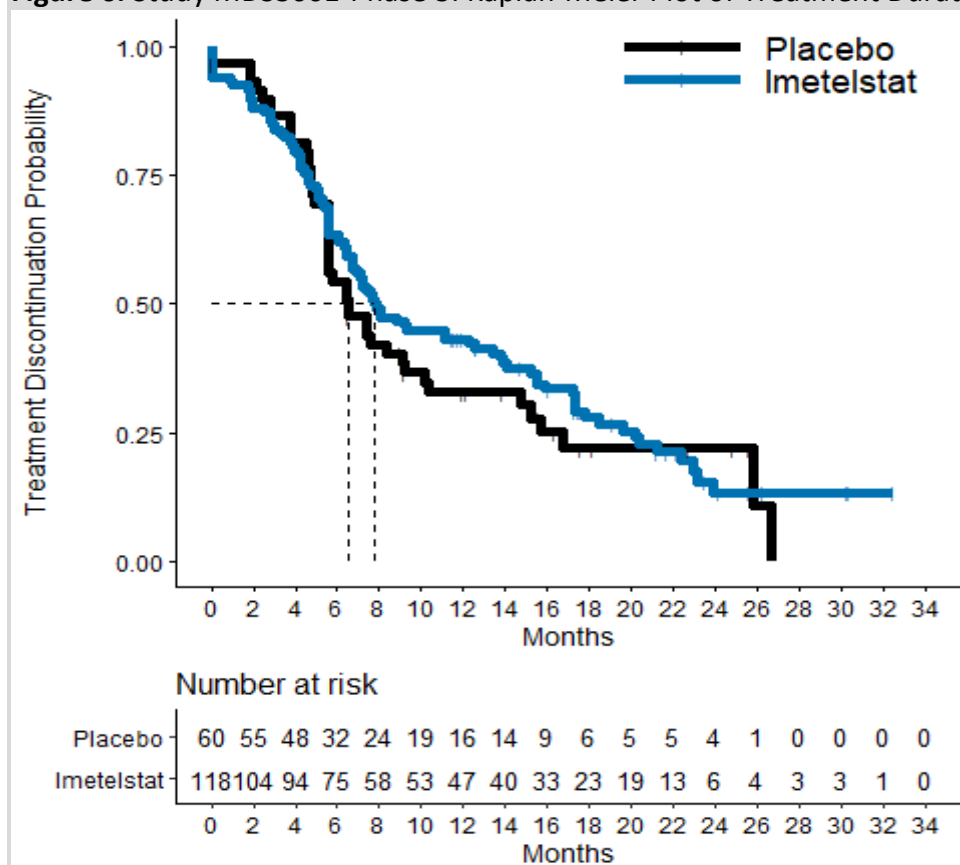
Clinical Reviewer Comment: With a very effective and safe therapy, one would expect to observe a much longer duration of treatment compared to placebo. However, patients treated with imetelstat had a similar duration of treatment as patients treated with placebo, as shown in Figure 6, and the median duration of treatment was only 8 cycles for patients treated with imetelstat, the same as placebo.

Table 15. Study MDS3001-Phase 3: Treatment Duration (ITT set)

Treatment	Imetelstat (N=118)	Placebo (N=60)
Discontinued	77%	75%
Lack of Efficacy	24%	42%
Patient refused further study treatment	14%	17%
Adverse event	16%	0%
Disease relapse	14%	2%
Progressive disease	6%	8%
Physician decision	2%	3%
Death	1%	3%
Lost to follow-up	1%	0%
Ongoing	23%	23%
Untreated	0%	2%
Median Time to Treatment Discontinuation , months (95% CI)	7.8 (6.5, 13.4)	6.5 (5.6, 9.2)
Median Number of Cycles Received (range)	8.0 (1, 34)	8.0 (1, 30)

Source: FDA analysis using ADDISP and ADSL datasets; Data cutoff: 13 October 2022

Figure 6. Study MDS3001-Phase 3: Kaplan-Meier Plot of Treatment Duration (ITT set)



Note: Duration of treatment was defined as the time from the first exposure to treatment to the last exposure to treatment (censored if no treatment discontinuation occurred; event if treatment was discontinued).

Source: FDA analysis using ADDISP and ADSL datasets; Data cutoff 13 October 2022

Protocol Violations/Deviations

Data:

Overall, 43.3% of subjects had major protocol deviations (Table tsidv01_p2), including 55 (46.6%) subjects in the imetelstat group and 22 (36.7%) subjects in the placebo group. Most of these deviations were due to : continuing dosing despite toxicity that required a dose hold, not dose reducing due to toxicity, dosing before availability of all required laboratory results, and restarting treatment after interruption > 28 days without Sponsor approval.

Incorrect stratification accounted for major protocol deviations in 12.7% of subjects in the imetelstat group and 10.0% in the placebo group (Table tsidv01_p2). Higher than expected volume of stratification errors was largely related to the baseline transfusion burden and attributed to the detailed calculation required by the investigator to determine the maximum

number of RBC units transfused over an 8-week period during the 16 weeks prior to randomization.

To reduce these errors, the medical monitor started to review the stratification for each subject prior to randomization. This corrective action was implemented early during the study, when only 24 subjects had been randomized, and the number of stratification errors was subsequently minimized.

The Applicant's Position:

Assessment of major protocol violations on the study results

Based on medical assessment, the major protocol deviations described above were concluded to have minimal impact on subject safety or data integrity in this study.

Despite the stratification errors at randomization, the data showed 2:1 allocation ratio was maintained for imetelstat and placebo groups within each of the strata, i.e. prior RBC transfusion burden (≤ 6 units, > 6 units) and IPSS category (low, INT-1). To assess the impact of the major protocol deviations on the efficacy results, sensitivity analyses of primary and secondary endpoints were performed in the Per Protocol analysis set (summarized in Table tefti02b_p2 and Table tefti04b_p2, respectively). The results demonstrated that these major protocol deviations had minimal impact on the data integrity in this study.

The FDA's Assessment:

As noted by the Applicant above, 43.3% of patients had major protocol deviations. Notably, incorrect stratification accounted for major protocol deviations in 12.7% of patients in the imetelstat group and 10.0% of patients in the placebo group. Sensitivity analyses of the primary endpoint 8-week RBC-TI and key secondary endpoint 24-week RBC-TI were performed in the per-protocol analysis set by the Applicant. Per these sensitivity analyses, the major protocol deviations do not appear to substantially impact the efficacy results. For potential impact on other endpoints, see discussion of OS results in "Efficacy Results – Secondary and other relevant endpoints" section below for more information.

Per CSR, "Overall, 43.3% of subjects had major protocol deviations. The proportion of subjects with major protocol deviations was higher in the imetelstat group (46.6%) compared to the placebo group (36.7%), which was mostly due to more frequent incorrect administration of study treatment in the imetelstat group (29.7%) versus the placebo group (13.3%). Among subjects in both treatment groups, major protocol deviations related to incorrect administration of study treatment included study treatment not held due to toxicity as per protocol (20 subjects in the imetelstat group, 3 subject in the placebo group), study treatment dose not reduced due to toxicity per protocol (13 subjects in the imetelstat group, 1 subject in the placebo group), treatment administered prior to availability of hematological or chemistry

lab results (7 subjects in the imetelstat group, 3 subject in the placebo group), study treatment interruption lasting > 28 days, and treatment restarted without Sponsor approval (5 subjects in the imetelstat group, 1 subject in the placebo group)...Other major protocol deviations included study drug not administered according to the protocol schedule (5 [4.2%] subjects in the imetelstat group and 4 [6.7%] subjects in the placebo group), hematology labs not done at scheduled visits (7 [5.9%] and 5 [8.3%] subjects, respectively), AEI/SAE not reported as per protocol (7 [5.9%] and 2 [3.3%] subjects, respectively), and subjects not satisfying the entry criteria after study entry (3 [2.5%] and 2 [3.3%] subjects, respectively)."

Table of Demographic Characteristics

Data:

Applicant Table 16: Demographic Characteristics (Phase 3, Intent-to-Treat Analysis Set)

	Imetelstat (N = 118)	Placebo (N = 60)	Total (N = 178)
Age (years)			
Mean (SD)	70.4 (8.82)	71.7 (8.95)	70.9 (8.86)
Median	71.5	73.0	72.0
Minimum, Maximum	44, 87	39, 85	39, 87
Age group, n (%)			
< 65 years	27 (22.9%)	9 (15.0%)	36 (20.2%)
≥ 65 years	91 (77.1%)	51 (85.0%)	142 (79.8%)
<75 years	83 (70.3%)	37 (61.7%)	120 (67.4%)
≥ 75 years	35 (29.7%)	23 (38.3%)	58 (32.6%)
Gender, n (%)			
Female	47 (39.8%)	20 (33.3%)	67 (37.6%)
Male	71 (60.2%)	40 (66.7%)	111 (62.4%)
Ethnicity, n (%)			
Hispanic or Latino	6 (5.1%)	5 (8.3%)	11 (6.2%)
Not Hispanic or Latino	100 (84.7%)	48 (80.0%)	148 (83.1%)
Unknown	1 (0.8%)	1 (1.7%)	2 (1.1%)
Not reported	11 (9.3%)	6 (10.0%)	17 (9.6%)
Race, n (%)			

Version date: June 2022 (ALL NDA/ BLA reviews)

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NDA/BLA Multi-disciplinary Review and Evaluation NDA 217779 imetelstat
 TRADENAME, imetelstat

	Imetelstat (N = 118)	Placebo (N = 60)	Total (N = 178)
White	95 (80.5%)	48 (80.0%)	143 (80.3%)
Black or African American	1 (0.8%)	2 (3.3%)	3 (1.7%)
Asian	8 (6.8%)	2 (3.3%)	10 (5.6%)
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Other	1 (0.8%)	1 (1.7%)	2 (1.1%)
Unknown	1 (0.8%)	1 (1.7%)	2 (1.1%)
Not reported	12 (10.2%)	6 (10.0%)	18 (10.1%)
Region, n (%)			
North America	13 (11.0%)	12 (20.0%)	25 (14.0%)
European Union	80 (67.8%)	38 (63.3%)	118 (66.3%)
Rest of world ^a	25 (21.2%)	10 (16.7%)	35 (19.7%)

SD = standard deviation.

^a Rest of World includes Israel, Republic of Korea, Russian Federation, Switzerland, Turkey, Ukraine, United Kingdom

Source: Table tsidm01_p2.

The Applicant's Position:

Demographic characteristics were balanced between the imetelstat and placebo groups ([Applicant Table 16](#)). The median age for all subjects was 72 years (range: 39 to 87 years) with a higher proportion of males (62.4%), consistent with the epidemiology for this patient population. The imetelstat group was slightly younger compared to the placebo group with 77% versus 85% of subjects being ≥ 65 years old and 30% versus 38% being ≥ 75 years old.

Study MDS3001 was designed as a global study; however, most of the subjects were from the EU and few were from North America. That said, there are no expected differences by region (US vs EU) given that MDS is predominantly observed in individuals who are white, male, and elderly, with the incidence increasing with age, all of which are consistent with the baseline demographics in MDS3001, with the majority being white, from Europe and North America, and ≥ 65 years. Furthermore, there are similar incidence and prevalence rates of MDS between the US and EU (see [Section 2](#)). Therefore, the MDS3001 study population can still be considered representative of this LR-MDS patient population as the epidemiology of MDS, clinical practice and methods of treatment are similar between the 2 regions.

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The FDA's Assessment:

FDA agrees with the demographic characteristics of the MDS3001-Phase 3 study population as noted in the Applicant's table above.

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

Data:

Applicant Table 17: Disease and Other Baseline Characteristics (Phase 3, Intent-to-Treat Analysis Set)

	Imetelstat (N = 118)	Placebo (N = 60)	Total (N = 178)
Time since initial diagnosis (years)			
Mean (SD)	4.834 (4.3173)	3.825 (3.9462)	4.494 (4.2120)
Median (Minimum, Maximum)	3.544 (0.10, 26.66)	2.762 (0.15, 25.68)	3.321 (0.10, 26.66)
< 2 years, n%	31 (26.3%)	22 (36.7%)	53 (29.8%)
≥ 2 years, n%	87 (73.7%)	38 (63.3%)	125 (70.2%)
Prior RBC transfusion burden per IWG 2006			
Mean (SD)	7.3 (3.56)	6.9 (2.40)	7.2 (3.21)
Median (Minimum, Maximum)	6.0 (4, 33)	6.0 (4, 13)	6.0 (4, 33)
≤6 units, n%	62 (52.5%)	33 (55.0%)	95 (53.4%)
>6 units, n%	56 (47.5%)	27 (45.0%)	83 (46.6%)
Total RBC transfusion units in 16 weeks prior to study entry			
Mean (SD)	11.4 (5.89)	10.5 (4.64)	11.1 (5.50)
Median	10.0	10.0	10.0
Minimum, Maximum	4, 54	4, 24	4, 54
Prior RBC transfusion burden per IWG 2018 (n%)			
Low transfusion burden (LTB) ^a	21 (17.8%)	18 (30.0%)	39 (21.9%)
High transfusion burden (HTB) ^a	97 (82.2%)	42 (70.0%)	139 (78.1%)
WHO classification (2008)			
RS+ (RARS/RCMD-RS/MDS/MPN-RS-T)	73 (61.9%)	37 (61.7%)	110 (61.8%)
RS- (Others)	44 (37.3%)	23 (38.3%)	67 (37.6%)
Central Bone marrow blasts, n (%)			
≤5%	117 (99.2%)	56 (93.3%)	173 (97.2%)
>5%	1 (0.8%)	1 (1.7%)	2 (1.1%)
Missing	0	3 (5.0%)	3 (1.7%)
IPSS category based on CRF ^b , n (%)			
Low	80 (67.8%)	39 (65.0%)	119 (66.9%)
Intermediate-1	38 (32.2%)	21 (35.0%)	59 (33.1%)
IPSS-R prognostic risk category ^c , n (%)			
Very low	3 (2.5%)	2 (3.3%)	5 (2.8%)
Low	87 (73.7%)	46 (76.7%)	133 (74.7%)
Intermediate	20 (16.9%)	8 (13.3%)	28 (15.7%)
High	1 (0.8%)	0	1 (0.6%)
Very high	0	0	0
Missing	7 (5.9%)	4 (6.7%)	11 (6.2%)
Number of cytopenias, n (%)			
0-1	93 (78.8%)	49 (81.7%)	142 (79.8%)
2-3	25 (21.2%)	11 (18.3%)	36 (20.2%)

Version date: June 2022 (ALL NDA/ BLA reviews)

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NDA/BLA Multi-disciplinary Review and Evaluation NDA 217779 imetelstat
 TRADENAME, imetelstat

	Imetelstat (N = 118)	Placebo (N = 60)	Total (N = 178)
Prior ESA use, n (%)			
Yes	108 (91.5%)	52 (86.7%)	160 (89.9%)
No	10 (8.5%)	8 (13.3%)	18 (10.1%)
Serum EPO level (mU/mL)			
N	113	58	171
Mean (SD)	361.25 (556.018)	472.44 (763.935)	398.96 (634.147)
Median (Minimum, Maximum)	174.86 (6.0, 4460.0)	277.00 (16.9, 5514.0)	184.10 (6.0, 5514.0)
≤ 500 mU/mL, n (%)	87 (73.7%)	36 (60.0%)	123 (69.1%)
> 500 mU/mL, n (%)	26 (22.0%)	22 (36.7%)	48 (27.0%)
Missing, n (%)	5 (4.2%)	2 (3.3%)	7 (3.9%)
ECOG score, n (%)			
0	42 (35.6%)	21 (35.0%)	63 (35.4%)
1	70 (59.3%)	39 (65.0%)	109 (61.2%)
2	6 (5.1%)	0	6 (3.4%)

CRF = case report form; ECOG = Eastern Cooperative Oncology Group; ESA = erythropoiesis-stimulating agent; FAB = French-American-British; HMA = hypomethylating agent; IPSS = International Prognostic Scoring System; IPSS-R = Revised International Prognostic Scoring System; MDS-u = myelodysplastic syndrome unclassifiable; RA = refractory anemia; RAEB = RA with excess blasts; RARS = RA with ringed sideroblasts; RBC = red blood cell; RCMD = refractory cytopenia with multilineage dysplasia; RS = ring sideroblasts; SD = standard deviation; WHO = World Health Organization.

^a Per revised IWG 2018 (Platzbecker, 2019) the LTB subject is a subject who received 3 to 7 RBC units in the 16 weeks prior to study entry in at least 2 transfusion episodes. The HTB subject is a subject who received ≥ 8 RBC units in the 16 weeks prior to study entry in at least 2 transfusion episodes.

^b Final per investigator

^c Derived by sponsor based on central lab cytogenetic data and local lab results for bone marrow blasts, Hgb, platelets, and neutrophils.

^e Derived by sponsor based on central lab cytogenetic data.

Source: Table tsidm01_p2, Table tsidc01_p2, Table tsidc02_p2.

The Applicant's Position:

Disease and other baseline characteristics were generally well balanced between the 2 treatment groups and were in line with those expected in patients with LR MDS with transfusion dependent anemia after ESA failure (Applicant Table 17). Median serum EPO level was lower in the imetelstat group (174.86 mu/ml) compared to the placebo group (277.00 mU/mL), with 22.0% and 36.7% of subjects, respectively, having serum EPO > 500 mU/mL.

Of importance, median prior RBC transfusion burden was 6.0 units per 8 weeks (range: 4 to 33 and 4 to 13 units per 8 weeks for the imetelstat and placebo groups, respectively). In the 16 weeks prior to study entry, the median total number of RBC transfusion units was 10.0 units (range: 4 to 54 and 4 to 24 units per 16 weeks, respectively) for the 2 treatment groups. Overall, a larger proportion of subjects in the imetelstat group (82.2%) were classified per IWG 2018 as high transfusion burden (HTB) (≥ 8 RBC units in the 16 weeks prior to study entry in at least 2 transfusion episodes) compared to the placebo group (70.0%).

Version date: June 2022 (ALL NDA/ BLA reviews)

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The FDA's Assessment:

FDA agrees with the Applicant's position regarding disease and other baseline characteristics of subjects in Study MDS3001-Phase 3.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment compliance

Imetelstat was administered by qualified site staff, and the details of each administration were recorded in the eCRF. In both Phase 3 and Phase 2 of the MDS3001 study, mean relative dose intensity with respect to the planned dose was > 99% (99.6 + 1.92 and 100.1 + 2.44, respectively; Table tex01b), indicating good treatment compliance.

Premedication

Per protocol, all subjects who received an infusion of study drug had to be premedicated with an antihistamine (diphenhydramine 25 to 50 mg or equivalent) and a corticosteroid (hydrocortisone 100 to 200 mg or equivalent), either IV or orally. Premedications were administered per local standard of care approximately 1 hour prior to study drug infusion.

Concomitant medications

The use of concomitant medication was reported for the majority of subjects in the imetelstat group (98.3%) and all subjects (100%) in the placebo group and were generally balanced between the treatment groups (Table tsicm05_p2) and consistent with expected for a LR MDS older patient population.

The most common concomitant medications in the imetelstat and placebo groups, respectively, were iron chelating agents (63.6% and 62.7%).

A larger proportion of subjects in the imetelstat group than in the placebo group required concomitant use of granulocyte colony stimulating factors (34.7% vs. 3.4%).

A summary of concomitant medications started during treatment is provided in Table tsicm06_p2, and a summary of pre-study medications ongoing during treatment is provided in Table tsicm07_p2.

Rescue medication

Not relevant to the product and disease under study.

The Applicant's Position:

Treatment compliance in the Phase 3 study was high with most subjects having received > 99% of the planned dose. Premedication with steroid and antihistamine was administered before each cycle to minimize occurrence if infusion-related reactions (IRRs).

The FDA's Assessment:

The majority of patients (211) had prior ESA therapy (Table 18). Patients treated on the imetelstat arm of the Phase 3 portion of the study received prior ESA marginally more frequently than patients on the placebo arm or in the Phase 2 portion.

Table 18: Study MDS3001: Prior and subsequent anti-neoplastic therapies and concomitant medications

	Imetelstat (Phase 2) N=57	Imetelstat (Phase 3) N=118	Placebo (Phase 3) N=60
Prior ESA	51 (89%)	108 (92%)	52 (87%)
Prior anti-neoplastic therapy	26 (47%)	20 (17%)	9 (15%)
Concomitant medications	54 (95%)	117 (99%)	60 (100%)
Subsequent anti-neoplastic therapy	24 (42%)	40 (34%)	25 (42%)

Data cutoff: 13 Oct 2022

Source: FDA analysis using ADCM dataset

Prior anti-neoplastic therapy was given to 26 (47%) of patients in Phase 2, 20 (17%) of patients receiving imetelstat in Phase 3, and 9 (15%) of patients receiving placebo in Phase 3 (Table 19). In the Phase 2 study, the most common prior medications included lenalidomide (12), HMAs (8), investigational agents (5), rigosertib (5), and luspatercept (5). In the Phase 3 study, luspatercept (7), danazol (5), and roxadustat (5) were the most commonly used prior medications in patients on the imetelstat arm and luspatercept (4) and danazol (2) the most commonly used in the placebo arm. Note that some agents used (i.e., roxadustat, rigosertib) are not approved in the US.

Table 19: Study MDS3001: Prior systemic therapy

	Imetelstat (Phase 2) N=57	Imetelstat (Phase 3) N=118	Placebo (Phase 3) N=60
Any	26 (47%)	20 (17%)	9 (15%)
Lenalidomide	12 (21%)	1 (0.8%)	0
HMAs	8 (14%)	0	1 (1.7%)
Luspatercept*	5 (9%)	7 (6%)	4 (7%)
Danazol	1 (1.8%)	5 (4.2%)	2 (3.3%)
Investigational	5 (9%)	0	0
Roxadustat*	0	5 (4.2%)	1 (1.7%)

NDA/BLA Multi-disciplinary Review and Evaluation NDA 217779 imetelstat
 TRADENAME, imetelstat

Cyclosporine	1 (1.8%)	3 (2.5%)	0
Other	7 (12%)	2 (1.7%)	2 (3.3%)
Rigosertib	5 (9%)	0	0

* Agents that increase hemoglobin but are not active against the underlying MDS

Data cutoff: 13 Oct 2022

Source: FDA analysis using ADCM dataset

Of note, patients in the Phase 2 study were more likely to have 5q deletions and were more likely to receive lenalidomide or HMAs compared to patients in the Phase 3 study. This can be attributed to the fact that the protocol was modified during the course of the Phase 2 portion of the study to exclude patients with prior exposure to lenalidomide or HMAs and patients with 5q- syndrome, including in the Phase 3 portion of the protocol. Among patients in the Phase 3 portion of the study, slightly more patients were treated with prior systemic therapy in the imetelstat arm, with relatively more receiving roxadustat. This agent is not approved in the US and the implications of prior use of this agent are unclear.

Prior medications of any type were used by the majority of patients on both parts of the study and in patients treated with either imetelstat or placebo.

Table 20: Study MDS3001: Commonly used prior medications other than ESA and systemic therapy for MDS, by study part and treatment arm

	Imetelstat (Phase 2) N=57	Imetelstat (Phase 3) N=118	Placebo (Phase 3) N=60
Any	47 (82%)	112 (95%)	54 (90%)
Iron chelating agents*	28 (49%)	64 (54%)	25 (42%)
Drugs for acid related disorders	20 (35%)	34 (29%)	20 (33%)
Acting on renin-angiotensin	14 (24.6%)	31 (26%)	22 (37%)
Vitamins	12 (21%)	28 (24%)	10 (17%)
Antianemic preparations**	12 (21%)	27 (23%)	15 (25%)
Beta-blockers	13 (23%)	26 (22%)	13 (22%)
Lipid modifying agents	8 (14%)	26 (22%)	17 (28%)
Drugs used in diabetes	11 (19%)	25 (21%)	11 (18%)
Analgesics	21 (37%)	24 (20%)	17 (28%)
Antithrombotic agents	6 (10.5%)	21 (18%)	10 (17%)
Diuretics	14 (24.6%)	18 (15%)	11 (18%)

Medication categories based on CMLVL2 except as noted

*CMLVL4

**Includes folic acid and B12, excludes ESA

Data cutoff: 13 Oct 2022

Source: FDA analysis using ADCM dataset

Version date: June 2022 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

The majority of patients on both parts of the study, regardless of treatment arm, started new concomitant medications during treatment (Table 21). Notably, antibacterials for systemic use and immunostimulants (including colony stimulating agents such as myeloid growth factors) were more commonly started during treatment for patients receiving imetelstat compared to placebo. This may be attributed to the increased rate of neutropenia and infections observed in the imetelstat arm (see Section 8.2.4 for further discussion of these issues).

Table 21: Study MDS3001: Commonly used concomitant medications started during treatment excluding pre-infusion medications, by study part and treatment arm

	Imetelstat (Phase 2) N=57	Imetelstat (Phase 3) N=118	Placebo (Phase 3) N=60
Any	51 (89%)	109 (92%)	52 (87%)
Antibacterials for systemic use	43 (75%)	48 (41%)	20 (33%)
Analgesics	33 (58%)	41 (25%)	23 (38%)
Immunostimulants*	20 (35%)	42 (36%)	2 (3%)
Vaccines	2 (3.5%)	47 (40%)	19 (32%)
Diuretics	13 (23%)	24 (20%)	9 (15%)
Corticosteroids for systemic use	14 (25%)	19 (16%)	5 (8%)
Drugs for acid related disorders	17 (30%)	23 (19%)	8 (13%)
Antithrombotic agents	12 (21%)	14 (12%)	13 (22%)
Psycholeptics	11 (19%)	13 (11%)	8 (13%)
Anti-inflammatory and anti-rheumatic products	8 (14%)	13 (11%)	5 (8%)
Drugs for constipation	13 (23%)	12 (10%)	10 (16%)
Antihistamines for systemic use	13 (23%)	5 (4%)	1 (2%)
Drugs for functional gastrointestinal disorders	12 (21%)	12 (10%)	4 (7%)
Mineral supplements	11 (19%)	14 (12%)	2 (3%)
Antianemic preparations**	5 (9%)	15 (13%)	4 (7%)

Medication categories based on CMLVL2

*Includes colony stimulating factors, interferons

**Includes folic acid, ferrous sulfate, ferritin, ferrous fumarate in combination with folic acid, B12; excludes ESA

Data cutoff: 13 Oct 2022

Source: FDA analysis using ADCM dataset

More patients in the Phase 2 portion of the study and the placebo arm of the phase 3 portion received at least one subsequent anti-neoplastic therapy compared to patients in the imetelstat Phase 3 portion (Table 22). The most common subsequent therapies included HMA, lenalidomide, luspatercept, cytotoxic chemotherapy, and investigational therapies.

Among patients treated on the Phase 2 portion of the study, the most common subsequent anti-neoplastic treatments were HMAs, lenalidomide, and luspatercept. Two patients in the Phase 2 portion of the study received subsequent total body irradiation, suggesting plans for subsequent HSCT. It is unclear whether subsequent cytotoxic chemotherapy was part of a planned HSCT regimen.

Among patients on the Phase 3 portion of the study, use of HMA, lenalidomide, and investigational therapies was more common among patients on the placebo arm compared to the imetelstat arm. Use of luspatercept was similar between the two arms.

A small number of patients on each arm received subsequent therapy with erythropoietin stimulating agents.

Table 22: Study MDS3001: Subsequent anti-neoplastic therapy by study arm

	Imetelstat (Phase 2) N=57	Imetelstat (Phase 3) N=118	Placebo (Phase 3) N=60
Any	24 (42%)	40 (34%)	25 (42%)
HMA	12 (21%)	9 (8%)	7 (12%)
Lenalidomide	6 (11%)	3 (2.5%)	4 (7%)
Luspatercept	6 (11%)	26 (22%)	14 (23%)
Cytotoxic chemo	5 (9%)	4 (3.4%)	1 (1.7%)
Investigational	5 (9%)	1 (0.8%)	5 (8%)
ESA	1 (1.8%)	4 (3.4%)	2 (3.3%)

Data cutoff: 13 Oct 2022

Source: FDA analysis using ADCM dataset

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

8-week RBC-TI rates are summarized in

[Applicant](#) Table 23 and shown in

[Applicant](#) Figure 10. Transfusion independence intervals for 8-week RBC IT responders are shown in [Applicant Figure 7](#). Subgroup analysis of the primary endpoint is shown in [Applicant Figure 8](#).

Applicant Table 23: Rate of 8-week RBC TI (Phase 3, Intent-to-Treat Analysis Set)

	Imetelstat (N = 118)	Placebo (N = 60)	% Difference (95% CI) ^a	P value ^b
8-week RBC TI (%)	47 (39.8%)	9 (15.0%)		
95% CI for response rate (%) ^c	(30.93%, 49.25%)	(7.10%, 26.57%)	24.8% (9.90%, 36.89%)	< 0.001

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; IPSS = International Prognostic Scoring System; RBC = red blood cell; TI = transfusion independence.

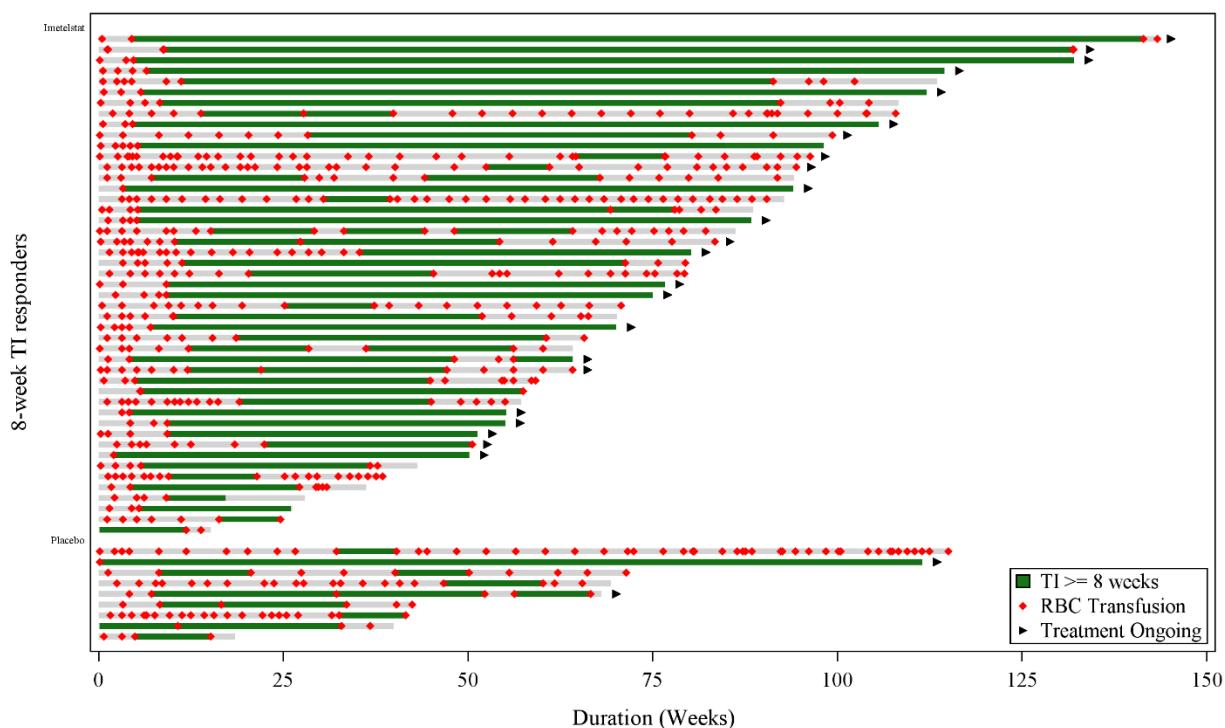
^a The 95% CI is based on Wilson Score method.

^b The P value is based on CMH controlling for prior RBC transfusion burden (≤ 6 vs. > 6 units RBC) and IPSS risk group (low vs. intermediate-1) applied to randomization.

^c Exact Clopper-Pearson confidence interval.

Source: Table tefti01a_p2.

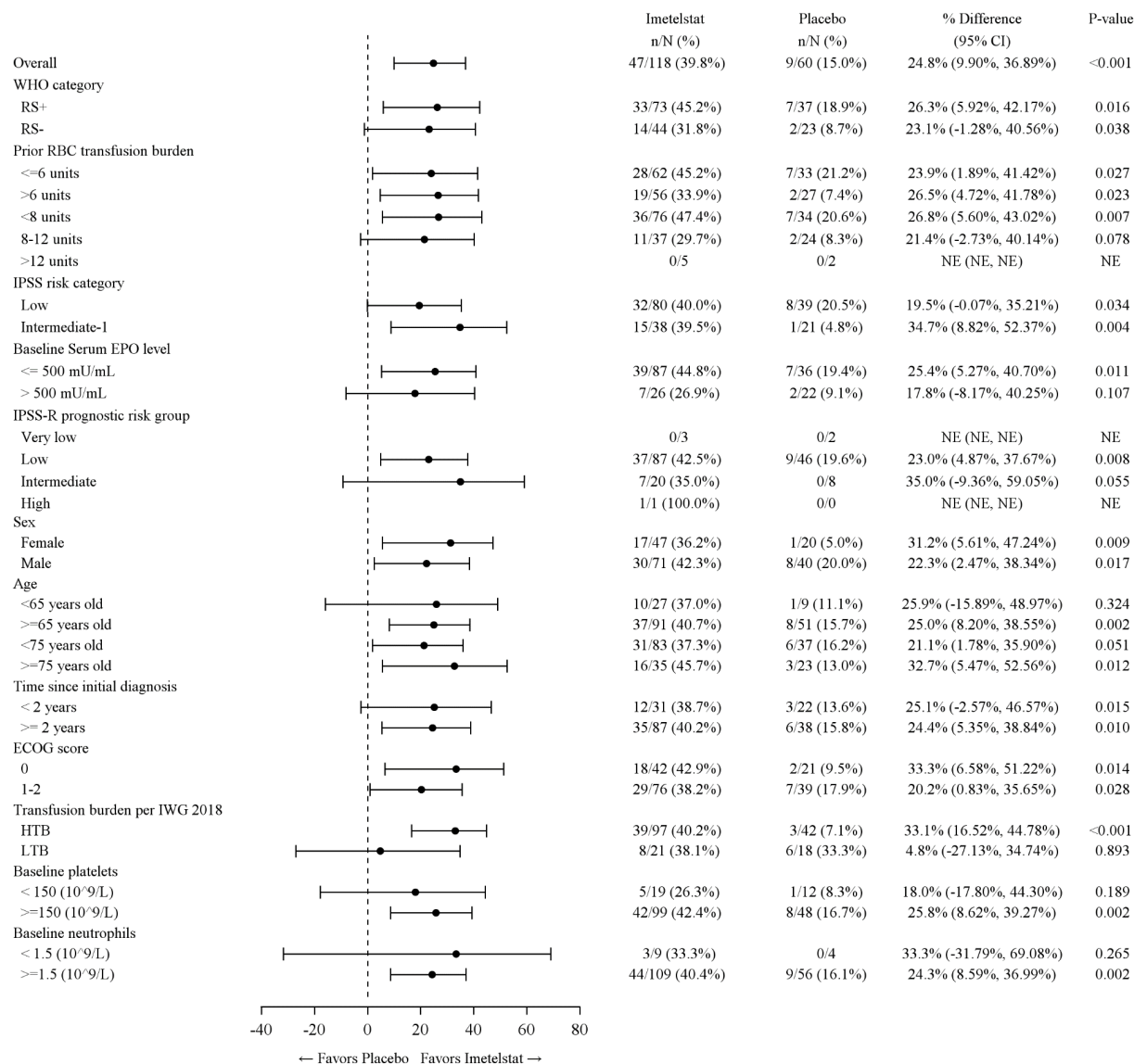
Applicant Figure 7: 8-week RBC TI Intervals (Phase 3, Intent-to-Treat 8-week TI Responder Analysis Set)



TI = transfusion independence; RBC = red blood cell

Source: Figure feftisw01a_p2

Applicant Figure 8: Rate of 8-Week RBC TI by Baseline Characteristics (Phase 3, Intent-to-Treat Analysis Set)



CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EPO = erythropoietin; HTB = high transfusion burden; IPSS = International Prognostic Scoring System; IPSS-R = revised International Prognostic Scoring System; IWG = International Working Group; LTB = low transfusion burden; NE = non-evaluable; RBC = red blood cell; RS = ring sideroblasts; TI = transfusion independence; WHO = World Health Organization.

Notes: The 95% CI is based on Wilson Score method.

The P value is based on CMH controlling for prior RBC transfusion burden (≤6 vs. >6 units RBC) and IPSS risk group (low vs. intermediate-1) applied to randomization.

Source: Figure fefti01a_p2.

The Applicant's Position:

The study met the primary endpoint with a highly statistically significant and clinically meaningful improvement in 8-week RBC TI rate in the imetelstat group (39.8% [47/118]) compared to the placebo group (15.0% [9/60]) (

[Applicant](#) Table 23 and

[Applicant](#) Figure 10). The difference in the rate of 8-week RBC TI between the 2 treatment groups was 24.8% (95% CI: 9.90%, 36.89%, $P < .001$).

In addition, subgroup analysis of 8-week TI based on demographics and the most relevant disease characteristics, showed an advantage for imetelstat over placebo in most subgroups tested. Statistically significant and clinically meaningful difference in 8-week RBC TI rates between the imetelstat and placebo groups was achieved irrespective of baseline RS status (26.3%, $P = .016$ [RS+] and 23.1%, $P = .038$ [RS-]), baseline RBC transfusion burden (23.9%, $P = .027$ [≤ 6 units] and 26.5%, $P = .023$ [> 6 units]), or IPSS disease category (19.5%, $P = .034$ [low] and 34.7%, $P = .004$ [intermediate-1]) ([Applicant Figure 8](#)).

Sensitivity analyses

Data

Sensitivity analyses were performed for the Phase 3 study to evaluate the robustness of the primary analysis and included:

- CMH test of 8-week based on the modified intent-to-treat (mITT) analysis set in the case there were subjects who were dosed but did not receive any assigned treatment
- CMH test of 8-week based on per-protocol (PP) analysis set
- CMH estimate of the odds ratio of 8-week RBC TI with the stratification factors and the associated 95% CI
- Comparison of 8-week RBC TI based on CMH test adjusted by values of prior RBC transfusion burden and IPSS risk group recorded on the eCRF
- Comparison of 8-week RBC TI based on CMH test without adjusting for the baseline stratification factors

Results of these analyses were supportive of the primary analysis (Table tefti02a_p2, Table tefti02b_p2, Table tefti02c_p2).

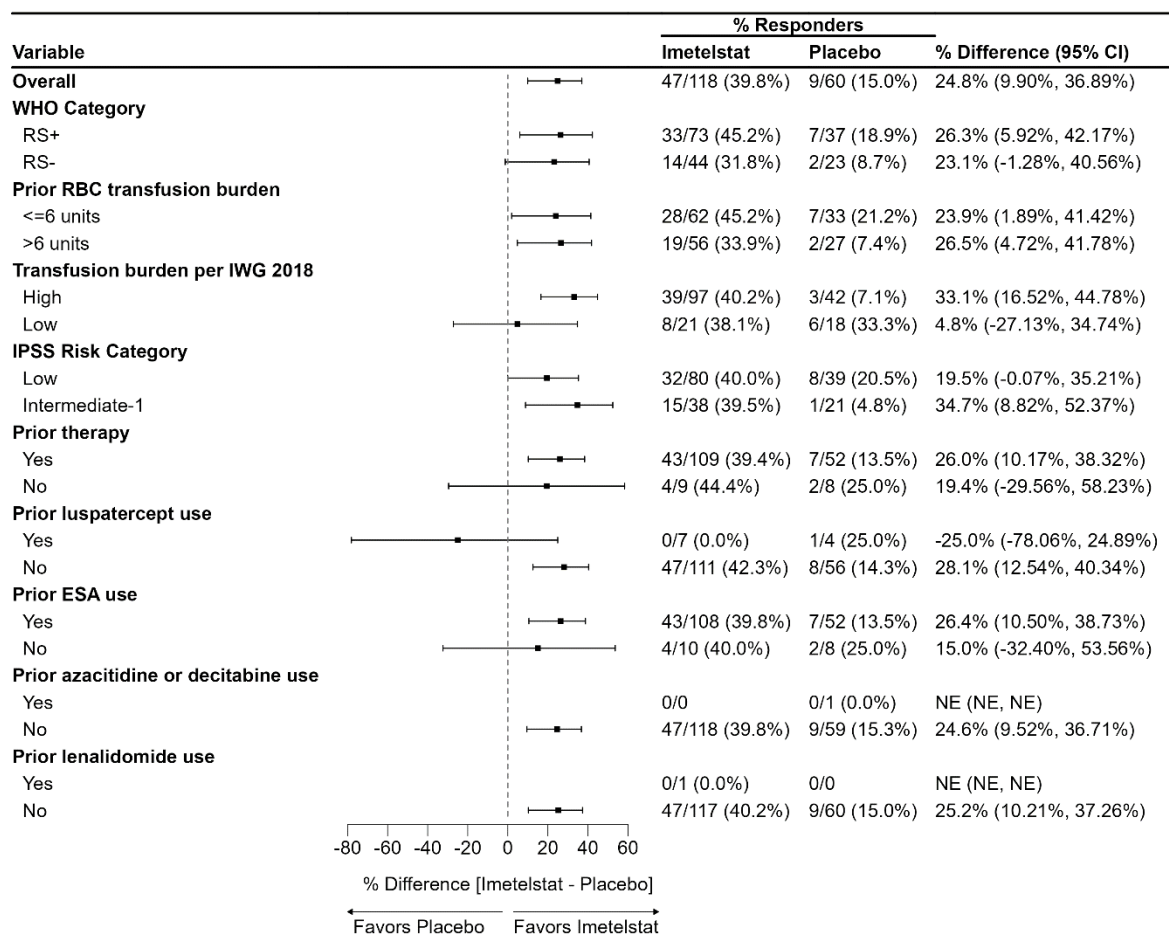
The FDA's Assessment:

FDA agrees that Study MDS3001-Part 2 (Phase 3) met its primary endpoint with a statistically significant improvement in 8-week RBC-TI rate in the imetelstat group compared to the placebo group (39.8% imetelstat versus 15.0% placebo; $p = <0.001$), equating to a rate difference of +24.8% (95% CI 9.9, 36.9) in favor of imetelstat. However, it should be noted that the clinical

meaningfulness of an 8-week RBC-TI period in the context of lower risk MDS is uncertain. In recent years, the general consensus among MDS experts has been that only a 16-week or longer period of transfusion independence is clinically meaningful (Platzbecker 2019). Therefore, the presumption in the use of the early outcome of 8-week RBC-TI is that the treatment effect seen early will persist for a more substantial period. Thus, the Applicant evaluated alternative definitions of RBC-TI reflecting greater durability, which are discussed in the “Efficacy Results – Secondary and other relevant endpoints” section below.

Subgroup analyses of 8-week RBC-TI in the Phase 3 study based on demographics and most relevant disease characteristics per FDA analysis are shown in Figure 9 below. These analyses showed a numerical advantage for imetelstat over placebo in most subgroups. However, the 8-week RBC-TI rate was higher with placebo in the subgroup of patients with prior luspatercept use, with 0/7 (0%) subjects treated with imetelstat achieving an 8-week RBC-TI versus 1/4 (25.0%) subjects treated with placebo, equating to a rate difference of -25.0% (95% CI -78.1%, 24.9%) in favor of placebo. In comparison, the 8-week RBC-TI rate in the Phase 2 study was 3/5 (60%) in patients previously treated with luspatercept, with 2 subjects achieving at least a 1-year RBC-TI. Given the small sample sizes in both Phase 3 and Phase 2, it is difficult to make any conclusions regarding efficacy of imetelstat in the subgroup of patients with prior luspatercept treatment.

Additionally, the treatment effect was marginal for subjects with lower transfusion burden at baseline (defined as 4-7 units RBCs in 16 weeks in at least 2 transfusion episodes), with a difference in 8-week RBC-TI rate of only +4.8% (95% CI -27.1, 34.7) between arms in favor of imetelstat.

Figure 9: MDS3001-Phase 3: Subgroup analysis of rate of 8-week RBC-TI

CI = Confidence Interval; NE = Not Evaluable

Source: FDA analysis based on ADSL and ADBDC datasets. Data cutoff: 13 Oct 2022.

Data Quality and Integrity

Data:

Consistency of Transfusion Practices

Additional analysis was performed in order to assess for any potential bias of study investigators for when RBC transfusions were prescribed. Per protocol, transfusions were administered as needed per investigator discretion and according to local standard practices. The protocol did not outline transfusion parameters, such as Hgb level threshold. Results of this analysis are summarized in [Applicant Table 24](#). Analysis performed evaluating the Hgb levels

Version date: June 2022 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

prior to receiving RBC transfusions on study demonstrated a median Hgb of 7.4 g/dL on imetelstat and 7.5 g/dL on placebo. Pre-study baseline Hgb levels leading to transfusions were also compared to on-study Hgb levels resulting in transfusions. This demonstrated a median change (pre-study vs. on-study) of -0.45 g/dL on imetelstat and -0.30 g/dL on placebo. Based on these data, while on treatment, there is no notable difference in investigators transfusion parameters between treatment groups, or within each group prior to enrollment compared to while on study.

Applicant Table 24: Summary of Pre-transfusion Hemoglobin (Phase 3, Intent-to-Treat Analysis Set)

	Imetelstat (N = 118)	Placebo (N = 59)
Pre-transfusion Hgb (g/dL)		
n	106	56
Mean (SD)	7.394 (0.6942)	7.470 (0.5925)
Median	7.390	7.501
Minimum, Maximum	4.70, 9.85	5.80, 8.75
Pre-transfusion Hgb – Pretreatment Hgb (g/dL)		
n	106	56
Mean (SD)	-0.435 (0.7495)	-0.353 (0.7184)
Median	-0.445	-0.295
Minimum, Maximum	-2.20, 1.43	-2.90, 1.02

Hgb = hemoglobin; RBC = red blood cell; SD = standard deviation.

Note Pre-transfusion Hgb is the last Hgb within 3 days of an RBC transfusion. RBC transfusions before the first transfusion in follow-up or subsequent anticancer therapy are considered. Hb values within 14 days of RBC transfusions are excluded due to impact of transfusions.

Source: Table tefhgb02_p2.

The Applicant's Position:

Overall Quality

Geron was the sponsor for the Phase 3 study. The monitoring was outsourced to a CRO and performed in accordance with the CRO's SOPs. The data submitted in this NDA are of adequate quality to perform the safety and efficacy review. Overall, there are no concerns regarding the integrity of data in this submission.

This study was conducted in accordance with the FDA and Health Canada regulations, the ICH E6 Guidelines for GCP, and applicable local, state, national laws. For EU member states, this includes Directive 201/20/EC, Directive 205/28/EC, and other directives as applicable as well as applicable local and national laws.

The Sponsor performed oversight of the data management of this trial, including approval of the CRO's data management and data quality plans.

An electronic data capture (EDC) vendor, (b) (4), developed and provided eCRFs for this study. The CRO, was responsible for data management of this trial, including quality checking of the data. The data were collected via EDC using eCRFs. A data quality plan was produced by the CRO that describes the quality checking to be performed on the data. The site was responsible for data entry into the EDC system. In the event of discrepant data, the CRO requested data clarification from the sites, which the sites resolved electronically in the EDC system. eCRFs and query resolution documentation was maintained in the EDC system's audit trail. System backups for data stored at the CRO was performed in accordance with the CRO's standard operating procedures.

Study sites were monitored by the CRO at regular intervals following the principles of GCP, regulatory, and ICH guidelines. Monitoring visits included review and inspection of the facilities and records relevant to the study, which included but were not limited to subject signed ICFs, source documentation, regulatory and essential documents, eCRFs, and drug accountability records. Between site visits, the sponsor maintained appropriate communications with the investigator site personnel.

During this study, 7 investigator site audits were conducted.

The FDA's Assessment:

Per protocol, transfusions were administered as needed per investigator discretion and according to local standard practice. Although there was no major difference in the mean and median pre-transfusion Hgb between the imetelstat and placebo groups as noted by the Applicant above, there were differences in 8-week RBC-TI rates by region of enrollment. The 8-week RBC-TI rate with imetelstat was much lower in the subgroup of patients enrolled at sites within the US compared to non-US sites, with a difference in response rate of only 12.5% for US subjects compared to 25.5% for non-US subjects (Table 38). Although no definitive conclusions can be drawn due to the small sample size of the subgroups and the lack of prespecified subgroup hypothesis testing, potential impact of region-specific patient or treatment-related factors cannot be ruled out.

Additionally, the Agency sent an information request to the Applicant requesting clarification on the time period during which RBC and platelet transfusions were required to be reported. Based on the Applicant's response to the Agency's information request, as of Protocol Amendment 7 (dated 2 Sept 2021), investigators were not reported to report RBC transfusions that occurred after the first RBC transfusion in the post-treatment follow-up period. In addition, the protocol did not mandate the collection of platelet transfusion data after the end of treatment as part of post-treatment follow-up; however, if subjects had ongoing Grade 3+ thrombocytopenia at the time of post-treatment follow-up and platelet transfusions were given as part of treatment for the AE of thrombocytopenia, investigators were to report the

transfusion in association with the thrombocytopenia AE. Given this, there may have been under-reporting of RBC and platelet transfusions that occurred after the end of treatment.

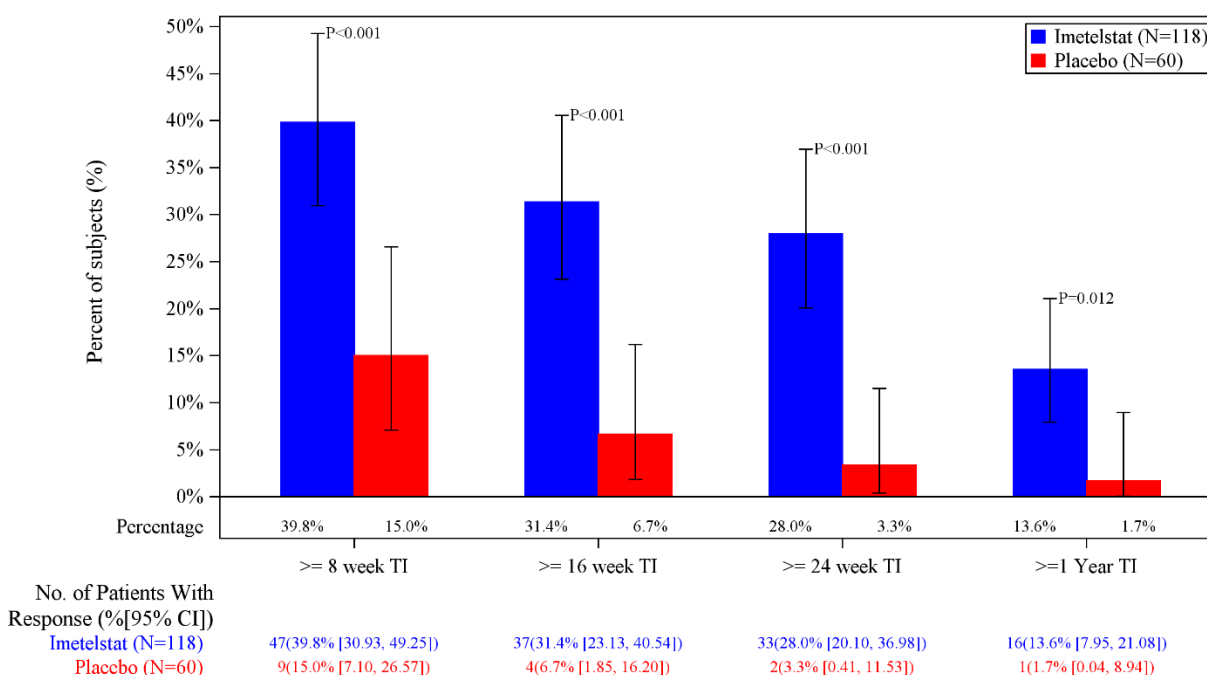
Efficacy Results – Secondary and other relevant endpoints

Data:

RBC IT rates, including 8- and 24-week TI (primary and key secondary endpoints) are shown in

[Applicant Figure 10](#). Though not explicit endpoints, TI rate for ≥ 16 weeks and 1 year was also significantly higher with imetelstat than placebo ($P < .001$ and $P = .012$, respectively).

Applicant Figure 10: Transfusion Independence in Imetelstat Versus Placebo-Treated Subjects With LR MDS (Phase 3; Intent-to-Treat Analysis Set)



Results from key secondary endpoints and other relevant endpoints are summarized below. Note nominal (unadjusted for multiplicity) p-values are shown throughout this document.

≥ 24 -week RBC TI

The key secondary endpoint of ≥ 24 -week RBC-TI rate is summarized in

[Applicant Table 25](#) and shown in

Applicant Figure 10. Subgroup analysis of > 24-week TI is shown in
 Applicant Figure 11.

Applicant Table 25: Rate of 24-week RBC TI (Phase 3, Intent-to-Treat Analysis Set)

Efficacy Endpoint Statistic	Imetelstat N = 118	Placebo N = 60
Transfusion Independence		
≥ 24-week TI, n (%)	33 (28.0%)	2 (3.3%)
95% CI for response rate ^a	(20.10%, 36.98%)	(0.41%, 11.53%)
% Difference (95% CI) ^b	24.6% (12.64%, 34.18%)	
p-value ^c	< 0.001	

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; IPSS = International Prognostic Scoring System; RBC = red blood cell;
 TI = transfusion independence.

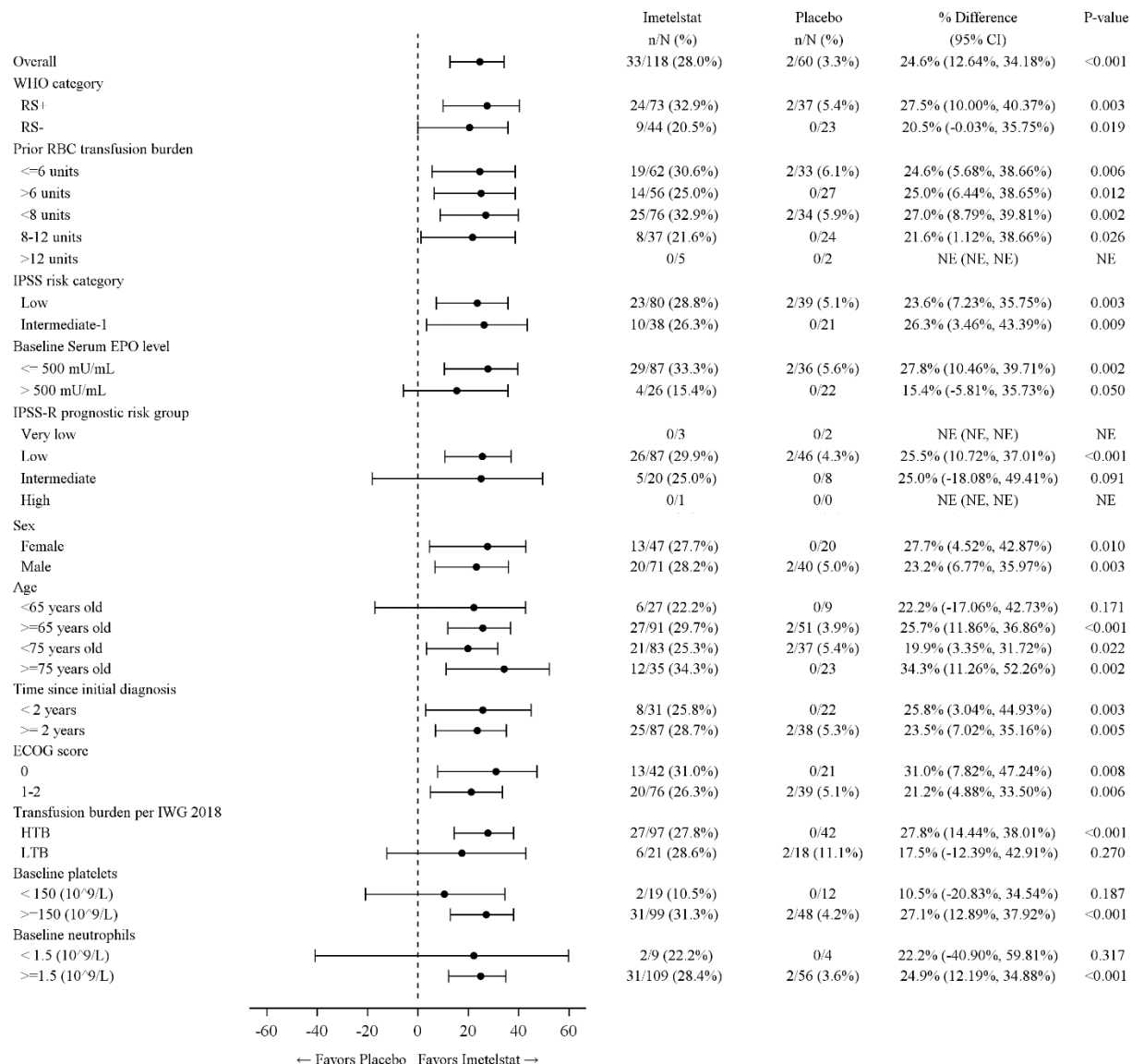
^a Exact Clopper-Pearson confidence interval.

^b The 95% CI is based on Wilson Score method.

^c The P value is based on CMH controlling for prior RBC transfusion burden (≤6 vs. >6 units RBC) and IPSS risk group (low vs. intermediate-1) applied to randomization.

Source: Table tefti05a_p2.

Applicant Figure 11: Rate of 24-Week RBC TI by Baseline Characteristics (Phase 3, Intent-to-Treat Analysis Set)



CI = confidence interval; CMH = Cochran-Mantel-Haenszel; EPO = erythropoietin; HTB = high transfusion burden; IPSS = International Prognostic Scoring System; IPSS-R = revised International Prognostic Scoring System; IWG = International Working Group; LTB = low transfusion burden; NE = non-evaluable; RBC = red blood cell; RS = ring sideroblasts; TI = transfusion independence; WHO = World Health Organization.

Notes: The 95% CI is based on Wilson Score method.

The P value is based on CMH controlling for prior RBC transfusion burden (≤6 vs. >6 units RBC) and IPSS risk group (low vs. intermediate-1) applied to randomization.

Source: Figure fefti02_p2.

Duration of RBC TI

Duration of ≥ 8 -week and ≥ 24 -week RBC TI is summarized in Applicant Table 26 and the KM curve for 8-week TI responders is shown in Applicant Figure 12.

Applicant Table 26: Duration of RBC TI (Phase 3, Intent-to-Treat Analysis Set)

Efficacy Endpoint Statistic	Imetelstat N = 118	Placebo N = 60
Duration of Transfusion Independence (weeks)		
8-week TI	47	9
Median (95% CI) ^a	51.6 (26.86, 83.86)	13.3 (8.00, 24.86)
Hazard ratio (95% CI) ^b	0.23 (0.091, 0.571)	
p-value ^c	< 0.001	
24-week TI	33	2
Median (95% CI) ^a	80.0 (51.57, NE)	NE (24.86, NE)
Hazard ratio (95% CI) ^b	0.59 (0.069, 5.103)	
p-value ^c	0.655	

CI = confidence interval; IPSS = International Prognostic Scoring System; NE = not estimable; RBC = red blood cell; TI = transfusion independence.

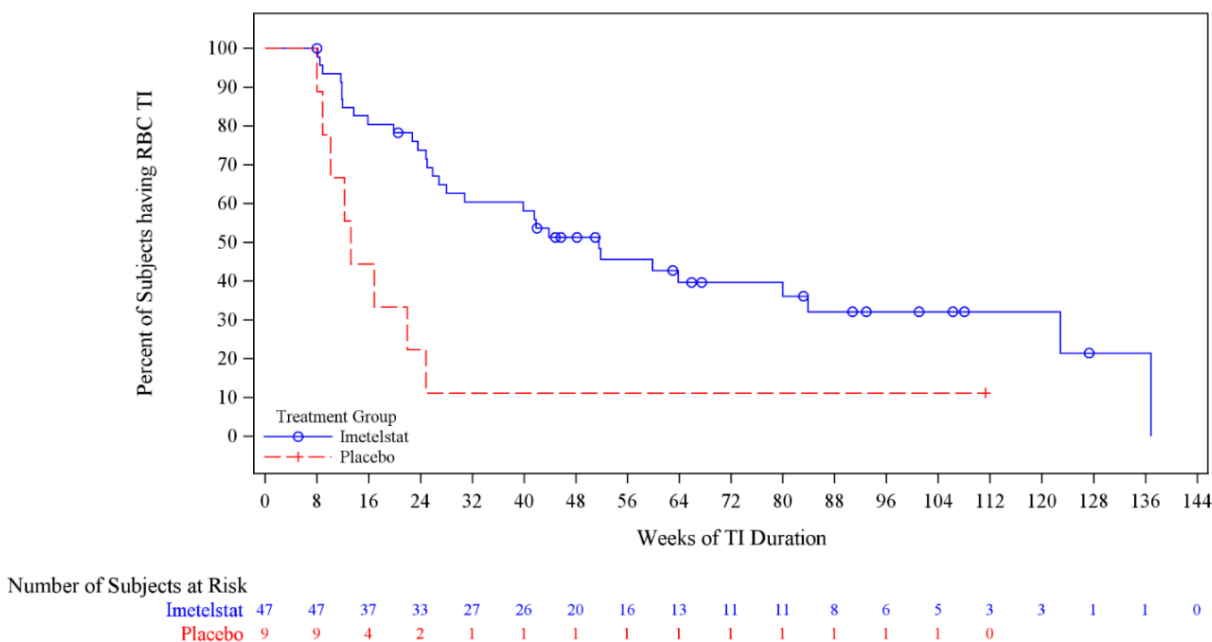
^a Based on Kaplan-Meier product limit estimates.

^b Hazard ratio and 95% CI are from the Cox proportional hazard model, stratified by prior RBC transfusion burden (≤ 6 vs. > 6 units RBC) and IPSS risk group (low vs. intermediate-1), with treatment as the only covariate.

^c P value (two-sided) for superiority of imetelstat versus placebo in hazard ratio, using stratified log-rank test.

Source: Table tefdti02_p2, Table tefdti01_p2.

Applicant Figure 12: Kaplan-Meier Plot of Duration of RBC TI (Phase 3, ITT 8-Week TI Responder Analysis Set)



The plot only includes responders.

ITT = intent-to-treat; RBC = red blood cell; TI = transfusion independence

Source: Figure fefdti02_p2.

Clinically meaningful durability of RBC TI for subjects who achieved 8-week RBC TI was achieved in the imetelstat group compared to placebo irrespective of baseline RS status (median 46.9 weeks versus 16.9 weeks, HR = 0.32, P = .035 [RS+] and median 51.6 weeks versus 11.2 weeks, HR 0.11, P = .062 [RS-]), baseline RBC transfusion burden (median 51.9 weeks versus 16.9 weeks, HR = 0.35, P = .035 [≤ 6 units] and median 39.9 weeks versus 8.4 weeks, HR = 0.04, P < .001 [> 6 units]), or IPSS risk category (median 43.9 weeks versus 15.1 weeks, HR = 0.26, P = .004 [low] and median 51.6 weeks versus 10.1 weeks, HR = 0.15, P = .128 [intermediate-1]) (Figure fefdti04_p2).

Additionally, imetelstat treatment had a favorable clinical benefit in durability of RBC TI across many other subgroups, for subjects who achieved 8-week RBC TI (Figure fefdti04_p2 and Table tefdti04_p2).

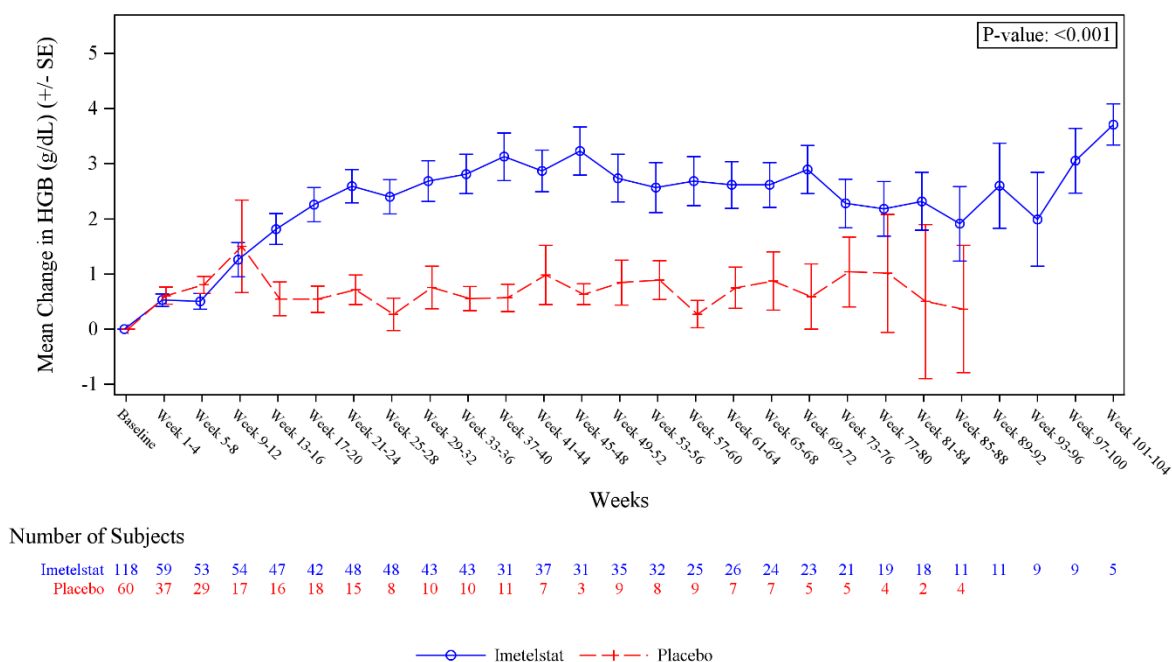
Change in Hemoglobin Levels

Imetelstat treatment led to a significant and sustained increase in Hgb levels (based on central laboratory results) compared to placebo (least squares [LS] mean difference in Hgb increase was 1.18 g/dL, 95% CI: 0.693, 1.665, P < .001; Table tefhgb01a_p2). Mean change from baseline in Hgb values over time, shown in Applicant Figure 13, was significantly higher with imetelstat

treatment than placebo, indicating clinical benefit with imetelstat even in subjects who did not achieve RBC TI.

Median Hgb rise in the longest TI period from pretreatment levels for 8-week RBC TI responders was 3.6 g/dL for the imetelstat group compared to 0.8 g/dL in the placebo group (Applicant Table 27). Median Hgb peak in the longest RBC TI interval was 11.3 g/dL in the imetelstat group compared to 8.9 g/dL in the placebo group.

Applicant Figure 13: Changes in Mean Hemoglobin Levels Over Time in Weeks (Phase 3, Intent-to-Treat Analysis Set)



HGB = hemoglobin; HI-E = hematologic improvement-erythroid; SE = standard error.

Notes: The mean changes from the minimum HGB of the values that were after 14 days of transfusions in the 8 weeks prior to the first dose date are shown.

Data points that have less than 4 subjects are not shown.

P-value is between treatment arms based on a mixed model for repeated measures with HGB change as dependent variable, week, stratification factors, min HGB in 8 weeks prior to first dose, and treatment arm as independent variables with autoregressive moving average (ARMA(1,1)) covariance structure.

Source: SCE Figure 12

Applicant Table 27: Change in Hgb Level in 8-week TI Responder (Phase 3, ITT 8-week TI Responder Analysis Set)

Efficacy Endpoint Statistic	Imetelstat N = 118	Placebo N = 60
Pretreatment Hgb level (g/dL)		

Efficacy Endpoint Statistic	Imetelstat N = 118	Placebo N = 60
n	47	9
Mean (SD)	7.871 (0.5524)	8.176 (0.8508)
Median (Minimum, Maximum)	7.917 (6.53, 9.23)	8.360 (6.23, 9.16)
Maximum Hgb value in the longest RBC TI interval excluding the first 2 weeks (g/dL)		
n	46	8
Mean (SD)	11.602 (2.5288)	8.900 (0.5292)
Median (Minimum, Maximum)	11.250 (8.00, 21.90)	8.850 (7.90, 9.70)
Hgb rise in the longest RBC TI interval (g/dL)^a		
n	46	8
Mean (SD)	3.738 (2.5794)	0.757 (0.6709)
Median (Minimum, Maximum)	3.550 (-0.07, 13.76)	0.800 (-0.16, 1.67)

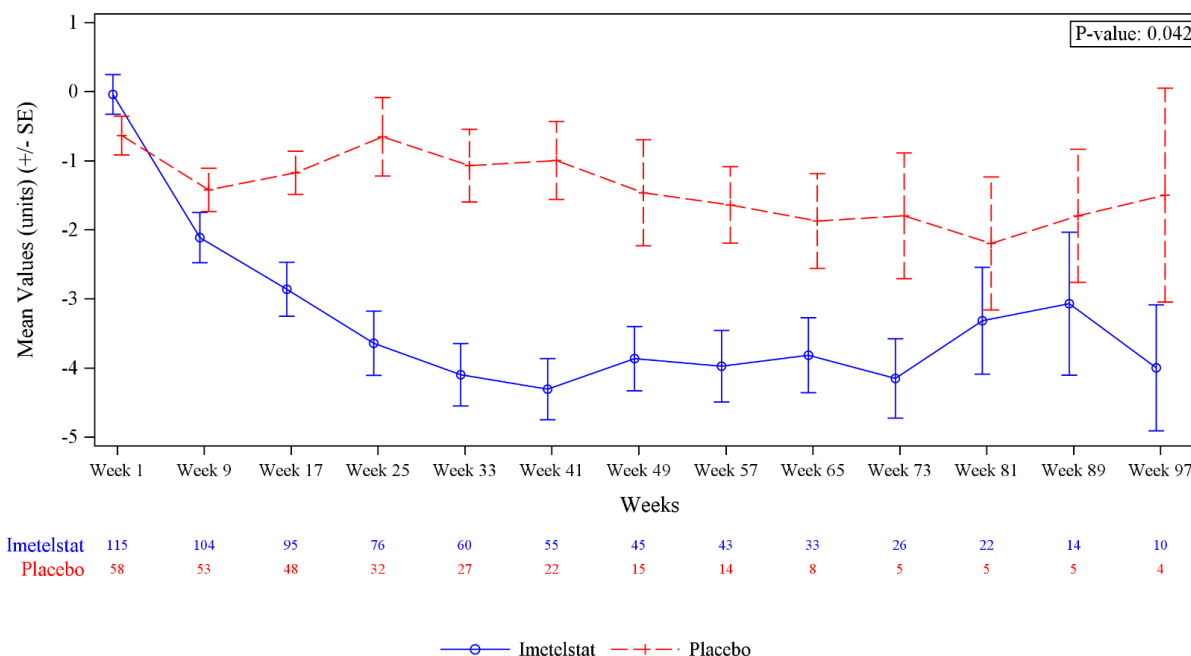
Hb = hemoglobin; RBC = red blood cell; SD = standard deviation; TI = transfusion independence.

^a The Hb rise = the maximum Hb value in the longest transfusion free interval excluding the first 2 weeks – the pretreatment Hb level. Pretreatment Hb level was defined as the average of all Hb values in the 8 weeks prior to the first dose date, including the value on the first dose date and excluding values that were within 14 days after transfusion (thus, considered to be influenced by transfusion) for all treated subjects. If there were no Hb values that met this definition of not being influenced by transfusions, then the baseline value was used. For subjects who have been randomized but not treated with any study drug, the last non-missing Hb, or the average if multiple values from the same date, from local or central lab collected on or before the randomization date was used for pretreatment Hb.

Change in Transfusion Burden

Mean absolute change from baseline in RBC transfusion burden during the best 8-week interval ([Applicant Figure 14](#)) for the imetelstat group was -4.3 units (range: -24 to 15) and for the placebo group -3.6 units (range: -11 to +2). Least squares mean absolute change in RBC units from prior transfusion burden for all subjects was significantly lower in the imetelstat group versus the placebo group, with the LS mean difference of -0.97 units (P = .042) (Table teftran12_p2).

Applicant Figure 14: Absolute Change in RBC Transfusion Units in 8-week Interval Over Time (Phase 3, Intent-to-Treat Analysis Set)



RBC = red blood cell, SE = standard error.

Notes: The point at week X represents the absolute change in RBC transfusion units in the post-baseline 8-week interval starting week X from the prior transfusion burden. Prior RBC transfusion burden is defined as the maximum number of RBC units transfused over any consecutive 8 weeks prior to study entry.

Data points that have less than 4 subjects are not shown.

P-value is between treatment arms based on a mixed model for repeated measures with change in transfusion reduction as dependent variable, week, stratification factors, prior transfusion burden, and treatment arm as independent variables with autoregressive moving average (ARMA(1,1)) covariance structure.

Source: SCE Figure 14.

Rate of HI-E Per Modified IWG 2018

Analysis of HI-E was performed using the revised 2018 IWG criteria, which is considered more clinically relevant in MDS than the previous IWG 2006 criteria (Platzbecker, 2019), as it emphasizes durability of response over a 16-week interval versus an 8-week interval used by the 2006 IWG criteria. HI-E results for both IWG 2006 and IWG 2018 are shown in Applicant Table 28. HI-E per IWG 2018 criteria was 42.2% in subjects treated with imetelstat vs. 13.3% with placebo (P < .001), reflecting the increased durability of the RBC-TI response with imetelstat (see also

Applicant Figure 10 for 16-week RBC TI rates). Among low transfusion burden (LTB) subjects (who received 3 to 7 RBC units in the 16 weeks prior to study entry), the HI-E response rate was 33.3% and 22.2% in imetelstat and placebo subjects, respectively (P = .562). Among HTB

subjects (who received ≥ 8 RBC units in the 16 weeks prior to study entry), 30.9% of imetelstat subjects and none in the placebo group had a major HI-E response ($P < .01$) and 44.3% of the imetelstat-treated subjects compared to 9.5% of the placebo-treated subjects had a minor HI-E response ($P < .001$).

The imetelstat group also demonstrated statistically significant differences compared to the placebo group in hematologic improvement per revised IWG 2018 criteria group across key subgroups, including RS status (27.7%, $P = .01$ [RS+] and 32.0%, $P = .007$ [RS-]), baseline RBC transfusion burden (23.8%, $P = .021$ [≤ 6 units] and 35.4%, $P = .003$ [> 6 units]), or IPSS disease category (29.6%, $P = .001$ [low] and 27.3%, $P = .026$ [intermediate-1]) (Table tefphi05_p2).

Subgroup analysis for the rate of hematologic improvement per modified IWG 2006 criteria (derived by the sponsor) is presented in Table tefhie02_p2 and Figure fefhie02_p2.

Applicant Table 28: Hematologic Improvement (Phase 3, ITT Aalysis Set)

Efficacy Endpoint Statistic	Imetelstat N = 118	Placebo N = 60
HI-E per IWG 2006, n (%)	75 (63.6%)	31 (51.7%)
95% CI for response rate ^a	(54.20%, 72.22%)	(38.39%, 64.77%)
% Difference (95% CI) ^b	11.9% (-4.10%, 27.56%)	
p-value ^c	0.112	
≥ 1.5 g/dL increase in Hgb lasting ≥ 8 weeks, n (%)	40 (33.9%)	6 (10.0%)
95% CI for response rate ^a	(25.44%, 43.19%)	(3.76%, 20.51%)
% Difference (95% CI) ^b	23.9% (9.98%, 34.95%)	
p-value ^c	< 0.001	
Transfusion reduction by ≥ 4 units/8 weeks, n (%)	71 (60.2%)	30 (50.0%)
95% CI for response rate ^a	(50.75%, 69.07%)	(36.81%, 63.19%)
% Difference (95% CI)	10.2% (-5.94%, 25.89%)	
p-value ^c	0.175	
HI-E per IWG 2018		
LTB^d subjects, n (%)	21 (17.8)	18 (30.0)
HI-E response (16-week RBC TI), n (%)	7 (33.3)	4 (22.2)
95% CI for response rate ^a	(14.59, 56.97)	(6.41, 47.64)
% Difference (95% CI) ^b	11.1 (-20.31, 38.96)	
p-value ^c	0.562	
HTB^d subjects, n (%)	97 (82.2)	42 (70.0)
Major HI-E response (16-week RBC TI), n (%)	30 (30.9)	0
95% CI for response rate ^a	(21.93, 41.12)	(0.00, 8.41)
% Difference (95% CI) ^b	30.9 (17.29, 41.24)	
p-value ^c	< 0.001	
Minor HI-E response (50% RBC units reduction in 16 weeks), n (%)	43 (44.3)	4 (9.5)

Efficacy Endpoint Statistic	Imetelstat N = 118	Placebo N = 60
95% CI for response rate ^a	(34.24, 54.77)	(2.66, 22.62)
% Difference (95% CI) ^b	34.8 (17.60, 47.05)	
p-value ^c	< 0.001	
LTB + HTB^d subjects, n (%)	118 (100.0)	60 (100.0)
HI-E response (16-week TI or 50% reduction in HTB subjects), n (%)	50 (42.4)	8 (13.3)
95% CI for response rate ^a	(33.33, 51.81)	(5.94, 24.59)
% Difference (95% CI) ^b	29.0 (14.23, 40.79)	
p-value ^c	< 0.001	

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; IPSS = International Prognostic Scoring System; IWG = International Working Group; RBC = red blood cell; TI = transfusion independence.

^a Exact Clopper-Pearson confidence interval.

^b The 95% CI is based on Wilson Score method.

^c The P value is based on CMH controlling for prior RBC transfusion burden (≤ 6 vs. > 6 units RBC) and IPSS risk group (low vs. intermediate-1) applied to randomization.

^d Per revised IWG 2018, LTB subject is a subject who received 3 to 7 RBC units in the 16 weeks prior to study entry in at least 2 transfusion episodes. HTB subject is a subject who received ≥ 8 RBC units in the 16 weeks prior to study entry in at least 2 transfusion episodes.

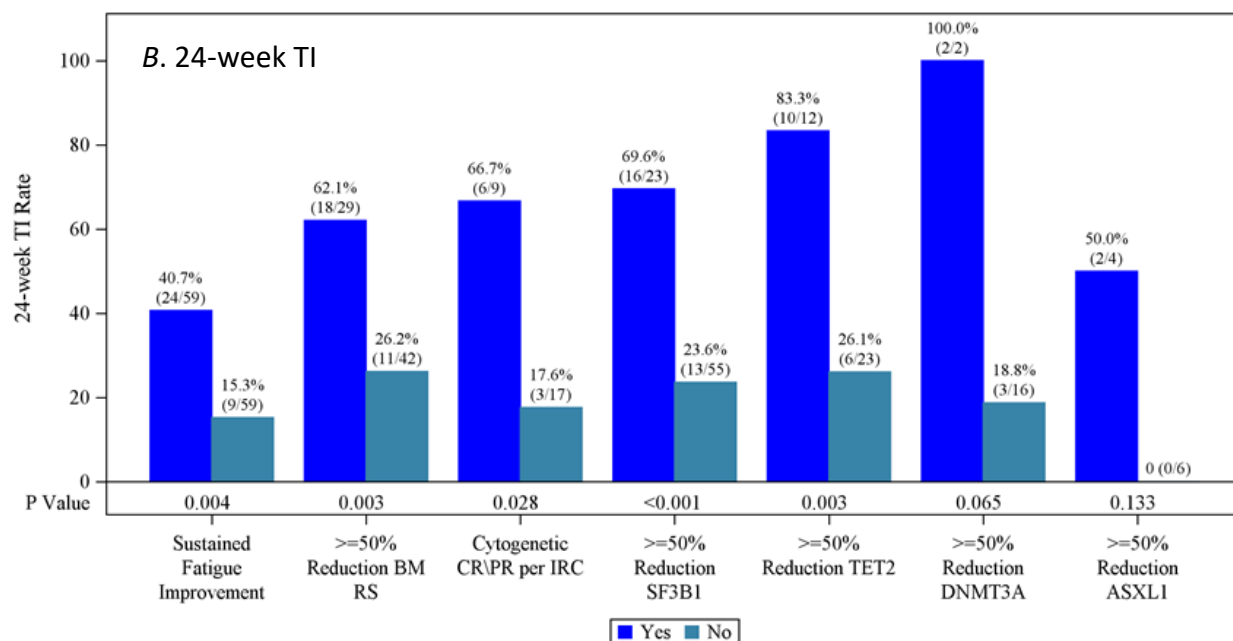
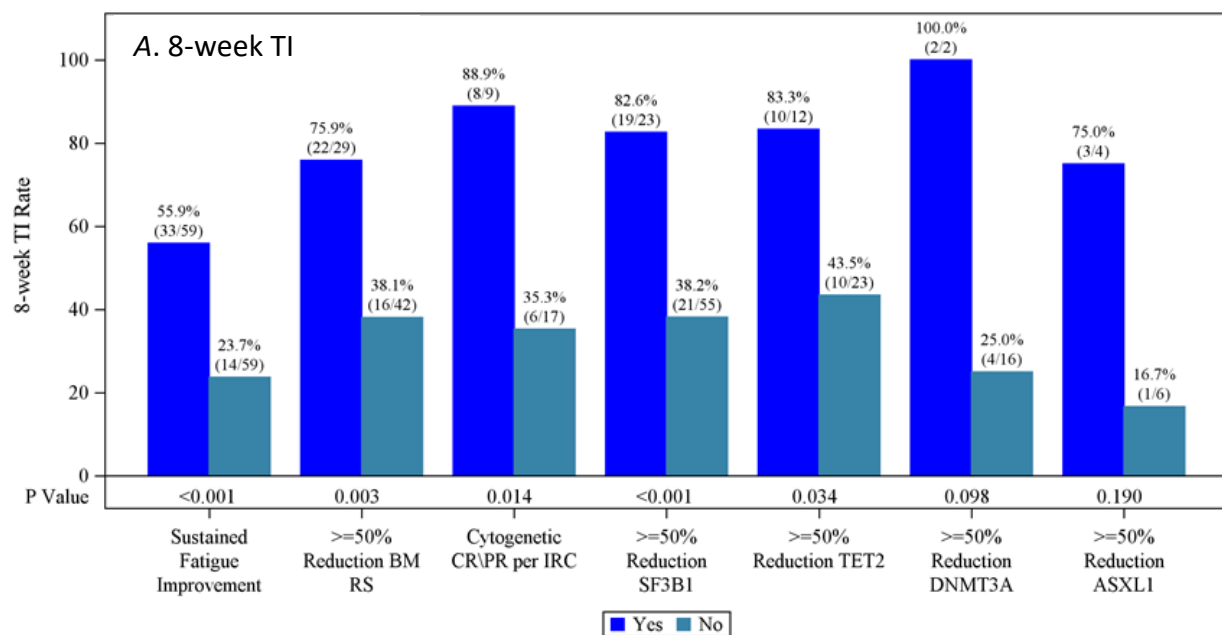
Source: Table tefphi03a_p2, Table tefphi01a_p2.

Additional Measures of Clinical Benefit Associated with Achieving TI

In addition to high rates of TI across various LR MDS subgroups with accompanying improvement in Hgb and reduction in transfusion burden among TI responders, subjects treated with imetelstat experienced other benefits. These include clinical benefits such as improvement in patient-reported symptoms of fatigue and lack of deterioration of dyspnea, as well as improvements in measures of LR MDS disease burden indicators such as cytogenetic responses, reduction of variant allele frequency (VAF) for mutations characteristic of MDS, and reduction in BM features of MDS such as RS+ cells.

Importantly, all the above measures of clinical benefit and evidence of disease modification were more likely to occur in subjects who experienced both ≥ 8 - and ≥ 24 -week TI ([Applicant Figure 15](#)). This association reinforces the conclusion that TI is an important outcome reflecting improvement in the signs and symptoms of LR MDS and that achieving TI results in additive clinical benefits across multiple efficacy endpoints.

Applicant Figure 15: 8- and 24-week TI in Imetelstat Treated Subjects by Associated Outcome Measures in Study MDS3001-Phase 3



BM = bone marrow; CR = complete response; IRC = Independent Review Committee; PR = partial response; RS = ring sideroblasts; TI = transfusion independence

P-value is calculated using Fisher exact test between yes vs no in each outcome

Source: Figure fefti04_p2 and Figure fefti05_p2

Cytogenetic Responses

A key characteristic of LR MDS is the absence of increased bone marrow blasts (IPSS low risk: < 5%; intermediate 1 risk: 5% to 10%; (Greenberg, 1997)). In the MDS3001-Phase 3 study, 97.2% of subjects had $\leq$ 5% BM (Applicant Table 17), thus the assessment of CR, PR or mCR by IWG 2006 criteria (which is generally applied only to patients with BM blasts > 5%), has limited applicability to this patient population.

Twenty-two percent (26/118) of subjects in the imetelstat group and 21.7% (13/60) in the placebo group had a baseline cytogenetic abnormality and were considered for cytogenetic response by IRC adjudication. Based on IRC adjudication, the cytogenetic response rate (cytogenetic CR + PR) was 9/26 (34.6%, 95% CI: 17.21%, 55.67%) in the imetelstat group and 2/13 (15.4%, 95% CI: 1.92%, 45.45%) in the placebo group (% difference 19.2%; 95% CI: -15.93%, 43.78%; P = .216) (Table tefbr02_p2). Despite not reaching statistical significance due to small sample size, objective cytogenetic responses favored the imetelstat group.

Association of Cytogenetic Responses with TI

In the imetelstat group, 88.9% (8/9) of the cytogenetic responders also achieved 8-week TI response compared to 50.0% (1/2) of cytogenetic responders in the placebo group (Applicant Figure 15A and Listing lefrs02_p2 and Listing lefres01_p2). Similar results were observed in subjects who achieved 24-week TI (Applicant Figure 15B).

Change in Mutation Burden

SF3B1 is one of the most frequent mutations found in MDS and is associated with the RS subtype (Malcovati, 2015; Tang, 2019; Jafari, 2020). It is also significantly associated with lower Hgb values, consistent with a high degree of ineffective erythropoiesis, higher neutrophil and platelet counts, and lower BM blasts in LR-MDS patients (Malcovati L, 2020). Mutations in *ASXL1*, *RUNX1*, *TP53*, *EZH2*, *ETV6* genes are also highly prevalent in MDS patients, and are associated with poorer outcomes (Bejar, 2011; Thol, 2011; Liang, 2019).

In the Phase 3 study, blood samples at baseline and every 12-week during treatment were collected for mutation analysis. One-hundred-sixteen subjects had the *SF3B1* mutation detected at baseline and at least 1 post-treatment mutation assessment, including 78 and 38 subjects in imetelstat and placebo group, respectively (SCE Section 3.2.4.3). Subjects in the imetelstat group had sustained reduction of *SF3B1* VAF over treatment duration compared to the placebo group, with 29.5% of imetelstat-treated subjects versus 2.6% of placebo-treated subjects achieving $\geq$ 50% reduction in *SF3B1* VAF. In addition, compared to placebo, a higher percentage of subjects in the imetelstat group achieved $\geq$ 50% VAF reduction in the mutation

biomarkers *TET2* (34.3% versus 8.3%), *DNMT3A* (11.1% versus 0%), and *ASXL1* (40.0% versus 16.7%) genes (Figure fefmsrdc01_p2).

Because *SF3B1* mutant MDS-initiating cells may arise from the hematopoietic stem and progenitor cells (Mian, 2015; Mortera-Blanco, 2017), the decrease in *SF3B1* mutation VAF suggests a reduction in the clonal burden of malignant stem and progenitor cells in the BM.

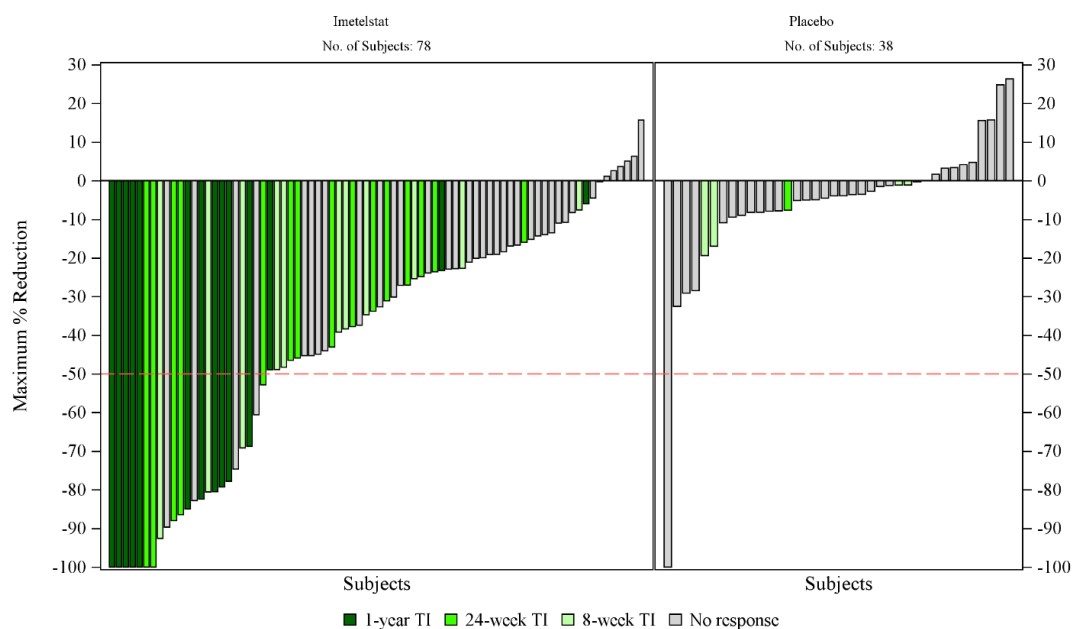
Correlation of Change in Mutation Burden with Clinical Benefit

In the imetelstat group, the proportion of RBC TI responders was significantly higher among subjects achieving $\geq 50\%$ *SF3B1* VAF reduction compared to those who did not (Applicant Figure 16A); the rate of 8-week RBC TI was 82.6% (19/23) versus 38.2% (21/55) (Applicant Figure 15A), 24-week TI was 69.6% (16/23) versus 23.6% (13/55) (Applicant Figure 15B), and 1-year TI was 47.8% (11/23) versus 5.5% (3/55), respectively ($P < 0.001$ in all comparisons; SCE Section 3.2.4.3). Similar results were also seen for *TET2*, *DNMT3A* and *ASXL1* VAF reduction with association to durable TI responses in imetelstat-treated subjects (SCE Section 3.2.4.3). Linear regression analysis showed a statistically significant correlation between RBC TI duration and *SF3B1* VAF reduction; the greater the maximum reduction of *SF3B1* VAF observed, the longer the TI duration achieved ($r = -0.549$, $P < 0.001$) (Applicant Figure 16B). The correlation between RBC TI duration and *TET2* ($r = -0.577$, $P < 0.001$), *DNMT3A* ($r = -0.545$, $P < .019$) and *ASXL1* ($r = -0.518$, $P = 0.125$) VAF reduction was also observed (SCE Section 3.2.4.3).

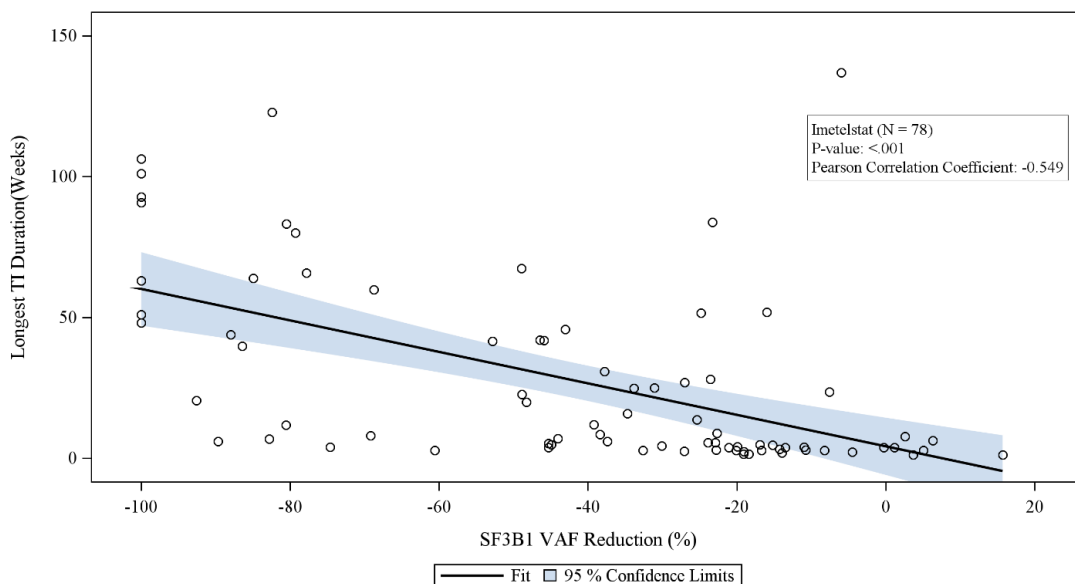
Importantly, there was a statistically significant negative correlation between *SF3B1* VAF reduction and level of Hgb in the imetelstat group where the greater the reduction in *SF3B1* VAF, the higher the increase in Hgb level ($r = -0.626$, $P < 0.001$).

Applicant Figure 16: Correlation of Clinical Endpoints and Change in VAF of *SF3B1* Mutations in Study MDS3001-Phase 3

A. Maximum VAF Reduction from Baseline *SF3B1* Mutation and Association with TI



B. Linear Regression Analysis of Duration of RBC TI on Maximum Percentage Reduction from Baseline in *SF3B1* VAF for Imetelstat-treated Subjects



RBC = red blood cell; TI = transfusion independence; VAF = variant allele frequency.

Note: The fitted line and p-value are based on linear regression with duration of RBC TI as dependent variable, and the maximum percentage reduction from baseline in *SF3B1* VAF as independent variable. The correlation

coefficient is based on Pearson Correlation. N represents imetelstat arm subjects in mutation biomarker analysis set who had detectable assessment ($\geq 5\%$) in SF3B1 at baseline and had any post-baseline mutation assessment. Note: The fitted line and p-value are based on linear regression with duration of RBC TI as dependent variable, and the maximum percentage reduction from baseline in SF3B1 VAF as independent variable. The correlation coefficient is based on Pearson Correlation. N represents imetelstat arm subjects in mutation biomarker analysis set who had detectable assessment ($\geq 5\%$) in SF3B1 at baseline and had any post-baseline mutation assessment. Source: SCE Figure 23, SCE Figure 24

Improvement in Bone Marrow Morphology

The imetelstat group had a greater maximum reduction in BM RS relative to baseline (-30.5%, range: -98%, 62%) compared to the placebo group (-4.0%, range: -94%, 44%). Overall, 29/71 (40.8%) subjects in the imetelstat group and 3/31 (9.7%) in the placebo group achieved $\geq 50\%$ reduction in central BM RS relative to baseline (Table tefbm04_p2).

Association of Improvement in BM Morphology with TI

In the imetelstat group, 75.9% (22/29) of the subjects who achieved $\geq 50\%$ reduction in central BM RS relative to baseline also achieved 8-week TI response, and 62.1% (18/29) achieved 24-week TI response (Table tefbm06_p2 and [Applicant Figure 15](#)).

Long-term Outcomes

At the time of the clinical cut off for the primary analysis of MDS3001 (13 Oct 2022), the median follow-up was 19.48 and 17.51 months in the imetelstat and placebo groups, respectively. At this time, the OS, PFS and time to AML progression data are considered preliminary, and subjects are still in survival follow-up. Results from the primary analysis demonstrated no detrimental impact of imetelstat treatment on PFS or OS (MDS3001 CSR Section 11.2.3.4 and MDS3001 CSR Section 11.2.3.6). Subjects are continuing in survival follow-up as part of an extension phase, until 5 years from the first dose of imetelstat or after 3 years of post-treatment follow-up (MDS3001 Protocol Amendment 8, Section 9.1.6).

Overall Survival

MDS3001 was not designed or powered to demonstrate an OS benefit, given that TI was the pre-specified primary endpoint. As of the cutoff date for the primary analysis, the proportion of subjects who died was similar between the two treatment groups (16.1% [19 subjects] in the imetelstat group and 13.3% [8 subjects] in the placebo group). Median OS has not been reached in either treatment group (HR = 1.07; 95% CI: 0.459, 2.476) (Table tefsur01_p2). Based on Kaplan-Meier estimates, the 1-year survival rate was 92.5% (95% CI: 85.49, 96.17) for the imetelstat group and 94.7% (95% CI: 84.49, 98.27) for the placebo group, and the 18-month survival rate was 88.7% (80.36, 93.66) and 84.8% (70.22, 92.61), respectively (Table tefsur01_p2). The Applicant is continuing ongoing data cleaning with the aim of providing additional OS data per the protocol-specified analysis that will occur in October 2023, which corresponds to 2 years after the last subject was randomized in the MDS3001-Phase 3 study.

Progression-free Survival

As of the data cutoff date for the primary analysis, based on Kaplan-Meier estimates, the 1-year PFS rate was 83.6% (95% CI: 74.06%, 89.81%) for the imetelstat group and 82.6% (95% CI: 66.06%, 91.60%) for the placebo group (Table tefpfs01a_p2).

Disease Progression and Time to Progression to AML

As of the data cutoff date for the primary analysis, ~10% of subjects in either treatment group had disease progression (12/118 in the imetelstat group and 6/60 in the placebo group). This included 2 (1.7%) subjects in the imetelstat group and 1 (1.7%) subject in the placebo group who had transformation to AML during follow-up (Table tefpd01_p2 and Table tefamlfs01_p2). Three additional subjects (2 in the imetelstat group and 1 in the placebo group) progressed to AML but were censored from the analysis of progression to AML because they received subsequent anti-cancer therapy before progression to AML (SCE Section 3.2.3.6).

The Kaplan-Meier estimate of the proportion of subjects without progression to AML was 97.9% (95% CI: 91.71%, 99.47%) at 6, 12 and 24 months for both treatment groups. Currently, the AML data are preliminary, and subjects are still being followed up (Table tefamlfs01_p2).

The Applicant's Position:

The MDS3001 Phase 3 study demonstrated a clear advantage for imetelstat compared to placebo in all of the key secondary endpoints, which further support the primary endpoint. Overall, the totality of the data from this Phase 3 study provides statistically persuasive and consistent efficacy findings, including the high and durable rates of TI together with additional clinical benefits for LR MDS patients. The durability of the transfusion independence response, accompanied by a significant increase in Hgb levels and reduction in transfusion burden are unprecedented and not observed with approved products in the MDS setting and as such are indicative of clinically relevant benefits that address the signs and symptoms of the disease in this heavily transfused patient population. These results were obtained in most key MDS subgroups including baseline RS status, baseline transfusion burden and IPSS risk category, demonstrating the breadth of activity seen with imetelstat.

Furthermore, achieving TI in response to imetelstat treatment was associated with a meaningful, sustained improvement in patient-reported fatigue compared with placebo. A significant association was observed between achieving RBC TI in response to imetelstat treatment and improvement in fatigue, which was not observed with placebo. This improvement in fatigue has not been observed in other studies of treatment for LR MDS.

Additionally, cytogenetic responses, decreases in mutation burden, decrease in BM RS+ cells and a correlation of these decreases with TI, further demonstrate the clinical benefit of

achieving TI and the possibility for imetelstat treatment to change longer term disease-based outcomes.

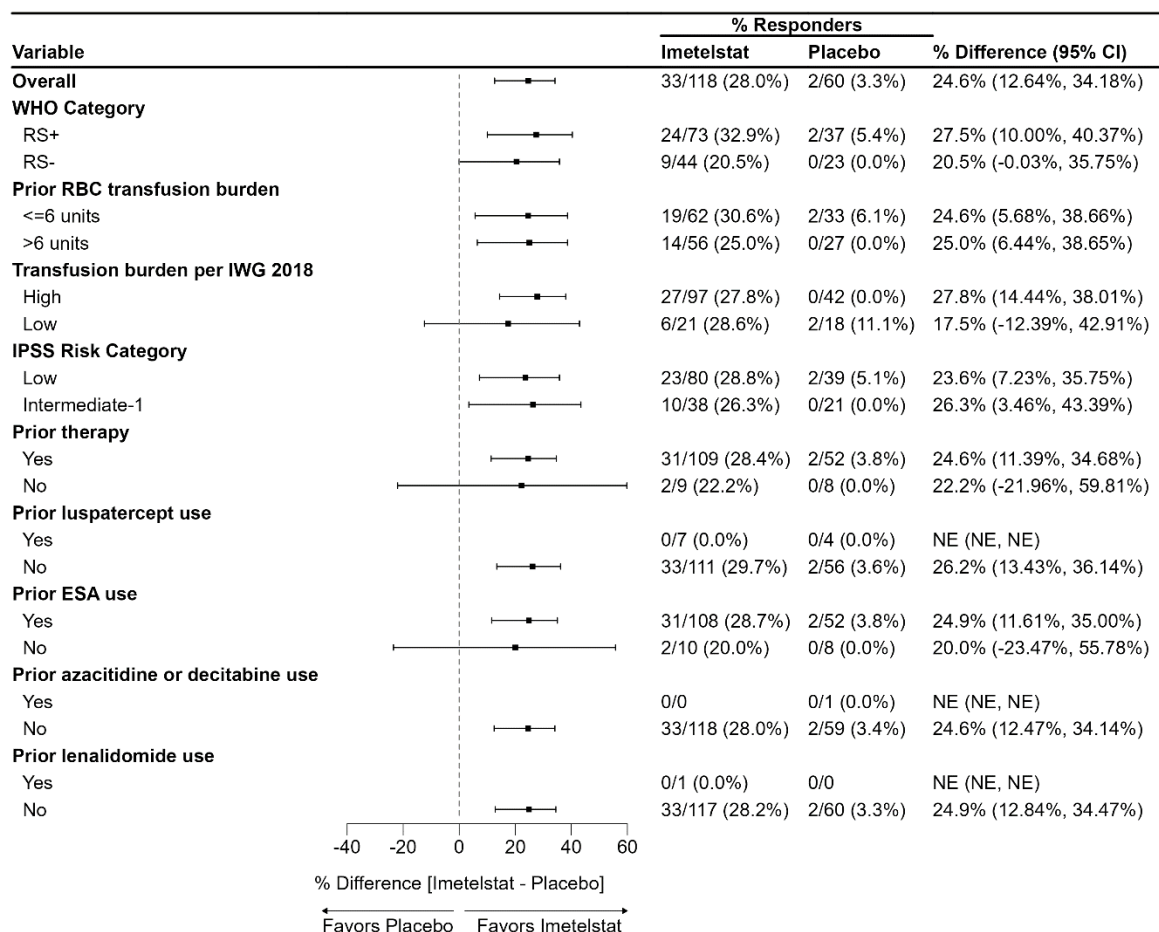
Though data for OS, PFS, and time to AML transformation in the Phase 3 study are preliminary, longer-term Phase 2 OS data indicates a possible improvement in survival compared with that reported in the literature. Given the evidence that indicates an association between reduction in transfusion burden and achieving TI with the improvement in longer-term clinical outcomes such as survival (De Witte, 2020; Santini, 2022, it is reasonable to anticipate that treatment with imetelstat would result in similar longer-term clinical benefits.

The FDA's Assessment:

24-week RBC TI

Although Study MDS3001 met its primary endpoint of 8-week RBC-TI as noted above, the presumption in the use of the early outcome of 8-week RBC-TI is that the treatment effect seen early will persist for a more substantial period. Thus, the Applicant evaluated alternative definitions of RBC-TI reflecting greater durability. In addition to the primary endpoint of 8-week RBC-TI, the Applicant evaluated the rates of RBC-TI lasting at least 24 weeks (24-week RBC-TI). The point estimate of the response rate decreased as the target duration of RBC-TI increased, with 28.0% (95% CI 20.1, 37.0) of imetelstat-treated subjects achieving 24-week RBC-TI vs. 3.3% (95% CI 0.4, 11.5) of placebo-treated subjects. However, the rate difference between the imetelstat and placebo groups was maintained at +24.6% (95% CI 12.6, 34.2) for 24-week RBC-TI. This is reassuring and suggests that imetelstat can lead to a clinically meaningful duration of RBC-TI in a subset of patients.

Subgroup analyses of 24-week RBC-TI in the Phase 3 study based on demographics and most relevant disease characteristics per FDA analysis are shown in Figure 17 below. These analyses showed a numerical advantage for imetelstat over placebo in most subgroups.

Figure 17: MDS3001-Phase 3: Subgroup analysis of rate of 24-week RBC-TI

CI = Confidence Interval; NE = Not Evaluable

Source: FDA analysis based on ADSL and ADBDC datasets. Data cutoff: 13 Oct 2022.

Duration of RBC-TI

The Applicant reports that the median duration of the longest RBC-TI interval was 51.6 weeks (95% CI 26.9, 83.9) for imetelstat versus 13.3 weeks (95% CI 8.0, 24.9) for placebo.

Clinical Reviewer comments:

The duration of RBC-TI was confirmed by the FDA; however, it should be noted that this metric applies only to the subgroup of patients who achieved an 8-week RBC-TI response, rather than the entire study population. As shown in Table 29, in the entire study population, the median duration of the longest RBC-TI interval per patient was substantially shorter: 5.0 weeks (95% CI 4.0, 7.7) with imetelstat versus 3.9 weeks (95% CI 3.6, 4.0) with placebo, which was only a 1.1 week difference. This minimal difference in the median duration of the longest RBC-TI interval

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between arms can be attributed to the fact that the majority of subjects in the imetelstat arm did not have an RBC-TI interval of 8 weeks or more.

Table 29: MDS3001-Phase 3: Duration of Longest RBC-TI Interval by Study Arm

Cohort	Treatment group	Median duration of the longest RBC-TI interval in weeks (95% CI)*
All subjects	Imetelstat (N=118)	5.0 (4.0, 7.7)
	Placebo (N=60)	3.9 (3.6, 4.0)
8-week RBC-TI responders	Imetelstat (N=47)	51.6 (26.9, 83.9)
	Placebo (N=9)	13.3 (8.0, 24.9)

* Calculated using the Kaplan-Meier method

Notes: ITT population; longest RBC-TI interval after randomization and before end of treatment visit, last dose + 30 days, and date of initiation of subsequent anticancer/antianemia therapy. Longest RBC-TI interval ended with next RBC transfusion, death, last transfusion status assessment, or initiation of subsequent anticancer/antianemia therapy, whichever occurred first.

Source: FDA analysis using ADTTEEF dataset

Data cutoff 13 October 2022

HI-E response

Hematologic improvement in the erythroid lineage (HI-E) per IWG 2006 criteria was a key secondary endpoint in the MDS3001-Phase 3 study. The definition of an HI-E response per IWG 2006 criteria is a hemoglobin increase by ≥ 1.5 g/dL with concurrent relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions over 8 weeks compared with the pre-treatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a hemoglobin of ≤ 9.0 g/dL pre-transfusion count in the RBC transfusion response evaluation (Cheson 2006).

These results were not adjudicated by the FDA. However, based on the Applicant's analysis, there was no significant difference in the proportion of subjects who achieved an HI-E response per IWG 2006 criteria in the Phase 3 trial, with an HI-E rate of 63.6% (75/118) for imetelstat versus 51.7% (31/60) for placebo, $p=0.112$. Additionally, transfusion reduction by ≥ 4 units/8 weeks (a component of the HI-E response) was achieved by 60.2% (71/118) of subjects receiving imetelstat versus 50% (30/60) of subjects receiving placebo.

Clinical Reviewer comment:

The high proportion of subjects who achieved an HI-E response and transfusion reduction in the placebo group is notable; these results suggest that a portion of hemoglobin rises and corresponding periods of transfusion reduction are due in part to natural fluctuations of the underlying disease, rather than a direct treatment effect.

The Applicant also evaluated HI-E per the updated IWG 2018 criteria (Platzbecker 2019). Based on these updated criteria, the rate of HI-E was 42.2% for the imetelstat group versus 13.3% with

placebo, which appears favorable for imetelstat. However, when evaluating the HI-E rate per IWG 2018 criteria according to baseline transfusion, the HI-E benefit for patients with low transfusion at baseline was marginal, as shown in Table 30. It should also be noted that evaluation of HI-E per IWG 2018 criteria was an ad hoc analysis without alpha allocation or multiplicity adjustment, therefore the results should be interpreted with caution.

Table 30: Study MDS3001-Phase 3: HI-E per IWG 2006 versus IWG 2018 criteria

	Imetelstat	Placebo	p value
HI-E per IWG 2006	75/118 (63.6%)	31/60 (51.7%)	0.112
HI-E per IWG 2018			
LTB subjects*	7/21 (33.3%)	4/18 (22.2%)	--
HTB subjects**			
Major HI-E response	30/97 (30.9%)	0/42 (0%)	--
Minor HI-E response	43/97 (44.3%)	4/42 (9.5%)	--

*LTB = low transfusion burden (requiring 3-7 RBC units in a 16-week baseline period in at least 2 transfusion episodes, max 3 units in 8 weeks)

**HTB = high transfusion burden (requiring ≥ 8 RBC units in a 16-week baseline period, or ≥ 4 units in 8 weeks)

Data cutoff 13 Oct 2022

Source: Study MDS001 Phase 3 CSR

Patient-reported outcomes

See discussion of PROs in “Efficacy Results – Secondary or exploratory COA (PRO) endpoints” section below.

Complete remission (CR) and partial remission (PR)

CR and PR per IWG 2006 criteria were secondary endpoints in Study MDS3001-Phase 3. According to the IWG 2006 criteria, CR is defined as bone marrow $\leq 5\%$ myeloblasts with normal maturation of all cell lines (persistent dysplasia will be noted) with peripheral blood counts as follows: hemoglobin ≥ 11 g/dL, platelets $\geq 100 \times 10^9/L$, neutrophils $\geq 1.0 \times 10^9/L$, and blasts 0%. PR is defined as all CR criteria if abnormal before treatment except bone marrow blasts decreased by $\geq 50\%$ over pretreatment but still $> 5\%$. In both cases, response must last at least 4 weeks (Cheson 2006).

For the Phase 3 study, an independent review committee (IRC) was established to assess blinded data and adjudicate CR, PR, and marrow CR (mCR) responses per the IWG 2006 criteria for subjects with $> 5\%$ baseline blasts per central pathology reviewer assessment and a CR, PR, mCR, or cytogenetic response per investigator assessment. However, the Applicant reported that only 2 of the total 178 randomized subjects (1 subject in each treatment group) had $> 5\%$ baseline marrow blasts and were therefore eligible for IRC adjudication, and neither of these 2 subjects achieved a CR, PR, or mCR per the IRC at the time of the primary analysis.

However, even when looking at CR and PR rates per investigator assessment, no subjects achieved a CR or PR response with imetelstat. It should be noted that 24% (28/118) subjects in the imetelstat arm were deemed not evaluable due to absent post-baseline bone marrow assessments.

Clinical reviewer comment:

In December 2023, the Applicant updated the IRC charter to allow subjects with baseline marrow blasts $\leq 5\%$ to be eligible for CR response, if they had at least one post-baseline bone marrow sample with central reviewer assessment. Based on this updated IRC charter, 83 subjects treated with imetelstat and 39 subjects treated with placebo were now eligible for CR response evaluation. Based on FDA adjudication of responses, at this “final analysis,” the CR rate was at best 7/118 (6%) for the imetelstat arm. However, significant limitations were noted during the adjudication process, such as excess time allowed between the marrow and CBC confirming CR and missing data. The Applicant reported a CR rate of 0 for the placebo arm.

Notably, duration of CR was not evaluable, because the IRC only assessed best response and no data was collected on date of relapse from CR. Because of this, and the limitations previously noted, it's unclear if these CRs were clinically meaningful.

Cytogenetic response

Cytogenetic complete response (CyCR) per IWG 2006 and updated IWG 2023 criteria is defined as the disappearance of baseline chromosomal abnormalities without the appearance of new ones. Cytogenetic partial response (CyPR) per IWG 2006 and updated IWG 2006 criteria is defined as a $\geq 50\%$ reduction in a baseline chromosomal abnormality (Cheson 2006; Zeidan 2023).

Clinical Reviewer comment:

Only a small number of subjects in Study MDS3001-Phase 3 had any baseline cytogenetic abnormalities: 26 subjects in the imetelstat arm, and 13 in the placebo arm. Of these, 6 subjects achieved a cytogenetic CR in the imetelstat arm and 1 achieved a cytogenetic CR in the placebo arm. However, nearly half of subjects in each treatment arm were not evaluable for cytogenetic response analysis, all but one due to lack of a post-baseline sample (Table 31). Furthermore, it should be noted that cytogenetic response was merely an exploratory endpoint in this study, and this is not an endpoint that reflects direct clinical benefit. Due to these significant limitations, no definitive conclusions can be drawn regarding cytogenetic response in this study.

Table 31: Study MDS3001-Phase 3: Cytogenetic response (ITT, per IRC)

	Imetelstat (N=26)	Placebo (N=13)
CyCR	6 (23.1%)	1 (7.7%)

NDA/BLA Multi-disciplinary Review and Evaluation NDA 217779 imetelstat
 TRADENAME, imetelstat

CyPR	4 (15.4%)	1 (7.7%)
Does not meet CyCR or CyPR criteria	4 (15.4%)	5 (38.5%)
Not evaluable	12 (46.2%)	6 (46.2%)

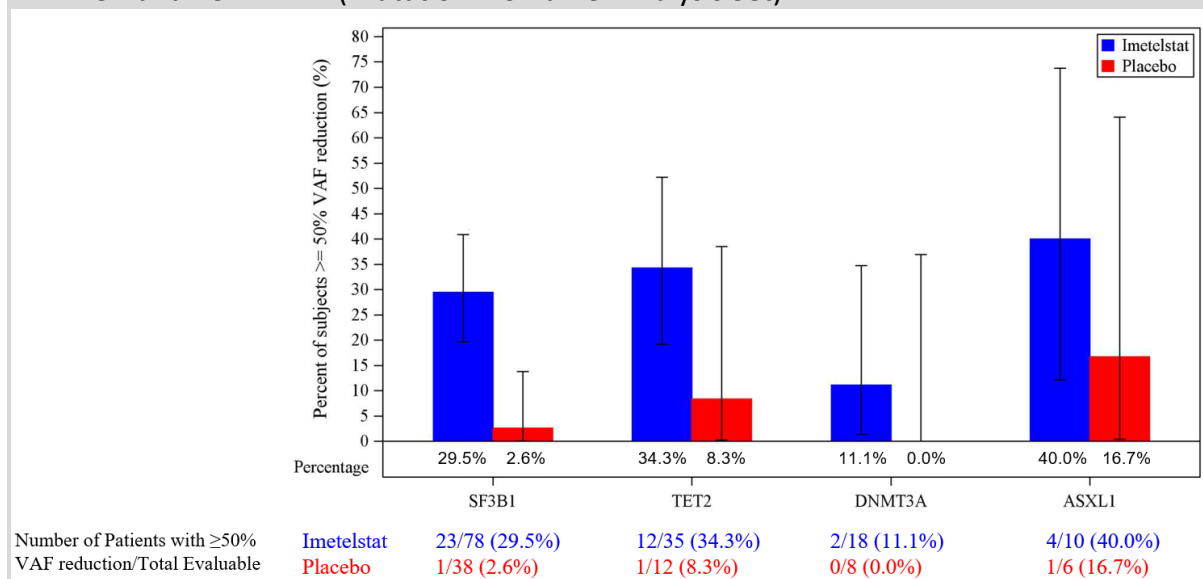
Data cutoff 13 Oct 2023

Source: Applicant's Response to FDA Information Request: Long-term Follow-up Efficacy Data

Change in Mutation Burden

The Applicant reports that more subjects receiving imetelstat achieved a 50% or greater variant allele frequency (VAF) reduction in SF3B1, one of the most frequent mutations found in MDS associated with the ringed sideroblasts subtype, with a trend toward VAF reduction in other mutations such as TET2, DNMT3A, and ASXL1, as shown in Figure 18.

Figure 18. MDS3001-Phase 3: Subjects Achieving $\geq 50\%$ Reduction from Baseline in SF3B1, TET2, DNMT3A and ASXL1 VAF (Mutation Biomarker Analysis Set)



Source: Study MDS3001 Phase 3 Clinical Study Report

Data cutoff 13 October 2022

Clinical Reviewer comment:

Despite the above results, reduction in mutation burden was an exploratory endpoint in Study MDS3001; the study was not designed to examine the impact of treatment on mutational burden. Furthermore, there are issues with the methodology of data collection. The next generation sequencing assay used for mutation analyses in the study has not been designed for VAF tracking. In addition, only a subset of patients had each relevant mutation at baseline and at least 1 post-baseline assessment making them evaluable for assessment. Samples for mutation analyses were collected from peripheral blood only, and at relatively sparse timepoints

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(every 12 weeks and at the time of suspected response or progression). This analysis is also based on maximal VAF reductions from baseline, which may have been achieved at any timepoint. Without serial data at distinct pre-specified intervals for all patients, it is difficult to examine associations between VAF changes and the dynamics of RBC transfusion independence. Additionally, it is unclear whether a $\geq 50\%$ VAF reduction in mutation burden is clinically significant, as there was no a priori well-justified rationale for use of this cutoff. Given the lack of evidence of a corresponding survival benefit, any impact on mutation burden does not appear to be of sufficient magnitude to result in a direct clinical benefit to the patient.

Overall Survival

Overall survival (OS) is considered both an efficacy and a safety endpoint. FDA requires collection and submission of OS data in oncology clinical trials to assess clinical benefit. Furthermore, one argument for therapeutically targeting transfusion-dependent anemia in subjects with lower-risk MDS is that higher RBC transfusion density has been reported to correlate with decreased overall survival (OS) (Santini et al. 2016). However, the association between a treatment-induced increased rate of RBC-transfusion independence and an improvement in OS has not been demonstrated in prospective studies.

In Study MDS3001-Phase 3, OS was included as a secondary endpoint, but no formal hypothesis testing was planned. Of note, no other trial has demonstrated an OS advantage in lower-risk MDS with transfusion-dependent anemia. The OS results at the time of the primary efficacy analysis and the most recent planned analysis are summarized in Table 32: below. At the time of the most recent analysis (data cutoff 5 January 2024), the median follow-up times were 32 and 28 months for the imetelstat and placebo groups, respectively. The stratified hazard ratio between the imetelstat and placebo arms was 0.98 (95% CI: 0.53, 1.82) (Table 32: and Figure 19). Median overall survival was 40 months (95% CI: 37, NE) for the imetelstat group and was not estimable for the placebo group. Numerically, a higher percentage of deaths was observed in the imetelstat arm both at the time of primary analysis (data cutoff 13 October 2022) and updated analysis (data cutoff 5 January 2024).

Statistical Reviewer Comment:

The upper bound of the stratified OS hazard ratio 95% confidence interval of 1.82 indicates that potential harm cannot be ruled out. The numerically higher percentage of deaths in the imetelstat arm is also concerning. Furthermore, it's important to note that incorrect stratification accounted for major protocol deviations in 12.7% of subjects in the imetelstat group and 10.0% of subjects in the placebo group, as noted in the "Protocol Violations/Deviations" section above. Therefore, the stratified hazard ratio should be interpreted with caution. Notably, the unstratified OS hazard ratio (data cutoff 5 January 2024) is 1.11 (95% CI 0.61, 2.03), again illustrating that potential harm cannot be ruled out.

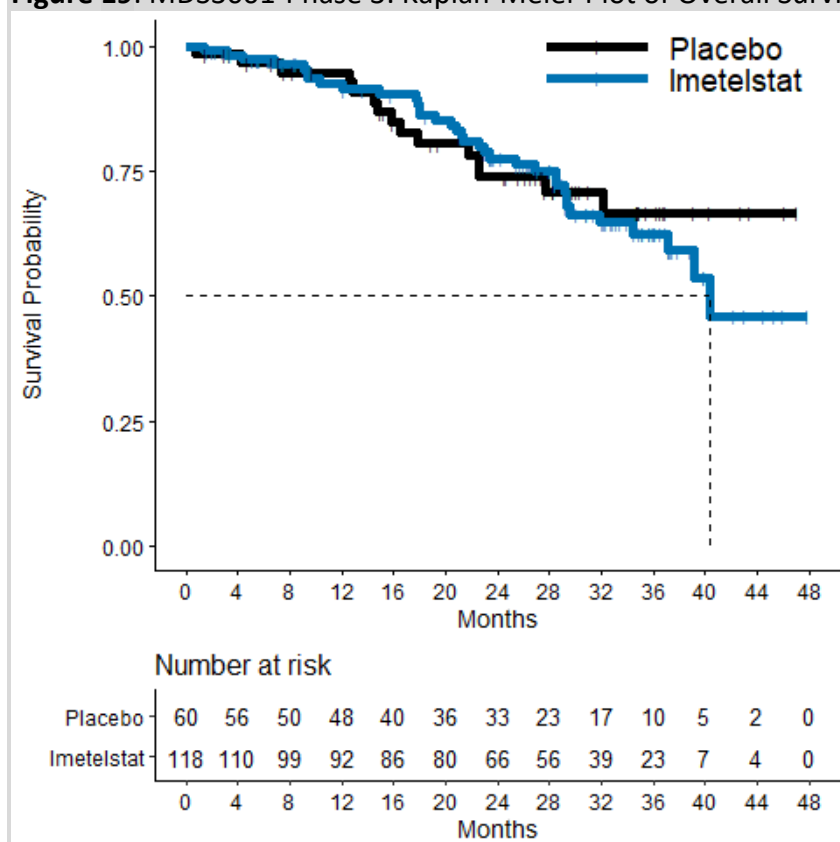
Table 32: MDS3001-Phase 3: Overall Survival (ITT Set) at Primary and Updated Analysis

Data Cutoff	Overall Survival	Imetelstat (N=118)	Placebo (N=60)
13 October 2022	Deaths, n (%)	19 (16.1%)	8 (13.3%)
	Hazard Ratio (95% CI) ¹	1.07 (0.46, 2.48)	
5 January 2024	Deaths, n (%)	35 (29.7%)	15 (25.0%)
	Censored, n (%)	83 (70.3%)	52 (86.7%)
	Adverse event	0	1 (1.7%)
	Lost to follow-up, n (%)	3 (2.5%)	2 (3.3%)
	Withdrawal by patient, n (%)	25 (21.2%)	16 (26.7%)
	Last date known alive, n (%)	55 (46.6%)	26 (43.3%)
	Hazard Ratio (95% CI) ¹	0.98 (0.53, 1.82)	

¹ Based on a Cox proportional hazards model with stratification factors.

Source: Study MDS3001 Phase 3 Clinical Study Report and Applicant's response to FDA Information Request: Long-term Follow up Efficacy Data; FDA analysis

Figure 19: MDS3001-Phase 3: Kaplan-Meier Plot of Overall Survival (ITT Set) at Updated Analysis



Source: FDA analysis using ADTTEEF dataset

Data cutoff 5 January 2024

Version date: June 2022 (ALL NDA/ BLA reviews)

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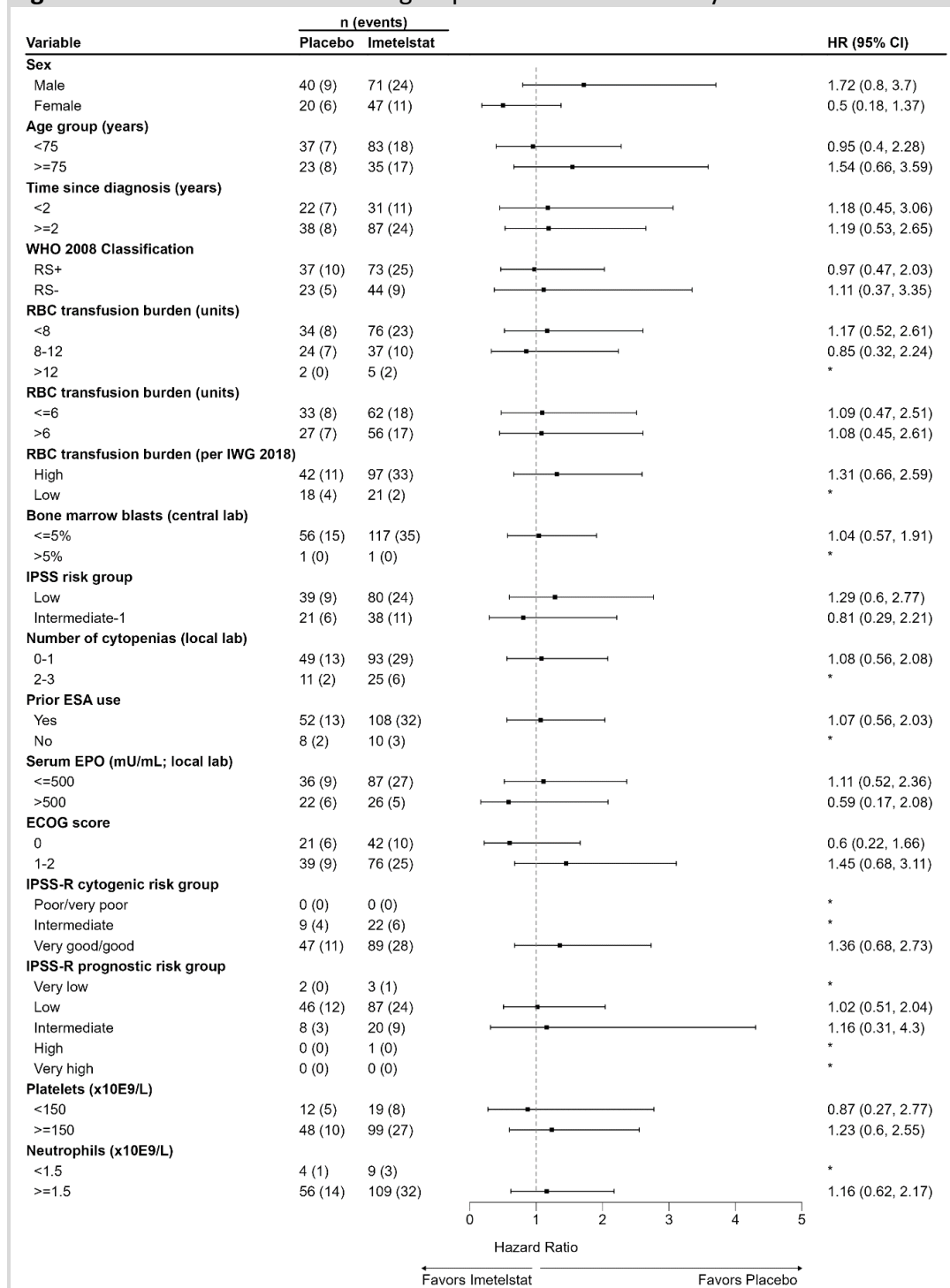
Clinical Reviewer comment:

Unlike growth factors such as ESAs which increase red blood cell count by targeting erythropoiesis, imetelstat is purported to have a direct effect on the underlying MDS through telomerase inhibition resulting in cell-cycle arrest, apoptosis, or senescence of malignant cells. However, these OS results are not supportive of a substantial disease-modifying treatment effect.

Figure 20 below shows OS subgroup analyses.

NDA/BLA Multi-disciplinary Review and Evaluation NDA 217779 imetelstat
 TRADENAME, imetelstat

Figure 20: MDS3001-Phase 3: Subgroup Overall Survival Analysis



* Results for subgroups with fewer than 10 total events were not reported

Source: FDA analysis using ADTTEF, ADSL, ADBDC datasets

Data cutoff 5 January 2024

Version date: June 2022 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Progression-free survival, disease progression, and progression to AML

The Applicant submitted a long-term efficacy update with data cutoff of 5 January 2024, including updated progression-free survival (PFS), disease progression, and progression to AML results. As of the most recent efficacy update (data cutoff 5 January 2024) with median follow-up of 32.2 months and 28.4 months in the imetelstat and placebo groups, respectively, the stratified PFS hazard ratio for imetelstat versus placebo was 0.85 (95% CI 0.44, 1.64), which is lower than the PFS hazard ratio at the time of primary analysis, which was 0.96 (95% CI 0.46, 2.04).

Clinical Reviewer comment:

It is important to note that the definition of PFS used for this analysis was per IWG 2006 criteria (Cheson 2006), which is “disease progression or death from MDS.” Disease progression per the IWG 2006 definition includes not only progression to AML, but also an increase in blasts, decrease in granulocyte or platelet count, reduction in hemoglobin by at least 2 g/dL, or transfusion dependence. This definition of disease progression and PFS has not been validated for MDS, therefore no meaningful conclusions can be drawn from the PFS analysis.

With regard to progression to AML, as of the most updated analysis (data cutoff 5 January 2024), there were only 2 progression to AML events in each treatment arm. Additionally, the AML data are preliminary as noted by the Applicant above. Therefore, no meaningful conclusions can be drawn at this time regarding progression to AML in Study MDS3001.

Dose/Dose Response

Data:

In the CSRs, study drug doses are expressed as milligrams of imetelstat sodium (the active substance), a salt of imetelstat. To convert a quantity of imetelstat salt to the equivalent quantity of imetelstat free acid, a factor of 0.9416 based on relative molar mass of the free acid form (4610 g/mol) to the sodium salt (4896 g/mol; $4610/4896 = 0.9416$) is applied (ie, 1 mg imetelstat sodium = 0.9416 mg imetelstat).

The use of the 7.1 mg/kg imetelstat (free acid, equivalent to 7.5 mg/kg imetelstat-sodium) dose q4w is supported by exposure-efficacy analyses using population PK ([Section 6.3.2.2](#) and [6.3.2.3](#)) as well as analysis of the primary endpoint of RBC TI in the Phase 2 and Phase 3 MDS3001 studies.

- In both the Phase 2 and Phase 3 studies, the majority of imetelstat-treated subjects achieved their first 8-week RBC TI interval while on the 7.1 mg/kg dose (81.0% and 74.5%, respectively; Applicant Table 33). Similar results were observed for the 24-week TI. Combined data from Phase 2 and Phase 3 indicate that 76.5% and 78.7% of imetelstat-treated subjects were on the 7.1 mg/kg dose at the onset of 8-week RBC TI and 24-week TI, respectively.

Applicant Table 33: Imetelstat Dose Level at the Onset of 8-Week or 24-Week RBC TI, RBC TI Responder Analysis Set (Study MDS3001 Phase 2, Phase 3)

	Imetelstat Dose ^a		
	7.1 mg/kg	5.6 mg/kg	4.4 mg/kg
8-week RBC TI n/m (%)			
Phase 2 ^b	17/21 (81.0)	2/21 (9.5)	1/21 (4.8)
Phase 3	35/47 (74.5)	11/47 (23.4)	1/47 (2.1)
Phase 2 ^b and Phase 3	52/68 (76.5)	13/68 (19.1)	2/68 (2.9)
24-week RBC TI n/m (%)			
Phase 2	11/14 (78.6)	2/14 (14.3)	1/14 (7.1)
Phase 3	26/33 (78.8)	7/33 (21.2)	0/33 (0)
Phase 2 and Phase 3	37/47 (78.7)	9/47 (19.1)	1/47 (2.1)

Source: Study MDS3001 CSR (Phase 3)/teftido01_p2; Study MDS3001 CSR (Phase 2)/teftido01_p1

^a Dose based on active moiety (free acid). To convert a quantity of imetelstat salt to the equivalent quantity of imetelstat, a factor of 0.9416 based on relative molar mass of the free acid form (4610 g/mol) to the sodium salt (4896 g/mol; $4610/4896 = 0.9416$) is applied (i.e., 1 mg imetelstat sodium = 0.9416 mg imetelstat)

^b One subject reached 8-week TI at 9.4 mg/kg imetelstat-sodium (8.9 mg/kg imetelstat free acid) since dose escalation prior to protocol amendment 2 was permitted.

The actual dose level on or before the first 8-week/24-week TI period is shown.

m = number of total responders; n = number of subjects; RBC = red blood cell; TI = transfusion independence.

- The mean (SD) relative dose intensity (calculated as the average of actual cumulative dose level per cycle and takes into consideration dose reductions) with respect to the 7.1 mg/kg dose of imetelstat (active moiety, equivalent to 7.5 mg/kg imetelstat-sodium) was 90.5 (± 11.8) in the Phase 3 study and 89.92 (± 14.15) in the target population of the Phase 2 study (Table tsix01_p2 and Table tsix01_p1). Because dose reductions were to decrease the dose to approximately 60% to 80% of the intended 7.1 mg/kg dose, a mean relative dose intensity $>80\%$ indicates subjects received 7.1 mg/kg for a greater proportion of the treatment course than for which they received a lower dose.
- The mean relative dose intensity with respect to the 7.1 mg/kg dose from the first dose until the onset of 8-week TI in both phases of the study was $> 95\%$ (96.8% and 95.2% in Phase 2 and Phase 3, respectively) (SCE Table 20) indicating that most subjects were receiving the 7.1 mg/kg dose in the 4 weeks leading to the start of TI. Additionally, the

mean relative dose intensity was 93.16% and 89.16% when 24-week and 1-year TI were achieved (Table tsix21_p2 and Table tsix22_p2).

- The mean dose intensity from the first dose until the start of the TI and achievement of the TI provides an indication of the dose intensity of imetelstat needed to elicit and maintain clinical benefit of 8-week RBC TI, 24-week RBC TI, or 1-year TI after initiating treatment.
- In the imetelstat group of the Phase 3 study, mean relative dose intensity with respect to the 7.1 mg/kg dose remained steady around 90% throughout treatment in 8-week TI responders while declining below 80% in non-responders (SCE Figure 25); therefore, subjects who achieved an 8-week TI response required less fewer dose reductions than non-responders. Additionally, it can be surmised that dose reduction prior to achieving TI may have diminished the likelihood of attaining a TI response.
- In Phase 3, 35 (74.5%) of the 47 imetelstat-treated 8-week RBC TI responders did not have any dose reductions during the TI period. Among the 12 (25.5%) 8-week RBC TI responders with at least 1 dose reduction to 5.6 mg/kg (equivalent to 6.0 mg/kg imetelstat-sodium), 6 (12.8%) responders had a second dose reduction to 4.4 mg/kg (equivalent to 4.7 mg/kg imetelstat-sodium). The median time from the first and second dose reduction to the end of TI (ie, first transfusion after TI period) was 46.79 weeks (range: 3.9 to 119.9) and 44.50 weeks (range: 8.3 to 114.9) respectively (SCE Table 21), indicating that dose reductions did not lead to immediate loss of response, and response was maintained for a median of > 10 months despite dose reductions.

The Applicant's Position:

While dose modifications occurred as mandated per protocol in both the Phase 2 and Phase 3 study, $\geq 90\%$ overall dose intensity of the 7.1 mg/kg dose was achieved over the treatment period for all subjects. In both MDS3001 Phase 2 and Phase 3, $> 75\%$ of subjects received 7.1 mg/kg at the time of onset of 8-week RBC TI, and $> 95\%$ mean relative dose intensity was demonstrated from the first dose until the achievement of 8-week RBC TI. Overall relative dose intensity throughout treatment was higher for 8-week RBC TI responders than non-responders, indicative of a greater need for dose reductions in non-responders that is supported by the dose reduction data. Furthermore, dose reduction did not lead to loss of TI response in either 8-week RBC TI or 24-week RBC TI responders.

In summary, the 7.1 mg/kg dose demonstrated favorable efficacy and was well tolerated by those who achieved at least 8- or 24-week RBC TI. When indicated, subsequent dose reductions in responders allow for continued dosing and maintenance of durable transfusion-free periods. In addition, the results from exposure-efficacy analyses suggest that imetelstat doses (and accordingly C_{avg}) lower than 7.1 mg/kg q4w may result in reduced clinical efficacy.

The FDA's Assessment:

Dose modifications in Study MDS3001

There was a high rate of dose modifications with imetelstat compared to placebo in Study MDS3001-Phase 3, as shown in Table 34 and Figure 21.

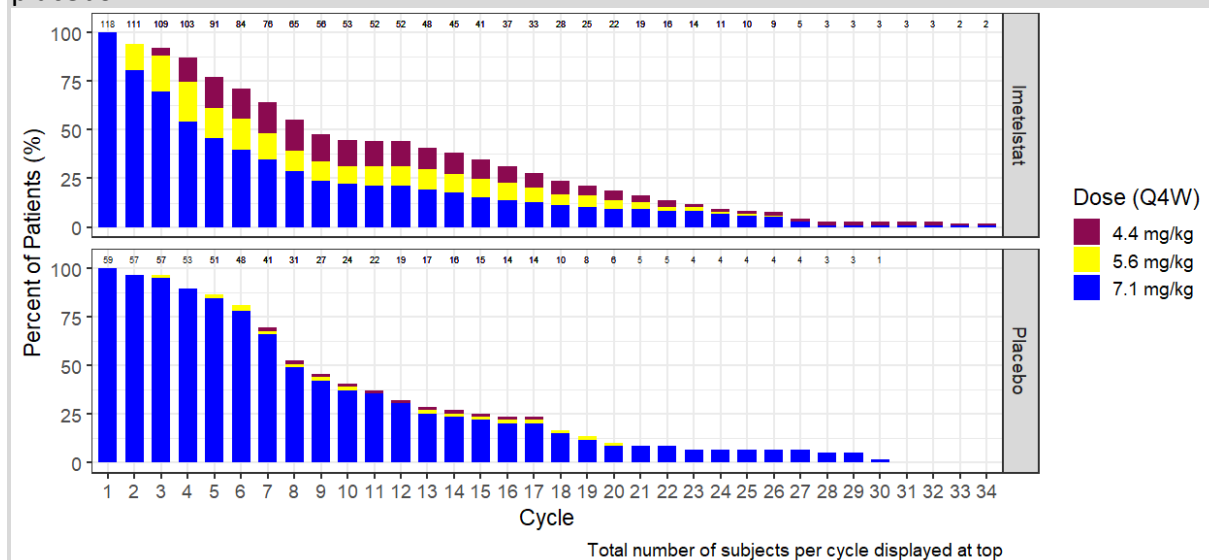
Table 34: MDS3001-Phase 3: High dose modification rate with imetelstat compared to placebo

	Imetelstat (N=118)	Placebo (N=59)
Dose delay by >3 days	73%	30.5%
Dose delay by >7 days	64%	22%
Dose reduction due to AE	49%	7%
Infusion interrupted, decreased rate, or aborted due to AE	6%	0
Discontinuation due to AE	14%	0

Source: FDA analysis using ADEX dataset

Data cutoff 13 October 2022

Figure 21: MDS3001-Phase 3: Higher rate of dose reduction with imetelstat compared to placebo



Source: FDA analysis using ADEX dataset

Data cutoff 13 October 2022

A total of 17 patients (14%) receiving imetelstat on the phase 3 portion of MDS3001 and zero receiving placebo discontinued treatment due to AEs. Reasons for imetelstat discontinuation included neutropenia (6 patients), thrombocytopenia (4 patients), cardiac failure/cardiac failure

congestive (2 patients), infections (2 patients), and malignancies other than MDS (3 patients). The start day of events leading to discontinuation ranged from day 25 to 267 and in cycles 1-12.

Dose reductions due to AE occurred in 58 patients (49%) receiving imetelstat in the phase 3 portion of the study and 4 patients (7%) receiving placebo. The majority of dose reductions in the imetelstat arm were related to neutropenia (39 patients) or thrombocytopenia (27 patients). Other reasons for dose reduction included leukopenia and transaminase increased, fatigue, and neutropenic sepsis (1 patient each). Reasons for dose reduction among patients receiving placebo included neutropenia (1 patient), transaminase increased (2 patients), and thrombocytopenia (1 patient)

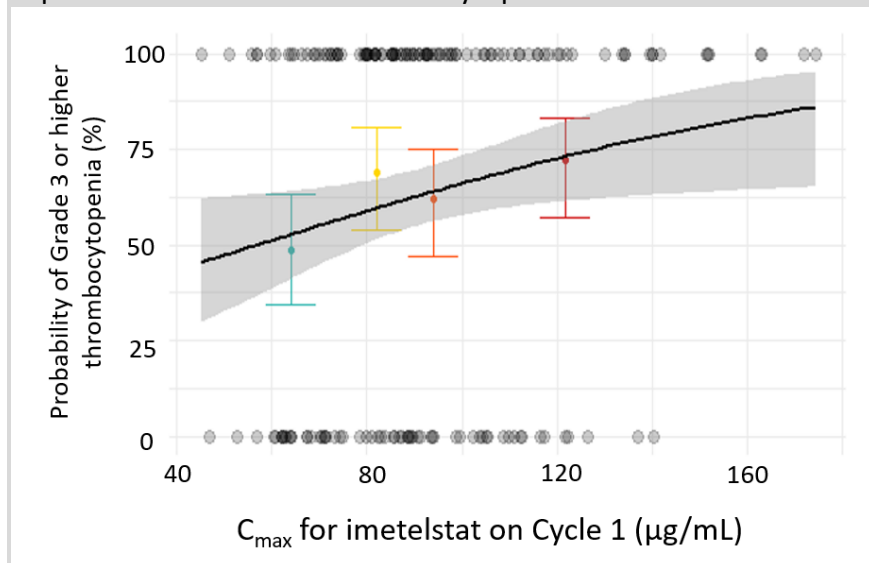
Dose exploration across the drug development program

Imetelstat doses of 0.4 mg/kg to 11 mg/kg, alone or in combination with other agents, and dosing schedules from weekly to every 4 weeks were explored in a variety of indications throughout the drug development program. However, the evaluation of imetelstat in MDS has been limited to two studies. The first study evaluated imetelstat as a single agent given to patients with MDS or MDS/MPN at a dose of 7.1 mg/kg weekly with the possibility to dose escalate to 8.9 mg/kg weekly. The second study, MDS3001, evaluated the effect of imetelstat at 7.1 mg/kg every 4 weeks in patients with lower risk MDS.

Exposure-response relationship between imetelstat and Grade 3-4 thrombocytopenia

In Study MDS3001-Phase 3, higher maximum plasma concentrations of imetelstat (C_{max}) correlated with a higher probability of Grade 3-4 thrombocytopenia, as shown in Figure 22, which supports the observation of higher rates of thrombocytopenia with imetelstat (Section 8.2.4). This finding suggests that the starting dose and regimen of imetelstat may be further optimized.

Figure 22: MDS3001-Phase 3: Positive exposure-response relationship between imetelstat exposure and Grade 3-4 thrombocytopenia



Source: FDA analysis using ER_THR.csv dataset
Data cutoff 13 October 2022

Exposure-response relationship between imetelstat and 8-week RBC-TI response

Although there was also a positive exposure-response relationship between the average plasma concentration of imetelstat (C_{avg}) and 8-week RBC-TI response, this analysis was significantly limited by the single dose and narrow exposure range studied in patients with MDS and is limited by confounding factors, such as frequent dose modifications and subjects dropping off treatment.

In summary, although other dose levels of imetelstat have been explored in myelofibrosis and solid tumors, dose exploration in MDS has been limited to a single dose level. Therefore, it is unclear whether the proposed starting dose is the optimal dose for the proposed indication, particularly in light of the high rate of dose modifications, toxicities, and low dose intensity with imetelstat seen in Study MDS3001. A post-marketing study of additional dose levels of imetelstat may be warranted.

Durability of Response

Data:

Median duration RBC TI was 51.6 weeks (95% CI: 26.86, 83.86; range: 8.0 to 136.9 weeks) in the imetelstat group versus 13.3 weeks (95% CI: 8.00, 24.86; range: 8.0 to 111.3 weeks) in the placebo group based on Kaplan-Meier estimates ([Applicant Table 26](#) and [Applicant Figure 12](#)). The hazard ratio between the treatment groups was 0.23 (95% CI: 0.091, 0.571, $P < 0.001$).

Version date: June 2022 (ALL NDA/ BLA reviews)

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Approximately 83% of 8-week RBC TI responders had a single continuous TI period, further demonstrating the durability of the response ([Applicant Figure 7](#)).

Additional evidence of long continuous TI achieved with imetelstat can be seen among the subjects who achieved 24- week RBC-TI. Median duration of RBC TI for these subjects was 80.0 weeks (95% CI: 51.57, non-estimable [NE]; range: 24.9 to 136.9) and NE (95% CI: 24.86, NE; range: 24.9, 111.3 weeks) in the placebo group ([Applicant Table 26](#)). The hazard ratio between the imetelstat and placebo treatment groups was 0.59 (95% CI: 0.069, 5.103, P= 0.655).

The Applicant's Position:

Transfusion dependence and high transfusion burden have been linked to reduced OS and PFS and increased risk of transformation to AML and subsequent achievement of TI with therapy has been shown to contribute to mitigation of those reductions. Therefore, achieving durable TI and thus alleviating the signs and symptoms associated with it, is an important clinical outcome in LR MDS. The durability of continuous RBC TI seen with imetelstat across LR MDS subgroups is unprecedented and has the potential to translate to positive long-term clinical outcomes such as OS.

The FDA's Assessment:

See FDA Assessment in "Efficacy Results – Secondary and other relevant endpoints" for comment on the duration of the longest RBC TI interval.

Persistence of Effect

Data:

As of the 13 Oct 2022 clinical cutoff date, the median follow-up time in Phase 3 was 19.48 and 17.51 months in the imetelstat and placebo groups, respectively (Table tsids07_p2).

The 1-year RBC TI rate (

[Applicant Figure 10](#)) and the duration of TI ([Applicant Figure 12](#)) were included to assess the durability of the effect of imetelstat on TI.

In Phase 3, 1-year RBC TI was achieved by 13.6% of imetelstat-treated subjects versus 1.7% of placebo-treated subjects, with the difference between the 2 treatment groups of 11.9% (95% CI: 1.86%, 19.87%, P = 0.012) (Table tefti07_p2 and (

Applicant Figure 10). While statistically significant compared with placebo, the imetelstat data are expected to mature further, with longer-term follow-up still ongoing in the study.

The Applicant's Position:

Transfusion dependence and high transfusion burden have been linked to reduced OS and PFS and increased risk of transformation to AML and subsequent achievement of TI with therapy has been shown to contribute to mitigation of those reductions. Therefore, achieving durable TI and thus alleviating the signs and symptoms associated with it, is an important clinical outcome in LR MDS. The durability of continuous RBC TI seen with imetelstat across LR MDS subgroups is unprecedented and has the potential to translate to positive long-term clinical outcomes such as OS.

The FDA's Assessment:

The Applicant provided an updated analysis of 1-year RBC-TI in the Phase 3 study with data cutoff of 13 October 2023, with a median time on study of 32.2 months for imetelstat-treated subjects and 28.4 months for placebo-treated subjects. Based on this updated data cutoff, the rate of 1-year RBC-TI is 17.8% (95% CI 11.4, 25.9) for imetelstat-treated subjects versus 1.8% (95% CI 0, 8.9) for placebo-treated subjects, with the difference between the 2 groups of 16.1% (95% CI 5.6, 24.6). This suggests that a small subset of patients may achieve a prolonged period of RBC-TI with imetelstat treatment. However, it should be noted that 1-year RBC-TI was not a prespecified endpoint in the study.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data:

Fatigue Measured by FACIT-Fatigue Score

The FACIT-Fatigue Scale is a QoL instrument that was included in the study to measure fatigue from the patient perspective. A higher score indicates improvement (i.e., less fatigue on the FACIT-Fatigue Scale).

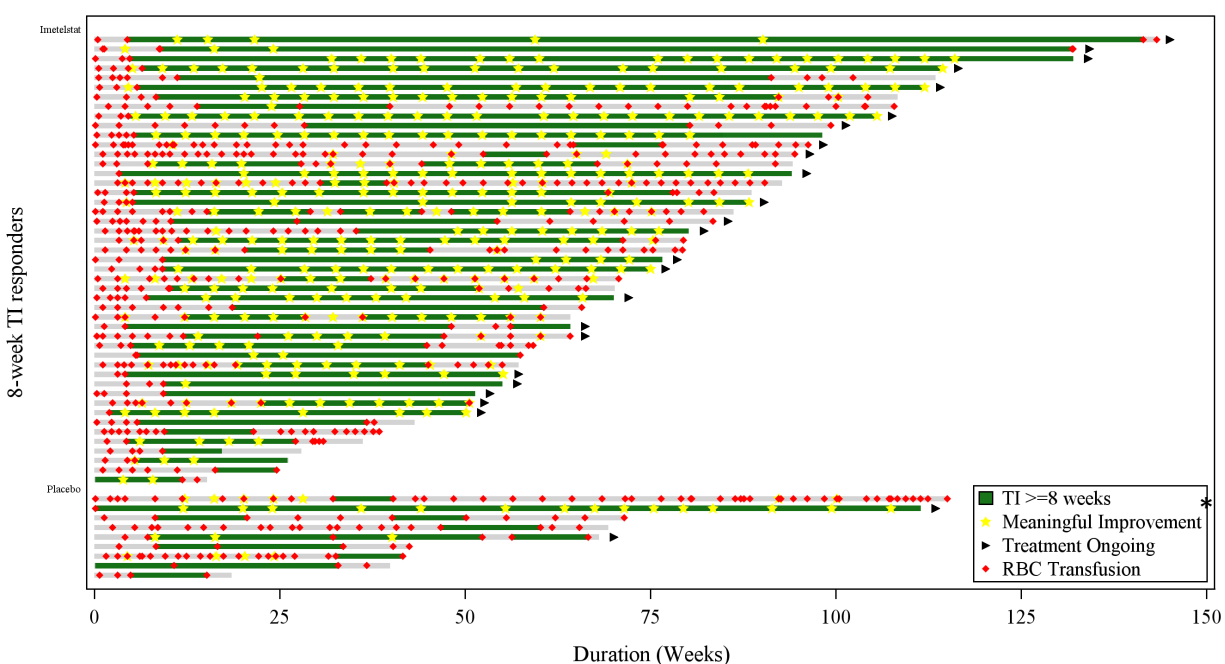
The results demonstrate that imetelstat treatment did not cause a clinically meaningful deterioration in fatigue compared to placebo; rather, subjects treated with imetelstat demonstrated favorable, sustained, meaningful improvement in fatigue (defined by a ≥ 3 -point increase on the FACIT Fatigue Scale for ≥ 2 consecutive non-missing treatment cycles) compared with placebo (50.0% in the imetelstat group compared with 40.4% in the placebo group) (SCE Section 3.2.4.1.2). Furthermore, imetelstat-treated subjects experienced a shorter median time to reported first sustained meaningful improvement in fatigue versus placebo; 28.3 vs 65.0 weeks, HR = 1.34 (95% CI, 0.82–2.20). After 12 weeks, more subjects in the imetelstat group reported improvement in the FACIT Fatigue Scale than placebo (SCE Section 3.2.4.1.3).

Additional analysis demonstrated that subjects who reported TEAE of Grade 3 or 4 neutropenia or thrombocytopenia had the same rates of sustained meaningful improvement in fatigue (42/80; 52.5% and 39/73; 53.4% respectively) as the total imetelstat population (50%) (SCE Section 3.2.4.1.2).

Association of Improvement in Fatigue with TI

Further analysis demonstrated that in the imetelstat group, a significantly higher proportion of 8-week and 24-week TI responders experienced sustained meaningful improvement in fatigue scores than non-responders (Applicant Figure 15). This association was not observed in the placebo group (Table tspqs71_p2 and Figure fspqs38_p2). The majority of the 8-week TI responders in the imetelstat group consistently had sustained meaningful improvement in FACIT Fatigue scores through the durable TI intervals, as indicated by the yellow stars in Applicant Figure 23.

Applicant Figure 23: TI Periods are Associated with Meaningful Improvement in FACIT-Fatigue Score in MDS3001 Phase 3



RBC = red blood cell; TI = transfusion independence

*Timepoint of meaningful improvement in fatigue when FACIT-Fatigue questionnaire completed

Source: SCE Figure 21

Other PRO Measures

Version date: June 2022 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Exploratory analyses were performed to investigate the impact of imetelstat on other PRO concepts of interest (COIs) that were identified as relevant for patients with LR MDS: physical function, dyspnea, pain, bruising, and systemic symptoms. The analyses suggested that subjects in the imetelstat group had better outcomes in terms of dyspnea than those in the placebo group. Although no improvement from baseline was observed for other pre-identified COIs, subjects in the imetelstat group showed no more deterioration in any of the pre-identified COIs than those in the placebo group (SCE Section 3.2.4.1.5).

The Applicant's Position:

Level of fatigue is an important patient-centered consideration for treatment of LR MDS as patients with chronic transfusion-dependent anemia suffer from exhaustive fatigue (Platzbecker, 2021). Fatigue was selected as the main PRO COI for study MDS3001 as it is a central concern to patients and treatment providers of LR MDS. Maintaining the same levels or avoiding deterioration in fatigue with treatment is an important therapeutic goal. The improvement in fatigue observed in subjects who achieved TI, indicates that imetelstat is targeting multiple core symptoms of LR MDS simultaneously, bringing greater clinical benefit to patients than current treatment options.

Existing Functional Assessment of Cancer Therapy – Anemia-Related Effects (FACT-An) and Quality of Life in Myelodysplasia Scale (QUALMS) composite scores (FACT-An total score, FACT-An Trial Outcome Index score, QUALMS physical burden score, and QUALMS total score) suggest better general health outcomes for subjects treated with imetelstat than those with placebo (SCE Section 3.2.4.1.5).

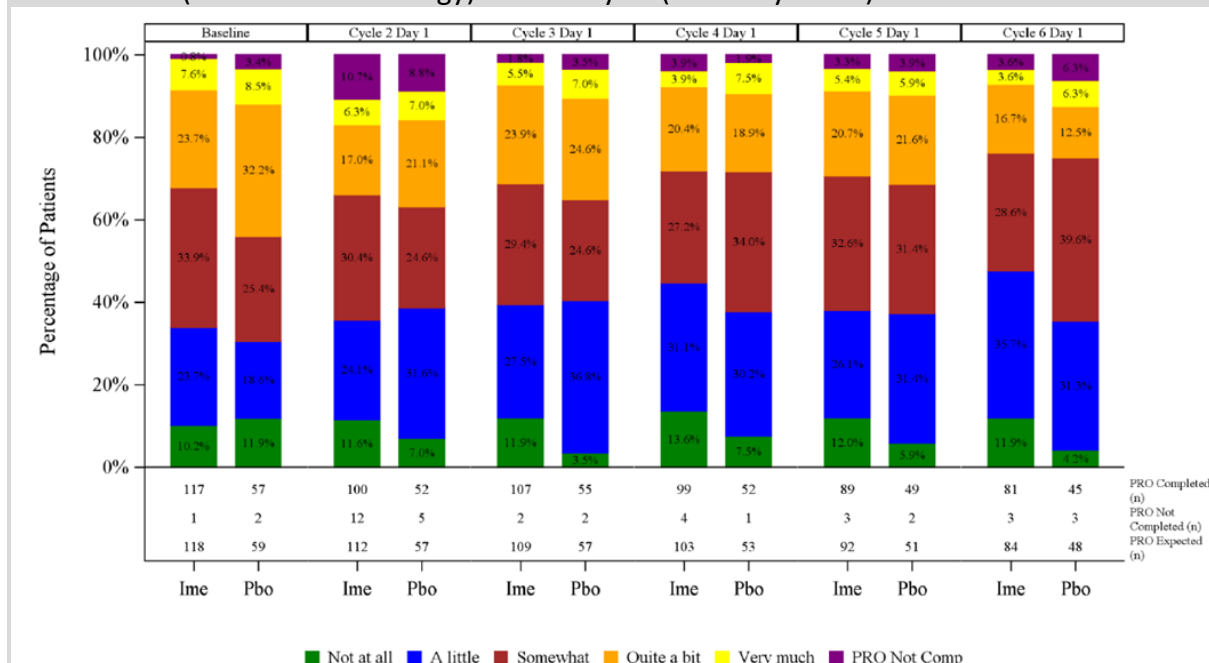
The FDA's Assessment:

Patient-generated disease symptom information was collected in MDS3001 using the FACT-Anemia and QUALMS measures, among other PRO measures. The assessment frequency was day 1 of each cycle until end of treatment and then every 12-16 weeks during follow up. Patient-reported outcomes (PRO) were included as non-multiplicity controlled exploratory endpoints.

The proportion of patients providing a response out of those expected to respond was >85% in both arms during the first year of the trial. FDA examined the patient-reported outcomes data for supportive evidence that treatment with imetelstat provided improvement in anemia related symptoms, however there was no clear evidence that patients treated with imetelstat experienced sustained improvement in fatigue or other anemia related symptoms. For example, the Applicant's PRO endpoint of interest was the proportion of patients who experienced deterioration in fatigue, with similar proportion in each arm observed (43% imetelstat versus 46% placebo). FDA examined categorical responses for key PRO items such as

the FACT-Anemia question GP1 “I have lack of energy” and noted similar results between arms during the first 6 months (Figure 24).

Figure 24: Study MDS3001-Phase 3: Bar plot of Distribution of Categorical Responses for FACT-An Item GP1 (I Have Lack of Energy) at Each Cycle (ITT analysis set)



Source: Applicant's Response to FDA Information Request dated 10 January 2024

Of note, there is no clear evidence that patients treated with imetelstat experienced sustained improvement in fatigue or other anemia related symptoms. Additionally, it should be noted that although patient-reported deterioration in fatigue results were similar between arms, more patients in the imetelstat arm experienced all grade fatigue per investigator AE reporting. More frequent assessment of patient-reported fatigue would have provided more comprehensive information, particularly the experience within cycles (and not just the seven days preceding Day 1 of a new cycle as recorded per the FACIT-Fatigue questionnaire). FDA notes the median duration of the longest episode of fatigue per investigator AE reporting was also much longer for patients treated with imetelstat, as shown in Table 35. Given the discrepancies between patient-reported and investigator-reported fatigue, as well as the fact that the PRO findings were purely exploratory in this study, no clear conclusions can be drawn regarding the impact of imetelstat on fatigue based on Study MDS3001.

Table 35: MDS3001-Phase 3: Analyses of fatigue according to different methods

	Imetelstat	Placebo
Patient-reported deterioration in fatigue for at least 2 consecutive cycles, as measured by FACIT-Fatigue ^a	51/118 (43%)	26/57 (46%)
Investigator-reported all grade fatigue ^b	34/118 (29%)	13/59 (22%)
Investigator-reported median duration of the longest episode of fatigue in weeks (range) ^c	19.1 (5, 39)	5.7 (2, NE)

^a Source: Study MDS3001 Phase 3 CSR: PRO report. Denominator includes only subjects with at least two consecutive non-missing PRO assessments.

^b Source: FDA analysis based on ADAE dataset. Denominator includes all treated subjects.

^c Source: Applicant's response to FDA Information Request Dated 22 January 2024. Denominator includes all treated subjects.

Data cutoff 13 October 2022

In order to support a marketing application, transfusion independence data should ideally be supported by evidence of direct clinical benefit to the patient (e.g., survival benefit, CR/PR benefit, or improvement in quality of life). Therefore, in the absence of a survival benefit or CR/PR benefit, the question of whether there is an improvement in patient experience becomes paramount. Although these PRO findings were purely exploratory and descriptive, FDA found no compelling evidence to support improvement in fatigue or other anemia related symptoms.

Additional Analyses Conducted on the Individual Trial

Data:

TA and hTERT Reduction and Association with TI Response

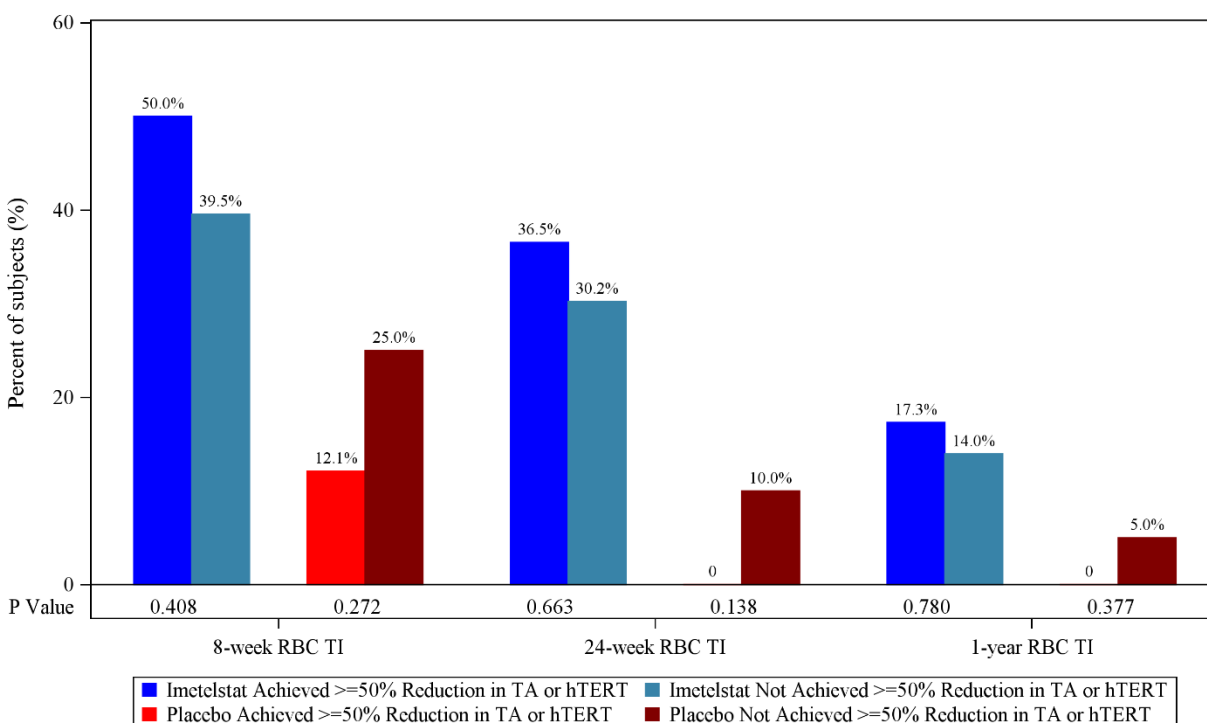
In both the pivotal Phase 3 study and the supportive Phase 2 study, imetelstat treatment induced a $\geq 50\%$ reduction from baseline in TA and hTERT mRNA levels (optimal pharmacodynamic effect). A $\geq 50\%$ reduction in TA was observed in 60% of subjects in the imetelstat group compared with 37.5% of subjects in the placebo group in the Phase 3 study and in 42.9% of subjects overall (N = 57) and in 23.1% of subjects in the target population (N = 38) of the Phase 2 study.

In the Phase 3 study, $\geq 50\%$ reduction from baseline in hTERT expression was similar among the imetelstat-treated (43.2%) and placebo-treated subjects (54.0%). In the Phase 2 study, a reduction of $\geq 50\%$ in hTERT expression was observed in 54.3% and 58.8% of subjects in the target population and overall population, respectively.

Optimal pharmacodynamic effect was associated with clinical response (8-week, 24-week, or 1-year RBC TI) (Applicant Figure 25). In the Phase 3 study, the rate of clinical response in the imetelstat group was higher in subjects who achieved the optimal pharmacodynamic effect compared with those who did not, but not statistically significant: for 8-week RBC TI (50% versus 39.5%; $P = .408$), 24-week RBC TI (36.5% versus 30.2%; $P = .663$), and 1-year RBC TI (17.3% versus 14.0%; $P = .780$). In contrast, in the placebo group, RBC TI rates were higher in subjects who did not have $\geq 50\%$ decrease from baseline in TA or hTERT. Similar results were observed in the target population the Phase 2 study: for 8-week TI (63.2% versus 18.8%; $P = 0.016$), 24-week TI (57.9% versus 6.3%; $P = 0.002$), and 1 year TI (52.6% versus 6.3%; $P = 0.004$) (MDS3001 CSR Phase 2 Section 11.2.4.1).

In the Phase 2 study, median duration of RBC TI was 68.4 weeks in subjects who achieved optimal pharmacodynamic effect compared to 5.5 weeks in subjects who did not ($HR = 0.326$), log-rank $P = 0.003$). Similar results were observed in the overall population (MDS3001 CSR Phase 2 Section 11.2.4.1).

Applicant Figure 25: Transfusion Independence by Optimal Pharmacodynamic Effect (Phase 3, Biomarker Analysis Set)



hTERT = human telomerase reverse transcriptase; RBC = red blood cell; TA = telomerase activity; TI = transfusion independence.

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Note: Biomarker Analysis Set includes all the subjects who received at least one dose of study drug and had baseline and at least one post-baseline assessment in either TA or hTERT were included.

P-value is from Fisher exact test within each treatment arm.

Source: MDS3001CSR Phase 3 Figure 10

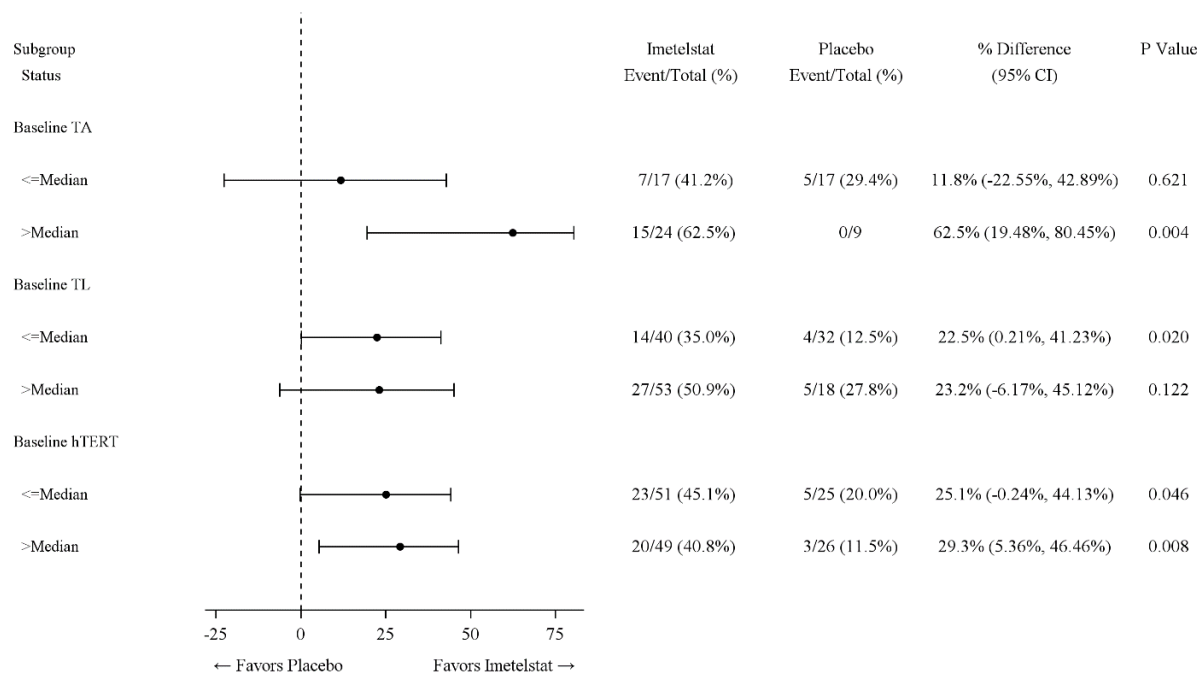
Association with TI

Additional analysis demonstrated that effect of imetelstat on TI response was associated with baseline TA levels. Subjects who had baseline TA level > median value had significantly higher rates of 8-week and 24-week RBC TI with imetelstat compared to Placebo treatment, with 8-week RBC TI rate of 62.5% (15/24, P = .004) and 24-week TI rate of 50% (12/24, P = .018) in imetelstat group vs. 0% in placebo group (0/9). In the subgroup with baseline TA level ≤ median value, compared to placebo, imetelstat also had higher rates of 8 week (41.2% vs. 29.4%; P = .621) and 24-week RBC TI (29.4% vs. 0%; P = .074), although these differences were not statistically significant ([Applicant Figure 26](#)). This suggests that patients with higher baseline TA level may be more susceptible to imetelstat treatment, which is consistent with mechanism of action of imetelstat.

Analyses based on baseline hTERT level yielded demonstrated that imetelstat had significantly superior RBC TI rates compared to placebo treatment regardless of baseline hTERT level: in the subgroup with higher hTERT level (> median value), 8-week RBC TI was 40.8% versus 11.5% (P = .008); 24-week RBC TI was 34.7% versus 0% (P < .001); in the subgroup with lower hTERT level (≤ median value), 8-week RBC TI was 45.1% versus 20% (P = .046); 24-week RBC TI was 29.4% versus 8% (P = .042). Within each treatment group, there was no significant difference in RBC TI responses between the hTERT subgroups ([Applicant Figure 26](#)).

In the imetelstat group, there was no significant difference in RBC TI responses between subjects with TL ≤ median value and subjects with TL > median value. However, in the subgroup with shorter TL (≤ median value), imetelstat treatment had significantly higher RBC TI response rates compared with placebo treatment: 8-week RBC TI was 35% versus 12.5% (P = .020); 24-week RBC TI was 32.5% versus 3.1% (P = .001) ([Applicant Figure 26](#)).

Applicant Figure 26: Forest Plot of Rate Difference for 8-week TI Between Treatment Arms by Baseline TA, TL, hTERT Status (Phase 3, Biomarker Analysis Set)



CMH = Cochran-Mantel-Haenszel; hTERT = human telomerase reverse transcriptase; IPSS = International Prognostic Scoring System; RBC = red blood cell; TA = telomerase activity; TI = transfusion burden; TL = telomere length.

Note: Mutation Biomarker Analysis Set (BAS) included all the subjects who received at least one dose of study drug and had C1D1 (baseline) mutation data available.

Comparison between treatment arms within each mutation status group.

The 95% CI was based on Wilson Score method with continuity correction.

P value is from CMH controlling for prior RBC transfusion burden (≤6 vs. >6 units RBC) and IPSS risk group (low vs. intermediate-1) applied to randomization.

Source: Figure fefbmfrti01a_p2

The Applicant's Position:

On-target activity of imetelstat was demonstrated by reductions in both TA and hTERT expression. An association between hTERT reduction from baseline and TI response was evident, with patients who achieved 8- or 24-week TI having significantly higher proportions of > 50% reduction in hTERT expression. Such an association was not observed with placebo.

Together, these results demonstrate that on-target activity of imetelstat results in clinical outcomes.

The FDA's Assessment:

FDA did not adjudicate reduction in telomerase activity (TA) and human telomerase reverse transcriptase (hTERT) expression, which was an exploratory endpoint in this study. Based on the Applicant's analyses reported above, FDA's interpretation is that $\geq 50\%$ reduction in TA was observed in both the imetelstat and placebo groups, though the rate was higher for the imetelstat group (50% vs 37.5%). However, $\geq 50\%$ reduction from baseline in hTERT expression was higher in placebo-treated subjects compared to imetelstat-treated subjects (54.0% vs 43.2%). Therefore, the mechanism of action of imetelstat cannot be determined with currently available data.

8.1.3. Integrated Review of Effectiveness

The FDA's Assessment:

The Applicant is seeking approval of imetelstat for the treatment of transfusion-dependent anemia in adult patients with low- to intermediate-1 risk MDS who have not responded to, or have lost response to, or are ineligible for ESA. This application is based primarily on the results of Study MDS3001-Phase 3. Study MDS3001-Phase 3 met the statistical goals for the primary endpoint of 8-week RBC-TI (39.8% imetelstat versus 15.0% placebo; $p = <0.001$) and key secondary endpoint 24-week RBC-TI (28.0% imetelstat versus 3.3% placebo; $p = <0.001$). Although the median duration of RBC-TI was only 5.0 weeks (95% CI 4.0, 7.7) for imetelstat versus 3.9 weeks (95% CI 3.6, 4.0) for placebo in all subjects, the median duration of RBC-TI in 8-week RBC-TI responders was 51.6 weeks (95% CI 26.9, 83.9) for imetelstat versus 13.3 weeks (95% 8.0, 24.9) for placebo, indicating that a subset of patients has a clinically meaningful duration of benefit.

While MDS3001-Phase 3 met its primary and key secondary endpoints, questions remain regarding the nature of these effects. Imetelstat is purported to have a direct effect on the underlying MDS through telomerase inhibition resulting in cell-cycle arrest, apoptosis, or senescence of malignant cells. However, a statistically significant treatment effect was not observed on the key secondary endpoint of HI-E per IWG 2006 criteria (63.6% vs. 51.7%) or other secondary endpoints reflective of a disease-modifying effect such as CR or PR (0% vs. 0% at the time of primary analysis; 5.9% at best vs. 0% at the time of updated analysis) and OS (HR=0.98 [95% CI: 0.53, 1.82] at most recent data cut). In addition, the patient-reported outcomes collected in Study MDS3001-Phase 3 did not reflect an improvement in fatigue or other anemia-related symptoms. There are also residual uncertainties regarding the impact of imetelstat on overall medical resource utilization (see Section 8.1.4 under Additional Efficacy Considerations) and the applicability of the trial results to the US population, given the limitations of the medical resource utilization analyses and lower RBC-TI rates in the US population compared to the non-US population. Additionally, very few patients in Study

MDS3001 had prior treatment with luspatercept, which is now approved for frontline treatment of transfusion-dependent anemia in patients with lower-risk MDS.

In conclusion, while a subset of patients appears to have a clinically meaningful benefit with imetelstat, it is important to weigh the potential benefits of imetelstat against the potential risks, which are further discussed in the safety review below.

8.1.4. Assessment of Efficacy Across Trials

Study MDS3001-Phase 2

Study Design

Part 1 of the MDS3001 study was designed as a single arm Phase 2 study. Initially ~30 subjects were planned to be enrolled. Per Amendment 2, enrollment was expanded to include ~22 additional subjects for a total planned enrollment of ~55 subjects. The open-label, single-arm design was considered appropriate to provide supportive safety data and demonstrate preliminary clinical benefit of treatment with imetelstat in MDS at 7.1 mg/kg (active moiety, equivalent to 7.5 mg/kg imetelstat-sodium) every 4 weeks in the Phase 2 setting and to support the initiation of the randomized, placebo-controlled Phase 3 part of the study (Part 2).

The primary objective of the Phase 2 study was to evaluate the efficacy and safety of imetelstat in transfusion-dependent subjects with low- or intermediate-1 risk MDS that is relapsed/refractory to ESA treatment.

The primary efficacy endpoint of the Phase 2 study was the rate of RBC TI lasting ≥ 8 weeks and was calculated as described for the pivotal Phase 3 study.

Key secondary endpoints of the Phase 2 study were:

- Safety of imetelstat in subjects with MDS (e.g., incidence, intensity, and type of AEs, vital signs measurements, clinical laboratory values, ECGs, and deaths)
- 24 week RBC TI rate, defined as the proportion of subjects without any RBC transfusion during at least any consecutive 24 weeks (168 days) starting from Study Day 1
- Time to the 8 week (or 24-week) RBC TI, defined as the interval from Study Day 1 to the first day of the first 8 week (or 24-week) RBC TI period
- Duration of RBC TI, defined as the first day of the longest RBC TI period to the date of the first RBC transfusion after the TI period started
- Rate of hematologic improvement, including HI-E, per modified IWG 2006
- Rates of CR, PR, or mCR per modified IWG 2006

- OS, defined as the interval from Study Day 1 to death from any cause. Survival time of living subjects was censored on the last date a subject was known to be alive or lost to follow-up.
- PFS, defined as the time interval from Study Day 1 to the first date of disease progression or death from any cause, whichever occurred first
- Time to progression to AML, defined as the interval from Study Day 1 to the date of AML diagnosis
- Amount and relative change in units of RBC transfusions
- Rate of myeloid growth factors usage, defined as the proportion of subjects who received any myeloid growth factors starting from Study Day 1; duration of myeloid growth factor administered starting from Study Day 1
- PK parameters (e.g., C_{max} , AUC0-t), and immunogenicity of imetelstat (e.g., antibodies to imetelstat)

The exploratory endpoints of the Phase 2 study were:

- TA and hTERT at baseline and the change from baseline, TL at baseline only
- Cytogenetic status at baseline and change over time for cytogenetic response
- Mutation status at baseline and change over time including at the time of suspected response (CR, PR, HI-E) or progressive disease

Primary Endpoints

Data:

8-week RBC-TI rates for the Target Population (N = 38) are summarized in [Applicant Table 36](#) and transfusion independence intervals for 8-week RBC IT responders in are shown in [Applicant Figure 27](#).

Subgroup analysis of the primary endpoint is shown in Applicant Figure 28.

Applicant Table 36: Rate of 8-week RBC TI (Phase 2 Study, All Treated Analysis Set)

	Target Population (N = 38)
8-week RBC TI, n (%)	16 (42.1%)
95% CI ^a for response rate (%)	(26.31%, 59.18%)

CI = confidence interval; RBC = red blood cell; TI = transfusion independence.

^a Exact Clopper-Pearson confidence interval.

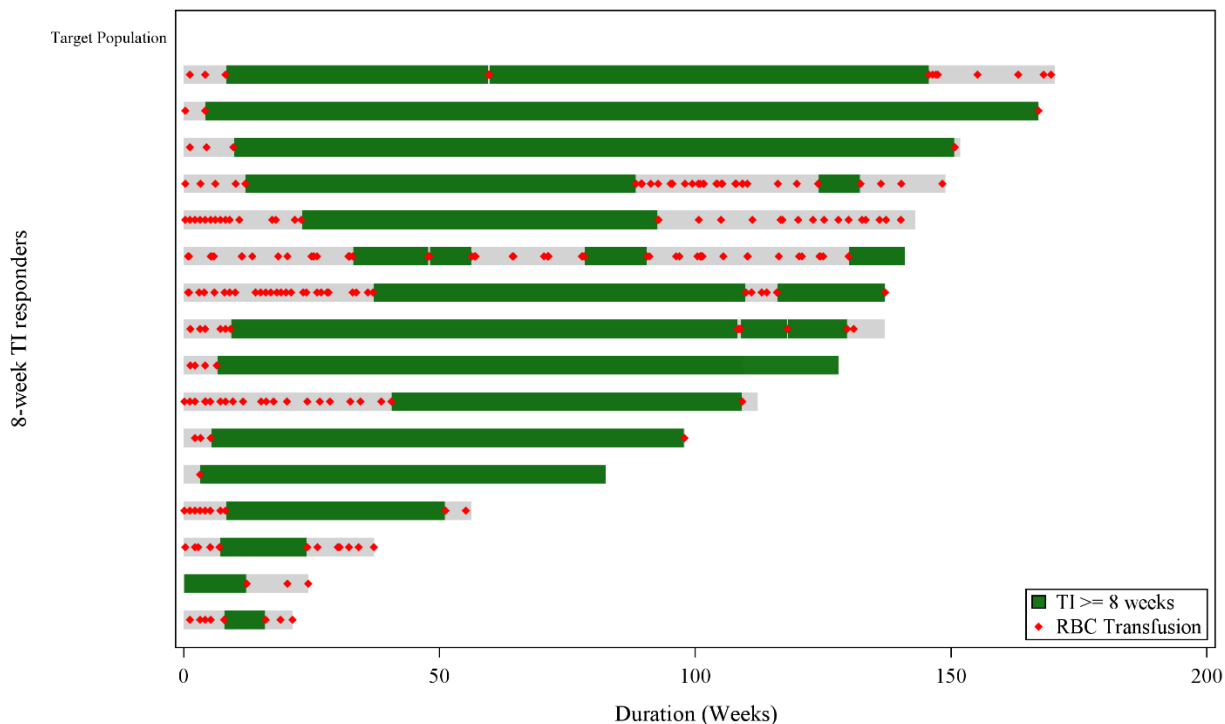
Note: The target population includes the subjects without prior HMA or lenalidomide use and non del(5q) in karyotype at baseline.

Source: Table *tefti01_p1*.

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Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Applicant Figure 27: 8-Week RBC TI Intervals (Phase 2 Study All Treated 8-week RBC TI Responder Analysis Set)

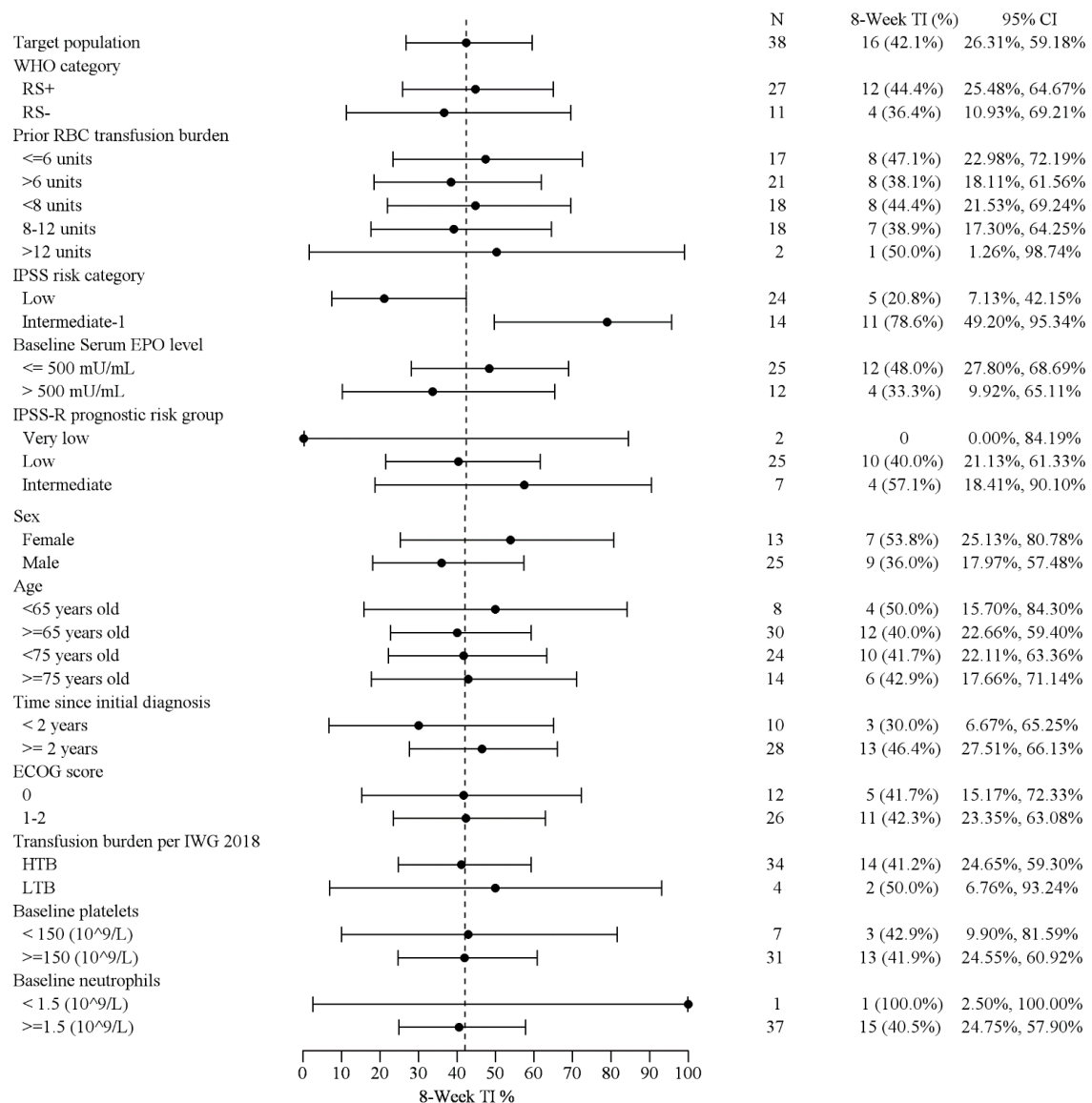


RBC = red blood cell; TI = transfusion independence.

Note: The target population includes the subjects without prior HMA or lenalidomide use and non del(5q) in karyotype at baseline.

Source: Figure feftisw01_p1.

Applicant Figure 28: Rate of 8-Week RBC TI by Baseline Characteristics (Phase 2, All Treated Analysis Set; Target Population)



CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EPO = erythropoietin; HTB = high transfusion burden; IPSS = International Prognostic Scoring System; IPSS-R = International Prognostic Scoring System-Revised; IWG = International Working Group; LTB = low transfusion burden; RBC = red blood cell; RS = ring sideroblasts; TI = transfusion independence; WHO = World Health Organization.

Note: The target population includes the subjects without prior HMA or lenalidomide use and non del(5q) in karyotype at baseline.

Source: Figure fefti01a_p1.

The Applicant's Position:

The Phase 2 study demonstrated a high rate of RBC TI lasting at least 8 weeks. Results obtained in the target population which is the same as the LR MDS population of the pivotal Phase 3 study, were consistent and supportive of the Phase 3 study. High rates of 8-week TI were observed in most key LR MDS subgroups including including RS status, baseline transfusion burden, and baseline serum EPO levels.

The FDA's Assessment:

Phase 2 study design

Study MDS3001-Part 1 (Phase 2) was a multicenter, single-arm, open-label trial evaluating imetelstat in patients with transfusion dependent anemia due to IPSS low- or intermediate-1 risk MDS who are relapsed/refractory to or ineligible for ESA.

The study initially planned to enroll about 30 subjects. However, upon review of the efficacy and safety data among 32 subjects, a higher RBC-TI rate was noted in a subset of 13 subjects with non-del(5q) karyotype and without prior treatment with either HMA or lenalidomide. Thus, the Phase 2 study was expanded with Amendment 2 to enroll an additional 25 subjects who met these criteria. Thus, there were a total of 57 subjects enrolled in the Phase 2 study, 38 of whom met these criteria (referred to as the "target population").

The starting dose was imetelstat sodium 7.5 mg/kg (equivalent to imetelstat 7.1 mg/kg) IV every 4 weeks. The study protocol initially allowed for dose escalation to imetelstat sodium 9.4 mg/kg, however it was noted that the higher dose was not associated with improved TI; therefore, as of Amendment 2, dose escalation was no longer allowed.

The primary efficacy endpoint was 8-week RBC-TI, defined as the proportion of subjects without any RBC transfusion during at least any consecutive 8 weeks (56 days) starting from Study Day 1 until subsequent anti-cancer therapy, if any. Study Day 1 was defined as the day of the first dose. Secondary and exploratory endpoints were as noted above by the Applicant.

Primary endpoint (8-week RBC-TI) results

The rate of 8-week RBC-TI was 42.1% (95% CI 26.3, 59.2) for the target population and 36.8% (95% CI 24.5, 50.7) for all subjects in the Phase 2 study, which is generally consistent with the 8-week RBC-TI rate observed in the Phase 3 study. Subgroup analyses are discussed in the "Subpopulations" section below.

Secondary and Other Endpoints

Data:

Applicant Table 37: Summary of Key Secondary Endpoints (Phase 2 Study, All Treated Analysis Set)

	Target Population (N = 38)
24-week RBC-TI, n (%)	12 (31.6%)
95% CI ^a for response rate (%)	(17.50%, 48.65%)
1-year RBC-TI, n (%)	11 (28.9%)
95% CI ^a for response rate (%)	(15.42%, 45.90%)
Duration of RBC-TI (weeks)	
8-week TI responders (n)	16
Median (95% CI)	74.5 (17.00, 99.00)
24-week TI responders (n)	12
Median (95% CI)	85.9 (68.43, 140.86)
Rate of hematologic improvement per modified IWG 2006	
Erythroid response (HI-E), n (%)	25 (65.8%)
95% CI for response rate	(48.65%, 80.37%)
Rate of hematologic improvement per revised IWG 2018	
LTB subjects, n (%)	4 (10.5%)
HI-E response (16-week RBC TI)	2 (50.0%)
95% CI for response rate	(6.76%, 93.24%)
HTB subjects, n (%)	34 (89.5%)
Major HI-E response (16-week RBC TI)	11 (32.4%)
95% CI for response rate	(17.39%, 50.53%)
Overall survival (months)	
Median (95% CI)	55.2 (38.08, NE)

CI = confidence interval; RBC = red blood cell; TI = transfusion independence.

^a Exact Clopper-Pearson confidence interval.

Note: The target population includes the subjects without prior HMA or lenalidomide use and non del(5q) in karyotype at baseline.

Source: Table tefti05_p1.

Key Secondary Efficacy Variables

- The rate of 24-week RBC TI in the target population was 31.6%. Among all subjects overall, the 24-week RBC TI rate was 24.6% (
- [Applicant Table 37](#)).
- Imetelstat demonstrated clinical benefit across all subgroups in the target population, including RS status (37.0% [RS⁺] and 18.2% [RS⁻]), baseline transfusion burden (35.3% [≤ 6 units] and 28.6% [> 6 units]), IPSS risk category (20.8% [low] and 50.0% [intermediate-1]),

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and baseline serum EPO levels (40.0% [≤ 500 mU/mL] and 16.7% [> 500 mU/mL]) (shown for the Target population in [Applicant Figure 28](#)). In both the target population and overall, over 91% of the subjects who achieved at least 24-week TI went on to achieve at least 1-year TI.

- Duration of RBC TI
 - Median duration of RBC TI among the 16 subjects in the target population who achieved 8-week RBC TI was 74.5 weeks. Among the 21 subjects in the overall subject population who achieved 8-week RBC TI, median duration of RBC TI was 69.6 weeks. Median duration of RBC TI among both the 12 subjects in the target population and the 14 subjects in the overall subject population who achieved 24-week RBC TI was 85.9 weeks.
- Hematologic improvement:
 - Imetelstat treatment led to a sustained increase in Hb levels. The median Hb rise from pretreatment in the longest RBC TI period for 8-week RBC TI responders was 3.96 g/dL in the target population and 3.75 g/dL in the overall subject population. Median Hb peak in the longest RBC TI interval was 11.6 g/dL in the target population and 11.4 g/dL in the overall subject population.
 - Median relative change from baseline in RBC transfusion burden during the best 8-week interval was -77.8% in the target population and -66.7% in the overall subject population.
 - The rate of HI-E per modified IWG 2006 criteria in the target population was 65.8%, which included 13 (34.2%) subjects with Hb increase ≥ 1.5 g/dL above pretreatment and lasting ≥ 8 weeks. Among all subjects overall, the rate of HI-E was 61.4%, which included 16 (28.1%) subjects with Hb increase ≥ 1.5 g/dL above pretreatment and lasting ≥ 8 weeks. One subject (2.6%) in the target population had HI-P. The HI-P in the overall subject population was 1.8%.
 - The rate of hematologic improvement per revised IWG 2018 criteria was also analyzed. Among subjects in the target population (LTB and HTB), the HI-E response rate was 50.0%. Among LTB subjects (n = 4), the HI-E response rate was 50.0%. Among HTB subjects (n = 34), 32.4% of subjects had a major HI-E response, and 50% of subjects had a minor HI-E response. HI-E rates were similar in the overall subject population.

Other Secondary Efficacy Variables

- Median time to 8-week RBC TI among the 16 subjects in the target population and 21 subjects in the overall subject population who achieved 8-week RBC TI was 8.3 weeks.
- Median time to 24-week RBC TI among the 12 subjects in the target population and 14 subjects in the overall subject population who achieved 24-week RBC TI was 8.8 weeks.
- Per investigator assessment, in the target population, 4 (10.5%) subjects had CR, 5 (13.2%) subjects had mCR, and no subjects had PR, for an overall response rate (CR + PR + mCR) of

23.7%. In the overall subject population, 5 (8.8%) subjects had CR, 7 (12.3%) subjects had mCR, and there were no subjects with PR, for an overall response rate of 21.1%. Of note, 91.2% of subjects in the overall subject population had $\leq 5\%$ bone marrow blasts at baseline but were still evaluated for CR/PR/mCR per investigator.

- Median OS was 55.2 months in the target population and 55.3 months in the overall subject population.
- Median estimated PFS was 34.2 months in both the target population and the overall subject population. Eleven (28.9%) subjects in the target population and 13 (22.8%) subjects in the overall subject population had disease progression.
- With post-treatment follow-up, 4 subjects, all in the target population, had reported progression to AML as of the cutoff date. Median estimated time to progression to AML was 44.2 months in the target population. In the overall subject population, the median estimated time to progression to AML was not reached.
- Thirteen (34%) subjects in the target population and 19 (33%) subjects in the overall subject population had at least 1 dose of myeloid growth factors as of the cutoff date.

Exploratory Efficacy Variables

- A reduction of $\geq 50\%$ in TA and hTERT (optimal pharmacodynamic effect) was observed in 23.1% and 54.3% of subjects, respectively, in the target population. In the overall population, 42.9% and 58.8% of subjects achieved TA and hTERT $\geq 50\%$ reduction from baseline, respectively. In the target population, a higher response rate was observed in subjects who achieved the optimal pharmacodynamic effect compared with those who did not, for 8-week RBC TI (63.2% versus 18.8%; $P = 0.016$), 24-week RBC TI (57.9% versus 6.3%; $P = 0.002$), and 1-year RBC TI (52.6% versus 6.3%; $P = 0.004$). Median duration of RBC TI was 68.4 weeks in subjects who achieved optimal pharmacodynamic effect compared to 5.5 weeks in subjects who did not ($HR = 0.326$, log-rank $P = 0.003$). Similar results were observed in the overall population.
- In the target population, among 31 subjects with baseline mutation data available, 27 had SF3B1 mutations, of whom 12 subjects also had post-treatment mutation data. Eleven subjects had a reduction (range: -9.8% to -93%) in SF3B1 VAF from baseline. The reduction of SF3B1 VAF was significantly correlated with TI duration; with a longer TI duration associated with a greater reduction in SF3B1 VAF (Pearson correlation coefficient $r = -0.71$; $P = 0.010$).
- There was no significant difference in 8-week, 24-week and 1-year TI rate in subjects with or without baseline mutations. There was no significant difference in durable TI rates for mutation defined subgroups based on genes involved in different biological functions, including splicing process, epigenetic regulation, or receptors/kinases.

The Applicant's Position:

In the Phase 2 study, imetelstat induced clinically meaningful and durable TI and a high HI-E rate in a population of heavily RBC transfusion-dependent, ESA-relapsed/refractory lower risk MDS, irrespective of the presence of RS. Correlations between on-target effects and decreased mutation and cytogenetic burden in responders suggest the potential for disease modification with imetelstat treatment. Imetelstat demonstrated an acceptable safety profile that was manageable and generally reversible, with no new safety signals or evidence of cumulative toxicity identified.

The results in the target population of this study are highly consistent and supportive of the pivotal Phase 3 study in the same LR MDS patient population.

The FDA's Assessment:

The rate of 24-week RBC-TI was 31.6% (95% CI 17.5, 48.7) for the target population and 24.6% (95% CI 14.1, 37.8) for all subjects in the Phase 2 study, which is generally consistent with the 24-week RBC-TI rate observed in the Phase 3 study. Subgroup analyses are discussed in the "subpopulations" section below.

The other secondary and exploratory endpoints in the Phase 2 study were not adjudicated by the FDA. However, based on the Applicant's analyses which are summarized above, the results were generally consistent with the results of the Phase 3 study. For example, the HI-E rate per IWG 2006 criteria was 65.8% in the target population and 61.4% in the overall population in Phase 2, which are similar to the HI-E rate of 63.6% observed for the imetelstat arm of the Phase 3 study.

However, it should be noted that the CR rate per investigator assessment was 10.5% for the target population and 8.8% for the overall population in the Phase 2 study, which is higher than the CR rate of 0% at the time of primary analysis in the Phase 3 study.

Lastly, it should be noted that time-to-event endpoints cannot be adequately assessed in a single-arm trial due to the lack of a placebo comparator; therefore, no definitive conclusions can be drawn based on the median PFS or median OS reported by the Applicant for the Phase 2 study above.

Subpopulations

Data:

Subgroup analyses were performed to assess the consistency and robustness of the treatment benefit mainly for the rate of RBC TI and the rate of HI-E. Subgroup analysis could be performed

for other selected efficacy and safety endpoints. The following subgroup variables and the cutoff values were subject to change if warranted to better represent the data.

- Sex (male versus female)
- Age (< 65 versus ≥ 65 years old; < 75 versus ≥ 75 years old)
- Time since initial diagnosis (< 2 versus ≥ 2 years)
- WHO Classification (RS+ versus RS-)
- Prior RBC transfusion burden (≤ 6 versus > 6 units RBC; < 8, 8 to 12, or 12 units RBC)
- Transfusion burden per IWG 2018 (HTB versus LTB)
- Baseline bone marrow blasts per central lab (≤ 5% versus > 5%)
- Baseline platelets (< 150 x10⁹/L versus ≥ 150 x10⁹/L)
- Baseline neutrophils (< 1.5 x10⁹/L versus ≥ 1.5 x10⁹/L versus)
- IPSS risk group (low risk versus intermediate-1 risk)
- Number of cytopenia (0 to 1 versus 2 to 3)
- Prior ESA use (yes versus no)
- Baseline serum EPO levels (≤ 500 versus > 500 mU/mL)
- Eastern Cooperative Oncology Group (ECOG) score (0 versus 1 to 2)
- IPSS-R cytogenetic risk groups (very good/good, intermediate, or poor/very poor) ([Greenberg, 2012](#))
- IPSS-R Prognostic risk groups (very low, low, intermediate, high, or very high) ([Greenberg, 2012](#))

Subgroup Analysis in Study MDS3001-Phase 3

Subgroup analysis is discussed in Efficacy Analysis of the Phase 3 study ([Section 8.1.2](#)).

Subgroup analysis of 8-week and 24-week TI (primary and key secondary endpoints) based on demographics and the most relevant disease characteristics, is shown in [Applicant Figure 8](#) and [Applicant Figure 11](#), respectively. Subgroup analyses for duration of response and HI-E are summarized in the sections describing the results for these endpoints ([Section 8.1.2](#)).

Subgroup Analysis in Study MDS3001-Phase 2

> 8-week and > 24-week RBC-TI

Imetelstat demonstrated comparable clinical benefit of > 8-week TI across most subgroups in the target population (N = 38), including RS status (44.4% [RS+] and 36.4% [RS-]), baseline transfusion burden (47.1% [≤ 6 units] and 38.1% [> 6 units]), and baseline serum EPO levels (48.0% [≤ 500 mU/mL] and 33.3% [> 500 mU/mL]).

Subgroup analysis by baseline characteristics for the target population is shown in [Applicant Figure 28](#). Subgroup analyses for the overall subject population is shown in [Figure fefti01a_p1](#).

Similarly, clinical benefit in terms of > 24-week TI was observed across all subgroups in the target population, including RS status (37.0% [RS+] and 18.2% [RS-]), baseline transfusion burden (35.3% [≤ 6 units] and 28.6% [> 6 units]), IPSS risk category (20.8% [low] and 50.0% [intermediate-1]), and baseline serum EPO levels (40.0% [≤ 500 mU/mL] and 16.7% [> 500 mU/mL]) (Table tefti06_p1 and Figure fefti02_p1).

The Applicant’s Position:

In the Phase 3 MDS3001 pivotal study, imetelstat demonstrated superiority compared to placebo in most key LR-MDS subgroups, including those based on RS status, baseline transfusion burden and baseline EPO levels, across several efficacy endpoints. The subgroup analyses for RBC-TI in the Phase 2 MDS3001 study were strongly supportive of those from the pivotal study and demonstrate the broad applicability of imetelstat as a therapeutic option in LR MDS.

The FDA’s Assessment:

The vast majority of subjects in Study MDS3001-Phase 3 (93%) were enrolled at non-US sites. The Agency sent an information request to the Applicant requesting information on efficacy by region. Based on the Applicant’s response to the Agency’s information request, the primary efficacy result varied greatly between the US and non-US sites. As shown in Table 38, the 8-week RBC-TI rate with imetelstat was much lower in the subgroup of patients enrolled at sites within the US compared to non-US sites, with a difference in response rate of only 12.5% for US subjects compared to 25.5% for non-US subjects.

Table 38: MDS3001-Phase 3: 8-week RBC-TI rate for United States versus Non-United States (ITT Set)

	Imetelstat	Placebo	Difference
United States 8-week RBC-TI (%) 95% CI	1/8 (12.5%) (0.3%, 52.7%)	0/5 (0%) (0%, 52.2%)	12.5% (-42.5%, 53.3%)
Non-United States 8-week RBC-TI (%) 95% CI	46/110 (41.8%) (32.5%, 51.6%)	9/55 (16.4%) (7.8%, 28.8%)	25.5% (9.6%, 38.2%)

Source: Applicant’s Response to FDA Information Request dated 2 October 2023

Regarding the region-specific population and treatment-related factors, the Applicant noted the following in the response to the information request dated 2 October 2023:

- **MDS diagnosis and Prognostic Factors.** “All enrolled subjects had their MDS diagnosis confirmed by a central pathology reviewer. There were no notable differences in disease

characteristics and prognostic factors between regions when taking into account the smaller numbers in NA and ROW [Rest of the World] compared with EU.”

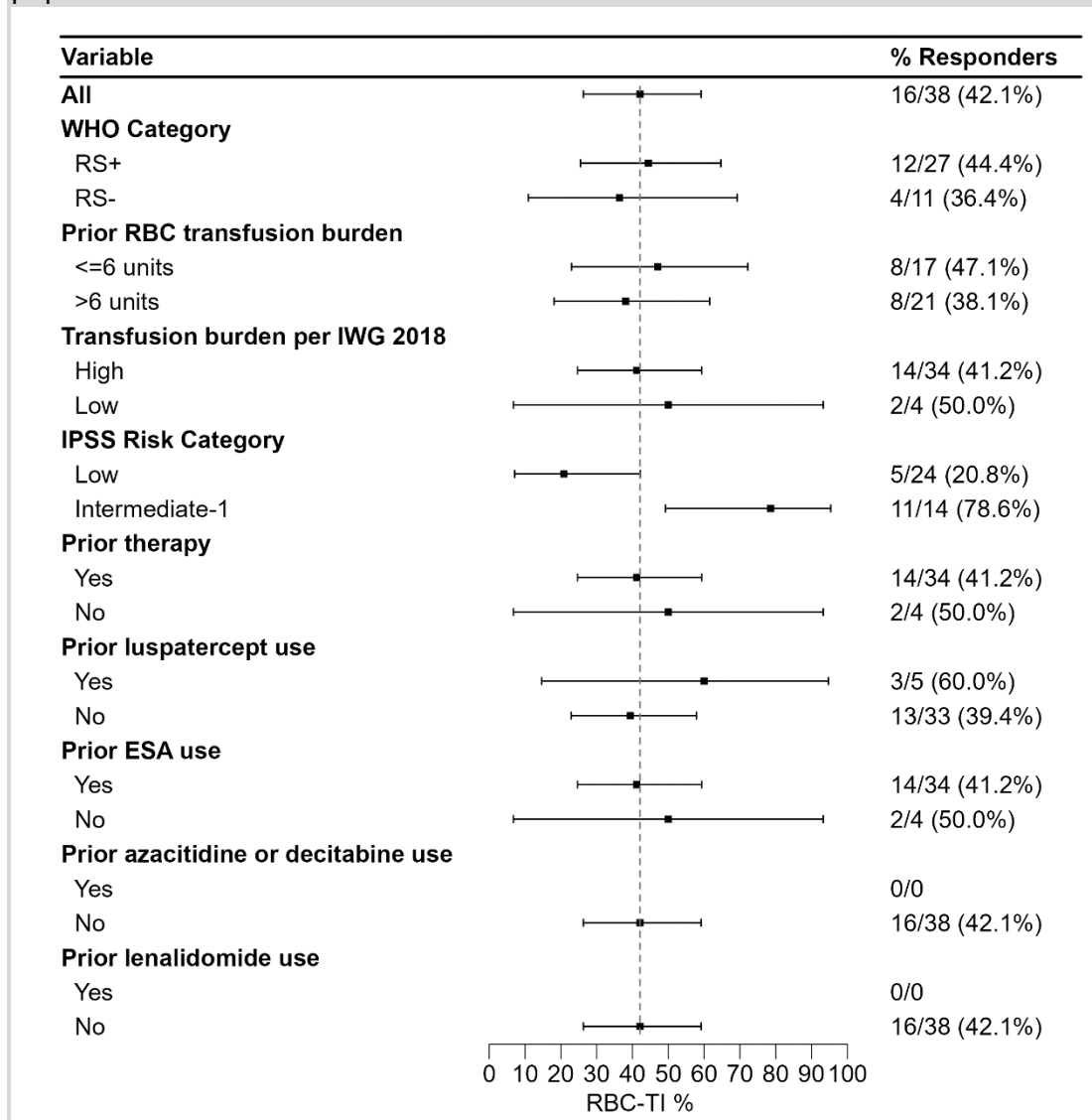
- **Concomitant medications.** “Regarding the potential impact of concomitant medication on regional TI rate differences, the use of iron chelators (IC) among imetelstat-treated subjects was higher in the EU (70%) and ROW (68%), compared with NA (15%), although there was no difference in use of IC between the imetelstat and placebo treated subjects, and no impact of IC use on the rates of 8-week TI. Growth factor usage for imetelstat-treated subjects was lower in NA compared to EU and ROW; however, this is likely due to the shorter duration of treatment of NA subjects (described in detail below). No other apparent trends of concomitant medications which could impact the efficacy across regions were identified.”
- **Transfusion Practices on study by region.** Analysis of baseline pretreatment Hgb levels by region showed no notable differences between regions in the study population (median Hgb 7.7 g/dL NA, 8.0 g/dL EU, 7.5 g/dL ROW) (Table 7). The on-study pre-transfusion Hgb was also similar between regions (median Hgb 7.6 g/dL NA, 7.4 g/dL EU, 7.2 g/dL ROW) (Table 7). These results are in line with guidelines and medical practice, as noted above. In addition, when baseline pretreatment Hgb levels leading to transfusions were also compared to on-study Hgb levels resulting in transfusions (pre-study versus on-study) the median change was comparable between regions and between imetelstat and placebo. Small differences can be attributed to the small sample sizes in NA and ROW and are not clinically meaningful. Based on these data, there are no notable regional differences in MDS3001 Phase 3 investigators’ transfusion practices between treatment groups on study or a change in Hgb levels leading to RBC transfusions while on study vs. pre-study.”
- **Treatment Duration.** “Overall, in the Phase 3 study, subjects in the NA region tended to stay on treatment for a shorter duration than those in other regions. Thirteen (11%) of 118 imetelstat-treated subjects were enrolled in NA, 8 of whom were enrolled in the US. The median treatment duration for these NA subjects was shorter compared with those in the EU and ROW (18 weeks, 53 weeks, and 26 weeks, respectively). Among the imetelstat-treated subjects in the US (n=8), it is notable that except for the 1 subject who was a long TI responder (treatment duration of 105.1 weeks at primary analysis), all other US subjects were treated for 6 cycles or less. Of these 7 subjects, 2 subjects received only 1 cycle, and 1 subject received 2 cycles. In NA, the availability of alternative treatment options such as hypomethylating agents and luspatercept, possibly impacted investigator and subject decision making to discontinue treatment earlier before achieving TI. Due to the small number of subjects and short treatment duration in the US, it is difficult to assess the efficacy of imetelstat in US subjects in isolation...”

Ultimately, no definitive conclusions can be drawn due to the small sample size of the subgroups and the lack of the prespecified subgroup hypothesis testing. However, potential

impact of region-specific patient or treatment-related factors cannot be ruled out. Residual uncertainty regarding applicability of the efficacy results to the US population remains.

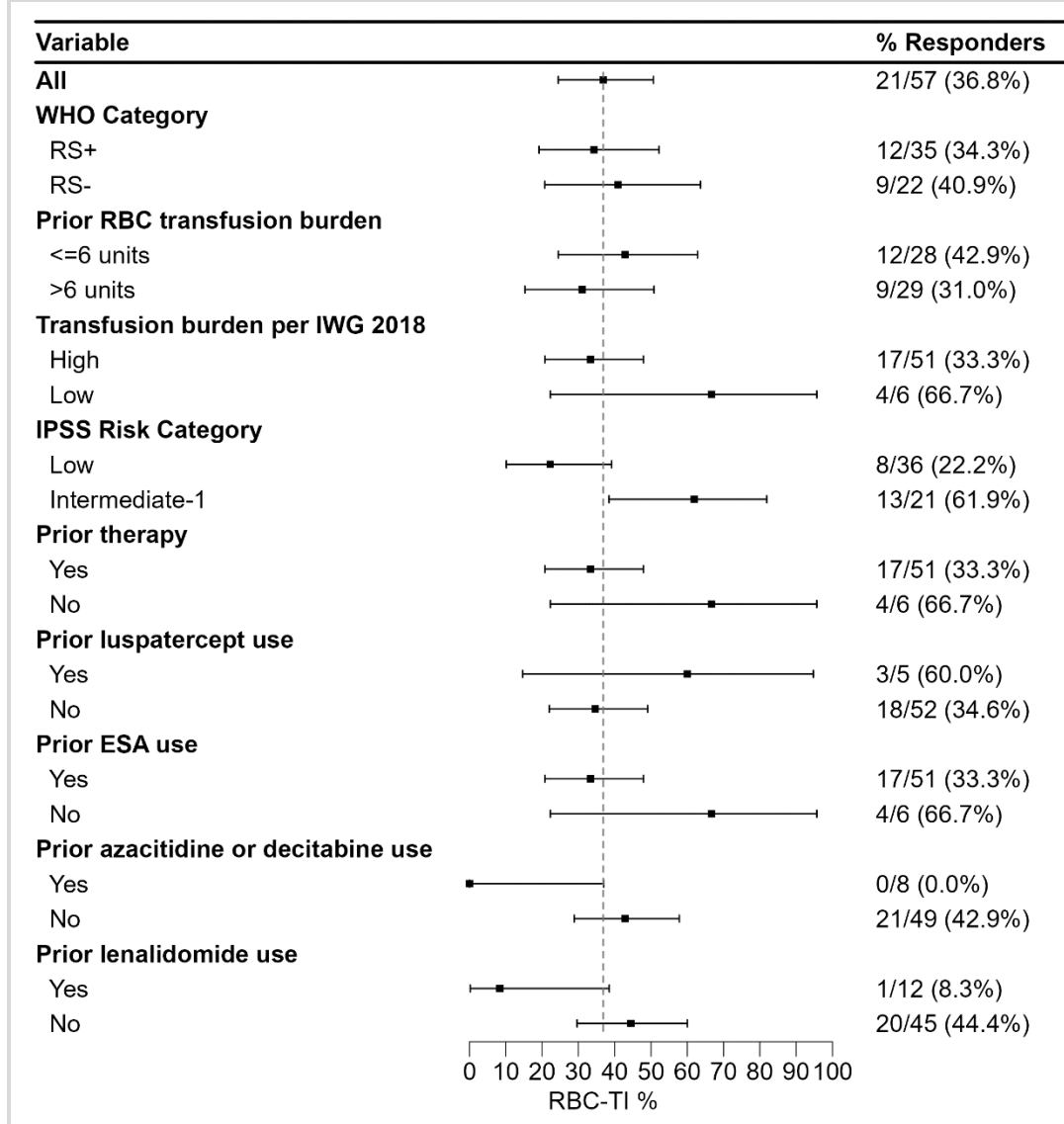
Subgroup analyses for 8-week RBC-TI in the target population and all subjects in the Phase 2 study are shown in Figure 29 and Figure 30, respectively. The rate of 8-week RBC-TI was similar across most subgroups, with a few notable exceptions. Subjects with IPSS low-risk MDS had a lower 8-week RBC-TI rate than subjects with IPSS intermediate-1 risk MDS. Additionally, subjects treated with prior hypomethylating agent (HMA) and/or lenalidomide had a substantially lower 8-week RBC-TI rate than other subgroups, with 0/8 (0%) of subjects with prior HMA achieving an 8-week RBC-TI and only 1/12 (8.3%) of subjects with prior lenalidomide achieving an 8-week RBC-TI.

Figure 29: Study MDS3001-Phase 2: Subgroup analyses of 8-week RBC-TI rate in the target population



Source: FDA analysis based on ADSL and ADBDC datasets. Data cutoff: 13 Oct 2022.

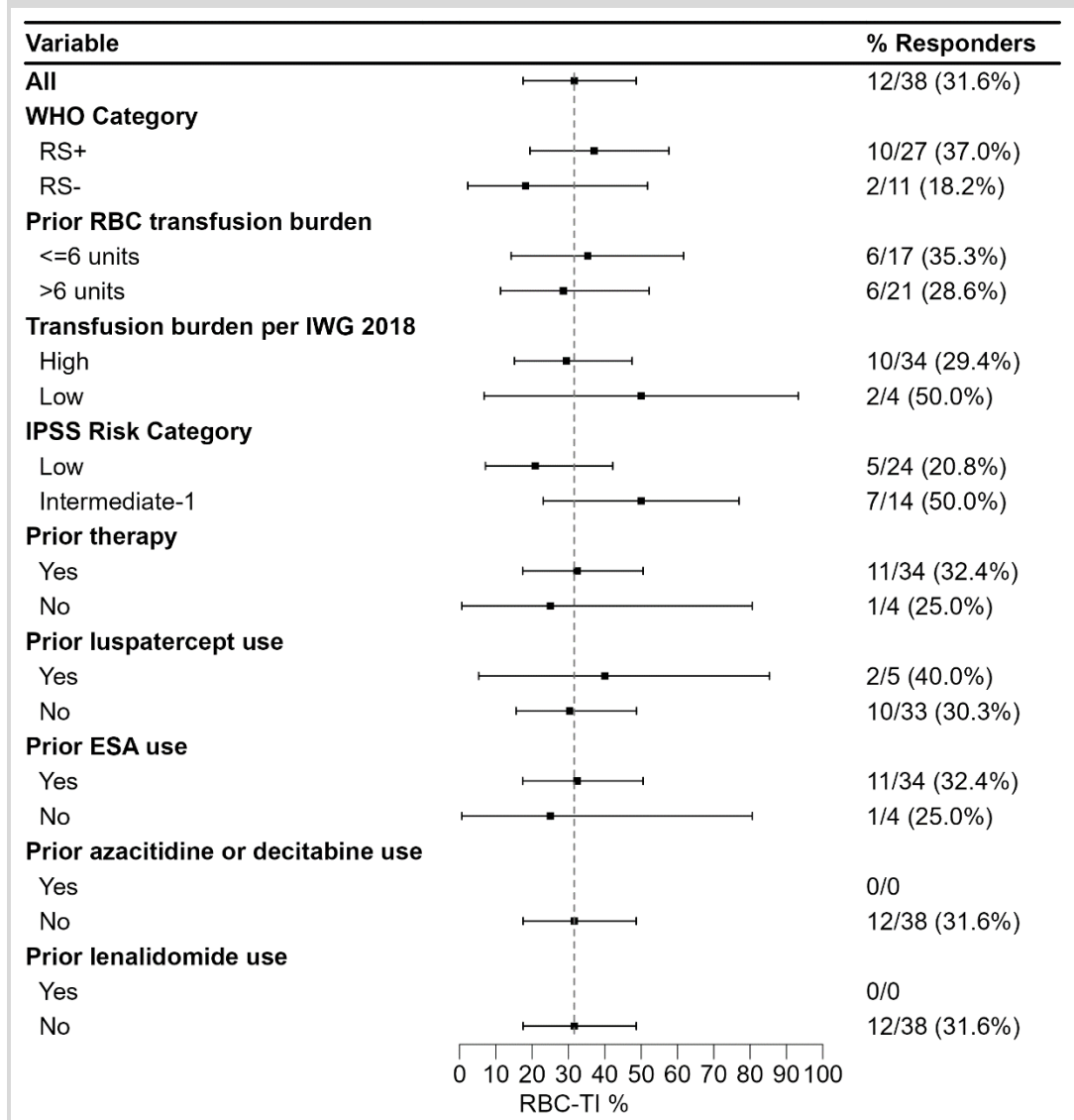
Figure 30: Study MDS3001-Phase 2: Subgroup analyses of 8-week RBC-TI rate in all subjects



Source: FDA analysis based on ADSL and ADBDC datasets. Data cutoff: 13 Oct 2022.

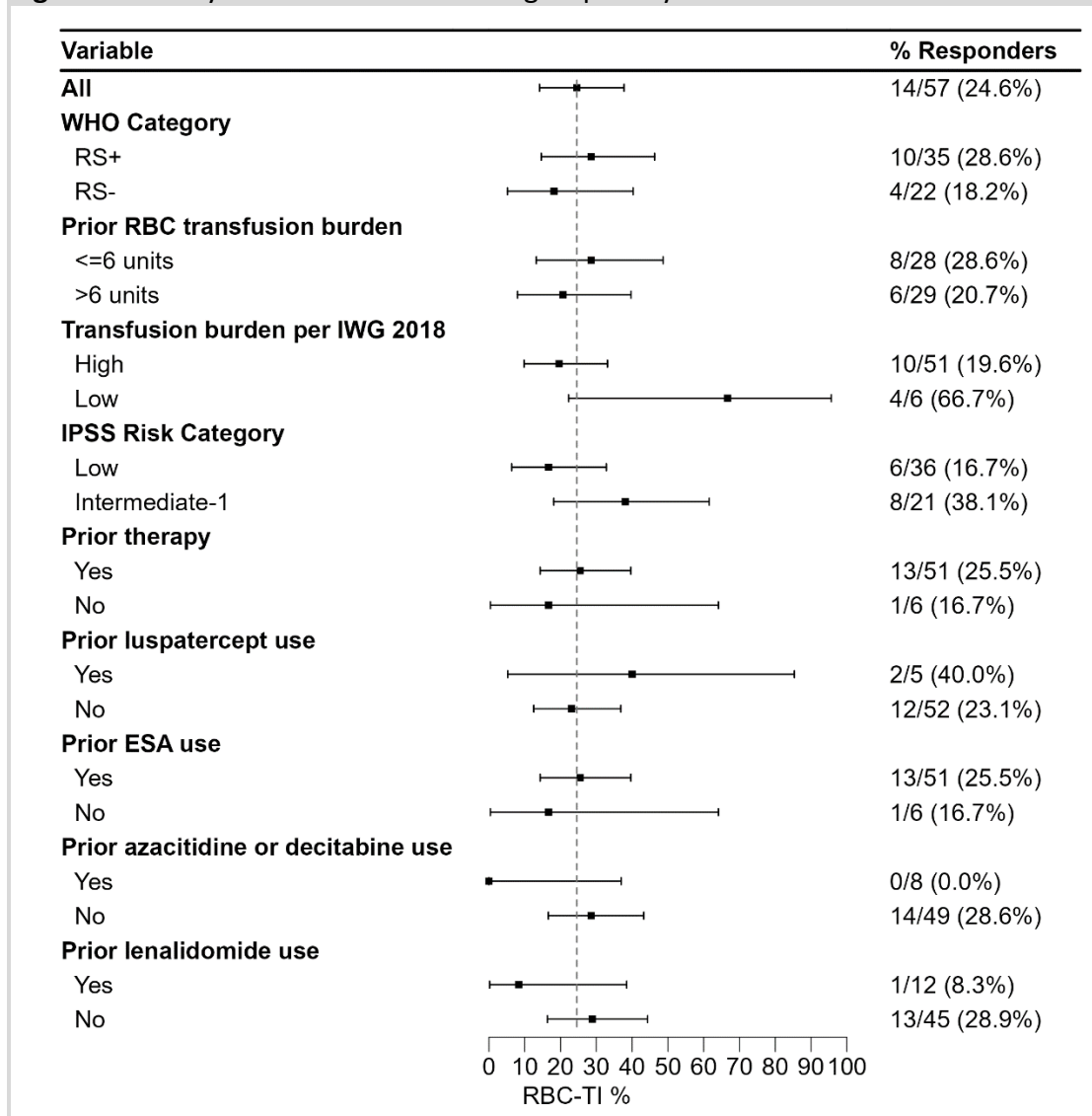
Subgroup analyses for 24-week RBC-TI in the target population and all subjects in the Phase 2 study are shown in Figure 31 and Figure 32, respectively. The results were similar to the subgroup analyses for 8-week RBC-TI. The rate of 24-week RBC-TI was similar across most subgroups with a few notable exceptions. Subjects with IPSS low-risk MDS had a lower 8-week RBC-TI rate than subjects with IPSS intermediate-1 risk MDS. Subjects treated with prior HMA and/or lenalidomide had a substantially lower 24-week RBC-TI rate than other subgroups, with 0/8 (0%) of subjects with prior HMA achieving a 24-week RBC-TI and only 1/12 (8.3%) of subjects with prior lenalidomide achieving a 24-week RBC-TI.

Figure 31: Study MDS3001-Phase 2: Subgroup analyses of 24-week RBC-TI rate in the target population



Source: FDA analysis based on ADSL and ADBDC datasets. Data cutoff: 13 Oct 2022.

Figure 32: Study MDS3001-Phase 2: Subgroup analyses of 24-week RBC-TI rate in all subjects



Source: FDA analysis based on ADSL and ADBDC datasets. Data cutoff: 13 Oct 2022.

Clinical Reviewer comments:

These subgroup analyses from the Phase 2 study suggest that patients with IPSS low risk disease benefit less from imetelstat treatment than patients with IPSS intermediate-1 risk disease. Additionally, the data suggest little to no efficacy of imetelstat in patients with prior HMA or lenalidomide, though the sample sizes are too small to make definitive conclusions. Of note, subjects with prior HMA or lenalidomide were excluded from the Phase 3 study, as previously noted.

Additional Efficacy Considerations

The FDA's Assessment:

Missing Data

The primary efficacy endpoint in Study MDS3001 was 8-week RBC TI rate, defined as the proportion of patients without any RBC transfusion during any consecutive 8 weeks (56 days) starting from the day of randomization. Reliable assessment of the patient transfusion status is essential for validity of such an endpoint. Potential missing data issues were assessed, and key aspects are summarized below.

Scheduled and Unscheduled Visits

Per Applicant's information request response, "According to the Time and Events schedule for MDS3001 Phase 3, cycle visits occurred every 4 weeks for study drug administration (i.e., Cycle X, Day 1; CXD1), and weekly for the first two cycles (i.e., additional visits on Day 8, Day 15 and Day 22 for Cycle 1 and Cycle 2). Therefore, the total number of scheduled visits per protocol for each subject is the total number of cycles (or doses) a subject received plus (+) an additional 6 Cycle 1 and Cycle 2 visits plus (+) the end of treatment visits plus (+) the visits in post treatment follow up until the first transfusion. A window of +/-3 days was allowed for visits. If a cycle delay occurred, it was not considered a missed dose or missed visit and the length of a cycle was extended, with Day 1 of the next cycle occurring on the day of study drug administration.

In addition to the total expected scheduled visits mentioned above, subjects could have unscheduled visits at any time for various reasons, for example, for monitoring of laboratory values. In the event laboratory values did not meet criteria for dosing on a scheduled visit, that visit became an unscheduled visit. If a subject had an unscheduled visit, the Transfusion Status Form was required to be completed."

Dataset Discrepancy Issues

Discrepancies between records in the CE (Clinical Events) and PR (procedures) datasets were identified. For the participants with the recorded response "Yes" to the question "Have there been any transfusions since the last visit?", the corresponding data appeared to be missing from the PR dataset. For example, for some patients there were multiple subsequent dates with the recorded "Yes" response to the question "Have there been any transfusions since the last visit?" without any corresponding transfusion data entries in the PR dataset.

Key Applicant's clarifications from a response to the information request: "As of Protocol Amendment 7 (dated 02 Sep 2021), investigators were not required to report transfusions that occurred after the first RBC transfusion in the PTFU period. All instances with CE data "Yes" and no concurrent PR data occurred after the first RBC transfusion in the follow-up phase or after the subsequent anti-cancer therapy, i.e., after the end date of the RBC Transfusion monitoring

period and did not affect the calculation of RBC TI interval, the primary efficacy endpoint or any TI based endpoint... Reconciliations between the Transfusion Status Form (CE dataset) and Transfusion Form (PR dataset) were performed and reviewed rigorously on a regular basis before the database lock. For the subjects with the recorded response “Yes” to the question “Have there been any transfusions since the last visit?” in the CE dataset, it was required to record all the transfusions in the PR dataset (e.g., the type of transfusion, the date and number of units transfused) between two consecutive visit dates (the current visit date and the last visit date in CE dataset). However, only the CE and PR data reported until the first transfusion in PTFU were relevant for assessments of TI rate and duration. Specifically, the reconciliation and missing transfusion data reviews focused on transfusion assessments from Study Day 1 until the first RBC transfusion was recorded in the follow-up phase (or the end of the TI duration)...Based on MDS3001 Phase 3 Study primary analysis data cut off (13 October 2022), of 5802 records from all subjects (imetelstat or placebo), the reconciliation listing identified only two discrepancies (0.03%) that may indicate missing transfusion records...Neither of these subjects were ≥ 8 - week TI responders.”

Statistical Reviewer Comment: As of Protocol Amendment 7 (dated 02 Sep 2021), investigators were not required to report transfusions that occurred after the first RBC transfusion in the PTFU period. Lack of adequate data precludes any assessment of an outcome related to the RBC transfusions after the first RBC transfusion in the PTFU period.

Data Collection

Per Applicant’s information request response, “Per protocol, transfusion data were required and collected during the entire treatment period, including at end of treatment (EOT), and in post-treatment follow up until the first transfusion in the follow-up phase (i.e., after the EOT visit). Transfusion status was actively assessed by completion of the Transfusion Status Form and detailed transfusion data was recorded at each visit (scheduled or unscheduled) on the Transfusions Form. During the post-treatment follow-up (PTFU) phase, transfusion data continued to be actively assessed and recorded in the same manner every 4 to 6 weeks until at least the first transfusion in follow-up.

The Transfusion Status Form contained the question “Have there been any transfusions since the last visit (including today)?”. This transfusion status question covered the entire period since the previously completed study visit (scheduled or unscheduled) up to and including the current visit. If the transfusion status question was answered as “Yes” then the site staff was required to record the pertinent transfusion data (e.g., the type of transfusion, the date and number of units transfused) since the last study visit on the Transfusions Form. The response to the transfusion status question was a required field in the Electronic Data Capture (EDC) system and it was not allowed to be left blank. Therefore, the question was asked, and responses were provided for all subjects (imetelstat or placebo) at almost all nonmissing visits ($\geq 98.6\%$). Only 1.1% and 1.4% of transfusion status data was missing in each arm respectively and these were

due to missed visits, all of which were during the additional weekly monitoring visits within the first 2 cycles where study drug was not administered.

Note, the transfusion status question covered the entire period between two consecutive study visits that actually occurred even if there was a missed visit or a delay between cycles. For example, if a subject missed Cycle 1 Day 8, then the transfusion status question at Cycle 1 Day 15 would cover the 14-day period from the date of Cycle 1 Day 1 up to and including the date of the Cycle 1 Day 15 visit. Therefore, the frequency at which the transfusion status question was asked and answered was at least once a cycle. Additionally, the transfusion status question was not asked in only 4 visits (0.2% of transfusion status data in imetelstat treated only), all either at EOT or at the first post-treatment follow-up visit.”

Quality Control for the Completeness of Transfusion Data

In addition to the active assessment of transfusion status in the EDC, several checks were in place to ensure completeness of transfusion data. An edit check was in place to query the site to record corresponding transfusions when the site answered affirmatively on the transfusion status form, but no corresponding transfusions were entered on the Transfusions Form during the intervening time period between the visits (scheduled or unscheduled). Additionally, the sponsor and the Contract Research Organization (CRO) medical monitors regularly reviewed patient hemoglobin levels compared to transfusion data and questioned any unexplained hemoglobin increases that did not accompany a reported transfusion, and vice versa, any transfusions reported without a preceding hemoglobin level. Queries were issued to record potentially missing transfusions or pre-transfusion hemoglobin levels, including in the event where a site may have inadvertently answered “No” to the initial question of “Have there been any transfusions since the last visit (including today)?” despite an observed increase in hemoglobin.

Summary

Per Applicant’s information request response,

- “The missing transfusion status data due to missed visits (1.1% and 1.4% in imetelstat and placebo arm respectively), all occurred during the additional weekly monitoring visits within the first 2 cycles (i.e., Cycle 1 and Cycle 2 Day 8, 15, 22) and were < 4 weeks from a previous visit.
- The four instances where transfusion status question was not asked occurred at EOT/Follow up 1, which would not have been considered in the calculation of TI. Additionally, the instances all occurred in subjects who did not achieve ≥ 8 -week TI, and, therefore, would not have impacted the accurate evaluation of transfusion independence rates or durations.

- The two instances of missing reported transfusion data occurred in subjects who did not achieve ≥ 8 -week TI, and, therefore, would not have impacted the accurate evaluation of transfusion independence rates or durations.”

Statistical Reviewer Comment: Missing data likely had minimal impact on the primary efficacy endpoint.

Medical resource utilization

For Study MDS3001-Phase 3, the Applicant reported that the total number of subjects who had at least 1 medical encounter (including both inpatient and outpatient encounters) was slightly higher in the imetelstat arm (56% versus 52%). This can be attributed to a higher number of subjects in the imetelstat arm requiring at least 1 hospitalization, as shown in Table 39, though the total number of medical encounters per patient was comparable between arms.

Table 39: MDS3001-Phase 3: Medical resource utilization

	Imetelstat (N=118)	Placebo (N=60)
Number of subjects with at least 1 outpatient encounter ^a	43 (36%)	24 (40%)
Number of subjects with at least 1 hospitalization	39 (33%)	14 (23%)
Total number of medical encounters (average per patient)	157 (1.3/patient)	96 (1.6/patient)

^a Outpatient encounters include emergency room visits, hospital outpatient visits, home care visits, laboratory visits, office visits, other visits

Source: Study MDS3001 Phase 3 Clinical Study Report

Data cutoff 13 October 2022

However, there are significant limitations with this analysis based on the methodological approach and potential for confounding resulting in limited interpretability of this data. Accurate assessment of transfusion and infusion visits is one of the key benefit-risk considerations in this clinical setting. Exclusion of protocol-mandated procedures, tests, and encounters limits the relevance of the medical resource utilization analysis due to the fact that all transfusions were excluded as protocol mandated (inclusive of RBC and platelet transfusion visits). Based on the limited data provided, there appears to be no significant reduction in medical resource utilization with imetelstat and further study would be required for validation.

8.1.5. Integrated Assessment of Effectiveness

Data:

Not applicable.

Version date: June 2022 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

The Applicant's Position:

Due to the differences in study design (open-label versus randomized and stratified, respectively), results from the Phase 2 and Phase 3 of Study MDS3001 were not pooled and integration of efficacy results was not performed.

The FDA's Assessment:

FDA concurs with this approach.

8.2. Review of Safety

Data:

The safety evaluation of imetelstat monotherapy in the treatment of hematologic malignancies is based on 5 clinical trials:

- The primary safety analysis is based on 1 placebo-controlled Phase 3 study in subjects with IPSS low or intermediate-1 risk MDS that is relapsed/refractory to or ineligible for ESA treatment (e.g., "lower-risk MDS" or LR MDS): MDS3001 (Phase 3 part)
- Phase 2 studies in subjects with hematologic malignancies (including LR MDS), MDS3001 (Phase 2 part), CP14B013, CP14B015, CP14B019, and MYF2001

In these 5 studies, a total of 391 subjects received treatment with imetelstat monotherapy. The following groupings are evaluated:

- MDS3001 Phase 3 imetelstat group (N = 118) versus placebo group (N = 59)
The **primary safety analysis** that will inform the label. All subjects treated with a starting dose of 7.1mg/kg imetelstat (equivalent to 7.5 mg/kg imetelstat-sodium) q4w (referred to as "Group A" in the SCS).
- MDS3001 Phase 2 imetelstat group (N = 57)
Data from the Phase 2 part of the MDS3001 study is confirmatory of the results observed in Phase 3. Data pooled from imetelstat-treated subjects in MDS3001 Phase 2 and Phase 3 provide a safety grouping of all subjects with LR MDS treated at 7.1 mg/kg imetelstat q4w (referred to as "Group B" in the SCS).
- Hematologic malignancy monotherapy grouping (N = 391)
Pooled data from all 5 studies (MDS3001, CP14B013, CP14B015, CP14B019, and MYF2001) and provides a safety grouping of subjects with all hematologic malignancies treated with imetelstat monotherapy (ie, monotherapy pool). Starting dose levels varied from 4.4mg/kg

to 8.9mg/kg imetelstat (equivalent to 4.7 mg/kg to 9.4 mg/kg imetelstat-sodium). MF subjects comprise approximately 40% of the pool. While differences in safety outcomes from the LR MDS pool are expected due to differences in underlying disease, these data increase the chances of detecting infrequent safety events that may not be observable in a smaller safety population (referred to as “Group C” in the SCS).

Total overall cumulative exposure to imetelstat monotherapy is 349.2 patient-years (PY) in the monotherapy pool (N = 391) and 105.7 PY in the MDS3001 Phase 3 imetelstat group (N = 118).

The Applicant’s Position:

Overall, the number of subjects treated and the total cumulative exposure to imetelstat as of the initial NDA submission provides an adequate database to assess the safety of imetelstat in patients with LR MDS.

The FDA’s Assessment:

The total number of patients in the integrated safety database is 795, of whom 243 were treated for MDS or MDS/MPN, 198 for myelofibrosis or other MPN, 57 for other hematologic neoplasms, and 284 for solid tumors. Within the general category of MPN, 169 patients had myelofibrosis, 9 blast phase MF/AML, 18 essential thrombocytopenia, and two polycythemia vera. Other hematologic malignancies included chronic lymphoproliferative disease (28) and multiple myeloma (42). Solid tumors included advanced or metastatic non-small cell lung cancer (105), locally recurrent or metastatic breast cancer (106), and relapsed or refractory solid tumors (75).

Treatment was highly variable, with patients receiving a variety of doses and dosing schedules of imetelstat and some patients receiving treatment in combination with other agents, including bevacizumab and paclitaxel. The dose of imetelstat used ranged from 0.4 mg/kg to 11.7 mg/kg. In addition, some patients were dosed based on body surface area at doses ranging from 20 mg/m² to 375 mg/m². Dosing schedules ranged from twice weekly to every 4 weeks. Details of each study and the dose used are described below. Note that doses in this section only refer to imetelstat sodium; the dose of 7.5 mg/kg of imetelstat sodium is equivalent to 7.1 mg/kg of imetelstat:

- 63935937MDS3001: Monotherapy with initial imetelstat dose of 7.5 mg/kg every 4 weeks or placebo in patients with MDS.
- 63935937MYF2001: Monotherapy with initial imetelstat dose of 9.4 mg/kg every 3 weeks or 4.7 mg/kg every 3 weeks in patients with MF; 48 patients dosed at 4.7 mg/kg and 59 at 9.4 mg/kg
- CP05-101 ST: 0.4-4.8 mg/kg weekly, 4.8-11.7 mg/kg days 1 and 8 of 21-day cycle, 9.4-11.7 mg/kg on day 1 of 21-day cycle in patients with advanced solid tumors.

- CP14A004: 3.2-14.0 mg/kg days 1, 8, and 15 of 21-day cycle initially planned, later modified to 3.2-7.2 mg/kg weekly and 6.0 mg/kg days 1 and 8 of 21-day cycle in patients with relapsed or refractory multiple myeloma.
- CP14A005: 3.2 mg/kg on day 1 of 21-day cycle, 3.2-7.5 mg/kg on days 1 and 8 of 21-day cycle in patients with non-small cell lung cancer.
- CP04-151 CLD: 20-240 mg/m² weekly in a 28-day cycle, 160-200 mg/m² with a shorter infusion time weekly in a 28-day cycle, 200 mg/m² days 1 and 8 of 3-week cycle in patients with chronic lymphoproliferative disease.
- CP14A010: 160-320 mg/m² on days 1, 8, and 15, 300 mg/m² on day 8, 300 mg on days 1 and 15, 375 mg/m² on days 1,8, and 15, 375 mg/m² on day 8 of 28-day cycles with bevacizumab or paclitaxel in patients with breast cancer.
- CP14A011: Combination therapy with bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma. Imetelstat was dosed at 160 or 200 mg/m².
- CP14B014: 300 mg/m² on day 1 of 21-day cycle with paclitaxel or bevacizumab in patients with breast cancer.

Clinical Reviewer comment: Patients who received imetelstat in doses determined by body surface area were excluded from dose specific investigations, as the dose in mg/m² could not be readily converted to a dose in mg/kg.

- CP14B012: 9.4 mg/kg on days 1 and 8 of 21-day cycle, with or without bevacizumab, on day 1 of a 21-day cycle in patients with non-small cell lung cancer
- CP14B013: Imetelstat dosed at 7.5 mg/kg on days 1 and 8 of 28-day cycle in patients with multiple myeloma; if lenalidomide maintenance was being used, it was continued.

Clinical Reviewer comments: This study is considered as monotherapy as lenalidomide was being given as ongoing therapy. Four of 9 patients received at least one dose of lenalidomide on study. These patients are not identified separately in the dataset.

- CP14B015: Monotherapy with imetelstat at a dose of 7.5 mg/kg or 9.4 mg/kg weekly in patients with essential thrombocytopenia or polycythemia vera.
- CP14B019: Arms A-D: 9.4 mg/kg on various schedules, arms E and G: 7.5 mg/kg every 28 days, arm F: 9.5 mg/kg cycles 1 and 2 followed by 7.5 mg/kg or 9.4 mg/kg depending on response; 18 patients treated on arms E and G, 62 on other arms. Of note, dose could be increased to 9.4 mg/kg if response criteria not met. Conditions under study included MF (arms A-C, E, F), MDS or MDS/MPN (arm G), and blast phase MF/AML (arm D).

Table 40: Patients in the ISS by underlying condition and dose

Dose/treatment	Overall	MDS	MPN	Other heme	Solid tumor
Total	795	243	178	88	286
Placebo	59	59	0	0	0
Imetelstat 7.1 mg q4w ¹	190	175	9	6	0
Imetelstat <7.1 mg/kg q4w ²	54	0	48	0	6
Imetelstat >7.1 mg/kg q4w ³	296	9	121	45	121
Combination ⁴	168	0	0	9	159
BSA based ⁵	28	0	0	28	0

Source: FDA analysis of ISS datasets

¹ Includes patients on trial MDS3001 (except placebo), CP14B019 arm E, and selected patients on study CP14B013*

² Includes MF2001 arm B, CP05-101 doses 0.4 mg/kg/week-1.6 mg/kg/wk

³ Includes MF2001 arm A, CP05-101-ST (all other doses), CP14A004, CP14B1012 (49 patients), CP14B013 (5 patients), CP14B015, CP14B019

⁴ Includes patients treated on trials CP14A005, CP14A010, CPA011, CP14B012, CP14B014

⁵ Includes CP04-151_CLD

*Patients treated after amendment to protocol who had prior transplant were treated with 7.5 mg/kg every 4 weeks.

Equivalent doses across different dosing schedules may be hard to determine as the peak concentration will vary more with dose but trough more with frequency of administration. In addition, a direct comparison between dosing by weight and by body surface area is difficult.

For the purposes of this review, dose (i.e., higher or lower than 7.5 mg/kg every 4 weeks) will be based on total dose per kilogram per 4 weeks. Thus, doses that are lower than 7.5 mg/kg may be higher if they are given more frequently. In addition, when dose escalation was allowed, the start dose is used to determine whether the dose is higher, lower, or equal to the proposed dose.

Four studies include at least one arm in which imetelstat was combined with other chemotherapeutic medications, including bevacizumab, bortezomib, and paclitaxel.

Overall, the safety database appears adequate to characterize the safety of imetelstat at a dose of 7.1 mg/kg every 4 weeks in patients with MDS. However, safety may not be fully characterizable in subpopulations. The safety of imetelstat in other conditions and at other doses and dosing schedules is outside of the scope of this NDA. However, the availability of data from other studies may be used to evaluate potential risks identified in the safety population of MDS3001 and assess the probability that these risks are associated with the drug versus the underlying condition. In particular, hematologic AEs are expected in patients with MDS and often with other hematologic malignancies but would not be expected to be seen due to the underlying condition in most patients with solid tumors. In addition, evaluation of AE in

different doses and dosing schedules may be helpful in defining whether a dose-response can be observed.

8.2.1. Safety Review Approach

The Applicant's Position:

The main focus of the safety evaluation will be MDS3001 study results and the Phase 3 data in particular. The monotherapy pool may be summarized to show consistency across indications or to examine rare events.

The clinical review of safety for this NDA is based on the following:

- Clinical study reports for the 4 clinical trials listed above
- Summary of Clinical Safety and pooled datasets
- Case Report Forms for and Safety Narratives for deaths, SAEs, adverse events of special interest (AESIs), and other TEAEs of clinical concern
- A planned 120-Day Safety Update that will include data from the remaining MDS3001 Phase 3 subjects who completed treatment since the clinical data cutoff date of the initial NDA filing.

Safety was evaluated by analysis of the incidence, intensity, and type of TEAEs, vital signs measurements, clinical laboratory values, ECGs, and deaths. All summaries and analyses were based on the Treated population, defined as all subjects who received at least one dose of study drug. All subjects were analyzed according to the treatment actually received. For analysis purposes, the following PTs were combined thrombocytopenia (thrombocytopenia + platelet count decreased), neutropenia (neutropenia + neutrophil count decreased), and leukopenia (leukopenia + white blood cell count decreased).

Across all studies, the primary risks associated with imetelstat treatment are neutropenia and thrombocytopenia, consistent with the on-target effects of imetelstat. These cytopenias have been well characterized and are manageable through appropriate dose modifications (including dose delays and reductions) that will be clearly outlined in product labeling, and monitored as per routine pharmacovigilance.

Furthermore, the risk of cytopenias is commonly seen with other therapies used for treatment of hematologic malignancies and MDS specifically and is to be expected as these malignancies originate in the BM. Peripheral blood cytopenias are a consequence of reducing disease burden by eliminating the malignant clone and temporarily reducing the amount of circulating hematopoietic cells until BM recovery. Therefore, hematologists and health care professionals

who care for patients with MDS are familiar with and skilled at the management of neutropenia and thrombocytopenia and their potential clinical complications of infections and bleedings.

The Applicant's Position:

The data presented is a comprehensive analysis of safety data that supports assessment of the safe and manageable use of imetelstat monotherapy 7.1 mg/kg q4w in the treatment of patients with LR MDS.

The FDA's Assessment:

FDA agrees that the primary safety analysis will be based on data from the MDS3001 study, including both part 1 (phase 2 portion) and part 2 (randomized, phase 3 portion). Data from other studies will be used to support the analysis of safety, including determining whether a correlation with dose is observed, whether AEs are observed consistently in different diseases and different populations, and screening for potential rare signals.

FDA agrees that cytopenias (thrombocytopenia, neutropenia, leukopenia) are much more commonly observed with use of imetelstat. However, we have concerns that the risks of neutropenia and thrombocytopenia are underappreciated by the Applicant. Details regarding the extent of cytopenias will be presented in the review. In addition, the statement that that the cytopenias are the result of clearing of the malignant clone is not well supported (see below for further details). This conclusion cannot be reached without evaluation of the frequency of cytopenias in patients who received imetelstat for solid tumors, the correlation between cytopenias and resolution of cytogenetic abnormalities or histologic bone marrow or peripheral blood changes (i.e., dysplasia), and the persistence of cytopenias or other evidence of the ability of the bone marrow to recover after use of imetelstat. To summarize data that will be presented below, there is strong evidence that neutropenia and thrombocytopenia in particular are due to drug toxicity and not to clearing of the malignant clone, which, as noted in the efficacy section, rarely occurs.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

In the MDS3001 Phase 3 study, the median duration of treatment for the imetelstat group (N = 118) was 33.93 weeks (range: 0.1 to 141.1 weeks) and for the placebo group (N = 59) was 28.29 weeks (range: 0.1 to 116.1 weeks) ([Applicant Table 42](#)). Subjects in the imetelstat and placebo groups received a median of 8 cycles of treatment (range: 1 to 34 and 1 to 30 cycles, respectively), and 40.7% of subjects in the imetelstat group and 28.8% of subjects in the

placebo group received more than 13 cycles of treatment. In the imetelstat and placebo groups, 68.6% and 69.5% of subjects, respectively, completed 24 weeks of treatment, and 44.9% and 28.8% of subjects, respectively, completed 48 weeks of treatment. Similar rates of treatment for imetelstat and placebo at 24 weeks are expected as subjects in a study tend to stay on for 24 weeks (approximately 6 months) and then, as expected, placebo subjects begin to drop off at a higher rate after 24 weeks due to lack of efficacy.

In the Phase 2 imetelstat group (N = 57), median duration of treatment was 32.29 weeks (range: 0.1 to 260.1 weeks) (Applicant Table 42). Subjects received a median of 8 cycles of treatment and 36.8% of subjects received more than 13 cycles. In Phase 2, 61.4% of subjects completed 24 weeks of treatment, and 38.6% of subjects, respectively, completed 48 weeks of treatment. Total cumulative exposure was 105.72 PY in the imetelstat group and 44.77 PY in the placebo group.

In the hematologic malignancies monotherapy grouping (N = 391), subjects were treated with imetelstat monotherapy for a cumulative total of 349.2 PY, including 118 subjects with LR MDS treated for 105.7 PY in Phase 3 of the main MDS3001 study, 57 subjects with LR MDS treated for 65.3 PY in Phase 2 of MDS3001, and 175 pooled subjects with LR MDS treated for 171.0 PY in Phase 2 and Phase 3 of the main MDS3001 study. Doses and dosing schedules of imetelstat used in the studies included in the safety analysis are listed in Applicant Table 43. Median duration of monotherapy treatment was 30.14 weeks (range: 0.1 to 263.4 weeks) (Table tex01c). Similar to the LR MDS pool, subjects in the Group C pool received a median of 8 cycles of treatment, and 37.3% of subjects in the overall population received more than 13 cycles. In the overall subject population, 60.6% of subjects completed 24 weeks of treatment, and 38.6% of subjects completed 48 weeks of treatment. Total cumulative PY of exposure was 349.22 PY.

Dose modifications other than dose reductions (e.g., infusion interruptions, dose delays) were not uniformly collected across studies in the Group C pool. In the overall pooled Group C population, 33.2% of subjects had a dose reduction, and most (30.2%) were due to AEs (Table tex03c).

Applicant Table 41: Safety Population, Size, and Denominators

Safety Database for the Study Drug ^a Individuals exposed to the study drug in this development program for the indication under review N ^b = 450		
Clinical Trial Groups	Imetelstat (n = 391)	Placebo (n = 59)
Controlled trials conducted for this indication ^c	118	59
All other than controlled trials conducted for this indication	273	

^a Study drug means the drug being considered for approval.

NDA/BLA Multi-disciplinary Review and Evaluation NDA 217779 imetelstat
 TRADENAME, imetelstat

^b N is the sum of all available numbers from the columns in the table

^c To be used in product's labeling

**Applicant Table 42: Summary of Treatment Exposure – Study MDS3001 – Phase 2 and 3
 (Treated Population)**

	Phase 3		Phase 2	Pooled
	Imetelstat (N = 118)	Placebo (N = 59)	Imetelstat (N = 57)	Imetelstat (N = 175)
Treatment duration (weeks)				
Mean (SD)	46.75 (34.304)	39.60 (29.196)	59.79 (59.048)	51.00 (44.170)
Median	33.93	28.29	32.29	33.43
Minimum, maximum	0.1, 141.1	0.1, 116.1	0.1, 260.1	0.1, 260.1
Number of treatment cycles received				
Mean (SD)	11.5 (8.14)	10.6 (7.08)	14.3 (13.79)	12.4 (10.37)
Median	8.0	8.0	8.0	8.0
Minimum, maximum	1, 34	1, 30	1, 66	1, 66
1-3 cycles, n (%)	15 (12.7%)	6 (10.2%)	10 (17.5%)	25 (14.3%)
4-6 cycles, n (%)	27 (22.9%)	12 (20.3%)	15 (26.3%)	42 (24.0%)
7-12 cycles, n (%)	28 (23.7%)	24 (40.7%)	11 (19.3%)	39 (22.3%)
≥13 cycles, n (%)	48 (40.7%)	17 (28.8%)	21 (36.8%)	69 (39.4%)
Dose interval (days) ^a				
Mean (SD)	31.2 (7.74)	28.7 (5.20)	31.4 (10.28)	31.3 (8.79)
Median	28.0	28.0	28.0	28.0
Minimum, maximum	21, 128	21, 133	22, 172	21, 172
Relative dose intensity with respect to planned dose				
Mean (SD)	99.608 (1.9243)	99.164 (2.2788)	100.100 (2.4405)	99.769 (2.1120)
Median	99.817	99.679	100.048	100.000
Minimum, maximum	84.49, 103.45	94.71, 105.10	89.87, 105.59	84.49, 105.59
Relative dose intensity with respect to the starting dose (%)				
Mean (SD)	90.495 (11.7921)	98.301 (4.6170)	91.137 (13.8300)	90.704 (12.4560)
Median	97.437	99.583	90.000	96.016
Minimum, maximum	(64.02, 103.42)	71.96, 105.10	(64.61, 122.44)	(64.02, 122.44)
Subjects completing 24 weeks of treatment, n (%)	81 (68.6%)	41 (69.5%)	35 (61.4%)	116 (66.3%)
Subjects completing 48 weeks of treatment, n (%)	53 (44.9%)	17 (28.8%)	22 (38.6%)	75 (42.9%)

SD = standard deviation

^a Dose interval is defined as the days between two consecutive dosing dates across all cycles.

Source: Table tex01a, Table tex01b

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Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Applicant Table 43: Hematologic Malignancies Study (Group C) Details

Disease Indication	Study Names (Phase)	Dose (mg/kg) ^d	Frequency	Subjects Treated with Imetelstat	Median Exposure (cycles)
MDS (N=175)	MDS3001 (Phase 2) ^a	7.1	Every 4 weeks	57	8
	MDS3001 (Phase 3)	7.1	Every 4 weeks	118	8
MPN (N=207)	CP14B015 (Phase 2) ^b	7.1	Weekly or as needed ^c	7	25
		8.9		13	14
	CP14B019 (Phase 2)	7.15	Every 3 or 4 weeks	18	5
		8.9		62	9
	MYF2001 (Phase 2)	4.4	Every 3 weeks	48	6
		8.9		59	11
MM (N=9)	CP14B013 (Phase 2)	7.1	Days 1, 8 every 4 weeks	4	4.5
		8.9		5	6
Total imetelstat-treated in Group C pool N = 391					
By dose group: 4.4 mg/kg N = 48, 7.1 mg/kg N = 204, 8.9 mg/kg N = 139					

Source: Table tex01a; CP14B013 CSR/Table 14.3.1; CP14B015 CSR/Table 14.1.3; CP14B019 CSR/Listing Isfex01; and MYF2001 CSR/Table tsfex01.

^a Dose could be elevated to 8.9 mg/kg prior to Amendment 2 (see MDS3001 CSR (Phase 3)/Section 9.8.1). Seven subjects had cycles at the dose level of 8.9 mg/kg, with a median of 4 cycles at that dose level (range: 1 to 31) (MDS3001 CSR (Phase 2)/Table tsfex08_p1).

^b Dose could be elevated to 11.0 mg/kg.

^c Based on hematologic response/toxicity.

MDS = myelodysplastic syndrome; MM = multiple myeloma; MPN = myeloproliferative neoplasm.

^d In the clinical study reports (CSRs), study drug doses are expressed as milligrams of imetelstat sodium (the active substance), a salt of imetelstat. Doses in this table (including the footnotes) are shown for the active moiety (free acid). To convert a quantity of imetelstat salt to the equivalent quantity of imetelstat, a factor of 0.9416 based on relative molar mass of the free acid form (4610 g/mol) to the sodium salt (4896 g/mol; $4610/4896 = 0.9416$) is applied (i.e., 1 mg imetelstat sodium = 0.9416 mg imetelstat).

The Applicant's Position:

In the MDS3001 Phase 3 study, the median duration of treatment was higher in the imetelstat group compared to the placebo group. Similar proportions of subjects in the imetelstat and placebo groups completed 24 weeks of treatment; however, more than a third of subjects in the imetelstat group completed 48 weeks of treatment compared to placebo. Rates for treatment discontinuations were similar for both groups however placebo was twice as likely to discontinue due to lack of efficacy while imetelstat subjects had a higher rate of discontinuation due to AEs, the majority of which were due to neutropenia and thrombocytopenia. Additionally, imetelstat had twice the rate of dose modifications compared to placebo including dose reductions which suggests that the dose modifications allowed subjects on imetelstat to stay on treatment longer.

Imetelstat exposure was similar in Phase 2 and Phase 3 in LR MDS subjects. Study duration and follow-up was longer in Phase 2.

The FDA's Assessment:

Assessment of the exposure to treatment for the imetelstat versus placebo arms is complicated by the fact that dose delays were more common in the imetelstat arm versus the placebo arm. Notably, the median number of cycles on each arm was similar, suggesting that the reason that there was a longer duration of treatment in the imetelstat arm was due to dose delays slowing the administration of treatment, leading to longer times but similar number of cycles.

Clinical Reviewer comments: Patients receiving imetelstat received the same median number of cycles but over a longer period of time. This suggests that the benefit-risk ratio may be problematic since one would expect a highly effective and tolerable treatment to result in a longer duration of treatment as measured by number of cycles received. A toxic treatment resulting in multiple delays would be expected to result in longer cycles due to treatment delays.

Relevant characteristics of the safety population:

Data:

Demographics were well-balanced between imetelstat and placebo groups and were consistent with the characteristics of patients in the proposed target indication. The median subject age of the imetelstat group was 71.5 years (range: 44 to 87 years) and in the placebo group was 73 years (range: 39 to 85 years), as anticipated for this subject population ([Applicant Table 44](#)). Most subjects in the imetelstat and placebo groups, respectively, were male (60.2% and 66.1%), White (80.5% and 79.7%) and not Hispanic or Latino (84.7% and 79.7%), reflecting the expected demographics of patients with MDS. Most subjects were enrolled at sites in the EU (67.8% and 64.4%), followed by the ROW (21.2% and 16.9%), and North America (11.0% and 18.6%). Median age at diagnosis in the imetelstat group was 66.71 years (range: 38.1 to 86.9 years) and in the placebo group was 69.29 years (range: 32.8 to 84.5 years) ([Applicant Table 45](#)). In the imetelstat and placebo groups, 47.5% and 45.8% of subjects, respectively, had a transfusion burden > 6 units per 8 weeks. The median baseline value for ANC was $2.63 \times 10^9/\text{L}$ and $2.80 \times 10^9/\text{L}$, respectively, and platelet count was $230 \times 10^9/\text{L}$ and $231 \times 10^9/\text{L}$, respectively. There was a higher proportion of subjects in the IPSS low risk (67.8% and 66.1%, respectively) vs Int-1 (33.2% and 33.9%, respectively). As required per the study entry criteria, all subjects had a baseline ECOG score of ≤ 2 , and most subjects in both groups ($\geq 94.9\%$) had a baseline score of ≤ 1 .

Demographics and baseline disease characteristics in the supportive MDS3001 Phase 2 study were highly consistent with Phase 3, with no major differences in any category. In the MDS Phase 2 imetelstat group (N = 57), median age was 71.0 years (range: 46 to 83 years); 75.4%

were ≥ 65 years old, and 31.6% were ≥ 75 years old ([Applicant Table 44](#)). Most subjects were White (82.1%) and not Hispanic or Latino (85.7%) and 56.1% were male. Most subjects were treated at sites in the EU (64.9%), followed by North America (21.1%) and ROW (14.0%). Median age at diagnosis was 66 years (range: 43.8 to 82.3 years) ([Applicant Table 45](#)). Overall, 50.9% subjects had a transfusion burden > 6 units per 8 weeks. The median baseline value for ANC was $2.90 \times 10^9/L$ (range: 1.5, 20.5) and platelet count was $297 \times 10^9/L$ (range: 89.3 to 800). A higher proportion of subjects were IPSS low risk (63.2%) versus Int-1 (36.8%). As required per the study entry criteria, all subjects had a baseline ECOG score of ≤ 2 , and most subjects (91.2%) had a baseline score of ≤ 1 .

In the hematologic malignancy monotherapy grouping (N = 391), demographics were similar to the pooled LR MDS subjects, except for a higher proportion of North America subjects (due to the MF studies), and a lower proportion from Europe (SCS Table 15 and Table tdm01c). Median age was 68.0 years (range: 21 to 93 years), 60.6% of subjects were male, 83.6% were White, and 81.0% were not Hispanic or Latino. Treatment was administered to 171 (43.7%) subjects at study sites in North America, 176 (45.0%) subjects in Europe, and 44 (11.3%) subjects in ROW. Subjects were distributed across renal function categories of normal (31.5%; 98 subjects), mildly impaired (36.7%; 114 subjects), moderately impaired (30.2%; 94 subjects), or severe (1.6%; 5 subjects), while most subjects had normal (61.1%; 239 subjects) or mildly impaired (30.7%; 120 subjects) hepatic function. Baseline characteristics for Group C differ based on the subjects' underlying disease (Table tdm02c).

Applicant Table 44: Demography and Other Baseline Characteristics – Study MDS3001 – Phase 2 and 3 (Group B Treated Population)

	Phase 3		Phase 2	Pooled
	Imetelstat (N = 118)	Placebo (N = 59)	Imetelstat (N = 57)	Imetelstat (N = 175)
Age (years)				
n	118	59	57	175
Mean (standard deviation)	70.42 (8.819)	71.69 (9.020)	70.12 (8.521)	70.32 (8.699)
Median	71.50	73.00	71.00	71.00
Minimum, maximum	44.0, 87.0	39.0, 85.0	46.0, 83.0	44.0, 87.0
Age group, n (%)				
n	118	59	57	175
<65	27 (22.9%)	9 (15.3%)	14 (24.6%)	41 (23.4%)
≥ 65	91 (77.1%)	50 (84.7%)	43 (75.4%)	134 (76.6%)
<75	83 (70.3%)	36 (61.0%)	39 (68.4%)	122 (69.7%)
≥ 75	35 (29.7%)	23 (39.0%)	18 (31.6%)	53 (30.3%)

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	Phase 3		Phase 2	Pooled
	Imetelstat (N = 118)	Placebo (N = 59)	Imetelstat (N = 57)	Imetelstat (N = 175)
Sex, n (%)				
Male	71 (60.2%)	39 (66.1%)	32 (56.1%)	103 (58.9%)
Female	47 (39.8%)	20 (33.9%)	25 (43.9%)	72 (41.1%)
Race, n (%)				
n	118	59	56	174
White	95 (80.5%)	47 (79.7%)	46 (82.1%)	141 (81.0%)
Asian	8 (6.8%)	2 (3.4%)	2 (3.6%)	10 (5.7%)
Black or African American	1 (0.8%)	2 (3.4%)	1 (1.8%)	2 (1.1%)
Other ^a	14 (11.9%)	8 (13.6%)	7 (12.5%)	21 (12.1%)
Ethnicity, n (%)				
n	118	59	56	174
Hispanic or Latino	6 (5.1%)	5 (8.5%)	1 (1.8%)	7 (4.0%)
Not Hispanic or Latino	100 (84.7%)	47 (79.7%)	48 (85.7%)	148 (85.1%)
Not reported	11 (9.3%)	6 (10.2%)	6 (10.7%)	17 (9.8%)
Unknown	1 (0.8%)	1 (1.7%)	1 (1.8%)	2 (1.1%)
Geographic region, n (%)				
n	118	59	57	175
North America	13 (11.0%)	11 (18.6%)	12 (21.1%)	25 (14.3%)
Europe	80 (67.8%)	38 (64.4%)	37 (64.9%)	117 (66.9%)
Rest of World	25 (21.2%)	10 (16.9%)	8 (14.0%)	33 (18.9%)
Renal impairment ^b , n (%)				
n	118	59	57	175
Normal (≥ 90 mL/min)	36 (30.5%)	15 (25.4%)	18 (31.6%)	54 (30.9%)
Mild (60 to <90 mL/min)	42 (35.6%)	24 (40.7%)	24 (42.1%)	66 (37.7%)
Moderate (30 to <60 mL/min)	39 (33.1%)	19 (32.2%)	15 (26.3%)	54 (30.9%)
Severe (< 30 mL/min)	1 (0.8%)	1 (1.7%)	0	1 (0.6%)
Hepatic impairment ^c , n (%)				
n	118	59	57	175
Normal	68 (57.6%)	39 (66.1%)	33 (57.9%)	101 (57.7%)
Mild	31 (26.3%)	14 (23.7%)	23 (40.4%)	54 (30.9%)
Moderate	17 (14.4%)	6 (10.2%)	1 (1.8%)	18 (10.3%)
Severe	2 (1.7%)	0	0	2 (1.1%)

Source: Table tdm01a, Table tdm01b

^a Other races include races recorded as other, unknown, or not reported.

^b Based on creatinine clearance.

^c Based on National Cancer Institute (NCI) classification

n = the number of subjects in each group with non-missing parameter value.

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**Applicant Table 45: Disease Characteristics at Baseline – Study MDS3001 – Phase 2 and 3
 (Group B Treated Population)**

	Phase 3		Phase 2	Pooled
	Imetelstat (N = 118)	Placebo (N = 59)	Imetelstat (N = 57)	Imetelstat (N = 175)
Age at diagnosis (years)				
n	118	59	57	175
Mean (standard deviation)	66.18 (9.809)	68.46 (9.948)	66.06 (7.980)	66.14 (9.230)
Median	66.71	69.29	66.13	66.62
Minimum, maximum	38.1, 86.9	32.8, 84.5	43.8, 82.3	38.1, 86.9
Disease diagnosis				
n	118	59	57	175
MDS	118 (100.0%)	59 (100.0%)	57 (100.0%)	175 (100.0%)
Red blood cell transfusion burden, n (%)				
n	118	59	57	175
≤ 6 units	62 (52.5%)	32 (54.2%)	28 (49.1%)	90 (51.4%)
> 6 units	56 (47.5%)	27 (45.8%)	29 (50.9%)	85 (48.6%)
IPSS risk category				
n	118	59	57	175
Low	80 (67.8%)	39 (66.1%)	36 (63.2%)	116 (66.3%)
Intermediate-1	38 (32.2%)	20 (33.9%)	21 (36.8%)	59 (33.7%)
Absolute neutrophil count (x10 ⁹ /L)				
n	118	59	57	175
Mean (standard deviation)	3.22 (2.790)	3.17 (1.618)	3.85 (3.282)	3.43 (2.965)
Median	2.63	2.80	2.90	2.69
Minimum, maximum	0.5, 26.8	0.9, 8.8	1.5, 20.5	0.5, 26.8
Platelet count (x10 ⁹ /L)				
n	118	59	57	175
Mean (standard deviation)	247.35 (112.050)	236.68 (94.911)	297.03 (167.156)	263.53 (134.090)
Median	230.00	231.00	251.00	239.00
Minimum, maximum	41.0, 630.0	91.0, 446.0	89.3, 800.0	41.0, 800.0
ECOG performance status				
n	118	59	57	175
0	42 (35.6%)	21 (35.6%)	21 (36.8%)	63 (36.0%)
1	70 (59.3%)	38 (64.4%)	31 (54.4%)	101 (57.7%)
0 or 1	112 (94.9%)	59 (100.0%)	52 (91.2%)	164 (93.7%)
2	6 (5.1%)	0	5 (8.8%)	11 (6.3%)
3	0	0	0	0

Source: Table tdm02a, Table tdm02b

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ECOG = Eastern Cooperative Oncology Group; IPSS = International Prognostic Scoring System; MDS = myelodysplastic syndromes; n = the number of subjects in each group with non-missing parameter value.

The Applicant's Position:

In the pivotal MDS3001 Phase 3 study, demographics and baseline characteristics were well balanced between the imetelstat and placebo groups and were similar to the safety population of the supportive Phase 2 study. The baseline characteristics of the MDS3001 subject population are consistent with that of the LR MDS patient population for which imetelstat is being proposed as treatment. The population of subjects with hematological malignancies in the monotherapy pool represents the mix of different indications studied and is provided mainly for signal detection in patients treated with imetelstat monotherapy.

The FDA's Assessment:

FDA has confirmed the numbers provided by the Applicant in Applicant Table 44 with the following clarifications:

- One patient in the open label imetelstat cohort had no value provided for race and ethnicity. It is noted that this patient was treated in France and that race and ethnicity are often not reported in France for legal reasons. Thus, the reviewer feels confident that this patient could be considered "not reported" for both values.
- Race and ethnicity are typically not reported in Germany for similar reasons. It is unclear how data regarding race and ethnicity were determined for patients in Germany (all of whom are listed as non-Hispanic white.) It is not clear whether the Applicant obtained the actual race and ethnicity for patients or if they made assumptions based on their expectations.
- The method used to derive renal and hepatic function are unclear and cannot be confirmed without further information.

Regarding the comparison between the imetelstat phase 2, imetelstat phase 3, and placebo safety populations, we have the following comments:

- Patients on the placebo arm are generally older, with a difference of about 1.5 years between the median ages of patients in the imetelstat versus placebo arms of the phase 3 portion of the study and fewer patients age <65 in the placebo arm compared to either imetelstat arm. This difference may be of importance, given that the overall survival analysis was not stratified by age.
- More patients in the placebo arm were male.
- The majority of patients in any arm were white and non-Hispanic, limiting evaluation of the effect of race on the safety profile of imetelstat.
- More patients in the placebo arm were treated in North America and fewer in rest of the world (other than the EU or North America) compared to imetelstat in the phase 3

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portion of the study. This may have implications for both the efficacy and the safety evaluations.

In addition to the baseline disease data provided by the Applicant, we would like to add the information described in Table 46 below.

Table 46: Baseline disease characteristics in patients in MDS3001

	Phase 3		Phase 2	Pooled
	Imetelstat (N = 118) n (%)	Placebo (N = 59) n (%)	Imetelstat (N = 57) n (%)	Imetelstat (N = 175) n (%)
Baseline ferritin				
Median	1380	1482	1490 ¹	1381 ¹
<2000 mcg/L	90 (76)	43 (73)	33 (58)	123 (70)
≥2000	28 (24)	16 (27)	23 (39)	51 (29)
Baseline monocyte count				
Median	280	260	NA	NA
<1000	105 (89)	53 (90)	NA	NA
≥1000	5 (4.2)	2 (3.4)	NA	NA
Unknown	8 (7)	4 (7)	57 (100)	NA
Bone marrow blasts at screening (local)				
<5%	101 (86)	55 (93)	41 (72)	142 (81)
≥5% ²	17 (14)	4 (7)	16 (28)	33 (19)
Range	0,10	0,10	0,10	0,10
Bone marrow blasts at screening (central)				
<5%	117 (99)	58 (98)	NA	NA
≥5% ²	1 (0.8)	1 (1.7)	NA	NA
Range	0,13.7	0,9	NA	NA
Baseline peripheral blood blasts				
None	102 (92)	51 (88)	42 (95)	144 (93)
Any	10 (8)	7 (12)	3 (5)	13 (7)
Median (% blasts/leukocytes)	0	0	0	0
Minimum, maximum	0,3	0,2	0,1	0,3
Unknown	6	1	12	18
Baseline hemoglobin, local (g/dl)				
Median (range)	8.5 (5.5,11.2)	8.3 (6.0,10.6)	8.6 (5.9,12.4)	8.5 (5.5,12.4)
<8	40 (34)	19 (32)	15 (26)	55
8-10	74 (63)	38 (64)	36 (63)	110
>10	4 (3.4)	2 (3.4)	6 (11)	10

	Phase 3		Phase 2	Pooled
	Imetelstat (N = 118) n (%)	Placebo (N = 59) n (%)	Imetelstat (N = 57) n (%)	Imetelstat (N = 175) n (%)
Baseline hemoglobin, central (g/dl)				
Median (range)	8.5 (5.8,10.8) ³	8.5 (6.0,10.5)	NA	NA
<8	29 (25)	14 (24)	NA	NA
8-10	79 (67)	44 (75)	NA	NA
>10	9 (8)	1 (1.7)	NA	NA

¹ Baseline ferritin missing for one patient in imetelstat phase 2 cohort

² ≥5% in either aspirate or biopsy on any screening marrow³ One patient did not have a baseline hemoglobin by central labs.

NA=not available

Of note, 8 patients ((b) (6)) had monocyte counts of ≥1000 and ≥10% at screening, suggesting a possible diagnosis of CMML using the 2016 criteria. Of these, three were considered screen failures, one was assigned to placebo but not treated, three ((b) (6)) were treated with imetelstat and one ((b) (6)) with placebo. Monocyte count was not documented for patients in part 1 of the study.

The percentage of patients with marrow blast counts of ≥5% varied considerably between the local and central laboratory assessments. Of note, local laboratory values for bone marrow blasts showed ≥5% blasts in more patients on the placebo as compared to the imetelstat arm of the phase 3 portion. In addition, more patients on the placebo arm had peripheral blasts. Median hemoglobin was similar between the two arms of the phase 3 component and did not vary significantly between the central and local assessments in terms of median value. Interestingly, more patients had a baseline hemoglobin of <8 g/dl per local labs in both arms of the phase 3 component of the study.

Adequacy of the safety database:

Data:

The size of the database for the MDS3001 Phase 3 safety population is adequate to provide an estimate of adverse reactions that may be associated with imetelstat use in the LR MDS population. The database from the total pooled population (N = 391) includes subjects with other hematologic malignancies (MF, MDS/MPN overlap, MM, ET, and polycythemia vera [PV]) and provides supportive safety. Demographic and baseline characteristics of subjects treated with imetelstat at the 7.1 mg/kg dose (equivalent to 7.5 mg/kg imetelstat-sodium) were generally representative of the LR MDS population. The duration of treatment in the overall LR MDS population is adequate to provide assessment of adverse reactions.

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The Applicant's Position:

The imetelstat safety database is considered to be adequate to assess the safety of the 7.1 mg/kg q4w dose and schedule.

The FDA's Assessment:

The safety database, including the data from MDS3001 and supportive data from other studies, is generally adequate to evaluate the safety of imetelstat at 7.1 mg/kg every 4 weeks in patients with lower risk MDS. However, the database does not contain adequate numbers of patients from underrepresented racial and ethnic populations and younger patients to characterize the risk in these subpopulations. In addition, comparison of the risk between other subpopulations (i.e., sex, transfusion burden) is limited. Finally, no conclusions can be drawn regarding the use of imetelstat in patients with an absolute neutrophil count of <500 or platelet count of <75,000, patients with moderate or severe organ impairment, or higher risk (IPSS-R intermediate, high, or very high risk) MDS and the findings of the safety review cannot be extrapolated to these populations.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

In the pivotal MDS3001, an independent DMC was established for the study to monitor safety data. In the Phase 3 study, the DMC periodically reviewed unblinded safety and efficacy data and made recommendations regarding the conduct of the study.

A HEC consisting of 3 hepatologists reviewed all investigator-reported AEs as well as all hepatic AEs and LFT laboratory abnormalities at least quarterly, or more frequently as needed. In general, the DMC and HEC recommendations were to continue study conduct without modifications.

The Sponsor performed oversight of the data management of this trial, including approval of the CRO's data management and data quality plans. The sites were responsible for data entry into the EDC system. In the event of discrepant data, the CRO requested data clarification from the sites, which the sites resolved electronically in the EDC system. eCRFs and query resolution documentation was maintained in the EDC system's audit trail. System backups for data stored at the CRO was performed in accordance with the CRO's standard operating procedures.

The Applicant's Position:

No meaningful concerns are anticipated in the quality and integrity of the submitted data; these were sufficiently complete to allow for a thorough review of safety. Furthermore, no data integrity concerns were reported following completion of site inspections; data in the CRFs and AE databases were consistent.

The FDA's Assessment:

In general, we agree that the data quality of the submission is adequate. However, several points required clarification:

We noted on analysis of the initial ADAE dataset that among 275 ADAE described for which the treatment emergent flag was not checked, the action taken with study treatment was described as drug withdrawn for 5 cases, drug interrupted for 7, unknown for one, and dose not changed for 89, suggesting that a total of 102 cases occurred while the patient was receiving medication. Among these 102 events, 43 occurred in 5 patients in the phase 2 imetelstat cohort, 52 in 15 patients in the imetelstat arm of the phase 3 portion of the study, and seven in four patients on the placebo arm. An IR was sent to the Sponsor to clarify this apparent discrepancy.

Of note, some patients had multiple reasons for treatment modification and may have events both described as treatment emergent and non-treatment emergent. When total number of patients affected was considered, no patient treated with imetelstat on the phase 3 arm had only non-TEAE as reason for treatment delay or dose modification and three out of 21 had only treatment non-emergent events as the reason for discontinuing treatment (that is, the rate of all events leading to discontinuation was 18% (21 patients), the rate of treatment emergent events only was 15% (18 patients), with one patient having both treatment emergent and treatment non-emergent events flagged as leading to treatment discontinuation.

The Applicant clarified that for situations in which the AE is described as not treatment emergent but an action was taken regarding the study medication, the AE occurred while treatment was on hold and further actions may have been required due to the AE, although it occurred in the absence of active treatment and therefore was not considered treatment emergent. For example, a patient whose treatment was held due to a treatment emergent AE may experience a further AE while medication was being held that led to treatment discontinuation.

Clinical Reviewer comment: The Applicant's rationale for not considering the events described above as treatment emergent is not entirely consistent with the definition of TEAE as described in the protocol. However, the effect on the total safety profile is relatively small. Also see section on treatment discontinuation for further information.

Another issue was a potential under-reporting of events. Specifically, patient (b) (6) a patient on the phase 2 portion of the study, experienced transaminase and bilirubin elevations consistent with a Hy's law case. The Applicant stated that this was not a Hy's law case as the abnormalities were related to sepsis. However, the patient had not had sepsis documented in the ADAE database. The Applicant's response follows:

"For patient (b) (6) the attribution for the events of transaminase and bilirubin elevations on days 231-235 due to sepsis was derived from the investigator's assessment in a follow up questionnaire. The investigator responded that the only SAE for this patient was the grade 3 Escherichia UTI which was responsible for the sepsis and transaminase elevations. The sepsis was not captured as an SAE in the safety database based on the investigator's response to the safety follow up report. An SAE of grade 3 Escherichia UTI was also reported in the clinical database, however, the event of sepsis was not reported in the clinical database and, therefore, does not appear in the ADAE dataset."

Clinical Reviewer comments: This response raises concerns about under-reporting of safety events. However, the OSI inspections did not reveal a systematic issue and therefore we consider that this is likely an isolated incident.

In summary, the data quality appears generally adequate, but there are minor issues that should be taken into account, particularly given the unexpectedly low number of events of infection and bleeding given the very severe and frequent cytopenias observed.

Categorization of Adverse Event

The Applicant's Position:

TEAEs, as reported in each study, were used for the safety analysis. The definition of TEAEs in each study were:

- MDS3001: 1) AEs that occurred or worsened after the first dose of study drug through the treatment phase and for 30 days following the last dose of study drug or until subsequent anti-cancer therapy if earlier; 2) any event that was considered study drug-related regardless of the start date of the event; or 3) any event that was presented at baseline but worsened in severity or was subsequently considered by the investigator to be study drug-related.
- MYF2001 and CP14B019: AEs that occurred or worsened after the first dose of study drug and within 30 days following the last dose of study drug.
- CP14B015: AEs that occurred or worsened after the first dose of study drug until 30 days after the last administration of study treatment or study discontinuation/termination, whichever occurred first.

- CP14B013: AEs that occurred or worsened after the first dose of study drug until 30 days after their last infusion of imetelstat or until initiation of alternate therapy for their MM, whichever occurred first.

All AEs were coded with system organ class (SOC) and PT according to MedDRA version 25.0. For analysis purposes, the following PTs were combined thrombocytopenia (thrombocytopenia + platelet count decreased), neutropenia (neutropenia + neutrophil count decreased), and leukopenia (leukopenia + white blood cell count decreased). The severity of AEs was graded 1 to 5 according to National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) as assigned in the original studies. For each subject and each TEAE, the worst severity recorded was attributed and used in the by-severity summaries.

Adverse events reflective of laboratory measurements were considered based on worsening of laboratory values, given the high prevalence of laboratory abnormalities in this subject population and higher degree of accuracy in the laboratory values compared to AE reporting, in order to provide the most conservative frequencies.

Adverse events of interest as defined in the MDS3001 protocol include liver function abnormalities based on laboratory data, and hepatic TEAEs (based on high level terms and hepatic PTs). In addition, other selected AEs of interest (thrombocytopenia and bleeding events, neutropenia and infections, IRRs), which were not specifically defined in the MDS3001 protocol, were identified based on the mechanism of action of imetelstat and the safety profile observed to date and have been monitored throughout the study. After the start of the COVID-19 pandemic in March 2020, events related to COVID-19 were also monitored as events of interest in Study MDS3001.

The FDA's Assessment:

In general, the Applicant's definition of treatment emergent AE is reasonable. We note that in addition to the preferred terms, some AE will be examined using grouped terms as noted in the appendix. In addition, as noted later in the safety section, some events that occur more than 30 days after the end of treatment are considered potentially related for the following reasons:

- A related AE occurred on treatment or within 30 days of treatment and there is evidence that the later, non-treatment related AE is related to the earlier TEAE. An example might include infections occurring >30 days after last dose but with neutropenia that began within 30 days of last dose and had not resolved at the time of the infection.
- The duration of cytopenias after end of treatment with imetelstat is unclear and events that may be related to cytopenias (infection, hemorrhage) may be related to treatment, despite occurring >30 days after end of treatment. This issue will be explored further below.

Routine Clinical Tests

The Applicant's Position:

In the pivotal MDS3001 Phase 3 study, clinical assessments including physical examinations and vital signs were taken at screening and pre-dose on Day 1 of every 28-day cycle. 12-lead ECG was assessed at Screening and Day 1 of Cycle 2. Samples for clinical laboratory assessments were collected at Screening, pre-dose on Cycle 1 Day 1, weekly during Cycle 1, and Cycle 2 and then pre-dose on Day 1 of every 28-day cycle until end of treatment. Local laboratories were used for routine safety laboratory parameters, and reference ranges for each laboratory were collected and used in the analysis. Clinical significance of laboratory values were determined by the investigator; clinically significant abnormalities were reported as AEs. The following laboratory parameters were assessed for safety: hematology, coagulation, and serum chemistry, including liver function tests.

The FDA's Assessment:

The Agency acknowledges the Applicant's description of the physical examination, vital signs, laboratory tests, and ECG evaluations performed as part of MDS3001. We note the following regarding their adequacy:

- The ECG assessments were inadequate to definitively assess the risk of QT prolongation with use of imetelstat. A further ventricular repolarization study to address this issue is underway. In addition, very little information is provided regarding the ECGs that were documented. With few exceptions, the only data provided was whether the ECG was read as normal or abnormal with or without clinical significance to the abnormality. The ventricular repolarization study should provide further information regarding cardiac issues that can be observed on ECG (rhythm, signs of stress) as well as QT interval information.
- Laboratory tests, including complete blood count (CBC) were performed less frequently after cycle 2. Therefore, the rate of cytopenias observed in each cycle may be biased by lack of evaluation in later cycles. Similarly, monitoring of hepatic function and other potential laboratory abnormalities was decreased after the first two cycles and may lead to missed findings of asymptomatic transaminase increases.

8.2.4. Safety Results

Deaths

Data:

In the MDS3001 Phase 3 study, the rate and causes of death (including during treatment and in the post-treatment follow-up period) were similar between the imetelstat group (16.1%; N = 118) and the placebo group (13.6%; N = 59) and most deaths occurred during follow-up ([Applicant Table 47](#)). One subject in each arm died during the treatment period and the events

were considered Grade 5 TEAEs (sepsis in the imetelstat-treated subject and aortic stenosis in the placebo-treated subject) (Table tae05a). Both events were considered unrelated to study treatment (Table tae05d).

In the MDS3001 Phase 3 post-treatment follow-up, 15.3% of subjects in the imetelstat group and 11.9% of subjects in the placebo group died ([Applicant Table 47](#)). The reported cause of death in 6 (5.1%) subjects in the imetelstat group and 2 (3.4%) subjects in the placebo group were non-TEAEs, all assessed as not related to study treatment and all occurred > 30 days after last dose of study treatment. Progressive disease was the reported cause of death in 1 (0.8%) and 3 (5.1%) subjects in the imetelstat and placebo groups, respectively. The cause of death was reported as “Other” for 11 (9.3%) subjects in imetelstat and 2 (3.4%) subjects in placebo and all of these deaths occurred ≥ 90 days from the last treatment dose. These deaths included events associated with the underlying disease or subsequent therapies, such as infections and clinical deterioration (7 subjects), unknown causes of death (3 subjects), and death from complications of hematopoietic stem cell transplant (2 subjects). These deaths all occurred ≥ 90 days from the last treatment dose.

There was a greater proportion of deaths overall in imetelstat-treated subjects in MDS3001 Phase 2 compared to MDS3001 Phase 3 imetelstat groups (47.4% vs 16.1%, respectively; [Applicant Table 47](#)), which is expected due to the approximately 3 years of longer median duration of time on study in Phase 2 (57.3 months vs 19.5 months, respectively). More subjects died during the treatment period with Grade 5 TEAEs in Phase 2 (5 subjects with one of the following events: cerebrovascular accident, COVID-19 pneumonia, femur fracture, neurodegenerative disorder, and thrombosis mesenteric vessel) compared to Phase 3 (1 subject with sepsis; Table tae05b). All of the events were considered unrelated to study treatment (Table tae05e). The remaining deaths occurred during post-treatment follow-up. In the Phase 2 post-treatment follow-up, 22 (38.6%) subjects died with reported cause of death of non-TEAE in 1 (1.8%) subject, progressive disease in 8 (14.0%) subjects, and “Other” in 13 (22.8%) subjects ([Applicant Table 47](#)). These deaths included events associated with the underlying disease or subsequent therapies, such as infections and clinical deterioration (10 subjects), unknown causes of death (2 subjects), and death from complications of hematopoietic stem cell transplant (1 subject).

After review of death from across all monotherapy studies in hematologic malignancies (N = 391), no patterns of fatal events or infrequent deaths of concern were apparent. There were higher proportions of deaths overall in the < 7.1 mg/kg and > 7.1 mg/kg groups (72.9% and 59.0%, respectively) compared to the 7.1 mg/kg group (29.9%) ([Applicant Table 48](#)), which corresponds with longer median times on study (41.6 months and 42.4 months vs 24.2 months, respectively). The following TEAEs that led to death (including death > 30 days after last dose) were reported in 1 subject each in the following dose groups (Table tae05c):

- < 7.1 mg/kg group: sepsis, head injury, and splenic infarction

- 7.1 mg/kg group: sepsis (MDS3001 Phase 3); cerebrovascular accident, COVID-19 pneumonia, femur fracture, neurodegenerative disorder, and thrombosis mesenteric vessel (MDS3001 Phase 2); and oesophageal varices haemorrhage and pneumonia
- > 7.1 mg/kg: acute respiratory failure, cardiac failure, haemorrhage, and respiratory failure

All of the events were considered unrelated to study treatment except for the haemorrhage in the > 7.1 mg/kg group, for which a brief narrative is provided below (Table tae05f). There were no fatal TEAEs in Study CP14B013 (Listing lae02a).

Applicant Table 47: Summary of Deaths and Causes of Deaths – Study MDS3001 – Phase 2 and Phase 3 (Treated Population)

	Phase 3		Phase 2	Imetelstat
	Imetelstat (N = 118)	Placebo (N = 59)	Imetelstat (N = 57)	Pooled (N = 175)
Overall deaths on study	19 (16.1%)	8 (13.6%)	27 (47.4%)	46 (26.3%)
Deaths during treatment ($\leq$ 30 days after last dose or > 30 days if death due to related TEAE)	1 (0.8%)	1 (1.7%)	5 (8.8%)	6 (3.4%)
Grade 5 TEAE	1 (0.8%)	1 (1.7%)	5 (8.8%)	6 (3.4%)
Deaths in post-treatment follow-up (> 30 days after last dose) ^a	18 (5.1%)	7 (11.9%)	22 (38.6%)	40 (22.9%)
Non-treatment-emergent adverse events	6 (5.1%)	2 (3.4%)	1 (1.8%)	7 (4.0%)
Progressive disease	1 (0.8%)	3 (5.1%)	8 (14.0%)	9 (5.1%)
Other	11 (9.3%)	2 (3.4%)	13 (22.8%)	24 (13.7%)

TEAE = treatment-emergent adverse event.

^a Deaths in post-treatment follow-up = overall deaths on study minus deaths during treatment.

Note: Death during Treatment include death events that occur after the first dose of study drug, through the treatment phase, and for 30 days following the last dose of study drug or until subsequent anti-cancer therapy if earlier or any death that is considered study drug-related regardless of the date.

Source: Table tae09a, Table tae09b

Applicant Table 48: Summary of Death and Causes of Death – Studies MDS3001, CP14B013, CP14B015, CP14B019, MYF2001 – Phase 2 and 3 Imetelstat (Group C Treated Population)

	Imetelstat ^f			
	<7.1 mg/kg ^a q4w (N = 48)	7.1 mg/kg ^b q4w (N = 204)	>7.1 mg/kg ^c q4w (N = 139)	Total Pooled (N = 391)
Overall deaths on study	35 (72.9%)	61 (29.9%)	82 (59.0%)	178 (45.5%)
Deaths during treatment (≤ 30 days after last dose or > 30 days if death due to related TEAE)	5 (10.4%)	7 (3.4%)	12 (8.6%)	24 (6.1%)
Grade 5 TEAEs	4 (8.3%)	6 (2.9%)	3 (2.2%)	13 (3.3%)
Progressive disease	0	0	2 (1.4%)	2 (0.5%)
Cause unknown	0	0	4 (2.9%)	4 (1.0%)
Other	1 (2.1%)	1 (0.5%)	3 (2.2%)	5 (1.3%)
Deaths in post-treatment follow-up (> 30 days after last dose) ^d	30 (62.5%)	54 (26.5%)	70 (50.4%)	154 (39.4%)
Non-treatment-emergent adverse events	2 (4.2%)	7 (3.4%)	1 (0.7%)	10 (2.6%)
Treatment-emergent adverse events ^e	0	2 (1.0%)	1 (0.7%)	3 (0.8%)
Progressive disease	15 (31.3%)	15 (7.4%)	32 (23.0%)	62 (15.9%)
Cause unknown	0	5 (2.5%)	14 (10.1%)	19 (4.9%)
Other	13 (27.1%)	25 (12.3%)	22 (15.8%)	60 (15.3%)

^a MYF2001 4.4mg/kg arm only

^b CP14B019 Arms E and G; MDS3001 Phase 2 and 3 (Imetelstat); CP14B015 and CP14B013 7.1 mg/kg arm

^c CP14B019 Arms A, B, D, and F; CP14B015, CP14B013, and MYF2001 8.9 mg/kg arm

^d Deaths in post-treatment follow-up = overall deaths on study minus deaths during treatment

^e TEAEs that led to death > 30 days after last dose.

^f 7.1 mg/kg active moiety (free acid), which is equivalent to 7.5 mg/kg imetelstat sodium.

Note: Death during Treatment include death events that occur after the first dose of study drug, through the treatment phase, and for 30 days following the last dose of study drug or until subsequent anti-cancer therapy if earlier or any death that is considered study drug-related regardless of the date.

q4w = once every 4 weeks; TEAE = treatment-emergent adverse event.

Source: Table tae09c

The Applicant's Position:

A review of the overall causes of death in the MDS3001 Phase 3 study indicates no increased mortality from imetelstat treatment as compared to placebo. Deaths during treatment occurred infrequently with only 1 death in each group, both of which were not related to study treatment. The majority of deaths occurred in post-treatment follow up ≥ 90 days from the last treatment dose and were generally balanced between both groups. All deaths in the post-treatment follow up period were considered unrelated to study treatment, were due to

underlying MDS and/or disease progression or complications from comorbidities and subsequent therapies. No early deaths were reported.

Results in the MDS3001 Phase 2 imetelstat group were consistent with MDS3001 Phase 3. A review of the overall causes of death shows that deaths occurred infrequently during imetelstat treatment (5 subjects experiencing Grade 5 TEAEs that were all not related to imetelstat treatment), with the majority of deaths occurring in post-treatment follow-up. All deaths in the post-treatment follow-up period were considered unrelated to study treatment and were due to underlying MDS and/or disease progression or complications from comorbidities and subsequent therapies.

A review of the deaths in the pooled monotherapy grouping does not suggest a causal relationship to imetelstat as these deaths are confounded by underlying disease and co-morbidities.

The Sponsor continues to actively follow all subjects to monitor for death on treatment and in post-treatment follow-up.

The FDA’s Assessment:

Overview: Updated information on overall survival was provided twice after the initial submission. First, in the 120-day safety update (data cut-off 10 May 2023) and then in an ad hoc overall survival update with data cut-off date of 5 Jan 2024. An overview of deaths documented at each time point is provided in Table 49. Of note, the number of patients who died was higher in the imetelstat arm of the phase 3 portion at each time point provided. In the phase 2 portion of the study, nearly half of patients have died. No further fatal events were reported in the imetelstat phase 2 arm between the 120-day safety update and the overall survival update. However, all patients on this portion of the study have completed or discontinued the study and the most recent end of study date was 2 October 2023, suggesting that the lack of further recorded deaths is related to lack of further follow up rather than to no further deaths occurring. It should be noted that due to differences in patient characteristics and follow up time, deaths in the phase 2 portion cannot be directly compared to those in the phase 3 portion. Deaths are described based on the time of submission, with the data from the initial submission provided first followed by the data in the 120-day safety update and the OS update.

Table 49: Deaths among patients treated on Study MDS3001.

	Imetelstat phase 2 N=57 N (%)	Imetelstat phase 3 N=118 N (%)	Placebo N=59 N (%)
Initial submission	27 (46)	19 (16)	8 (14)
120-day safety	28 (49)	29 (25)	13 (22)
OS update	28 (49)	35 (30)	15 (25)

Source: FDA analysis

Data from initial submission:

As noted by the Applicant, a higher percentage of patients in the imetelstat arm died on study compared to patients in the placebo arm, with death by the time of data cut-off occurring in 19 (16%) of patients on the imetelstat arm and 8 (14%) of patients on the placebo arm. Of these, two (one in each arm) occurred on treatment or within 30 days of last dose of imetelstat/placebo. However, it is noted that some fatal events began within 30 days of last dose of the investigational product, although death was delayed to >30 days, suggesting a potential relationship to the study drug. Brief narratives of the events and table with the FDA's adjudication of the events are below.

Table 50: Deaths on the phase 3 portion of MDS3001 by study arm and FDA adjudication of relationship to study drug

Patient ID	Treatment arm	Fatal event	FDA adjudication
Treatment emergent adverse events (within 30 days of last dose of imetelstat)			
(b) (6)	Imetelstat	Sepsis	Related
Non-treatment emergent adverse events (greater than 30 days since last dose of imetelstat)			
(b) (6)	Imetelstat	COVID-19 pneumonia	Unlikely related
	Imetelstat	Progression to AML	Unlikely related
	Imetelstat	Cardiorenal syndrome	Unlikely related
	Imetelstat	Cardiac failure, GI hemorrhage	Unlikely related
	Imetelstat	Cardiac failure	Unlikely related
	Imetelstat	GI hemorrhage, metastatic tumor	Unlikely related
	Imetelstat	Septic shock	Not related
	Imetelstat	Clinical degradation	Not related
	Imetelstat	Respiratory insufficiency	Unlikely related
	Imetelstat	Pneumonia	Not related
	Imetelstat	Multiple organ failure	Unlikely related
	Imetelstat	GVHD	Not related
	Imetelstat	Sudden death	Unlikely related
	Imetelstat	Unknown cause	Unlikely related
	Imetelstat	Unknown cause	Unlikely related
	Imetelstat	Lung neoplasm, embolic stroke	Unlikely related
	Imetelstat	Disease progression	Not related
	Imetelstat	Respiratory insufficiency	Not related
	Placebo	Aortic stenosis	Not related
	Placebo	COVID-19, multiple organ dysfunction	Not related
	Placebo	CHF	Not related

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(b) (6)	Placebo	Septic shock	Not related
	Placebo	Progressive disease	Not related
	Placebo	Complications of transplant	Not related
	Placebo	Disease progression	Not related
	Placebo	Disease progression	Not related

Data cut-off date: 13 October 2022

Narratives for events in the imetelstat arm described in the table above follow:

(b) (6) was a 72 y/o M with IPSS low risk MDS with baseline RBC transfusion requirement of 8 units/8 weeks and prior use of ESA. He was randomized to imetelstat and received 23 cycles of imetelstat total. On day 619 (C23 D1) he developed grade 3 neutropenia, anemia, and thrombocytopenia which worsened to grade 4 by day 633. Imetelstat was given despite low counts, which was a major protocol deviation. On study day 644, he developed grade 4 sepsis. He died on day 649 of acute respiratory failure, septic shock, pneumonia, and cardiac ischemia.

Clinical Reviewer comments: Neutropenia is an AE associated with use of imetelstat and fatal sepsis in the context of neutropenia in a patient on active treatment with imetelstat is considered related to the drug.

(b) (6) 78 y/o M with IPSS intermediate-1 MDS with baseline transfusion burden of 6 units/8 weeks, prior treatment with luspatercept randomized to imetelstat arm. The patient had grade 3 decreased leukocytes and grade 2 neutropenia on study day 15. On study day 16, a grade 1 upper respiratory tract infection was reported. On study day 20, bacterial pneumonia and congestive heart failure were reported. On study day 29, leukocyte count was grade 1 and neutropenia had resolved. COVID-19 pneumonia was documented on day 35 and was fatal on day 42.

Clinical Reviewer comments: The event of COVID-19 pneumonia occurred more than 30 days after the last dose of imetelstat (given on day 1 of cycle 1). However, it is noted that the patient appears to have had an unresolved bacterial pneumonia at the time of death which may have increased his vulnerability to COVID-19, despite an apparently normal neutrophil count at the time of infection. In addition, the patient's leukopenia had not entirely resolved at last documented evaluation and his neutrophil count had not increased appropriately for a serious infection, suggesting some level of immune dysfunction. In summary, the event is considered unlikely related due to timing, prior pneumonia that occurred during a neutropenic episode, and comorbid cardiac failure that occurred on treatment.

(b) (6) 83 y/o F with intermediate-1 MDS and a baseline transfusion burden of 8 units/8 weeks, previously treated with ESA, randomized to imetelstat. The patient had a history of myelofibrosis and splenectomy. She received 4 cycles of imetelstat total and withdrew due to

worsening of myelofibrosis and development of peripheral blood blasts on study day 125. Other AE noted included asthenia, malnutrition, abdominal pain, and stomatitis. She died on study day 131, with death attributed to AML.

Clinical Reviewer comments: No bone marrow biopsy results after the initial screening biopsy are provided and therefore cannot confirm the diagnosis of AML. However, peripheral blood blasts were noted on the last laboratory evaluation on study. Of note, last neutrophil and platelet counts were normal or decreased to grade 1, which may call the attribution of death to AML into question. The patient's general physical condition (malnutrition, asthenia) may have contributed to the death.

(b) (6) 75 y/o M with low risk MDS with baseline transfusion burden of <6 units/8 weeks who was randomized to imetelstat arm of study. The patient discontinued treatment on study day 555 due to lack of efficacy (last dose of study medication day 527). Grade 2 neutropenia was noted at the time of last dose of imetelstat and was persistent through the last laboratory value on study on day 555. He developed gram negative bacteremia and cardiorenal decompensation on about day 562 of the study and died on day 583, with death attributed to cardiorenal syndrome. Adverse events of thrombocytopenia and neutropenia were noted during the study, with the last ANC on study showing grade 2 neutropenia.

Clinical Reviewer comments: Although the neutropenia noted at about the time the patient developed fatal bacteremia and cardiorenal syndrome was not severe, it may have contributed to the event. In addition, the patient had a normal baseline neutrophil count, suggesting that the neutropenia could be attributed to use of imetelstat. Thus, this event is considered possibly related.

(b) (6) 83 y/o M with low risk MDS and baseline transfusion burden of 6 units/8 weeks who was randomized to imetelstat. The patient had a past medical history of myocardial ischemia and myocardial infarction, but no documented history of cardiac insufficiency. The patient had a normal platelet count at baseline. On study day 25, he developed grade 4 GI hemorrhage, and a bleeding duodenal ulcer was found. Platelet count on study day 22 (last count prior to event) was 207 and platelet count documented during the event was 164. Coagulation profile was not documented, but INR was noted to be increased (grade 1) at end of study labs on day 59 with a normal baseline. He was successfully treated for the ulcer but fell during hospitalization on study day 29 and grade 4 deconditioning and cardiac failure were reported on days 36 and 47, respectively. Treatment was withdrawn on day 59 (second planned dose was not given). The patient died on day 95 due to multiple medical issues including cardiac insufficiency, deconditioning, and GI hemorrhage.

Clinical Reviewer comments: This patient had multiple medical issues. The patient had platelet counts in the normal or grade 1 thrombocytopenic range except for a single value of 68 (grade

2) on day 80 of the study. Grade 3-4 cardiac insufficiency was seen more frequently on the imetelstat arm of the study and may have contributed to death. However, death occurred >90 days after the last (and only) dose of imetelstat and the GI hemorrhage was not known to be associated with thrombocytopenia, leading to doubt about the connection. Thus, this death is considered unlikely related to treatment.

(b) (6) 65 y/o M with low risk MDS and baseline transfusion burden of 19 units/8 weeks randomized to the imetelstat arm. The patient had a history of left ventricular failure and cardiac failure as well as iron overload. The patient received 4 cycles of imetelstat. On study day 80, an SAE of pneumonia was reported, and he was treated with antibiotics, steroids, and furosemide. Cycle 4 was delayed due to the pneumonia, but started on study day 113. On study day 131, an SAE of cardiac failure was reported. On study day 190, treatment was withdrawn due to cardiac failure and the subject died of this AE on study day 208.

Clinical Reviewer comments: The patient has a history of pre-existing cardiac issues which complicate the assessment of the reported fatal cardiac failure. Use of imetelstat may have worsened the cardiac failure, leading to death given that the AE was reported only on study day 131. Overall, this event is considered unlikely related due to multiple confounders and the time between last dose and death.

(b) (6) 71 y/o M with intermediate-1 MDS and baseline transfusion burden of <6 units/8 weeks experienced GI hemorrhage on day 621 and died on study day 647, 105 days after the last dose of imetelstat was given. The patient had a history of vocal cord and prostate cancer, and the bleeding was suspected to be related to metastatic disease. The patient had experienced thrombocytopenia during treatment with a platelet count of 89 (grade 1) on the day of the GI hemorrhage and 48 (grade 2) on day 603 (last evaluation prior to event).

Clinical Reviewer comments: This patient had a history of metastatic solid malignancy which is likely to have been the major factor leading to the event of fatal GI bleeding. However, some contribution of drug related thrombocytopenia cannot be ruled out.

(b) (6) 66 y/o M with low risk MDS and baseline transfusion burden of 6 units/8 weeks with prior therapy with ESA was randomized to the imetelstat arm and received a total of 8 cycles of therapy. The patient withdrew from treatment on study day 253 due to lack of efficacy. Neutrophil count was reported as within normal limits at that time. The patient died of septic shock on study day 622.

(b) (6) 69 y/o M with low risk MDS and baseline transfusion burden of 8 units/8 weeks previously treated with ESA was randomized to imetelstat and received a total of 6 cycles of therapy. The patient had baseline grade 4 neutropenia, grade 2 anemia, and grade 1 thrombocytopenia. Multiple cycles were delayed due to neutropenia. Treatment was

withdrawn due to neutropenia on study day 260. The patient died on study day 548 with death being attributed to clinical degradation.

(b) (6) 87 y/o M with intermediate-1 MDS and baseline transfusion burden of >6 units/8 weeks who was randomized to imetelstat. The patient died of respiratory insufficiency on study day 451, 245 days after last dose of imetelstat.

(b) (6) 64 y/o F with intermediate-1 MDS and a baseline transfusion burden of >6 units/8 weeks randomized to the imetelstat arm. The patient died of pneumonia on study day 892, 646 days after the last dose of study medication.

Clinical Reviewer comments: Given the long time period between last treatment and death in these patients, the fatal events are considered not related to imetelstat.

(b) (6) 73 y/o F with low risk MDS and a baseline transfusion burden of 7 units/8 weeks, previously treated with ESA who was randomized to imetelstat. The patient died of multiple organ failure on study day 313, 93 days after last dose of imetelstat. The patient had multiple AEs of diarrhea during treatment as well as diverticulosis, neutropenia, and thrombocytopenia. AEs that were not documented to have resolved prior to death included diarrhea, abdominal pain, diverticulosis, and hyperferritinemia. The last neutrophil count documented on study was 780 (grade 3).

Clinical Reviewer comments: Given the time between the last dose of medication and the fatal event of multiple organ failure, a relationship between imetelstat and the fatal event is unlikely. However, given that events leading up to multiple organ failure could be prolonged, a relationship cannot be ruled out entirely and the event is therefore considered unlikely related.

(b) (6) 61 y/o M with low risk MDS and transfusion burden of ≤ 6 units/8 weeks treated with imetelstat died of CMV infection and graft versus host disease on study day 771, 525 days after last dose. The patient withdrew from treatment on day 274 due to progressive disease and underwent HSCT on study day 470.

(b) (6) 83 y/o M with intermediate risk disease and baseline transfusion burden of >6 units/8 weeks randomized to the imetelstat arm. The patient is described as having had "sudden death on the bus" on study day 542, 304 days after last treatment with imetelstat. The patient was noted to have experienced thrombocytopenia while on study, but this AE resolved by study day 175. Of note, he had an AE of dizziness reported as well as two falls on study days 413 and 505.

Clinical Reviewer comments: The sudden death of a patient on clinical trial examining use of a novel therapy is always of concern. Possible reasons for sudden death might include QT prolongation, intracranial hemorrhage, and cardiac events. However, it is unlikely that the

effects of imetelstat would last nearly a year after the last dose was given. The underlying condition and potentially other medications are more likely causes of the event of sudden death.

(b) (6) 83 y/o F with low-risk disease and a baseline transfusion burden of >6 units/8 weeks who was randomized to imetelstat died of unknown cause on study day 712, 248 days after last dose of imetelstat. The patient discontinued treatment due to relapse. No further details were provided regarding events leading to the patient's death. AEs reported during the patient's treatment included pyrexia, fatigue, and thrombocytopenia, all of which had resolved by day 464.

(b) (6) 86 y/o M with intermediate-1 MDS with a transfusion burden of >6 units/8 weeks randomized to imetelstat died of unknown cause on study day 278, 109 days after the last treatment dose. The patient is described as having "died at home in his sleep". It was noted that no autopsy was performed. Treatment was discontinued due to lack of efficacy. The only AEs noted during treatment were neutropenia and thrombocytopenia.

Clinical Reviewer comments: The long interval between last dose of imetelstat and death and lack of unresolved AEs or AEs likely to result in long term complications during treatment make it highly unlikely that these patients' deaths were related to treatment.

(b) (6) 72 y/o M with low risk MDS with baseline transfusion burden of 8 units/8 weeks who was randomized to imetelstat and received 5 cycles of treatment. The patient died on study day 283, 90 days after last treatment, due to complications of embolic stroke. He withdrew from treatment on study day 180 due to a new diagnosis of a lung neoplasm. He was noted to have developed atrial fibrillation while on study (on study day 3), as well as neutropenia and thrombocytopenia. The atrial fibrillation is noted to have resolved. No prior history of atrial fibrillation or other cardiac issues was noted.

Clinical Reviewer comments: This patient had at least two risk factors for embolic stroke: atrial fibrillation and lung neoplasm. Although the event of atrial fibrillation documented resolved, atrial fibrillation may be intermittent and may have returned at a later time. The timing of the initial diagnosis of atrial fibrillation is suggestive of a possible relationship to imetelstat. Conversely, solid tumors are frequently associated with thrombosis and the diagnosis of lung neoplasm may have contributed. Overall, it is not possible to definitively rule in or out a contribution from imetelstat and the event is considered unlikely related.

(b) (6) 85 y/o F with low risk MDS and baseline transfusion burden of ≤6 units/8 weeks randomized to imetelstat and treated with 5 cycles before discontinuing due to lack of efficacy died of progressive disease on study day 368, 241 days after last dose of imetelstat. AEs while on study were notable for cytopenias, UTIs, and an episode of QTc prolongation.

Clinical Reviewer comments: Given the long time between last dose and death as well as the diagnosis of progressive disease, this event is considered not related to imetelstat.

(b) (6) 83 y/o M with low risk MDS with a baseline transfusion burden of ≤ 6 units/8 weeks randomized to imetelstat died of respiratory insufficiency on study day 286, 228 days after the last dose of imetelstat. The patient discontinued treatment after 3 doses due to thrombocytopenia and lymphopenia. Past medical history included chronic kidney disease, MI, hypertension, atrial fibrillation, and Parkinson's disease. The patient was noted to have had CHF and respiratory insufficiency during treatment. However, both were noted as resolved.

Clinical Reviewer comments: Given the amount of time between last treatment and death as well as the multiple comorbid conditions, this death is considered unrelated to imetelstat.

The following further deaths on study were reported in the 120-day safety update (data cut-off date 10 May 2023) and overall survival update (data cut-off date 5 Jan 2024). Very little information was provided concerning these events, making attribution difficult. Of note, the submission did not include narratives of the deaths, including the death on study. The Applicant later provided a narrative for this event in response to an IR.

Table 51: Deaths in patients receiving imetelstat on the phase 3 portion of MDS3001 described in safety and survival updates

Deaths reported on the 120-day safety update imetelstat arm of phase 3 portion of study			
Patient ID	Treatment arm	Fatal event	FDA adjudication
(b) (6)	Imetelstat	Cardiac decompensation	Unlikely related
	Imetelstat	Lung cancer	Not related
	Imetelstat	Progressive disease	Not related
	Imetelstat	"Another illness"	Not assessable
	Imetelstat	Unknown	Not assessable
	Imetelstat	Multiorgan failure	Not related
	Imetelstat	Unknown	Unlikely related
	Imetelstat	COVID-19 pneumonia	Not related
	Imetelstat	Assisted dying program	Not related
	Imetelstat	Unknown	Not assessable
Deaths reported in overall survival update imetelstat arm of phase 3 portion of study			
(b) (6)	Imetelstat	Progressive disease	Not related
	Imetelstat	Cardiovascular arrest	Unlikely related
	Imetelstat	Fragility	Unlikely related
	Imetelstat	Progressive disease	Not related
	Imetelstat	Unknown	Not assessable
	Imetelstat	Myocardial infarction	Unlikely related

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*Death occurred (b) (6) but was not reported until the OS update
Data cutoff date for 120-day safety update: 10 May 2023
Data cutoff date for overall survival update: 5 January 2024

Patient (b) (6) was a 73 y/o F who died of myocardial infarction on study day 685, 7 days after last dose of imetelstat. The patient experienced cystitis, neutropenia, and back pain while on study. Neutropenia was not noted in the ADAE dataset but was documented in the 120-day safety update. No cardiac disease was documented in the ADAE dataset; however, data cut-off was earlier than that of the survival dataset which did not include further AE updates.

A narrative was provided in response to an IR which noted that the patient had a history of hypercholesterolemia and smoking as well as COVID-19 infection 6 months prior to start of study. It was noted that the last hemoglobin prior to the event was 8.2 g/dl. The patient was admitted to the hospital hemodynamically unstable on study day 685 and experienced cardiac arrest shortly thereafter. No details of symptoms or prior cardiac issues was provided. Death was attributed to myocardial infarction and was assessed by the investigator as not related to imetelstat.

Clinical Reviewer comments: No increase in arterial occlusive disease was noted with use of imetelstat in patients on study MDS3001. However, the risk of other cardiac conditions is equivocal and a contribution of imetelstat to the death is difficult to entirely rule out.

Patient (b) (6) was a 75 y/o M who died of cardiac decompensation on study day 1230, 500 days after last dose of imetelstat. The patient was noted to have discontinued treatment in (b) (6) due to disease relapse and died (b) (6). No AE were reported after day 693, at which time dizziness and atrial fibrillation were reported. Last hematologic labs on study day 842 showed no ongoing neutropenia or thrombocytopenia.

Clinical Reviewer comments: The long time between last treatment and death makes a causal relationship to imetelstat unlikely. However, treatment emergent atrial fibrillation, dizziness, and angina were reported and could be factors that contributed to the later cardiac decompensation.

Patient (b) (6) was a 65 y/o M with MDS and a history of passive smoke exposure who died on study day 1190, 200 days after the last dose of imetelstat of lung cancer. Stage 4 lung adenocarcinoma, including cerebral metastases, was diagnosed on day 1018. The subject ended participation due to progressive MDS at about this time.

Patient (b) (6) was a 69 y/o M with MDS who died of progressive disease 673 days after last dose of study medication.

Clinical Reviewer comments: In the absence of evidence of carcinogenicity associated with imetelstat, these events are considered unrelated. However, if further non-clinical testing reveals a mutagenic or clastogenic signal, further evaluation to rule out the risk of worsening disease or risk of secondary malignancy may be needed.

Patient (b) (6) was a 74 y/o F who died of “another illness” on study day 890, 191 days after last dose of imetelstat. It is noted that the patient experienced esophageal varices, splenomegaly, and portal hypertension, all of which were described as unresolved at the time of last contact, while on treatment.

Clinical Reviewer comments: In the absence of further information, the relationship to imetelstat cannot be assessed.

Patient (b) (6) was a 68 y/o M who died of multiple organ failure on study day 888, 744 days after last dose of imetelstat on study. This patient had multiple episodes of neutropenia and thrombocytopenia reported while on treatment, but no events reported after study day 192. No lab values for neutrophils or platelets were reported after study day 276, at which time the patient had normal platelet and neutrophil counts.

Clinical Reviewer comments: The last reported neutrophil and platelet counts were normal, reducing the probability that the event is related to use of imetelstat, although in the absence of information about events leading to the event of multiple organ failure, the possibility cannot be completely ruled out.

Patient (b) (6) was a 77 y/o F who died of unknown cause on study day 820, 294 days after the last dose of study medication. The patient experienced multiple bouts of neutropenia and infection during the course of treatment. Last neutrophil count showed resolution of neutropenia to grade 0 on study day 683. The patient was noted to have received further therapy directed against MDS.

Clinical Reviewer comments: It is unlikely that the death was related to imetelstat given the normalization of neutrophils and further treatment. However, in the absence of information about the cause of death, a relationship cannot be entirely ruled out.

Patient (b) (6) was a 71 y/o M who died of COVID-19 pneumonia on study day 635, 541 days after last treatment with imetelstat. The patient experienced multiple grade 3-4 cytopenias (neutropenia, thrombocytopenia, hemoglobin decreased, and leukopenia). The patient had continued thrombocytopenia at last value evaluated (day 633). The last neutrophil count documented was on day 288 and was normal at that time. The patient was noted to have had subsequent anti-neoplastic therapy.

Clinical Reviewer comments: The normalization of neutrophil count, further treatment, and long time between last treatment with imetelstat and death suggest that the fatal event of COVID-19 was not related to treatment.

Patient (b) (6) was a 78 y/o M who died on study day 538, 409 days after last treatment with imetelstat. Cause of death was listed as medical assistance in dying program. The subject was noted to have received subsequent anti-neoplastic therapy. The patient experienced multiple AE of neutropenia, thrombocytopenia, and leukopenia during treatment as well as transaminase increased, nosebleed, and anal fissure. The patient was noted to have continued grade 3 neutropenia and thrombocytopenia at last lab values on day 175.

Clinical Reviewer comments: The cause of death in this patient was not related to imetelstat. However, the events leading up to the decision to request medical assistance in dying is unknown and thus component of quality of life being lowered by adverse events associated with imetelstat cannot be ruled out.

Patient (b) (6) was an 81 y/o F who died of unknown cause on day 549 of study participation. The treatment end day was reported to be day 183, making the time between end of treatment and death >1 year. The subject was reported to have experienced hepatitis, COVID-19, troponin increased, E coli urosepsis, and multiple episodes of cytopenias (leukopenia, neutropenia, thrombocytopenia) during treatment or within 30 days of end of treatment. Events of troponin increased and hepatitis were considered to be not resolved and resolved with sequelae, respectively.

Clinical Reviewer comments: Although the time between last dose of study medication and death makes the relationship to imetelstat unlikely, in the absence of any information on cause of death and with ongoing AE or sequelae of AE at last documentation of status make it difficult to rule out a relationship entirely.

Patient (b) (6) was a 75 y/o M reported to have died of progressive disease on study day 1128, 217 days after last treatment was given.

Patient (b) (6) was a 70 y/o M reported to have died of progressive disease on study day 867, 810 days after the last treatment with imetelstat.

Clinical Reviewer comments: There is no clear evidence to suggest that imetelstat worsens the underlying disease of MDS and therefore deaths from progressive disease are considered not related. However, it must be noted that disease status at time of death was not adjudicated by the FDA.

Patient (b) (6) was a 71 y/o M who died of cardiovascular arrest on study day 900, 74 days after the last dose of imetelstat. The patient experienced TEAE of bladder papilloma, bone pain, fatigue, GGT increased, hematuria, hyperferritinemia, influenza, fall, and multiple episodes of neutropenia and thrombocytopenia. Two episodes of neutropenia were considered resolved with sequelae or had no information regarding resolution and one of thrombocytopenia was listed as not resolved at last evaluation.

Clinical Reviewer comments: Given the lack of resolution or resolution only with sequelae of cytopenias at last evaluation, the non-specific nature of the cause of death, a relationship is unlikely, but not ruled out.

Patient (b) (6) was an 81 y/o F whose death was attributed to fragility. The patient died on study day 868, 341 days after last treatment. The patient experienced anorexia, back pain, marrow edema, constipation, infections including COVID-19 and E coli infection, hypertension, lumbar vertebral fracture, syncope, and multiple episodes of neutropenia and thrombocytopenia during treatment. All events except for constipation were considered resolved or recovered at last evaluation.

Clinical Reviewer comments: Given the long time period between last treatment and death and absence of unresolved AE at last evaluation, the patient's death is unlikely to have been related to imetelstat. However, a contribution of deconditioning due to fracture that may be related cannot be entirely ruled out.

Patient (b) (6) was an 81 y/o M who died of unknown cause on study day 699, 564 days after last dose of imetelstat.

Clinical Reviewer comments: This death appears unlikely to be related to imetelstat but cannot be assessed completely due to lack of information.

Deaths on phase 2 portion of study

Twenty-seven deaths (47%) were reported among patients in part 1 (phase 2) portion of the study, including 5 deaths on treatment. Causes of death among patients who died during treatment included cerebrovascular accident, femur fracture, thrombosis of mesenteric vessel, COVID-19 pneumonia, and neurodegenerative disorder.

Among the 22 patients who died after the end of treatment, time from last dose of study treatment to death ranged from 60 to 1937 days. Death was attributed to progressive disease in 8 patients, in whom time from last dose to death ranged from 387 to 1446 days. Narratives for patients whose death occurred >365 days after last dose of treatment or who died of

progressive disease or transplantation complications will not be included here unless review of AEs suggests that an ongoing AE may have contributed to the death.

Table 52: Patients on the phase 2 portion of MDS3001 who have died up to data cut off

Patient ID	Time since last treatment	Cause of death	Relationship to imetelstat
(b) (6)	15	Cerebrovascular accident	Unlikely related
	3	Thrombosis mesenteric vessel	Unlikely related
	26	Neurodegenerative disorder	Possibly related
	4	Complications of femur fracture	Probably related
	19	COVID-19 pneumonia	Possibly related
	313	Distributive shock, abdominal ischemia	Not related
	509	Progressive disease	Not related
	729	COVID-19	Not related
	678	Progressive disease	Not related
	801	Complications of spinal insufficiency	Not related
	1195	Unknown	Not related
	178	Post-transplant complications	Not related
	1035	Progressive disease	Not related
	728	Progressive disease	Not related
	919	Progressive disease	Not related
	1937	Unknown	Not related
	1341	Cardiac decompensation	Unlikely related
	1446	Progressive disease	Not related
	269	Congestive heart failure	Unlikely related
	1005	Cardiogenic shock with multiorgan failure	Not related
	159	Transitional cell carcinoma	Possibly related
	1117	Progressive disease	Not related
	947	Febrile neutropenia/ P aeruginosa	Not related
	299	CHF and hepatic encephalopathy	Possibly related
	60	Probable fulminant sepsis	Unlikely related
	246	Cardiogenic shock	Unlikely related
Events documented in the survival update			
(b) (6)		Progressive disease	Not related

Data cut-off dates 13 October 2022 (initial submission) and 5 January 2024 (survival update)

Relevant narratives are below:

(b) (6) 82 y/o F with MDS treated with imetelstat for >1 year was hospitalized on study day 1186 for a grade 4 cerebrovascular accident. CT showed vascular thrombus and no hemorrhage, and the patient underwent thrombectomy. The patient had multiple AEs while on study, including neutropenia, thrombocytopenia, leukopenia, transaminases increased, and multiple infectious and bleeding events. Platelet count on study day 1176 (last documented prior to event) was 139. On day 1187, the platelet count was 257. No platelet transfusions were documented. The patient died on study day 1192 after being transitioned to palliative care only.

(b) (6) 62 y/o F with IPSS low risk MDS with a transfusion burden of 5 units/8 weeks died of thrombosis of mesenteric vessel on study day 953, 3 days after last dose of imetelstat. The patient did not have thrombocytopenia documented as an AE prior to the event and last documented platelet count on study was 400 on study day 951.

Clinical Reviewer comments: Thrombosis was not increased overall in patients receiving imetelstat. However, the timing of the events (within a few days of last dose of study medication) makes a relationship hard to definitively rule out, especially in light of the relatively young age of one of the patients.

(b) (6) 67 y/o F with low risk MDS and a past medical history notable for hypertension, chronic gastritis, and cholecystitis, with a transfusion burden of 6 units/8 weeks died of neurodegenerative disorder on study day 391, 26 days after her last dose of study medication. The patient was stated to have been asymptomatic on study day 390 but was found dead on study day 391. The death certificate listed "Senile degeneration of the brain" as the cause of death. No autopsy was performed. Last platelet count documented on study was 56 on study day 367. Of note, the patient had a bleeding episode requiring RBC transfusion (hemorrhoidal hemorrhage) on study day 314, with the last platelet count prior to this event being 117 on study day 309.

Clinical Reviewer comments: The diagnosis of neurodegeneration is unexpected in a patient with no apparent history of neurologic disorder of any sort and who was asymptomatic one day prior to the fatal event. Given that no autopsy was performed and in light of the patient's history of severe bleeding at a platelet count of >100, an acute intracranial hemorrhage cannot be ruled out. Thus, the death is considered possibly related to imetelstat.

(b) (6) 81 y/o F with intermediate-1 MDS with a transfusion burden of 8 units per 8 weeks died of complications of femur fracture on day 1042 of the study, 4 days after her last dose of study medication. The patient's course of therapy was complicated by multiple infectious issues and cardiac failure. On study day 1038, cycle 33 of imetelstat was administered. On study day 1039, the patient experienced a femoral fracture. The details of how the fracture occurred were not provided. The patient withdrew from treatment and died on study day 1042.

Clinical Reviewer comments: Patients receiving imetelstat had a higher rate of fractures and severe fractures compared to those receiving placebo. Thus, this death is considered probably related.

(b) (6) 58 y/o M with low risk MDS and baseline transfusion burden of 9 units/8 weeks as well as past medical history notable for hypertension, cardiomyopathy, Gilbert's syndrome, and splenomegaly, died on study day 1278 from COVID-19 pneumonia. The patient was found to have progressive disease on study day 1259. At that time, his hemoglobin was 4.7 g/dl, platelets were 80,000 and ANC 2870. However, his marrow showed 42% blasts. He discontinued treatment at that time, with last dose of imetelstat being given on that day. On study day 1269, he was diagnosed with COVID-19 pneumonia. His white blood count was $0.8 \times 10^9/L$ at that time. He was treated aggressively for COVID pneumonia, but died on study day 1278, 19 days after the last dose of imetelstat.

Clinical Reviewer comments: Given the state of the underlying disease at the time of the AE as well as the potential for COVID-19 to cause severe disease even in non-immunosuppressed individuals, the death due to COVID-19 pneumonia is unlikely related to treatment. However, we cannot rule out the possibility that imetelstat treatment contributed to the death.

(b) (6) 58 y/o M with MDS, IPSS and baseline transfusion requirement not specified, died on study day 428 of distributive shock at the time of acute ischemic abdomen, 313 days after last treatment with imetelstat. No narrative was provided for this patient. The patient was noted to have received subsequent therapy for MDS, but the details were not provided.

Clinical Reviewer comments: Given the amount of time between last dose and the report of subsequent treatment for MDS, the death is considered not related to imetelstat.

(b) (6) 80 y/o F with low risk MDS, RBC transfusion requirement not provided, treated on the phase 2 portion of the study (part 1), receiving a total of 4 cycles of imetelstat. On study day 98, she developed grade 3 cardiac failure. Evaluation for coronary artery disease showed mild CAD which did not explain the decrease in ejection fraction. On study day 195, cardiac MRI showed an ejection fraction of 50% and evidence of iron overload. Deferasirox treatment was started. The event of cardiac failure was stated to have ended on study day 238. On study day 1433, the patient died of cardiac decompensation stated to be related to anemia and MDS.

Clinical Reviewer comments: Although the time between last treatment and the fatal event is long and there were confounding factors, notably anemia and MDS, a contribution of imetelstat cannot be ruled out as the patient developed cardiac failure on study and residual cardiac insufficiency may have contributed to the fatal event.

(b) (6) 60 y/o F with low risk MDS, transfusion burden not stated, and history of iron overload was treated with imetelstat on part 1 of the study. On study day 6, grade 3 anemia was reported (baseline grade 2) and transfusions were given with improvement in anemia. The patient experienced repeated episodes of cytopenia during treatment and was dose reduced several times due to this. On study day 814, the patient was withdrawn due to thrombocytopenia. No cardiac issues were noted during treatment, although non-cardiac chest pain was noted on days 649 and 651. On study day 1053, the patient died of congestive heart failure. No details of events between end of treatment and death were provided.

Clinical Reviewer comments: The long time period between end of treatment and death, confounding issues of iron overload and chronic anemia, and lack of evidence of worsening of cardiac function on study make it less likely that imetelstat was the cause of the fatal event. However, the patient had no past medical history of cardiac disease and a decrease in ejection fraction that was not noted in the AE dataset during treatment cannot be ruled out. Overall, the event is adjudicated as unlikely related.

(b) (6) 79 y/o M with intermediate risk MDS and baseline transfusion burden of 10 units/8 weeks treated with imetelstat on part 1 of the study. The patient experienced thrombocytopenia requiring dose decrease to 4.7 mg/kg in cycle 6 but received treatment at this dose through cycle 23. On study day 590, a UTI was reported and treated with ciprofloxacin. On day 599, hematuria was reported and workup for possible transitional cell carcinoma was started. On study day 630, a grade 3 SAE of transitional cell carcinoma was reported. The patient underwent nephroureterectomy and treatment with imetelstat resumed. On study day 748, biopsy of a supraclavicular LN showed metastatic transitional cell carcinoma and the patient was removed from treatment on study day 765. He was treated palliatively for the transitional cell carcinoma with radiation. He died on study day 896 of transitional cell carcinoma.

Clinical Reviewer comments: The patient appears to have developed transitional cell carcinoma while on treatment with imetelstat and an increased risk of malignancy in patients receiving imetelstat cannot be ruled out (see section 8.2.9). Therefore, this event is considered possibly related to imetelstat.

(b) (6) 80 y/o M with low risk MDS with a baseline transfusion burden of 14 units/8 weeks and a PMH that includes angina and hypertension, treated on part 1 of the study died of congestive heart failure and hepatic encephalopathy on study day 349, 299 days after last dose of imetelstat. The patient was admitted to the hospital for grade 3 CHF on study day 80. Grade 1-2 AST and ALT elevations were reported on days 80 and 81 as well. On study day 82, febrile neutropenia was diagnosed and on study day 106, bronchoalveolar lavage demonstrated disseminated tuberculosis. The patient was treated with quadruple therapy for TB and the

event was reported to have resolved on study day 294. On study day 255, the subject withdrew from treatment due to CHF. He died on study day 349 of CHF and hepatic encephalopathy.

Clinical Reviewer comments: The patient has risk factors for CHF, including history of stable angina and hypertension. However, no CHF was reported prior to start of imetelstat. The issue of hepatic impairment is not discussed in the narrative. However, it is notable that the patient experienced transaminase elevations at the same time as the CHF was noted. Overall, the events of CHF and hepatic impairment are possibly related to imetelstat, although attribution is confounded by the underlying disease, possible iron overload, concurrent infections, and concomitant medications.

(b) (6) 78 y/o M with low risk MDS and baseline transfusion burden of 9 units/8 weeks treated with imetelstat on phase 2 component of study. Past medical history included hemosiderosis. The patient experienced neutropenia and thrombocytopenia during treatment, including events that required dose modification. On study day 744 (cycle 23 day 28), he had grade 3 thrombocytopenia and treatment was withdrawn due to the AE. Last neutrophil count on study (day 772) was 3400. Last neutrophil count on treatment (day 744) was 2300. The patient died of probable sepsis on day 777.

Clinical Reviewer comment: The patient died approximately 60 days after the last treatment with imetelstat. Neutrophil count was normal at the time of last evaluation prior to end of treatment and prior to death. The event of probable fulminant sepsis is therefore considered unlikely related to treatment, although a subtle continued immune defect cannot be ruled out.

(b) (6) 63 y/o M with low risk MDS and baseline transfusion burden of 10 units/8 weeks treated with imetelstat on part 1 of the study, died of cardiogenic shock 246 days after last dose of study medication. The patient received a total of 6 cycles of imetelstat and was discontinued on study day 246 due to grade 2 thrombocytopenia. On study day 330, the patient had a bone marrow biopsy that showed progressive disease (7% blasts). The patient died on day 457, with death attributed to cardiogenic shock. No information on events between day 330 and day 457 was provided. No AE related to cardiac function were noted during treatment.

Clinical Reviewer comments: The long time between last dose and death as well as lack of cardiac related AEs make it unlikely that the event of cardiogenic shock was related to treatment with imetelstat, but the possibility cannot be entirely ruled out.

One additional death (patient (b) (6)) was reported in the survival update, bringing the number of deaths among patients on the phase 2 portion of the study to 28 (49%). The final death reported was attributed to progressive disease and occurred >1 year after the end of treatment. The patient was noted to have received subsequent treatment for MDS.

In summary, more deaths occurred in the imetelstat arm of the phase 3 portion of the study compared to the placebo portion. Few deaths occurred on study, although at least one fatal adverse drug reaction due to sepsis was documented in the imetelstat arm. However, several deaths related to infection occurred in patients who had documented leukopenia or neutropenia less than 30 days after the end of treatment, although the actual death did not occur for more than 30 days. In addition, the time needed for full recovery of cytopenias after cessation of imetelstat is uncertain and deaths due to infection or bleeding may be related to imetelstat use even if they occur >30 days after the end of treatment. Finally, a subtle change in the disease or residual normal bone marrow leading to an increased risk of issues related to cytopenias (infection, bleeding) cannot be ruled out.

Deaths on the phase 2 portion of the study cannot be directly compared to those on the phase 3 portion. However, it is notable that several deaths on treatment or within 30 days of treatment occurred in the phase 2 portion of the study, including at least one death which appears likely to have been related to intracranial hemorrhage, one due to infection (COVID-19), and one due to complications of fracture, each of which is related to adverse events that appear to be linked to use of imetelstat (see below for further details).

Finally, although the majority of fatal events do not have an apparent relationship to imetelstat use, there is a consistent trend towards more events in the imetelstat arm that is concerning, but no definite risk has been identified at this time.

Serious Adverse Events

Data:

In the pivotal MDS3001 Phase 3 study, serious TEAEs were reported in 32.2% of subjects in the imetelstat group (N = 188) and 22.0% of subjects in the placebo group (N = 59) ([Applicant Table 53](#)). In both groups, the frequency of SAEs was highest in the Infections and infestations SOC (11.9% and 13.6%, respectively).

In the MDS3001 Phase 3 imetelstat group (N = 118), the most commonly reported SAEs were anaemia, cardiac failure, and pneumonia (2.5% each). Treatment-related SAEs were reported in 5.1% of subjects in the imetelstat group (Table tae02m). No treatment-related SAE was reported in more than 1 subject. One subject discontinued treatment due to treatment-related SAEs of Grade 4 sepsis and Grade 3 atrial fibrillation (along with concurrent non-serious Grade 3 renal abscess) (Listing lae02e).

In the MDS3001 Phase 3 placebo group (N = 59), the most commonly reported SAEs were COVID-19 pneumonia (5.1%) and abscess limb (3.4%). No subjects in the placebo group had a treatment-related SAE and no SAEs led to discontinuation of study treatment.

In the MDS3001 Phase 2 imetelstat group (N = 57), treatment-emergent SAEs were reported in 47.4% of subjects ([Applicant Table 53](#)). The most commonly reported SAE was femur fracture (5.3% of subjects), followed by cardiac failure, pneumonia, and thrombocytopenia in 3.5% of subjects each. All other SAEs were reported in 1 subject each. Treatment-related SAEs were reported in 15.8% of subjects (Table tae02n). Thrombocytopenia (2 [3.5%] subjects) was the only treatment-related SAE reported in more than 1 subject. Two treatment-related SAEs led to study drug withdrawal (Grade 3 cardiac failure and Grade 3 diarrhea), and all events resolved (Listing lae02c).

In subjects across all monotherapy studies in hematologic malignancies (N = 391), treatment-emergent SAEs were reported in 47.8% of subjects (Table tae03f). The most commonly reported SAEs in subjects across monotherapy studies were anaemia (13.6%; driven by MF studies), pneumonia (4.3%), and dyspnoea (1.8%). Treatment-related SAEs were reported in 15.1% of subjects (Table tae02o). Treatment-related SAEs reported in more than 1 subject included anaemia (5.1%), febrile neutropenia (1.8%), thrombocytopenia (1.0%), dyspnoea (0.8%), and chills, fatigue, pneumonia, IRR, and headache (0.5% each).

Across all hematologic monotherapy studies (N = 391), 6 subjects had treatment-related SAEs that led to study drug withdrawal (Listing lae02c). In addition to the 3 subjects with treatment-related SAEs that led to study drug withdrawal in Study MDS3001, there were 3 subjects in the MYF2001 8.9 mg/kg group with 1 treatment-related SAE each (Grade 5 haemorrhage), Grade 3 pancytopenia, and Grade 3 aneurysm ruptured).

Applicant Table 53: Summary of Treatment-emergent SAEs That Occurred in ≥ 2 subjects Overall – Study MDS3001 – Phase 2 and Phase 3 (Treated Population)

System Organ Class Preferred Term	Phase 3		Phase 2	Imetelstat
	Imetelstat (N = 118)	Placebo (N = 59)	Imetelstat (N = 57)	Pooled (N = 175)
Subjects with ≥ 1 treatment-emergent SAE	38 (32.2%)	13 (22.0%)	27 (47.4%)	65 (37.1%)
Infections and infestations	14 (11.9%)	8 (13.6%)	10 (17.5%)	24 (13.7%)
Pneumonia	3 (2.5%)	1 (1.7%)	2 (3.5%)	5 (2.9%)
COVID-19 pneumonia	2 (1.7%)	3 (5.1%)	1 (1.8%)	3 (1.7%)
Sepsis	2 (1.7%)	0	1 (1.8%)	3 (1.7%)
Urinary tract infection	2 (1.7%)	0	1 (1.8%)	3 (1.7%)
Febrile neutropenia	1 (0.8%)	0	1 (1.8%)	2 (1.1%)
Abscess limb	0	2 (3.4%)	0	0
Cardiac disorders	7 (5.9%)	3 (5.1%)	3 (5.3%)	10 (5.7%)
Cardiac failure	3 (2.5%)	0 ^a	2 (3.5%)	5 (2.9%)
Atrial fibrillation	2 (1.7%)	0	0	2 (1.1%)

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System Organ Class Preferred Term	Phase 3		Phase 2	Imetelstat
	Imetelstat (N = 118)	Placebo (N = 59)	Imetelstat (N = 57)	Pooled (N = 175)
Blood and lymphatic system disorders	4 (3.4%)	0	5 (8.8%)	9 (5.1%)
Anaemia	3 (2.5%)	0	1 (1.8%)	4 (2.3%)
Thrombocytopenia	0	0	2 (3.5%)	2 (1.1%)
Injury, poisoning and procedural complications	4 (3.4%)	1 (1.7%)	6 (10.5%)	10 (5.7%)
Femur fracture	2 (1.7%)	1 (1.7%)	3 (5.3%)	5 (2.9%)
Hip fracture	1 (0.8%)	0	1 (1.8%)	2 (1.1%)
Gastrointestinal disorders	4 (3.4%)	2 (3.4%)	7 (12.3%)	11 (6.3%)
Oesophageal varices haemorrhage	1 (0.8%)	0	1 (1.8%)	2 (1.1%)
General disorders and administration site conditions	4 (3.4%)	0	0	4 (2.3%)
Pyrexia	2 (1.7%)	0	0	2 (1.1%)
Nervous system disorders	2 (1.7%)	0	4 (7.0%)	6 (3.4%)
Syncope	2 (1.7%)	0	0	2 (1.1%)

SAE = serious adverse event.

^a One subject in the placebo group also had an SAE of Grade 3 cardiac failure congestive.

Note: Adverse events were coded using MedDRA) Version 25.0.

Source: Table tae02g, Table tae02h

The Applicant's Position:

The most frequently reported SAEs in the Phase 3 imetelstat group occurred in ≤ 2.5% of subjects each and included anaemia, cardiac failure, and pneumonia. The most commonly reported SAEs in the placebo group were COVID-19 pneumonia and abscess limb.

There were no major differences in the types and frequencies of SAEs reported in the MDS3001 Phase 2 imetelstat group compared to MDS3001 Phase 3 imetelstat group, and no major differences from the overall monotherapy pool, except for lower incidence of COVID-19 SAEs as most of the corresponding studies were completed prior to the start of the pandemic.

The FDA's Assessment:

A total of 156 SAEs were observed in 78 patients, including 27 (47%) receiving imetelstat in the phase 2 portion of the study, 38 (32%) receiving imetelstat in the phase 3 portion of the study, and 13 (22%) receiving placebo (Table 54).

In general, the risk of SAEs appeared to be higher in the phase 2 portion of the study, possibly related to differences in patient characteristics at baseline. However, overall, SAE were higher in patients receiving imetelstat in either part of the study compared to placebo.

The risk of SAEs of cytopenias (anemia, thrombocytopenia, neutropenia), infections including sepsis, cardiac failure, hypertension, and fractures were more commonly seen in patients treated with imetelstat on either part of the study compared to placebo. Neutropenia and complications of neutropenia (infections) were more common in patients receiving imetelstat in either study cohort compared to placebo. Thrombocytopenia as an SAE was seen in the phase 2 portion of the study, but not in either arm of the phase 3 portion. However, SAE of hemorrhage was seen more often in the imetelstat cohorts.

Table 54: Serious adverse events by study arm

Event term	Imetelstat phase 2 N=57	Imetelstat phase 3 N=118	Placebo N=59	RD
Any	27 (47)	38 (32)	13 (22)	+10.2
Sepsis*	3 (5)	5 (4.2)	0	+4.2
Fracture*	4 (7)	4 (3.4)	1 (1.7)	+1.7
Pneumonia	2 (3.5)	4 (3.4)	2 (3.4)	0
Cardiac failure*	3 (5)	3 (2.5)	1 (1.7)	+0.8
Anemia***	2 (3.5)	3 (2.5)	0	+2.5
Hemorrhage**	6 (11)	3 (2.5)	1 (1.7)	+0.8
Hypertension*	1 (1.8)	1 (0.8)	0	+0.8
Thrombocytopenia*	2 (3.5)	0	0	0

Source: FDA analysis

Data cut-off date 13 October 2022

RD=risk difference between imetelstat phase 3 and placebo

*Grouped term

**Narrow SMQ

***HLGT

No additional SAE were reported in the 120-day safety update.

Clinical Reviewer comments: Cytopenias and events associated with cytopenias (bleeding, cardiac failure, infections) were more common SAE in the imetelstat arm. This is expected given the known risk profile of imetelstat but does highlight that the cytopenias may have serious consequences for patients receiving imetelstat. SAE of hemorrhage and sepsis were less common in patients receiving imetelstat on the phase 3 portion of the study versus the phase 2. This may reflect differences in the patient populations or differences in reporting and the decision to label an event as serious or not.

Serious fractures were also more common among patients receiving imetelstat compared to placebo. The reason for this finding is unclear and should be correlated with results of overall risk profile.

Hypertension and cardiac failure as SAEs were rare in the imetelstat groups but were consistently observed with imetelstat and not seen or more rarely seen in the placebo arm of the phase 3 portion of the study. These findings may suggest a cardiac or vascular risk related to imetelstat. However, correlation with overall findings is needed.

Also see overall AE, grade 3+ AE, and treatment modification for AEs for further characterization of events.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

In the MDS3001 Phase 3 imetelstat group (N = 118), 14.4% of subjects discontinued imetelstat treatment due to a TEAE ([Applicant Table 55](#)). The median time to study treatment discontinuation due to a TEAE was 21.1 weeks (range: 2.3 to 44.0) in the imetelstat group (MDS3001 CSR [Phase 3]/Table tsix18_p2). The most commonly reported TEAE leading to study treatment withdrawal was neutropenia in 5.1% of subjects, followed by thrombocytopenia in 3.4% of subjects. All other TEAEs leading to study treatment withdrawal in the imetelstat group were reported in 1 subject each. Eleven (9.3%) subjects had TEAEs leading to imetelstat discontinuation that were considered related to imetelstat, including 6 subjects with Grade 3/4 neutropenia, 4 subjects with Grade 2/3 thrombocytopenia, and 1 subject each with Grade 4 sepsis, Grade 3 renal abscess, Grade 3 atrial fibrillation, and Grade 2 pruritus (MDS3001 CSR [Phase 3]/Listing lsfae01_p2).

No subjects in the MDS3001 Phase 3 placebo group (N = 59) discontinued study treatment due to a TEAE.

In the MDS3001-Phase 2 imetelstat group (N = 57), 28.1% subjects discontinued study treatment due to a TEAE ([Applicant Table 55](#)). The most commonly reported TEAE leading to study treatment withdrawal was thrombocytopenia in 12.3% of subjects, followed by neutropenia in 8.8% of subjects. All other TEAEs leading to study treatment withdrawal were reported in 1 subject each. The median time to the first TEAE that led to study treatment withdrawal was 29.9 weeks (range: 1.6 to 112.7 weeks) (MDS3001 CSR [Phase 2]/Table tsix18_p1). Nine subjects had TEAEs leading to study treatment withdrawal that were considered related to treatment, including 5 subjects with Grade 3/4 thrombocytopenia, 3 subjects with Grade 3/4 neutropenia, 1 subject with Grade 3 cardiac failure, and 1 subject with Grade 3 diarrhoea (Listing lae02d).

In the pool of subjects from all hematologic malignancy monotherapy studies (N = 391), 17.1% of subjects discontinued study treatment due to a TEAE (Table tae02r). Similar to LR MDS subjects, the most commonly reported TEAEs leading to study treatment withdrawal were thrombocytopenia in 4.6% of subjects and neutropenia in 4.3% of subjects. Other TEAEs leading

to study treatment withdrawal that were reported in ≥ 2 subjects included leukocytosis, cardiac failure, and dyspnoea (0.8% each); and leukopenia, asthenia, and sepsis (0.5% each).

Applicant Table 55: Treatment-emergent Adverse Events Leading to Treatment Withdrawal – Study MDS3001 – Phase 2 and Phase 3 (Treated Population)

System Organ Class / Preferred Term	Phase 3		Phase 2	Imetelstat
	Imetelstat (N = 118)	Placebo (N = 59)	Imetelstat (N = 57)	Pooled (N = 175)
Subjects experiencing TEAE leading to withdrawal from treatment	17 (14.4%)	0	16 (28.1%)	33 (18.9%)
Blood and lymphatic system disorders	10 (8.5%)	0		
Neutropenia	6 (5.1%)	0	5 (8.8%)	11 (6.3%)
Thrombocytopenia	4 (3.4%)	0	7 (12.3%)	11 (6.3%)
Anaemia	1 (0.8%)	0	0	1 (0.6%)
Cardiac disorders	2 (1.7%)	0		
Cardiac failure	1 (0.8%)	0	1 (1.8%)	2 (1.1%)
Atrial fibrillation	1 (0.8%)	0	0	1 (0.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (1.7%)	0	1 (1.8%)	3 (1.7%)
Lung neoplasm malignant	1 (0.8%)	0	0	1 (0.6%)
Myelofibrosis	1 (0.8%)	0	0	1 (0.6%)
Transitional cell carcinoma	0	0	1 (1.8%)	1 (0.6%)
Gastrointestinal disorders	1 (0.8%)	0	1 (1.8%)	2 (1.1%)
Gastrointestinal haemorrhage	1 (0.8%)	0	0	1 (0.6%)
Diarrhoea	0	0	1 (1.8%)	1 (0.6%)
General disorders and administration site conditions	1 (0.8%)	0	0	1 (1.8%)
Asthenia	1 (0.8%)	0	0	1 (0.6%)
Infections and infestations	1 (0.8%)	0	1 (1.8%)	2 (1.1%)
Renal abscess	1 (0.8%)	0	0	1 (0.6%)
Sepsis	1 (0.8%)	0	0	1 (0.6%)
Pneumonia	0	0	1 (1.8%)	1 (0.6%)
Injury, poisoning and procedural complications	1 (0.8%)	0	1 (1.8%)	2 (1.1%)
Joint dislocation	1 (0.8%)	0	0	1 (0.6%)
Craniocerebral injury	0	0	1 (1.8%)	1 (0.6%)
Psychiatric disorders	1 (0.8%)	0	0	1 (0.6%)
Disorientation	1 (0.8%)	0	0	1 (0.6%)
Respiratory, thoracic and mediastinal disorders	1 (0.8%)	0	0	1 (0.6%)
Dyspnoea	1 (0.8%)	0	0	1 (0.6%)

System Organ Class / Preferred Term	Phase 3		Phase 2	Imetelstat
	Imetelstat (N = 118)	Placebo (N = 59)	Imetelstat (N = 57)	Pooled (N = 175)
Skin and subcutaneous tissue disorders	1 (0.8%)	0	0	1 (0.6%)
Pruritus	1 (0.8%)	0	0	1 (0.6%)

TEAE = treatment-emergent adverse event.

Note: Medical Dictionary for Regulatory Activities (MedDRA) v25.0 was used for TEAE coding.

Source: Table tae02p, Table tae02q

The Applicant's Position:

Overall, reasons for discontinuation of imetelstat were similar across studies with cytopenias being the most common TEAEs leading to drug withdrawal. In the MDS3001 Phase 3 pivotal study, the proportion of subjects who withdrew from treatment due to AEs was relatively low (< 20%) due to added measures for managing cytopenias implemented in the study. The remaining TEAEs leading to treatment discontinuation occurred in 1 subject each without any prevalent SOC.

The FDA's Assessment:

Treatment discontinuation due to adverse events was required in 36 patients on study, all of whom received imetelstat. In addition, treatment discontinuation or withholding was required for non-treatment emergent AEs in 9 patients. The Sponsor clarified that in these cases, treatment was being held due to a TEAE and further events led to treatment withdrawal or further dose delay.

Although we agree that the Sponsor's approach seems reasonable in general, further evaluation of non-TEAE leading to treatment modification, including discontinuation and continued withholding, was undertaken to determine whether TEAE may have contributed to the later non-TEAE (e.g., neutropenia contributing to later infection). Fourteen non-TEAE that led to dose modification in 9 patients and any relevant related events are described below:

- Patient (b) (6) was treated on the phase 2 portion of the study. The patient experienced congestive heart failure leading to treatment discontinuation on study day 234. Treatment was interrupted for this patient at day 106 due to disseminated tuberculosis. Neutropenia of up to grade 3 was noted in this patient.
- Patient (b) (6) was treated on the imetelstat arm of the phase 3 portion of the study. The patient experienced study drug interruption due to thrombocytopenia on days 139-160 of the study. It is noted that treatment was initially interrupted due to thrombocytopenia occurring on treatment at day 133.
- Patient (b) (6) was treated on the placebo arm of the phase 3 portion of the study had treatment was interrupted on study day 126 in this patient due multiorgan failure that

was ultimately fatal. Treatment had been previously interrupted due to COVID-19 pneumonia. No neutropenia was reported.

- Patient (b) (6) was treated on the imetelstat arm of the phase 3 portion of the study and had treatment discontinued due to development of B-cell lymphoma on study day 267. Treatment had previously been interrupted due to COVID-19 infection.
- Patient (b) (6) was treated on the imetelstat arm of the phase 3 portion of the study and had treatment discontinued on study day 42 due to COVID-19 pneumonia that was ultimately fatal. It is unclear when or whether treatment was stopped since no other events that led to dose modification were documented. The last event documented as treatment emergent was bacterial pneumonia occurring on day 27.
- Patient (b) (6) was treated with imetelstat on the phase 3 component of the study and had treatment withdrawn due to cardiac failure congestive and physical deconditioning on study day 94. The patient had previously experienced GI bleeding and left femur dislocation on study days 25 and 29. The action taken with study drug for these events was also listed as treatment discontinued. The events of congestive cardiac failure and physical deconditioning were listed as starting on days 47 and 36, respectively.
- Patient (b) (6) was treated on the imetelstat arm of the phase 3 component of the study and had treatment interrupted due to febrile neutropenia on day 216. Treatment was interrupted on study day 210-211 for the treatment emergent events of thrombocytopenia and neutropenia.
- Patient (b) (6) was treated on the placebo arm of the phase 3 component and had study treatment interrupted due to thrombocytopenia that started on days 345 and 356. The patient had previously had treatment interrupted on day 303 due to thrombocytopenia.
- Patient (b) (6) was treated on the imetelstat arm of the phase 3 component and had treatment discontinued due to hepatic cirrhosis that was first documented on study day 413. Treatment had been previously interrupted due to cirrhosis and ascites noted on study day 361.

Clinical Reviewer comments: One patient on the imetelstat phase 2 portion of the study discontinued due to a non-TEAE. Of note, this patient had previously interrupted treatment due to disseminated tuberculosis and discontinuation was due to cardiac failure, which could be related to disseminated TB. However, this is speculative.

Among patients on the imetelstat phase 3 portion of the study, four discontinued treatment due to non-TEAE, including one patient each with congestive heart failure and physical deconditioning, hepatic cirrhosis, COVID-19 pneumonia, and B-cell lymphoma. All events that were considered non-treatment emergent were documented as starting within 2 months of the last dose of study medication.

Treatment was held in one patient on the placebo arm due to thrombocytopenia and treatment continued to be withheld after >30 days due to continued thrombocytopenia. This patient later discontinued participation due to progressive disease.

Table 56: Treatment emergent adverse events leading to treatment discontinuation by study arm

	Imetelstat N=57 n (%)	Imetelstat Ph 3 N=118 n (%)	Placebo N=59 n (%)	RD*
Overall	16 (28)	17 (14)	0	+14
Neutropenia	5 (9)	6 (5)	0	+5
Thrombocytopenia	7 (12)	4 (3.4)	0	+3.4
Infection**	1 (1.8)	1 (0.8)	0	+1.7

*Risk difference between imetelstat phase 3 arm and placebo

**Event in SOC infections and infestations

Source: FDA analysis

Based on initial submission data cut-off date **13 October 2022**

	Imetelstat N=57 n (%)	Imetelstat Ph 3 N=118 n (%)	Placebo N=59 n (%)	RD*
Overall	16 (28)	18 (15)	2 (3.4)	+12
Neutropenia	5 (9)	6 (5)	0	+5
Thrombocytopenia	7 (12)	5 (4.2)	0	+4.2
Infection**	1 (1.8)	1 (0.8)	1 (1.7)	-0.8

*Risk difference between imetelstat phase 3 arm and placebo

**Event in SOC infections and infestations

Source: FDA analysis

Based on 120-day safety update, data cut-off date **10 May 2023**

No treatment discontinuations were required for TEAE in the placebo arm. In the imetelstat arm of the phase 3 component and in the imetelstat phase 2 component, neutropenia, thrombocytopenia, and infection were the most common reasons for treatment discontinuation. All other events leading to treatment discontinuation occurred in a single patient.

Clinical Reviewer comments: Patients receiving imetelstat were more likely to need to discontinue due to AE, primarily cytopenias, compared to patients who received placebo. Among patients who discontinued due to AEs that occurred or worsened while not receiving treatment, discontinuation was frequently due to events related to TEAE, including infectious complications, thrombocytopenia, and cirrhosis.

Overall, treatment discontinuation was seen more frequently in patients receiving imetelstat, suggesting that there were issues with tolerance of the medication.

Dose Interruption/Reduction Due to Adverse Effects

Data:

In the MDS3001 Phase 3 imetelstat group (N = 118), 68.6% of subjects had TEAEs leading to cycle delay, and neutropenia (50.8%) and thrombocytopenia (33.1%) were the most frequently reported ([Applicant Table 57](#)). The median time to cycle delay due to a TEAE in the imetelstat group was 4.0 weeks (range: 2.0 to 84.0 weeks). TEAEs leading to dose reduction were reported for 49.2% of subjects, with neutropenia (33.1%) and thrombocytopenia (22.9%) the most commonly reported ([Applicant Table 58](#)). The median time to imetelstat dose reduction due to a TEAE was 10.5 weeks (range: 2.0 to 78.9 weeks).

In the MDS3001 Phase 3 placebo group (N = 59), 23.7% of subjects had a TEAE that led to cycle delay, including COVID-19, ALT increased, COVID-19 pneumonia, diarrhoea, and gastroenteritis in 2 (3.4%) subjects each. Four (6.8%) subjects had a TEAE that led to dose reduction. The median time to cycle delay due to an AE was 6.4 weeks (range: 3.0 to 48.0 weeks) and median time to dose reduction was 14.6 weeks (range: 6.4 to 47.0 weeks) (MDS3001 CSR [Phase 3]/Table tsix18_p2).

In the MDS3001-Phase 2 study (N = 57), 66.7% subjects had TEAEs that led to cycle delay, and neutropenia (49.1%) and thrombocytopenia (40.4%) were the most frequently reported ([Applicant Table 57](#)). The median time to the first TEAE that led to cycle delay was 4.0 weeks (range: 2.0 to 88.0 weeks) (MDS3001 CSR [Phase 2]/Table tsix18_p1). A total of 52.6% subjects had TEAEs that led to dose reduction ([Applicant Table 58](#)). The majority of dose reductions were due to neutropenia (43.9%) and thrombocytopenia (28.1%). Overall, the type and frequency of TEAEs leading to cycle delay or dose reduction were consistent between the Phase 2 and Phase 3 imetelstat groups.

For subjects in the total hematologic malignancy monotherapy group (N = 391), TEAEs leading to dose reduction were reported in 31.5% of subjects. The majority of dose reductions in Group C were due to neutropenia (19.4%) and thrombocytopenia (15.6%) subjects (Table tae02u).

Applicant Table 57: Treatment-emergent Adverse Events Leading to Cycle Delay in 2 or More Subjects in Any Treatment Group – Study MDS3001 – Phase 2 and Phase 3 (Treated Population)

System Organ Class Preferred Term	Phase 3		Phase 2	Imetelstat
	Imetelstat (N = 118)	Placebo (N = 59)	Imetelstat (N = 57)	Pooled (N = 175)
Subjects experiencing TEAE leading to cycle delay	81 (68.6%)	14 (23.7%)	38 (66.7%)	119 (68.0%)
Blood and lymphatic system disorders	76 (64.4%)	3 (5.1%)	34 (59.6%)	110 (62.9%)
Neutropenia	60 (50.8%)	1 (1.7%)	28 (49.1%)	88 (50.3%)
Thrombocytopenia	55 (46.6%)	1 (1.7%)	23 (40.4%)	78 (44.6%)
Leukopenia	4 (3.4%)	0	6 (10.5%)	10 (5.7%)
Anaemia	2 (1.7%)	1 (1.7%)	1 (1.8%)	3 (1.7%)
Infections and infestations	17 (14.4%)	7 (11.9%)	8 (14.0%)	25 (14.3%)
COVID-19	9 (7.6%)	2 (3.4%)	0	9 (5.1%)
Urinary tract infection	3 (2.5%)	0	2 (3.5%)	5 (2.9%)
Bronchitis	0	1 (1.7%)	2 (3.5%)	2 (1.1%)
General disorders and administration site conditions	6 (5.1%)	2 (3.4%)	0	6 (3.4%)
Pyrexia	3 (2.5%)	0	0	3 (1.7%)
Respiratory, thoracic and mediastinal disorders	4 (3.4%)	0	2 (3.5%)	6 (3.4%)
Epistaxis	2 (1.7%)	0	0	2 (1.1%)
Investigations	3 (2.5%)	2 (3.4%)	2 (3.5%)	5 (2.9%)
Aspartate aminotransferase increased	2 (1.7%)	1 (1.7%)	1 (1.8%)	3 (1.7%)
Alanine aminotransferase increased	1 (0.8%)	2 (3.4%)	0	1 (0.6%)
Renal and urinary disorders	3 (2.5%)	0	2 (3.5%)	5 (2.9%)
Renal impairment	2 (1.7%)	0	0	2 (1.1%)
Gastrointestinal disorders	2 (1.7%)	4 (6.8%)	3 (5.3%)	5 (2.9%)
Diarrhoea	0	2 (3.4%)	0	0

TEAE = treatment-emergent adverse event.

Note: Medical Dictionary for Regulatory Activities (MedDRA) v25.0 was used for TEAE coding.

Source: Table tsfae18_p2, Table tae02z

Applicant Table 58: Treatment-emergent Adverse Events Leading to Dose Reduction – Study MDS3001 – Phase 2 and Phase 3 (Treated Population)

System Organ Class Preferred Term	Phase 3		Phase 2	Imetelstat
	Imetelstat (N = 118)	Placebo (N = 59)	Imetelstat (N = 57)	Pooled (N = 175)
Subjects experiencing TEAE leading to dose reduction	58 (49.2%)	4 (6.8%)	30 (52.6%)	88 (50.3%)
Blood and lymphatic system disorders	56 (47.5%)	2 (3.4%)	30 (52.6%)	86 (49.1%)
Neutropenia	39 (33.1%)	1 (1.7%)	25 (43.9%)	64 (36.6%)
Thrombocytopenia	27 (22.9%)	1 (1.7%)	16 (28.1%)	43 (24.6%)
Leukopenia	2 (1.7%)	0	3 (5.3%)	5 (2.9%)
General disorders and administration site conditions	1 (0.8%)	0	0	1 (0.6%)
Fatigue	1 (0.8%)	0	0	1 (0.6%)
Infections and infestations	1 (0.8%)	0	0	1 (0.6%)
Neutropenic sepsis	1 (0.8%)	0	0	1 (0.6%)
Investigations	1 (0.8%)	2 (3.4%)	1 (1.8%)	2 (1.1%)
Alanine aminotransferase increased	1 (0.8%)	2 (3.4%)	0	1 (0.6%)
Aspartate aminotransferase increased	1 (0.8%)	1 (1.7%)	1 (1.8%)	2 (1.1%)
Gamma-glutamyltransferase increased	0	2 (3.4%)	0	0

TEAE = treatment-emergent adverse event

Note: Medical Dictionary for Regulatory Activities (MedDRA) v25.0 was used for TEAE coding.

Source: Table tsfae16_p2, Table tae02t.

The Applicant's Position:

Most dose delays and dose reductions with imetelstat treatment were due to neutropenia or thrombocytopenia. These dose modifications enabled subjects to stay on study drug as demonstrated by the overall low number of discontinuations in comparison to dose modifications. In the Phase 3 study, dose reductions of imetlestat occurred later during treatment (median 10.5 weeks [range: 2.0 to 78.9 weeks]), suggesting that subjects were able to receive the full planned dose of 7.1 mg/kg imetelstat long enough to achieve a response (see Dose/Dose Response in [Section 8.1.2](#)).

The FDA's Assessment:

The table below shows the incidence of dose reductions and most common reasons for requirement of dose reduction in patients on MDS3001. Other AE of interest leading to dose

reductions in one patient each in the imetelstat arm of the phase 3 portion included transaminase elevation and neutropenic sepsis.

Table 59: Common treatment emergent adverse events leading to dose reductions by study arm and part of study

	Imetelstat N=57 n (%)	Imetelstat Ph 3 N=118 n (%)	Placebo N=59 n (%)	Risk difference*
Any	30 (53)	58 (49)	4 (7)	+42
Neutropenia	25 (44)	39 (33)	1 (1.7)	+31
Thrombocytopenia	16 (28)	27 (23)	1 (1.7)	+21
Leukopenia	3 (5)	2 (1.7)	0	+2.3

*Risk difference between patients treated on the imetelstat arm of the phase 3 portion of the study and those treated with placebo

Source: FDA analysis

Data cut-off date 13 October 2022

Table 60: Median (range) number of dose reductions, time to dose reduction, and number (%) of patients requiring cycle delay due to adverse events

	Imetelstat N=30 ¹	Imetelstat Ph 3 N=58 ¹	Placebo N=4
Total number of events	64	106	8
NPP (median (range))	2 (1,5)	2 (1,4)	2 (1,3)
TTE (median (range))	71 (1,845)	99 (15,554)	104 (49,330)
# events in cycles 1-3 (n (%)) ²	37 (58)	66 (62)	1 (13)
# patients in cycles 1-3 (n (%)) ³	23 (77)	38 (66)	1 (25)
Duration (median (range))	11 (3,400)	10 (2,88)	15 (4,35)
Cycle delay? (n (%)) ²	58 (91)	94 (89)	5 (63)

NPP=number per patient; TTE=time to event; Cycles 1-3 indicates events occurring in cycles 1-3

1 Includes only patients who required dose reduction

2 Percentage indicates percent of events

3 Percentage indicates number of patients who experienced events in cycles 1-3 out of the total number of patients experiencing at least one event

Source: FDA analysis

Data cut-off 13 October 2022

There were more TEAE leading to dose decrease among patients treated with imetelstat on the phase 2 portion of the study as well as in the imetelstat arm of the phase 3 portion of the study compared to placebo, with 49% of patients on the imetelstat arm experiencing at least one dose reduction versus 7% on the placebo arm. Common TEAE leading to dose reduction included neutropenia, thrombocytopenia, and leukopenia. The number of events per patient and duration of events were similar in the imetelstat arm and placebo arm of the phase 3 portion of the study. However, the number of events requiring cycle delay as well as dose

reduction was higher in the imetelstat arm, with 89% of events leading to dose reduction in the imetelstat arm also requiring treatment delay, compared to 63% in the placebo arm.

Of note, the majority of events leading to dose reduction in the imetelstat arm (66%) occurred in cycles 1-3, whereas only one event in the placebo arm occurred in cycles 1-3.

Clinical Reviewer comment: The requirement for dose reduction generally occurred early in the course of treatment with imetelstat, although the time to the event was similar in the imetelstat and placebo arms.

Table 61: Treatment emergent adverse events leading to treatment interruption or delay by study arm.

	Imetelstat N=57 n (%)	Imetelstat Ph 3 N=118 n (%)	Placebo N=59 n (%)	RD ¹
Any	37	92 (78)	15 (25)	+53
Infusion interrupted	5 (9)	7 (6)	0	+6
Infusion aborted	4 (7)	1 (0.8) ²	0	+0.8
Cycles 1-3 ³	25 (44)	72 (61)	10 (17)	+44
Specific TEAE				
Thrombocytopenia	21 (36)	56 (47)	0	+47
Neutropenia	24 (42)	59 (50)	0	+50
Infections	10 (18)	19 (16)	8 (14)	+2
Leukopenia	5 (9)	4 (3.4)	0	+3.4
Hepatic toxicity ⁴	1 (1.8)	3 (2.5)	2 (3.4)	-0.8

¹ Risk difference between imetelstat phase 3 arm and placebo

² The action taken associated with this event was “Drug withdrawn”

³ Number of patients requiring dose delay in cycles 1-3

⁴ Includes hepatotoxicity, AST increased, ascites

Source: FDA analysis

Data cut-off date October 2022

TEAE leading to treatment interruption or delay occurred in the majority of patients receiving imetelstat on either arm. On the phase 3 portion of the study, the risk difference between imetelstat and placebo was +53. Infusion interruptions or abortions were relatively uncommon, occurring in 6% and <1%, respectively, of patients on the imetelstat arm of the phase 3 portion and no patients on the placebo arm. Similar to dose reduction, a large number of the events leading to treatment interruption occurred in cycles 1-3.

The most common reasons for treatment delay in patients receiving imetelstat was neutropenia or thrombocytopenia. No patient receiving placebo required a treatment delay for neutropenia or thrombocytopenia. Other common reasons for treatment delay included

leukopenia, infections, and hepatotoxicity. With the exception of hepatotoxicity, each of these events were more common in the imetelstat arm.

Clinical Reviewer comments: Patients receiving imetelstat had a high probability of requiring dose reduction, treatment delay, or both during the study, with nearly half and over ¾ of patients on the imetelstat arm of the phase 3 component requiring dose reduction and treatment delay, respectively. Neutropenia, thrombocytopenia, and infections were the cause of treatment delay or dose reduction in the majority of cases in the imetelstat arm, whereas neutropenia or thrombocytopenia leading to dose modification was rare in the placebo arm.

Treatment modifications, including dose decrease, were seen most commonly in cycles 1-3. However, some patients required treatment modification as late as cycle 13 or greater, suggesting that there are ongoing tolerability issues with imetelstat.

Overall, the dose modification data suggest that the dose of imetelstat used in this study is not tolerable and that, at minimum, close monitoring would be needed to ensure that patients do not develop life threatening complications from treatment.

Significant Adverse Events

Data:

Grade 3/4 TEAEs were reported in 90.7% subjects in the MDS3001 Phase 3 imetelstat group (N = 118) and 47.5% subjects in the MDS3001 Phase 3 placebo group (N = 59) ([Applicant Table 62](#)). The most commonly reported Grade 3/4 TEAE was neutropenia, reported in 67.8% and 3.4% of subjects in the imetelstat and placebo groups, respectively, followed by thrombocytopenia (61.9% and 8.5%, respectively), and anaemia (19.5% and 6.8%, respectively). Most of these events were considered related to study treatment ([Applicant Table 55](#)). See [Section 8.2.5](#) for further discussion of neutropenia and thrombocytopenia. Grade 3/4 TEAEs were most commonly reported in the Blood and lymphatic system disorders SOC in both the imetelstat (83.9%) and placebo (16.9%) groups.

In the MDS3001 Phase 2 imetelstat group (N = 57), Grade 3/4 TEAEs were reported in 87.7% of subjects ([Applicant Table 62](#)). The most commonly reported Grade 3/4 TEAE was neutropenia, reported in 59.6% of subjects, followed by thrombocytopenia in 54.4% of subjects, and anaemia and leukopenia in 19.3% of subjects each. Most of these events were considered related to study treatment ([Applicant Table 58](#)). Grade 3/4 TEAEs were most commonly reported in the Blood and lymphatic system disorders SOC (70.2%).

In the overall monotherapy grouping (N = 391), Grade 3/4 TEAEs were reported in 88.2% subjects (Table tae04c). As in the LR MDS subjects, the most commonly reported Grade 3/4 TEAEs were thrombocytopenia (46.8%), neutropenia (45.3%), anaemia (33.2%), leukopenia (12.5%), and fatigue (5.9%). All other Grade 3/4 TEAEs were reported in < 5% of subjects. Most of these events were considered related to study treatment (Table tae04i).

Applicant Table 62: Treatment-emergent Adverse Events with Worst Severity of Grade 3 or Grade 4 Reported in ≥ 5% of Subjects in Any Group – Study MDS3001 – Phase 2 and Phase 3 (Treated Population)

System Organ Class Preferred Term	Phase 3		Phase 2	Pooled
	Imetelstat (N = 118) n (%)	Placebo (N = 59) n (%)	Imetelstat (N = 57) n (%)	Imetelstat (N = 175) n (%)
Subjects with any Grade 3 or Grade 4 TEAE	106 (89.8%)	27 (45.8%)	45 (78.9%)	151 (86.3%)
Blood and lymphatic system disorders	99 (83.9%)	10 (16.9%)	40 (70.2%)	139 (79.4%)
Neutropenia	80 (67.8%)	2 (3.4%)	34 (59.6%)	114 (65.1%)
Thrombocytopenia	73 (61.9%)	5 (8.5%)	31 (54.4%)	104 (59.4%)
Anaemia	23 (19.5%)	4 (6.8%)	11 (19.3%)	34 (19.4%)
Leukopenia	9 (7.6%)	0	11 (19.3%)	20 (11.4%)
Febrile neutropenia	1 (0.8%)	0	3 (5.3%)	4 (2.3%)
Investigations	6 (5.1%)	2 (3.4%)	7 (12.3%)	13 (7.4%)
Alanine aminotransferase increased	3 (2.5%)	2 (3.4%)	3 (5.3%)	6 (3.4%)
Aspartate aminotransferase increased	0	0	3 (5.3%)	3 (1.7%)
Vascular disorders	3 (2.5%)	2 (3.4%)	8 (14.0%)	11 (6.3%)
Hypertension	3 (2.5%)	0	5 (8.8%)	8 (4.6%)
Injury, poisoning and procedural complications	5 (4.2%)	1 (1.7%)	7 (12.3%)	12 (6.9%)
Femur fracture	2 (1.7%)	1 (1.7%)	3 (5.3%)	5 (2.9%)
Musculoskeletal and connective tissue disorders	2 (1.7%)	4 (6.8%)	5 (8.8%)	7 (4.0%)
Back pain	1 (0.8%)	1 (1.7%)	3 (5.3%)	4 (2.3%)
Infections and infestations	12 (10.2%)	8 (13.6%)	12 (21.1%)	24 (13.7%)
Bronchitis	0	0	3 (5.3%)	3 (1.7%)
COVID-19 pneumonia	2 (1.7%)	3 (5.1%)	0	2 (1.1%)

Source: Table tae04a, Table tae04b, Table tae02a, Table tae02b

Note: Medical Dictionary for Regulatory Activities (MedDRA) v25.0 was used for TEAE coding.

PT = preferred term; TEAE = treatment-emergent adverse event

The Applicant's Position:

The most commonly reported Grade 3/4 TEAEs in MDS3001 Phase 3 imetelstat-treated subjects were neutropenia and thrombocytopenia, reported in approximately 2/3 of subjects, and approximately half of all subjects had Grade 3/4 TEAEs considered related to imetelstat. These events are manageable with cycle delays and dose reductions and are generally reversible (see [Section 8.2.5](#)). The most commonly reported Grade 3/4 TEAEs in the placebo group were thrombocytopenia and anaemia, reported in < 10% each.

The type and frequency of Grade 3/4 events reported in Phase 2 and in the overall hematological malignancy grouping were similar to those in the Phase 3 imetelstat group.

No new safety signals were observed following review of the overall hematologic malignancy monotherapy grouping.

The FDA's Assessment:

Grade 3+ AEs were observed more frequently in patients treated with imetelstat in the phase 2 and phase 3 portions of the study compared to placebo (Table 63).

Differences of greater than 50 percent units were observed in grade 3-4 AE of neutropenia and thrombocytopenia in the imetelstat arm of the phase 3 portion compared to the placebo arm, with a similar frequency of events seen in the phase 2 study. Anemia and leukopenia were less common in imetelstat treated patients, but a large risk difference was seen when compared with patients treated with placebo.

Sepsis, hypertension, fractures, and cardiac failure were seen more frequently in the imetelstat treated cohorts, although the differences compared to placebo were smaller than the differences in grade 3 or higher cytopenias. As noted earlier, SAE of cardiac failure, sepsis, hypertension, and fractures were seen more frequently in patients treated with imetelstat compared to placebo.

Four patients in the phase 2 cohort and three in the imetelstat arm of the phase 3 component had grade 3 or higher events of neoplasm. All events consisted of a secondary malignancy or premalignant condition, rather than a complication or progression of the underlying MDS. Specific events included cholangiocarcinoma, hepatocellular carcinoma, transitional cell carcinoma of the bladder, renal cell carcinoma, bladder papilloma, and lung neoplasm. Of note, lung carcinoma and transitional cell carcinoma each occurred in two patients.

Table 63: Grade 3-4 treatment emergent adverse events by study phase and arm

Adverse event	Imetelstat Phase 2 N=57	Imetelstat Phase 3 N=118	Placebo N=59	RD
Any	50 (88)	107 (91)	28 (47)	+44
Any excluding neutropenia and thrombocytopenia	40 (70)	64 (54)	23 (39)	+16
Neutropenia	34 (60)	80 (68)	2 (3.4)	+65
Thrombocytopenia	31 (54)	73 (62)	5 (9)	+53
Anemia	13 (23)	23 (20)	4 (7)	+13
Leukopenia	11 (19)	9 (8)	0	+8
Sepsis	3 (5)	5 (4.2)	0	+4.2
Hypertension	5 (9)	4 (3.4)	0	+2.5
Neoplasms	4 (7)	3 (2.5)	0	+2.5
Fractures	4 (7)	4 (3.4)	1 (1.7)	+1.7

Cardiac failure	3 (5)	5 (3.4)	1 (1.7)	+1.7

RD=risk difference between imetelstat arm of phase 3 portion of the study and placebo

Source: FDA analysis

Data cut-off date 10 May 2023

Clinical Reviewer comments: Grade 3-4 AE were higher in patients receiving imetelstat versus placebo in the phase 3 portion of the study. Since the majority of events in the imetelstat arm were neutropenia and thrombocytopenia, an analysis of events when these terms were excluded was performed and showed a continued, if smaller, difference between study arms. Similar rates of grade 3-4 AE in the phase 2 portion of the study support the possibility of causality.

We note that the laboratory data (see below) do not support a higher incidence of grade 3-4 hemoglobin decreased in the imetelstat arm. The reason for the higher rate of the adverse event of anemia being reported is unclear. In addition, cardiac failure was seen more frequently as a SAE and as a grade 3-4 event but was not higher overall. Thus, the relationship between imetelstat and cardiac failure is uncertain.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Adverse Events

An overview of TEAEs for subjects in Phase 2 and Phase 3 of MDS3001 is provided in [Applicant Table 64](#) and for all subjects in the hematologic malignancy monotherapy grouping in [Applicant Table 65](#).

Applicant Table 64: Overview of Treatment-emergent Adverse Events – Study MDS3001 – Phase 2 and Phase 3 (Treated Population)

Subjects with ≥ 1:	Phase 3		Phase 2	Pooled
	Imetelstat (N = 118)	Placebo (N = 59)	Imetelstat (N = 57)	Imetelstat (N = 175)
TEAE ^a				
Any	117 (99.2%)	59 (100.0%)	56 (98.2%)	173 (98.9%)
Grade 3 or higher	107 (90.7%)	28 (47.5%)	50 (87.7%)	157 (89.7%)
Grade 5 (fatal)	1 (0.8%)	1 (1.7%)	5 (8.8%)	6 (3.4%)
Study drug-related TEAE ^b				
Any	97 (82.2%)	20 (33.9%)	50 (87.7%)	147 (84.0%)
Grade 3 or higher	85 (72.0%)	6 (10.2%)	43 (75.4%)	128 (73.1%)
Grade 5 (fatal)	0	0	0	0
Treatment-emergent SAE	38 (32.2%)	13 (22.0%)	27 (47.4%)	65 (37.1%)
Study drug-related treatment-emergent SAE	6 (5.1%)	0	9 (15.8%)	15 (8.6%)

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Subjects with ≥ 1 :	Phase 3		Phase 2	Pooled
	Imetelstat (N = 118)	Placebo (N = 59)	Imetelstat (N = 57)	Imetelstat (N = 175)
TEAE leading to treatment discontinuation	17 (14.4%)	0	16 (28.1%)	33 (18.9%)
Study drug-related TEAE leading to treatment discontinuation	11 (9.3%)	0	9 (15.8%)	20 (11.4%)
TEAEs leading to infusion interruption/abortion	7 (5.9%)	0	6 (10.5%)	13 (7.4%)
TEAEs leading to dose reduction or cycle delays	83 (70.3%)	14 (23.7%)	38 (66.7%)	121 (69.1%)

SAE = serious adverse event; TEAE = treatment-emergent adverse event.

^a Treatment-emergent AEs are defined as events that occur or worsen after the first dose of study drug.

Treatment-emergent events that were identified for each individual study are used for the pooled analyses.

^b Study drug relationship is based on investigator assessment.

Source: Table tae01a, Table tae01b

Applicant Table 65: Overview of Treatment-emergent Adverse Events – Studies MDS3001, CP14B013, CP14B015, CP14B019, MYF2001 – Phase 2 and 3 Imetelstat (Treated Population)

Subjects with ≥ 1 :	Imetelstat ^f			
	<7.1 mg/kg ^a q4w (N = 48)	7.1 mg/kg ^b q4w (N = 204)	>7.1 mg/kg ^c q4w (N = 139)	Total Pooled (N = 391)
TEAE ^d				
Any	47 (97.9%)	202 (99.0%)	139 (100.0%)	388 (99.2%)
Grade 3 or higher	38 (79.2%)	180 (88.2%)	127 (91.4%)	345 (88.2%)
Grade 5 (fatal)	3 (6.3%)	8 (3.9%)	4 (2.9%)	15 (3.8%)
Study drug-related TEAE ^e				
Any	29 (60.4%)	174 (85.3%)	122 (87.8%)	325 (83.1%)
Grade 3 or higher	18 (37.5%)	138 (67.6%)	79 (56.8%)	235 (60.1%)
Grade 5 (fatal)	0	0	1 (0.7%)	1 (0.3%)
Treatment-emergent SAE	21 (43.8%)	89 (43.6%)	82 (59.0%)	192 (49.1%)
Study drug-related treatment-emergent SAE	6 (12.5%)	25 (12.3%)	51 (36.7%)	82 (21.0%)
TEAE leading to treatment discontinuation	10 (20.8%)	36 (17.6%)	21 (15.1%)	67 (17.1%)
Study drug-related TEAE leading to treatment discontinuation	2 (4.2%)	21 (10.3%)	17 (12.2%)	40 (10.2%)

q4w = once every 4 weeks; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

^a MYF2001 4.4 mg/kg arm only

^b CP14B019 Arms E and G; MDS3001 Phase 2 and 3 (Imetelstat); CP14B015 and CP14B013 7.5 mg/kg arm

^c CP14B019 Arms A, B, D, and F; CP14B015, CP14B013, and MYF2001 8.9 mg/kg arm

^d Treatment-emergent AEs are defined as events that occur or worsen after the first dose of study drug.

Treatment-emergent events that were identified for each individual study are used for the pooled analyses.

^e Study drug relationship is based on investigator assessment.

^f Doses in this table (including the footnotes) are shown for the active moiety (free acid). To convert a quantity of imetelstat salt to the equivalent quantity of imetelstat, a factor of 0.9416 based on relative molar mass of the free acid form (4610 g/mol) to the sodium salt (4896 g/mol; 4610/4896 = 0.9416) is applied (i.e., 1 mg imetelstat sodium = 0.9416 mg imetelstat).

Note: Medical Dictionary for Regulatory Activities (MedDRA) v25.0 was used for TEAE coding.

Source: Table tae01c

Common Adverse Events

In the MDS3001 Phase 3 imetelstat group (N = 118), the most commonly reported TEAEs by PT were thrombocytopenia (75.4%) and neutropenia (73.7%), followed by anaemia (20.3%), asthenia (18.6%), and COVID-19 (15.3%) (Applicant Table 66). In the placebo group (N = 59), the most commonly reported TEAEs by PT were asthenia and oedema peripheral in (13.6% each), and diarrhoea, constipation, and pyrexia (11.9% each).

The SOC with the highest incidence of TEAEs in the MDS3001 Phase 3 imetelstat group was Blood and lymphatic system disorders (89.0%), followed by Infections and infestations (42.4%), General disorders and administration site conditions (41.5%), and Gastrointestinal disorders (34.7%). In the Phase 3 placebo group, the highest incidence of TEAEs were in the SOC of General disorders and administration site conditions (47.5%), Gastrointestinal disorders (40.7%), Infections and infestations (33.9%), and Metabolism and nutrition disorders (25.4%). The most commonly reported TEAEs by PT in the Phase 2 imetelstat group were neutropenia (66.7%) and thrombocytopenia (61.4%), followed by anaemia (24.6%), headache (22.8%), and leukopenia and pyrexia (19.3% each) (Applicant Table 66). In the Phase 2 imetelstat group, the highest incidence of TEAEs were in the SOC of Blood and lymphatic system disorders (77.2%), Infections and infestations (57.9%), General disorders and administration site conditions (54.4%), and Gastrointestinal disorders and Musculoskeletal and connective tissue disorders (49.1%) each.

In the overall hematologic malignancy monotherapy grouping (N = 391), the types and frequencies of any-grade TEAEs differed based on the subjects' underlying disease. Compared to MDS3001, higher incidences of fatigue and gastrointestinal events (diarrhoea, nausea) were reported, as well as lower rates of cytopenias, due to lower rates reported in MF and ET/PV subjects in Studies MYF2001, CB14B019, and CB14B015.

Applicant Table 66: Treatment-emergent Adverse Events Reported in ≥ 10% in Any Group – Study MDS3001 – Phase 2 and Phase 3 (Treated Population)

System Organ Class Preferred Term	Phase 3		Phase 2	Pooled
	Imetelstat (N = 118)	Placebo (N = 59)	Imetelstat (N = 57)	Imetelstat (N = 175)
Subjects experiencing at least one TEAE	117 (99.2%)	59 (100.0%)	56 (98.2%)	173 (98.9%)
Blood and lymphatic system disorders	105 (89.0%)	14 (23.7%)	40 (70.2%)	149 (85.1%)

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 TRADENAME, imetelstat

System Organ Class Preferred Term	Phase 3		Phase 2	Pooled
	Imetelstat (N = 118)	Placebo (N = 59)	Imetelstat (N = 57)	Imetelstat (N = 175)
Thrombocytopenia	89 (75.4%)	6 (10.2%)	35 (61.4%)	124 (70.9%)
Neutropenia	87 (73.7%)	4 (6.8%)	38 (66.7%)	125 (71.4%)
Anaemia	24 (20.3%)	6 (10.2%)	14 (24.6%)	38 (21.7%)
Leukopenia	12 (10.2%)	1 (1.7%)	11 (19.3%)	23 (13.1%)
Infections and infestations	50 (42.4%)	20 (33.9%)	33 (57.9%)	83 (47.4%)
COVID-19	18 (15.3%)	4 (6.8%)	0	18 (10.3%)
Urinary tract infection	7 (5.9%)	2 (3.4%)	10 (17.5%)	17 (9.7%)
Nasopharyngitis	1 (0.8%)	2 (3.4%)	7 (12.3%)	8 (4.6%)
Bronchitis	0	1 (1.7%)	7 (12.3%)	7 (4.0%)
General disorders and administration site conditions	49 (41.5%)	28 (47.5%)	31 (54.4%)	80 (45.7%)
Asthenia	22 (18.6%)	8 (13.6%)	6 (10.5%)	28 (16.0%)
Oedema peripheral	13 (11.0%)	8 (13.6%)	8 (14.0%)	21 (12.0%)
Fatigue	11 (9.3%)	5 (8.5%)	7 (12.3%)	18 (10.3%)
Pyrexia	9 (7.6%)	7 (11.9%)	11 (19.3%)	20 (11.4%)
Gastrointestinal disorders	41 (34.7%)	24 (40.7%)	28 (49.1%)	69 (39.4%)
Diarrhoea	14 (11.9%)	7 (11.9%)	10 (17.5%)	24 (13.7%)
Constipation	9 (7.6%)	7 (11.9%)	8 (14.0%)	17 (9.7%)
Nausea	7 (5.9%)	3 (5.1%)	7 (12.3%)	14 (8.0%)
Abdominal pain	7 (5.9%)	2 (3.4%)	6 (10.5%)	13 (7.4%)
Vomiting	2 (1.7%)	1 (1.7%)	7 (12.3%)	9 (5.1%)
Musculoskeletal and connective tissue disorders	35 (29.7%)	13 (22.0%)	28 (49.1%)	63 (36.0%)
Back pain	10 (8.5%)	4 (6.8%)	10 (17.5%)	20 (11.4%)
Muscle spasms	4 (3.4%)	0	6 (10.5%)	10 (5.7%)
Nervous system disorders	34 (28.8%)	14 (23.7%)	24 (42.1%)	58 (33.1%)
Headache	15 (12.7%)	3 (5.1%)	13 (22.8%)	28 (16.0%)
Investigations	32 (27.1%)	9 (15.3%)	21 (36.8%)	53 (30.3%)
Alanine aminotransferase increased	14 (11.9%)	4 (6.8%)	10 (17.5%)	24 (13.7%)
Aspartate aminotransferase increased	11 (9.3%)	4 (6.8%)	8 (14.0%)	19 (10.9%)
Respiratory, thoracic and mediastinal disorders	21 (17.8%)	8 (13.6%)	18 (31.6%)	39 (22.3%)

Version date: June 2022 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

System Organ Class Preferred Term	Phase 3		Phase 2	Pooled
	Imetelstat (N = 118)	Placebo (N = 59)	Imetelstat (N = 57)	Imetelstat (N = 175)
Dyspnoea	10 (8.5%)	5 (8.5%)	6 (10.5%)	16 (9.1%)
Cough	0	2 (3.4%)	6 (10.5%)	6 (3.4%)
Renal and urinary disorders	10 (8.5%)	3 (5.1%)	13 (22.8%)	23 (13.1%)
Haematuria	2 (1.7%)	0	6 (10.5%)	8 (4.6%)

TEAE = treatment-emergent adverse event.

Note: Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0.

Source: Table tsfae03_p2, Table tae02b

Adverse Drug Reactions

All TEAEs were reviewed in the initial selection of adverse drug reactions (ADRs) for imetelstat primarily based on the MDS3001 Phase 3 study due to the double-blind placebo-controlled design and the inclusion of the population for which imetelstat is intended. The initial focus was TEAEs (all grades) that occurred with a frequency of $\geq 5\%$ in the imetelstat group, occurring $\geq 2\%$ higher in the imetelstat group compared to placebo ([Applicant Table 67](#)). These cut offs were determined based on the size of the population being treated in the MDS3001 Phase 3 study. In addition, the TEAEs occurring $< 5\%$ but $> 2\%$ were reviewed and assessed for inclusion based on severity and relevance. All Grade 3 or higher TEAEs and serious TEAEs occurring $\geq 2\%$ of subjects in the imetelstat group were also reviewed. To ensure the identification of any potential signals for less common events, all TEAEs not meeting these criteria were also reviewed. PTs were grouped where appropriate. Selection was based on the magnitude of difference in incidence between imetelstat and placebo, biological plausibility, consistency in time to onset, dechallenge/rechallenge/ information, the presence of alternative explanations, nonclinical data, and frequency expected in the treated population along with applied medical judgement.

Adverse events reflective of laboratory measurements were considered based on worsening of laboratory values, given the high prevalence of laboratory abnormalities in this subject population and higher degree of accuracy in the laboratory values compared to AE reporting, in order to provide the most conservative frequencies ([Applicant Table 68](#)).

Applicant Table 67: Adverse Reactions (≥ 5%) in Patients Receiving Imetelstat with a Difference Between Groups ≥ 2% in MDS3001 Phase 3

System Organ Class Preferred term	Imetelstat N = 118		Placebo N = 59	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
General disorders and administration site conditions				
Asthenia ^a	32 (27.1%)	0	13 (22.0%)	1 (1.7%)
Nervous system disorders				
Headache	15 (12.7%)	1 (0.8%)	3 (5.1%)	0
Musculoskeletal and connective tissue disorders				
Arthralgia	10 (8.5%)	0	2 (3.4%)	1 (1.7%)
Immune system disorders				
Infusion related reactions	9 (7.6%)	2 (1.7%)	2 (3.4%)	0
Skin and subcutaneous tissue disorders				
Pruritus	7 (5.9%)	0	1 (1.7%)	0
Respiratory, thoracic and mediastinal disorders				
Epistaxis	7 (5.9%)	0	0	0
Vascular disorders				
Haematoma	6 (5.1%)	0	0	0

Source: MDS3001 CSR (Phase 3)/Table adr02

^a Includes Asthenia and Fatigue

Applicant Table 68: Laboratory Abnormalities Worsened Since Baseline in Study MDS3001 Phase 3

Laboratory Parameter	Imetelstat N = 118				Placebo N = 59			
	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Hematology								
Thrombocytopenia	19 (16.1%)	17 (14.4%)	51 (43.2%)	26 (22.0%)	10 (16.9%)	5 (8.5%)	3 (5.1%)	2 (3.4%)
Neutropenia	5 (4.2%)	19 (16.1%)	55 (46.6%)	29 (24.6%)	9 (15.3%)	15 (25.4%)	3 (5.1%)	1 (1.7%)
Chemistry								
AST increased	50 (42.4%)	6 (5.1%)	1 (0.8%)	0	10 (16.9%)	2 (3.4%)	1 (1.7%)	0
ALP increased	48 (40.7%)	5 (4.2%)	0	0	7 (11.9%)	0	0	0

Source: MDS3001 CSR (Phase 3)/Table adr01

ALP = alkaline phosphatase; AST = aspartate aminotransferase

The Applicant's Position:

The most commonly reported TEAEs in the MDS3001 Phase 3 imetelstat group were thrombocytopenia and neutropenia, reported in approximately 3/4 of subjects, and approximately 2/3 of subjects had thrombocytopenia and neutropenia considered related to imetelstat. These were also the most commonly reported Grade 3/4 TEAEs. Thrombocytopenia and neutropenia occurred more frequently during the early months of treatment and decreased over time, suggesting a lack of cumulative toxicity. The most commonly reported TEAEs in the placebo group were asthenia and oedema peripheral, reported in < 15% of subjects. The most commonly reported Grade 3/4 TEAEs in the placebo group were thrombocytopenia and anaemia, reported in < 10% each.

Grade 3/4 TEAEs are manageable with cycle delays and dose reductions and are generally reversible (discussed [Section 8.2.5](#)).

The profile of any-grade TEAEs reported in Phase 2, including the most common TEAEs, the timing of TEAEs, and the profile of treatment-related TEAEs, was similar to and supportive of the Phase 3 results.

No new safety signals were observed after review of the broader hematologic malignancy monotherapy population of 391 subjects that would alter the safety profile and management of imetelstat treatment.

The FDA's Assessment:

We do not agree with the Applicant's overall assessment of adverse events as described above. In particular, the Sponsor's analysis minimizes or fails to document the extent and severity of a number of adverse events, including cytopenias, infection, and bleeding, and does not comment on several potential signals as discussed below.

Table 69: Treatment emergent adverse events overview

TEAE	Imetelstat N=118 n (%)	Placebo N=59 n (%)	Risk difference
Overall TEAE	117 (99)	59 (100)	-0.8
Serious Adverse Events	38 (32)	13 (22)	+10
Grade 3-4 TEAE	107 (91)	28 (47)	+44
Grade 3-4 TEAE excluding neutropenia and thrombocytopenia	64 (54)	23 (39)	+16
Fatal TEAE	1 (0.8)	1 (1.7)	-0.8
Deaths (including not related to TEAE)	19 (16)	8 (14)	+2
TEAE leading to any dose modification	102 (86)	15 (25)	+61
Discontinuation	17 (14)	0	+14
Dose decrease	58 (49)	4 (7)	+42
Dose interruption	92 (78)	15 (25)	+53

Source: FDA analysis

Data cut-off date 13 October 2022

As the table above makes clear, the rate of SAE, grade 3-4 TEAE, and AE leading to dose modifications of any type (discontinuation, decrease, or interruption) are higher in the imetelstat arm. Because cytopenias are a significant risk with imetelstat and might obscure other issues, the rate of grade 3-4 AEs excluding neutropenia and thrombocytopenia was examined and a higher rate of grade 3-4 AEs was still observed in the imetelstat arm. It is important to note that none of the grade 3-4 events of neutropenia or thrombocytopenia were considered by the Applicant to be SAE. The rate of AEs described in the 120-day safety update is provided below for completeness. No substantial change in the overall pattern of AE was observed.

Table 70: Treatment emergent adverse events overview, 120-day safety update

TEAE	Imetelstat N=118 n (%)	Placebo N=59 n (%)	Risk difference
Overall TEAE	117 (99)	59 (100)	-0.8
Serious Adverse Events	38 (32)	13 (22)	+10
Grade 3-4 TEAE	108 (92)	29 (49)	+43

Grade 3-4 TEAE excluding neutropenia and thrombocytopenia	67 (57)	24 (41)	+16
Fatal TEAE	1 (0.8)	2 (3.4)	-0.8
Deaths on study (including non-TEAE)	28 (24)	13 (22)	+2
TEAE leading to any dose modification	103 (87)	15 (25)	+62
Discontinuation	18 (15)	2 (3.4)	+12
Dose decrease	58 (49)	4 (7)	+42
Dose interruption	94 (80)	15 (25)	+55

Source: FDA analysis

Data cut-off date 10 May 2023

Clinical Reviewer comments: Imetelstat showed more severe toxicity, including SAE, grade 3-4 AE, and TEAE leading to dose modification than placebo. Further details will be discussed below.

Specific commonly occurring TEAE are described below in Table 71 and Table 72.

Table 71: Adverse events by frequency, treatment phase, and study arm (initial submission)

Adverse event	Imetelstat Phase 2 N=57	Imetelstat Phase 3 N=118	Placebo N=59	RD
Any	56 (98)	117 (99)	59 (100)	-1
Neutropenia ¹	38 (67)	87 (74)	4 (7)	+67
Thrombocytopenia ¹	35 (61)	89 (75)	6 (10)	+65
Anemia ²	26 (28)	24 (20)	6 (10)	+10
Hepatic disorders ¹	16 (28)	30 (25)	9 (15)	+10
Infections ³	33 (58)	50 (42)	20 (33)	+9
Hemorrhage ⁴	19 (33)	24 (21)	7 (12)	+9
Leukopenia	11 (19)	12 (10)	1 (1.7)	+8
Arthralgia/myalgia ¹	18 (32)	29 (25)	10 (17)	+8
Headache	13 (23)	15 (13)	3 (5)	+8
Fatigue ¹	14 (25)	34 (29)	13 (22)	+7
Syncope ¹	1 (1.8)	7 (6)	1 (1.7)	+4.3
Pruritus ¹	2 (3.5)	7 (6)	1 (1.7)	+4.3
Sepsis ¹	3 (5)	5 (4.2)	0	+4.2
COVID-19 ¹	1 (1.8)	21 (18)	8 (14)	+4
Atrial fibrillation	0	6 (5.1)	1 (1.7)	+3.4
Fractures ¹	6 (11)	6 (5)	1 (1.7)	+3.3
Neoplasms ³	5 (9)	7 (6)	2 (3.3)	+2.7
Hypertension ¹	5 (9)	3 (2.5)	0	+2.5
Renal dysfunction ¹	2 (3.5)	5 (4.2)	1 (1.7)	+2.5

¹Custom grouped term

NDA/BLA Multi-disciplinary Review and Evaluation NDA 217779 imetelstat
 TRADENAME, imetelstat

²High level grouped term

³ SOC

⁴Narrow SMQ

RD=risk difference comparing imetelstat phase 3 to placebo

Source: FDA analysis

Data cut-off date 13 October 2022

Table 72: Treatment emergent adverse events by frequency, study phase, and arm (120-day safety update)

Adverse event	Imetelstat Phase 2 N=57	Imetelstat Phase 3 N=118	Placebo N=59	RD
Any	56 (98)	117 (99)	59 (100)	-0.8
Neutropenia ¹	38 (67)	89 (75)	5 (9)	+66
Thrombocytopenia ¹	35 (61)	89 (75)	6 (10)	+65
Infections ²	33 (58)	55 (47)	20 (34)	+13
Anemia ³	26 (28)	26 (22)	7 (12)	+10
Hemorrhage ⁴	19 (33)	26 (22)	7 (12)	+10
Fatigue ¹	14 (25)	34 (29)	12 (20)	+9
Hepatic disorders ¹	16 (28)	31 (26)	10 (17)	+9
Leukopenia	11 (19)	12 (10)	1 (1.7)	+8
Headache	13 (23)	15 (13)	3 (5)	+8
Syncope ¹	4 (7)	9 (8)	1 (1.7)	+6.3
Arthralgia/myalgia ¹	18 (32)	30 (25)	11 (19)	+6
COVID-19 ¹	1 (1.8)	22 (19)	8 (14)	+5
Neoplasms ²	5 (9)	9 (8)	2 (3.4)	+4.6
Fractures ¹	6 (11)	6 (5)	1 (1.7)	+4.3
Pruritus	2 (3.5)	7 (6)	1 (1.7)	+4.3
Atrial fibrillation	0	7 (6)	1 (1.7)	+4.3
Sepsis ¹	3 (5)	5 (4.2)	0	+4.2
Bone pain	0	4 (3.4)	0	+3.4
Hypertension ¹	5 (9)	4 (3.4)	0	+3.4
Renal dysfunction ¹	2 (3.5)	5 (4.2)	1 (1.7)	+2.5
Abdominal pain ¹	14 (25)	14 (12)	7 (12)	0
Pneumonia ¹	6 (11)	6 (5)	3 (5)	0
URI ¹	13 (23)	10 (8)	5 (8)	0
VTE ¹	0	2 (1.7)	1 (1.7)	0
Cardiac failure ¹	3 (5)	4 (3.4)	3 (5)	-1.6
AOE ¹	4 (7)	4 (3.4)	4 (7)	-3.6
Dizziness ¹	7 (12)	10 (8)	7 (12)	-4

¹ Custom grouped term

² SOC

Version date: June 2022 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

3 High level grouped term

4 Broad SMQ

RD=risk difference between patients who received imetelstat in the phase 3 portion of the study and placebo

Source: FDA analysis

Data cut-off date 10 May 2023

Cytopenias were more common overall in patients treated with imetelstat in both parts 1 and 2 of the study compared to those treated with placebo. Of note, anemia was at least 10 percent units higher in both imetelstat groups. However, we note that this finding was not confirmed in the laboratory data (below). Cytopenias will be discussed in further detail in the laboratory findings section of the review.

Issues that might be expected to co-occur with cytopenias, including sepsis, hemorrhage, and fatigue, were seen more frequently in patients treated with imetelstat as well. COVID-19 infections were more common in patients treated with imetelstat in part 2, but not in part 1, probably reflecting the timing of enrollment and treatment in each part of the study. A more detailed comparison of infectious complications is described below in Table 104.

In addition, patients receiving imetelstat were more likely to experience hepatic disorders compared to patients receiving placebo. This finding was consistent across both cohorts of patients receiving imetelstat. Also see laboratory results for further discussion of hepatotoxicity.

Musculoskeletal issues, including fractures and arthralgia/myalgia, were seen more commonly in patients treated with imetelstat compared to placebo, across both cohorts of patients receiving imetelstat, suggesting a potential causative connection, although the mechanism of action is not clear.

Although SAE of cardiac failure was more common in patients treated with imetelstat, there was little difference in the overall rate of cardiac failure among patients treated with imetelstat compared to placebo, with a risk difference of +1.7 units for patients treated in part 1 and +1.8 units in patients treated on part 2. In addition, hypertension and atrial fibrillation were observed more commonly among patients receiving imetelstat than those receiving placebo.

The neurologic events of headache and syncope were more common in patients receiving imetelstat compared to placebo. In addition, pruritus and renal dysfunction were observed more frequently in patients treated with imetelstat.

Clinical Reviewer comments: Review of the adverse events occurring in trial MDS3001 reveal potential risks of cytopenias, hepatic toxicity, cardiac toxicity, fractures, and arthralgia/myalgia. Cytopenias and related AEs, musculoskeletal toxicities, and hepatic toxicity were consistently seen more frequently in patients treated with imetelstat and the risk differences were generally

high. Cardiac toxicity, neurologic events, renal dysfunction, and pruritus were seen more frequently in patients treated with imetelstat, but with smaller risk differences and, for some events, with inconsistent results (i.e., more frequent events in one of the imetelstat cohorts.) See below for correlation with events in the ISS overall and in other subpopulations.

In order to further characterize the risk of TEAE in patients receiving imetelstat, an analysis of patients in the integrated safety database was performed. As noted above, patients in the ISS were treated for a variety of malignancies, including solid tumors, MDS, myeloproliferative neoplasms, and other hematologic malignancies. In addition, multiple doses and dosing schedules were examined in various tumor types and imetelstat was given with other chemotherapeutic agents in some studies. Of note, of studies which currently have data available, only MDS3001 included a placebo arm. Thus, all patients who received placebo were being treated for lower risk MDS. (Also see section 8.2.3 above for details of the grouping of imetelstat doses.) Combination regimens were excluded as there is significant confounding related to other chemotherapeutics used.

Table 73: Treatment emergent adverse events in overall development program by dose

	Low dose N=54	Recommended dose N=190	High dose N=296	Placebo N=59
Any	53 (98)	188 (99)	296 (100)	59 (100)
Any gr 3-4	41 (76)	168 (88)	242 (82)	28 (47)
Any fatal	4 (7)	6 (3)	25 (8)	1 (0.8)
Neutropenia ¹	6 (11)	138 (73)	275 (93)	4 (7)
Thrombocytopenia	11 (20)	137 (72)	184 (62)	6 (10)
Infections ²	21 (39)	86 (45)	119 (40)	20 (34)
Fatigue ¹	23 (43)	62 (33)	190 (64)	13 (22)
Arthralgia/myalgia ¹	22 (41)	56 (30)	119 (40)	10 (17)
Abdominal pain ¹	19 (35)	31 (16)	90 (30)	7 (12)
Hemorrhage ³	12 (22)	50 (26)	142* (47)	7 (12)
Pruritus ¹	12 (22)	10 (5)	30 (10)	1 (1.7)
Dizziness ¹	7 (13)	30 (16)	49 (17)	8 (14)
Anemia ⁴	16 (30)	48 (25)	125 (42)	6 (10)
Headache	6 (11)	28 (15)	45 (15)	3 (5)
Hepatic disorders ¹	3 (6)	50 (26)	108 (36)	9 (15)
Fractures ¹	0	13 (7)	8 (2.7)	1 (1.7)

*Includes all terms in SMQ hemorrhage, including laboratory terms. When laboratory terms are removed, 61 (21%) of patients experienced a bleeding event.

¹ Grouped term

² SOC infections and infestations

³ Broad SMQ haemorrhage

⁴ High level grouped term

Source: FDA analysis

Data cut-off date 13 October 2022

Fatal TEAEs in the lower dose group included head injury, splenic infarct, sepsis, and disease progression. Deaths in the recommended dose group were due to sepsis, COVID-19 pneumonia, femur fracture, neurodegenerative disorder, cerebrovascular accident, and thrombosis mesenteric. All occurred on trial MDS3001 and are discussed above. Among the 27 events leading to death in 25 patients treated at doses higher than 7.1 mg/kg/4 weeks, 7 were due to disease progression, five to hemorrhage, four to infection (sepsis in three, pneumonia in one), and three to cardiac arrest.

Clinical Reviewer comments: AE described in the ISS generally supported the findings from MDS3001. Of note, the rate of grade 3-4 AE, hemorrhage, infections, neutropenia, and thrombocytopenia were higher even in the lowest dose group compared to placebo. The rate of neutropenia and thrombocytopenia increased dramatically between the low dose and the standard/high doses, and an apparent dose/response was seen for all of these issues.

In addition, fatigue, arthralgia/myalgia, pruritus, dizziness, and anemia were higher at all doses of imetelstat compared to placebo. Hepatic disorders and fractures were higher in the two higher doses compared to either low dose or placebo.

These results should be interpreted with caution as differences in underlying condition, supportive care, and other factors may have contributed to the observed differences. However, in general, the findings from the ISS support those from MDS3001 and in particular the comparison of imetelstat phase 3 dose with placebo.

Specific issues identified in the review of the safety data are described below. Note that issues previously identified by the Applicant (thrombocytopenia, neutropenia, infusion related reaction, and hepatic toxicity) are discussed below in section 8.2.5.

Fractures

Fractures were observed more frequently in patients receiving imetelstat compared to those receiving placebo, as noted above.

In patients receiving imetelstat on the phase 2 portion of the study, six patients experienced fractures, including femur fracture, hip fracture, thoracic vertebral fracture, radius fracture, rib fracture, skull fracture, spinal compression fracture, and wrist fracture. Of these, only femur fracture, which was documented in three patients, occurred in more than one patient. Grade 3-4 events were documented in four patients and one fatal event of femur fracture was noted.

In the phase 3 portion of the study, fractures were documented in 6 (5%) of patients on the imetelstat arm, including two femur fractures and one each hand fracture, hip fracture, humerus fracture, and lumbar vertebrae fracture. One humerus fracture was documented in the placebo arm. Grade 3-4 events were documented in four patients on the imetelstat arm. No fatal events were documented. The one patient in the placebo arm who experienced a fracture had two grade 3 fractures. None of the fractures in either arm were associated with documented falls or other specific trauma.

In the ISS dataset, fractures were documented in 21 (3.9%) patients receiving imetelstat at any dose, including 12 (2.2%) patients in whom grade 3-4 events occurred and one death as noted above. All events occurred in patients receiving 7.1 mg/kg/4 weeks or higher and all occurred in patients receiving monotherapy.

Clinical Reviewer comments: The reason for the increased rate of fractures in patients who received imetelstat is unclear. It is noted that only one event was associated with a documented fall. However, fractures were observed in patients receiving imetelstat in both parts of MDS3001 as well as in patients who received imetelstat in other studies.

Fatigue

Fatigue was documented in 29% of patients in the imetelstat of the phase 3 portion of MDS3001 and 20% of patients on the placebo arm. A relatively high rate of fatigue (25%) was noted in the phase 2 portion as well. Fatigue was observed frequently in the ISS, with an apparent increase in incidence at higher doses, including a rate of 64% in patients who received more than 7.1 mg/kg/4 weeks and 33% in the overall population of patients who received imetelstat at 7.1 mg/kg/4 weeks. No grade 3-4 events of fatigue were observed in the imetelstat arm of the phase 3 portion of MDS3001. However, 30 (10%) of patients who received >7.1 mg/kg/4 weeks experienced grade 3 fatigue.

Clinical Reviewer comment: The higher incidence of fatigue in the imetelstat arm along with the apparent dose/effect in patients on the overall development program suggest a potential causal connection between use of imetelstat and fatigue. This effect may be somewhat ameliorated by the improved hemoglobin observed in patients with MDS.

Arthralgia/myalgia

Arthralgia and myalgia were seen more frequently in the imetelstat phase 3 arm compared to the placebo arm (25% and 19%, respectively). Arthralgia and myalgia were high in the phase 2 portion of MDS3001 as well (32%) and was elevated in patients in the total development program.

Clinical Reviewer comments: Infusion related reactions (IRR) may explain some of the increased incidence of arthralgia/myalgia in patients receiving imetelstat. However, not all events were associated with IRR and there may be a risk of arthralgia/myalgia with imetelstat use.

Cardiac Issues

The risk of cardiac TEAE with imetelstat is ambiguous. A marginally higher rate of events in the SOC cardiac disorders was observed (15% in imetelstat, 14% in placebo). A higher incidence of some events, including atrial fibrillation and hypertension, was observed with use of imetelstat. Conversely, aortic occlusive events were less common in patients receiving imetelstat (3.4% for imetelstat versus 7% for placebo). In addition, the rate of cardiac failure overall was not higher with treatment with imetelstat, but the risk of grade 3-4 cardiac failure was elevated. Syncope, which could be due to neurologic or cardiac issues, was higher in the imetelstat arm.

Clinical Reviewer comments: No conclusions can be drawn regarding risk of cardiac events and use of imetelstat. Further observations in the post-marketing setting, including longer term follow up of patients on MDS3001, other clinical trials, and in the non-clinical trial setting may identify or definitively refute a signal.

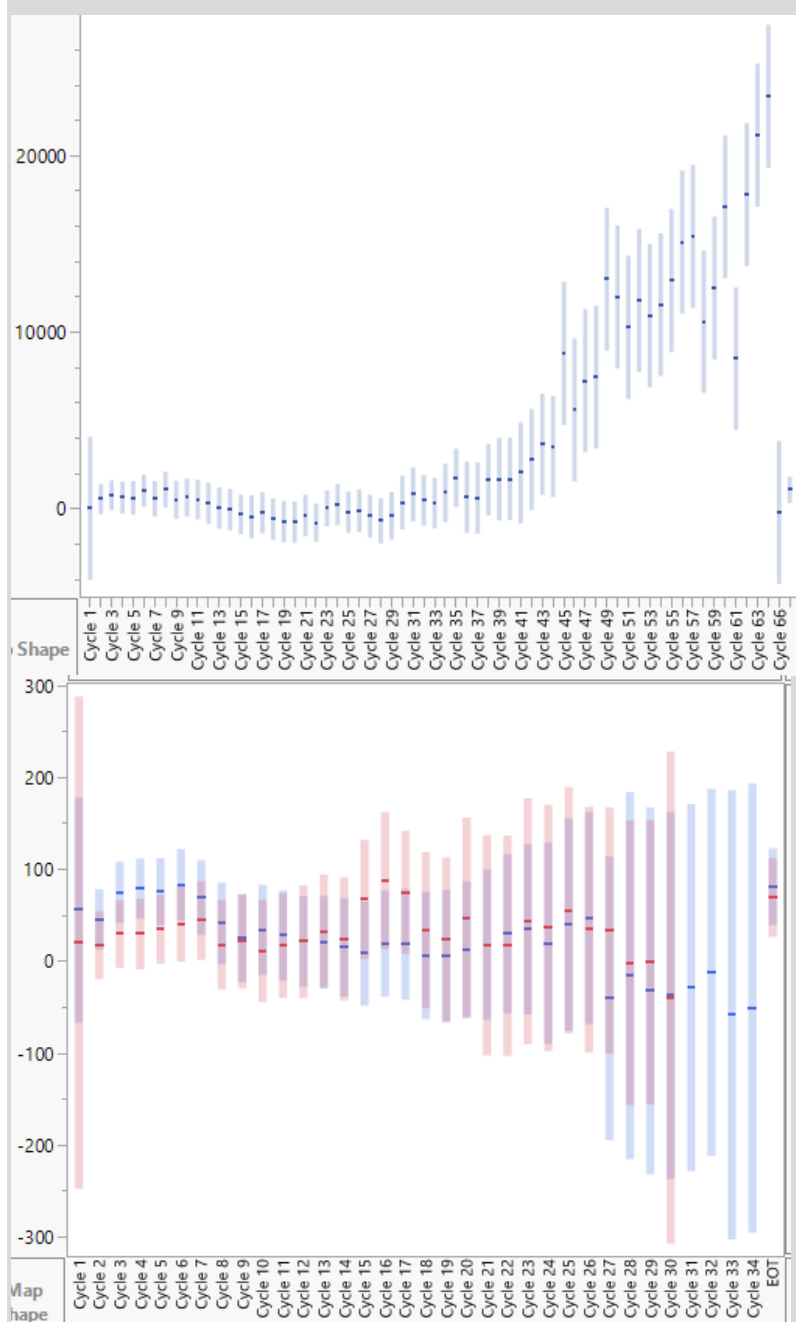
Iron Overload

The definitive test for iron overload, cardiac and hepatic MRI, was not performed in study MDS3001. Therefore, any data on changes in iron overload are tentative and may not reflect changes in total body iron.

Iron overload based on TEAE was evaluated using a custom term including preferred terms hyperferritinaemia, iron overload, serum ferritin increased, blood iron increased, hemochromatosis, and hemosiderosis. Using these terms, iron overload was documented in 7 (6%) of patients on the imetelstat arm and 8 (14%) in the placebo arm.

Ferritin was collected during the trial, although day and cycle of collection varies. Overall patterns of change in ferritin are shown below. For patients on the phase 2 portion of the study, ferritin was stable to slightly decreased compared to baseline until about cycle 39, when increased values were seen (Figure 40, part A). It should be noted that few patients continued treatment to later cycles and that this may confound the results. Ferritin levels were essentially overlapping for patients on the phase 3 part of the study (Figure 33, part B).

Figure 33: Ferritin levels during treatment for patients on a) phase 2 portion of MDS3001 and b) phase 3 portion of MDS3001. Imetelstat is represented in blue, placebo in red.



Source: FDA analysis

Based on laboratory values for ferritin from the initial submission data cut-off date 10 May 2023

Clinical Reviewer comment: No definitive conclusions can be drawn regarding the rate of iron overload observed with use of imetelstat. Based on the limited data available, there does not appear to be a major decrease in iron overload in patients receiving imetelstat. Longer term

follow up, more accurate diagnostic measures, and focus on iron status in patients who achieve long term transfusion independence may help clarify the issue.

Laboratory Findings

Laboratory findings are presented for the LR MDS population (Safety Groups A and B).

Data:

Hematology

Neutropenia

Based on laboratory assessment, most subjects (108/118 [91.5%]) in the MDS3001 Phase 3 imetelstat group (N = 118) had worsening neutropenia from baseline while on treatment ([Applicant Table 74](#)). In the placebo group (N = 59), 28/59 (47.5%) subjects had worsening neutropenia from baseline while on treatment. In the imetelstat and placebo groups, 46.6% and 5.1% of subjects, respectively, had decreased neutrophils at a maximum CTCAE Grade 3, and 24.6% and 1.7% of subjects, respectively, at a maximum CTCAE Grade 4. Median time to onset of Grade 3 or Grade 4 decreased neutrophils was 4.43 weeks (range: 1.0 to 81.0 weeks) in the imetelstat group and 13.00 weeks (range: 3.0 to 23.0 weeks) in the placebo group (Table tlab06a). Median duration of Grade 3/4 neutropenia was 1.86 weeks (range: 0.0, 15.9) in the imetelstat group and 3.36 weeks (range: 1.0, 13.9) in the placebo group.

In the MDS3001 Phase 3 imetelstat group (N = 118), 226 (81.0%) of 279 Grade 3/4 neutropenia events resolved to Grade ≤ 2 and 49 (90.7%) of Grade 4 neutropenia events resolved to Grade ≤ 3 in under 4 weeks ([Applicant Table 75](#)). In the placebo group (N = 59), 3 (50.0%) of Grade 3/4 neutropenia events resolved to Grade ≤ 2 and 1 (100.0%) Grade 4 neutropenia event resolved to Grade ≤ 3 in under 4 weeks.

Most subjects in the MDS3001 Phase 2 imetelstat group (N = 57) (93.0% of subjects) had worsening neutropenia from baseline while on treatment. Overall, 84.6% of Grade 3/4 neutropenia events resolved to Grade ≤ 2 in under 4 weeks, which included 91.4% of Grade 4 neutropenia events (Table tlab06b). Median duration of Grade 3/4 neutropenia events was 2.00 weeks (range: .01, 16.7) (Table tsflb01_p1).

Thrombocytopenia

Based on hematology laboratory measures, 95.8% of subjects in the MDS3001 Phase 3 imetelstat group (N = 118) had worsening thrombocytopenia from baseline while on treatment ([Applicant Table 74](#)). In the placebo group (N = 59), 33.9% of subjects had worsening thrombocytopenia from baseline while on treatment. Median time to onset of Grade 3 or Grade 4 decreased platelets was 6.00 weeks (range: 1.7 to 88.3 weeks) in the imetelstat group and 15.14 weeks (range: 6.4 to 40.6 weeks) in the placebo group (Table tlab06a). Median duration of Grade 3/4 thrombocytopenia was 1.43 weeks (range: 0.1, 12.6) in the imetelstat groups and 2.00 weeks (range: 0.3, 22.3) in the placebo group (Table tsflb01_p2).

In the imetelstat group (N = 118), 183 (86.3%) of 212 Grade 3/4 thrombocytopenia events resolved to Grade ≤ 2 and 40 (85.1%) of 47 Grade 4 thrombocytopenia events resolved to Grade ≤ 3 in under 4 weeks ([Applicant Table 75](#)). In the placebo group (N = 59), 4 (44.4%) of 9 Grade 3/4 thrombocytopenia events resolved to Grade ≤ 2 . Among 3 Grade 4 thrombocytopenia events, none resolved to Grade ≤ 3 in under 4 weeks and 2 were ongoing as of the data cutoff date.

In the MDS3001 Phase 2 imetelstat group (N = 57), most subjects (91.2%) had worsening thrombocytopenia while on treatment ([Applicant Table 74](#)). Median time to onset of Grade 3 or Grade 4 decreased platelets was 4.0 weeks (range: 2.0 to 89.7 weeks) (Table tlab06b). Overall, 90.8% of Grade 3/4 thrombocytopenia events resolved to Grade ≤ 2 in under 4 weeks, which included 96.8% of Grade 4 thrombocytopenia events ([Applicant Table 75](#)). Median duration of Grade 3/4 thrombocytopenia events was 1.29 weeks (range: 0.1, 15.0) (Table tsflb01_p1).

Applicant Table 74: Worst Toxicity for Neutropenia and Thrombocytopenia on Treatment – Study MDS3001 – Phase 2 and Phase 3 (Treated Population)

	Phase 3		Phase 2	Pooled
	Imetelstat (N = 118) n (%)	Placebo (N = 59) n (%)	Imetelstat (N = 57) n (%)	Imetelstat (N = 175) n (%)
Neutropenia grade at baseline				
Grade 0	97 (82.2%)	49 (83.1%)	47 (82.5%)	144 (82.3%)
Grade 1	12 (10.2%)	7 (11.9%)	9 (15.8%)	21 (12.0%)
Grade 2	8 (6.8%)	2 (3.4%)	1 (1.8%)	9 (5.1%)
Grade 3	0	1 (1.7%)	0	0
Grade 4	1 (0.8%)	0	0	1 (0.6%)
Worst neutropenia grade on treatment				
Grade 1	5 (4.2%)	9 (15.3%)	5 (8.8%)	10 (5.7%)
Grade 2	19 (16.1%)	15 (25.4%)	11 (19.3%)	30 (17.1%)
Grade 3	55 (46.6%)	3 (5.1%)	17 (29.8%)	72 (41.1%)
Grade 4	29 (24.6%)	1 (1.7%)	20 (35.1%)	49 (28.0%)
Same as baseline	10 (8.5%)	31 (52.5%)	4 (7.0%)	14 (8.0%)
Thrombocytopenia grade at baseline				
Grade 0	99 (83.9%)	48 (81.4%)	48 (84.2%)	147 (84.0%)
Grade 1	16 (13.6%)	11 (18.6%)	9 (15.8%)	25 (14.3%)
Grade 2	2 (1.7%)	0	0	2 (1.1%)
Grade 3	1 (0.8%)	0	0	1 (0.6%)
Grade 4	0	0	0	0
Worst thrombocytopenia grade on treatment				

	Phase 3		Phase 2	Pooled
	Imetelstat (N = 118) n (%)	Placebo (N = 59) n (%)	Imetelstat (N = 57) n (%)	Imetelstat (N = 175) n (%)
Grade 1	19 (16.1%)	10 (16.9%)	7 (12.3%)	26 (14.9%)
Grade 2	17 (14.4%)	5 (8.5%)	12 (21.1%)	29 (16.6%)
Grade 3	51 (43.2%)	3 (5.1%)	21 (36.8%)	72 (41.1%)
Grade 4	26 (22.0%)	2 (3.4%)	12 (21.1%)	38 (21.7%)
Same as baseline	5 (4.2%)	39 (66.1%)	5 (8.8%)	10 (5.7%)

Source: Table tlab02a, Table tlab06a, Table tlab02b, Table tlab06b

Note: Worsening is defined as Common Terminology Criteria for Adverse Events (CTCAE) grade elevated after baseline.

Applicant Table 75: Reversibility of Grade 3 or 4 Neutropenia and Thrombocytopenia Events by Lab Assessment During the Study – Study MDS3001 – Phase 2 and Phase 3 (Treated Population)

	Phase 3		Phase 2	Pooled
	Imetelstat (N = 118) n (%)	Placebo (N = 59) n (%)	Imetelstat (N = 57) n (%)	Imetelstat (N = 175) n (%)
Grade 3/4 neutropenia events	279	6	136	415
Resolved ≥ 4 weeks ^a	40 (14.3%)	2 (33.3%)	18 (13.2%)	58 (14.0%)
Resolved < 4 weeks ^a	226 (81.0%)	3 (50.0%)	115 (84.6%)	341 (82.2%)
Ongoing ^c	13 (4.7%)	1 (16.7%)	3 (2.2%)	16 (3.9%)
Grade 4 neutropenia events	54	1	35	89
Resolved ≥ 4 weeks ^b	3 (5.6%)	0	2 (5.7%)	5 (5.6%)
Resolved < 4 weeks ^b	49 (90.7%)	1 (100.0%)	32 (91.4%)	81 (91.0%)
Ongoing ^c	2 (3.7%)	0	1 (2.9%)	3 (3.4%)
Grade 3/4 thrombocytopenia events	212	9	120	332
Resolved ≥ 4 weeks ^a	17 (8.0%)	1 (11.1%)	9 (7.5%)	26 (7.8%)
Resolved < 4 weeks ^a	183 (86.3%)	4 (44.4%)	109 (90.8%)	292 (88.0%)
Ongoing ^c	12 (5.7%)	4 (44.4%)	2 (1.7%)	14 (4.2%)
Grade 4 thrombocytopenia events	47	3	31	78
Resolved ≥ 4 weeks ^b	2 (4.3%)	1 (33.3%)	1 (3.2%)	3 (3.8%)
Resolved < 4 weeks ^b	40 (85.1%)	0	30 (96.8%)	70 (89.7%)
Ongoing ^c	5 (10.6%)	2 (66.7%)	0	5 (6.4%)

Source: Table tlab05a, Table tlab05b

^a Grade 3/4 cytopenia resolved to ≤ Grade 2.

^b Grade 4 cytopenia resolved to Grade ≤ 3.

^c Ongoing may include events ongoing at time of study discontinuation or death or ongoing at the time of study cutoff. A subject can report multiple events for each lab assessment.

Coagulation

In the MDS3001 Phase 3 imetelstat group (N = 118), most subjects were within normal range at baseline for aPTT and prothrombin INR (92.8% and 76.6%, respectively) and remained within normal range during treatment (75.3% and 84.0%, respectively) (Table tlab06g, Table tlab02g). In the Phase 2 imetelstat group (N = 57), most subjects were within normal range at baseline for aPTT and prothrombin INR (88.7% and 74.5%, respectively) and remained within normal range during treatment (67.9% and 58.8%, respectively) (Table tlab06h, Table tlab02h)).

Liver Function Tests

In the MDS3001 Phase 3 imetelstat group (N = 118), worsening toxicity grades during treatment were reported for ALT (46/117 [39.3%] subjects), AST (57/118 [48.3%] subjects), ALP (53/118 [44.9%] subjects), and bilirubin (46/118 [39.0%] subjects) ([Applicant Table 76](#)). In the placebo group (N = 59), worsening toxicity grades during treatment were reported for ALT (22/59 [37.3%] subjects), AST (13/59 [22.0%] subjects), ALP (7/59 [11.9%] subjects), and bilirubin (23/59 [39.0%] subjects). There were no subjects with Grade 4 toxicities in liver function tests. All liver function test abnormalities resolved during the study.

In the MDS3001 Phase 2 imetelstat group (N = 57), worsening toxicity grades during treatment were reported for ALT (27 [47.4%] subjects), AST (27 [47.4%] subjects), ALP (19 [33.3%] subjects), and bilirubin (27 [47.4%] subjects) ([Applicant Table 76](#)).

Applicant Table 76: Maximum Postbaseline CTCAE Grade, Worsened Since Baseline for Liver Function Tests by Cycle and Overall – Study MDS3001 – Phase 2 and Phase 3 (Treated Population)

	Phase 3		Phase 2	Pooled
	Phase 3 (N = 118) n (%)	Placebo (N = 59) n (%)	Imetelstat (N = 57) n (%)	Imetelstat (N = 175) n (%)
Worst on treatment				
Alanine aminotransferase				
n	117	59	57	174
No worsening	71 (60.7%)	37 (62.7%)	30 (52.6%)	101 (58.0%)
1	36 (30.8%)	16 (27.1%)	18 (31.6%)	54 (31.0%)
2	6 (5.1%)	3 (5.1%)	6 (10.5%)	12 (6.9%)
3	4 (3.4%)	3 (5.1%)	3 (5.3%)	7 (4.0%)
4	0	0	0	0
Alkaline phosphatase				
n	118	59	57	175
No worsening	65 (55.1%)	52 (88.1%)	38 (66.7%)	103 (58.9%)
1	48 (40.7%)	7 (11.9%)	17 (29.8%)	65 (37.1%)
2	5 (4.2%)	0	2 (3.5%)	7 (4.0%)

	Phase 3		Phase 2	Pooled
	Phase 3 (N = 118) n (%)	Placebo (N = 59) n (%)	Imetelstat (N = 57) n (%)	Imetelstat (N = 175) n (%)
3	0	0	0	0
4	0	0	0	0
Aspartate aminotransferase				
n	118	59	57	175
No worsening	61 (51.7%)	46 (78.0%)	30 (52.6%)	91 (52.0%)
1	50 (42.4%)	10 (16.9%)	21 (36.8%)	71 (40.6%)
2	6 (5.1%)	2 (3.4%)	3 (5.3%)	9 (5.1%)
3	1 (0.8%)	1 (1.7%)	3 (5.3%)	4 (2.3%)
4	0	0	0	0
Bilirubin				
n	118	59	57	175
No worsening	72 (61.0%)	36 (61.0%)	30 (52.6%)	102 (58.3%)
1	28 (23.7%)	15 (25.4%)	18 (31.6%)	46 (26.3%)
2	17 (14.4%)	7 (11.9%)	7 (12.3%)	24 (13.7%)
3	1 (0.8%)	1 (1.7%)	2 (3.5%)	3 (1.7%)
4	0	0	0	0

Source: Table tlab02d, Table tlab02e

Note: Worsened defined as CTCAE grade elevated after baseline. The Grade 1-4 summaries categorize subjects according to the maximum grade among those laboratory values that have worsened since baseline.
 CTCAE = Common Terminology Criteria for Adverse Events.

The Applicant's Position:

Hematology

Neutropenia

Grade 3/4 neutropenia is very common with imetelstat and occurred more frequently during the first few cycles. These events are manageable with dose modifications and growth factor support and generally reversible. Few subjects discontinued imetelstat due to neutropenia. Moreover, the number of events of febrile neutropenia or significant infections was low across all 3 safety groups ([Applicant Table 62](#) and Table tae04c), severe infections were generally not associated with severe neutropenia, and most were not related to imetelstat treatment ([Applicant Table 102](#)). Management of neutropenia will be included in the proposed product labeling and these events will be monitored with routine post-marketing pharmacovigilance. Neutropenia as an AESI is further discussed in [Section 8.2.4](#).

Thrombocytopenia

Grade 3/4 thrombocytopenia is very common with imetelstat treatment and occurred more frequently during the first few cycles. These events are manageable with cycle delays and dose

reductions and are generally reversible. Few subjects discontinued imetelstat due to thrombocytopenia. Moreover, the number of significant bleeding events was low, the events were assessed by the investigator as not related to imetelstat treatment, and most were not associated with severe thrombocytopenia ([Applicant Table 95](#)). Monitoring for thrombocytopenia will be included in the proposed product labeling and these events will be monitored with routine post-marketing pharmacovigilance. Thrombocytopenia as an AESI is further discussed in [Section 8.2.4](#).

Coagulation

Not applicable.

Liver Function Tests

Hepatic events were primarily low grade and reversible elevations of ALT, AST, and bilirubin, have been observed in both imetelstat and placebo-treated subjects, with no apparent dose effects. No cases meeting Hy's law criteria were observed.

Hepatic events as AESIs are further discussed in [Section 8.2.4](#).

The FDA's Assessment:

We do not agree with the assessment above, which underestimates the significance and extent of cytopenias, coagulation abnormalities, and hepatic function abnormalities as well as not documenting any evaluation of electrolytes or creatinine. Details of the laboratory abnormalities are below.

Overview

Changes in hematologic, coagulation, and chemistry labs were seen in MDS3001 with differences observed between the imetelstat and placebo arms of the phase 3 portion of the trial in multiple areas. The major changes are summarized in Table 77 below.

There was a major increase in neutrophil count decreased and platelet decreased, both overall and when only grade 3-4 abnormalities were included. In addition, leukocyte count decreased was observed more commonly in patients receiving imetelstat. Of note, no difference was observed between rates of hemoglobin decreased overall or grade 3-4 only. Prolonged activated partial thromboplastin time (PTT) was seen in 22% of patients in the imetelstat arm, including two who had grade 3 prolongations.

High rates of creatinine increased, alkaline phosphatase increased, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), bilirubin increased, hyperkalemia, and hyponatremia were observed in patients on the phase 3 portion of the study. Of these, AST, ALT, and AP increased were more common in the imetelstat arm.

Table 77: Overview of common laboratory abnormalities in patients treated on the phase 3 portion of MDS3001.

Laboratory abnormality	Imetelstat N=118 (%)		Placebo N=59 (%)		Risk difference	
	All Grade	Grade 3-4	All Grade	Grade 3-4	All Grade	Grade 3-4
Hematology						
Platelets decreased	97	65	34	8	+63	+57
Leukocytes decreased	94	53	59	1.7	+36	+51
Neutrophils decreased	92	72	47	7	+45	+64
Hemoglobin decreased	64	64	64	64	0	0
PTT prolonged	26*	1.0*	17*	3.8*	+9	-2.8
PT prolonged	34*	1.0*	30*	2.2*	+4	-1.2
Chemistry						
Creatinine increased	77	0	75	0	+2	0
Alkaline phosphatase increased	48	0	12	0	+36	0
Aspartate aminotransferase increased	53	0.8	22	1.7	+31	-0.8
Alanine aminotransferase increased	43	3.4	37	5	+6	-1.6
Bilirubin increased	39	0.8	39	1.7	0	-0.8
Hyperkalemia	24	1.7	25	5	-1	-3.4
Hyponatremia	22	2.5	22	0	0	+2.5

Abnormalities occurring in >20% on either arm included. Only values that represent change compared to baseline and which occurred on treatment were included.

Source: FDA analysis using ADLB dataset

Data cutoff 10 May 2023

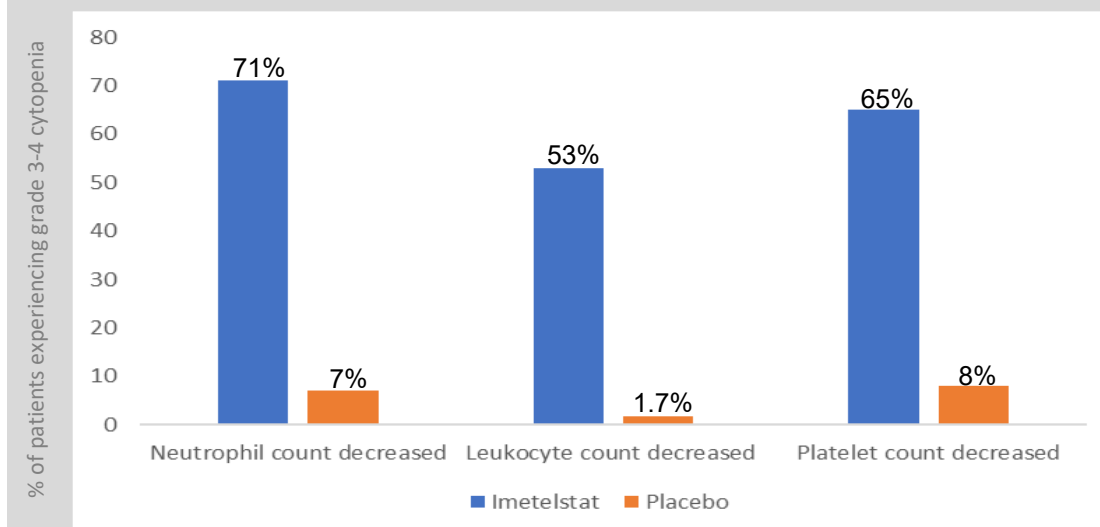
*Does not include data for patients who had no normal range defined.

Cytopenias

Based on reporting of TEAE, cytopenias, including neutropenia, thrombocytopenia, anemia, and leukopenia were seen more frequently in patients receiving imetelstat compared to those receiving placebo.

Individual cytopenias will be discussed below. This section gives a brief overview of the effects of imetelstat on hematopoiesis overall. Patients treated with imetelstat experienced more TEAEs of neutropenia, thrombocytopenia, and leukopenia, as well as more grade 3 or higher events compared to patients treated with placebo. More adverse events of anemia were reported in patients on the imetelstat arm compared to placebo as well, but the rate of hemoglobin decreased as per the laboratory datasets were similar (see below for further discussion). The rate of post-baseline laboratory abnormalities of neutropenia, thrombocytopenia, and leukopenia, however, were all higher in the imetelstat arm compared to the placebo arm (Figure 34). Laboratory values will be used to discuss the rate of cytopenias unless otherwise specified.

Figure 34: Percent of patients with grade 3-4 cytopenias and at least one grade decrease in relevant laboratory value on phase 3 portion of MDS3001



Includes only those values that represent a worsening of at least one grade compared to baseline.
 Source: FDA analysis using ADLB dataset
 Data cutoff 13 October 2022

Per Applicant's analysis shown in Table 79, the median duration of individual events of Grade 3-4 neutropenia and thrombocytopenia was just under two weeks in the imetelstat arm (Table 79). However, some patients experienced multiple events. For example, 77 patients with Grade 3-4 thrombocytopenia in the imetelstat arm experienced 212 events in total. The median total time in cytopenia among those who experienced at least one event in the imetelstat arm, defined as the sum of durations of all cytopenia events for each patient, was 4.9 weeks for Grade 3-4 neutropenia and 3.0 weeks for Grade 3-4 thrombocytopenia.

In order to confirm that the differences observed were not related to the underlying disease rather than to imetelstat, an analysis of the rate of cytopenias in the ISS laboratory database was undertaken.

Table 78: Cytopenias by dose in the ISS

	Low dose N=54	Recommended dose N=190	High dose N=296
Neutrophils decreased	14 (26)	169 (89)	150 (51)
Platelets decreased	26 (48)	178 (94)	220 (74)
Leukocytes decreased	22 (41)	174 (92)	172 (58)
Hemoglobin decreased	26 (48)	124 (65)	179 (60)

Source: FDA analysis
 Data cut-off date 13 October 2022

Clinical Reviewer comments: The rate of cytopenias was generally somewhat lower in the ISS, although the overall rate was still quite high. This may indicate that patients with MDS are more vulnerable to cytopenias compared to patients with solid tumors. However, it is clear that patients who have solid tumors and hematologic malignancies other than MDS also experience frequent cytopenias when treated with imetelstat.

Table 79: Duration of neutropenia and thrombocytopenia

	Imetelstat (N=118)	Placebo (N=59)
Duration of Grade 3-4 neutropenia		
Number (%) of patients with an event*	86 (73%)	5 (8%)
Median in weeks individual events (range)	1.9 (0, 15.9)	2.2 (1.0, 4.6)
Total number of events	279	6
Duration of Grade 3-4 thrombocytopenia		
Number (%) of patients with an event	77 (65%)	5 (8%)
Median in weeks individual events (range)	1.3 (0.1, 12.6)	2.0 (0.3, 11.6)
Total number of events	212	9

* An event occurred after the last exposure to treatment + 30 days in two patients in the imetelstat arm and one patient in the placebo arm. The duration of Grade 3-4 neutropenia analyses includes these patients in imetelstat (N = 84 + 2 = 86) and placebo (N = 4 + 1 = 5) arms.

Note: Median in weeks individual events was defined as the time from onset of worsened Grade 3+ local laboratory result from baseline grade to the day of first subsequent Grade 2 or lower local laboratory result before subsequent anticancer therapy (if any) or study discontinuation. Each subject may have had more than one cytopenia and these results are based on each separate occurrence.

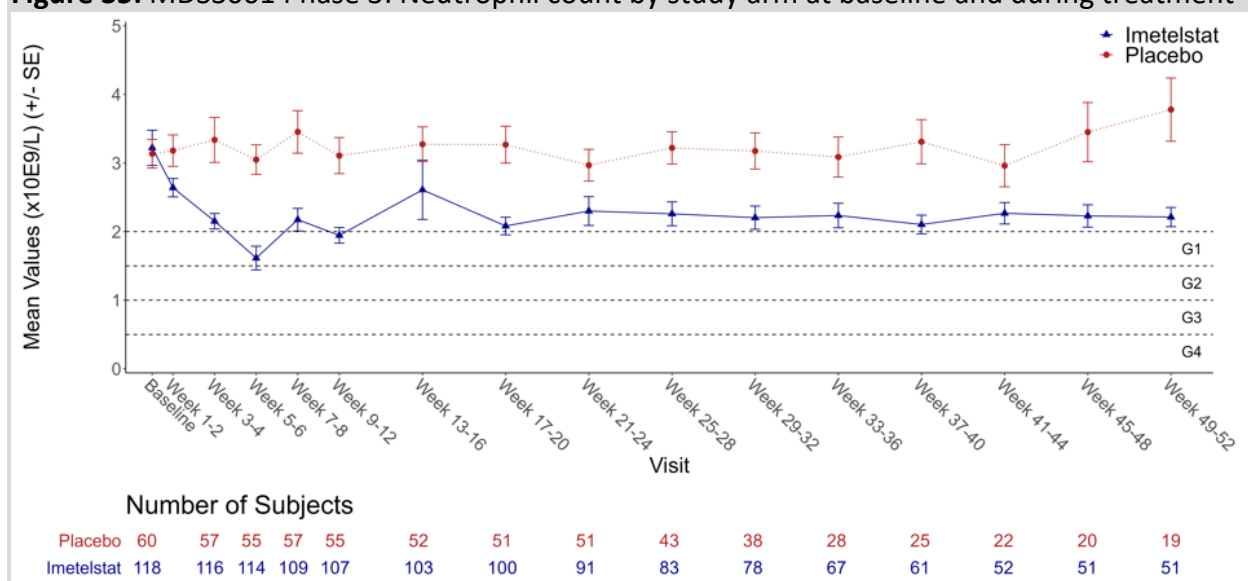
Source: Applicant's response to information request dated 21 December 2023
 Data cutoff 13 October 2022

Clinical Reviewer comments: With the exception of hemoglobin decreased, cytopenias were observed more commonly in the imetelstat arm compared to the placebo arm of MDS3001 phase 3. Hemoglobin decreased was similar between the two arms, although for unclear reasons the rate of anemia reported as a TEAE was higher in the imetelstat arm.

Neutropenia

Neutropenia was observed more commonly in the imetelstat arm compared to the placebo arm. Changes in mean neutrophil rate over time is shown in Figure 35. Neutrophil count is similar between the arms at baseline but decreases in the imetelstat arm by weeks 1-2 and does not return to baseline at any time during treatment. The mean value for neutrophils is unchanged or increased during the study for patients in the placebo arm.

Figure 35: MDS3001 Phase 3: Neutrophil count by study arm at baseline and during treatment



Source: FDA analysis using ADLB dataset
 Data cutoff 13 October 2022

In addition, more patients experienced shifts of 3-4 grades in their neutrophil count on the imetelstat arm as compared to the placebo arm. As noted in Table 80, any grade worsening was seen in almost all (92%) of patients in the imetelstat arm and in about half (53%) of patients on the placebo arm. Most events in the placebo arm were grade 1-2 worsening, whereas 60% of patients in the imetelstat arm had a three-grade worsening in neutrophil count compared to baseline at least once during the study and 17% had a four-grade worsening.

Table 80: MDS3001-Phase 3: Neutrophil count decrease by grade and study arm

	Imetelstat N=118	Placebo N=59
Any grade worsening	109 (92%)	31 (53%)
1 grade	97 (82%)	31 (53%)
2 grades	98 (83%)	18 (31%)
3 grades	71 (60%)	3 (5%)
4 grades	20 (17%)	2 (3.4%)

Source: FDA analysis using ADLB dataset
 Data cutoff 13 October 2022

In order to assess the persistence of events of neutropenia, neutrophil count was assessed by cycle number. In general, the rate of neutropenia decreases in the later cycles. However, it remained high (Table 81). In cycles 1-3, 88% of patients on the imetelstat arm had a worsening of neutrophil count, including 42 (36%) who had a grade 3-4 worsening. In the placebo arm, 24 (41%) of patients experienced a worsening of neutrophil count, all of which were one or two

grade decreases. In later cycles, 69-74% of patients in the imetelstat arm experienced worsening of neutropenia compared to baseline, including 13-15% who experienced a 3-4 grade decrease. In the placebo arm, 21-25% of patients experienced worsening of neutropenia, most of which was accounted for by one or two grade decreases.

Table 81: MDS3001-Phase 3: Neutrophil count grade change by cycle and study arm*

Cycle	Grade change	Imetelstat n/N (%)	Placebo n/N (%)
1-3	Any	104/118 (88%)	24/59 (41%)
	1-2	88%	41%
	3-4	36%	0
4-6	Any	71/103 (69%)	11/53 (21%)
	1-2	65%	21%
	3-4	13%	0
7-12	Any	56/76 (74%)	10/41 (24%)
	1-2	72%	24%
	3-4	13%	2.4%
13+	Any	33/48 (69%)	4/16 (25%)
	1-2	69%	25%
	3-4	15%	0

*Denominator ranged from 48-118 for imetelstat and 16-59 for placebo and represents number of patients who had at least one value for neutrophils documented in the relevant cycles.

Source: FDA analysis using ADLB dataset

Data cutoff 13 October 2022

The total percentage of patients who experienced a grade 3-4 neutropenia which represents a decrease from baseline of any grade is shown below (Table 82). The percentage of patients with grade 3-4 neutrophil count decreased was higher in the first cycle of treatment but was fairly stable in later cycles. Few patients in the placebo arm experienced grade 3-4 neutropenia. The apparent increase in cycles 13+ is probably related to the small number of total patients in the study at that time (17 patients had at least one value evaluated in cycle 13 or later).

Table 82: MDS3001-Phase 3: Percentage of patients with grade 3-4 neutropenia by cycle and study arm.

Cycle	Imetelstat	Placebo
Any cycle	72%	7%
Cycles 1-3	65%	3.4%
Cycles 4-6	35%	3.8%
Cycles 7-12	32%	0%
Cycles 13+	39%	6%

FDA analysis

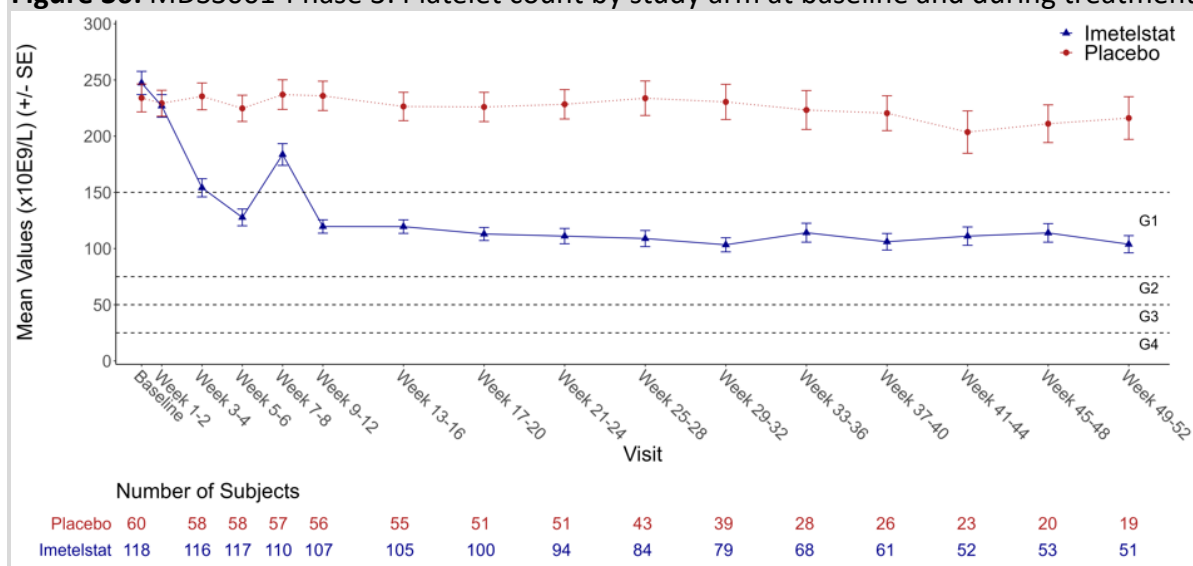
Data cut-off 13 May 2023

In summary, neutropenia and grade 3-4 neutropenia were more common in the imetelstat arm, with grade 3-4 decreased neutrophil counts seen most frequently in the first three cycles of treatment but with continued risk of neutropenia throughout treatment.

Thrombocytopenia

Thrombocytopenia was frequently observed in patients treated with imetelstat (Figure 36). As with neutropenia, mean platelet count was similar between arms initially but decreased in the imetelstat arm while staying constant in the placebo arm during treatment. Of note, the mean platelet count in the imetelstat arm decreased to grade 1 thrombocytopenia and remained in this range throughout the study.

Figure 36: MDS3001-Phase 3: Platelet count by study arm at baseline and during treatment



Source: FDA analysis using ADLB dataset
 Data cutoff 13 October 2022

More patients on the imetelstat arm experienced worsening of platelet count during therapy, including decreases of platelet count of three or four grades from baseline, with 57% of patients in the imetelstat arm experiencing a three-grade worsening in platelet count compared to 7% of patients in the placebo arm (Table 83).

Table 83: MDS3001-Phase 3: Platelet count decrease by grade and study arm

	Imetelstat N=118	Placebo N=59
Any grade worsening	113 (96%)	27 (46%)

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1 grade	113 (96%)	22 (37%)
2 grades	90 (76%)	9 (15%)
3 grades	67 (57%)	4 (7%)
4 grades	20 (17%)	2 (3.4%)

Includes all laboratory values collected from first value after start of treatment (cycle 1 day 8) through end of treatment visit.

Source: FDA analysis using ADLB dataset

Data cutoff date 13 October 2022

Changes in platelet count by cycle and study arm are described in Table 84. Eighty-eight to 93% of patients in the imetelstat arm experienced a platelet decrease of at least one grade compared to their baseline platelet count with little variation between cycles. Platelet count decreases of three to four grades were seen in 41% of patients in the first three cycles and 24-26% of patients in subsequent cycles. In the placebo arm, 15-26% of patients experienced an any grade decrease in platelet count compared to baseline and only a single decrease of 3-4 grades was seen at any time during the study.

Table 84: MDS3001-Phase 3: Platelet count grade change by cycle and study arm*

Cycle	Grade change	Imetelstat n/N (%)	Placebo n/N (%)
1-3	Any	109/118 (92%)	9/59 (15%)
	1-2	92%	15%
	3-4	41%	0%
4-6	Any	93/103 (90%)	12/53 (23%)
	1-2	90%	23%
	3-4	25%	0%
7-12	Any	71/76 (93%)	7/41 (17%)
	1-2	92%	17%
	3-4	26%	2.4%
13+	Any	42/48 (88%)	5/19 (26%)
	1-2	88%	26%
	3-4	24%	0

*Denominator ranged from 48-118 for imetelstat and 19-59 for placebo and represents number of patients who had at least one value for platelets documented in the relevant cycles.

Source: FDA analysis using ADLB dataset

Data cutoff 13 October 2022

The total percentage of patients with grade 3-4 platelet decreased and who experienced a decrease in platelet count from baseline, regardless of grade, based on laboratory data is shown below (Table 85).

Table 85: MDS3001 Phase 3: Grade 3-4 platelet decreased by cycle and treatment arm.

Cycle	Imetelstat	Placebo
Any cycle	65%	8%
Cycles 1-3	48%	1.7%
Cycles 4-6	31%	3.8%
Cycles 7-12	33%	4.9%
Cycles 13+	24%	0

FDA Analysis

Data cut-off date 13 May 2023

As with neutropenia, thrombocytopenia was observed most frequently in the first three cycles of treatment but was relatively stable in later cycles of treatment in the imetelstat arm. Platelet count decrease increased slightly over time in the placebo arm, but this is based on very small numbers of patients.

Coagulation Parameters

Activated partial thromboplastin time (PTT) was documented as prolonged in 26% (25/98) of patients on the imetelstat arm who had a PTT documented with a normal range provided. In addition, 7 patients had at least one PTT documented with no normal range provided. Of these, three patients had values that were >38 and were increased by at least 1 from baseline and one patient had a value of 114. Among patients on the placebo arm, 9 out of 52 (17%) experienced PTT Prolongation. Most events for both arms were grade 1-2.

Among patients receiving imetelstat, 96 had PT/INR values recorded with normal ranges provided. Of these, 33/96 (34%) had PT prolongation. Among patients receiving placebo, 14/46 with documented normal ranges had PT prolongation. One patient in each arm had a PT prolongation of grade 3.

Table 86: MDS3001 Phase 3: PTT and PT by study arm

	Imetelstat		Placebo	
	Overall	Grade 3-4	Overall	Grade 3-4
PTT prolonged	25/98 (26%)	1 (1%)	9/52 (17%)	2 (3.8%)
PT prolonged	33/96 (34%)	1 (1%)	14/46 (30%)	1/46 (2.2%)

Source: FDA analysis

Twenty-nine patients (25%) on the imetelstat arm and 18 (31%) on the placebo arm received anti-thrombotic agents at some point during treatment. Among patients on the imetelstat arm, this included two patients receiving vitamin K antagonists, thirteen direct factor Xa inhibitors, and nine heparin group medications, most commonly enoxaparin. Among patients on placebo, 18 (31%) received any anti-thrombotic agent, including one who received a vitamin K antagonist, 7 who received a direct factor Xa inhibitor, one who received a direct thrombin

inhibitor, and 5 who received a heparin group medication, most commonly enoxaparin. On the imetelstat arm, 12 patients both received at least one anti-thrombotic medication (heparin group, vitamin K antagonist, or factor Xa inhibitor) and had at least one elevation of PT or PTT. Of note, the patient who had a grade 3 prolongation of PTT was not prescribed the medication at the time the grade 3 PTT Prolongation was documented. Seven patients on the placebo arm both received anti-thrombotics and had at least one prolongation of PT or PTT.

Clinical Reviewer comments: Although some patients who experienced PT or PTT Prolongation were treated with various anti-thrombotics, the timing and extent of PT and PTT prolongation were not explained by anti-thrombotic use.

Vital Signs

Data:

There did not appear to be any clinically significant mean or median changes in weight, pulse, systolic blood pressure, diastolic blood pressure, or temperature in the MDS3001 Phase 3, Phase 2, or pooled imetelstat groups.

The Applicant's Position:

No clinically relevant changes in vital signs were observed.

The FDA's Assessment:

The Agency does not agree with the Applicant's assessment of the vital signs data. Details are below.

Blood pressure

Systolic blood pressure:

Systolic blood pressure elevations were observed in the majority of patients at baseline and during the study. At baseline, any elevation in systolic blood pressure was seen in 67% of patients receiving imetelstat in either phase of the study and 57% of patients receiving placebo, with the majority of patients in each cohort having grade 1 SBP (SBP of 120-<140) (Table). Blood pressure measurements on cycle 2 day 1 and cycle 4 day 1 were compared to evaluate changes in SBP over time. At cycle 2 day 1, any blood pressure elevation was seen in fewer patients in the imetelstat phase 2 portion and more patients in both arms of the phase 3 component. By cycle 4 day 1, elevations in SBP were seen in 75% of patients in the imetelstat arm of the phase 3 portion and 53% of patients in the placebo arm. No clear pattern of change in grade was observed.

Table 87: Systolic blood pressure by study arm

Timing	Severity	Imetelstat Phase 2 N (%)	Imetelstat Phase 3 N (%)	Placebo N (%)
Baseline (N)		57	118	59
	Any	38 (67)	79 (67)	34 (57)
	Grade 1 (120-<140)	25 (44)	47 (40)	21 (36)
	Grade 2 (140-<160)	10 (18)	28 (24)	11 (19)
	Grade 3 (160+)	3 (5)	4 (3.4)	2 (3.4)
Cycle 2 d1 (N)		56	112	57
	Any	29 (52)	78 (70)	40 (70)
	Grade 1 (120-<140)	13 (23)	50 (45)	31 (54)
	Grade 2 (140-<160)	13 (23)	21 (19)	9 (16)
	Grade 3 (160+)	3 (5)	5 (4.5)	0
Cycle 4 d1 (N)		47	103	53
	Any	23 (49)	77 (75)	28 (53)
	Grade 1 (120-<140)	14 (30)	49 (48)	14 (26)
	Grade 2 (140-<160)	8 (17)	23 (22)	13 (25)
	Grade 3 (160+)	1 (2.1)	5 (4.9)	1 (1.9)

Source: FDA analysis

Data cut-off date 13 October 2022

Diastolic blood pressure:

A smaller number of patients experienced elevations in DBP at baseline, with 18% of patients in the phase 2 portion, 9% of the imetelstat arm of the phase 3 portion, and 12% of patients in the placebo arm. The rate of overall diastolic hypertension increased slightly in both imetelstat cohorts at cycle 2 and cycle 4, with a slight decrease seen in the placebo arm. No clear trend towards increased grade of DBP elevations was seen.

Table 88: Diastolic blood pressure by study arm

Timing	Severity	Imetelstat Phase 2	Imetelstat Phase 3	Placebo
Baseline (N)		57	118	59
	Any	10 (18)	11 (9)	7 (12)
	Grade 1 (80-<90)	9 (16)	9 (8)	7 (12)
	Grade 2 (90-<100)	1(1.8)	1 (0.8)	0
	Grade 3 (100+)	0	1 (0.8)	0
Cycle 2 d1 (N)		56	111	57
	Any	10 (18)	12 (11)	5 (9)
	Grade 1 (80-<90)	10 (18)	10 (9)	4 (7)
	Grade 2 (90-<100)	0	2 (1.8)	1 (1.8)
	Grade 3 (100+)	0	0	0
Cycle 4 d1 (N)		47	103	53

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	Any	11 (23)	15 (15)	5 (9)
	Grade 1 (80-<90)	10 (21)	14 (14)	3 (6)
	Grade 2 (90-<100)	1 (2.1)	0	2 (3.8)
	Grade 3 (100+)	0	1 (1)	0

Source: FDA analysis

Data cut-off date 13 October 2022

In order to clarify the significance of the changes in blood pressure observed, a shift table showing changes in blood pressure in patients who were evaluated at baseline and cycle 4 day 1 were produced (Table 89). Overall, more patients in the phase 3 portion of the study had shifts of at least one grade in their SBP. Patients in the imetelstat arm had more increases in SBP and more grade 2 increases compared to placebo, although it is notable that the only patient with a 3-grade increase received placebo. Similarly, shifts in DBP grade were slightly more common in the imetelstat arm of the phase 3 portion of the study, including one grade 3 event.

Table 89: Shift tables showing changes in blood pressure at cycle 4 day 1 by study arm and blood pressure measurement

Variable	Category	Any grade N (%)	1 grade N (%)	2 grades N (%)	3 grades N (%)
SBP	Imetelstat P2 (N=47)	6 (13)	4 (9)	2 (4.3)	0
	Imetelstat P3 (N=103)	38 (37)	32 (31)	6 (6)	0
	Placebo (N=53)	15 (28)	14 (26)	0	1 (1.9)
DBP	Imetelstat	4 (9)	4 (9)	0	0
	Imetelstat P3	11 (11)	10 (10)	0	1 (1)
	Placebo	5 (9)	4 (8)	1 (1.9)	0

P2=phase 2; P3=phase 3

Source: FDA analysis

Data cut-off date 13 October 2022

Clinical Reviewer comments: A trend towards more hypertension and more shifts towards higher grades of hypertension was seen in the imetelstat arm of the phase 3 portion of the study compared to placebo. This correlates with the higher rates of hypertension seen in the ADAE dataset. Overall, the data suggest a possible risk of hypertension with use of imetelstat, although few patients appear to have had severe elevations in their blood pressure.

Temperature

At least one post-baseline temperature of <35° C was reported in 8 patients, four of whom had baseline temperatures of <35° C. Among patients who had a temperature of <35° C and a baseline temperature of ≥35° C, three were on the imetelstat phase 2 portion of the study, one on the imetelstat arm of the phase 3 portion of the study.

Twenty-four patients had at least one post-baseline temperature of $\geq 37.5^{\circ}\text{C}$, including 9 on the phase 2 portion of the study, eight on the imetelstat arm of the phase 3 portion of the study, and 7 on the placebo arm.

Overall, no consistent increase or decrease in temperature was observed in patients treated with imetelstat.

Clinical Reviewer comments: While fever and hypothermia were observed in a few patients, this is most likely consistent with infection or other systemic condition. No clear effect of imetelstat on temperature was observed.

Heart Rate

Median heart rate (measured as peripheral pulse) on treatment for patients on the imetelstat phase 3 arm was 73 beats per minute (BPM) (range 42-151 BPM), with a baseline of 74 BPM (60-124 BPM). Twenty-one patients had at least one value of < 60 BPM, with no baseline values below 60 BPM. The timing of the incidents of bradycardia was variable, ranging from an unscheduled vital signs check on cycle 1 day 1 to cycle 28 day 1. No TEAE of bradycardia were reported, although bundle branch block was reported in one patient. Heart rates of > 110 BPM were reported in four patients, one of whom had an elevated baseline heart rate.

Median heart rate on treatment for patients on the placebo arm of the phase 3 portion of the study was 76 (range 18-117), with a baseline of 75 (53-106). Sixteen (27%) of patients had a heart rate of < 60 BPM at some time during the study. Of these, 11 had baseline of > 60 bpm. Note that this includes one patient who had two values of 18 BPM recorded. Five patients had at least one heart rate of > 110 BPM noted, none of whom had baseline heart rates of > 100 BPM.

Clinical Reviewer comments: No major effects of imetelstat on heart rate/pulse are apparent from the data.

Electrocardiograms (ECGs)

Data:

Based on subjects in hematological monotherapy studies, key findings for the clinical assessment of the proarrhythmic potential of imetelstat based on a review of the events included in the SMQ Torsade de pointes/QT prolongation with the additional PT of Seizure (Group C; N = 391) are as follows:

- Four (1.0%) subjects experienced events of ECG QT prolonged. Two subjects experienced non-serious Grade 3 events (1 of which also experienced a Grade 1 event) and 2 subjects experienced a Grade 1 event (Listing lae03c). All 4 ECG QT prolonged

events were considered not related to imetelstat by the investigator. One of the subjects was from the MDS3001 Phase 3 imetelstat group (N = 118).

- One subject in the MDS3001 Phase 3 imetelstat group had a Grade 3 TEAE of ECG QT prolonged on Study Day 49 resulting in study drug interruption after receiving nitrofurantoin and furosemide on Study Days 48 and 49, respectively, for a Grade 2 urinary tract infection. Both events were considered unrelated to study treatment by the investigator, the ECG resolved without treatment on Study Day 51, and imetelstat treatment continued.
- In addition, a review of the associated events of ECG QTc Prolongation showed 10 (2.6%) subjects with events of syncope (6 [1.5%] were Grade 3), 3 subjects (0.8%) with events of cardiac arrest (2 [0.5%] were Grade 5 and 1 (0.3%) was Grade 4), 1 (0.3%) subject with an event of multiple organ dysfunction syndrome (Grade 4), 1 (0.3%) subject with an event of loss of consciousness (Grade 1), 1 (0.3%) subject with an event of seizure (Grade 3), and 1 (0.3%) subject with an event of ventricular tachycardia (Grade 1) (Table tcardae01c, Listing lcardae01c).
 - The majority of these events were considered not related to imetelstat including the 2 fatal (Grade 5) cardiac arrest events in MF subjects (discussed below).
 - One MDS/MPN subject from Study CP14B019 had an unrelated Grade 5 cardiac arrest following an esophagogastroduodenoscopy for Grade 3 upper gastrointestinal hemorrhage 26 days after the last dose of imetelstat.
 - One post-ET MF subject from Study CP14B019 had an unrelated Grade 5 cardiac arrest in the setting of disease progression and Grade 4 sepsis 31 days after the first and last dose.
 - Additionally, sponsor review of these associated events identified confounding by the underlying disease, underlying cardiac history including prior syncopal episodes, cardiac valve abnormalities, hypertension, and atrial fibrillation, concurrent anemia and other co-morbid conditions such as diabetes mellitus, advanced age and procedural complication. Therefore, an association of these events with QTC prolongation due to imetelstat is unlikely.

Applicant Table 90: Cardiac Treatment-emergent Adverse Events by System Organ Class and Preferred Term – Studies MDS3001, CP14B013, CP14B015, CP14B019, MYF2001 – Phase 2 and Phase 3 Imetelstat (Treated Population)

System Organ Class Preferred Term	Imetelstat ^d			
	<7.1 mg/kg ^a q4w (N = 48)	7.1 mg/kg ^b q4w (N = 204)	>7.1 mg/kg ^c q4w (N = 139)	Total Pooled (N = 391)
Subjects with ≥ 1 cardiac TEAE	0	16 (7.8%)	5 (3.6%)	21 (5.4%)
Nervous system disorders	0	11 (5.4%)	1 (0.7%)	12 (3.1%)
Syncope	0	9 (4.4%)	1 (0.7%)	10 (2.6%)

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System Organ Class Preferred Term	Imetelstat ^d			
	<7.1 mg/kg ^a q4w (N = 48)	7.1 mg/kg ^b q4w (N = 204)	>7.1 mg/kg ^c q4w (N = 139)	Total Pooled (N = 391)
Loss of consciousness	0	1 (0.5%)	0	1 (0.3%)
Seizure	0	1 (0.5%)	0	1 (0.3%)
Cardiac disorders	0	2 (1.0%)	2 (1.4%)	4 (1.0%)
Cardiac arrest	0	1 (0.5%)	2 (1.4%)	3 (0.8%)
Ventricular tachycardia	0	1 (0.5%)	0	1 (0.3%)
Investigations	0	3 (1.5%)	1 (0.7%)	4 (1.0%)
Electrocardiogram QT prolonged	0	3 (1.5%)	1 (0.7%)	4 (1.0%)
General disorders and administration site conditions	0	0	1 (0.7%)	1 (0.3%)
Multiple organ dysfunction syndrome	0	0	1 (0.7%)	1 (0.3%)

Source: Table tcardae01c

^a MYF2001 4.4 mg/kg (active moiety, equivalent to 4.7 mg/kg imetelstat sodium) arm only

^b CP14B019 Arms E and G; MDS3001 Phase 2 and 3 (Imetelstat); CP14B015 and CP14B013 7.1 mg/kg arm

^c CP14B019 Arms A, B, D, and F; CP14B015, CP14B013, and MYF2001 8.9 mg/kg (active moiety, equivalent to 9.4 mg/kg imetelstat sodium) arm

^d Doses in this table (including the footnotes) are shown for the active moiety (free acid). To convert a quantity of imetelstat salt to the equivalent quantity of imetelstat, a factor of 0.9416 based on relative molar mass of the free acid form (4610 g/mol) to the sodium salt (4896 g/mol; 4610/4896 = 0.9416) is applied (i.e., 1 mg imetelstat sodium = 0.9416 mg imetelstat).

Note: Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0.

Note: Cardiac events searched by Torsade de pointes/QT prolongation or PT = Seizure.

PT = preferred term; q4w = once every 4 weeks; TEAE = treatment-emergent adverse event.

The Applicant's Position:

Overall, based on the current knowledge of imetelstat from nonclinical safety pharmacology assessments and the relevant clinical cardiac safety data, and supported by the limited proarrhythmic potential for other ODNs, imetelstat is not likely to prolong the QT interval.

The FDA's Assessment:

At least one ECG was performed, and some data was provided for all patients on study MDS3001. However, the data are extremely sparse. ECG were collected routinely only at baseline and cycle 2, day 1, severely limiting any conclusions that can be drawn regarding the long term or cumulative effects of imetelstat on cardiac function.

Among patients treated with imetelstat on the phase 2 portion, all patients had a documented baseline ECG, 52 had a cycle 2 day 1 ECG, and ECG at all other timepoints were collected for 1-2 patients. The only information provided was a description of the ECG as "normal", "abnormal clinically insignificant", and "abnormal clinically significant". At baseline, 36 ECG were described as normal, 21 abnormal, clinically insignificant. At cycle 2 day 1, 19 were considered abnormal,

Version date: June 2022 (ALL NDA/ BLA reviews)

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

clinically insignificant. Of these, 7 had normal baseline ECGs. No further information regarding the specific change or how clinical significance was determined was provided.

Among patients receiving imetelstat on the phase 3 portion, all (118) patients received at least 1 ECG. Overall interpretation was available for 117 patients at baseline, 93 at cycle 2 day 1, and 11 at cycle 1 day 22. At baseline, 76 ECG were interpreted as normal and 41 as abnormal, clinically insignificant. At cycle 2 day 1, 68 ECG were interpreted as normal, 24 as abnormal, clinically insignificant, and one as abnormal, clinically significant. The baseline ECG was normal for 7 of the patients whose cycle 2 day 2 ECG were abnormal clinically insignificant and abnormal clinically insignificant for the patient whose cycle 2 day 1 ECG was abnormal clinically significant. Overall, two patients had ECG at any time documented as abnormal clinically significant.

Forty-nine patients who received placebo had cycle 2 day 1 ECG with results of the interpretation available. Of these, 28 were considered normal and 21 abnormal, clinically insignificant. Two patients with abnormal ECG had normal baseline ECG and one had an ECG read as abnormal, clinically significant.

Clinical Reviewer comments: A small number of patients receiving imetelstat experienced a change in their ECG from normal to abnormal clinically insignificant and one changed from abnormal clinically insignificant to abnormal clinically significant. The interpretation of this finding is limited by lack of information about specific changes and how clinical significance was determined. No definitive conclusions can be drawn regarding the effect of imetelstat on cardiac events as diagnosed by ECG. Also see AE evaluation.

QT

Data:

See above under ECGs. A thorough QT study has not been conducted.

The Applicant's Position:

A randomized double-blinded placebo-controlled clinical ventricular repolarization/QTc substudy is ongoing in subjects with MDS under Study MDS3001. Analyses of ECG parameters and the relationship between imetelstat exposure and the QT/QTc interval will be conducted on approximately 45 LR MDS subjects. Results will be provided upon completion of the study with an integrated risk assessment of nonclinical and clinical data to fully characterize the proarrhythmic potential of imetelstat.

The FDA's Assessment:

QT information was available on only a single patient in study MDS3001. This patient was treated with imetelstat on the phase 3 portion of the study. Their baseline QTcF was 423 ms.

QTcF values were taken in triplicate on cycle 1 day 1 pre-dose and 2, 4, 6, 8, and 24 hours post-dose as well as cycle 2 day 1. The mean values are provided in the table below.

Table 91: QT values from one patient treated with imetelstat

Time	Value	Change versus baseline
Baseline	423	NA
Pre-dose	423	0
2 hours post-dose	428	+5
4 hours post-dose	426	+3
6 hours post-dose	411	-12
8 hours post-dose	417	-6
24 hours post-dose	409	-14
Cycle 2 day 1	407	-12

Source: FDA analysis

Data cut-off date 13 May 2023

In addition, electrocardiogram QT elevation was documented as a TEAE in two patients on the imetelstat arm of the phase 3 portion of the study, including one patient who had a grade 3 event.

Clinical Reviewer comments: No evidence of QT prolongation was observed with the single patient in whom data were provided. However, since data are available for a single patient at early timepoints, no definitive conclusions can be made concerning the risk of QT prolongation with use of imetelstat.

Immunogenicity

Data:

There was no discernable effect of ADA on imetelstat PK (Applicant Figure 47), safety, or efficacy (See Section 6.3).

The Applicant's Position:

ADA do not impact the overall benefit/risk profile of imetelstat.

The FDA's Assessment:

Baseline screening for ADA (screening or cycle 1 day 1) was available for 226 patients on study MDS3001. The screen was positive for 10 patients. However, confirmatory testing was negative for all patients involved. At least one post-baseline value was available for 217 patients. Of these, 40 patients had at least one positive value at any time post-start of treatment and 28 had positive confirmatory evaluations, including 12 who were treated on the phase 2 portion of the study and 16 who were treated on the imetelstat arm of the phase 3 portion of the study.

Peak titers ranged from 10-80, with a median of 10. The dose of imetelstat was escalated in two patients ((b) (6) and (b) (6)). All other patients had dose maintained or decreased.

Clinical Reviewer comments: Imetelstat appears to be immunogenic with positive ADA being observed as soon as study day 85.

8.2.5. Analysis of Submission-Specific Safety Issues

Specific safety issues are presented in the LR MDS population.

8.2.5.1 Hepatic Adverse Events and LFT Elevations

Data:

Hepatic Events

Approximately 43% and 35% of subjects in the MDS3001 Phase 3 imetelstat and placebo groups, respectively, had a medical history of conditions associated with iron overload (hyperferritinaemia, haemosiderosis, haemochromatosis, and iron overload), and approximately 14% and 10% of subjects in the 2 groups, respectively, had a history of hepatobiliary disorders. In addition, 64% and 63% of subjects, respectively, were on iron chelating agents at the time of entering the study or while on treatment.

In the MDS3001 Phase 3 imetelstat group (N = 118), hepatic TEAEs (any grade) were reported in 28.8% of subjects ([Applicant Table 92](#)). The most commonly reported hepatic TEAE in subjects in the imetelstat group was ALT increased in 11.9% of subjects, followed by AST increased and hyperbilirubinaemia (9.3% each), blood ALP increased (4.2%), and gamma-glutamyl transferase (GGT) increased (3.4%). Seventeen (14.4%) subjects had hepatic TEAEs considered related to imetelstat (Table taesi01a). Eight (6.8%) subjects had a Grade 3/4 hepatic event, including 3 (2.5%) subjects with Grade 3 hepatic events considered related to imetelstat. One subject had a serious Grade 4 oesophageal varices haemorrhage (Listing lae02b). Median time to onset of the Grade 3/4 hepatic events was 198 days (range: 1 to 633 days) in the imetelstat group and 113 days (range: 85 to 330) in the placebo group (Table taesi03a). There were no other serious events and no Grade 5 events. One subject had a dose reduction due to Grade 2 events of ALT increased and AST increased (not related to imetelstat). No subjects discontinued treatment due to hepatic events.

In the MDS3001 Phase 3 placebo group (N = 59), hepatic TEAEs (any grade) were reported in 16.9% of subjects and Grade 3/4 TEAEs were reported in 5.1% of subjects with median time to onset of 113 days (range: 85 to 330 days) (Table taesi03a) ([Applicant Table 92](#)). The most commonly reported hepatic TEAE in subjects in the placebo group was hyperbilirubinaemia in 10.2% of subjects, followed by ALT and AST increased (6.8% each), and GGT increased (3.4%). Four (6.8%) subjects had events considered related to study treatment (Table tasei01a). There

were no Grade 4 or Grade 5 hepatic TEAEs and no hepatic SAEs in the placebo group (Listing lae02b). Two subjects had dose reductions due to hepatic TEAEs (Grade 2/3 events of ALT increased, AST increased and GGT increased) all of which were considered related to study treatment. No subjects discontinued study treatment due to a hepatic TEAE.

In the Phase 2 imetelstat group (N = 57), hepatic TEAEs (any grade) were reported in 31.6% of subjects, and Grade 3 events were reported in 12.3% of subjects ([Applicant Table 92](#)). The most commonly reported event in subjects was ALT increased in 17.5% of subjects, followed by AST increased (14.0%), hyperbilirubinaemia (8.8%), hepatomegaly (5.3%), and blood ALP increased (3.5%). Nine subjects had hepatic events considered related to imetelstat (Table taesi01b). Median time to onset of the Grade 3/4 hepatic events was 439 days (range: 8 to 769 days) (Table taesi03b). Two subjects had SAEs: 1 subject with Grade 3 events of cholecystitis, biliary colic, and oesophageal varices haemorrhage; 1 subject with Grade 3 events of hepatocellular carcinoma and hepatic cancer (Table taesi04b, Listing lae02b). All of the events were unrelated to imetelstat. There were no Grade 5 hepatic events. No subjects discontinued treatment due to hepatic events.

Applicant Table 92: Treatment-emergent Adverse Events of Interest Per Protocol Criteria: Hepatic Event – Study MDS3001 – Phase 2 and Phase 3 (Treated Population)

Category Preferred Term	Imetelstat - Phase 3 (N = 118) n (%)		Placebo – Phase 3 (N = 59) n (%)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Subjects with ≥1 hepatic TEAE	34 (28.8%)	8 (6.8%)	10 (16.9%)	3 (5.1%)
Alanine aminotransferase increased	14 (11.9%)	3 (2.5%)	4 (6.8%)	2 (3.4%)
Aspartate aminotransferase increased	11 (9.3%)	0	4 (6.8%)	0
Hyperbilirubinaemia	11 (9.3%)	1 (0.8%)	6 (10.2%)	1 (1.7%)
Blood alkaline phosphatase increased	5 (4.2%)	0	1 (1.7%)	0
Gamma-glutamyltransferase increased	4 (3.4%)	0	2 (3.4%)	1 (1.7%)
Ascites	2 (1.7%)	0	0	0
Hepatic steatosis	2 (1.7%)	0	0	0
Portal hypertension	2 (1.7%)	0	0	0
Biliary cyst	1 (0.8%)	0	0	0
Bilirubin conjugated increased	1 (0.8%)	1 (0.8%)	0	0
Cholelithiasis	1 (0.8%)	0	0	0
Hepatic cirrhosis	1 (0.8%)	0	0	0
Hepatitis	1 (0.8%)	1 (0.8%)	0	0
Hepatomegaly	1 (0.8%)	0	0	0
Hepatotoxicity	1 (0.8%)	1 (0.8%)	0	0
International normalised ratio increased	1 (0.8%)	0	0	0
Jaundice hepatocellular	1 (0.8%)	0	0	0

Category Preferred Term	Imetelstat - Phase 3 (N = 118) n (%)		Placebo – Phase 3 (N = 59) n (%)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Oesophageal varices haemorrhage	1 (0.8%)	1 (0.8%)	0	0
Prothrombin time prolonged	1 (0.8%)	0	0	0
Transaminases increased	1 (0.8%)	0	0	0
Varices oesophageal	1 (0.8%)	0	0	0
Hypoalbuminaemia	0	0	1 (1.7%)	0

Source: Table taesi02a, Table taesi04a

Note: Medical Dictionary for Regulatory Activities (MedDRA) v25.0 was used for TEAE coding.

SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Liver Function Test Abnormalities

No subjects in Study MDS3001 met Hy's law criteria.

In the Phase 3 of the MDS3001 study, 2 subjects, both in the imetelstat group (N = 188), met the laboratory criteria for Hy's law, ie, ALT or AST Grade ≥ 2 ($> 3.0 \times \text{ULN}$) with concurrent (within 7 days) bilirubin Grade ≥ 2 ($> 2.0 \times \text{ULN}$); however, an alternative etiology for these LFT elevations was established: deferasirox hepatotoxicity in 1 subject, and in the other subject, multiple risk factors for LFT alterations and possibly deferasirox-induced liver injury. These cases were reviewed by the HEC and determined not to be Hy's law cases.

In the MDS3001 Phase 2 imetelstat group (N = 59), 1 subject met the laboratory criteria for Hy's law, ie, ALT or AST Grade ≥ 2 ($> 3.0 \times \text{ULN}$) with concurrent (within 7 days) bilirubin Grade ≥ 2 ($> 2.0 \times \text{ULN}$); however, an alternative etiology for the LFT elevations was established (sepsis). The case was reviewed by the HEC and determined not to be a Hy's law case.

Additional findings based on laboratory are provided in [Section 8.2.4](#) under the "Laboratory Findings" heading.

Applicant Table 93: Treatment-emergent Adverse Events of Interest Per Protocol Criteria: Liver Function Abnormalities – Study MDS3001 – Phase 2 and Phase 3 (Treated Population)

LFT Abnormality	Phase 3		Phase 2	Pooled
	Imetelstat (N = 118) n (%)	Placebo (N = 59) n (%)	Imetelstat (N = 57) n (%)	Imetelstat (N = 175) n (%)
ALT Grade ≥ 3 ($>5.0 \times \text{ULN}$), n (%)	4 (3.4%)	3 (5.1%)	3 (5.3%)	7 (4.0%)
AST Grade ≥ 3 ($>5.0 \times \text{ULN}$), n (%)	1 (0.8%)	1 (1.7%)	3 (5.3%)	4 (2.3%)
Bilirubin Grade ≥ 3 ($>3.0 \times \text{ULN}$), n (%)	3 (2.5%)	1 (1.7%)	2 (3.5%)	5 (2.9%)
ALP Grade ≥ 3 ($>5.0 \times \text{ULN}$), n (%)	0	0	0	0

	Phase 3		Phase 2	Pooled
	Imetelstat (N = 118) n (%)	Placebo (N = 59) n (%)	Imetelstat (N = 57) n (%)	Imetelstat (N = 175) n (%)
LFT Abnormality				
ALT or AST Grade ≥ 2 ($>3.0 \times$ ULN) with Bilirubin Grade $\geq 2.0 \times$ ULN within 7 days, n (%)	2 (1.7%)	0	1 (1.8%)	3 (1.7%)

Source: Table tlab07d and Table tlab07e

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; LFT = liver function test; ULN = upper limit of normal.

The Applicant's Position:

Hepatic events were primarily low grade and reversible elevations of ALT, AST, and bilirubin, have been observed in both imetelstat and placebo-treated subjects, with no apparent dose effects. No cases meeting Hy's law criteria were observed. The hepatic events and laboratory abnormalities in the MDS population are confounded by the high background rate of hepatic dysfunction due to iron overload from chronic transfusions in this transfusion-dependent patient population as well as the concomitant use of iron chelating agents, alcohol, antibiotics, and concurrent infections associated with hepatic abnormalities. Hepatic events were manageable and generally reversible, with few dose reductions and treatment discontinuations due to hepatic events observed across all imetelstat treated subjects.

The FDA's Assessment:

Hepatic Disorders

As noted above, a higher rate of hepatic disorders was observed in the imetelstat arm compared to the placebo arm of the phase 3 portion. The relative incidence of transaminase elevation and increased bilirubin were discussed in further detail in the laboratory data section, above. In summary, higher rates of transaminase (AST and ALT) elevation and alkaline phosphatase elevation were observed in the imetelstat arm of the study, although the rate of bilirubin increased was similar between the imetelstat and placebo arms.

Overall, TEAE in the general category of hepatic disorders were observed in 31 (26%) patients in the imetelstat arm of the phase 3 portion (based on the 120-day update), compared to 10 (17%) in patients on the placebo arm. The most common TEAE noted were transaminase elevation, hyperbilirubinemia, and GGT increased. A variety of other events of hepatic disorders were observed in the imetelstat arm, including hepatic cirrhosis, hepatic steatosis, and portal hypertension in two patients each and hepatitis, hepatomegaly, hepatotoxicity, jaundice hepatocellular, and varices esophageal in one patient each in the imetelstat arm. No abnormalities apart from laboratory abnormalities (including hyperbilirubinemia) were noted in the placebo arm. In the phase 2 portion of the study, 16 (28%) patients experienced at least one hepatic disorder. Again, investigations were the most common abnormalities. In addition,

hepatomegaly was seen in 3 (5%) patients and hepatic cirrhosis and chronic hepatitis in one patient each.

Two events meeting the laboratory definition of Hy's law cases were observed in the imetelstat arm of the phase 3 portion of the study. Of these, one was in a patient who had abnormalities in bilirubin at baseline and had no clear pattern of worsening during treatment. The other patient developed transaminase and bilirubin elevation while being treated with imetelstat and deferasirox simultaneously. The abnormalities resolved when both medications were stopped. Imetelstat was not restarted, although a milder increase in transaminases was seen after restarting deferasirox.

Clinical Reviewer comments: Of the two patients who met laboratory criteria for Hy's law in the imetelstat portion of the phase 3 part of the study, one had baseline abnormalities. The second patient had abnormalities that occurred on treatment and were consistent with Hy's law. The finding was confounded by the coadministration of deferasirox. Given the positive de-challenge and the finding of more hepatic disorders in the imetelstat arm, the finding is suspicious for a possible Hy's law case.

One additional patient on the phase 2 portion of the study experienced laboratory abnormalities consistent with Hy's law. Per the Applicant, these laboratory abnormalities occurred in the setting of sepsis (noting again that sepsis was not documented for this patient in the ADAE dataset, although a UTI that could be a precursor to sepsis was documented).

Clinical Reviewer comments: Overall, the data suggest that imetelstat has at least minor hepatotoxicity. Liver function should be monitored in patients receiving imetelstat.

8.2.5.2 Thrombocytopenia and Bleeding Events

Data:

Thrombocytopenia

Thrombocytopenia findings based on laboratory data are summarized in [Section 8.2.4](#) under the "Laboratory Findings" heading.

In the MDS3001 Phase 3 imetelstat group (N = 118), thrombocytopenia (any grade) was reported in 75.4% of subjects, including 61.9% of subjects with Grade 3/4 thrombocytopenia ([Applicant Table 94](#)). Most events occurred in the earlier months of treatment and rates decreased over time for any grade and Grade 3/4 thrombocytopenia, suggesting a lack of cumulative toxicity. Grade 4 thrombocytopenia was reported in 24 subjects (Listing lae02e), and 67.8% of subjects had events that were considered related to imetelstat treatment. In the imetelstat group, thrombocytopenia led to cycle delay in 46.6% of subjects, dose reduction in 22.9% of subjects, and discontinuation of imetelstat in 3.4% of subjects. Median time to cycle delay due to thrombocytopenia was 6 weeks (range: 2.9 to 71.7) and median time to dose

reduction was 16 weeks (range: 2.9 to 64) (MDS3001 CSR [Phase 3]/Table tsix18a_p2).
 Subjects who discontinued treatment due to thrombocytopenia occurred later in treatment
 (≥ 150 days) (MDS3001 CSR [Phase 3]/Table 61).

In the placebo group (N = 59), thrombocytopenia (any grade) was reported in 10.2% of subjects, including 8.5% of subjects with Grade 3/4 thrombocytopenia (Applicant Table 94). Grade 4 thrombocytopenia was reported in 3.4% of subjects, and 5.1% of subjects had events that were considered related to study treatment (Listing lae02e). In the placebo group, thrombocytopenia led to cycle delay in 1 (1.7%) subject and dose reduction in 1 (1.7%) subject; no subjects in the placebo group discontinued treatment due to thrombocytopenia.

There were no Grade 5 events of thrombocytopenia and no SAEs of thrombocytopenia reported in either of the MDS3001 Phase 3 treatment groups.

In the MDS3001 Phase 2 imetelstat group (N = 57), thrombocytopenia (any grade) was reported in 61.4% of subjects, including 54.4% of subjects with Grade 3/4 thrombocytopenia (Applicant Table 94). Grade 4 thrombocytopenia was reported in 12 subjects, and most events were considered related to imetelstat treatment (Listing lae02e). There were no Grade 5 events of thrombocytopenia.

Applicant Table 94: Treatment-emergent Adverse Events: Thrombocytopenia – Study MDS3001 – Phase 2 and Phase 3 (Treated Population)

Subjects with Thrombocytopenia:	Phase 3		Phase 2	Pooled
	Imetelstat (N = 118)	Phase 3 (N = 59)	Imetelstat (N = 57)	Imetelstat (N = 175)
Any TEAE, n (%)	89 (75.4%)	6 (10.2%)	35 (61.4%)	124 (70.9%)
0 to <3 months, n/N (%)	74/118 (62.7%)	3/59 (5.1%)	32/57 (56.1%)	106/175 (60.6%)
3 to <6 months, n/N (%)	55/104 (52.9%)	4/55 (7.3%)	18/49 (36.7%)	73/153 (47.7%)
6 to <12 months, n/N (%)	39/85 (45.9%)	3/41 (7.3%)	16/37 (43.2%)	55/122 (45.1%)
≥ 12 months, n/N (%)	20/49 (40.8%)	0/16	9/22 (40.9%)	29/71 (40.8%)
Treatment-related TEAE, n (%)	80 (67.8%)	3 (5.1%)	33 (57.9%)	113 (64.6%)
Grade 3 or 4 TEAE, n (%)	73 (61.9%)	5 (8.5%)	31 (54.4%)	104 (59.4%)
0 to <3 months, n/N (%)	46/118 (39.0%)	1/59 (1.7%)	16/57 (28.1%)	62/175 (35.4%)
3 to <6 months, n/N (%)	20/104 (19.2%)	2/55 (3.6%)	6/49 (12.2%)	26/153 (17.0%)
6 to <12 months, n/N (%)	16/85 (18.8%)	2/41 (4.9%)	7/37 (18.9%)	23/122 (18.9%)
≥ 12 months, n/N (%)	6/49 (12.2%)	0/16	4/22 (18.2%)	10/71 (14.1%)
Grade 5 TEAE, n (%)	0	0	0	0
Treatment-emergent SAE, n (%)	0	0	2 (3.5%)	2 (1.1%)
TEAE that led to cycle delay, n (%)	55 (46.6%)	1 (1.7%)	23 (40.4%)	78 (44.6%)
TEAE that led to dose reduction, n (%)	27 (22.9%)	1 (1.7%)	16 (28.1%)	43 (24.6%)

Subjects with Thrombocytopenia:	Phase 3		Phase 2	Pooled
	Imetelstat (N = 118)	Phase 3 (N = 59)	Imetelstat (N = 57)	Imetelstat (N = 175)
TEAE that led treatment withdrawal, n (%)	4 (3.4%)	0	7 (12.3%)	11 (6.3%)

Source: Table tae02a, Table tae02b (TEAEs, Grade 3/4, Grade 5), Table tae07a, Table tae07b (TEAEs over time), Table tae02j, Table tae02k (related), Table tae02g, Table tae02h (SAEs), Table tae02y, Table tae02z (cycle delay), Table tae02s, Table tae02t (dose reduction), and Table tae02p, Table tae02q (treatment withdrawal).
 SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Bleeding Events

To investigate the temporal association between decreased platelet counts based upon laboratory results and concurrent bleeding AEs, subjects with decreased platelet counts by laboratory value were identified and assessed if a bleeding event occurred within ± 7 days of the laboratory result. In the MDS3001 Phase 3 imetelstat group (N = 118), 65.3% of subjects had Grade 3 or Grade 4 decreased platelets while on study treatment, and 7.6% of subjects had a Grade 1 or Grade 2 bleeding event within ± 7 days of the laboratory result ([Applicant Table 95](#)). These included Grade 1 events of haematoma (in 2 subjects), epistaxis (in 2 subjects), and gingival bleeding, haematuria, ecchymosis, and contusion (in 1 subject each), and Grade 2 gastrointestinal haemorrhage (in 1 subject) (MDS3001 CSR [Phase 3]/Listing lsflb14a_p2). None of the subjects in the MDS3001 Phase 3 imetelstat group had Grade 3 or Grade 4 or serious bleeding events associated with Grade 3/4 decreased platelets.

In the MDS3001 Phase 3 placebo group (N = 59), 8.5% of subjects had Grade 3 or Grade 4 decreased platelets while on study treatment, and none of them had a bleeding event within ± 7 days of the laboratory result ([Applicant Table 95](#)).

In the MDS3001 Phase 2 imetelstat group (N = 57), 57.9% of subjects had Grade 3 or Grade 4 decreased platelets while on imetelstat treatment, and 14.0% of subjects had a bleeding event within ± 7 days of the laboratory result ([Applicant Table 95](#)). Two subjects had Grade 3 bleeding events associated with Grade 3/4 decreased platelets (serious haematoma and non-serious post procedural haemorrhage; both not related to imetelstat). Two subjects had serious bleeding events associated with Grade 3/4 decreased platelets (Grade 3 haematoma and Grade 2 rectal haemorrhage; both not related to imetelstat) (MDS3001 CSR [Phase 2]/Listing lsflb14_p1). Among subjects with any grade of decreased platelets, 9 subjects had associated Grade 3/4 or serious bleeding events.

Applicant Table 95: Subjects with Grade 3 or Grade 4 Decrease in Platelets and Bleeding Events Within 7 Days – Study MDS3001 – Phase 2 and Phase 3 (Group B Treated Population)

	Phase 3		Phase 2	Pooled
	Imetelstat (N = 118) n (%)	Placebo (N = 59) n (%)	Imetelstat (N = 57) n (%)	Imetelstat (N = 175) n (%)
Number of subjects with Grade 3/4 platelets on treatment, n (%)	77 (65.3%)	5 (8.5%)	33 (57.9%)	110 (62.9%)
Grade 3/4 platelets with any bleeding events within +/- 7 days	9 (7.6%)	0	8 (14.0%)	17 (9.7%)
With Grade 1/2 bleeding events	9 (7.6%)	0	6 (10.5%)	15 (8.6%)
With Grade 3/4 bleeding events	0	0	2 (3.5%)	2 (1.1%)
With serious bleeding events	0	0	2 (3.5%)	2 (1.1%)

Source: Table tlab07ba, Table tlab07b

The Applicant's Position:

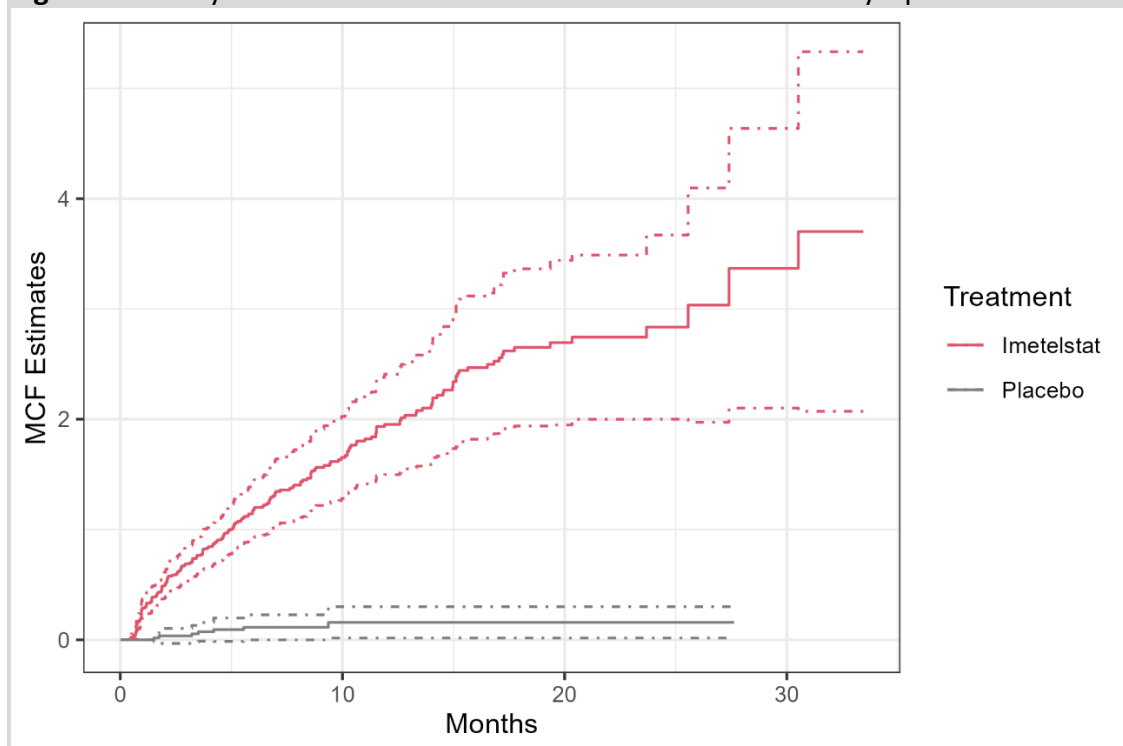
Grade 3/4 thrombocytopenia is very common with imetelstat treatment and occurred more frequently during the first few cycles. These events are manageable with cycle delays and dose reductions and are generally reversible. Few subjects discontinued imetelstat due to thrombocytopenia. Moreover, the number of significant bleeding events was low, the events were assessed by the investigator as not related to imetelstat treatment, and most were not associated with severe thrombocytopenia. Monitoring for thrombocytopenia will be included in the proposed product labeling and these events will be monitored with routine post-marketing pharmacovigilance.

The FDA's Assessment:

Figure 40 shows mean number of Grade 3+ thrombocytopenia events over time estimated with a mean cumulative function (nonparametric). Mean number of Grade 3+ thrombocytopenia events by 12 months is 1.95 (95% CI: 1.50, 2.41) in the imetelstat group and 0.16 (95% CI: 0.02, 0.30) in the placebo group with a difference of 1.79 (95% CI: 1.32, 2.27) between the groups. Mean number of Grade 3+ thrombocytopenia events by 24 months is 2.84 (95% CI: 2.00, 3.67) in the imetelstat group and 0.16 (95% CI: 0.02, 0.30) in the placebo group with a difference of 2.68 (95% CI: 1.83, 3.52) between the groups. These results show a higher frequency of recurrent Grade 3+ thrombocytopenia events in the imetelstat group compared to the placebo group.

Statistical Reviewer Comment: The mean cumulative function results based on FDA analysis match the results based on the code provided by the Applicant in response to the information request (sent on 22 January 2024). The results reported by the Applicant in the response to the information request have some minor discrepancies. These discrepancies have no impact on overall conclusions.

Figure 37: Study MDS3001: Mean Number of Grade 3+ Thrombocytopenia Events over Time



Note: Dotted lines show 95% confidence interval; events starting on or before the last dose date + 30 days, date of subsequent treatment, or date of death were considered

Source: FDA analysis using ADAEIR dataset

Data cutoff 13 Oct 2022

The total incidence of thrombocytopenia will be discussed further in the laboratory section, below. The following will discuss the consequences of thrombocytopenia, including requirement for platelet transfusion, treatment modifications, and hemorrhagic events.

Dose modifications for thrombocytopenia were required more frequently in the imetelstat arm compared to the placebo arm (Table 96). At least one dose modification was required in 54% of patients receiving imetelstat compared to 3.4% of those receiving placebo, including 3.4% versus 0% requiring treatment discontinuation due to thrombocytopenia. Note that thrombocytopenia refers to the adverse event of thrombocytopenia as dose modification for laboratory findings was not documented.

Table 96: Thrombocytopenia in patients on MDS3001 by treatment arm

	Imetelstat N=118 (%)	Placebo N=59 (%)
Any dose modification	54	3.4
Dose reduction	23	1.7
Treatment interruption	47	1.7
Treatment discontinuation	3.4	0

Source: FDA analysis using ADAE dataset
 Data cutoff date 13 October 2022

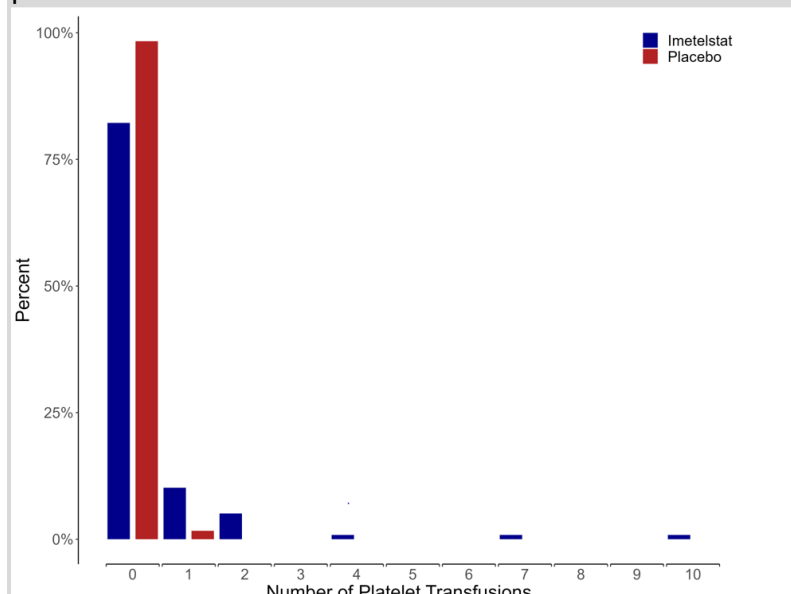
Platelet transfusions were given more frequently in patients on the imetelstat arm as shown in Table 97 and Figure 38, with 21 (18%) patients in the imetelstat arm and 1 (2%) in the placebo arm receiving at least one platelet transfusion. In addition, patients on the imetelstat arm required up to 10 separate transfusions whereas the patient on the placebo arm received platelets only once.

Table 97: Rate of platelet transfusion by study arm

	Imetelstat (N=118)	Placebo (N=60)
Subjects requiring platelet transfusion on-treatment, n (%)	21 (18%)	1 (2%)
Number of platelet transfusions, median (range)	1 (1, 10)	-- (1)

Source: FDA analysis using ADCM and ADTIPR datasets
 Data cutoff date 13 October 2022

Figure 38: Histogram of platelet transfusion requirements by study arm in patients on MDS3001 phase 3



Source: FDA analysis using ADTIPR dataset
 Data cutoff 13 October 2022

Patients on the imetelstat arm experienced more adverse events of hemorrhage compared to those on the placebo arm, with 22% of patients in the imetelstat arm and 12% in the placebo arm experiencing at least one hemorrhage (Table 98). No specific site of bleeding dominated; however, epistaxis, hematoma, contusion, and GI bleeding were common events. All of these events were more common in the imetelstat arm except for contusion. Grade 3-4 events were rare but did occur in three patients on the imetelstat arm and one on the placebo arm. All grade 3-4 events were related to GI bleeding, except for one grade 3 hematuria in the imetelstat arm.

Table 98: Hemorrhagic events in patients on MDS3001 by study arm and severity

Adverse Event	Imetelstat N=118 (%)		Placebo N=59 (%)		Risk difference	
	All Grade	Grade 3-4	All Grade	Grade 3-4	All Grade	Grade 3-4
Any Hemorrhage	22	2.5	12	1.7	+10.2	+0.8
Epistaxis	7	0	0	0	+6.8	0
Hematoma	6	0	0	0	+5.9	0
Contusion	0.8	0	5	0	-3.4	0
GI Hemorrhage	4.2	1.7	3.4	1.7	+0.8	0

Source: FDA analysis using ADAE dataset
 Data cutoff date 13 October 2022

Thrombocytopenia and hemorrhagic events were seen frequently in patients receiving imetelstat in the ISS, with an increase in incidence as the dose of imetelstat increased. The finding is most notable in patients who received a higher dose of imetelstat.

Table 99: Thrombocytopenia and hemorrhagic events by dose level in the overall development program

	Low dose N=54	Standard dose N=190	High dose N=296	Placebo N=59
Thrombocytopenia	11 (21)	137 (73)	184 (62)	6 (10)
Hemorrhage	12 (22)	50 (26)	153 (52)	7 (12)
Grade 3-4 hemorrhage	1 (1.9)	11 (6)	62 (21)	1 (1.7)
Fatal hemorrhage	0	0	5 (1.7)	0

Source: FDA analysis using ADAE dataset

Data cutoff date 13 October 2022

A total of 138 patients receiving >7.1 mg/kg/4 weeks of imetelstat experienced at least one event in the broad SMQ of hemorrhage. When laboratory terms were removed, this decreased to 98 (33%). However, grade 3-4 hemorrhagic events were seen in 62 (21%) patients and fatal events were seen in 5 (1.7%) of patients who received >7.1 mg/kg/4 weeks of imetelstat. Fatal events included hemorrhage, hemorrhage intracranial (2), esophageal varices hemorrhage, and upper GI hemorrhage.

In summary, platelet decreases were observed in over 90% of patients receiving imetelstat (by laboratory values, Table 83). The mean platelet count on the imetelstat arm decreased and did not improve to baseline in subsequent cycles, despite a higher rate of platelet transfusion in the imetelstat arm. Finally, hemorrhage was observed more frequently in patients receiving imetelstat. Overall, the risk of thrombocytopenia is high in patients receiving imetelstat.

Clinical Reviewer comments: The incidence of thrombocytopenia was much higher in the imetelstat arm of the phase 3 portion of MDS3001 compared to the placebo arm. This finding is confirmed by a high incidence of thrombocytopenia in patients who received imetelstat in the phase 2 portion of the study and in various studies in the ISS. There appears to be a dose-response relationship based on the incidence of thrombocytopenia compared to dose in the ISS; however, the relationship is confounded by the wide variety of underlying conditions being treated. Bleeding events and platelet transfusion were more common with imetelstat compared to placebo in MDS3001 and the ISS confirmed that bleeding events were observed throughout the developmental program, including fatal hemorrhagic events. Although no fatal hemorrhagic events were identified in MDS3001, the reviewer feels that the death attributed to “neurological degeneration” in the phase 2 portion of the study was consistent with death due to an intracranial hemorrhage, although no testing that could have confirmed this diagnosis (i.e., imaging, autopsy) was reported.

We disagree with the Applicant’s statement that events of thrombocytopenia occurred primarily in the early cycles. Although some decrease in incidence was observed after the first 3 cycles,

the rates of thrombocytopenia remained high. In addition, the less frequent CBC in later cycles may confound the comparison. Also see laboratory section above for further details.

Overall, thrombocytopenia is a common and severe risk of imetelstat use and careful monitoring and treatment is needed to prevent severe or fatal hemorrhage.

8.2.5.3 Neutropenia and Infections

Data:

Neutropenia

Neutropenia findings based on laboratory data are summarized in [Section 8.2.4](#) under the “Laboratory Findings” heading.

In the MDS3001 Phase 3 imetelstat group (N = 118), neutropenia (any grade) was reported in 73.7% of subjects, including 67.8% of subjects with Grade 3/4 neutropenia ([Applicant Table 100](#)). Grade 4 neutropenia was reported in 24 subjects (Listing lae02e). Treatment-related neutropenia was reported in 64.4% of subjects. In the imetelstat group, neutropenia led to dose reduction in 33.1% of subjects, cycle delay in 50.8% of subjects, and discontinuation of study treatment in 5.1% of subjects. Median time to cycle delay due to neutropenia was 4.21 weeks (range: 2.0 to 119.0) and median time to dose reduction was 8.14 weeks (range: 2.0 to 78.9) (MDS3001 CSR [Phase 3]/Table tsix18a_p2). Treatment discontinuation due to neutropenia occurred later in treatment (≥ 100 days) in all but 1 subject (MDS3001 CSR [Phase 3]/Table 65). TEAEs of neutropenia occurred at highest incidence during the first 3 months of treatment and decreased in frequency over time, suggesting a lack of cumulative toxicity.

In the placebo group (N = 59), neutropenia (any grade) was reported in 6.8% of subjects, including 3.4% of subjects with Grade 3/4 neutropenia ([Applicant Table 100](#)). One subject had Grade 4 neutropenia (Listing lae02e). Treatment-related neutropenia was reported in 5.1% of subjects. One (1.7%) subject had a dose reduction due to neutropenia, and 1 (1.7%) subject had a cycle delay due to neutropenia. No subjects in the placebo group discontinued study treatment due to neutropenia.

There were no Grade 5 events of neutropenia and no SAEs of neutropenia reported in either MDS3001 Phase 3 treatment group.

In the MDS3001 Phase 2 imetelstat group (N = 57), neutropenia (any grade) was reported in 66.7% of subjects, including 59.6% of subjects with Grade 3/4 neutropenia. TEAEs of neutropenia occurred at the highest incidence during the first 3 months of treatment and decreased in frequency over time, suggesting a lack of cumulative toxicity. Most events of neutropenia were considered related to imetelstat treatment. One subject had an SAE of Grade 4 neutropenia considered related to imetelstat that led to dose reduction. There were no

Grade 5 events of neutropenia. Neutropenia led to cycle delay in 49.1% of subjects, dose reduction in 43.9% of subjects, and discontinuation of imetelstat in 8.8% of subjects. All discontinuations due to neutropenia occurred later in treatment (> 100 days on study) (Listing Isfae09_p1).

Applicant Table 100: Treatment-emergent Adverse Events: Neutropenia – Study MDS3001 – Phase 2 and Phase 3 (Group B Treated Population)

Subjects with Neutropenia:	Phase 3		Phase 2	Pooled
	Imetelstat (N = 118)	Placebo (N = 59)	Imetelstat (N = 57)	Imetelstat (N = 175)
Any TEAE, n (%)	87 (73.7%)	4 (6.8%)	38 (66.7%)	125 (71.4%)
0 to <3 months, n/N (%)	84/118 (71.2%)	3 (5.1%)	34/57 (59.6%)	118/175 (67.4%)
3 to <6 months, n/N (%)	49/104 (47.1%)	3 (5.5%)	19/49 (38.8%)	68/153 (44.4%)
6 to <12 months, n/N (%)	33/85 (38.8%)	1 (2.4%)	13/37 (35.1%)	46/122 (37.7%)
≥12 months, n/N (%)	17/49 (34.7%)	1 (6.3%)	5/22 (22.7%)	22/71 (31.0%)
Treatment-related TEAE, n (%)	76 (64.4%)	3 (5.1%)	32 (56.1%)	108 (61.7%)
Grade 3 or 4 TEAE, n (%)	80 (67.8%)	2 (3.4%)	34 (59.6%)	114 (65.1%)
0 to <3 months, n/N (%)	62/118 (52.5%)	0	22/57 (38.6%)	84/175 (48.0%)
3 to <6 months, n/N (%)	26/104 (25.0%)	2 (3.6%)	9/49 (18.4%)	35/153 (22.9%)
6 to <12 months, n/N (%)	16/85 (18.8%)	0	4/37 (10.8%)	20/122 (16.4%)
≥12 months, n/N (%)	7/49 (14.3%)	0	1/22 (4.5%)	8/71 (11.3%)
Grade 5 TEAE, n (%)	0	0	0	0
Treatment-emergent SAE, n (%)	0	0	1 (1.8%)	1 (0.6%)
TEAE that led to cycle delay, n (%)	60 (50.8%)	1 (1.7%)	28 (49.1%)	88 (50.3%)
TEAE that led to dose reduction, n (%)	39 (33.1%)	1 (1.7%)	25 (43.9%)	64 (36.6%)
TEAE that led treatment withdrawal, n (%)	6 (5.1%)	0	5 (8.8%)	11 (6.3%)

Source: Table tae02a, Table tae02b (TEAEs, Grade 3/4, Grade 5), Table tae07a, Table tae07b (TEAEs over time), Table tae02j, Table tae02k (related), Table tae02g, Table tae02h (SAEs), Table tae02y, Table tae02z (cycle delay), Table tae02s, Table tae02t (dose reduction), and Table tae02p, Table tae02q (treatment withdrawal).
 SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Infections

In the MDS3001 Phase 3 imetelstat group (N = 118), treatment-emergent infections (any grade) were reported in 42.4% of subjects, and 10.2% of subjects had Grade 3/4 infections ([Applicant Table 101](#)). The most commonly reported infection was COVID-19 in 15.3% of subjects), followed by urinary tract infection in 5.9% of subjects and pneumonia in 3.4% subjects. Four (3.4%) subjects had Grade 4 infections (1 subject each with COVID-19 pneumonia and Enterococcal sepsis, and 2 subjects with sepsis, 1 of which was considered related to study treatment) (Listing lae2e). Median time to onset of first Grade 3/4 infection 142.0 days (range: 20 to 644 days) (Table taesi03j). Six subjects had infections considered related to study treatment, including sinusitis, pneumonia bacterial, pneumonia, renal abscess, sepsis, urinary

tract infection, and neutropenic sepsis (Table tae02j). Serious infections were reported in 11.9% of subjects, the most common of which was pneumonia in 3 (2.5%) subjects (Table tae02g).

In the MDS3001 Phase 3 placebo group (N = 59), 33.9% of subjects had infections, including 13.6% of subjects with Grade 3/4 infections ([Applicant Table 101](#)). Median time to first Grade 3/4 infection was 142.0 days (range: 20 to 644 days) (Table taesi03j). The most commonly reported infection was COVID-19 in 4 (6.8%) subjects. One subject had a Grade 4 infection of listeriosis, considered not related to study treatment (Listing lae02e). There were no infections considered related to study treatment in the placebo group, and no Grade 5 infections. Serious infections were reported in 13.6% of subjects, the most common of which was COVID-19 pneumonia in 5.1% of subjects. Median time to onset of first Grade 3/4 infection in the placebo group was 61.5 days (range: 15 to 638 days) (Table tae02g).

In the MDS3001 Phase 2 imetelstat group (N = 57), treatment-emergent infections (any grade) were reported in 57.9% of subjects in the overall subject population, and 21.1% of subjects had Grade 3/4 infections (Table taesi02t). The most commonly reported infection was urinary tract infection (17.5%), followed by bronchitis and nasopharyngitis (12.3% each). Ten subjects had Grade 3 infections, and 6 subjects had Grade 4 infections, one of which was considered related to study treatment (urinary tract infection) (MDS3001 CSR [Phase 2]/Section 12.4.4.2.2.2). One subject had a Grade 5 infection of COVID-19 pneumonia considered not related to study treatment.

To investigate the temporal association between decreased neutrophil counts based upon laboratory results and concurrent infection AEs, subjects with decreased neutrophil counts by laboratory value were identified and assessed if an infection event occurred within ± 7 days of the laboratory result. In the MDS3001 Phase 3 imetelstat group, 72.0% of subjects had Grade 3 or Grade 4 decreased neutrophils while on study treatment, and 7.6% of subjects had an infection within ± 7 days of the laboratory result ([Applicant Table 102](#)). Three subjects with sepsis events had Grade 3/4 infections associated with Grade 3/4 neutropenia, all of which were reported as SAEs (Listing llab05a). In the placebo group (N = 59), among the 6.8% of subjects with Grade 3 or Grade 4 decreased neutrophils while on study treatment, 1 (1.7%) subject had a Grade 4 infection within ± 7 days of the laboratory result ([Applicant Table 102](#) and Listing llab05a).

Applicant Table 101: Treatment-emergent Adverse Events of Interest: Infections Reported in ≥ 5% of Either Group or Reported Serious in Any Subject – Study MDS3001 – Phase 3 Imetelstat Versus Placebo (Group A Treated Population)

Preferred Term	Imetelstat – Phase 3 (N = 118) n (%)			Placebo – Phase 3 (N = 59) n (%)		
	Any Grade	Grade 3/4	SAE	Any Grade	Grade 3/4	SAE
Subjects with any infection TEAE	50 (42.4%)	12 (10.2%)	14 (11.9%)	20 (33.9%)	8 (13.6%)	8 (13.6%)
COVID-19	18 (15.3%)	0	0	4 (6.8%)	0	0
Urinary tract infection	7 (5.9%)	2 (1.7%)	2 (1.7%)	2 (3.4%)	0	0
Pneumonia	4 (3.4%)	3 (2.5%)	3 (2.5%)	2 (3.4%)	1 (1.7%)	1 (1.7%)
Gastroenteritis	3 (2.5%)	0	0	2 (3.4%)	1 (1.7%)	1 (1.7%)
COVID-19 pneumonia	2 (1.7%)	2 (1.7%)	2 (1.7%)	3 (5.1%)	3 (5.1%)	3 (5.1%)
Erysipelas	2 (1.7%)	0	1 (0.8%)	0	0	0
Sepsis	2 (1.7%)	1 (0.8%)	2 (1.7%)	0	0	0
Clostridium difficile infection	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Enterococcal sepsis	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Gastroenteritis clostridial	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Infection	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Neutropenic sepsis	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Pneumonia bacterial	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Pseudomembranous colitis	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Abscess limb	0	0	0	2 (3.4%)	2 (3.4%)	2 (3.4%)
Arthritis bacterial	0	0	0	1 (1.7%)	1 (1.7%)	1 (1.7%)
Listeriosis	0	0	0	1 (1.7%)	1 (1.7%)	1 (1.7%)

Source: Table taesi02s, Table tae02g

Note: Medical Dictionary for Regulatory Activities (MedDRA) v25.0 was used for TEAE coding.

SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Applicant Table 102: Subjects with Grade 3 or Grade 4 Decrease in Neutrophils and Infection Events Within 7 Days – Study MDS3001 – Phase 2 and Phase 3 (Treated Population)

	Phase 3		Phase 2	Pooled
	Imetelstat (N = 118) n (%)	Placebo (N = 59) n (%)	Imetelstat (N = 57) n (%)	Imetelstat (N = 175) n (%)
Number of subjects with Grade 3/4 neutrophils on treatment	85 (72.0%)	4 (6.8%)	37 (64.9%)	122 (69.7%)
Grade 3/4 neutrophils with any infection event within +/- 7 days	9 (7.6%)	1 (1.7%)	11 (19.3%)	20 (11.4%)
With Grade 1/2 infection events	6 (5.1%)	0	10 (17.5%)	16 (9.1%)
With Grade 3/4 infection events	3 (2.5%)	1 (1.7%)	3 (5.3%)	6 (3.4%)

	Phase 3		Phase 2	Pooled
	Imetelstat (N = 118) n (%)	Placebo (N = 59) n (%)	Imetelstat (N = 57) n (%)	Imetelstat (N = 175) n (%)
With serious infection events	3 (2.5%)	1 (1.7%)	1 (1.8%)	4 (2.3%)

Source: Table tlab07a, Table tlab07b

The Applicant's Position:

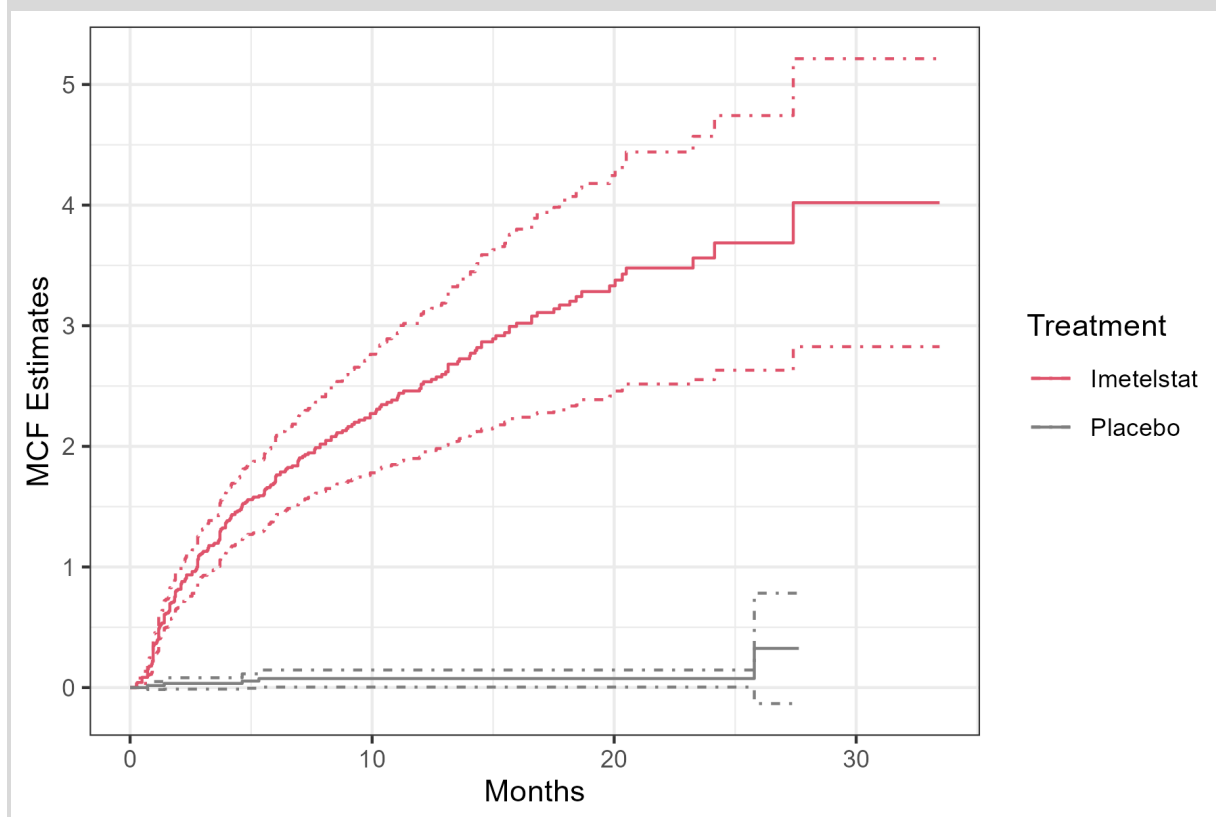
Grade 3/4 neutropenia is very common with imetelstat and occurred more frequently during the first few cycles. These events are manageable with dose modifications and growth factor support and generally reversible. Few subjects discontinued imetelstat due to neutropenia. Moreover, the number of events of febrile neutropenia or significant infections was low, severe infections were generally not associated with severe neutropenia, and most were not related to imetelstat treatment. Management of neutropenia will be included in the proposed product labeling and these events will be monitored with routine post-marketing pharmacovigilance.

The FDA's Assessment:

Figure 39 shows mean number of Grade 3+ neutropenia events over time estimated with a mean cumulative function (nonparametric). Mean number of Grade 3+ neutropenia events by 12 months is 2.48 (95% CI: 1.91, 3.04) in the imetelstat group and 0.07 (95% CI: 0.00, 0.15) in the placebo group with a difference of 2.40 (95% CI: 1.83, 2.97) between the groups. Mean number of Grade 3+ thrombocytopenia events by 24 months is 3.56 (95% CI: 2.55, 4.57) in the imetelstat group and 0.07 (95% CI: 0.00, 0.15) in the placebo group with a difference of 3.49 (95% CI: 2.48, 4.50) between the groups. These results show a higher frequency of recurrent Grade 3+ neutropenia events in the imetelstat group compared to the placebo group.

Statistical Reviewer Comment: The mean cumulative function results based on FDA analysis match the results based on the code provided by the Applicant in response to the information request (sent on 22 January 2024). The results reported by the Applicant in the response to the information request have some minor discrepancies. These discrepancies have no impact on overall conclusions.

Figure 39. Study MDS3001: Mean Number of Grade 3+ Neutropenia Events over Time



Note: Dotted lines show 95% confidence interval; events starting on or before the last dose date + 30 days, date of subsequent treatment, or date of death were considered

Source: FDA analysis using ADAEIR dataset

Data cutoff 13 Oct 2022

The total incidence of neutropenia and grade 3-4 neutropenia will be discussed further in the laboratory section below. This section will concentrate on clinical consequences of neutropenia, including neutropenia requiring dose modification, infections, and neutropenia requiring concomitant medications to ameliorate the risks associated with neutropenia.

Dose modification for neutropenia was required more frequently in patients receiving imetelstat compared to placebo (Table 103). In the imetelstat arm, 59% of patients required at least one dose modification, including 5% who required treatment discontinuation for neutropenia. In the placebo arm, one patient required dose modification, and none required treatment discontinuation for neutropenia. Note that neutropenia refers to the adverse event of neutropenia as dose modification for laboratory findings was not documented.

Table 103: Dose modification for neutropenia by study arm for patients on the phase 3 portion of MDS3001

	Imetelstat N=118 (%)	Placebo N=59 (%)
Any dose modification	59	1.7
Dose reduction	33	1.7
Treatment interruption	50	1.7
Treatment discontinuation	5	0

Source: FDA analysis using ADAE dataset
 Data cutoff date 13 October 2022

Patients receiving imetelstat had more events in the SOC infections and infestations compared with patients on the placebo arm. Sepsis, UTIs, and bacterial infections were more common in the groups treated with imetelstat in both parts 1 and 2. Viral infections and COVID-19 were more common in the imetelstat arm of part 2, but not in part 1, possibly due to most patients in part 1 receiving treatment prior to the SARS-CoV2 pandemic.

Table 104: Infectious treatment emergent adverse events

Adverse event	Imetelstat N=118 (%)		Placebo N=59 (%)		Risk Difference	
	All Grade	Grade 3-4	All Grade	Grade 3-4	All grade	Grade 3-4
Infections*	47	11	34	14	+8.5	-2.6
Viral infections**	24	1.7	14	5	+10.2	-3.4
Bacterial infections**	7	3.4	5	3.4	+1.7	0
Pathogen not specified**	25	7	27	9	-1.7	-1.7
Specific infections						
COVID-19†	19	1.7	12	5	+6.9	-3.3
UTI	9	1.7	5	0	+3.4	+1.7
URI†	8	0	7	0	+1	0
Pneumonia†	5	3.4	5	3.4	0	0
Sepsis†	4.2	4.2	0	0	+4.2	+4.2

RD=risk difference between imetelstat phase 3 and placebo

*SOC Infections and infestations

**HLGT

***HLT

†Grouped term

Source: FDA analysis using ADAE dataset

Data cutoff date 13 October 2022

Clinical Reviewer comments: The increase in infections and in serious infections such as sepsis indicate that the neutropenia observed with imetelstat has clinical consequences. As noted

below, use of granulocyte colony stimulating agents was far more common among patients treated with imetelstat versus those treated with placebo, possibly ameliorating the risk of infection to some degree.

More patients receiving imetelstat required myeloid growth factor support, with 42 (36%) of patients on the imetelstat arm requiring myeloid growth factor support at any time after start of therapy versus two patients in the placebo arm Table 105 and Figure 40. Among patients who received growth factor support, the number of episodes for which it was required ranged from 1 to 23, with a median of 3 times. Of the two patients on the placebo arm who required growth factor support, one received it once, the other 7 times.

Table 105: Myeloid growth factor use by study arm in patients on phase 3 component of MDS3001

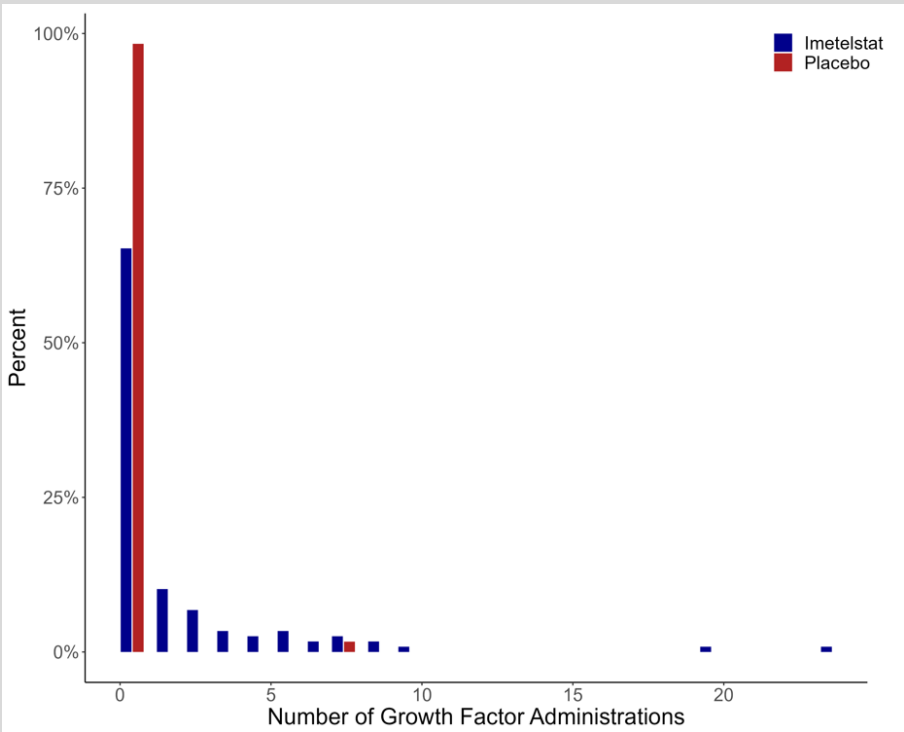
	Imetelstat (N=118)	Placebo (N=60)
Subjects requiring myeloid growth factor on-treatment, n (%)	42 (36%) *	2 (3%)
Frequency of myeloid growth factor administration, median (range)	3 (1, 23)	-- (1, 7)

* Includes one patient who started growth factor 3 days after last dose of study drug

Source: FDA analysis using ADCM and ADTIPR datasets

Data cutoff date 13 October 2022

Figure 40: MDS3001 Phase 3: Histogram of patients requiring myeloid growth support by study arm



Source: FDA analysis using ADCM dataset
Data cutoff 13 October 2022

Use of any anti-infective (including vaccines) was documented in 75 (64%) of patients receiving imetelstat and 35 (59%) of those receiving placebo (Table 106). If vaccines were excluded, systemic anti-infective treatment was used in 50 (42%) of patients on the imetelstat arm and 20 (34%) of patients on the placebo arm. Antibiotic use was documented in 43 (36%) of patients receiving imetelstat and 19 (32%) of patients receiving placebo. Antiviral medication use was documented in 12 (10%) patients receiving imetelstat and 3 (5%) of patients receiving placebo.

Table 106: MDS3001 Phase 3: Use of anti-infective agents by study arm

	Imetelstat N=118 (%)	Placebo N=59 (%)
Any anti-infective	64	59
Any except vaccines	42	34
Antibiotics	36	32
Anti-virals	10	5

Source: FDA analysis using ADCM dataset
Data cutoff date 13 October 2022

Clinical Reviewer comments: Despite a much higher use of anti-infective medications and myeloid growth factor, the rate of infections was higher in the imetelstat arm of the phase 3 portion of MDS3001. In addition, patients on the phase 2 portion had a high rate of infection, further demonstrating that there is an increased risk of infection with use of imetelstat.

8.2.5.4 Infusion-Related Reactions

Data:

In the MDS3001 Phase 3 imetelstat group (N = 118), IRRs (any grade) were reported in 7.6% of subjects, and Grade 3 events were reported in 1.7% of subjects ([Applicant Table 107](#)). Median time to onset of the Grade 3 events was 106.5 days (range: 85 to 128 days) in the 2 subjects with Grade 3 IRRs (Table taesi03g). The most commonly reported IRR was headache in 4.2% of subjects. All events were considered related to study treatment. There were no Grade 4 or Grade 5 events. One subject had an IRR of serious Grade 3 hypertensive crisis described briefly below

- Subject (b) (6) had an SAE of Grade 3 hypertensive crisis on Study Day 85 considered related to imetelstat (Listing lae02c). The subject had an ongoing medical history of hypertension. The subject's blood pressure was 135/54 mmHg at the start of the infusion. Prior to the infusion, the subject received premedication with steroid, but not the antihistamine (reason not specified). Approximately 1 hour into the infusion, her blood pressure was 206/87 mmHg, and the infusion was interrupted. She was treated with nitroglycerin. Approximately 30 minutes later, her blood pressure was 169/69 mmHg, and the infusion was restarted. The infusion was interrupted a second time (blood pressure 203/84 mmHg) and then restarted again (blood pressure 184/71 mmHg). At the conclusion of the infusion, her blood pressure was 209/91 mmHg and she was treated with nifedipine. Three days later, the hypertension improved to Grade 1, and there were no further events of hypertension in subsequent cycles. The subject continued treatment at a reduced dose of 4.4 mg/kg (active moiety, equivalent to 4.7 mg/kg imetelstat-sodium) due to thrombocytopenia and neutropenia. The subject discontinued imetelstat on Study Day 322 due to lack of efficacy.

In the placebo group (N = 59), 3.4% of subjects had IRR events. All events were Grade 1 and considered related to study treatment. There were no serious events.

Five (4.2%) subjects in the imetelstat group had IRRs that led to study treatment interruption (Table taesi01o). One subject in the imetelstat group discontinued imetelstat due to an IRR event of Grade 2 pruritus. No subjects in the placebo group had a treatment delay or discontinuation due to an IRR. No subject in either treatment group had a dose reduction due to an IRR event. IRRs were managed by symptom relief (steroids, antihistamines, blood pressure medications and pain medication).

In the MDS3001 Phase 2 imetelstat group (N = 57), IRR (any grade) were reported in 10.5% of subjects, and Grade 3/4 events were reported in 7.0% of subjects (Table taesi02n). Median time to onset of the Grade 3/4 events was 520.5 days (range: 379 to 1197 days) in the 4 subjects with Grade 3/4 IRRs (Table taesi03h). The most commonly reported IRR was back pain in 5.3% of subjects, followed by chest pain and hypotension (3.5% each). There were no Grade 4 or Grade 5 events and no serious events (Table taesi01n). Imetelstat was interrupted in 5 subjects due to an IRR. No subjects discontinued treatment due to an IRR. Infusion-related reactions were managed by symptom relief (steroids, antihistamines, blood pressure medications and pain medications). The occurrence of IRR was similar in the Phase 2 and Phase 3 imetelstat groups.

Applicant Table 107: Treatment-emergent Adverse Events: Infusion Related Reaction Events – Study MDS3001 – Phase 3 Imetelstat Versus Placebo (Group A Treated Population)

Category Preferred Term	Imetelstat- Phase 3 (N = 118) n (%)			Placebo – Phase 3 (N = 59) n (%)		
	Any Grade	Grade 3/4	SAE	Any Grade	Grade 3/4	SAE
Any IRR TEAE	9 (7.6%)	2 (1.7%)	1 (0.8%)	2 (3.4%)	0	0
Headache	5 (4.2%)	0	0	0	0	0
Abdominal pain	1 (0.8%)	0	0	0	0	0
Arthralgia	1 (0.8%)	0	0	0	0	0
Asthenia	1 (0.8%)	0	0	0	0	0
Back pain	1 (0.8%)	0	0	0	0	0
Bone pain	1 (0.8%)	0	0	0	0	0
Diarrhoea	1 (0.8%)	0	0	0	0	0
Erythema	1 (0.8%)	0	0	0	0	0
Hypertensive crisis	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Malaise	1 (0.8%)	0	0	0	0	0
Non-cardiac chest pain	1 (0.8%)	1 (0.8%)	0	0	0	0
Pruritus	1 (0.8%)	0	0	0	0	0
Urticaria	1 (0.8%)	0	0	0	0	0
Chest pain	0	0	0	1 (1.7%)	0	0
Cough	0	0	0	1 (1.7%)	0	0
Pyrexia	0	0	0	1 (1.7%)	0	0

Source: Table taesi02m, Table taesi04g

Note: Medical Dictionary for Regulatory Activities (MedDRA) v25.0 was used for TEAE coding.

IRR = infusion-related reaction; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

The Applicant's Position:

The incidence of IRRs in the imetelstat studies was low (< 15%) across the program and most events were Grade 1/2. The introduction of protocol mandated premedication with hydrocortisone and diphenhydramine has reduced the incidence and severity of IRRs. IRRs were managed by dose interruptions and symptom relief. There were no Grade 4 or 5 events or dose reductions due to IRRs. One subject had an IRR of serious Grade 3 hypertensive crisis in setting of not receiving premedication with an antihistamine, that led to treatment discontinuation. Two other subjects discontinued treatment due IRR events: Grade 2 pruritis in 1 subject, and Grade 3 dyspnoea and Grade 2 arthritis in the other subject. The most commonly reported IRR in imetelstat-treated LR MDS subjects was headache. Recommendations for premedication and management of IRRs will be included in the proposed product labeling.

The FDA's Assessment:

No events under the PT of infusion related reaction (IRR) or cytokine release syndrome were reported in the ADAE dataset for patients on either part or arm of MDS3001. However, symptoms associated with IRR were observed frequently in patients receiving imetelstat on MDS3001. The Applicant reported IRR based on their grouped term occurred in 17 patients, including 6 (11%) in the phase 2 portion of the study, 9 (8%) receiving imetelstat in the phase 3 portion, and 2 (3.4%) on the placebo arm of the phase 3 portion. Preferred terms commonly associated with IRR included back pain, headache, bone pain, and chest pain. IRR resulted in drug discontinuation in one patient and treatment interruption in 10 patients.

As noted by the Applicant, one of these events was considered grade 3. Among the preferred terms noted by the Applicant as related to IRR, six events in 6 patients, all of whom received imetelstat, were grade 3. These events included hypertension, hypertensive crisis, hypotension, non-cardiac chest pain, headache, and back pain.

Events considered to be related to IRR by the Applicant occurred in 91 (12%) of patients in the ISS dataset, including 30 who had IRR as the PT provided for the event. Treatment was withdrawn in 10 patients due to IRR.

Some adverse events that may be associated with IRR were more common in patients receiving imetelstat including headache, pruritus, fatigue, and arthralgia/myalgia. However, it is difficult to be certain how many of these events were related to IRR and how many were independent risks of imetelstat.

Clinical Reviewer comments: Overall, there appears to be a significant risk of IRR with use of imetelstat. A warning and precaution statement is planned for the label and recommendations for premedication will be provided.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Data:

FACIT-Fatigue Score

Additional analysis of the FACIT-Fatigue Score described in [Section 8.1.2](#) demonstrated that subjects who reported TEAE of Grade 3 or 4 neutropenia or thrombocytopenia had the same rates of sustained meaningful improvement in fatigue (42/80; 52.5% and 39/73; 53.4% respectively) as the total imetelstat population (50%) (SCE Section 3.2.4.1.2).

The Applicant's Position:

Treatment-emergent neutropenia and thrombocytopenia had no impact on improvement in fatigue observed in subjects who achieved TI.

The FDA's Assessment:

See the "Efficacy Results – Secondary or Exploratory COA (PRO) endpoints" section above for FDA discussion regarding the FACIT-Fatigue score and other PRO endpoints related to disease symptoms.

FDA also examined patient-reported tolerability data from the FACT GP5 item "I am bothered by side effects of treatment" and found that patients treated with imetelstat did not report increased side effects compared to placebo. This is likely because the full side effect profile of imetelstat includes non-symptomatic AEs such as cytopenias and is further discussed in detail in Section 3.4.

8.2.7. Safety Analyses by Demographic Subgroups

Data:

Age

In the imetelstat group (N =118), 77.1% subjects were ≥ 65 years old. Events reported more frequently in subjects ≥ 65 years old than in subjects < 65 years old included thrombocytopenia (79.1% vs 63.0%, respectively), and infections (48.4% vs 22.2%, respectively). In the placebo group (N = 59), 84.7% subject were ≥ 65 years old. Events reported more frequently in subjects ≥ 65 years old than in subjects < 65 years old included thrombocytopenia (12.0% vs 0%, respectively), and infections (40.0% vs 0%, respectively). There were no differences of ≥ 10% of subjects in SAEs, hepatic events, bleeding events, or IRRs.

In the imetelstat group (N =118), 29.7% subjects were ≥ 75 years old. Events reported more frequently in subjects ≥ 75 years old than in subjects < 75 years old included thrombocytopenia (82.9% vs 72.3%, respectively) and SAEs (44.8% vs 28.1%, respectively), driven by serious

infections (20.7% vs 9.0%, respectively). In the placebo group (N = 59), 39.0% subjects were $\geq$ 75 years old. Events reported more frequently in subjects $\geq$ 75 years old included SAEs (38.1% vs 13.2%, respectively) and serious infections (23.8% vs 7.9%, respectively). There were no differences of $\geq$ 10% of subjects in hepatic events, bleeding events, infections (any grade), or IRRs.

Sex

In the imetelstat group (N =118), 60.2% of subjects were males and 39.8% of subjects were females. There were no differences of $\geq$ 10% of subjects in the subgroup analysis by sex for thrombocytopenia, neutropenia, SAEs, hepatic events, bleeding events, infections, or IRRs.

Renal Function

In the imetelstat group (N =118), subjects at baseline were distributed across the renal function categories of normal (30.5%), mild impairment (35.6%), or moderate impairment (33.1%). There was no trend of worse toxicity in increasingly renally impaired subjects. There were no differences of $\geq$ 10% of subjects across $\geq$ 2 subgroups in thrombocytopenia, SAEs, bleeding events, infections (any grade), or IRRs.

Hepatic Function

In the imetelstat group (N =118), most subjects had normal (57.6%) or mild (26.3%) hepatic impairment at baseline. Fewer subjects had moderate hepatic impairment (14.4%), and thus interpretation of results in this subgroup should be made with caution. There was no trend of worse toxicity in increasingly hepatically impaired subjects.

Race, Ethnicity, ECOG Performance Status (PS)

Most subjects were White (80.5%), Not Hispanic (84.7%), and ECOG PS 0 or 1 (94.9%) at baseline.

The Applicant's Position:

No clinically significant differences in safety from the overall population were observed in the subgroup analysis, including rate and intensity of TEAEs, SAEs, and events of interest in imetelstat-treated subjects based on age, sex, race/ethnicity, ECOG PS, mild to moderate hepatic impairment, or mild to moderate renal impairment. The analysis of race, ethnicity, and ECOG PS subgroups were not meaningful due to the disproportionate number of subjects who were White, Not Hispanic, and ECOG PS 0 or 1 at baseline, consistent with the characteristics of patients in the proposed indication.

The FDA's Assessment:

FDA evaluated risk of TEAE and grade 3-4 AE by sex, race, ethnicity, and age (<65 years, $\geq$ 65 years of age). Results are below.

Sex

A total of 92 patients treated on trial MDS3001 were female, including 25 (35%) in the phase 2 component, 47 (40%) in the phase 3 imetelstat arm, and 20 (34%) on the phase 3 placebo arm. Comparison of AE by sex and study arm for the phase 3 portion of the study is provided in Table 108. Results were generally similar for the phase 2 portion of the study.

Table 108: Treatment emergent events by sex and study arm

	Female			Male		
	Imetelstat N=47	Placebo N=20	RD	Imetelstat N=71	Placebo N=39	RD
Overall	46 (98)	20 (100)	-2	71 (100)	39 (100)	0
Grade 3+	42 (89)	8 (40)	+49	66 (93)	21 (54)	+39
Neutropenia	39 (83)	2 (10)	+73	50 (70)	3 (8)	+62
Thrombocytopenia	34 (72)	2 (10)	+62	55 (78)	4 (10)	+68
Arthralgia/myalgia	15 (32)	2 (10)	+22	15 (21)	9 (23)	-2
Infections	22 (47)	6 (30)	+17	33 (47)	14 (36)	+11
Hemorrhage	10 (21)	1 (5)	+16	16 (23)	6 (15)	+8
Leukopenia	6 (13)	0	+13	6 (9)	1 (2.6)	+6.4
Fatigue	14 (30)	4 (20)	+10	20 (28)	8 (21)	+7
COVID-19	9 (19)	2 (10)	+9	13 (18)	6 (15)	+3
Hypertension	4 (9)	0	+9	0	0	0
Iron overload	4 (9)	0	+9	3 (4.2)	8 (21)	-16.8
Diarrhea	6 (13)	1 (5)	+8	8 (11)	6 (15)	-4
UTI	6 (13)	1 (5)	+8	2 (2.8)	1 (2.6)	+0.2
Pruritus	4 (9)	0	+9	3 (4.2)	1 (2.6)	+1.6
Headache	8 (17)	2 (10)	+7	7 (10)	1 (2.6)	+7.4
Peripheral edema	8 (17)	2 (10)	+7	6 (9)	6 (15)	-6
Syncope	3 (6)	0	+6	5 (7)	1 (2.6)	+4.4
Fractures	3 (6)	0	+6	3 (4.2)	1 (2.6)	+1.6
Hepatic disorders	13 (28)	5 (25)	+3	18 (25)	5 (13)	+12

Source: FDA analysis

Data cut-off date 13 May 2023

We disagree with the Applicant's statement that no differences of >10 percent units between the rate of AE between sexes. Overall, men were more likely to have grade 3+ TEAE in both arms of the phase 3 part of the study. Women had a larger risk difference for grade 3+ events (+49 percent units versus +39), but both sexes showed a major increase in risk in the imetelstat arm. Risk difference was >10 percent units higher in female patients compared to male for neutropenia, arthralgia/myalgia, iron overload, and peripheral edema. Infections were more

common in female patients, with a particularly notable higher rate of UTIs, possibly related to the higher rate of neutropenia.

The risk difference was positive for female patients and negative for male patients for iron overload, peripheral edema, diarrhea, and arthralgia/myalgia. The significance of this finding is unclear given the small total number of patients who experienced these TEAE but could suggest areas for post-marketing evaluation.

Overall, the risk was similar between female and male patients, although some events, including neutropenia, arthralgia/myalgia, iron overload, hypertension, infections, and diarrhea appear to be more common in female patients whereas hepatic disorders appeared to be more common in male patients.

Age

The effect of age on risk of TEAE was examined using the age cut-off of 65 (<65 or ≥65 years). The overview of major differences in risk are described below in Table 109.

Table 109: Risk of TEAE by age and study arm

	Age <65			Age ≥65		
	Imetelstat N=27	Placebo N=9	RD	Imetelstat N=91	Placebo N=50	RD
Overall	26 (96)	9 (100)	-4	91 (100)	50 (100)	0
Grade 3+	24 (89)	1 (11)	+78	84 (92)	28 (47)	+45
Neutropenia	19 (70)	0	+70	70 (77)	5 (10)	+67
Thrombocytopenia	17 (63)	0	+63	72 (79)	6 (12)	+53
Hepatic disorders	11 (41)	0	+41	20 (22)	10 (20)	+2
Infections	9 (33)	0	+33	46 (51)	20 (40)	+11
Arthralgia/myalgia	7 (26)	1 (11)	+15	23 (25)	10 (20)	+5
COVID-19	4 (15)	0	+15	18 (20)	8 (16)	+4
Nausea	4 (15)	0	+15	4 (4.4)	3 (6)	-1.6
Leukopenia	3 (11)	0	+11	9 (10)	1 (2)	+8
Pruritus	3 (11)	0	+11	4 (4.4)	1 (2)	+2.4
Hemorrhage	5 (19)	1 (11)	+8	21 (23)	6 (12)	+11
Headache	4 (15)	1 (11)	+4	11 (12)	2 (4)	+8
Fractures	1 (3.7)	0	+3.7	5 (6)	1 (2)	+4
UTI	1 (3.7)	0	+3.7	7 (8)	2 (4)	+4
Fatigue	6 (22)	2 (22)	0	28 (31)	10 (20)	+11
Sepsis	0	0	0	5 (6)	0	+6
Syncope	0	0	0	8 (9)	1 (2)	+7

Atrial fibrillation	0	1 (11)	-11	7 (8)	0	+8

Source: FDA analysis

Dat cut-off date 13 May 2023

Overall, the rate of TEAE, grade 3+ TEAE, neutropenia, and thrombocytopenia were high in both age groups. Grade 3+ TEAE were seen more commonly in the older age group, but only one patient on the placebo arm in the younger age cohort experienced a grade 3+ TEAE, such that the risk difference was much higher for younger patients (+78) versus older patients (+45). Hepatic disorders were seen more commonly in younger patients and only slightly more commonly in imetelstat than in placebo in older patients. Additional TEAE observed more commonly compared to placebo in younger patients (risk difference >5 percent units) included infections, arthralgia/myalgia, COVID-19, nausea, pruritus, leukopenia, and hemorrhage. Among older patients, the rate of TEAE was higher in imetelstat for infections, arthralgia/myalgia, leukopenia, hemorrhage, fatigue, syncope, sepsis, and atrial fibrillation.

Neutropenia and infections were more common in imetelstat than in placebo in both younger and older patients. Of note, infections were not observed in the placebo arm for younger patients and in 33% of patients in the imetelstat arm. Although the total number of infections was higher in older patients, the difference between study arms was less than in younger patients. The finding was supported by high rates of neutropenia and infection in patients on the phase 2 portion of the study, where 8/14 (57%) of patients had neutropenia or infections.

Similarly, thrombocytopenia was high in both younger and older patients, but the difference was +10 percent units in younger patients compared to older patients. Hemorrhage was more common (>5 percent units) in both younger and older patients.

Hepatic disorders, including transaminase and other laboratory abnormalities, were more commonly seen in younger patients and a large difference between study arms was seen in younger, but not older, patients.

In general, the results of the phase 2 component of the study supported the results of the phase 3 portion, with younger patients experiencing high rates of cytopenias, infections, hemorrhage, and hepatic disorders.

Clinical Reviewer comments: No major increase in risk was observed for older patients. However, major risks such as overall TEAE, grade 3+ TEAE, neutropenia, infections, thrombocytopenia, hemorrhage, and hepatic toxicity were seen commonly in both older and younger patients. Strikingly, no infections were reported in younger patients receiving placebo while 33% of younger patients experienced at least one documented infection, highlighting the risk of neutropenia. In addition, only one of the patients experienced grade 3+ TEAE whereas almost 90% receiving imetelstat experienced at least one grade 3+ TEAE.

Race and Ethnicity

TEAE rates were examined by race and ethnicity.

A total of 12 patients were identified as of Hispanic or Latino ethnicity, including one on the phase 2 portion of the study, 6 on the imetelstat arm of phase 3, and 5 on the placebo arm. In general, no major differences were seen compared with the overall population or with the subpopulation identified as non-Hispanic, with the exception of fatigue, which was notably high in the Hispanic population (50%), but given the small number of patients, no conclusions can be drawn from this finding.

A total of 4 patients identified as African American or black (1 in each imetelstat arm, two in placebo). This was considered too small a population to be able to draw any conclusions so the results from this analysis will not be shown.

Twelve patients were identified as Asian, including two in the phase 2 portion of the study, 8 on the imetelstat arm of the phase 3 portion, and 2 on the placebo arm. Hepatic disorders were notably common in the imetelstat arms including 1 out of 2 (50%) of patients on the phase 2 portion, 5 out of 8 (63%) on the imetelstat arm of the phase 3 portion, and no patient on placebo. However, again, the number of patients is too small to draw definitive conclusions.

Clinical Reviewer comments: The number of patients in traditionally underrepresented ethnic and racial groups are too low to draw any conclusions regarding the safety of imetelstat in these populations.

8.2.8. Specific Safety Studies/Clinical Trials

Data:

Not applicable

The Applicant's Position:

A randomized double-blinded placebo-controlled clinical ventricular repolarization/QTc substudy is ongoing in subjects with MDS under Study MDS3001. Analyses of ECG parameters and the relationship between imetelstat exposure and the QT/QTc interval will be conducted on approximately 45 LR MDS subjects. Results will be provided upon completion of the study with an integrated risk assessment of nonclinical and clinical data to fully characterize the proarrhythmic potential of imetelstat.

The FDA's Assessment:

No data are available at this time from the ventricular repolarization/QTc substudy.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Data:

Not applicable.

The Applicant's Position:

Refer to [Section 5.5.3](#) Carcinogenicity, in Nonclinical Pharmacology / Toxicology, for information on the potential carcinogenicity of imetelstat.

The FDA's Assessment:

A higher rate of events in the SOC "neoplasms, benign, malignant and unspecified" was observed in the imetelstat arm of the phase 3 portion of MDS3001 compared to the placebo arm. In addition, the rate of events in this SOC was higher in the phase 2 portion.

Table 110: Incidence of neoplasms in patients treated with imetelstat on the phase 3 portion of MDS3001 and in the overall development program

	Imetelstat*	Placebo
Initial ADAE dataset	8 (7)	2 (3.4)
120-day update	10 (8)	2 (3.4)
ISS	36 (5)	2 (3.4)
ISS-low dose	1(1.9)	NA
ISS-standard dose	14 (7)	NA
ISS-high dose	15 (5)	NA

*Includes patients in the imetelstat arm of the phase 3 portion of the study for initial ADAE dataset and 120-day update rows; includes all patients who received imetelstat in the ISS row

Source: FDA analysis

Data cut-off 10 May 2023

Note that in the table above, events were not restricted to treatment emergent events since neoplasms can develop long after the exposure. Events occurring prior to start of treatment were excluded.

Events in the neoplasms SOC were more common in the imetelstat arm of MDS3001. Although not directly comparable, the ISS showed a higher number of events in the standard and high dose groups compared to placebo or to the low dose group. However, no single malignancy dominated. Neoplasms observed included myelofibrosis, acute myeloid leukemia, lymphoma, and a wide variety of solid tumors.

Clinical Reviewer comments: Overall, there is not strong clinical evidence of carcinogenicity for imetelstat. However, there is a small increase in the overall incidence of malignancies in patients who received imetelstat in the phase 3 portion of MDS3001 and the number of events appears to be increasing over time (i.e., more events in the 120-day follow up in the imetelstat arm but not in the placebo arm.) Longer follow up of the outcomes of patients treated with imetelstat may help resolve this issue.

Human Reproduction and Pregnancy

Data:

There are no available clinical data on the use of imetelstat in pregnant women. In embryo-fetal development toxicity studies, imetelstat was not teratogenic. However, administration of imetelstat to pregnant mice and rabbits during the period of organogenesis resulted in embryo-lethal effects at maternal exposures that ranged from approximately 2.5-times and 19.2-times, respectively, the human exposure at the recommended clinical dose.

The Applicant's Position:

There are no data available for imetelstat in pregnant women. Females of reproductive potential should be advised of the potential risk of miscarriage and to use effective contraception for at least 1 week after the final dose of treatment with imetelstat.

The FDA's Assessment:

We agree that no pregnancies were reported in the data provided by the Applicant and that therefore no conclusions can be drawn based on clinical data. Also see review of non-clinical data.

Pediatrics and Assessment of Effects on Growth

Data:

Not applicable.

The Applicant's Position:

There are limited studies of imetelstat in pediatric patients. A request for deferral for the initiation of pediatric studies was included in the NDA submission. In the agreed amended iPSP (FDA letter dated 14 March 2023), the proposed pediatric indication is for treatment, in combination with fludarabine and cytarabine, of pediatric patients with relapsed or refractory AML or MDS, including juvenile myelomonocytic leukemia (JMML), from >1 year to ≤18 years of age.

The FDA's Assessment:

Agree that there is no data on pediatric patients at this time. The age of the youngest patient in the ISS was reported as 21 years of age. However, we note that a phase 2 study of imetelstat in

children with recurrent or refractory nervous system malignancies has been published (Salloum 2016). Notable AE reported from this study include neutropenia, thrombocytopenia, transaminase elevations, and CNS hemorrhage, including two fatal events. No specific issues with growth or development were reported.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Data:

Not applicable.

The Applicant's Position:

There is no clinical experience with overdose with imetelstat.

Imetelstat has no pharmacological properties that would promote its use for abuse or misuse for illegal purposes and no drug abuse or dependence has been observed in the clinical studies. There is no evidence of withdrawal or rebound associated with imetelstat discontinuation in the clinical studies.

The FDA's Assessment:

No overdoses were reported in study MDS3001. A trend towards more frequent AE appeared to be seen in the ISS, suggesting that overdose may pose a significant risk. There were no reports of withdrawal or rebound in MDS3001. It is unlikely based on mechanism of action, use, primary effects, and adverse events profile that imetelstat has a high risk of abuse. Drugs that increase hemoglobin have some risk of being abused as performance enhancing drugs. However, since imetelstat appears to act on the malignant clone in MDS, it is unlikely that it would be misused in this manner.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Data:

Not applicable.

The Applicant's Position:

There is no postmarketing experience with imetelstat.

The FDA's Assessment:

FDA agrees that there is no postmarketing experience with imetelstat.

Expectations on Safety in the Postmarket Setting

Data:

The most commonly reported TEAEs in the MDS3001 Phase 3 imetelstat group were thrombocytopenia (75.4%) and neutropenia (73.7%), and the most commonly reported TEAEs related to imetelstat were thrombocytopenia (67.8%) and neutropenia (64.4%).

The most commonly reported Grade 3/4 TEAEs in the imetelstat group were neutropenia (67.8%) and thrombocytopenia (61.9%), and the most commonly reported Grade 3/4 TEAEs related to imetelstat were neutropenia (58.5%) and thrombocytopenia (54.2%). The majority of Grade 3/4 cytopenia resolved in < 4 weeks, and decreased in frequency over time.

The Applicant's Position:

The most common adverse reactions were reversible cytopenias (neutropenia and thrombocytopenia), consistent with the mechanism of action and on-target effect of imetelstat, but with minimal clinical sequelae as shown by a low incidence of serious bleeding events and infections. Cytopenias were generally Grade 3/4.

Cytopenias occurred more frequently during the first few cycles and were of short duration.

These events were manageable with cycle delays and dose reductions for thrombocytopenia, and with dose modifications and growth factor support for neutropenia.

These risks can be effectively managed by health care providers and with information provided in the Prescribing Information (USPI).

The FDA's Assessment:

FDA agrees that it is likely that severe and potentially life-threatening neutropenia and thrombocytopenia will be seen in the post-marketing setting. We are concerned that in the absence of intense monitoring and rapid response to these issues provided in the clinical trial setting the risk of hemorrhagic events and infection may be higher than expected based on the trial results. The need for careful monitoring of blood counts and prompt response, including dose modification, if severe neutropenia or thrombocytopenia are seen will ameliorate this risk.

In addition, infusion related reaction is expected to occur as frequently or more frequently in the post-marketing setting as in the clinical trial setting. Guidance for pre-medication will be included in the label to reduce this risk.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

The safety profile of imetelstat has been well characterized and is consistent across the safety data pooled from MDS and hematological malignancies. LR MDS is a serious and life-threatening disease, and imetelstat treatment in these subjects demonstrated manageable and acceptable adverse events.

The median duration of treatment with imetelstat was 33.93 weeks and ~50% of subjects in the imetelstat group completed 48 weeks of treatment, indicating that imetelstat at the proposed 7.5 mg/g dose was tolerable.

The adverse event profile of imetelstat is characterized by hematological toxicities specifically thrombocytopenia and neutropenia, which were also the most frequently occurring Grade 3/4 TEAEs. Neutropenia and thrombocytopenia with imetelstat treatment are, in part, an indicator of on-target activity and are also common events in MDS. Despite being common, few events of thrombocytopenia and/or neutropenia led to discontinuation of study therapy, and no fatal cytopenia events occurred in the pivotal study.

Grade 3/4 thrombocytopenia and neutropenia events were short lived (median duration < 2 weeks) and > 80% of cases resolved to Grade ≤ 2 in under 4 weeks. The number of severe (Grade 3/4) bleeding events and events of febrile neutropenia, or severe infections, was low and generally assessed by the investigator as not related to imetelstat treatment. No severe bleeding events were associated with severe thrombocytopenia and severe infections were generally not associated with severe neutropenia.

Management of thrombocytopenia and neutropenia using regular monitoring of blood cell counts and dose modifications as well as monitoring for the clinical consequences (bleeding and infection) are included in Section 5 Warning and Precautions and Section 2 Dose modifications of the US USPI. These events will also be monitored with routine post-marketing pharmacovigilance.

Infusion-related reactions are also included under Section 5 (Warning and Precautions) of the USPI. IRRs were generally mild and premedication with hydrocortisone and diphenhydramine is required under Section 2.2 of the USPI.

Identified ADRs for imetelstat include thrombocytopenia, neutropenia, AST increased, ALP increased, asthenia, headache, arthralgia, infusion related reactions, pruritus, epistaxis, and hematoma.

The FDA's Assessment:

There are several safety concerns with the use of imetelstat in the setting of lower risk MDS.

The most serious concerns are the increased number of deaths on study in the imetelstat arm and the risk of neutropenia and thrombocytopenia and accompanying risks of infection and hemorrhage.

The number of deaths was higher on the imetelstat arm at all timepoints evaluated. Although the differences were not statistically significant and the majority of the deaths were >30 days

post-treatment and often years post-treatment, the consistent trend is concerning. At minimum, harm cannot be ruled out.

Grade 3-4 neutropenia was seen in most patients receiving imetelstat on either portion of the study. Although deaths on study were rare, one death due to sepsis was seen in the phase 3 portion and another due to COVID-19 in the phase 2 portion of the study. In addition, the possibility of ongoing neutropenia after the end of treatment cannot be ruled out and thus deaths occurring >30 days after the end of treatment may be related, as noted in section 8.2.4. Use of neutrophil growth factor support and antibiotics was more common in the imetelstat arm. Despite this, infections were more common in the imetelstat arm of the phase 3 portion of the study compared to placebo. Although not directly comparable, there was a higher risk of infection in the phase 2 portion than was seen in either arm of the phase 3 portion. This could be related to different baseline populations or to increased experience with the risk of cytopenias and more aggressive prophylaxis and treatment in the phase 3 portion of the study.

Similarly, grade 3-4 thrombocytopenia was observed frequently in patients treated with imetelstat and hemorrhagic events were more common in patients treated with imetelstat compared to placebo. No confirmed fatal hemorrhagic events were reported, although the narrative of one death in the phase 2 component was suspicious for intracranial hemorrhage and grade 4 hemorrhagic events were reported. Patients on the imetelstat arm were more likely to receive platelet transfusions and aggressive management of thrombocytopenia, which may have reduced the risk of bleeding during the study. However, platelet transfusion holds risks, including the risk of transfusion reaction and antibody formation. The risks associated with more platelet transfusions must be balanced against the benefit of fewer red blood cell transfusions.

Other events that occurred more frequently in the imetelstat arm included hepatotoxicity, fatigue, arthralgia/myalgia, fractures, infusion related reaction, PTT prolongation, and headache. The effect of imetelstat on cardiac function was unclear: no increase in risk of arterial occlusive disease was observed with imetelstat, but rates of atrial fibrillation and hypertension were higher. In addition, more grade 3+ cardiac failure was seen in the imetelstat arm, although the total rate of cardiac failure was not elevated.

In summary, there are significant risks to the use of imetelstat in patients with lower risk MDS. These risks must be considered carefully in the context of any benefit observed in terms of red blood cell transfusion reduction.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

Overall Survival: Harm Cannot be Ruled Out

The latest estimate (5 January 2024) of the overall survival hazard ratio was 0.98 (95% CI: 0.53, 1.82) based on the Cox proportional hazards model with stratification factors and 1.11 (95% CI: 0.61, 2.03) based on the model without stratification factors. Both point estimates are close to 1 and the upper bounds of the confidence intervals are close to 2, suggesting that potential harm cannot be ruled out.

Given the patients still remaining on study, at most 55 events could be observed in the imetelstat arm and at most 26 events could be observed in the placebo arm. Per protocol, patients “will be followed in the Extension Phase for at least 5 years from the first dose of imetelstat received in Part 2 of the main study (including treatment and follow-up), or 3 years of post-treatment follow-up from the last dose of study treatment, whichever occurs later, or until death, withdrawal of consent, study termination, or until a subject is lost to follow-up.” Due to a limited planned follow-up, not all patients remaining on study might reach an event. Monitoring the survival status and death narratives throughout the Extension Phase will be important for continued reassessment of the potential harm to patients.

Frequency and Duration of Cytopenia

There are several ways to estimate frequency and duration of cytopenia. These outcomes are inherently complex to describe with a single summary because not all patients will experience cytopenia, and those who will, may experience multiple instances of varying duration. FDA has conducted various time-to-event analyses, including mean cumulative function, among others (see Section 8.2.5 *Analysis of Submission-Specific Safety Issues*). Based on these additional analyses, our conclusions regarding safety remain consistent with the other results, indicating potential increased cytopenia risk for patients on the imetelstat treatment.

Residual Uncertainty on the Applicability to the US Population

In the US population of Study MDS3001 (Phase 3), one out of eight patients (12.5%, 95% CI: 0.3%, 52.7%), achieved 8-week RBC-TI in the imetelstat group and none out of five patients (0%, 95% CI: 0%, 52.2%), achieved 8-week RBC-TI in the placebo group. No definitive conclusions can be drawn due to the small sample size of the subgroups.

Potential impact of region-specific patient or treatment-related factors cannot be ruled out. Residual uncertainty regarding applicability of the efficacy results to the US population remains.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The Applicant is seeking approval of imetelstat for the treatment of transfusion-dependent anemia in adult patients with low- to intermediate-1 risk MDS who have not responded to, or have lost response to, or are ineligible for ESA. This application is based primarily on the results of Study MDS3001-Phase 3. Study MDS3001-Phase 3 met the statistical goals for the primary endpoint of 8-week RBC-TI (39.8% imetelstat versus 15.0% placebo; $p < 0.001$) and key secondary endpoint 24-week RBC-TI (28.0% imetelstat versus 3.3% placebo; $p < 0.001$). Although the median duration of RBC-TI was only 5.0 weeks (95% CI 4.0, 7.7) for imetelstat versus 3.9 weeks (95% CI 3.6, 4.0) for placebo in all subjects, the median duration of RBC-TI in 8-week RBC-TI responders was 51.6 weeks (95% CI 26.9, 83.9) for imetelstat versus 13.3 weeks (95% 8.0, 24.9) for placebo, indicating that a subset of patients has a clinically meaningful duration of benefit. The Phase 2 results for 8-week and 24-week RBC-TI support the Phase 3 results.

While MDS3001-Phase 3 met its primary and key secondary endpoints, questions remain regarding the nature of these effects. Imetelstat is purported to have a direct effect on the underlying MDS through telomerase inhibition resulting in cell-cycle arrest, apoptosis, or senescence of malignant cells. However, a statistically significant treatment effect was not observed on the key secondary endpoint of HI-E per IWG 2006 criteria (63.6% vs. 51.7%) or other secondary endpoints reflective of a disease-modifying effect such as CR or PR (0% vs. 0% at the time of primary analysis; 5.9% at best vs. 0% at the time of updated analysis) and OS (HR=0.98 [95% CI: 0.53, 1.82] at most recent data cut). In addition, the patient-reported outcomes collected in Study MDS3001-Phase 3 did not reflect an improvement in fatigue or other anemia-related symptoms. There are also residual uncertainties regarding the impact of imetelstat on overall medical resource utilization and the applicability of the trial results to the US population, given the limitations of the medical resource utilization analyses and lower RBC-TI rates in the US population compared to the non-US population. Additionally, very few patients in Study MDS3001 had prior treatment with luspatercept, which is now approved for frontline treatment of transfusion-dependent anemia in patients with lower-risk MDS.

A high rate of cytopenias was observed in the imetelstat arm of MDS3001-Phase 3. Such cytopenias may require further management and elevate a patient's risk for infection or bleeding. The incidence of at least one Grade 3-4 neutropenia event was 71% in the imetelstat arm and 7% in the placebo arm. Myeloid growth factors were required in 36% of patients in the imetelstat arm compared to 3% in the placebo arm. Similarly, the incidence of at least one Grade 3-4 thrombocytopenia event was 65% in the imetelstat arm and 8% in the placebo arm. Platelet transfusions were required in 18% of patients in the imetelstat arm compared to 2% in the placebo arm. It is worth noting that cytopenias occurred regardless of whether a patient responded to imetelstat or not. As most patients do not respond to imetelstat, there is a

substantial risk of exposing patients to toxicity with no durable RBC-TI. In contrast, worsening Grade ≥ 3 neutropenia occurred in 7% of patients on the placebo arm, as did worsening Grade ≥ 3 thrombocytopenia in 8% of patients.

Additional potential risks with imetelstat treatment were identified in MDS3001-Phase 3, particularly events related to cytopenia events. For instance, at least one occurrence of any all-grade infection was higher in the imetelstat arm than the placebo arm (47% vs. 34%). Grade 3-4 infections was similar between the two arms (11% vs. 14%). In addition, at least one occurrence of any all-grade hemorrhage was higher in the imetelstat arm than the placebo arm (22% vs. 12%). Grade 3-4 hemorrhage was similar between the two arms (2.5% vs. 1.7%). Other toxicity signals were identified in MDS3001-Phase 3, such as an increased incidence of at least one any grade fatigue event, although this signal is not reflected in patient-reported outcomes.

The potential benefits and risks should be weighed in the context of residual uncertainties. For instance, there is residual uncertainty regarding the optimal dose of imetelstat given the limited dose exploration in the target population and high rate of dose modifications observed in Study MDS3001. This is notable given that dose reductions due to AE occurred in 49% of patients in the imetelstat arm vs. 7% in the placebo arm. In addition, while the increased risk of cytopenias with imetelstat treatment seems apparent, other risks such as fractures may be increased with imetelstat treatment, though such risks are less well-understood. These uncertainties are due in part to the nature of the development program, which includes only one randomized trial in LR-MDS and limited dose-optimization for this indication.

Overall, treatment with imetelstat is associated with risks that might be considered substantial. Therefore, FDA held an Oncologic Drugs Advisory Committee (ODAC) meeting on 14 March 2024 for discussion of whether the benefits of imetelstat outweigh the risks for the proposed indication. The AC voted that the potential benefits of imetelstat outweigh the risks. Given this, in addition to the high unmet need for the proposed patient population, the Agency has concluded that the benefits of imetelstat outweigh the risks for the treatment of adult patients with IPSS low- to intermediate-1 risk MDS with transfusion-dependent anemia requiring 4 or more red blood cell units over 8 weeks who have not responded to or have lost response to or are ineligible for ESA. FDA recommends granting regular approval to imetelstat for this indication. PMR/PMC recommendations are noted in the “Postmarketing Requirements and Commitments” section below.

8.4.1. Approach to Substantial Evidence of Effectiveness

Select from the options below to indicate how substantial evidence of effectiveness (SEE) was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication (*enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response*):
RYTELO is indicated for the treatment of adult patients with low- to intermediate-1 risk myelodysplastic syndromes (MDS) with transfusion-dependent anemia requiring 4 or more red blood cell units over 8 weeks who have not responded to or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESA).
2. SEE was established with (*check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE*)
 - a. Adequate and well-controlled clinical investigation(s):
 - i. ☐ Two or more adequate and well-controlled clinical investigations, **OR**
 - ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations
 - OR**
 - b. ☒ One adequate and well-controlled clinical investigation and confirmatory evidence^{1,2,3}
 - OR**
 - c. ☐ Evidence that supported SEE from a prior approval (*e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch*)²
3. Complete response, if applicable
 - a. ☐ SEE was established
 - b. ☐ SEE was not established (*if checked, omit item 2*)

¹ FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (2019)

² FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (1998)

³ Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence (2023)]

X

X

Primary Statistical Reviewer

Statistical Team Leader

X

X

Primary Clinical Reviewer

Clinical Team Leader

APPEARS THIS WAY ON ORIGINAL

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

Summary provided by Division of Advisory Committee and Consultant Management (DACCM) with edits for clarity.

NDA 217779 was discussed by the Oncologic Drugs Advisory Committee (ODAC) on 3/14/2024. There was 1 discussion question and 1 voting question.

Collectively, the Committee members agreed that Study MDS3001 met the statistical goals for the primary endpoint of achievement of red blood cell transfusion independence (RBC-TI) for 8 weeks and the secondary endpoint of RBC-TI for 24 weeks. When it comes to overall safety, the Committee acknowledged the occurrences of cytopenia shown in the data but expressed that these toxicities are not foreign in the population studied and can be well controlled in a real-world setting.

Some members noted the lack of measurable outcomes in the study. They suggested for the applicant to establish a true surrogate, in further studies, so a measurable quality of life (QOL) benefit can be captured in the population studied. Other members noted that transfusion independence (TI) is a QOL metric.

The Committee highlighted the current challenges of MDS patients and the limited options available to manage the disease. The members pointed out that avoiding transfusion as long as possible reduces toxicity and cost, which are considered meaningful outcomes in the MDS community. Although the data did not show any markers of overall survival or imetelstat preventing the transitioning of MDS to acute myelogenous leukemia, the Committee agreed that the possibility of achieving TI up to 6 months is remarkable to the population affected.

The voting question was “Do the results of imetelstat outweigh its risks for the treatment of transfusion-dependent anemia in adult patients with IPSS low- to intermediate-risk MDS who have not responded to or have lost response to or are ineligible for erythropoiesis-stimulating agents?”

Vote Result: Yes: 12 No: 2 Abstain: 0

The majority of the Committee voted “Yes”, that imetelstat’s benefits outweigh its risks for the treatment of transfusion dependent anemia in adult patients with International Prognosis Scoring System low- to intermediate-1 risk MDS who have not responded to or have lost response to or are ineligible for erythropoiesis-stimulating agents.

The Committee members who voted “Yes”, agreed that the study met its primary and secondary endpoints. Although the Committee acknowledged the severity of the side effects observed from imetelstat in the study, the members discussed that these episodes can be well-controlled in a real world setting as the intended population is already closely monitored by specialists who are familiar with neutropenia and thrombocytopenia. One member stated that hematologists are no strangers to neutropenia, and although neutropenia cannot be mitigated, to have an option where patients can potentially benefit is promising in the management of MDS. Another member expressed that the long-term consequences of transfusion dependence are debilitating enough, and the demonstration shown of imetelstat’s ability to reduce the number of transfusions is “impressive.”

Two Committee members voted “No”, that the data shown did not convince them of imetelstat’s benefits (RBC-TI for eight weeks) outweighing its risks (i.e., cytopenia). Although there was an agreement that the primary and secondary endpoints were met, these members were not persuaded by the trial’s outcome relative to the safety profile observed. Please see the transcript for details of the Committee’s discussion.

10 Pediatrics

The Applicant's Position:

Geron has an agreed amended iPSP (FDA letter dated 14 March 2023). The proposed pediatric indication is for treatment, in combination with fludarabine and cytarabine, of pediatric patients with relapsed or refractory AML or MDS, including JMML, from >1 year to ≤18 years of age. A request for waiver to exclude the youngest subset of pediatric patients, from birth to 1 year of age, based on the rare incidence of myeloid malignancies (AML, MDS, and JMML) in this subset was submitted with the NDA submission. A request for deferral for the initiation of pediatric studies and a population PK exposure-response analysis was also included in the NDA submission.

The FDA's Assessment:

The submission is an original NDA for a new active ingredient, for treatment of an adult cancer, and directed at a molecular target substantially relevant to the growth or progression of a pediatric cancer, and therefore is subject to the FDARA amendment to PREA. The agreed iPSP included 2 studies to provide an assessment of PK, safety, and preliminary efficacy in pediatric patients with relapsed/refractory acute myeloid leukemia, myelodysplastic syndrome, or juvenile myelomonocytic leukemia treated in combination with chemotherapy. The PREA PMR reflects (b) (4)

Additional details of a PREA PMR required under the FDARA amendment is detailed in the PMR section.

11 Labeling Recommendations

Data:

FDA modified sections of the labeling as described below. See the approval letter for final labeling.

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	Applicant's Proposed Labeling	FDA's proposed Labeling
Indications and Usage (1)	TRADENAME is indicated for the treatment of transfusion-dependent anemia in adult patients with low- to intermediate-1 risk myelodysplastic syndromes (MDS) who have failed to respond or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESA).	FDA modified the indication to state that TRADENAME is indicated for the treatment of adult patients with low-to intermediate-1 risk myelodysplastic syndromes (MDS) with transfusion-dependent anemia requiring 4 or more red blood cell units over 8 weeks who have not responded to or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESA).
Dosage and Administration Recommended Dosage (2.1)	Recommended dosage is 7.1 mg/kg administered as an intravenous (IV) infusion over 2 hours every 4 weeks (b) (4)	FDA agreed with the recommended dosage. FDA modified the treatment discontinuation statement to state that Rytelo should be discontinued if a patient does not experience a decrease in RBC transfusion burden after 24 weeks of treatment (administration of 6 doses) or if unacceptable toxicity occurs at any time.
Dosage and Administration Premedication Instructions (2.2)	Within at least (b) (4) prior to dosing, premedicate with diphenhydramine and hydrocortisone, or	FDA agreed.

	equivalent, to prevent or reduce potential infusion-related reactions Monitor patients for adverse reactions (ARs) for at least one hour after the infusion has been completed	
Dosage and Administration Dose Modifications for Adverse Reactions (2.3)	Recommended dose reductions for Grade 3 and 4 adverse reactions (Table 1) First dose reduction is to 5.6 mg/kg every 4 weeks Second dose reduction is to 4.4 mg/kg every 4 weeks Management of Grade 3 and 4 ARs may require temporary dose delay, dose reduction, or treatment discontinuation, as presented in Tables 2 & 3 Treatment should be permanently discontinued if the patient cannot tolerate the lowest dose level of 4.4 mg/kg Dose Modifications for Hematologic (Grade 3 and 4) Adverse Reactions Monitor complete blood cell counts prior to (b) (4) TRADENAME, weekly for the first two cycles, prior to each cycle thereafter, and as clinically indicated (b) (4) (b) (4) Delay the next cycle if absolute neutrophil count is less than $1.0 \times 10^9/L$ and	FDA agreed with the recommended dose reductions. FDA modified recommendations in the tables to note that after either 3rd or 4th occurrence, the drug should be permanently discontinued for grade 3 or 4 ARs.

	platelets are less than $50 \times 10^9/L$ Modify dose as described in Table 2 Dose Modifications for Non-hematologic Adverse Reactions Dose modifications for infusion-related reactions and other adverse drug reactions, including elevated liver function tests (LFTs), are described in Table 3	FDA generally agreed except as noted above regarding permanent discontinuation for grade 3 or 4 ARs after the 3rd or 4th occurrence as noted in tables 2 and 3.
Dosage and Administration Preparation and Administration (2.4)	Lyophilized powder in a single-dose vial for IV infusion only; must be reconstituted and diluted Does not contain a preservative (b) (4) calculate dose (total mg) based on patient's body weight (kg) determine number of vials needed to achieve required dose (b) (4) Table 4 Reconstitute (b) (4) Table 4 (b) (4) In-use storage times: Not to exceed 18 hours when stored at 20°C to 25°C* Not to exceed 48 hours when stored at 2°C to 8°C*	FDA modified this section to improve clarity and readability, removed trailing zeros throughout, and rounded the concentration of final reconstituted solution to one decimal point.

	(b) (4)	Additionally, the statement (b) (4) as proposed by the applicant was removed because postmarketing reports have shown (b) (4)
Dosage Forms and Strengths (3)	Two Strengths: For injection: 47 mg of imetelstat (b) (4) For injection: 188 mg of imetelstat (b) (4) Supplied as a white to off-white or slightly yellow lyophilized powder in a single-dose vial for reconstitution.	FDA removed (b) (4) as it is included in section 11. FDA agreed with the physical description.
Contraindications (4)	None	FDA agreed.
Warnings and Precautions Thrombocytopenia (5.1)	New or worsening Grade 3 or 4 thrombocytopenia, based on laboratory values, occurred in 65.2% of MDS patients treated with TRADENAME Median time to onset: 6 weeks Median duration: (b) (4) Monitor for bleeding (b) (4)	FDA modified to streamline information, remove any negative data statements, and recommend monitoring of blood counts weekly for the first 2 cycles, and prior to and 7-10 days after the start of each cycle thereafter. FDA added cross reference to section 6.1 Adverse Reactions.

	Monitor complete blood cell counts and (b) (4) Section 2.3	
Warnings and Precautions Neutropenia (5.2)	New or worsening Grade 3 or 4 neutropenia, based on laboratory values, occurred in 71.2% of MDS patients treated with TRADENAME. Median time to onset (b) (4) (b) (4) Monitor for infections, including sepsis, (b) (4) (b) (4) Monitor complete blood cell counts and (b) (4) Section 2.3 Administer growth factors and anti-infective therapies or prophylaxis as appropriate	FDA modified to streamline information, remove any negative data statements, and recommend monitoring of blood counts weekly for the first 2 cycles, and prior to and 7-10 days after the start of each cycle thereafter. FDA added cross reference to section 6.1 Adverse Reactions.
Warnings and Precautions Infusion-related Reactions (5.3)	Infusion-related reactions occurred in (b) (4) % of MDS patients treated with TRADENAME (b) (4) (b) (4) Manage symptoms with supportive care and infusion interruptions or decrease infusion rate per Section 2.3	FDA modified this section to add grade 3 or 4 infusion-related reactions, as well as to add premedication recommendations.
Warnings and Precautions Embryo-Fetal Toxicity (5.4)	N/A	FDA added a W&P 5.4 for embryo-fetal toxicity because of the findings in the fetal development toxicity studies and the need for contraception.

Adverse Reactions (6)	The following clinically significant ARs are described elsewhere in the labeling: Thrombocytopenia Neutropenia Infusion-related Reactions	FDA agreed.
Adverse Reactions Clinical Trials Experience (6.1)	Safety was evaluated in one (b) (4) randomized, double-blind, placebo-controlled trial (TRADENAME, n=118; placebo, n=59) Median time on treatment 7.8 months (range, (b) (4) months); 68.6% of patients exposed to TRADENAME 24 weeks or longer; 44.9% exposed for 48 weeks or longer Treatment discontinuation due to an AR occurred in (b) (4) patients Dose delays due to an AR occurred in (b) (4) patients (b) (4) Dose reductions due to an AR occurred in 49.2% (b) (4) of patients (b) (4)	FDA revised and reordered to be consistent with oncology labeling to present information in 6.1 for oncology products in a consistent manner and to make this information more accessible and useful to healthcare providers. Changes to the data were made after FDA review and adjudication.

	(b) (4)	FDA revised the laboratory abnormalities table to include columns for All grades and Grade 3 or 4 laboratory abnormalities. Laboratory terms, not AE terms were used in the table.
Drug Interactions (7)	This section was not included in the initial submission in the US Prescribing Information	FDA agreed.
Use in Specific Populations Pregnancy (8.1)	(b) (4)	FDA modified to state that imetelstat can cause embryonic or fetal harm when administered to a pregnant woman. FDA added that in rabbits the dose of 28.2 mg/kg was maternally toxic based on mortality. Other edits in the section made to align with labeling recommendations for consistency with PLLR formatting.
Use in Specific Populations Lactation (8.2)	Advise women not to breastfeed during treatment and for 1 week after the final dose	FDA generally agreed but modified “final” to “last”.
Use in Specific Populations Females and Males of Reproductive Potential (8.3)	Pregnancy Testing: verify the pregnancy status of females of reproductive potential before starting treatment Contraception: advise use of effective contraception	FDA agreed but modified “final” to “last”.

	during treatment and for at least 1 week after the final dose Infertility: based on findings in animals, may impair fertility in females of reproductive potential	
Use in Specific Populations Pediatric Use (8.4)	Safety and effectiveness in pediatric patients have not been established	FDA agreed.
Use in Specific Populations Geriatric Use (8.5)	No differences in safety or efficacy observed between older (≥ 65 years) and younger patients	FDA generally agreed.
Use in Specific Populations Renal Impairment (8.6)	(b) (4)	FDA removed this subsection as there no recommended dose adjustments and the data are presented in subsection 12.3.
Use in Specific Populations Hepatic Impairment (8.7)		FDA removed this subsection as there no recommended dose adjustments and the data are presented in subsection 12.3.
Description (11)	Imetelstat is a telomerase inhibitor for intravenous use	FDA generally agreed but removed the last sentence (b) (4)

	Molecular formulas for both the sodium salt and active moiety are included Inactive ingredients may be added during manufacturing: sodium carbonate anhydrous (47 mg preparation) or sodium carbonate monohydrate (188 mg preparation) hydrochloric acid (to adjust to pH of 7.0 to 8.5) (b) (4)	duplicative with information presented earlier in the section.
Clinical Pharmacology Mechanism of Action (12.1)	(b) (4)	FDA modified this section to remove any potentially promotional statements and to provide clarity and simplicity.

		(b) (4)
Clinical Pharmacology Pharmacodynamics (12.2)		FDA removed (b) (4) FDA added that with higher imetelstat exposure, there is a higher incidence of grade 3 and 4 thrombocytopenia in patients with MDS.
Clinical Pharmacology Pharmacokinetics (12.3) Distribution		FDA modified this section to improve clarity and for consistency with labeling of other oncologic drugs; (b) (4) were removed. (b) (4)
Clinical Pharmacology Pharmacokinetics (12.3) Elimination	Geometric mean (CV%) apparent half-life in plasma is approximately 4.9 hours (b) (4) %	FDA generally agreed with geometric mean (CV%) findings but modified the language within the Elimination heading to be more concise and to remove (b) (4).

	(b) (4)	
Clinical Pharmacology Pharmacokinetics (12.3) Special populations	No clinically significant differences in PK based on age (21 to 87 years), sex, race, or mild to moderate renal/hepatic impairment PK (b) (4) severe renal impairment, end-stage renal disease, or severe hepatic impairment	FDA corrected the subheading title to Specific Populations and edited to align with recommendations in Guidance.
Clinical Pharmacology Pharmacokinetics (12.3) Drug interaction studies	(b) (4)	FDA added subsection headings for in vitro studies, CYP enzymes, and transporter systems and removed (b) (4)
Clinical Pharmacology Immunogenicity (12.6)	(b) (4)	FDA removed (b) (4) FDA agreed that there were no significant effect of ADA

	(b) (4)	on the PK, safety, or efficacy of Rytelo among patients in the IMerge who developed ADA.
Nonclinical Toxicology Carcinogenesis, Mutagenesis, Impairment of Fertility (13.1)	Studies examining the carcinogenic potential have not been conducted Imetelstat is not mutagenic in vitro in the bacterial mutagenicity assay or clastogenic in vitro in the chromosomal aberrations assay (b) (4) Uterine endometrial atrophy was exhibited in female monkeys at a mean exposure approximately (b) (4)-times the human exposure (based in AUC) at the recommended clinical dose; and was absent following a 14-week recovery period, (b) (4)	FDA modified to improve clarity, add that fertility studies have not been conducted with imetelstat, and removed (b) (4)
Clinical Studies Myelodysplastic Syndromes (MDS) (14.1)	Efficacy was assessed in MDS3001, a (b) (4) randomized, double-blinded placebo-controlled trial (b) (4)	FDA generally agreed with the efficacy data but added baseline median peripheral blood counts, removed duplicative information, added missing demographic

	Relevant baseline disease characteristics for the ITT population were included in Table 7 Efficacy was established after a median follow up of 19.5 months (range: 1.4 to 36.2) in the imetelstat group and 17.5 months (range: 0.7 to 34.3) in the placebo group Improvement in rate of 8-week RBC TI (b) (4) Improvement in rate of 24-week RBC TI (b) (4)	information, and edited for clarity.
How Supplied/Storage and Handling How Supplied (16.1)	A white to off-white or slightly yellow, lyophilized powder (b) (4) (b) (4) NDC 82959-112-01: 47 mg NDC 82959-111-01: 188 mg	FDA modified this section to remove clutter and duplicative information. FDA put the carton information into a table to improve readability. FDA removed (b) (4) FDA removed separate subsections 16.1 and 16.2 as they are not required; the

		formatting was changed to underlined headings.
How Supplied/Storage and Handling Storage (16.2)	Store refrigerated in carton; Do not freeze No preservative	“No preservative” was moved into the How Supplied section within the first sentence so that this information is not overlooked
Patient Counseling Information (17)	Thrombocytopenia and Neutropenia: Advise of the risk; Inform that blood counts will be routinely monitored and dose delays or reductions may be given as needed; Instruct to notify immediately if signs or symptoms occur Infusion-related Reactions (IRRs): Inform that IRRs can occur and that premedication (b) (4) will be given; Advise (b) (4) Lactation: Advise women not to breastfeed during treatment and for 1 week after the final dose (b) (4) Advise of the potential risk (b) (4) Advise to use effective contraception during treatment and for at least 1 week after the final dose	FDA generally agreed but modified the section to align with changes made to the corresponding sections in the USPI, including (b) (4) <i>Embryo-Fetal Toxicity.</i>

The Applicant’s Position:

Draft labeling submitted as part of the NDA describes the indication, usage, contraindications, warnings and precautions, adverse reactions, use in specific populations, clinical pharmacology, and clinical efficacy. The data presented in the IMerge (MDS3001) Phase 3 study in patients with low- to intermediate-1 risk myelodysplastic syndromes (MDS) who have transfusion-dependent anemia and have failed to respond or have lost response to or are ineligible for

erythropoiesis-stimulating agents (ESA) demonstrate the favorable benefit risk of imetelstat and support the proposed indication in this high unmet need population.

The FDA's Assessment:

FDA modified the USPI as described in the table above; additionally, the applicant proposed a Patient Package Insert (PPI) but the FDA determined that a Medication Guide would be required. The Medication Guide was reviewed by the patient labeling team within the Division of Medical Policy Programs; see separate review in DARRTS for details. In general, the information contained within the Medication Guide aligns with information in the USPI.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

FDA determined that REMS is not needed for this application.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

A total of 6 PMRs and one post-marketing commitment (PMC) are planned for this application.

PMR #1: Pediatric study(ies) to be conducted under the FDARA amendment to PREA. A clinical trial to examine the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of imetelstat in combination with chemotherapy in pediatric patients > 1 year old with acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) will be required.

PMRs #2 and #3: Carcinogenicity studies in rats and mice, respectively. Because of the potential for prolonged survival in the proposed patient population, the risk of carcinogenicity must be characterized.

PMR #4: Long-term safety of imetelstat in Study MDS3001-Phase 3. Because the long-term safety of imetelstat is unknown, extended follow-up of Study MDS3001 to establish safety of long-term treatment with imetelstat in patients with low or intermediate risk MDS is required, including the risk of neutropenia, thrombocytopenia, infections, and bleeding.

PMR #5: Randomized trial of at least two dosages of imetelstat in patients with lower risk MDS. Dosages lower than the proposed recommended dosage, 7.1 mg/kg every 4 weeks as a 2-hour infusion, have not been evaluated in patients with low or intermediate-1 risk myelodysplastic syndromes (LR-MDS). A randomized trial comparing at least 2 dosages of imetelstat in patients with LR-MDS will be required to potentially minimize the serious risks of imetelstat treatment including neutropenia and thrombocytopenia and other serious adverse events and improve tolerability while maintaining clinical benefit to patients. Additionally, given that the duration of neutropenia and thrombocytopenia after treatment discontinuation with imetelstat is unknown, extended follow up of patients in this trial to evaluate the effects of imetelstat on myelosuppression after treatment discontinuation is warranted. The study should enroll sufficient patients in the United States to establish efficacy and safety in relevant ethnic and racial populations in the US.

PMR #6: Evaluation of the risk of QT prolongation through completion of the ventricular repolarization substudy of MDS3001 Phase 3.

PMC #1: Exploratory analyses to identify markers that may predict response to imetelstat to achieve transfusion independence. A small number of patients receiving imetelstat experienced long-term transfusion independence, however predictors of response are currently unknown.

FDA PMC/PMR Checklist for Trial Diversity and US Population Representativeness		
The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed?
☐	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age diversity of the U.S. population for the proposed indication.	☒ Yes ☐ No
☐	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g., race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	☒ Yes ☐ No
☐	Other considerations (e.g., PK/PD), if applicable:	☐ Yes ☒ No

14 Division Director (DHOT) (NME ONLY)

X

APPEARS THIS WAY ON ORIGINAL

15 Division Director (OCP)

X

APPEARS THIS WAY ON ORIGINAL

16 Division Director (OB)

X

APPEARS THIS WAY ON ORIGINAL

17 Division Director (Clinical)

X

APPEARS THIS WAY ON ORIGINAL

18 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.

X

19 Appendices

19.1. References

The Applicant's References:

Adès, L, Itzykson R, Fenaux P. Myelodysplastic syndromes. *Lancet*. Jun 28 2014;383(9936):2239-52. doi:10.1016/S0140-6736(13)61901-7

Ahn, JE, Karlsson MO, Dunne A, Ludden TM. Likelihood based approaches to handling data below the quantification limit using NONMEM VI. *J Pharmacokinet Pharmacodyn*. Aug 2008;35(4):401-21. doi:10.1007/s10928-008-9094-4

Baerlocher, GM, Haubitz M, Braschler TR, Brunold C, Burington B, Oppliger Leibundgut E, Go N. Imetelstat inhibits growth of megakaryocyte colony-forming units from patients with essential thrombocythemia. *Blood Adv*. Nov 26 2019;3(22):3724-3728. doi:10.1182/bloodadvances.2019000167

Beal, SL. Ways to fit a PK model with some data below the quantification limit. *J Pharmacokinet Pharmacodyn*. Oct 2001;28(5):481-504. doi:10.1023/a:1012299115260

Bejar, R, Steensma DP. Recent developments in myelodysplastic syndromes. *Blood*. Oct 30 2014;124(18):2793-803. doi:10.1182/blood-2014-04-522136

Bejar, R, Stevenson K, Abdel-Wahab O, Galili N, Nilsson B, Garcia-Manero G, Kantarjian H, Raza A, Levine RL, Neuberg D, Ebert BL. Clinical effect of point mutations in myelodysplastic syndromes. *N Engl J Med*. Jun 30 2011;364(26):2496-2506. doi:10.1056/NEJMoa1013343

Berman, CL, Cannon K, Cui Y, Kornbrust DJ, Lagrutta A, Sun SZ, Tepper J, Waldron G, Younis HS. Recommendations for safety pharmacology evaluations of oligonucleotide-based therapeutics. *Nucleic Acid Therapeutics*, . Aug 2014;24(4):291-301. doi:10.1089/nat.2013.0477

Bonate, PL, Strougo A, Desai A, Roy M, Yassen A, van der Walt JS, Kaibara A, Tannenbaum S. Guidelines for the quality control of population pharmacokinetic-pharmacodynamic analyses: an industry perspective. *AAPS J*. Dec 2012;14(4):749-58. doi:10.1208/s12248-012-9387-9

Braga Lemos, M, Rodrigues SR, Schroeder T, Kulasekararaj AG, Matos JE, Tang D. Association between red blood cell transfusion dependence and burden in patients with myelodysplastic syndromes: A systematic literature review and meta-analysis. *Eur J Haematol*. Jul 2021;107(1):3-23. doi:10.1111/ejh.13619

Brennan SK, Wang Q, Tressler R, Harley C, Go N, Bassett E, et al. Telomerase inhibition targets clonogenic multiple myeloma cells through telomere length-dependent and independent mechanisms. *PLoS One*. 2010;5(9):e12487.

Briatore, F, Barrera G, Pizzimenti S, Toaldo C, Casa CD, Laurora S, Pettazzoni P, Dianzani MU, Ferrero D. Increase of telomerase activity and hTERT expression in myelodysplastic syndromes. *Cancer Biol Ther*. May 2009;8(10):883-839. doi:10.4161/cbt.8.10.8130

Bruedigam, C, Bagger FO, Heidel FH, Paine Kuhn C, Guignes S, Song A, Austin R, Vu T, Lee E, Riyat S, Moore AS, Lock RB, Bullinger L, Hill GR, Armstrong SA, Williams DA, Lane SW. Telomerase inhibition effectively targets mouse and human AML stem cells and delays relapse following chemotherapy. *Cell Stem Cell*. Dec 4 2014;15(6):775-790. doi:10.1016/j.stem.2014.11.010

Carraway, HE, Saygin C. Therapy for lower-risk MDS. *Hematology Am Soc Hematol Educ Program*. Dec 4 2020;2020(1):426-433. doi:10.1182/hematology.2020000127

Cavagnaro, J, Berman C, Kornbrust D, White T, Campion S, Henry S. Considerations for assessment of reproductive and developmental toxicity of oligonucleotide-based therapeutics. *Nucleic Acid Ther*. 2014/10// 2014;24(5):313-325. doi:10.1089/NAT.2014.0490

Cheson, BD, Greenberg PL, Bennett JM, Lowenberg B, Wijermans PW, Nimer SD, Pinto A, Beran M, de Witte TM, Stone RM, Mittelman M, Sanz GF, Gore SD, Schiffer CA, Kantarjian H. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood*. Jul 15 2006;108(2):419-425. doi:10.1182/blood-2005-10-4149

Crooke, RM, Graham MJ, Martin MJ, Lemonidis KM, Wyrzykiewicz T, Cummins LL. Metabolism of antisense oligonucleotides in rat liver homogenates. *J Pharmacol Exp Ther*. Jan 2000;292(1):140-149.

de Swart, L, Crouch S, Hoeks M, Smith A, Langemeijer S, Fenaux P, Symeonidis A, Cermak J, Hellstrom-Lindberg E, Stauder R, Sanz G, Mittelman M, Holm MS, Malcovati L, Madry K, Germing U, Tatic A, Savic A, Almeida AM, Gredelj-Simec N, Guerci-Bresler A, Beyne-Rauzy O, Culligan D, Kotsianidis I, Itzykson R, van Marrewijk C, Blijlevens N, Bowen D, de Witte T, Participants ER. Impact of red blood cell transfusion dose density on progression-free survival in patients with lower-risk myelodysplastic syndromes. *Haematologica*. Mar 2020;105(3):632-639. doi:10.3324/haematol.2018.212217

De Witte, T, Malcovati L, Fenaux P, Bowen D, Symeonidis A, Mittelman M, Stauder R, Sanz G, Cermak J, Langemeijer S, Hellstrom-Lindberg E, Germing U, Skov Holm M, Madry K, Tatic A, Medina Almeida A, Savic A, Mandac Rogulj I, Itzykson R, Hoeks M, Gravidahl Garelius H, Culligan D, Kotsianidis I, Ades L, Van de Loosdrecht AA, Van Marrewijk C, Yu G, Crouch S, Smith A. Novel dynamic outcome indicators and clinical endpoints in myelodysplastic syndrome; the European LeukemiaNet MDS Registry and MDS-RIGHT project perspective. *Haematologica*. Nov 1 2020;105(11):2516-2523. doi:10.3324/haematol.2020.266817

DeZern, AE, Dalton WB. How low risk are low risk myelodysplastic syndromes? *Expert Rev Hematol*. Jan 2022;15(1):15-24. doi:10.1080/17474086.2022.2029698

FDA. Food and Drug Administration, Draft Guidance for Industry: Clinical Pharmacology Considerations for the Development of Oligonucleotide Therapeutics. 2022.

Fenaux, P, Haase D, Santini V, Sanz GF, Platzbecker U, Mey U, clinicalguidelines@esmo.org
EGCEa. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment
and follow-up(dagger☆). *Ann Oncol*. Feb 2021;32(2):142-156.
doi:10.1016/j.annonc.2020.11.002

Fenaux, P, Platzbecker U, Mufti GJ, Garcia-Manero G, Buckstein R, Santini V, Diez-Campelo M,
Finelli C, Cazzola M, Ilhan O, Sekeres MA, Falantes JF, Arrizabalaga B, Salvi F, Giai V, Vyas P,
Bowen D, Selleslag D, DeZern AE, Jurcic JG, Germing U, Gotze KS, Quesnel B, Beyne-Rauzy O,
Cluzeau T, Voso MT, Mazure D, Vellenga E, Greenberg PL, Hellstrom-Lindberg E, Zeidan AM,
Ades L, Verma A, Savona MR, Laadem A, Benzohra A, Zhang J, Rampersad A, Dunshee DR, Linde
PG, Sherman ML, Komrokji RS, List AF. Luspatercept in Patients with Lower-Risk Myelodysplastic
Syndromes. *N Engl J Med*. Jan 9 2020;382(2):140-151. doi:10.1056/NEJMoa1908892

Foran, JM, Shammo JM. Clinical presentation, diagnosis, and prognosis of myelodysplastic
syndromes. *Am J Med*. Jul 2012;125(7 Suppl):S6-13. doi:10.1016/j.amjmed.2012.04.015

Garcia-Manero, G. Myelodysplastic syndromes: 2014 update on diagnosis, risk-stratification,
and management. *Am J Hematol*. Jan 2014;89(1):97-108. doi:10.1002/ajh.23642

Gaus, HJ, Owens SR, Winniman M, Cooper S, Cummins LL. On-line HPLC electrospray mass
spectrometry of phosphorothioate oligonucleotide metabolites. *Anal Chem*. Feb 1
1997;69(3):313-9. doi:10.1021/ac960557q

Geary, RS. Antisense oligonucleotide pharmacokinetics and metabolism. *Expert opinion on drug
metabolism & toxicology*. Apr 2009;5(4):381-391. doi:10.1517/17425250902877680

Geary, RS, Yu RZ, Levin AA. Pharmacokinetics of phosphorothioate antisense
oligodeoxynucleotides. *Curr Opin Investig Drugs*. 2001;2(4):562-573.

Germing, U, Schroeder T, Kaivers J, Kundgen A, Kobbe G, Gattermann N. Novel therapies in low-
and high-risk myelodysplastic syndrome. *Expert Rev Hematol*. Oct 2019;12(10):893-908.
doi:10.1080/17474086.2019.1647778

Greenberg, P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, Sanz M, Vallespi T, Hamblin T,
Oscier D, Ohyashiki K, Toyama K, Aul C, Mufti G, Bennett J. International scoring system for
evaluating prognosis in myelodysplastic syndromes. *Blood*. Mar 15 1997;89(6):2079-88.

Greenberg, PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Sole F, Bennett JM, Bowen D,
Fenaux P, Dreyfus F, Kantarjian H, Kuendgen A, Levis A, Malcovati L, Cazzola M, Cermak J,
Fonatsch C, Le Beau MM, Slovak ML, Krieger O, Luebbert M, Maciejewski J, Magalhaes SM,
Miyazaki Y, Pfeilstocker M, Sekeres M, Sperr WR, Stauder R, Tauro S, Valent P, Vallespi T, van de
Loosdrecht AA, Germing U, Haase D. Revised international prognostic scoring system for
myelodysplastic syndromes. *Blood*. Sep 20 2012;120(12):2454-2465. doi:10.1182/blood-2012-
03-420489

Griffey, RH, Greig MJ, Gaus HJ, Liu K, Monteith D, Winniman M, Cummins LL. Characterization
of oligonucleotide metabolism in vivo via liquid chromatography/electrospray tandem mass

NDA/BLA Multi-disciplinary Review and Evaluation NDA 217779 imetelstat
TRADENAME, imetelstat

spectrometry with a quadrupole ion trap mass spectrometer. *Journal of mass spectrometry : JMS*. Mar 1997;32(3):305-313. doi:10.1002/(sici)1096-9888(199703)32:3<305::aid-jms482>3.0.co;2-r

Harley, CB. Telomerase and cancer therapeutics. *Nat Rev Cancer*. Mar 2008;8(3):167-179. doi:10.1038/nrc2275

Hellstrom-Lindberg, E, van de Loosdrecht A. Erythropoiesis stimulating agents and other growth factors in low-risk MDS. *Best Pract Res Clin Haematol*. Dec 2013;26(4):401-10. doi:10.1016/j.beha.2013.09.007

Herbert, BS, Gellert GC, Hochreiter A, Pongracz K, Wright WE, Zielinska D, Chin AC, Harley CB, Shay JW, Gryaznov SM. Lipid modification of GRN163, an N3'-->P5' thio-phosphoramidate oligonucleotide, enhances the potency of telomerase inhibition. *Oncogene*. Aug 4 2005;24(33):5262-5268. doi:10.1038/sj.onc.1208760

Hochberg, Y. A sharper Bonferroni procedure for multiple tests of significance. *Biometrika*. 1988;75(4):800--802.

Hohaus, S, Voso MT, Orta-La Barbera E, Cavallo S, Bellacosa A, Rutella S, Rumi C, Genuardi M, Neri G, Leone G. Telomerase activity in human hematopoietic progenitor cells. *Haematologica*. May-Jun 1997;82(3):262-268.

ICH S1A. International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use, Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals. 1995.

ICH S4. International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use, Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing). 1998.

ICH S9. International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use, Nonclinical Evaluation for Anticancer Pharmaceuticals S9 Current Step 4 version. 2009.

Jafari, PA, Sadeghian MH, Miri HH, Sadeghi R, Bagheri R, Lavasani S, Souri S. Prognostic significance of SF3B1 mutations in patients with myelodysplastic syndromes: A meta-analysis. *Crit Rev Oncol Hematol*. Jan 2020;145:102832. doi:10.1016/j.critrevonc.2019.102832

Kazmi, F, Sensenhauser C, Greway T. Characterization of the In Vitro Inhibitory Potential of the Oligonucleotide Imetelstat on Human Cytochrome P450 Enzymes with Predictions of In Vivo Drug-Drug Interactions. *Drug Metab Dispos*. Jan 2019;47(1):9-14. doi:10.1124/dmd.118.084103

Kazmi, F, Yerino P, McCoy C, Parkinson A, Buckley DB, Ogilvie BW. An Assessment of the In Vitro Inhibition of Cytochrome P450 Enzymes, UDP-Glucuronosyltransferases, and Transporters by Phosphodiester- or Phosphorothioate-Linked Oligonucleotides. *Drug Metab Dispos*. Aug 2018;46(8):1066-1074. doi:10.1124/dmd.118.081729

Kelaidi, C, Park S, Sapena R, Beyne-Rauzy O, Coiteux V, Vey N, Stamatoullas A, Choufi B, Delaunay J, Gourin MP, Cheze S, Ravoet C, Ferrant A, Escoffre-Barbe M, Aljassem L, Raffoux E, Itzykson R, Ades L, Dreyfus F, Fenaux P. Long-term outcome of anemic lower-risk myelodysplastic syndromes without 5q deletion refractory to or relapsing after erythropoiesis-stimulating agents. *Leukemia*. Jun 2013;27(6):1283-90. doi:10.1038/leu.2013.16

Levin AA and Henry SP. Toxicology of Oligonucleotide Therapeutics and Understanding the Relevance of the Toxicities, Chapter 24, Preclinical safety evaluation of biopharmaceuticals: a science-based approach to facilitating clinical trials In: Cavagnaro JA, ed. 2008.

Liang, S, Zhou X, Pan H, Yang Y, Shi L, Wang L. Prognostic value of DNMT3A mutations in myelodysplastic syndromes: a meta-analysis. *Hematology (Amsterdam, Netherlands)*. Dec 2019;24(1):613-622. doi:10.1080/16078454.2019.1657613

Ma, W, Mason C, Chen P, Jiang Q, Delos Santos N, Lazzari E, Morris S, Mondala P, Isquith J, Huang F, Balaian L, Jamieson C. Telomerase Inhibition Impairs Self-Renewal of β -Catenin Activated Myeloproliferative Neoplasm Progenitors. Abstract. *Blood*. 2017/12/08/2017;130(Suppl 1):2860. doi:10.1182/blood.V130.Suppl_1.2860.2860

Ma, X. Epidemiology of myelodysplastic syndromes. *Am J Med*. Jul 2012;125(7 Suppl):S2-5. doi:10.1016/j.amjmed.2012.04.014

Malcovati, L, Karimi M, Papaemmanuil E, Ambaglio I, Jadersten M, Jansson M, Elena C, Galli A, Walldin G, Della Porta MG, Raaschou-Jensen K, Travaglino E, Kallenbach K, Pietra D, Ljungstrom V, Conte S, Boveri E, Invernizzi R, Rosenquist R, Campbell PJ, Cazzola M, Hellstrom Lindberg E. SF3B1 mutation identifies a distinct subset of myelodysplastic syndrome with ring sideroblasts. *Blood*. Jul 9 2015;126(2):233-41. doi:10.1182/blood-2015-03-633537

Malcovati, L, Porta MG, Pascutto C, Invernizzi R, Boni M, Travaglino E, Passamonti F, Arcaini L, Maffioli M, Bernasconi P, Lazzarino M, Cazzola M. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. *J Clin Oncol*. Oct 20 2005;23(30):7594-603. doi:10.1200/JCO.2005.01.7038

Malcovati L, SK, Papaemmanuil E, et al. SF3B1-mutant MDS as a distinct disease subtype: a proposal from the International Working Group for the Prognosis of MDS. *Blood*. May 27 2020;136(2):157-170. doi:10.1182/blood.2021012067

Mascarenhas, J, Komrokji RS, Palandri F, Martino B, Niederwieser D, Reiter A, Scott BL, Baer MR, Hoffman R, Odenike O, Vannucchi AM, Bussolari J, Zhu E, Rose E, Sherman L, Dougherty S, Sun L, Huang F, Wan Y, Feller FM, Rizo A, Kiladjian JJ. Randomized, Single-Blind, Multicenter Phase II Study of Two Doses of Imetelstat in Relapsed or Refractory Myelofibrosis. *J Clin Oncol*. Sep 10 2021;39(26):2881-2892. doi:10.1200/JCO.20.02864

Mian, SA, Rouault-Pierre K, Smith AE, Seidl T, Pizzitola I, Kizilors A, Kulasekararaj AG, Bonnet D, Mufti GJ. SF3B1 mutant MDS-initiating cells may arise from the haematopoietic stem cell compartment. *Nat Commun*. Dec 8 2015;6:10004. doi:10.1038/ncomms10004

Mittelman, M, Oster HS, Hoffman M, Neumann D. The lower risk MDS patient at risk of rapid progression. *Leuk Res.* Dec 2010;34(12):1551-5. doi:10.1016/j.leukres.2010.05.023

Mortera-Blanco, T, Dimitriou M, Woll PS, Karimi M, Elvarsdottir E, Conte S, Tobiasson M, Jansson M, Douagi I, Moarii M, Saft L, Papaemmanuil E, Jacobsen SEW, Hellstrom-Lindberg E. SF3B1-initiating mutations in MDS-RSs target lymphomyeloid hematopoietic stem cells. *Blood.* Aug 17 2017;130(7):881-890. doi:10.1182/blood-2017-03-776070

Mosoyan, G, Kraus T, Ye F, Eng K, Crispino JD, Hoffman R, Iancu-Rubin C. Imetelstat, a telomerase inhibitor, differentially affects normal and malignant megakaryopoiesis. *Leukemia.* Nov 2017;31(11):2458-2467. doi:10.1038/leu.2017.78

NCCN. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes, Version 3.

Neukirchen, J, Schoonen WM, Strupp C, Gattermann N, Aul C, Haas R, Germing U. Incidence and prevalence of myelodysplastic syndromes: data from the Dusseldorf MDS-registry. *Leuk Res.* Dec 2011;35(12):1591-6. doi:10.1016/j.leukres.2011.06.001

Newcombe, RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. *Stat Med.* Apr 30 1998;17(8):873-90. doi:10.1002/(sici)1097-0258(19980430)17:8<873::aid-sim779>3.0.co;2-i

Pang WW, Pluvineau JV, Price EA, Sridhar K, Arber DA, Greenberg PL, Schrier SL, Park CY, Weissman IL. Hematopoietic stem cell and progenitor cell mechanisms in myelodysplastic syndromes. *Proc Natl Acad Sci U S A.* 2013 Feb 19;110(8):3011-6.

Platzbecker, U, Fenaux P, Ades L, Giagounidis A, Santini V, van de Loosdrecht AA, Bowen D, de Witte T, Garcia-Manero G, Hellstrom-Lindberg E, Germing U, Stauder R, Malcovati L, Sekeres MA, Steensma DP, Gloaguen S. Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials. *Blood.* Mar 7 2019;133(10):1020-1030. doi:10.1182/blood-2018-06-857102

Platzbecker, U, Hofbauer LC, Ehninger G, Holig K. The clinical, quality of life, and economic consequences of chronic anemia and transfusion support in patients with myelodysplastic syndromes. *Leuk Res.* May 2012;36(5):525-36. doi:10.1016/j.leukres.2012.01.006

Platzbecker, U, Kubasch AS, Homer-Bouthiette C, Prebet T. Current challenges and unmet medical needs in myelodysplastic syndromes. *Leukemia.* Aug 2021;35(8):2182-2198. doi:10.1038/s41375-021-01265-7

Raza, A, Reeves JA, Feldman EJ, Dewald GW, Bennett JM, Deeg HJ, Dreisbach L, Schiffer CA, Stone RM, Greenberg PL, Curtin PT, Klimek VM, Shammo JM, Thomas D, Knight RD, Schmidt M, Wride K, Zeldis JB, List AF. Phase 2 study of lenalidomide in transfusion-dependent, low-risk, and intermediate-1 risk myelodysplastic syndromes with karyotypes other than deletion 5q. *Blood.* Jan 1 2008;111(1):86-93. doi:10.1182/blood-2007-01-068833

Santini, V, Almeida A, Giagounidis A, Gropper S, Jonasova A, Vey N, Mufti G, Buckstein R, Mittelman M, Platzbecker U, Shpilberg O, Ram R, del Canizo C, Gattermann N, Ozawa K, Zhong J, Seguy F, Hoenekopp A, Beach CL, Fenaux P. Efficacy and Safety of Lenalidomide (LEN) Versus Placebo (PBO) in RBC-Transfusion Dependent (TD) Patients (Pts) with IPSS Low/Intermediate (Int-1)-Risk Myelodysplastic Syndromes (MDS) without Del(5q) and Unresponsive or Refractory to Erythropoiesis-Stimulating Agents (ESAs): Results from a Randomized Phase 3 Study (CC-5013-MDS-005). *Blood*. 2014;124(21):409. doi:10.1182/blood.V124.21.409.409

Santini, V, Giagounidis A, Pelligra CG, Franco-Villalobos C, Tang D, Morison J, Beach CL, Hu A, Platzbecker U, Fenaux P. Impact of Lenalidomide Treatment on Overall Survival in Patients With Lower-Risk, Transfusion-Dependent Myelodysplastic Syndromes. *Clin Lymphoma Myeloma Leuk*. Sep 2022;22(9):e874-e883. doi:10.1016/j.clml.2022.05.001

Shammas, MA, Koley H, Bertheau RC, Neri P, Fulciniti M, Tassone P, Blotta S, Protopopov A, Mitsiades C, Batchu RB, Anderson KC, Chin A, Gryaznov S, Munshi NC. Telomerase inhibitor GRN163L inhibits myeloma cell growth in vitro and in vivo. *Leukemia*. Jul 2008;22(7):1410-1418. doi:10.1038/leu.2008.81

Singhal, D, Kutyna MM, Chhetri R, Wee LYA, Hague S, Nath L, Nath SV, Sinha R, Wickham N, Lewis ID, Ross DM, Bardy PG, To LB, Reynolds J, Wood EM, Roxby DJ, Hiwase DK. Red cell alloimmunization is associated with development of autoantibodies and increased red cell transfusion requirements in myelodysplastic syndrome. *Haematologica*. Dec 2017;102(12):2021-2029. doi:10.3324/haematol.2017.175752

Tang, Y, Miao M, Han S, Qi J, Wang H, Ruan C, Wu D, Han Y. Prognostic value and clinical feature of SF3B1 mutations in myelodysplastic syndromes: A meta-analysis. *Crit Rev Oncol Hematol*. Jan 2019;133:74-83. doi:10.1016/j.critrevonc.2018.07.013

Tefferi, A, Al-Kali A, Begna KH, Patnaik MM, Lasho TL, Rizo A, Wan Y, Hanson CA. Imetelstat therapy in refractory anemia with ring sideroblasts with or without thrombocytosis. *Blood cancer journal*. Mar 11 2016;6(3):e405. doi:10.1038/bcj.2016.13

Thol, F, Friesen I, Damm F, Yun H, Weissinger EM, Krauter J, Wagner K, Chaturvedi A, Sharma A, Wichmann M, Gohring G, Schumann C, Bug G, Ottmann O, Hofmann WK, Schlegelberger B, Heuser M, Ganser A. Prognostic significance of ASXL1 mutations in patients with myelodysplastic syndromes. *J Clin Oncol*. Jun 20 2011;29(18):2499-506. doi:10.1200/JCO.2010.33.4938

Visser, O, Trama A, Maynadie M, Stiller C, Marcos-Gragera R, De Angelis R, Mallone S, Tereanu C, Allemani C, Ricardi U, Schouten HC, Group RW. Incidence, survival and prevalence of myeloid malignancies in Europe. *Eur J Cancer*. Nov 2012;48(17):3257-66. doi:10.1016/j.ejca.2012.05.024

Volpe, VO, Garcia-Manero G, Komrokji RS. Myelodysplastic Syndromes: A New Decade. *Clin Lymphoma Myeloma Leuk*. Jan 2022;22(1):1-16. doi:10.1016/j.clml.2021.07.031

Wan, Z, Han B. High-dose regimens of hypomethylating agents promote transfusion independence in IPSS lower-risk myelodysplastic syndromes: a meta-analysis of prospective studies. *Aging*. Mar 26 2021;13(8):11120-11134. doi:10.18632/aging.202767

Wang, X, Hu CS, Petersen B, Qiu J, Ye F, Houldsworth J, Eng K, Huang F, Hoffman R. Imetelstat, a telomerase inhibitor, is capable of depleting myelofibrosis stem and progenitor cells. *Blood Adv*. Sep 25 2018;2(18):2378-2388. doi:10.1182/bloodadvances.2018022012

Yu, RZ, Kim TW, Hong A, Watanabe TA, Gaus HJ, Geary RS. Cross-species pharmacokinetic comparison from mouse to man of a second-generation antisense oligonucleotide, ISIS 301012, targeting human apolipoprotein B-100. *Drug Metab Dispos*. Mar 2007;35(3):460-8. doi:10.1124/dmd.106.012401

Zeidan, AM, Linhares Y, Gore SD. Current therapy of myelodysplastic syndromes. *Blood Rev*. Sep 2013;27(5):243-59. doi:10.1016/j.blre.2013.07.003

Zeidan, AM, Shallis RM, Wang R, Davidoff A, Ma X. Epidemiology of myelodysplastic syndromes: Why characterizing the beast is a prerequisite to taming it. *Blood Rev*. Mar 2019;34:1-15. doi:10.1016/j.blre.2018.09.001

The FDA's References:

Bernard E, Tuechler H, Greenberg PL, et al. Molecular international prognostic scoring system for myelodysplastic syndrome. *NEJM Evid* 2022;1(7):EVIDoa2200008 Epub 2022 Jun 12

Bersanelli M, Travaglino E, Meggendorfer M, Matteuzzi T, Sala C, Mosca E, Chiereghin C, Di Nanni N, Gnocchi M, Zampini M, Rossi M, Maggioni G, Termanini A, Angelucci E, Bernardi M, Borin L, Bruno B, Bonifazi F, Santini V, Bacigalupo A, Voso MT, Oliva E, Riva M, Ubezio M, Morabito L, Campagna A, Saitta C, Savevski V, Giampieri E, Remondini D, Passamonti F, Ciceri F, Bolli N, Rambaldi A, Kern W, Kordasti S, Sole F, Palomo L, Sanz G, Santoro A, Platzbecker U, Fenaux P, Milanesi L, Haferlach T, Castellani G, Della Porta MG. Classification and Personalized Prognostic Assessment on the Basis of Clinical and Genomic Features in Myelodysplastic Syndromes. *J Clin Oncol*;39(11):1223-1233.

Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. *Blood* 2006;108(2):419-25.

Cutler CS, Lee SJ, Greenberg P, et al. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk myelodysplasia is associated with improved outcome. *Blood* 2004;104(2):579-85.

Fenaux P, Giagounidis A, Selleslag D, et al. A randomized phase 3 study of lenalidomide versus placebo in RBC transfusion-dependent patients with low-/intermediate-1 risk myelodysplastic syndromes with del5q. *Blood* 2011;118(14):3765-76.

Fenaux P, Haase D, Santini V, et al. Myelodysplastic syndromes: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. *Ann Oncol* 2021;32(2):142-56.

Garcia-Manero G, Santini V, Almedia A, et al. Phase III, randomized, placebo-controlled trial of CC-486 (oral azacitidine) in patients with lower-risk myelodysplastic syndromes. *J Clin Oncol* 2021;39(13):1426-36.

Garcia-Manero G. Myelodysplastic syndromes: 2023 update on diagnosis, risk-stratification, and management. *Am J Hematol.* 2023;98(8):1307-25.

Greenberg P, Cox C, LeBeau M, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 1997;89(6):2079-88.

Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood* 2012;120(12):2454-65.

Greenberg PL, Rigsby CK, Stone RM et al. NCCN Task Force: Transfusion and iron overload in patients with myelodysplastic syndromes. *J Natl Compr Cancer Netw* 2009;7 Suppl 9:S1-16.

Koreth J, Pidala J, Perez WS, et al. Role of reduced-intensity conditioning allogeneic hematopoietic stem-cell transplantation in older patients with de novo myelodysplastic syndromes: an international collaborative decision analysis. *J Clin Oncol* 2013;31(21):2662-70.

Mo A, Poynton M, Wood E, et al. Do anemia treatments improve quality of life and physical function in patients with myelodysplastic syndromes? A systematic review. *Blood Rev* 2023;61:101114

Ogawa S. Genetics of MDS. *Blood*;133(10):1049-1059.

Park S, Grabar S, Kelaidi C, et al. Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: the GFM experience. *Blood* 2008;111(2):574-82.

Platzbecker U, Fenaux P, Adès L, et al. Proposals for revised IWG 2018 hematological response criteria in patients with MDS included in clinical trials. *Blood* 2019;133(10):1020-1030.

Salloum R, Hummel TR, Kumar SS, et al. A molecular biology and phase II study of imetelstat (GRN163L) in children with recurrent or refractory central nervous system malignancies: a pediatric brain tumor consortium study. J Neurooncol 2016;129(3):443-51.

Sanchez-Garcia J, Falantes J, Perez AM, et al. Prospective randomized trial of 5 days azacitidine versus supportive care in patients with lower-risk myelodysplastic syndromes without 5q deletion and transfusion-dependent anemia. Leuk Lymphoma 2018;59(5):1095-1104.

Santini V Treatment of low-risk myelodysplastic syndromes. Hematology Am Soc Hematol Educ Program 2016;2016(1):462-9.

SEER Cancer Statistics Explorer Network, SEER*Explorer, updated June 8, 2023, accessed August 16, 2023

U.S Food and Drug Administration. Clinical review, December 31, 2019, BLA 761136 Rebolozy (luspatercept); 2020. Available at:
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/761136Orig2s000MedR.pdf

U.S. Food and Drug Administration. Dacogen, Full Prescribing Information. Available at:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/021790s025lbl.pdf

U.S. Food and Drug Administration Inqovi, Full Prescribing Information. Available at:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/212576s003lbl.pdf

U.S. Food and Drug Administration. Vidaza Full Prescribing Information. Available at:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/050794s035lbl.pdf

Ye L, Mei C, Ren Y, et al. Lower-dose decitabine improves clinical response compared with best supportive care in lower-risk MDS patients: a prospective, multicenter phase 2 study. J Cancer 2021;12(10):2975-81.

Zeidan AM, Platzbecker U, Bewersdorf JP, et al. Consensus proposal for revised International Working Group 2023 response criteria for higher-risk myelodysplastic syndromes. Blood 2023;141(17):2047-2061.

19.2. Financial Disclosure

The Applicant's Position:

All investigators participating in study MDS3001 were assessed for equity interest, significant payments, proprietary interests and other compensation. None of the investigators out of 1057 total investigators had financial interests to disclose. Additionally, there were 17 investigators for whom the applicant was not able to obtain signed financial disclosure, but did

not have reportable financial disclosure and either did not have or enroll patients in the study, did not participate in the study or did not open sites for the study. A statement of due diligence in cases where the applicant was unable to obtain a signed financial disclosure form from the investigator is included as an attachment to FDA Form 3454 provided with the NDA submission.

Covered Clinical Study (Name and/or Number): MDS3001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>1057 investigators at sites which enrolled subjects plus 19 investigators who either did not have or enroll patients in the study, did not participate in the study, or did not open sites for the study</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
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) <u>19</u>		
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.

The FDA's Assessment:

The FDA concurs.

19.3. Nonclinical Pharmacology/Toxicology

Data:

N/A

The Applicant's Position:

N/A

The FDA's Assessment:

There are no additional Pharmacology/Toxicology data.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Population PK Analysis

19.4.1.1. Executive Summary

The FDA's Assessment:

In general, the applicant's population PK (popPK) analysis is considered acceptable for the purpose of characterizing the PK profile of imetelstat in adult patients with hematologic malignancies or solid tumors. The applicant's analyses were verified by the reviewer, with no significant discordance identified. More specifically, the model was used to support the current submission as outlined in Table 111.

Table 111: Specific Comments on Applicant's Final Population PK model

Utility of the final model			Reviewer's Comments
Support applicant's proposed labeling statements about intrinsic and extrinsic factors	Intrinsic factor	No clinically significant differences in the PK of imetelstat were observed based on age (21 to 87 years), sex, race, mild to moderate renal impairment (CrCL 30 to < 90 mL/min), mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin > 1x to 1.5x ULN and any AST), or moderate hepatic impairment (total bilirubin > 1.5x to 3x ULN and any AST). The PK of imetelstat have not been studied in patients with severe renal impairment (CrCL 15 and < 30 mL/min), end-stage renal disease, or severe	The statement is acceptable. The applicant included 14 severe renal impairment patients (minimum CrCL: 25 mL/min; N=7 in MDS patient), and 4 severe hepatic impairment patient (N=3 in MDS patient) in the popPK dataset. No significant effect was observed for these patients with severe renal impairment or hepatic impairment based on PopPK analysis. A population size of N=4 for severe hepatic

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		hepatic impairment (total bilirubin > 3x ULN and any AST).	impairment may not be enough subjects to draw reliable conclusion.

19.4.1.2. PPK Assessment Summary

The Applicant's Position:

General Information			
Objectives of PPK Analysis	- To quantitatively describe imetelstat PK in the indicated population - To identify and quantify the effects of covariates, which contribute significantly to the between-subject variability in PK for imetelstat - To derive individual exposure parameters to be used for the E-R analyses, including Cycle 1 C_{max}, Cycle 1 AUC, and C_{avg} up to the time of the event		
Studies, Populations, and Doses Included	Study	Population	Dose Levels*
	CP04-151	Chronic lymphoproliferative disease	19, 38, 75, 151, 226 mg/m ² qw over *6 h IV infusion 151, 188 mg/m ² qw 188 mg/m ² Days 1 and 8 q3w
	CP05-101	Solid tumors	0.4, 0.8, 1.5, 3.0, 4.5 mg/kg qw 4.5, 5.6, 7.1, 8.9, 11.0 mg/kg Days 1 and 8 q3w 8.9, 11.0 mg/kg q4w
	CP14A004	Multiple myeloma	3.0, 1.5, 5.6, 6.8 mg/kg qw 5.6 mg/kg Days 1 and 8 q3w
	CP14B015	Essential thrombocythemia, polycythemia vera	7.1, 8.9 mg/kg qw

Version date: June 2022 (ALL NDA/ BLA reviews)

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

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 TRADENAME, imetelstat

		CP14B013	Multiple myeloma	7.1, 8.9 mg/kg Days 1 and 8 q4w
		MYF2001	Myelofibrosis	4.4, 8.9 mg/kg q3w
		MDS3001	Myelodysplastic syndromes	7.1 mg/kg q4w
		*All dose levels are 2 h IV infusion unless otherwise indicated.		
Population Characteristics (Applicant Table 112)	General	Age: median 67.0 years (range: 21.0-87.0 years) Weight median 75.0 kg (range: 44.0-161.0 kg) Male: 247/424 (58.3%) Race: White/Caucasian: 342/424 (80.7%) Black/African American: 31/424 (7.3%) Asian: 16/424 (3.8%) Other: 2/424 (0.5%) Unknown: 33/424 (7.8%)		
	Organ Impairment	Hepatic Impairment (NCI-ODWG based on bilirubin and AST): Normal: 256/424 (60.4%) Mild: 119/424 (28.1%) Moderate: 24/424 (5.7%) Severe: 3/424 (0.9%) Missing: 22/424 (5.2%) Renal Impairment (based on CrCL): Normal: 156/424 (36.8%) Mild: 147/424 (34.7%) Moderate: 115/424 (27.1%) Severe: 6/424 (1.4%)		
	Pediatrics (if any)	Not applicable		

No. of Patients, PK Samples, and BLQ		See Applicant Table 113	
Sampling Schedule	Rich Sampling	Study	Serial PK Schedule
		CP04-151	6 h infusion: Cycle 1 Day 1 pre-dose; 1, 2, and 4 h post-SOI; EOI; and 0.25, 0.5, 1, 2, 3, 4, and 18 h post-EOI 2 h infusion: Cycle 1 Day 1 pre-dose; 1 h post-SOI; EOI; and 1, 2, 3, 6, 10, 14, 18, and 22 h post-EOI
		CP05-101	Cycle 1 Day 1: pre-dose, 1 h post-SOI, 5 minutes post-EOI, and 3, 4, 6, 8, 12, 16, 20, and 24 h post-SOI
		CP14B015	Cycle 1 Day 1: pre-dose, EOI, and 3, 4, 8, 14, and 26 h post-SOI
		MYF2001	Cycle 1 Day 1: pre-dose and 1, 2, 3-5, 6-10, 12-16, and 18-24 h post-SOI
		MDS3001 (Phase 2)	Cycle 1 Day 1: pre-dose and 1, 2, 3, 4, 6-8, and 22-26 h post-SOI
		EOI = end of infusion; SOI = start of infusion	
	In ITT Population	Study	Sparse PK Schedule
		MDS3001 (Phase 2)	Cycle 1 Day 1: pre-dose and 2, 3-6 h post-SOI Cycle 4 Day 1: pre-dose and 2, 3-6 h post-SOI Cycle 7, 10, etc. Day 1: pre-dose or 2 h post-SOI
		MDS3001 (Phase 3)	Cycle 1 Day 1: 2, 4-5, 6-7 h post-SOI Cycle 2+: 2 h post-SOI
Covariates Evaluated	Static	Age, sex, race, malignancy type, baseline spleen volume, hepatic impairment category, renal impairment category, ADA status	
	Time-varying	Body weight, CrCL, Albumin, total bilirubin, AST, ALT, dose, time, ADA status	
Final Model	Summary		Acceptability [FDA's comments]
Software and Version	NONMEM® program version 7.4 (ICON Development Solutions, Ellicott City, MD); Pirana version 2.9.8 (Certara, Princeton, NJ); Visual predictive checks (VPCs) were conducted using R version 4.1.3 (http://www.r-project.org).		Acceptable
Model Structure	2-compartment TMDD model with saturable binding/distribution and dose- and time-dependent elimination from the central compartment (Applicant Figure 41).		Acceptable

	The model was parameterized in terms of CL, V_c, transfer rate from the peripheral to the central compartment (K_{back}), total concentration of target (B_{max}), binding rate constant (K_{on}), dissociation rate constant (K_{off}), and internalization rate constant (K_{int}). Theory based allometric exponents of 0.75 for CL, 1 for V_c, and -0.25 from K_{back} were applied to body weight to account for the effect of body size. Interindividual variability was included on CL, V_c, B_{max}, and residual variability.	
Model Parameter Estimates	See Applicant Table 114	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	All fixed effects were estimated with sufficient precision. Effectively, relative standard errors (RSE) were lower than 11% for system related parameters. Condition number of the final model was 23.9, which is substantially less than 1000, supporting the fact that the popPK model developed is unlikely to be overparametrized (Bonate, 2012). Residual variability was quantified to be 22.2%. All random effects were also estimated with sufficient precision with RSE lower than 10%.	The Applicant updated their PopPK model based on Applicant IR response to the information request sent on Apr. 15, 2014. The correct residual variability based on new model should be 21.8%.
BLQ for Parameter Accuracy	BLQs were retained in the dataset and were treated using the M3 method (Beal, 2001; Ahn, 2008).	Acceptable
GOF, VPC	Applicant Figure 42, Applicant Figure 43, Applicant Figure 44	Acceptable
Significant Covariates and Clinical Relevance	There was no evidence for trends or differences in random effects (ETA) on CL across hepatic impairment categories (Applicant Figure 45), renal impairment categories (Applicant Figure 46), or the range of CrCL (Applicant Figure 46). The covariate analysis revealed the following significant covariates: malignancy type MF and spleen volume on B_{max}; sex, time, malignancy	Acceptable

	type MF and dose on CL; and malignancy type MM and sex on V _c . A forest plot of C _{max} and AUC estimates and 90% CIs across statistically significant covariates is provided in Applicant Figure 48 .	
Analysis Based on Simulation (optional)	Individual derived secondary PK parameters [C _{max} , AUC _{0-28d} , apparent half-life (t _{1/2}), and steady state volume of distribution (V _{ss}) at Cycle 1] were estimated by NCA of the individual concentration-time profiles simulated using the post-hoc primary PK parameters from the popPK model for the N = 170 subjects with MDS (Applicant Table 115).	Acceptable
Labeling Language	Description	Acceptability [FDA's comments]
8.6 Renal Impairment	(b) (4)	Acceptable
8.7 Hepatic Impairment		Acceptable
12.3 Pharmacokinetics	(b) (4) the geometric mean (coefficient of variation [CV] %) maximum concentration (C_{max}) in plasma was (b) (4) The area under the concentration-time	The Applicant's original PopPK model was developed based on DV2 and LDV2 calculated using the molecular weight of imetelstat free acid (4610 g/mol).

	curve from time 0 to 28 days (AUC_{0-28}) was (b) (4) <u>Distribution</u> Following a single intravenous dose of 7.1 mg/kg of TRADENAME administered over 2 hours in patients with MDS, the geometric mean (CV%) volume of distribution (b) (4) <u>Elimination</u> The geometric mean (CV%) apparent half-life for imetelstat in plasma is approximately 4.9 hours (b) (4) <u>Special populations</u> No clinically significant differences in the PK of imetelstat were observed based on age (21 to 87 years), sex, race, mild to moderate renal impairment (CrCL 30 to < 90 mL/min), mild hepatic impairment (total bilirubin $\leq$ ULN and AST > ULN, or total bilirubin > 1x to 1.5x ULN and any AST), or moderate hepatic impairment (total bilirubin > 1.5x to 3x ULN and any AST). The PK of imetelstat have not been studied in patients with severe renal impairment (CrCL 15 and < 30 mL/min), end-stage renal disease, or severe hepatic impairment (total bilirubin > 3x ULN and any AST).	However, per applicant IR response to the information request sent on Apr. 15, 2014, the correct molecular weight should be imetelstat sodium salt (4896 g/mol) given that the PK analyte is imetelstat sodium. The Applicant is asked to update the final PopPK model and associated analysis plot using the correct DV2 and LDV2. The reviewer has reviewed the updated PopPK model and deemed it acceptable. The following parameters should be corrected based on new model: Cmax 89.5 mcg/mL (27.3% CV) AUC_{0-28}: 559 h.mcg/mL (43.2% CV) Vss: 14.1 L (27.2% CV) T_{half}: 4.9 hours (43.2% CV)
12.6 Immunogenicity	Among the study participants who developed anti-drug antibodies, there was no clinically significant effect of ADA on the PK, safety, or efficacy of TRADENAME.	

Applicant Table 112: Summary of Baseline Characteristics and Laboratory Values in the Dataset, Stratified by Study

Characteristic	Statistic	CP04-151	CP05-101	CP14A004	CP14B013	CP14B015	MDS3001	MYF2001	All Subjects
Absolute eGFR (mL/min)	N	21	72	19	10	20	170	104	416
	Mean (SD)	86.9 (30.1)	97.4 (36.3)	72.8 (24.7)	99.4 (39.2)	84.8 (27.0)	81.8 (28.8)	74.3 (26.1)	83.0 (30.6)
	Median (Min, Max)	76.2 (50.5, 181)	93.4 (32.1, 228)	67.9 (35.9, 113)	81.6 (61.7, 171)	82.2 (30.4, 128)	79.1 (31.5, 218)	73.4 (27.8, 149)	79.2 (27.8, 228)
Age (years)	N	22	72	19	13	20	171	107	424
	Mean (SD)	63.2 (10.7)	60.2 (10.7)	60.7 (9.09)	59.9 (7.55)	58.2 (15.1)	70.3 (8.70)	67.2 (9.18)	66.1 (10.5)
	Median (Min, Max)	63.0 (43.0, 81.0)	63.0 (29.0, 79.0)	62.0 (44.0, 73.0)	62.0 (40.0, 68.0)	57.5 (21.0, 83.0)	71.0 (44.0, 87.0)	68.0 (31.0, 86.0)	67.0 (21.0, 87.0)
Alanine Aminotransferase (U/L)	N	22	72	19	13	20	170	107	423
	Mean (SD)	32.1 (33.2)	31.9 (26.5)	19.8 (12.0)	19.9 (9.27)	31.0 (16.0)	34.4 (27.1)	22.5 (15.5)	29.6 (24.0)
	Median (Min, Max)	19.0 (11.0, 142)	24.0 (6.00, 135)	17.0 (7.00, 56.0)	18.0 (12.0, 45.0)	27.5 (12.0, 65.0)	26.2 (3.00, 175)	18.6 (7.00, 128)	22.0 (3.00, 175)
Albumin (g/dL)	N	22	72	19	13	20	168	106	420
	Mean (SD)	3.95 (0.556)	3.77 (0.497)	4.02 (0.470)	3.99 (0.415)	4.16 (0.401)	4.28 (0.461)	3.92 (0.489)	4.06 (0.514)
	Median (Min, Max)	4.10 (2.30, 4.70)	3.80 (2.50, 4.70)	4.10 (3.00, 5.00)	4.00 (3.10, 4.60)	4.10 (3.20, 4.90)	4.30 (1.60, 6.20)	3.97 (2.60, 5.49)	4.10 (1.60, 6.20)
Aspartate Aminotransferase (U/L)	N	22	72	19	13	20	171	107	424
	Mean (SD)	39.1 (32.9)	38.2 (24.3)	29.0 (13.6)	22.7 (9.72)	32.4 (14.4)	25.9 (15.3)	31.7 (13.7)	30.5 (18.4)
	Median (Min, Max)	30.0 (15.0, 169)	32.0 (12.0, 156)	26.0 (13.0, 68.0)	20.0 (9.00, 47.0)	27.5 (15.0, 72.0)	22.0 (7.00, 98.4)	29.0 (11.0, 84.0)	26.0 (7.00, 169)
Baseline Spleen Volume (cm ³)	N	0	0	0	0	0	0	107	107
	Mean (SD)	NC (NC)	NC (NC)	NC (NC)	NC (NC)	NC (NC)	NC (NC)	3240 (1390)	3240 (1390)
	Median (Min, Max)	NC	NC	NC	NC	NC	NC	3170 (726, 7610)	3170 (726, 7610)
Bilirubin (mg/dL)	N	22	72	19	13	20	171	107	424

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	Mean (SD)	0.693 (0.370)	0.512 (0.819)	0.389 (0.197)	0.392 (0.185)	0.438 (0.199)	1.05 (0.608)	0.952 (0.460)	0.838 (0.624)
	Median (Min, Max)	0.610 (0.100, 1.80)	0.400 (0.100, 7.00)	0.300 (0.200, 1.00)	0.300 (0.200, 0.800)	0.400 (0.200, 1.00)	0.920 (0.292, 4.37)	0.900 (0.240, 2.29)	0.700 (0.100, 7.00)
BMI (kg/m²)	N	21	72	19	10	20	170	104	416
	Mean (SD)	26.2 (4.18)	26.6 (6.71)	31.1 (6.12)	31.2 (6.99)	28.0 (5.52)	27.1 (4.42)	26.0 (4.41)	27.0 (5.19)
	Median (Min, Max)	25.2 (20.5, 35.3)	25.6 (14.7, 48.2)	28.9 (23.2, 47.0)	31.3 (20.2, 42.4)	27.9 (18.3, 43.3)	26.4 (17.9, 41.6)	25.6 (18.4, 41.0)	26.4 (14.7, 48.2)
BSA (m²)	N	21	72	19	10	20	170	104	416
	Mean (SD)	1.88 (0.234)	1.86 (0.264)	1.96 (0.245)	1.93 (0.198)	1.95 (0.214)	1.84 (0.211)	1.88 (0.219)	1.87 (0.226)
	Median (Min, Max)	1.94 (1.41, 2.28)	1.80 (1.43, 2.72)	1.93 (1.62, 2.64)	1.96 (1.61, 2.21)	1.96 (1.57, 2.29)	1.82 (1.36, 2.36)	1.88 (1.38, 2.35)	1.86 (1.36, 2.72)
Creatinine (mg/dL)	N	22	72	19	13	20	171	107	424
	Mean (SD)	0.993 (0.311)	0.880 (0.292)	1.14 (0.395)	0.896 (0.273)	0.978 (0.283)	0.962 (0.331)	1.09 (0.378)	0.988 (0.343)
	Median (Min, Max)	0.995 (0.500, 1.70)	0.800 (0.400, 1.80)	1.00 (0.700, 2.00)	0.860 (0.560, 1.50)	0.894 (0.570, 1.59)	0.894 (0.390, 2.32)	1.00 (0.440, 2.42)	0.900 (0.390, 2.42)
Creatinine Clearance (mL/min)	N	22	72	19	13	20	171	107	424
	Mean (SD)	84.4 (35.1)	98.2 (38.0)	84.1 (29.0)	108 (47.2)	94.0 (35.2)	78.6 (29.3)	73.2 (28.6)	82.7 (33.2)
	Median (Min, Max)	76.4 (41.5, 184)	95.2 (25.2, 224)	80.1 (41.1, 128)	92.6 (55.5, 194)	91.2 (34.9, 158)	76.1 (29.7, 175)	68.6 (25.4, 160)	77.8 (25.2, 224)
Estimated Glomerular Filtration Rate (ml/min/1.73m²)	N	22	72	19	13	20	171	107	424
	Mean (SD)	79.9 (27.8)	91.4 (34.8)	63.9 (19.7)	84.4 (25.0)	74.9 (21.5)	77.4 (27.4)	68.8 (23.3)	77.2 (28.2)
	Median (Min, Max)	69.9 (51.2, 162)	84.6 (33.9, 223)	62.6 (32.6, 97.6)	74.8 (56.4, 134)	72.4 (33.6, 110)	74.1 (26.8, 224)	67.2 (25.3, 144)	73.6 (25.3, 224)
Height (cm)	N	21	72	19	10	20	170	104	416
	Mean (SD)	170 (10.6)	169 (8.44)	168 (12.0)	166 (11.2)	172 (10.7)	167 (9.51)	171 (9.98)	169 (9.81)

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	Median (Min, Max)	170 (152, 187)	170 (146, 184)	167 (148, 193)	166 (145, 189)	170 (156, 194)	168 (136, 190)	172 (146, 192)	170 (136, 194)
Weight (kg)	N	22	72	19	13	20	171	107	424
	Mean (SD)	75.8 (16.1)	76.5 (22.6)	87.6 (20.0)	88.3 (23.6)	82.3 (16.5)	75.9 (15.2)	75.8 (15.5)	77.2 (17.6)
	Median (Min, Max)	79.2 (47.3, 106)	71.7 (44.0, 161)	86.6 (62.4, 154)	83.3 (62.0, 147)	83.2 (56.0, 115)	74.0 (45.0, 116)	75.0 (45.0, 124)	75.0 (44.0, 161)
Sex: Male	N (%)	15 (68.2%)	43 (59.7%)	8 (42.1%)	5 (38.5%)	9 (45.0%)	100 (58.5%)	67 (62.6%)	247 (58.3%)
Sex: Female	N (%)	7 (31.8%)	29 (40.3%)	11 (57.9%)	8 (61.5%)	11 (55.0%)	71 (41.5%)	40 (37.4%)	177 (41.7%)
Race: Unknown	N (%)	2 (9.09%)	1 (1.39%)	0 (0%)	0 (0%)	0 (0%)	21 (12.3%)	9 (8.41%)	33 (7.78%)
Race: White/Caucasian	N (%)	16 (72.7%)	60 (83.3%)	15 (78.9%)	8 (61.5%)	18 (90.0%)	137 (80.1%)	88 (82.2%)	342 (80.7%)
Race: Black/African-American	N (%)	4 (18.2%)	10 (13.9%)	4 (21.1%)	5 (38.5%)	2 (10.0%)	2 (1.17%)	4 (3.74%)	31 (7.31%)
Race: Asian	N (%)	0 (0%)	1 (1.39%)	0 (0%)	0 (0%)	0 (0%)	10 (5.85%)	5 (4.67%)	16 (3.77%)
Race: Other	N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.585%)	1 (0.935%)	2 (0.472%)
Ethnicity: Hispanic or Latino	N (%)	2 (9.09%)	1 (1.39%)	0 (0%)	1 (7.69%)	0 (0%)	7 (4.09%)	10 (9.35%)	21 (4.95%)
Ethnicity: Unknown	N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	20 (100%)	20 (11.7%)	12 (11.2%)	52 (12.3%)
Ethnicity: Not Hispanic or Latino	N (%)	20 (90.9%)	71 (98.6%)	19 (100%)	12 (92.3%)	0 (0%)	144 (84.2%)	85 (79.4%)	351 (82.8%)
Baseline Spleen Volume Collected Flag: No	N (%)	22 (100%)	72 (100%)	19 (100%)	13 (100%)	20 (100%)	171 (100%)	0 (0%)	317 (74.8%)
Baseline Spleen Volume Collected Flag: Yes	N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	107 (100%)	107 (25.2%)
Anti-Drug Antibodies Subject Level: Missing	N (%)	22 (100%)	72 (100%)	19 (100%)	13 (100%)	20 (100%)	11 (6.43%)	107 (100%)	264 (62.3%)
Anti-Drug Antibodies Subject Level: Negative	N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	160 (93.6%)	0 (0%)	160 (37.7%)
Anti-Drug Antibodies Occurrence: N/A	N (%)	22 (100%)	72 (100%)	19 (100%)	13 (100%)	20 (100%)	0 (0%)	0 (0%)	146 (34.4%)
Anti-Drug Antibodies Occurrence: No	N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	145 (84.8%)	85 (79.4%)	230 (54.2%)

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Anti-Drug Antibodies Occurrence: Yes	N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	26 (15.2%)	22 (20.6%)	48 (11.3%)
Anti-Drug Antibodies by Visit: Missing	N (%)	22 (100%)	72 (100%)	19 (100%)	13 (100%)	20 (100%)	18 (10.5%)	107 (100%)	271 (63.9%)
Anti-Drug Antibodies by Visit: Negative	N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	153 (89.5%)	0 (0%)	153 (36.1%)
Hepatic Function: Normal	N (%)	18 (81.8%)	62 (86.1%)	18 (94.7%)	13 (100%)	17 (85.0%)	83 (48.5%)	98 (91.6%)	309 (72.9%)
Hepatic Function: Mild impairment	N (%)	4 (18.2%)	9 (12.5%)	1 (5.26%)	0 (0%)	3 (15.0%)	66 (38.6%)	9 (8.41%)	92 (21.7%)
Hepatic Function: Severe impairment	N (%)	0 (0%)	1 (1.39%)	0 (0%)	0 (0%)	0 (0%)	2 (1.17%)	0 (0%)	3 (0.708%)
Hepatic Function: Moderate impairment	N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	19 (11.1%)	0 (0%)	19 (4.48%)
Hepatic Function: Missing	N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.585%)	0 (0%)	1 (0.236%)
Renal Function: Normal	N (%)	6 (27.3%)	42 (58.3%)	9 (47.4%)	7 (53.8%)	11 (55.0%)	53 (31.0%)	28 (26.2%)	156 (36.8%)
Renal Function: Mild impairment	N (%)	10 (45.5%)	18 (25.0%)	4 (21.1%)	5 (38.5%)	5 (25.0%)	65 (38.0%)	40 (37.4%)	147 (34.7%)
Renal Function: Moderate impairment	N (%)	6 (27.3%)	11 (15.3%)	6 (31.6%)	1 (7.69%)	4 (20.0%)	52 (30.4%)	35 (32.7%)	115 (27.1%)
Renal Function: Severe impairment	N (%)	0 (0%)	1 (1.39%)	0 (0%)	0 (0%)	0 (0%)	1 (0.585%)	4 (3.74%)	6 (1.42%)
Solid Tumor Type: Yes	N (%)	0 (0%)	72 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	72 (17.0%)
Solid Tumor Type: No	N (%)	22 (100%)	0 (0%)	19 (100%)	13 (100%)	20 (100%)	171 (100%)	107 (100%)	352 (83.0%)
Malignancy Type: Solid tumors	N (%)	0 (0%)	72 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	72 (17.0%)
Malignancy Type: CLD	N (%)	22 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	22 (5.19%)
Malignancy Type: MF	N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	107 (100%)	107 (25.2%)
Malignancy Type: MDS	N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	171 (100%)	0 (0%)	171 (40.3%)
Malignancy Type: MM	N (%)	0 (0%)	0 (0%)	19 (100%)	13 (100%)	0 (0%)	0 (0%)	0 (0%)	32 (7.55%)
Malignancy Type: ET/PV	N (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	20 (100%)	0 (0%)	0 (0%)	20 (4.72%)

Version date: June 2022 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

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Dose Flag: Dose between 4.4 to 8.9 mg/kg	N (%)	6 (27.3%)	40 (55.6%)	16 (84.2%)	13 (100%)	20 (100%)	171 (100%)	68 (63.6%)	334 (78.8%)
Dose Flag: Dose not between 4.4 to 8.9 mg/kg	N (%)	16 (72.7%)	32 (44.4%)	3 (15.8%)	0 (0%)	0 (0%)	0 (0%)	39 (36.4%)	90 (21.2%)

Note: dose levels are expressed in terms of active moiety in this table.

Source: popPK/E-R Report Appendix Table 7

Applicant Table 113: Summary of Samples Included and Excluded in the Analysis for Final popPK Model

Study	Study ID	Number of Subjects		Number of Imetelstat PK Observations			
		Included	Excluded	Quantifiable	BLQ (N(%))	Exclusions*	Erroneous & Outliers
CP14A004	1	19	1	110	67 (37.9)	23	9
CP05-101	2	72	3	586	132 (18.4)	143	0
CP04-151	3	22	6	272	108 (28.4)	148	13
CP14B013	4	13	0	40	6 (13.0)	13	0
CP14B015	5	20	0	222	41 (15.6)	42	0
MYF2001	6	107	0	1054	19 (1.77)	63	6
MDS3001	7	171	63**	1717	1 (0.0582)	307	0
Subtotal		424	73	4001	374 (8.55)	739	28
Included/Total		424 / 497		4375 / 5142			

BLQ observations were included for popPK model development with M3 method.

Total Observations = all post-dose PK records excluding missing concentration values.

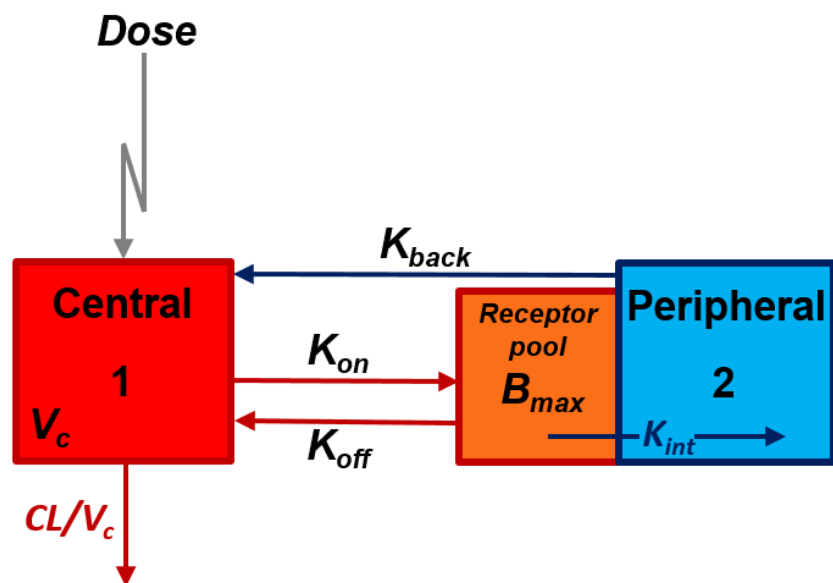
Total Observations = all PK records excluding missing concentration values.

*Reasons for exclusion include: Pre-dose observation; Erroneous samples; Outlier; Missing date/time; Missing AMT; PK without dosing; Specimen condition is ">552-day stability"; Imputed time to nominal; unable to calculate INFDUR; Unusual profile; Imputed Dose time or infusion duration; Record specific miss-matches between historical dataset.

**59 of the 63 subjects excluded were placebo subjects.

Source: popPK/E-R Report Appendix Table 2

Applicant Figure 41: Imetelstat 2-Compartment TMDD Model with Saturable Binding Schematic



Abbreviations: CL, clearance; V_c , volume of central compartment; K_{int} , internalization rate constant; K_{back} , transfer rate constant from peripheral to central compartments, K_{on} , binding rate constant; K_{off} , dissociation rate constant; B_{max} , total concentration of target.

Source: popPK/E-R Report, Figure 1

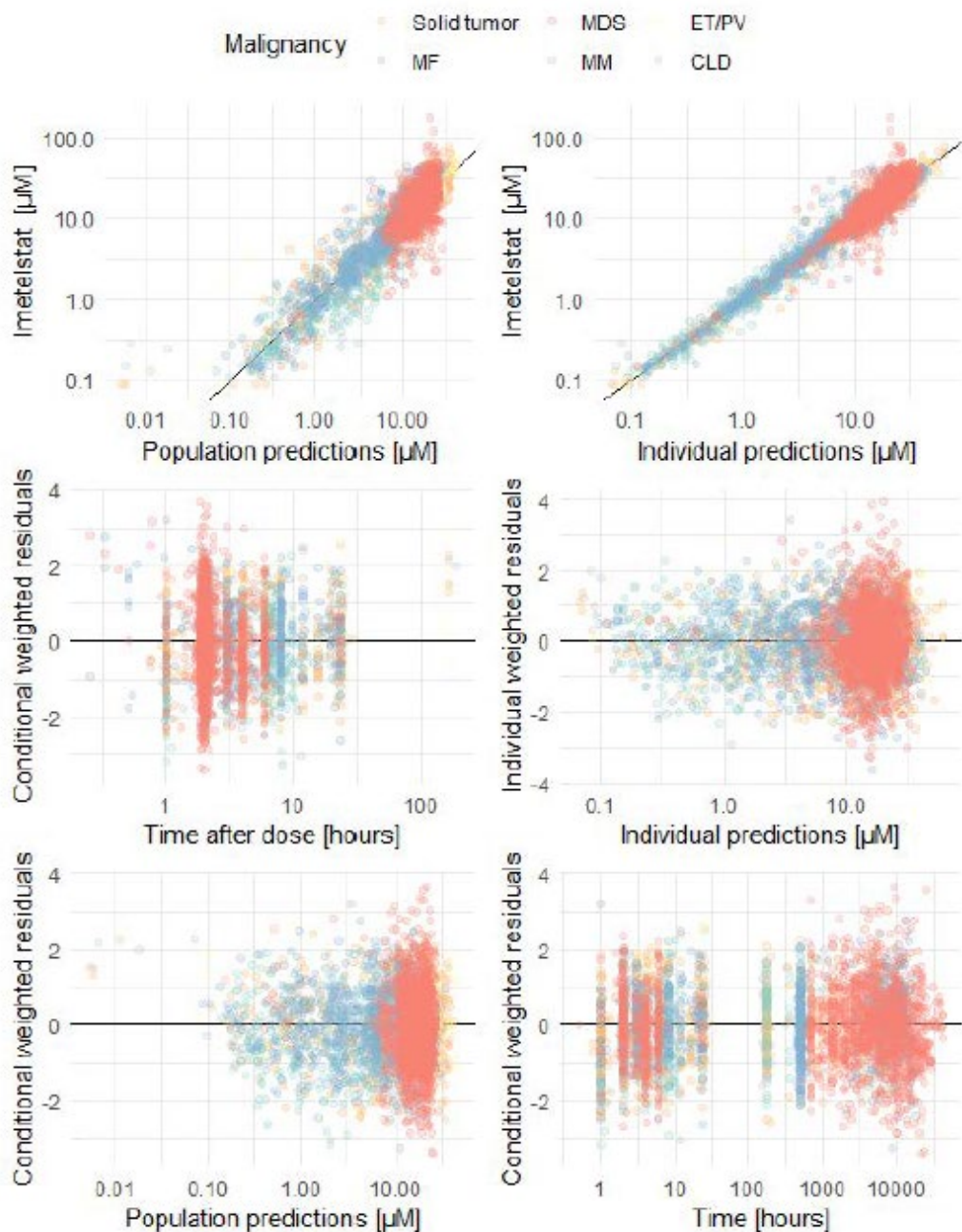
Applicant Table 114. Parameter Estimates for the Final PopPK Model of Imetelstat

Parameter [units]	Value	RSE [%]	Shrinkage [%]
Clearance [L/h/70kg]	0.969	3.38	-
Central volume [L/70kg]	3.91	2.54	-
Transfer rate from the peripheral to central compartment [1/h/70kg]	0.0305	8.13	-
Total concentration of target [μM]	15.5	6.80	-
Internalization rate constant [L/h/70 kg]	0.0864	10.6	-
Binding rate constant [L ² /(μM·h)]	0.157	8.58	-
Dissociation rate constant [L/h]	0.608	10.8	-
Effect of spleen volume on total concentration of target	0.672	29.6	-
Effect of MF malignancy on total concentration of target	1.35	7.18	-
Effect of MM malignancy on central volume	-0.239	27.4	-
Effect of dose on clearance	-0.390	9.79	-
Effect of MF on clearance	0.650	8.45	-
Effect of sex on clearance	-0.313	16.1	-
Effect of time on clearance	6190	6.11	-
Effect of sex on central volume	-0.121	27.0	-
Inter-individual variability on clearance [CV%]	43.6	4.26	10.4
Correlation between ETA on clearance and central volume [r]	55.6	10.4	-
Inter-individual variability on central volume [CV%]	25.4	6.01	19.6
Inter-individual variability on total concentration of target [CV%]	43.5	9.27	44.1
Inter-individual variability residual variability [CV%]	55.5	4.04	16.7
Residual variability [CV%]	22.2	3.88	13.2

Abbreviations: RSE, relative standard error; CV, coefficient of variation; MF, myelofibrosis; MM, multiple myeloma.

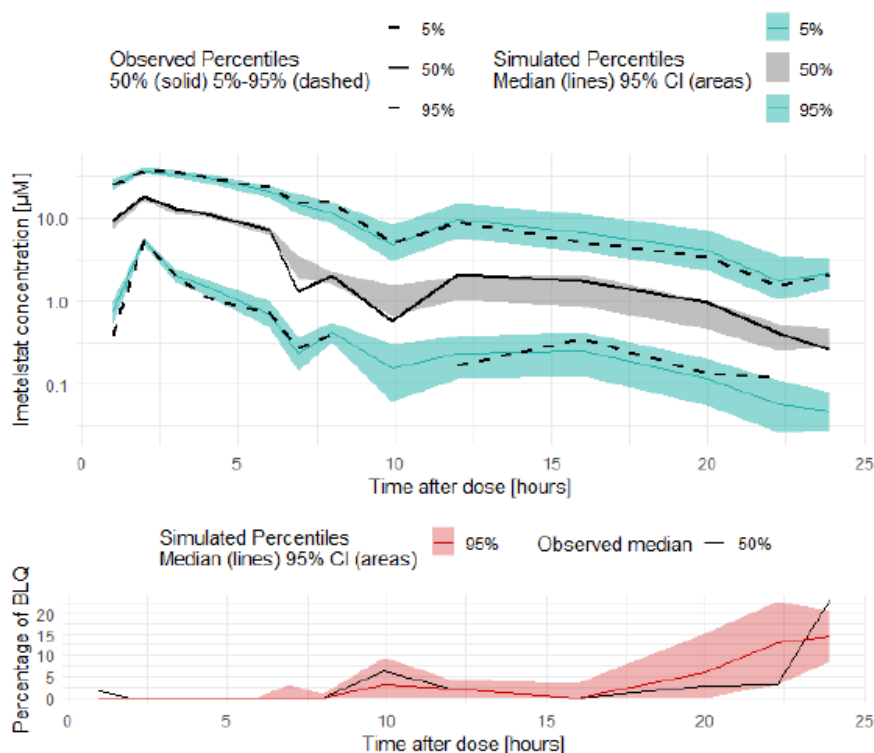
Source: popPK/E-R Report Table 1

Applicant Figure 42: Goodness of Fit Plots for the Final PopPK Model of Imetelstat



Source: popPK/E-R Report Figure 2

Applicant Figure 43: Visual Predictive Check for the Final PopPK Model of Imetelstat Including the Overall Population

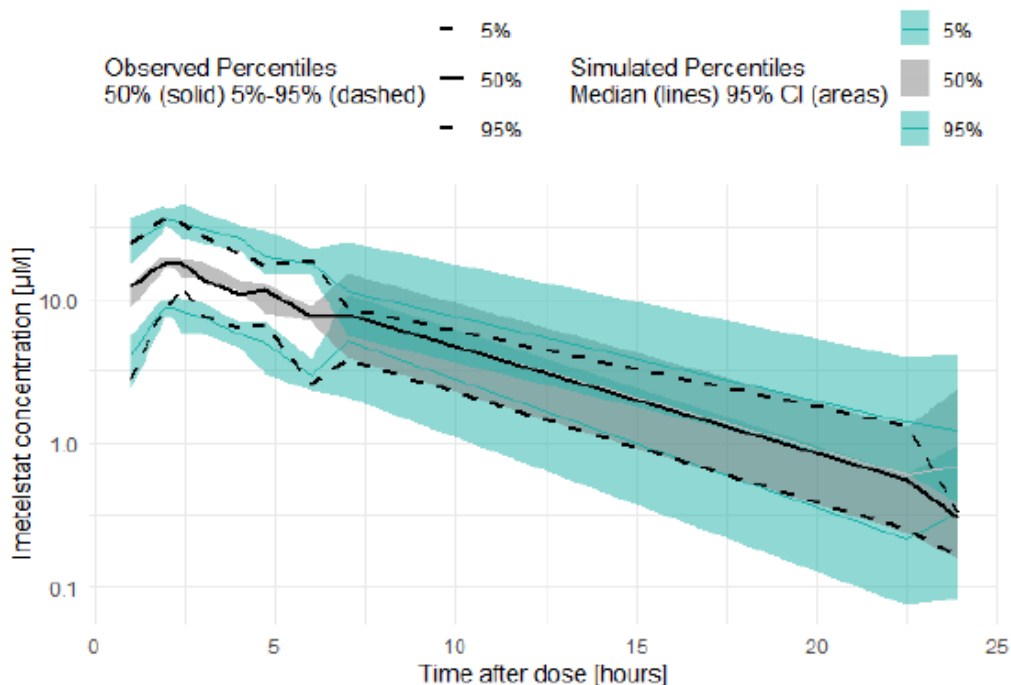


Abbreviation: BLQ, below the limit of quantification.

Solid and dashed lines represent the median and the 5th and 95th percentile of observed data. Gray and green shaded areas represent the 95% CI of the median and the 5th and 95th percentile simulated from the updated model. The lack line in the bottom panel represents the observed percentage of BLQ, and the red shaded are the predictions from the model.

Source: popPK/E-R Report Figure 3

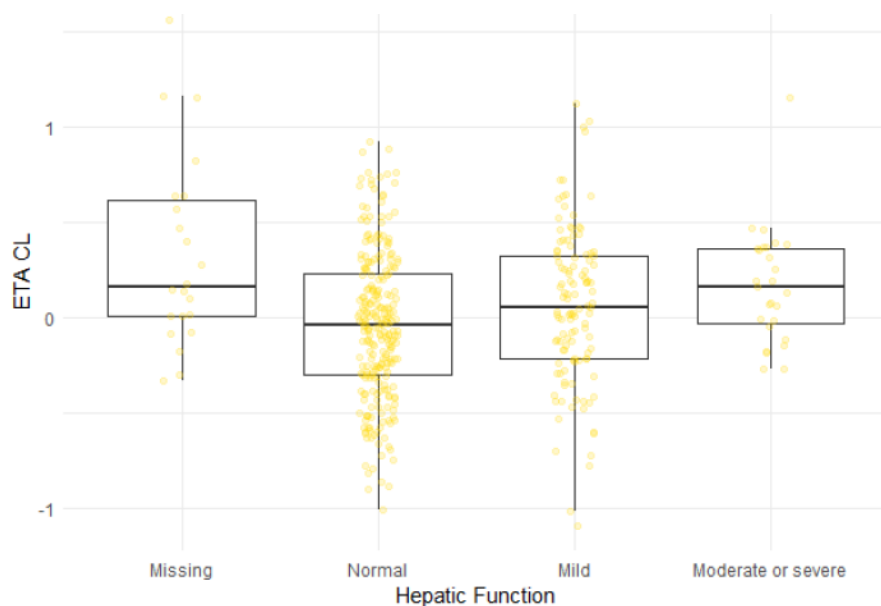
Applicant Figure 44: Visual Predictive Check for the Final PopPK Model of Imetelstat in Patients with MDS



Solid and dashed lines represent the median and the 5th and 95th percentile of observed data. Gray and green shaded areas represent the 95% CI of the median and the 5th and 95th percentile simulated from the updated model.

Source: popPK/E-R Report Figure 4

Applicant Figure 45: Clearance Random Effects (ETA) vs Hepatic Function Category from Final PopPK Model



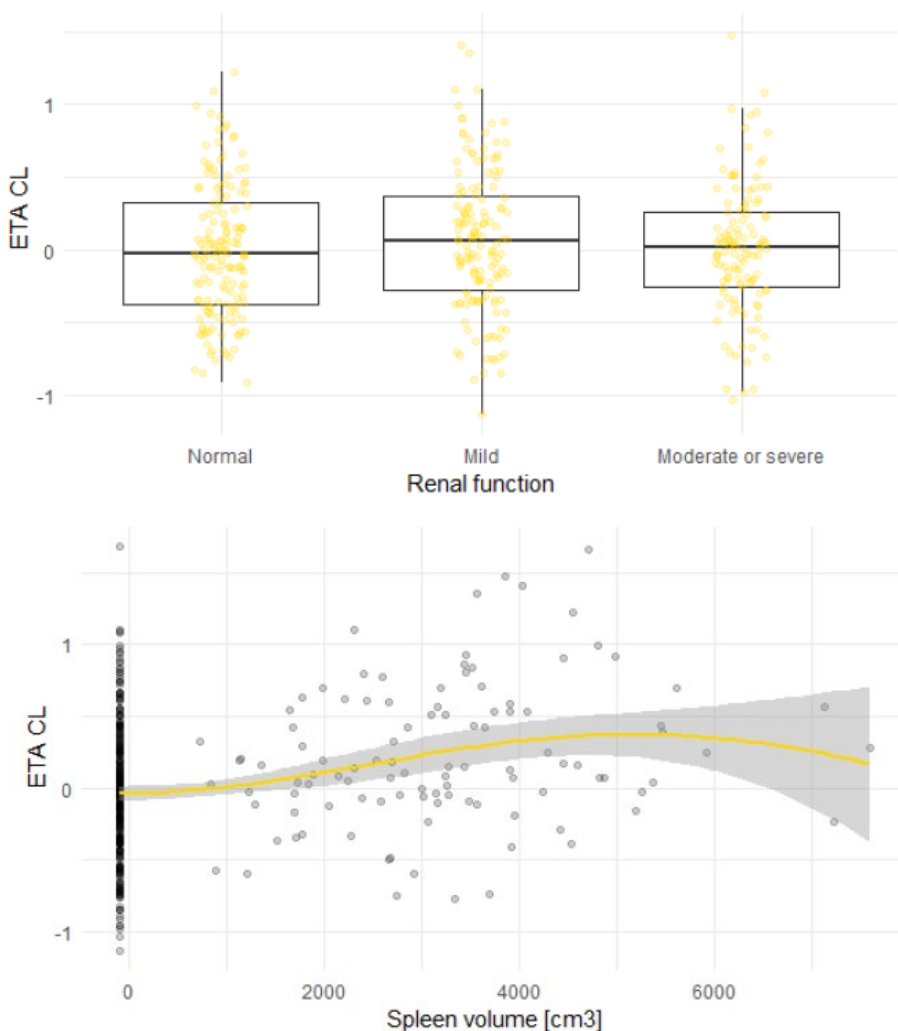
AST = aspartate aminotransferase; CL = clearance; ULN = upper limit of normal.

Hepatic impairment categorization based on total bilirubin and AST ([Ramalingam 2010](#)).

Normal = bilirubin $\leq$ ULN and AST $\leq$ ULN. Mild hepatic impairment = bilirubin $\leq$ ULN and AST $>$ ULN, or bilirubin $>$ 1.0x – 1.5x ULN and any AST. Moderate hepatic impairment = bilirubin $>$ 1.5x – 3.0x ULN and any AST. Severe hepatic impairment = bilirubin $>$ 3.0x and any AST.

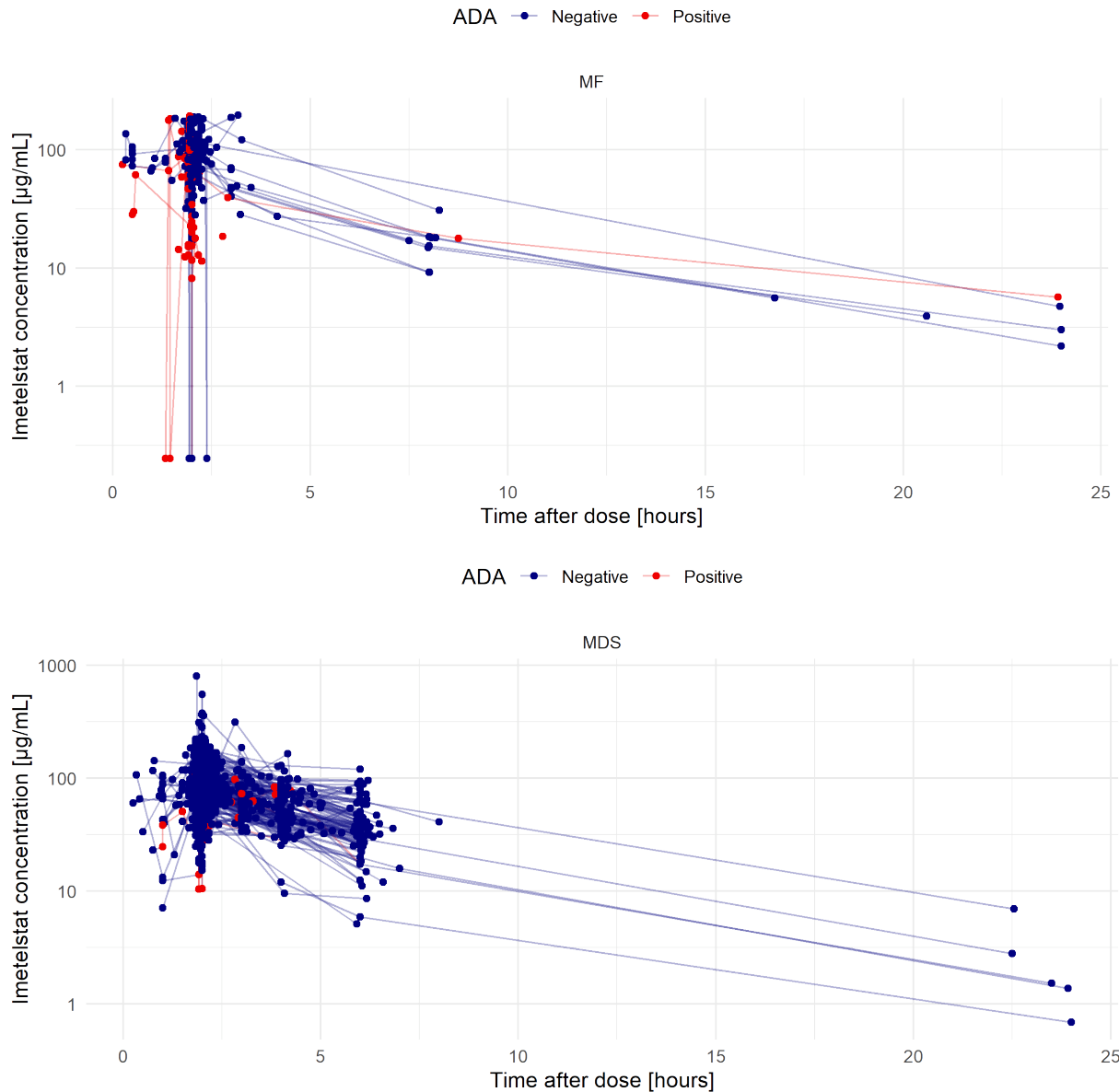
Source: popPK/E-R Report Appendix Figure 27

Applicant Figure 46: Clearance Random Effects (ETA) vs Renal Function Category (top panel) and vs Creatinine Clearance (bottom panel) from Final PopPK Model



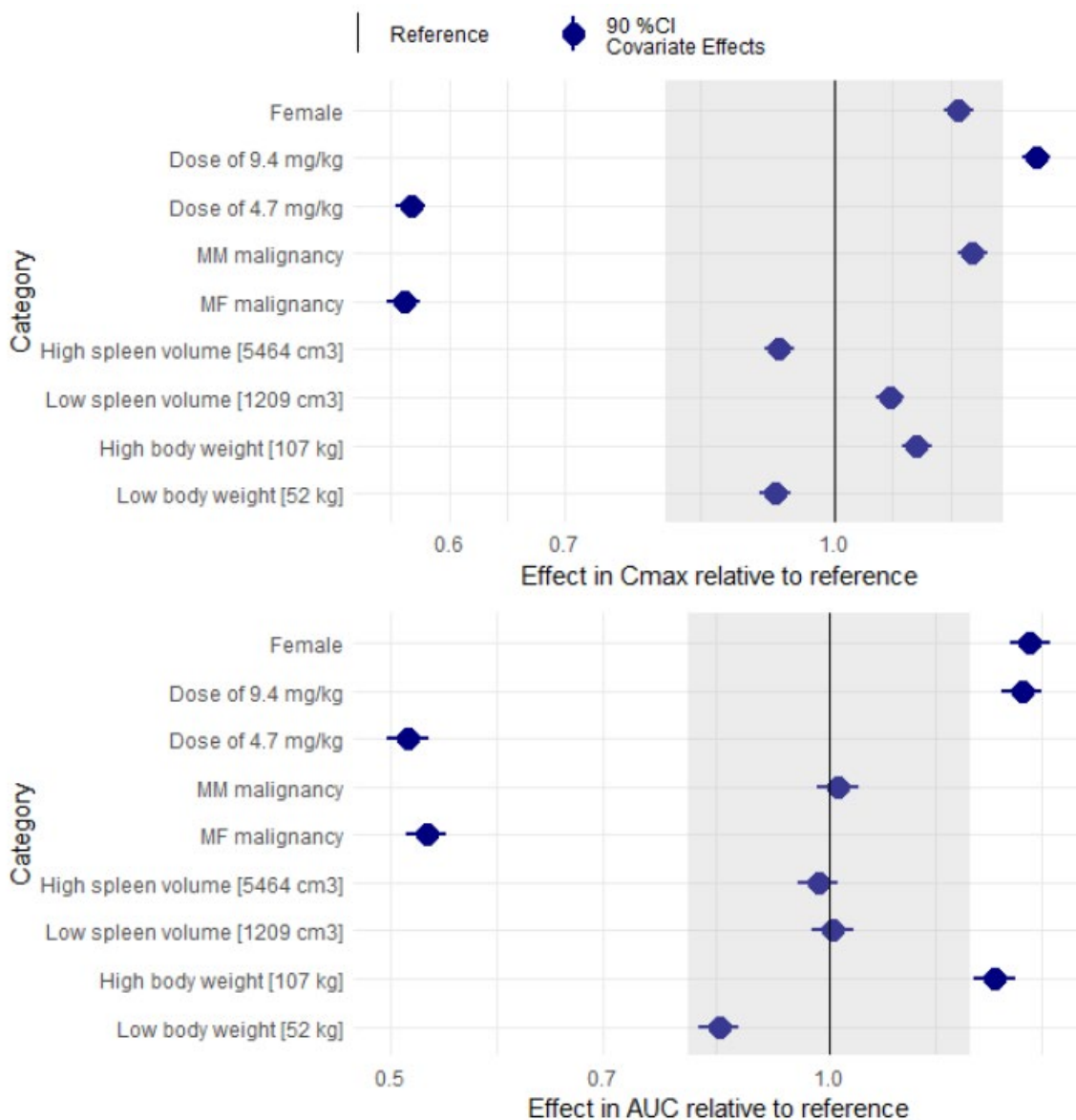
CL = clearance; CrCL = creatinine clearance. Renal impairment categorization based on CrCL ([US FDA 2020](#)). Normal renal function = CrCL ≥ 90 mL/min. Mild impairment = CrCL ≥ 60 to < 90 mL/min. Moderate impairment = CrCL ≥ 30 to < 60 mL/min. Severe impairment = CrCL ≥ 15 to < 30 mL/min.
 Source: popPK/E-R Report, Appendix Figure 6, Appendix Figure 7

Applicant Figure 47: Observed Imetelstat Concentrations vs Time After Dose by Time-Varying ADA Status (Study MDS3001 and MYF2001, popPK dataset)



ADA = anti-drug antibodies; MDS = myelodysplastic syndrome; MF = myelofibrosis.
 Observed imetelstat concentrations vs. time after dose from the final popPK dataset. X-axis is truncated at 24 hours after dose.
 Concentration records with missing ADA status were removed from the plots.
 Top panel is for Study MYF2001. Bottom panel is for MDS3001.
 Source: Integrated Summary of Immunogenicity, Figure 2

Applicant Figure 48: Effects of Significant Covariates on Imetelstat Exposure



Abbreviations: Cmax, maximum concentration; AUC, area under the concentration time curve; MM, multiple myeloma; MF: myelofibrosis. Comparisons are based on geometric mean ratio for 1000 simulated subjects for each category. Gray shading indicates 80 to 125% relative to reference population. Reference was a male, MDS malignancy, weighing 70 kg, and receiving 7.5 mg/kg of imetelstat. Dose levels expressed in terms of imetelstat sodium.

Source: popPK/E-R Report, Figure 5

Applicant Table 115: Summary Statistics of the Derived PK Parameters of Imetelstat Determined by Non-Compartmental Analysis in Subjects from Study MDS3001

Parameter	Median	Geometric mean	Geometric CV
AUC	546	554	43.4
C _{max}	88.6	89.2	27.2
t _{1/2}	5.00	4.90	45.5
V _{ss}	11.2	11.5	26.1

Abbreviations: AUC, Cycle 1 area under the concentration time curve in h x µg/mL; C_{max}, Cycle 1 maximum concentration in x µg/mL; t_{1/2}, apparent half-life in hours; CV, coefficient of variation; V_{ss}, volume of distribution at steady state.

Source: popPK/E-R Report Table 3

The FDA's Assessment:

The PopPK analysis included pooled data from seven studies comprising 424 subjects with multiple myeloma (MM), chronic lymphoproliferative disease (CLD), solid tumor malignancies, essential thrombocythemia (ET), polycythemia vera (PV), myelofibrosis (MF), or myelodysplastic syndrome (MDS). Brief descriptions of the study included are presented in Table 116.

Table 116: Summary of Studies with PK Sampling Included in Population PK Analysis

Study #	Study Description	Number of Subjects in PopPK Analysis and Subject Type	Dose(s)
Study #CP14A004	Phase 1, open-label, multi-center, sequential dose cohort, dose escalation study	Patients with Refractory or Relapsed Multiple Myeloma, N=19	3.2, 4.8, 6.0, 7.2 mg/kg imetelstat administered over 2 hours by IV infusion weekly; 6.0 mg/kg on Days 1 and 8 every 21 days
Study #CP05-101	Phase 1, open-label, sequential dose cohort, dose escalation study	Patients with Refractory or Relapsed Solid Tumor Malignancies, N=72	2-hour IV infusion at the following dose levels: 0.4, 0.8, 1.6, 3.2, and 4.8 mg/kg, weekly on a 4-week cycle; 4.8, 6, 7.2, 9.4, and 11.7 mg/kg on Days 1 and 8 of each 3-week dosing cycle; and 9.4 and 11.7 mg/kg on Day 1 in a 4-week cycle.
Study #CP04-151	Phase 1, open-label, sequential dose cohort, dose escalation study	Patients with Chronic Lymphoproliferative Disease, N=22	20, 40, 80, 160, and 240 mg/m ² imetelstat administered over 6 hours by IV infusion weekly; 160 and 200 mg/m ² imetelstat administered over 2 hours weekly; 200 mg/m ² imetelstat administered over 2 hours on Days 1 and 8
Study #CP14B013	Phase 2, open-label study	Patients with Previously Treated Multiple Myeloma, N=13	9.4 mg/kg imetelstat administered over 2 hours by IV infusion on Days 1 and 8 every 28 days. Dose may be reduced to 7.5 mg/kg due to Grade 3/4 cytopenias
Study #CP14B015	Phase 2, open-label study	Patients with Essential Thrombocythemia or Polycythemia Vera who Require Cytoreduction and Have Failed or are Intolerant to Previous Therapy, or who Refuse Standard Therapy; N=20	7.5-11.7 mg/kg imetelstat administered over 2 hours by IV infusion weekly or as needed based on hematologic response
Study #MYF2001	Phase 2, randomized, single-blind, multi-center study	Patients with Intermediate-2 or High-Risk Myelofibrosis (MF) Relapsed/Refractory to Janus Kinase (JAK) Inhibitor,	9.4 mg/kg (Arm A) or 4.7 mg/kg (Arm B) imetelstat administered over 2 hours by IV infusion every 21 days

NDA/BLA Multi-disciplinary Review and Evaluation NDA 217779 imetelstat
 TRADENAME, imetelstat

		N=107	
Study #MDS3001	Phase 2/3, multi-center, 2-part study; Part 1 was an open-label, single-arm design and Part 2 was a double-blind, randomized placebo-controlled design	Patients with IPSS Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS) that is Relapsed/Refractory to Erythropoiesis-Stimulating Agent (ESA) Treatment, N=171	7.5 mg/kg starting dose of imetelstat administered over 2 hours by IV infusion every 28 days (subjects whose dose was previously escalated could continue at the 9.4 mg/kg dose)

Source: Table adapted from Appendix Table 1 in Population Pharmacokinetic and Exposure-Response Analyses for Imetelstat in Patients with Hematologic Malignancies or Solid Tumors

NONMEM 7.4 and Pirana version 2.9.8 was used for PopPK modeling. R (version 4.1.3) were used for exploratory and post-modeling analyses. BLQ were retained in the dataset and were treated using the M3 method. Applicant Table 112 provides summary statistics of the baseline demographic covariates in the analysis dataset.

Base model

The PK of imetelstat was best characterized with a 2-compartment TMDD model with saturable binding. Models were estimated using a sequential process that implied ITS, SAEM, and IMP (with EONLY=1 option) algorithms. The structural model is illustrated in Applicant Figure 41

Covariate analysis

Covariates were evaluated using a forward additional following by backward elimination steps. Significant (p value ≤ 0.01 in likelihood ratio test and/or improvement in diagnostic plots) covariates identified in the forward addition steps are: the effect of spleen volume and myelofibrosis malignancy on Bmax (total target concentration); the effect of time-variant ADA, dose, myelofibrosis malignancy, sex, time, CrCL on CL; the effect of sex and multiple myeloma malignancy on Vc. The backward elimination step used a more stringent criteria (p value ≤ 0.001 in likelihood ratio test), the effect of time-variant ADA and CrCL on CL were dropped off from the model.

Final Model

The parameter estimates for the final PopPK models are listed in Applicant Table 114. The goodness-of-fit (GOF) plot for the final PopPK model are shown in Applicant Figure 42. The visual predictive check (VPC) plot for the final PopPK model is shown in Applicant Figure 43 and Applicant Figure 44.

PPK Review Issues

The Applicant's original PopPK model was developed based on DV2 and LDV2 calculated using the molecular weight of imetelstat free acid (4610 g/mol). However, per applicant IR response to the information request sent on Apr. 15, 2014, the correct molecular weight should be imetelstat sodium salt (4896 g/mol) given that the PK analyte is imetelstat sodium. The Applicant is asked to update the final PopPK model and associated analysis plot using the

correct DV2 and LDV2. The reviewer has reviewed the updated PopPK model and deemed it acceptable. The updated PopPK estimates are similar to original model. Overall, the incorrect calculation based on wrong molecular weight will not cause significant impact to the review outcome.

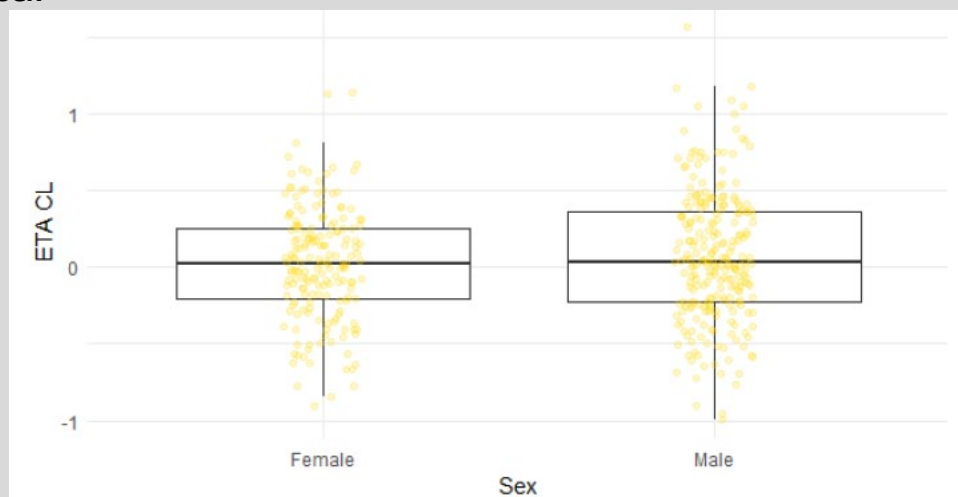
The reviewer deems the updated model provides a good description of imetelstat PK data. Based on the PopPK model, the effect of time on clearance is modeled with Emax equation (see below) and the T_{50} is estimated to be 6190 hours, or approximately 9 cycles of treatment.

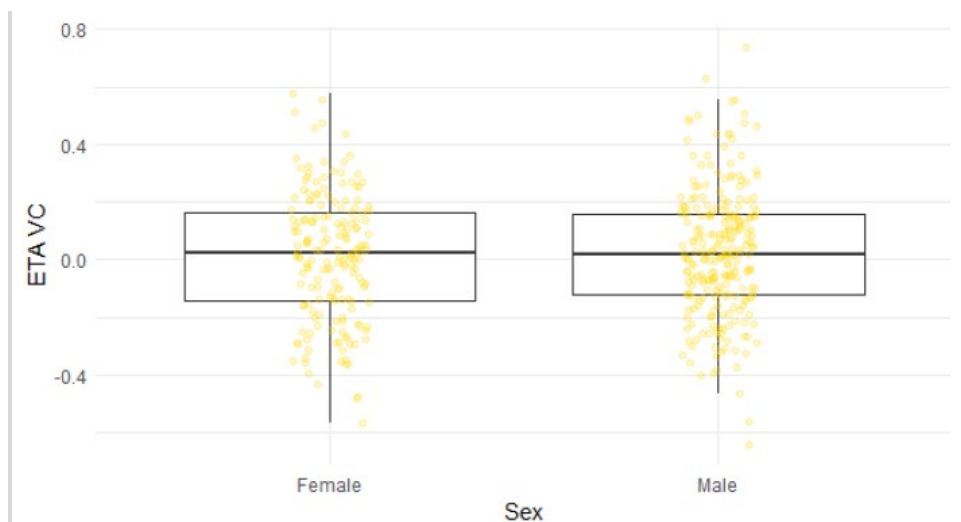
$$\text{Time effect} = 1 - \frac{\text{Time}}{T_{50} + \text{Time}}$$

Because of large T_{50} estimates, the time dependency of CL is very small and not significant. The impact of covariates included in the final PPK model was evaluated using forest plots of relative changes in steady state exposure using a male subject weighing 70 kg with MDS malignancy type receiving 7.5 mg/kg imetelstat as reference (Applicant Figure 48). Based on the analysis, dose and MF malignancy type can impact imetelstat exposure greater than 80-125% range. However, the reviewer deems the estimated effect of dose on clearance mainly comes from data in other non-MDS patient population as there is only one dose (7.5 mg/kg) studied in MDS patient. In addition, based on the box plots of post-hoc ETAs versus categorical baseline covariates for final popPK model, sex, race (white vs other), hepatic and renal functions (normal, mild, moderate or severe), should not significantly impact imetelstat clearance and volume distribution (Figure 49).

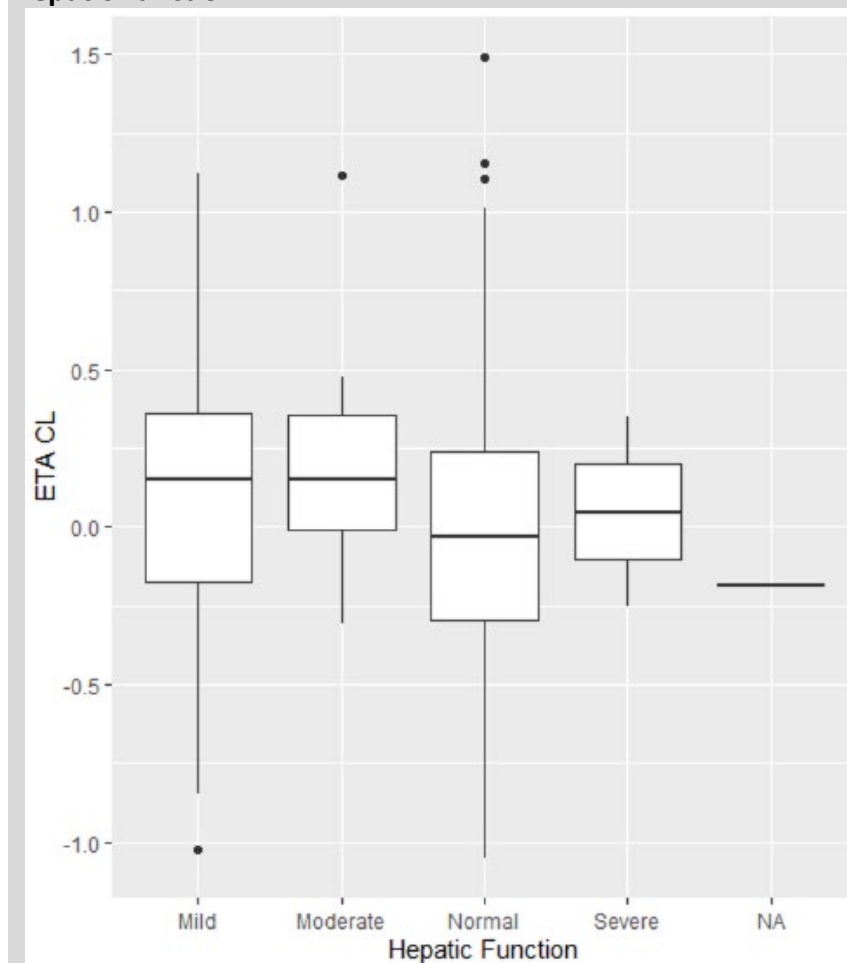
Figure 49: Box Plots of Post-hoc ETAs vs Categorical Baseline Covariates for the Final PopPK Model for Imetelstat

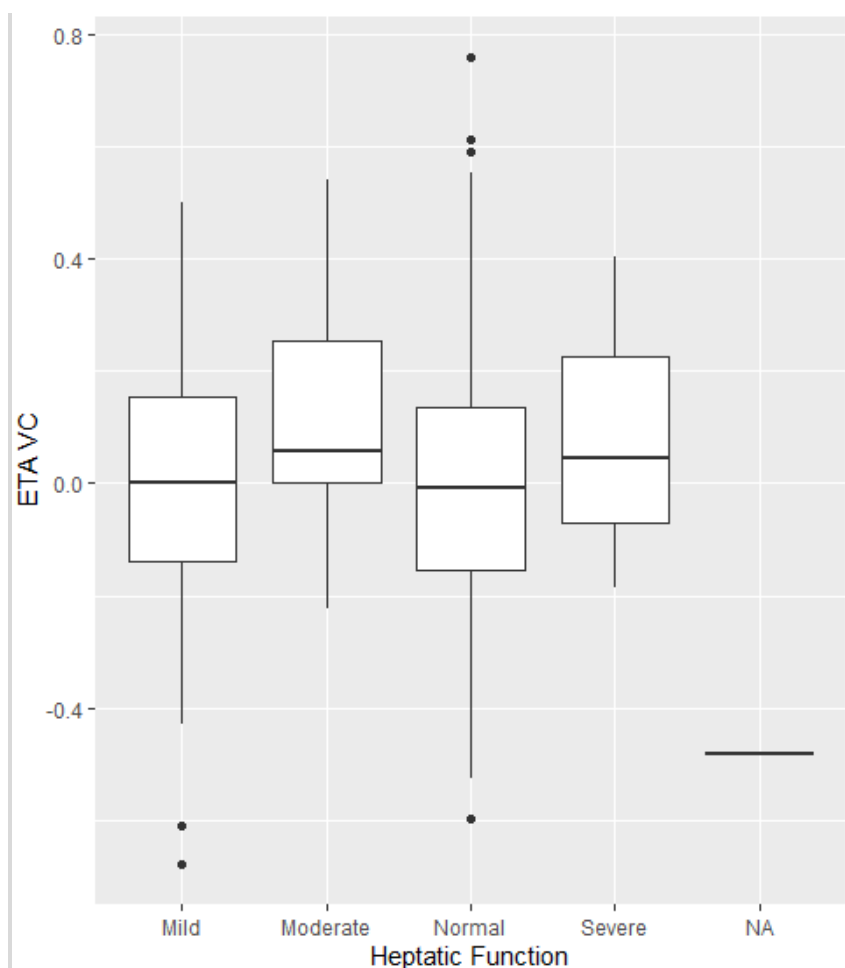
Sex

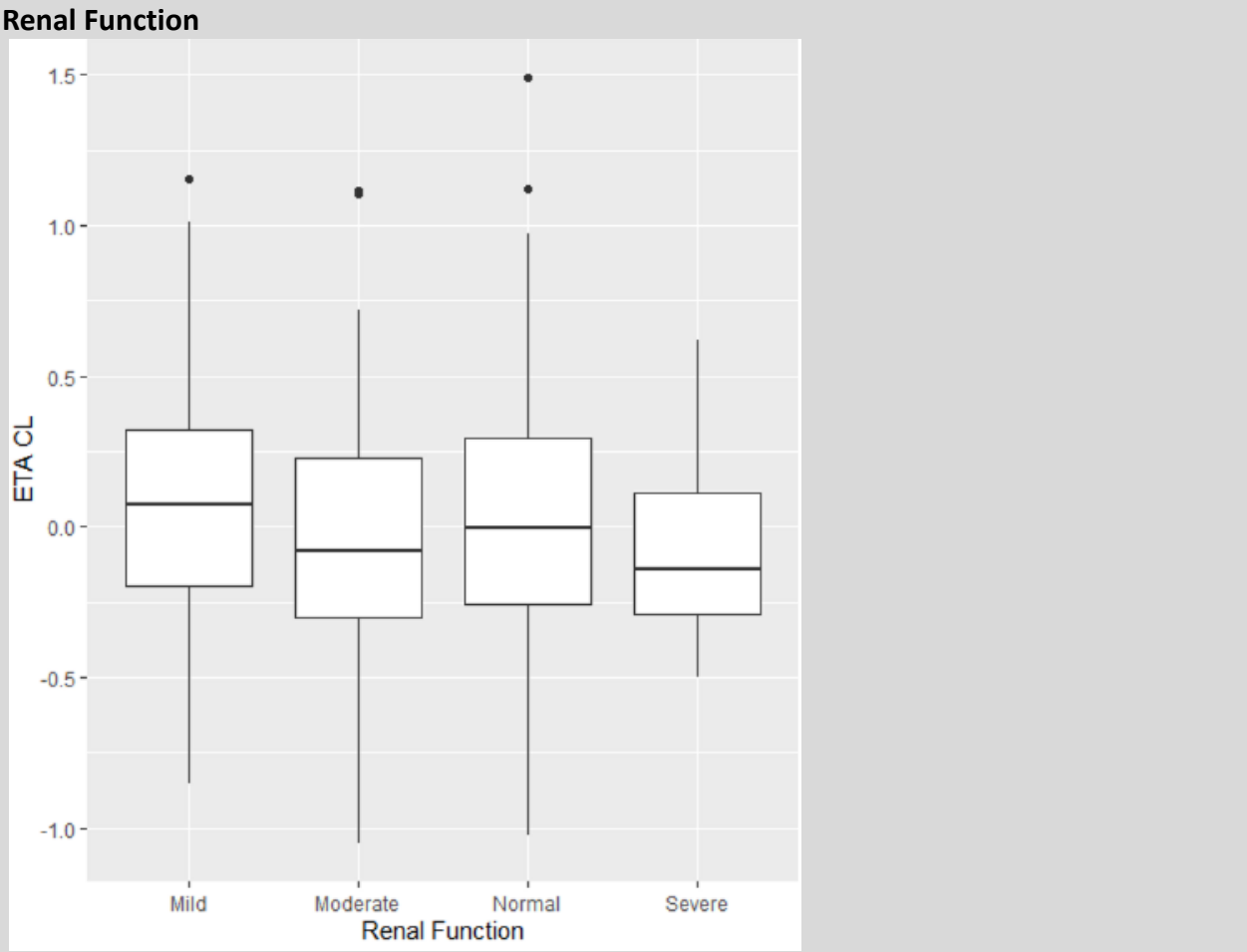


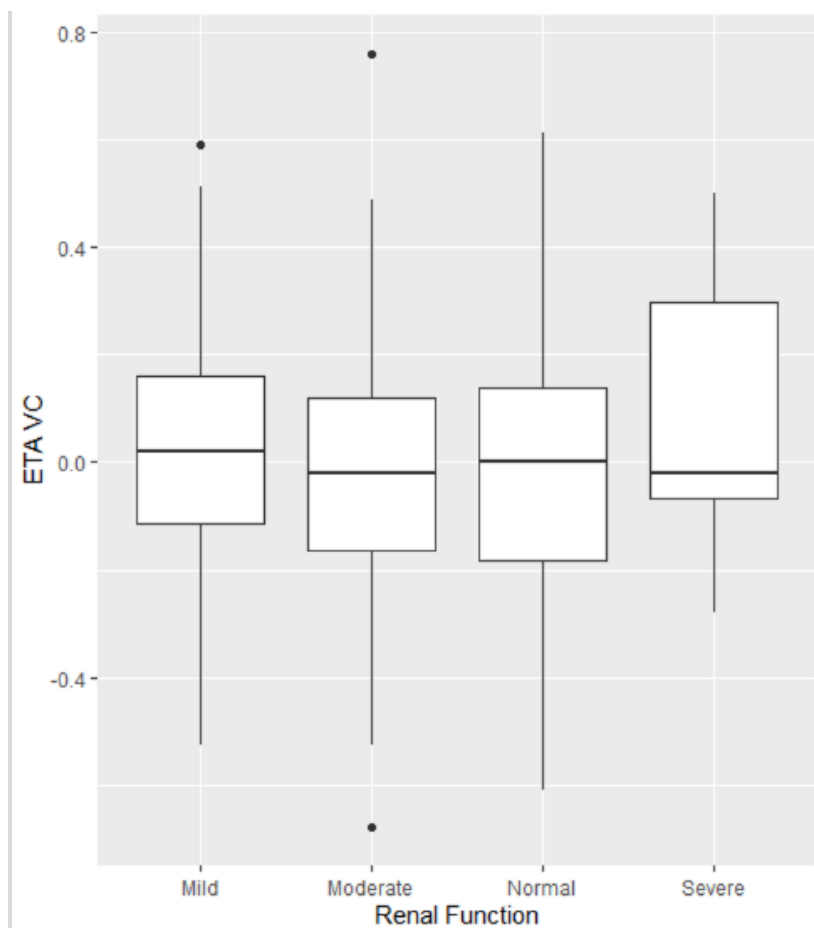


Hepatic Function

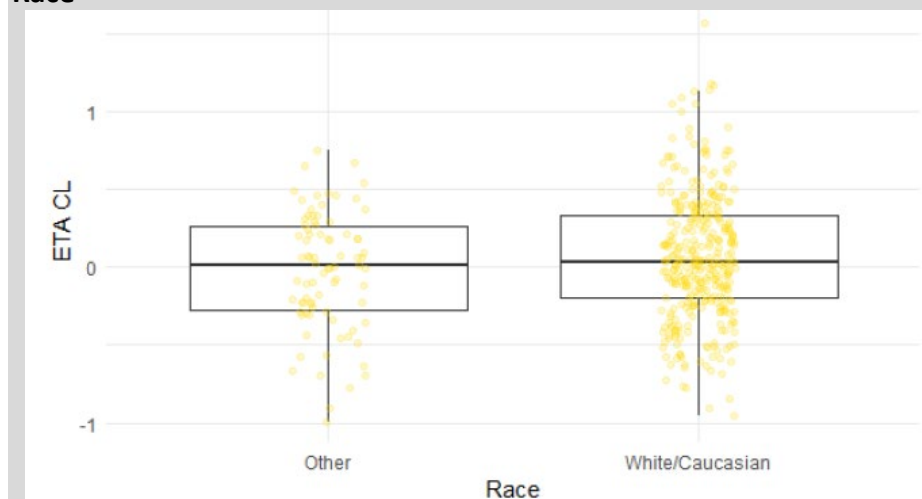


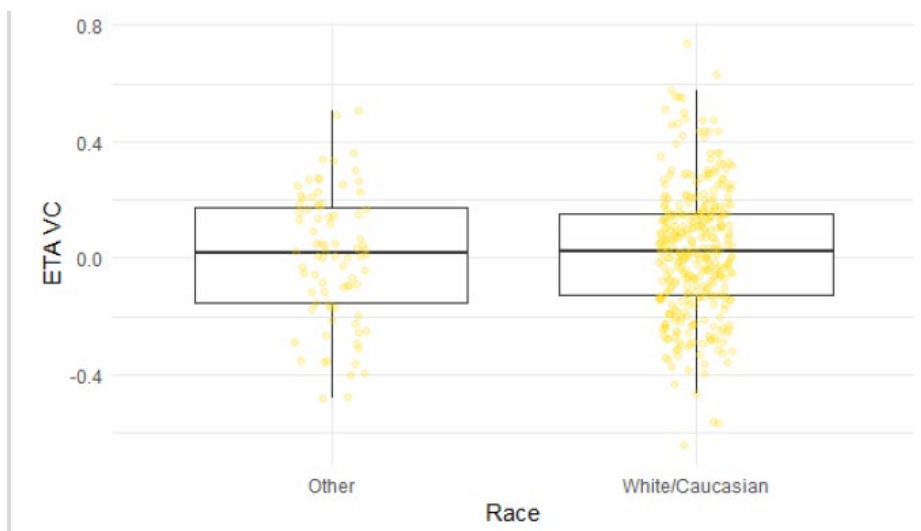






Race





“NA” means missing data.

Source: Appendix Figure 1, Addendum, PopPK modeling and ER analysis for Imetelstat in Patients with Hematologic Malignancies or Solid Tumors, Apr 24; FDA reviewer’s analysis for hepatic and renal function.

The reviewer verified that the Applicant’s updated PopPK analysis submitted on Apr 24, 2024, using the imetelstat sodium salt (4896 g/mol) to calculate dependent variable (DV2), log transformed DV2 (LDV2) is acceptable. The updated final popPK model estimates and summary statistics of the derived PK parameters of Imetelstat determined by non-compartmental analysis in subjects from Study MDS 3001 based on updated model are comparable to those submitted in original submission and are listed in tables below.

Table 117: Parameter Estimates for the updated final PopPK model of Imetelstat

Parameter [units]	Value	RSE [%]	Shrinkage [%]
Clearance [L/h/70kg]	1.00	3.50	-
Central volume [L/70kg]	4.08	2.55	-
Transfer rate from the peripheral to central compartment [1/h/70kg]	0.0253	7.58	-
Total concentration of target [µM]	15.0	7.08	-
Internalization rate constant [L/h/70 kg]	0.103	9.08	-
Binding rate constant [L ² /(µM·h)]	0.159	8.52	-
Dissociation rate constant [L/h]	0.609	10.7	-
Effect of spleen volume on total concentration of target	0.772	27.3	-
Effect of MF malignancy on total concentration of target	1.44	7.25	-
Effect of MM malignancy on central volume	-0.233	28.3	-
Effect of dose on clearance	-0.401	9.69	-
Effect of MF on clearance	0.511	10.9	-
Effect of sex on clearance	-0.299	17.1	-
Effect of time on clearance	5880	6.37	-
Effect of sex on central volume	-0.122	27.3	-
Inter-individual variability on clearance [CV%]	43.7	4.36	11.4%
Correlation between ETA on clearance and central volume [r]	0.545	10.9	-
Inter-individual variability on central volume [CV%]	25.7	6.02	20.4%
Inter-individual variability on total concentration of target [CV%]	45.8	9.44	44.5%
Inter-individual variability residual variability [CV%]	54.6	3.98	16.1%
Residual variability [CV%]	21.8	3.82	12.9%

Abbreviations: CV, coefficient of variation; MF, myelofibrosis; MM, multiple myeloma; RSE, relative standard error.

Source: Table 1, Addendum, PopPK modeling and ER analysis for Imetelstat in Patients with Hematologic Malignancies or Solid Tumors, Apr 24

Table 118: Summary Statistics of the Derived PK Parameters of Imetelstat Determined by Non-compartmental Analysis in subjects from Study MDS 3001 based on updated PopPK model

Parameter	Geometric mean	Geometric CV
AUC	559	43.2
C _{max}	89.5	27.3
t _{1/2}	4.94	43.2
V _{ss}	14.1	27.2

Abbreviations: AUC, Cycle 1 area under the concentration time curve (h x µg/mL); C_{max}, Cycle 1 maximum concentration (x µg/mL); CV, coefficient of variation; t_{1/2}, apparent half-life (in hours); V_{ss}, steady state volume of distribution.

Source: Table 2, Addendum, PopPK modeling and ER analysis for Imetelstat in Patients with Hematologic Malignancies or Solid Tumors, Apr 24

19.4.2. Exposure-Response Analysis

19.4.2.1. ER (efficacy) Executive Summary

The FDA's Assessment:

The Applicant conducted ER analysis using the data from 156 patients in study #MDS3001 for ER efficacy analysis. The efficacy endpoints include: 1) Proportion of subjects with ≥ 8 week red blood cell (RBC) transfusion independence (TI); and 2) Proportion of subjects with ≥24 week. The applicant's ER analysis is based on original PopPK model developed based on DV2 and LDV2 calculated using the molecular weight of imetelstat free acid (4610 g/mol). However, per

applicant IR response to the information request sent on Apr. 15, 2014¹, the correct molecular weight should be imetelstat sodium salt (4896 g/mol) given that the PK analyte is imetelstat sodium. The applicant is asked to update the final PopPK model and associated analysis plot using the correct DV2 and LDV2, and repeat ER analysis if significant discordancy was observed between the updated PK exposure predictions and original exposure predictions at the individual level. The applicant submitted the IR response on 4/25/2024. The reviewer has reviewed the updated PopPK model and deemed it acceptable. The updated PopPK estimates are similar to original model. In addition, there is high concordance ($r^2=0.999-1.00$) between exposure metrics for MDS patients derived from original and updated PopPK model. Thus, the incorrect calculation based on wrong molecular weight will not cause significant impact to the ER efficacy analysis outcome. The applicant did not repeat the ER analysis and the reviewer deems it is acceptable. Overall, the applicant's E-R analysis is considered acceptable for the purpose of characterizing the ER relationship of imetelstat and its efficacy endpoints (Table 119).

Table 119: Specific Comments on Applicant's E-R Analysis

Utility of the final model		Reviewer's Comments
Support applicant's proposed labeling statements about E-R Analysis	N/A	Based on ER analysis, higher imetelstat Cycle 1 Cmax is associated with higher incidence of Grade 3&4 thrombocytopenia in MDS patients. Higher imetelstat Cavg up to the event is associated with higher proportion of subjects with ≥8-week and 24-week RBC transfusion independence. However, the exposure response analyses are limited by the narrow dose/exposure range in Study MDS3001. The E-R analysis for efficacy has additional limitations due to potential confounding effect caused by dose modification and patient drop-out.

19.4.2.2. ER (efficacy) Assessment Summary

The Applicant's Position:

General Information	
Goal of ER analysis	To explore the relationship between efficacy endpoints and imetelstat exposure and to develop an E-R model for: • Proportion of subjects with ≥ 8-week RBC TI • Proportion of subjects with ≥ 24-week RBC TI
Study Included	Efficacy E-R analyses were conducted for the target population [non-del (5q) karyotype and without prior treatment with

¹ DARTS, NDA 217779, 4/18/2024, Clinical Pharmacology/Response to Information Request

Version date: June 2022 (ALL NDA/ BLA reviews)

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

		either hypomethylating agents or lenalidomide] in Phase 2 and Phase 3 of Study MDS3001.
Endpoint		<i>Primary:</i> proportion of subjects achieving ≥8-week RBC TI <i>Secondary:</i> proportion of subjects achieving ≥24-week RBC TI
No. of Patients (total, and with individual PK)		N = 156 subjects in target population in MDS3001 Phase 2 and Phase 3 N = 152 included in E-R efficacy analysis for C_{avg} N = 151 included in E-R efficacy for Cycle 1 C_{max} and AUC
Population Characteristics (Applicant Table 112)	General	Age: median 71.0 years (range: 44.0-87.0 years) Weight median 74.0 kg (range: 45.0-116 kg) Male: 100/171 (58.5%) Race: White/Caucasian: 137/171 (80.1%) Black/African American: 2/171 (1.7%) Asian: 10/171 (5.9%) Other: 1/171 (0.6%) Unknown: 21/171 (12.3%) Note: population characteristics provided for N = 171 subjects in Study MDS3001 included in final popPK dataset; not restricted to N = 152 in the target population
	Pediatrics (if any)	Not applicable
Dose(s) Included		All subjects received a starting dose of 7.1 mg/kg q4w. Subjects may have been dose reduced to 5.6 or 4.4 mg/kg or escalated to 8.9 mg/kg (Phase 2 portion only) in subsequent treatment cycles.
Exposure Metrics Explored (range)		• Cycle 1 C_{max} • Cycle 1 AUC_{0-21d} • C_{avg} up to the time of the event (or during the entire treatment period for subjects that did not have the event) Both linear and $\log_{10}$ forms of each exposure metric were evaluated in exploratory E-R analyses. Box plots of the distribution of the exposure metrics for E-R efficacy are provided in Applicant Figure 50 and Applicant Figure 51.
Covariates Evaluated		bilirubin, AST, ALT, age, body weight, albumin, neutrophil count at baseline, platelet count at baseline, sex, race, malignancy type, WHO2001 RS category at baseline, RBC transfusion burden at baseline, and IPSS risk category at baseline
Final Model Parameters		Summary Acceptability

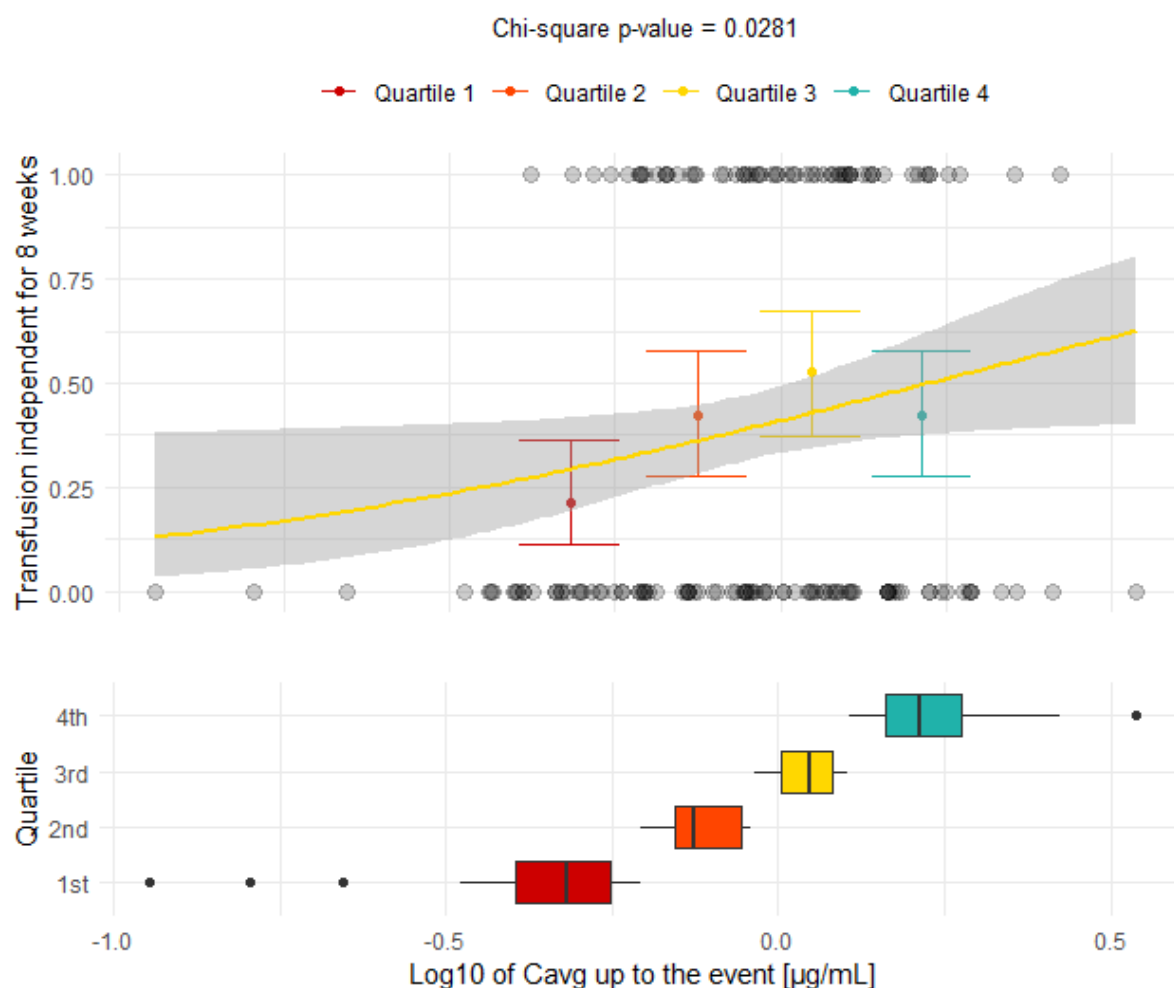
		[FDA's comments]
Model Structure	Univariate and multivariate linear logistic regression analyses were conducted. A summary of E-R efficacy analyses completed and p values for all 3 exposure metrics (C_{max} , AUC, C_{avg}) is provided in Applicant Table 120 . Figures and tables are provided below for $\log_{10} C_{avg}$, which had a significant E-R relationship with efficacy endpoints.	Acceptable
Visualization of E-R relationships	$\log_{10} C_{avg}$ and ≥ 8-Week TI: Applicant Figure 50 $\log_{10} C_{avg}$ and ≥ 24-Week TI: Applicant Figure 51	Acceptable
Model Evaluation	$\log_{10} C_{avg}$ and ≥ 8-Week TI: There was a significant positive E-R relationship ($p=0.0281$) between the proportion of subjects with ≥ 8 -week TI and $\log_{10} C_{avg}$ (Applicant Figure 50). The relationship remained significant in multivariate analysis ($p=0.0211$) (Applicant Table 121). $\log_{10} C_{avg}$ and ≥ 24-Week TI: There was a significant positive E-R relationship ($p=0.0396$) between the proportion of subjects with ≥ 24 -week TI and $\log_{10} C_{avg}$ (Applicant Figure 51 , Applicant Table 122).	Acceptable
Covariates and Clinical Relevance	$\log_{10} C_{avg}$ and ≥ 8-Week TI: IPSS risk category at baseline (Applicant Table 121) $\log_{10} C_{avg}$ and ≥ 24-Week TI: None (Applicant Table 122)	Acceptable
Simulation for Specific Population	Not applicable	
Overall Clinical Relevance for ER	There is a significant positive efficacy E-R relationship in Study MDS3001 driven by imetelstat C_{avg} , which suggests that lower exposures may result in lower efficacy.	Acceptable
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	Not applicable	N/A

Applicant Table 120: Summary of Completed Exposure-Efficacy Analyses

Endpoint	Studies	Analysis Type	p-value		
			C _{avg}	C _{max}	AUC
Efficacy					
≥8-Week Transfusion Independence	MDS3001	Univariate	*0.0281 ^l	0.899 ^l	0.741 ^l
		Multivariate	*0.0211 ^l	-	-
≥24-week Transfusion Independence	MDS3001	Univariate	*0.0396 ^l	0.423 ^l	0.777 ^l
		Multivariate	*0.0396 ^l	-	-

Analysis Type: univariate or multivariate logistic regression. Endpoints were assessed as probability of subjects meeting specified event. Exposure metrics included C_{max} for Cycle 1, AUC for Cycle 1, and C_{avg} up to time of event for responders and up to end of treatment for non-responders. Log-transformed exposure metrics are indicated with ^l. P values were computed from the likelihood ratio test. *Indicates a significant (p_{LRT} <0.05) and positive E-R relationship (probability of meeting endpoint increases with increasing exposure); - indicates analysis not done.
 Source: Module 2.7.2, Table 18 (note: table was adapted for the assessment aid to remove safety endpoints)

Applicant Figure 50: Shape of the Relationship between Log_{10} of C_{avg} and Proportion of Subjects with (Responders) or without (Non-Responders) ≥ 8 -Week RBC Transfusion Independence



NOTE: p value computed with the likelihood ratio test.

Upper panel: Symbols: individual response data; Colored dots and error bars: median and 95% CI of the probability of response in each quartile of exposure of the observed data (red, orange, yellow and green refers to 1st, 2nd, 3rd, 4th quartile); gold line and grey shaded area: smoothed line fitted to the data using a logistic regression and its corresponding 95% prediction interval. The error bars represent the 95% CI computed using the Wilson method for the median exposure at each quartile.

Bottom panel (boxplots): Middle line: median. Lower and upper hinges: first and third quartiles (the 25th and 75th percentiles). Upper whisker extends from the hinge to the largest value no further than 1.5 * IQR from the hinge. The lower whisker extends from the hinge to the smallest value at most 1.5 * IQR of the hinge. Symbols: individual data points outside the whiskers.

Source: popPK/E-R Report, Figure 21

Applicant Table 121: Summary Statistics of the Final Multiple Logistic Regression for Proportion of Subjects with (Responders) or without (Non-Responders) $\geq$ 8-Week RBC Transfusion Independence

Term	Estimate	2.5%	97.5%	Standard error	Statistic	p value
(Intercept)	-0.616	-1.05	-0.201	0.215	-2.86	0.00422
*Log ₁₀ of C _{avg}	1.76	0.257	3.39	0.794	2.22	0.0267
IPSSR	0.721	0.0257	1.43	0.356	2.02	0.0431

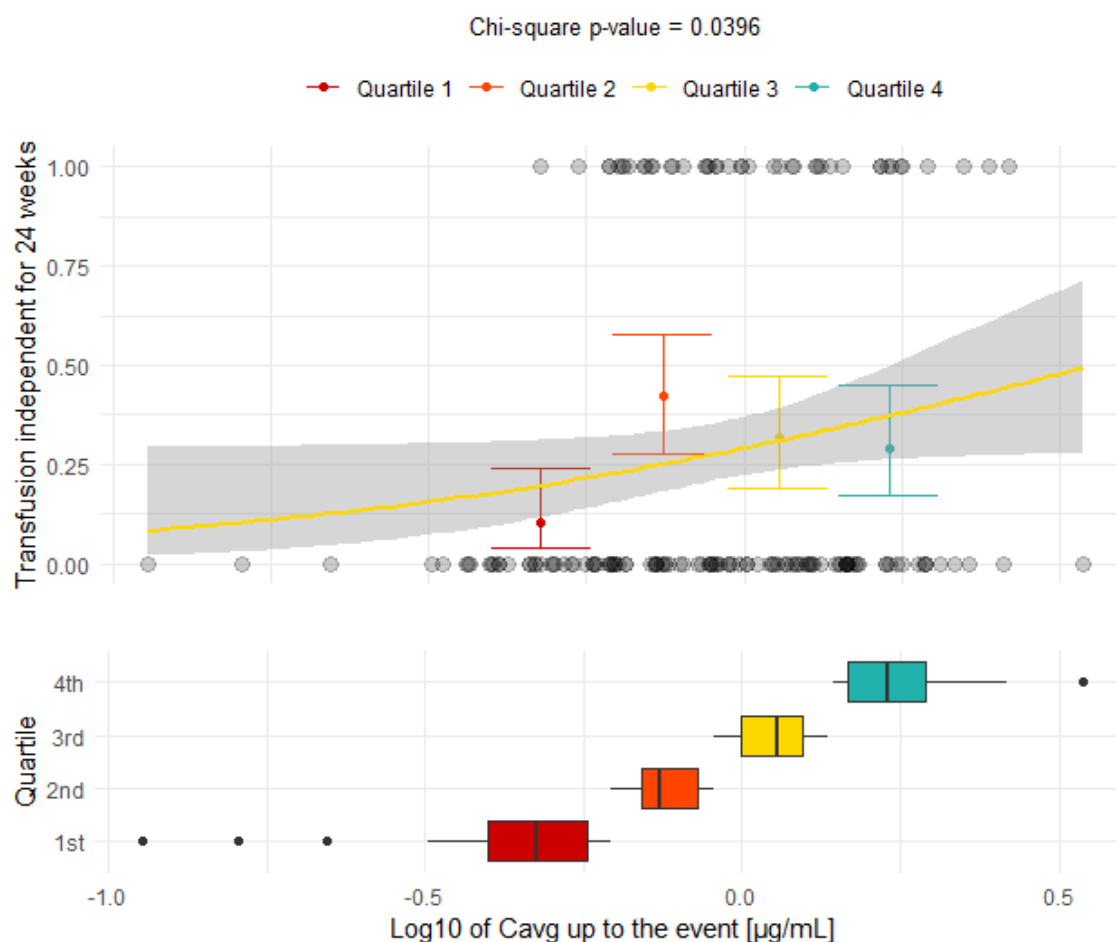
Abbreviations: IPSSR, IPSS risk category at baseline; C_{avg}, average concentration; 2.5%, percentile 2.5th; 97.5%, percentile 97.5th.

P value based on Wald test.

*P value based on LRT test was 0.0211.

Source: popPK/E-R Report, Table 23

Applicant Figure 51: Shape of the Relationship between Log_{10} of C_{avg} and Proportion of Subjects with (Responders) or without (Non-Responders) ≥ 24 -Week RBC Transfusion Independence



NOTE: p value computed with the likelihood ratio test.

Upper panel: Symbols: individual response data; Colored dots and error bars: median and 95% CI of the probability of response in each quartile of exposure of the observed data (red, orange, yellow and green refers to 1st, 2nd, 3rd, 4th quartile); gold line and grey shaded area: smoothed line fitted to the data using a logistic regression and its corresponding 95% prediction interval. The error bars represent the 95% CI computed using the Wilson method for the median exposure at each quartile.

Bottom panel (boxplots): Middle line: median. Lower and upper hinges: first and third quartiles (the 25th and 75th percentiles). Upper whisker extends from the hinge to the largest value no further than 1.5 * IQR from the hinge. The lower whisker extends from the hinge to the smallest value at most 1.5 * IQR of the hinge. Symbols: individual data points outside the whiskers.

Source: popPK/E-R Report Figure 34

Applicant Table 122: Summary Statistics of the Final Multiple Logistic Regression for Proportion of Subjects with (Responders) or without (Non-Responders) $\geq$ 24-Week RBC Transfusion Independence

Term	Estimate	2.5%	97.5%	Standard error	Statistic	p value
(Intercept)	-0.889	-1.26	-0.538	0.183	-4.87	0.00000114
*Log ₁₀ of C _{avg}	1.60	0.0743	3.24	0.804	1.99	0.0463

Abbreviations: C_{avg}, average concentration; 2.5%, percentile 2.5th; 97.5%, percentile 97.5th.

P value based on Wald test.

*P value based on LRT test was 0.0396.

Source: popPK/E-R Report Table 43

The FDA's Assessment:

The Applicant conducted E-R analysis for primary efficacy endpoint proportion of subjects with $\geq$ 8-week RBC TI and key secondary endpoint proportion of subjects with $\geq$ 24-week RBC TI. A total of 152 subjects with MDS were included in the analysis. E-R relationship was characterized using univariate and multivariate logistic regression models. For key primary efficacy endpoint, positive E-R relationship was identified for Log₁₀ of C_{avg} up to the event and proportion of subjects $\geq$ 8-Week RBC TI (Applicant Figure 50, Applicant Table 121). Similar relationship was identified using key secondary endpoint Log₁₀ of C_{avg} up to the event and proportion of subjects $\geq$ 24-Week RBC TI (Applicant Figure 51, Applicant Table 122). No significant E-R relationship was detected using other exposure metrics including C_{max} and AUC on Cycle 1. The reviewer verified that the ER for efficacy analysis is acceptable.

19.4.2.3. ER (safety) Executive Summary

The FDA's Assessment:

The Applicant conducted E-R analysis using the data from pooled dataset from all studies and 156 patients in study MDS3001 for ER safety analysis. The safety endpoints include: 1) Proportion of subjects with Grade 3/4 neutropenia; 2) Proportion of subjects with Grade 3/4 thrombocytopenia; 3) Proportion of subjects with resolution of first grade 3/4 neutropenia in less than 2 weeks and 4 weeks; and 4) Proportion of subjects with resolution of first grade 3/4 thrombocytopenia in less than 2 weeks and 4 weeks.

The Applicant's ER analysis is based on original PopPK model developed based on DV2 and LDV2 calculated using the molecular weight of imetelstat free acid (4610 g/mol). However, per applicant IR response to the information request sent on Apr. 15, 2014², the correct molecular weight should be imetelstat sodium salt (4896 g/mol) given that the PK analyte is imetelstat sodium. The applicant is asked to update the final PopPK model and associated analysis plot using the correct DV2 and LDV2, and repeat ER analysis if significant discordancy was observed between the updated PK exposure predictions and original exposure predictions at the individual level. The applicant submitted the IR response on 4/25/2024. The reviewer has reviewed the updated PopPK model and deemed it acceptable. The updated PopPK estimates are similar to original model. In addition, there is high concordance ($r^2=0.999-1.00$) between exposure metrics for MDS patients derived from original and updated PopPK model. Thus, the incorrect calculation based on wrong molecular weight will not cause significant impact to the ER safety analysis outcome. The applicant did not repeat the ER analysis and the reviewer deems it is acceptable.

Overall, the applicant's E-R analysis is considered acceptable for the purpose of characterizing the E-R relationship of imetelstat and its safety endpoints.

19.4.2.4. ER (safety) Assessment Summary

The Applicant's Position:

General Information	
Goal of ER analysis	To explore the relationship between safety endpoints and imetelstat exposure and to develop an E-R model for: Proportion of subjects with Grade 3/4 neutropenia worsening from baseline (based on lab value)

² DARTS, NDA 217779, 4/18/2024, Clinical Pharmacology/Response to Information Request

Version date: June 2022 (ALL NDA/ BLA reviews)

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

	• Proportion of subjects with Grade 3/4 thrombocytopenia worsening from baseline (based on lab value) • Proportion of subjects with resolution of first Grade 3/4 neutropenia event to Grade ≤ 2 in <2 weeks • Proportion of subjects with resolution of first Grade 3/4 neutropenia event to Grade ≤ 2 in <4 weeks • Proportion of subjects with resolution of first Grade 3/4 thrombocytopenia to Grade ≤ 2 event in <2 weeks • Proportion of subjects with resolution of first Grade 3/4 thrombocytopenia to Grade ≤ 2 event in <4 weeks
Study Included	Safety E-R analyses were conducted for all 7 studies in the popPK analysis and for Study MDS3001 alone. The two approaches enable a comprehensive understanding of imetelstat exposure-safety relationships across the wide investigated dose/exposure range for a full characterization of the E-R relationship as well as a focused analysis of the recommended imetelstat 7.1 mg/kg q4w dosing regimen in the indicated population. Only analyses from MDS3001 alone which investigated the E-R in the indicated population receiving the recommended imetelstat dosing regimen are presented below.
Population Included	For all 7 studies: Patients with myelodysplastic syndromes, chronic lymphoproliferative disease, solid tumors, multiple myeloma, essential thrombocythemia/polycythemia vera, myelofibrosis For MDS3001 alone: patients with MDS
Endpoints	• Proportion of subjects with Grade 3/4 neutropenia worsening from baseline (based on lab value) • Proportion of subjects with Grade 3/4 thrombocytopenia worsening from baseline (based on lab value) • Proportion of subjects with resolution of first Grade 3/4 neutropenia event to Grade ≤ 2 in <2 weeks • Proportion of subjects with resolution of first Grade 3/4 neutropenia event to Grade ≤ 2 in <4 weeks • Proportion of subjects with resolution of first Grade 3/4 thrombocytopenia to Grade ≤ 2 event in <2 weeks • Proportion of subjects with resolution of first Grade 3/4 thrombocytopenia to Grade ≤ 2 event in <4 weeks

No. of Patients (total, and with individual PK)		N = 175 subjects in MDS3001 Phase 2 and Phase 3 N = 170 included in E-R safety analysis Refer to popPK/E-R Report for subject exclusions and rationale.
Population Characteristics (Applicant Table 112)	General	Age: median 71.0 years (range: 44.0-87.0 years) Weight median 74.0 kg (range: 45.0-116 kg) Male: 100/171 (58.5%) Race: White/Caucasian: 137/171 (80.1%) Black/African American: 2/171 (1.7%) Asian: 10/171 (5.9%) Other: 1/171 (0.6%) Unknown: 21/171 (12.3%)
	Organ impairment	Hepatic Impairment (NCI-ODWG based on bilirubin and AST): Normal: 256/424 (60.4%) Mild: 119/424 (28.1%) Moderate: 24/424 (5.7%) Severe: 3/424 (0.9%) Missing: 22/424 (5.2%) Renal Impairment (based on CrCL): Normal: 156/424 (36.8%) Mild: 147/424 (34.7%) Moderate: 115/424 (27.1%) Severe: 6/424 (1.4%)
	Pediatrics (if any)	Not applicable
Dose(s) Included		All subjects received a starting dose of 7.1 mg/kg q4w in Study MDS3001. Subjects may have been dose reduced to 5.6 or 4.4 mg/kg or escalated to 8.9 mg/kg (Phase 2 portion only) in subsequent treatment cycles. Note: dose levels expressed in terms of imetelstat sodium.
Exposure Metrics Explored (range)		• Cycle 1 C_{max} • Cycle 1 AUC_{0-21d} • C_{avg} up to the time of the event (or during the entire treatment period for subjects that did not have the event) Both linear and $\log_{10}$ forms of each exposure metric were evaluated in exploratory E-R analyses.

	Box plots of the distribution of the exposure metrics for E-R safety are provided in Applicant Figure 52 through Applicant Figure 55.	
Covariates Evaluated	bilirubin, AST, ALT, age, body weight, albumin, neutrophil count at baseline, platelet count at baseline, sex, race, and malignancy type	
Final Model Parameters	Summary	Acceptability [FDA's comments]
Model Structure	Univariate and multivariate linear logistic regression analyses were conducted. A summary of the completed E-R safety analyses and p-values for all 3 exposure metrics (C_{max}, AUC, C_{avg}) is provided in Applicant Table 123. Figures and tables are provided below for the relationship between proportion of subjects with Grade 3/4 neutropenia or thrombocytopenia and imetelstat exposure in MDS3001 alone. Additional analyses including, including those for pooled studies, are provided in the popPK/E-R Report.	Acceptable
Visualization of E-R relationships	$\log_{10} C_{max}$ and Grade 3/4 Neutropenia: Applicant Figure 52 $\log_{10}$ AUC and Grade 3/4 Neutropenia: Applicant Figure 53 $\log_{10} C_{max}$ and Grade 3/4 Thrombocytopenia: Applicant Figure 54 $\log_{10}$ AUC and Grade 3/4 Thrombocytopenia: Applicant Figure 55	Acceptable
Model Evaluation	<u>Grade 3/4 Neutropenia:</u> In MDS3001 alone, there were no significant positive E-R relationship between the probability of Grade	Acceptable

	3/4 neutropenia and any exposure metric (Applicant Figure 52, Applicant Figure 53). In addition, no E-R relationship was seen between the probability of resolution of the first Grade 3/4 neutropenia event to Grade ≤ 2 in less than 2 weeks or in less than 4 weeks and imetelstat exposure prior to the event (Cycle 1 C_{max} or AUC) in Study MDS3001 (Applicant Table 123). Grade 3/4 Thrombocytopenia: In MDS3001 alone, there was a significant positive E-R relationship between the probability of Grade 3/4 thrombocytopenia and C_{max} (Applicant Figure 54, Applicant Table 124, $p_{LRT}=0.0192$ in univariate analysis, $p_{LRT}=0.0195$ in multivariate analysis) and a trend for a positive relationship with AUC (Applicant Figure 55, $p_{LRT}=0.0894$ in univariate analysis, $p_{LRT}=0.0594$ in multivariate analysis). In Study MDS3001, no significant E-R relationship was seen between the probability of resolution of the first Grade 3/4 thrombocytopenia event to Grade ≤ 2 in less than 2 weeks or in less than 4 weeks and imetelstat exposure (Cycle 1 C_{max} or AUC) (Applicant Table 123).	
Covariates and Clinical Relevance	Grade 3/4 Neutropenia: C_{max}: albumin, neutrophils at baseline, platelets at baseline Grade 3/4 Thrombocytopenia: C_{max}: platelets at baseline	Acceptable
Simulation for Specific Population	Not applicable.	N/A

Overall Clinical Relevance for ER	Multivariate E-R analyses for safety using laboratory data collected for imetelstat 7.1 mg/kg q4w in MDS3001 Phase 2 and Phase 3 demonstrated no significant E-R relationship for Grade 3/4 neutropenia and a positive E-R relationship for Grade 3/4 thrombocytopenia (statistically significant for C_{max} $p_{LRT}=0.0195$, approaching significance for AUC $p_{LRT}=0.0594$). Investigations of toxicity in identified subpopulations in MDS3001 Phase 2 and Phase 3 with potentially higher imetelstat exposure showed no clear trends between incidence of Grade 3/4 thrombocytopenia and increasing body weight quartiles or between sex. These analyses support that these subpopulations are not expected to be at increased risk of Grade 3/4 thrombocytopenia, and along with low rates of high-grade bleeding events in MDS patients in Study MDS3001, support the limited clinical impact of the characterized exposure-safety relationships. Further, E-R analyses showed no significant E-R relationship between subjects recovering from Grade 3/4 neutropenia or thrombocytopenia and imetelstat exposure in MDS3001 Phase 2 and Phase 3 with more subjects recovering within 4 weeks compared to 2 weeks, supporting the 4-week schedule. Taken together, the results from ER analyses support the favorable	Acceptable

	benefit-risk profile of the recommended dosing regimen of imetelstat 7.1 mg/kg q4w.	
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	Not applicable	N/A

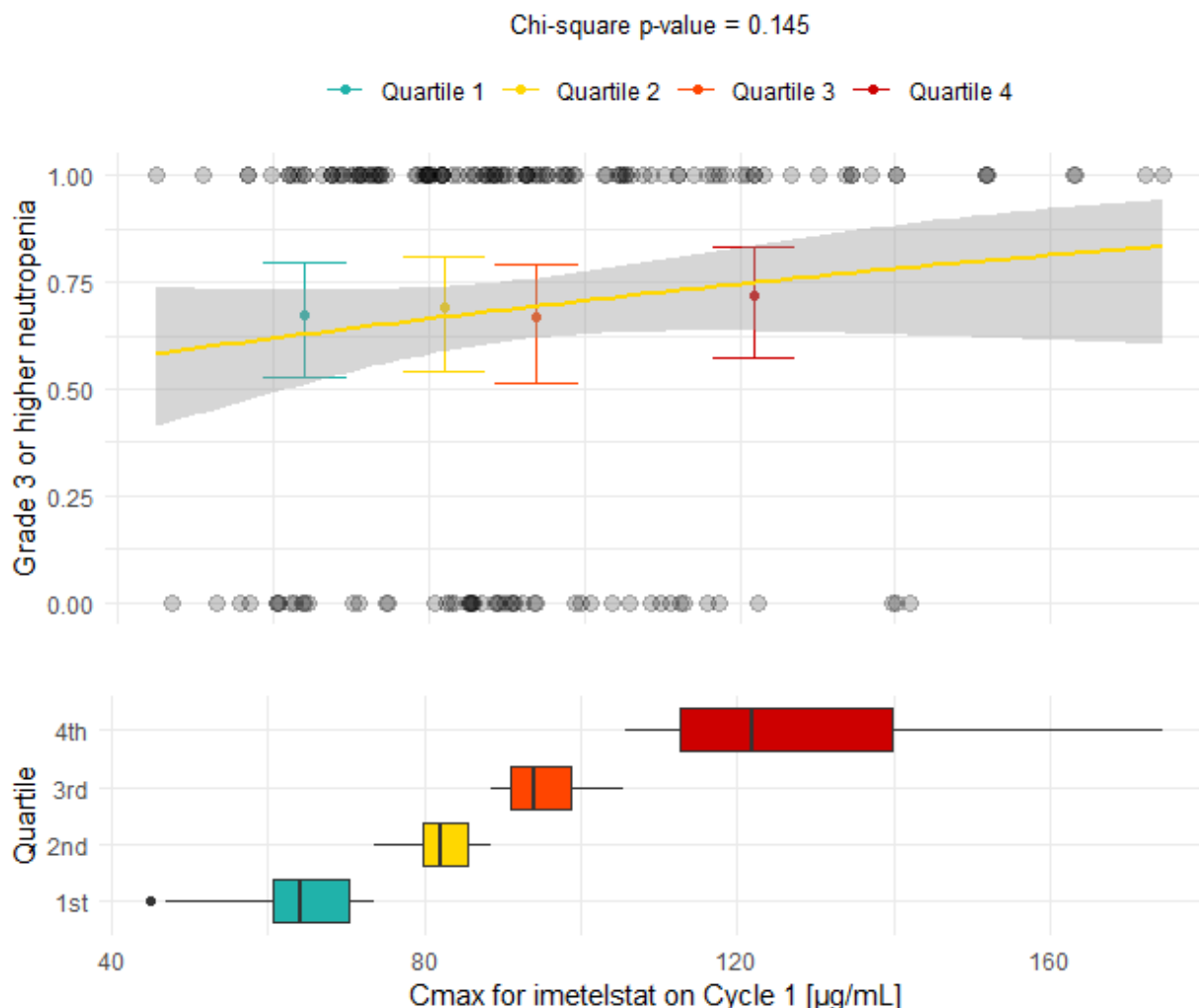
Applicant Table 123: Summary of Completed Exposure-Safety Analyses

Endpoint	Studies	Analysis Type	p-value		
			C _{avg}	C _{max}	AUC
Safety					
Grade 3/4 Neutropenia	MDS3001	Univariate	0.749	0.145	0.827
		Multivariate	-	0.136	0.565
First Grade 3/4 Neutropenia Event Recovery in <2 Weeks	MDS3001	Univariate	-	0.817	0.523
First Grade 3/4 Neutropenia Event Recovery in <4 Weeks	MDS3001	Univariate	-	0.662	0.742
Grade 3/4 Thrombocytopenia	MDS3001	Univariate	0.998	*0.0192	0.0894
		Multivariate	-	*0.0195	0.0594
First Grade 3/4 Thrombocytopenia Event Recovery in <2 Weeks	MDS3001	Univariate	-	0.884	0.554
First Grade 3/4 Thrombocytopenia Event Recovery in <4 Weeks	MDS3001	Univariate	-	0.869	0.730
Grade 3/4 Neutropenia	All	Univariate	0.792 ^l	*<0.0001 ^l	*0.00304 ^l
		Multivariate	-	*0.0437 ^l	*0.0457 ^l
Grade 3/4 Thrombocytopenia	All	Univariate	0.184 ^l	*<0.0001 ^l	0.581 ^l
		Multivariate	-	*<0.0001 ^l	*0.00139 ^l

Analysis Type: univariate or multivariate logistic regression. Endpoints were assessed as probability of subjects meeting specified event. Exposure metrics included C_{max} for Cycle 1, AUC for Cycle 1, and C_{avg} up to time of event for responders and up to end of treatment for non-responders. Log-transformed exposure metrics are indicated with ^l. P values were computed from the likelihood ratio test. *Indicates a significant (p_{LRT} <0.05) and positive E-R relationship (probability of meeting endpoint increases with increasing exposure); - indicates analysis not done.

Source: Module 2.7.2, Table 18 (note: table was adapted for the assessment aid to remove efficacy endpoints)

Applicant Figure 52: Shape of the Relationship between Cycle 1 C_{max} and Proportion of Subjects with Grade 3/4 Neutropenia (Study MDS3001)



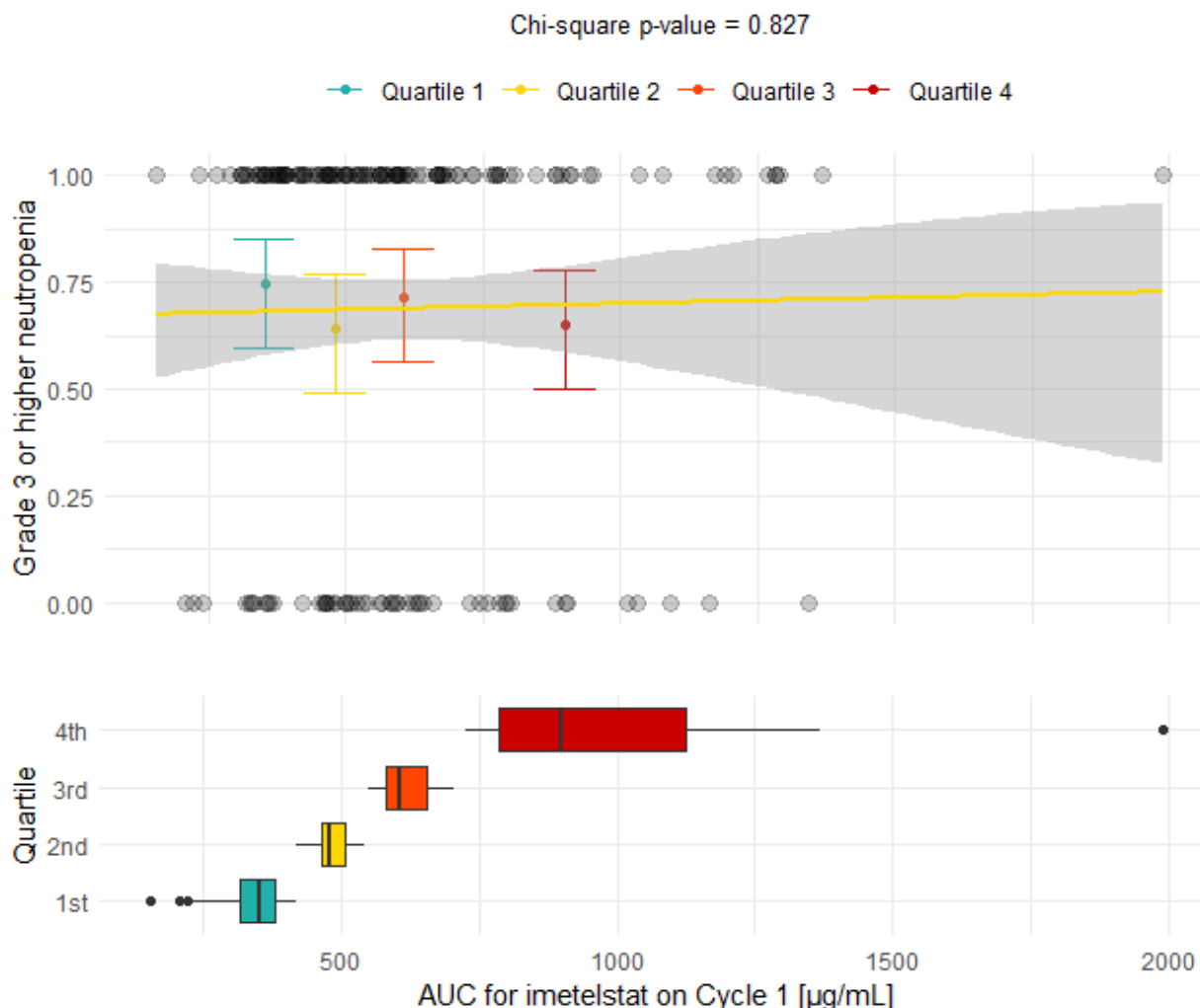
NOTE: p value computed with the likelihood ratio test.

Upper panel: Symbols: individual response data; Colored dots and error bars: median and 95% CI of the probability of response in each quartile of exposure of the observed data (green, yellow, orange and red refers to 1st, 2nd, 3rd, 4th quartile); gold line and grey shaded area: smoothed line fitted to the data using a logistic regression and its corresponding 95% prediction interval. The error bars represent the 95% CI computed using the Wilson method for the median exposure at each quartile.

Bottom panel (boxplots): Middle line: median. Lower and upper hinges: first and third quartiles (the 25th and 75th percentiles). Upper whisker extends from the hinge to the largest value no further than 1.5 * IQR from the hinge. The lower whisker extends from the hinge to the smallest value at most 1.5 * IQR of the hinge. Symbols: individual data points outside the whiskers.

Source: popPK/E-R Report Figure 51

Applicant Figure 53: Shape of the Relationship between Cycle 1 AUC and Proportion of Subjects with Grade 3/4 Neutropenia (Study MDS3001)



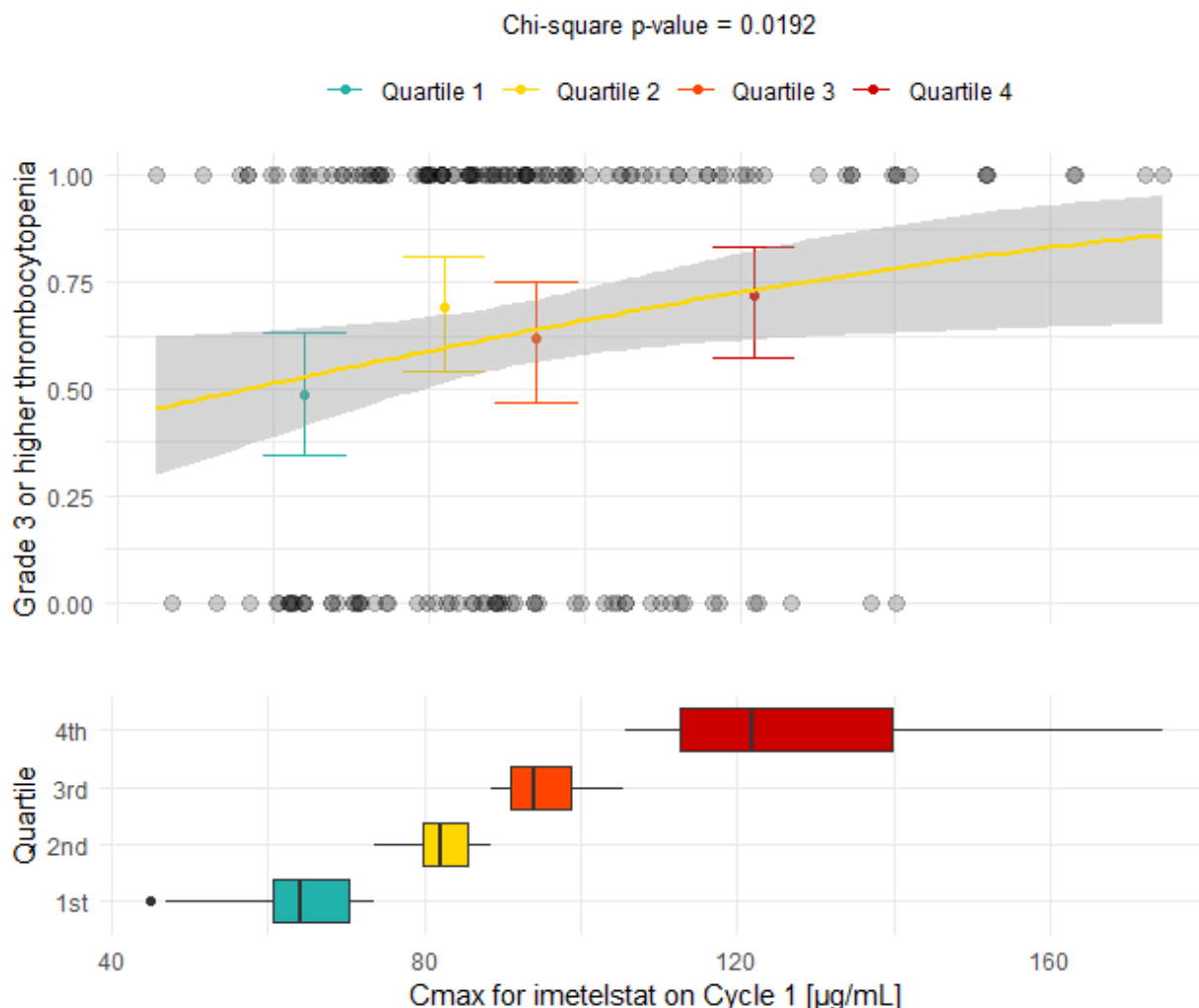
NOTE: p value computed with the likelihood ratio test.

Upper panel: Symbols: individual response data; Colored dots and error bars: median and 95% CI of the probability of response in each quartile of exposure of the observed data (green, yellow, orange and red refers to 1st, 2nd, 3rd, 4th quartile); gold line and grey shaded area: smoothed line fitted to the data using a logistic regression and its corresponding 95% prediction interval. The error bars represent the 95% CI computed using the Wilson method for the median exposure at each quartile.

Bottom panel (boxplots): Middle line: median. Lower and upper hinges: first and third quartiles (the 25th and 75th percentiles). Upper whisker extends from the hinge to the largest value no further than 1.5 * IQR from the hinge. The lower whisker extends from the hinge to the smallest value at most 1.5 * IQR of the hinge. Symbols: individual data points outside the whiskers.

Source: popPK/E-R Report Figure 55

Applicant Figure 54: Shape of the Relationship between Cycle 1 C_{max} and Proportion of Subjects with Grade 3/4 Thrombocytopenia (Study MDS3001)



NOTE: p value computed with the likelihood ratio test.

Upper panel: Symbols: individual response data; Colored dots and error bars: median and 95% CI of the probability of response in each quartile of exposure of the observed data (green, yellow, orange and red refers to 1st, 2nd, 3rd, 4th quartile); gold line and grey shaded area: smoothed line fitted to the data using a logistic regression and its corresponding 95% prediction interval. The error bars represent the 95% CI computed using the Wilson method for the median exposure at each quartile.

Bottom panel (boxplots): Middle line: median. Lower and upper hinges: first and third quartiles (the 25th and 75th percentiles). Upper whisker extends from the hinge to the largest value no further than 1.5 * IQR from the hinge. The lower whisker extends from the hinge to the smallest value at most 1.5 * IQR of the hinge. Symbols: individual data points outside the whiskers.

Source: popPK/E-R Report Figure 78

Applicant Table 124: Summary Statistics of the Final Multiple Logistic Regression for Proportion of Subjects with Grade 3/4 Thrombocytopenia (Study MDS3001)

Term	Estimate	2.5%	97.5%	Standard error	Statistic	p value
(Intercept)	0.717	-0.783	2.23	0.763	0.940	0.347
*C _{max}	0.0166	0.00259	0.0317	0.00740	2.24	0.0252
Platelets at baseline	-0.00632	-0.00952	-0.00353	0.00152	-4.15	0.0000327

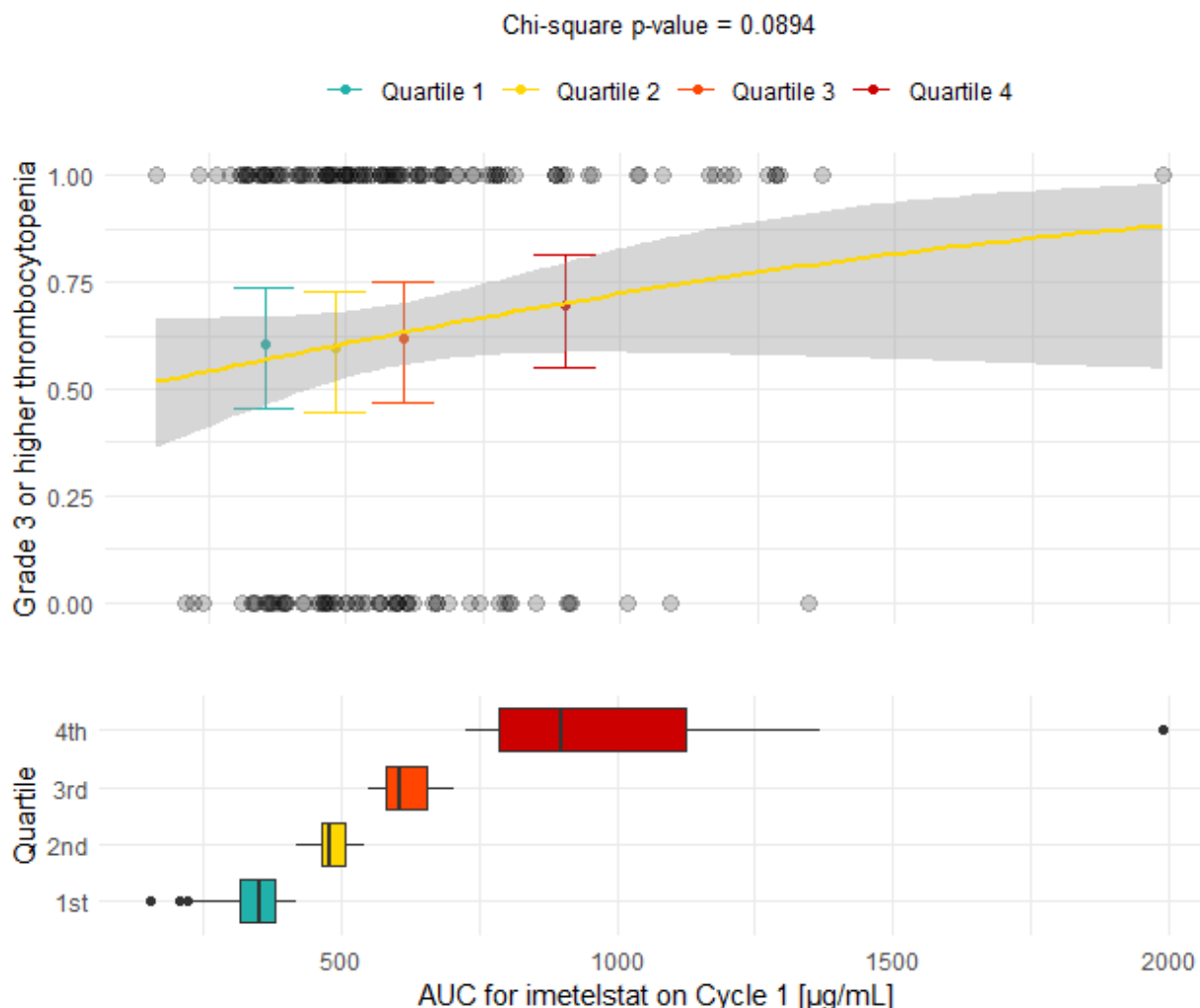
Abbreviations: C_{max}, maximum concentration; 2.5%, percentile 2.5th; 97.5%, percentile 97.5th.

NOTE: p value based on Wald test.

*P value computed with the LRT was 0.0195.

Source: popPK/E-R Report Table 125

Applicant Figure 55: Shape of the Relationship between Cycle 1 AUC and Proportion of Subjects with Grade 3/4 Thrombocytopenia (Study MDS3001)



NOTE: p value computed with the likelihood ratio test.

Upper panel: Symbols: individual response data; Colored dots and error bars: median and 95% CI of the probability of response in each quartile of exposure of the observed data (green, yellow, orange and red refers to 1st, 2nd, 3rd, 4th quartile); gold line and grey shaded area: smoothed line fitted to the data using a logistic regression and its corresponding 95% prediction interval. The error bars represent the 95% CI computed using the Wilson method for the median exposure at each quartile.

Bottom panel (boxplots): Middle line: median. Lower and upper hinges: first and third quartiles (the 25th and 75th percentiles). Upper whisker extends from the hinge to the largest value no further than 1.5 * IQR from the hinge. The lower whisker extends from the hinge to the smallest value at most 1.5 * IQR of the hinge. Symbols: individual data points outside the whiskers.

Source: popPK/E-R Report, Figure 82

The FDA's Assessment:

E-R relationship was characterized using univariate and multivariate logistic regression models for safety endpoints related to Grade 3/4 neutropenia and thrombocytopenia. Among all tested exposure metrics (cycle 1 AUC, cycle 1 C_{max}, C_{avg}), positive E-R relationship was only identified between C_{max} /Log₁₀C_{max} and Grade 3/4 thrombocytopenia in MDS patients (Applicant Figure 54, Applicant Table 124). A positive trend for neutropenia was also observed for cycle 1 C_{max} in pooled safety patient population. The reviewer verified that the ER for safety analysis is acceptable.

19.4.2.5. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

Exposure-Response (E-R) efficacy analyses support the imetelstat 7.1 mg/kg q4w dose and dosing regimen. Results from multivariate E-R efficacy analyses based on MDS3001 Phase 2 and Phase 3 demonstrated a statistically significant positive E-R relationship between imetelstat C_{avg} and the primary efficacy endpoint, 8-week TI rate (p_{LRT}=0.0211), and the key secondary endpoint, 24-week TI rate (p_{LRT}=0.0396). These outcomes support that imetelstat doses (and accordingly C_{avg}) lower than 7.1 mg/kg q4w may result in reduced clinical efficacy. Multivariate E-R analyses for safety using laboratory data collected for imetelstat 7.1 mg/kg q4w in MDS3001 Phase 2 and Phase 3 demonstrated no significant E-R relationship for Grade 3/4 neutropenia and a positive E-R relationship for Grade 3/4 thrombocytopenia (statistically significant for C_{max} p_{LRT}=0.0195, approaching significance for AUC p_{LRT}=0.0594). Investigations of toxicity in identified subpopulations in MDS3001 Phase 2 and Phase 3 with potentially higher imetelstat exposure showed no clear trends between incidence of Grade 3/4 thrombocytopenia and increasing body weight quartiles or between sex. These analyses support that these subpopulations are not expected to be at increased risk of Grade 3/4 thrombocytopenia, and along with low rates of high-grade bleeding events in MDS patients in Study MDS3001, support the limited clinical impact of the characterized exposure-safety relationships. Further, E-R analyses showed no significant E-R relationship between subjects recovering from Grade 3/4 neutropenia or thrombocytopenia and imetelstat exposure in MDS3001 Phase 2 and Phase 3 with more subjects recovering within 4 weeks compared to 2 weeks, supporting the 4-week schedule. Taken together, the results from ER analyses support the favorable benefit-risk profile of the recommended dosing regimen of imetelstat 7.1 mg/kg q4w.

The FDA's Assessment:

Although the Applicant's ER analysis is deemed acceptable, we need to be cautious when use this ER analysis to guide benefit-risk assessment due to the following reasons: 1) only one dose level 7.5 mg/kg is tested in pivotal study in MDS patients thus the studied imetelstat exposure

range is limited; 2) frequent dose modification and subject drop off may confound the ER for efficacy analysis result. Only Cavg but not Cmax and AUC, was found associated with two efficacy endpoints in ER for efficacy analysis. The reviewer deems the ER for safety analysis can still reflect the trend despite in limited drug exposure range that the higher imetelstat Cmax is correlated with higher incidence of Grade 3/4 Thrombocytopenia.

19.4.3. Mutational analyses in Study MDS3001

The FDA's Assessment

Baseline mutation status and treatment response: The Applicant conducted exploratory studies to investigate associations between mutational status in MDS-related genes at baseline and clinical response. Mutational status was examined in DNA from peripheral blood leukocytes with the LeukoVantage® MDS gene panel, which detects mutations by targeted sequencing in 36 genes that are frequently mutated in MDS. Overall, 98% of patients in the study had at least one somatic mutation at baseline, and mutation frequencies were similar in the imetelstat and placebo groups (Table 125). The observed mutation frequencies at baseline are in agreement with estimates from the literature (Ogawa 2019, Bersanelli 2021). The Applicant's exploratory analysis focused on six genes that are frequently mutated in low-risk MDS. Analysis by individual gene showed that in imetelstat-treated patients, the average 8-week RBC TI rate was 36.8% higher in patients with *SF3B1* mutations in comparison to patients without *SF3B1* mutations ($p = 0.001$). In patients who received placebo, the average 8-week RBC TI rate in patients with and without *SF3B1* mutations were similar. The presence of a mutation in *SF3B1* was associated with a 32.5% increase in 8-week RBC TI in comparison to the corresponding patients who received placebo. The patterns of *SF3B1* mutations in imetelstat-treated and placebo groups were similar and consistent with reports from the literature (PMID: 37007111), with the most common mutations in *SF3B1* being K700E (46%) followed by "hotspot" mutations H662 (13%), R625 (10%), and K666 (9%). *SF3B1* mutations lead to RNA splicing alterations, and there is no clear mechanistic relationship between mutant *SF3B1* and the target of imetelstat hTERT that would account for the observed difference in response rates. In both imetelstat-treated patients and placebo-treated patients, 8-week RBC TI rates were similar between patients with or without mutations in *TET2*, *ASXL1*, *DNMT3A*, *CUX1*, and *SRSF2*. In the subgroups of patients without baseline mutations in *TET2*, *ASXL1*, *DNMT3A*, *CUX1*, or *SRSF2*, 8-week RBC TI rates were higher in imetelstat-treated patients in comparison to placebo-treated patients ($p < 0.05$ for all comparisons); results were similar in the mutation positive subgroups but these comparisons were limited by the small number of patients in each of the mutation positive subgroups (Table 125). Together, this exploratory analysis suggests that baseline mutations in *SF3B1* are associated with increases in 8-week RBC TI rate in patients treated with imetelstat. However, given the exploratory nature of this analysis that included multiple

comparisons, the lack of a mechanistic rationale, and the fact that patients without *SF3B1* mutations did respond, no clinical action is recommended based on this finding.

Table 125: 8-week RBC TI rate vs baseline mutation status in Study MDS3001.

Gene	Mutation Status	8-week RBC TI							
		Imetelstat (N=110)			Placebo (N=55)			% Difference Between Treatment Arms (95% CI) ^{b,e}	P Value Between Treatment Arms ^{b,d}
		Event/Total (%)	% Difference Within Treatment Arm (95% CI) ^{a,e}	P Value Within Treatment Arm ^{a,c}	Event/Total (%)	% Difference Within Treatment Arm (95% CI) ^{a,e}	P Value Within Treatment Arm ^{a,c}		
Overall		43/110 (39.1%)			8/55 (14.5%)			24.5% (8.99%, 36.96%)	0.002
Mutation Status	Yes	43/107 (40.2%)	40.2% (-29.43%, 50.13%)	0.279	8/54 (14.8%)	14.8% (-80.04%, 27.67%)	>0.999	25.4% (9.55%, 37.98%)	0.002
	No	0/3			0/1			NE (NE,NE)	NE
SF3B1 mutation	Yes	40/82 (48.8%)	36.8% (13.61%, 51.06%)	0.001	7/43 (16.3%)	7.2% (-27.77%, 24.51%)	>0.999	32.5% (13.82%, 46.85%)	0.001
	No	3/25 (12.0%)			1/11 (9.1%)			2.9% (-32.02%, 24.99%)	0.687
TET2 mutation	Yes	20/40 (50.0%)	15.7% (-4.70%, 34.97%)	0.153	3/14 (21.4%)	8.9% (-12.87%, 39.69%)	0.413	28.6% (-5.18%, 50.96%)	0.138
	No	23/67 (34.3%)			5/40 (12.5%)			21.8% (3.21%, 36.73%)	0.018
ASXL1 mutation	Yes	5/18 (27.8%)	-14.9% (-35.18%, 12.87%)	0.298	0/6	-16.7% (-30.76%, 32.43%)	0.575	27.8% (-23.47%, 53.59%)	0.174
	No	38/89 (42.7%)			8/48 (16.7%)			26.0% (8.58%, 39.99%)	0.003
DNMT3A mutation	Yes	6/19 (31.6%)	-10.5% (-31.58%, 16.50%)	0.450	2/9 (22.2%)	8.9% (-14.23%, 47.28%)	0.607	9.4% (-32.33%, 40.26%)	0.754
	No	37/88 (42.0%)			6/45 (13.3%)			28.7% (11.21%, 42.19%)	0.001
CUX1 mutation	Yes	5/14 (35.7%)	-5.1% (-29.37%, 25.18%)	0.778	1/7 (14.3%)	-0.6% (-20.10%, 43.86%)	>0.999	21.4% (-27.38%, 53.12%)	0.860
	No	38/93 (40.9%)			7/47 (14.9%)			26.0% (8.78%, 39.45%)	0.004
SRSF2 mutation	Yes	2/11 (18.2%)	-24.5% (-42.81%, 10.95%)	0.193	0/4	-16.0% (-29.66%, 45.00%)	>0.999	18.2% (-44.07%, 52.25%)	0.083
	No	41/96 (42.7%)			8/50 (16.0%)			26.7% (9.83%, 40.13%)	0.002

^a Comparison between mutation status groups within each treatment arm.

^b Comparison between treatment arms within each mutation status group.

^c P value is from Fisher exact test.

^d P value is from Cochran-Mantel-Haenszel (CMH) controlling for prior RBC transfusion burden (<=6 vs. >6 units RBC) and IPSS risk group (low vs. intermediate-1) applied to randomization.

^e The 95% CI is based on Wilson Score method with continuity correction. TI: transfusion independence. CI: confidence interval.

Source: Study 63935937MDS3001 CSR, Table TEFMSTI01_P2 (note: table was adapted for the assessment aid to show the analysis of six genes).

19.4.4. Bioanalytical Methods

The FDA's Assessment

Imetelstat plasma concentrations were quantified using a hybridization enzyme-linked immunosorbent assay (ELISA). The method involved competition of imetelstat and a 3'-labelled digoxigenin analogue for a complementary oligonucleotide sequence containing biotin at the 3' end, with an ELISA used for detection. The resulting complex was captured onto the surface of a neutravidin-coated microtiter plate. The measurement of the digoxigenin-labelled probe was performed after reaction with anti-digoxigenin antibody conjugated to alkaline phosphatase, which catalyzed the fluorescent AttoPhos® substrate. Fluorescence intensity was measured using a Spectramax Gemini fluorescence plate reader.

The method was initially validated for the detection of imetelstat in human K3EDTA plasma (report #320026), then re-validated for the detection of imetelstat in human K2EDTA plasma (report #340713) with respect to specificity (interference check/selectivity), dilution linearity (including prozone assessment), working calibration range, lower and upper limit of quantitation (LLOQ and ULOQ), intra- and inter-assay precision and accuracy, and stability. Re-validations were performed for this method to assess long-term stability (report #345814 and #3450124), selectivity in hemolyzed human plasma (report #345814), antibody interference (report #3450124), selectivity in healthy, lipemic, and disease state plasma, intra- and inter-assay precision and accuracy using a compressed curve range of 100 to 400 nM imetelstat in neat plasma, stock solution stability in buffer, and imetelstat stability in human whole blood (report #3450278). The method was re-validated in 2022 (Validation report #3451131) in compliance with the 2018 FDA Guidance on Bioanalytical Method Validation. The validated parameters included selectivity at the LLOQ concentration, linearity assessments, extended long-term stability and specificity and stability in the presence of ruxolitinib. All clinical studies involved the measurement of imetelstat concentrations in human (K2EDTA) plasma.

The method validation summaries and the bioanalytical report for the pivotal study MDS3001 are provided in Table 126 and Table 127 below.

Table 126: Bioanalytical Method Validation Summary for Imetelstat Quantification

Bioanalytical validation report	To support analysis of samples from CP04-151, CP05-101, CP05-101, CP14A004, CP14A011, CP14B012, CP14B013, CP14B015	
Materials used for calibration curve	Imetelstat sodium: Geron Corporation, Batch MM040713	
Validated assay range	75.0 to 500 nM (0.75 to 5.00 nM after 100-fold dilution)	
Minimum required dilutions	100-fold dilution applied prior to analysis	
Regression model & weighting	4-Parameter Logistics Fit (4-PL) no weighting regression	
Validation parameters	Method validation summary	
Calibration curve performance during accuracy & precision	Number of standard calibrators	8
	Cumulative accuracy (%bias)	-5.5 to 7.1

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	Cumulative precision (%CV)	0.540 to 7.150
QCs performance during accuracy & precision	Intra-assay accuracy (%bias)	-6.4 to 17
	Intra-assay precision (%CV)	0.9 to 11.3
	Percent total error (TE)	≤ 40% at LLOQ and ≤ 30% at the other levels
Selectivity & matrix effect	<u>Acceptance Criteria:</u> Results were considered acceptable if 5 out of 6 unspiked plasma lots were below the LLOQ and if imetelstat-spiked plasma samples had a mean recovery within 75 to 125% of the theoretical concentration. <u>Normal Human Plasma Results:</u> Six lots of blank normal human plasma were assayed unspiked and spiked with imetelstat to a final concentration of 120 nM. The mean recovery of the 6 plasma lots was 99.8%. <u>CLL Patient Plasma Results:</u> Six lots of blank human plasma from CLL patients were assayed unspiked and spiked with imetelstat to a final concentration of 120 nM. The mean recovery of the 6 plasma lots was 106.3%.	
Hemolysis effect	<u>Acceptance Criteria:</u> Selectivity in 5% (v/v) hemolyzed human plasma (K₂EDTA) was considered acceptable if the unspiked 5% (v/v) hemolyzed plasma lot tested was below the LLOQ and if the mean concentration had recoveries within 80 to 120% of their theoretical concentration at each concentration. <u>Results:</u> The tested blank sample gave a mean concentration below the LLOQ (0.75 nM) and the imetelstat spiked samples gave mean concentrations within 80 to 120% of theoretical. Mean recovery at 1.20 nM and 2.50 nM were 103.0% and 87.1%, respectively.	
Interference & specificity	<u>Interference:</u> Based on results obtained from the dilution linearity assessments, no interference from the matrix was evident. No observed interference with PANK-1 antibody up to the maximum tested concentration of 1.000 µg/mL PANK-1 sample. <u>Observed %bias:</u> -24.2 to 2.7% (excluding 2.500 nM imetelstat /1.000 µg/mL PANK-1 sample that had a %bias of -28.4%*) <i>* reviewer's comment: acceptable after evaluation on the impact of deviation</i>	
Dilution linearity & hook effect	Up to 131-fold with blank human plasma (K ₂ EDTA)	
Bench-top/process stability	24 hours in human plasma (K ₃ EDTA) at room temperature and at 4°C	
Freeze-Thaw stability	24 hours in human plasma (K ₃ EDTA) after 4 freeze-thaw cycles at approximately -80°C	
Long-term storage	998 days in human plasma (K ₂ EDTA) in a freezer set to maintain -80°C 113 days in human plasma (K ₂ EDTA) in a freezer set to maintain -20°C 358 days in dilution buffer 649 days in 1x PBS buffer	

Table 127: Bioanalytical Method Modifications and Cross Validation Summary for Imetelstat Quantification – Reduced Range Partial Validation

Bioanalytical method review summary	To support analysis of samples from 63935937-MYF2001 and 63935937MDS3001
Method description	The method described in Table X was re-validated with respect to additional parameters including selectivity in lipemic plasma or selectivity in disease state

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	plasma, intra- and inter-assay precision and accuracy using a compressed curve range (100 nM to 400 nM), dilution linearity assessments, extended long-term stability and specificity and stability in the presence of ruxolitinib, etc..	
Materials used for calibration curve	Imetelstat sodium: Geron Corporation, multiple batches Ruxolitinib: Geron Corporation, 0568069; 30-Nov-2023 (3451131)	
Validated assay range	100 to 400 nM (1-4 uM after 100-fold dilution)	
Minimum required dilutions (MRDs)	100-fold dilution applied prior to analysis	
Regression model & weighting	4-Parameter Logistics Fit (4-PL) no weighting regression	
Validation parameters	Method validation summary	
Calibration curve performance during accuracy & precision	Number of standard calibrators	7 to 8
	Cumulative accuracy (%bias)	-3.4 to 7.9%
	Cumulative precision (%CV)	0.63 to 7.1
QCs performance during accuracy & precision	Intra-assay accuracy (%RE)	-1.7 to 28.2* (*Reviewer's comment: considered acceptable after evaluation on the impact of deviation)
	Intra-assay precision (%CV)	0.2 to 19.2
	Inter-assay accuracy (%bias)	1.8 to 14.3
	Inter-assay precision (%CV)	3.6 to 14.8
	Percent total error (TE)	5.7 to 29.1
Selectivity & matrix effect	<u>Acceptance Criteria:</u> At least 80% of blank lots < LLOQ and at least 80% of spiked samples within 80 to 120% of their theoretical concentration. <u>Normal Human Plasma Results:</u> All blank samples (10 of 10 lots) gave concentration results below the LLOQ, and 100% of spiked lots (10 of 10 lots) gave recoveries within 80 to 120% of the theoretical concentration with CV(%) ≤20% for each replicate. <u>Myelofibrosis Patient Plasma Results:</u> All blank samples (10 out of 10 lots) gave concentration results below the LLOQ; 10 out of 10 lots spiked at 150 nM and 8 out of 10 lots spiked at 300 nM were within ±20% of the theoretical concentration. <u>Normal Human Plasma Results:</u> All tested blank samples gave concentration results below the LLOQ and 100% of the human plasma (K₂EDTA) spiked lots tested gave recoveries within ± 25% relative error with CV (%) ≤20% for each replicate at the LLOQ level and 100% of the spiked lots tested gave recoveries within ± 20% relative error with CV (%) ≤ 20% for each replicate at the high QC level.	
Hemolysis effect	In 5% (v/v) hemolyzed human plasma, the tested blank sample gave a concentration result below the LLOQ of the method and the Imetelstat spiked lot gave recoveries within ±25% relative error and CV(%) between replicates ≤20% when tested at 100 nM (LLOQ) and within ±20% relative error and CV(%) between replicates ≤20% when tested at 300 nM (HQC).	
Lipemic effect	All blank samples (10 out of 10 lots) gave concentration results below the LLOQ; 10 out of 10 lots spiked at 150 nM and 8 of 10 lots spiked at 300 nM were within ±20% of the theoretical concentration. Observed theoretical (spiked lots): 102.7 to 118.8. However, additional assessment in Report 3451131 (3 replicates at 100 nM or 300	

Version date: June 2022 (ALL NDA/ BLA reviews)

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

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 TRADENAME, imetelstat

	nM) suggested that the method is likely not selective for Imetelstat in the presence of lipemic matrix and all future samples identified for lipemia will be flagged and results be reported “for information purposes only”
Interference & specificity	<u>Specificity in the Presence of Ruxolitinib</u> : The %RE was within $\pm 25\%$ and precision was $\leq 20\%$ for imetelstat at both the LLOQ and the ULOQ in matrix in the presence of 2002 nM of non-specific compound ruxolitinib.
Dilution linearity & hook effect	Up to 500-fold with blank human plasma (K ₂ EDTA)
Bench-top/process stability	Imetelstat is stable in the presence of ruxolitinib in human plasma (K ₂ EDTA) for 20 hours and 32 minutes at ambient room temperature.
Freeze-Thaw stability	Imetelstat is stable in the presence of ruxolitinib in human plasma (K ₂ EDTA) after 5 freeze-thaw cycles in a freezer set to maintain -80°C.
Long-term storage	Imetelstat is stable in the presence of ruxolitinib in human plasma (K ₂ EDTA) for 56 days in a freezer set to maintain -80°C. Imetelstat is stable in human plasma (K ₂ EDTA) for 1542 days (for 0.734 µg/mL) to 1549 days (for 1.47 µg/mL) in a freezer set to maintain -80°C.
Method performance in clinical study# 63935937MDS3001 Part 1	
Assay passing rate	100% (36 of 36 batches)
Standard curve performance	Cumulative bias range (%bias): -4.7 to 9.5 Cumulative precision (%CV): 1.3 to 10.0
QC performance	Cumulative bias range (%bias): -6.7 to 4.0 Cumulative precision (%CV): 3.5 to 14.0
Method reproducibility	63 study samples were selected for incurred sample reanalysis (ISR). ISR was successfully conducted with a pass rate of 93.7% (59/63 samples assessed meeting ISR acceptance). ISR was deemed acceptable if 67% of the reanalyzed samples had results within 30% of the original result.
Study sample analysis/ stability	A total of 714 human plasma (K ₂ EDTA) samples were received and stored in a freezer set to maintain -80°C until analysis. Of these 714 plasma samples, 570 were analyzed. All study samples were analyzed within the proven stability period. Calibration standards and QC samples were sub-sampled and stored in a freezer set to maintain -80°C
Method performance in clinical study# 63935937MDS3001 Part 1 and Part 2	
Assay passing rate	84.4% (103 of 122 batches)
Standard curve performance	Cumulative bias range (%bias): -18.7 to 5 Cumulative precision (%CV): 3.1 to 19.0
QC performance	Cumulative bias range (%bias): -1.4 to 4.3 Cumulative precision (%CV): 5.9 to 10.5
Method reproducibility	140 study samples were selected for incurred sample reanalysis (ISR). ISR was successfully conducted with a pass rate of 82.0% (115/140 samples assessed meeting ISR acceptance). ISR was deemed acceptable if 67% of the reanalyzed samples had results within 30% of the original result.
Study sample analysis/stability	A total of 2982 human plasma (K ₂ EDTA) samples were received and stored in a freezer set to maintain -80°C until analysis. Of these 2982 plasma samples, 651 placebo samples were not analyzed. All study samples were analyzed within the proven

Version date: June 2022 (ALL NDA/ BLA reviews)

Disclaimer: In this document, the sections labeled as “Data” and “The Applicant’s Position” are completed by the Applicant and do not necessarily reflect the positions of the FDA.

	stability period. Calibration standards and QC samples were sub-sampled and stored in a freezer set to maintain -80°C

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:

Custom grouped terms used in the review and preferred terms included in the grouped terms are described in Table 128. Note that only preferred terms for which were reported for at least one patient in any dataset (initial dataset for MDS3001, 120-day update, ISS) are included.

Table 128: Custom grouped terms

Grouped term	Preferred terms
Abdominal pain	Abdominal discomfort, abdominal distension, abdominal pain, abdominal pain lower, abdominal pain upper, gastritis, gastroenteritis, gastritis, gastroenteritis, gastrointestinal pain
Aortic occlusive events	Angina pectoris, aortic arteriosclerosis, aortic stenosis, arteriosclerosis coronary artery, extremity necrosis, intermittent claudication, myocardial infarction, peripheral ischaemia, renal artery stenosis, subclavian artery stenosis
Arthralgia/myalgia	Arthralgia, back pain, bone pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain, pain in extremity, pain in jaw, pelvic pain, sacral pain
Atrial arrhythmias	Atrial fibrillation, atrial flutter
Cardiac failure	Cardiac failure, cardiac failure congestive
COVID-19	Asymptomatic COVID-19, COVID-19, COVID-19 pneumonia, SARS-CoV-2 antibody test positive
Dizziness	Dizziness, dizziness postural, nystagmus, vertigo, vertigo postural
Fatigue	Asthenia, fatigue, malaise
Fractures	Femur fracture, hand fracture, hip fracture, humerus fracture, lumbar vertebral fracture, radius fracture, rib fracture, skull fracture, spinal compression fracture, thoracic vertebral fracture, wrist fracture
Hepatic disorders	Alanine aminotransferase increased, aspartate aminotransferase increased, bilirubin conjugated increased, blood bilirubin increased, chronic hepatitis, gamma-glutamyltransferase increased, hepatic cirrhosis, hepatic steatosis, hepatitis, hepatomegaly, hepatotoxicity, hyperbilirubinaemia, jaundice hepatocellular, portal hypertension, varices oesophagus
Hypertension	Hypertension, hypertensive crisis, hypertensive emergency
Infusion related reaction	Abdominal pain, arthralgia, back pain, bone pain, diarrhea, erythema, headache, hypertensive crisis, malaise, non-cardiac chest pain, pruritus, urticaria*

Iron overload	Blood iron increased, haemochromatosis, haemosiderosis, hyperferritinaemia, iron overload, serum ferritin increased
Neutropenia	Neutropenia, febrile neutropenia, neutrophil count decreased
Pneumonia	Atypical pneumonia, pneumonia, pneumonia bacterial, respiratory tract infection bacterial, respiratory tract infection viral
Pruritus	Eye pruritus, injection site pruritus, pruritus, pruritus allergic
Renal dysfunction	Acute kidney injury, chronic kidney injury, creatinine renal clearance decreased, renal failure, renal impairment
Sepsis	Bacterial sepsis, Enterococcal sepsis, Escherichia bacteraemia, Escherichia sepsis, neutropenic sepsis, sepsis, urosepsis
Syncope	Fall, loss of consciousness, orthostatic hypotension, presyncope, syncope
Thrombocytopenia	Thrombocytopenia, platelet count decreased
Upper respiratory tract infection	Influenza, nasopharyngitis, pharyngitis, sinusitis, upper respiratory tract infection
Urinary tract infections	Cystitis, Escherichia urinary tract infection, renal abscess, urinary tract infection
Venous thromboembolism	Deep vein thrombosis, phlebitis, phlebitis superficial

*Only events considered related to infusion related reactions were included in this category

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Signatures

DISCIPLINE	REVIEWER	OFFICE/ DIVISION	SECTIONS	AUTHORED/ APPROVED
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DBIX: Division of Biometrics IX; DCPI: Division of Cancer Pharmacology I; DHMI: Division of Hematologic Malignancies I; DPM: Division of Pharmacometrics; DTPM: Division of Translational and Precision Medicine; OB: Office of Biostatistics; OCP: Office of Clinical Pharmacology; OOD: Office of Oncologic Diseases				

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