FDA Briefing Document

NDA # 217779

Drug name: Imetelstat

Applicant: Geron Corporation

Oncology Drugs Advisory Committee Meeting

March 14, 2024

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the imetelstat new drug application (NDA) 217779 to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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Glossary

AC	Advisory Committee
AML	acute myeloid leukemia
ANC	absolute neutrophil count
BD	Briefing Document
BRF	Benefit-Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
ESA	erythropoiesis stimulating agents
FDA	Food and Drug Administration
Hgb	hemoglobin
IA	integrated assessment
IPSS	International Prognosis Scoring System
IRC	independent review committee
MDS	myelodysplastic syndromes
RBC	red blood cell
RBC-TI	red blood cell – transfusion independence
REMS	risk evaluation and mitigation strategy
RPM	Regulatory Project Manager
SAP	Statistical Analysis Plan
SD	standard deviation
RBC	red blood cell
TD	transfusion dependence
TI	transfusion independence

1 Executive Summary

1.1 Purpose/Objective of the AC Meeting

The Applicant is seeking approval of imetelstat (proposed trade name RYTELO) 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).

The Food and Drug Administration (FDA) is convening this Advisory Committee (AC) meeting to discuss whether the efficacy of imetelstat demonstrated on Study 63935937MDS3001 (Study MDS3001) in adult patients with lower-risk MDS outweigh the risks of treatment.

1.2 Context for Issues to be Discussed at the AC

Myelodysplastic syndromes (MDS) are a heterogeneous group of disorders resulting from the clonal expansion of a hematopoietic progenitor, causing bone marrow dysplasia, ineffective hematopoiesis, and risk of transformation to acute myeloid leukemia (AML). For lower-risk MDS, median survival has been reported to range from 2 to >10 years, depending on a number of clinical factors such as age.[1,2] Most patients with lower-risk MDS are affected by anemia and anemia-related symptoms, which may negatively impact health-related quality of life.[3] Anemia and transfusion dependence have also been reported to correlate with shorter survival in patients with MDS.[4]

Typical frontline therapy for transfusion-dependent anemia due to lower-risk 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). Additionally, lenalidomide is approved for the treatment of transfusion-dependent anemia in the subset of patients with lower-risk 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.[5]

1.3 Brief Description of Issues for Discussion at the AC

FDA approval requires that a drug is safe and effective for use under the conditions prescribed, recommended, or suggested in the product's labeling (FD&C Act section 505(d) [21 U.S.C. § 355(d)]); such evidence must be generated by one or more adequate and well-controlled investigations and results must be sufficiently robust and compelling. Because all drugs have adverse effects, the demonstration of safety requires showing that the benefits of the drug outweigh its risks in the intended population.

The Division of Hematologic Malignancies I is seeking an ODAC meeting to facilitate discussion regarding the NDA for imetelstat, which was submitted based on results of a single randomized, Phase 3 trial in patients with lower-risk MDS who have not responded to or have lost response to or are ineligible for ESAs with a primary endpoint of 8-week RBC transfusion independence, with supportive results from a single-arm Phase 2 trial. Specifically, FDA requests discussion on whether the magnitude and durability of benefit are sufficient to outweigh the potential risks of imetelstat considering the safety profile.

1.4 Draft Points for Consideration

- Discuss the efficacy of imetelstat for the proposed patient population based on the results of the MDS3001 trial considering the safety profile.
- Do the benefits of imetelstat outweigh its risks for the treatment of transfusion-dependent anemia in adult patients with IPSS low- to intermediate-1 risk MDS who have not responded to or have lost response to or are ineligible for erythropoiesis-stimulating agents (ESA)?

2 Introduction and Background

2.1 Background of the Condition

Myelodysplastic syndromes (MDS) are a heterogeneous group of disorders resulting from the clonal expansion of a hematopoietic progenitor, causing bone marrow dysplasia, ineffective hematopoiesis, and risk of transformation to acute myeloid leukemia (AML). The most commonly utilized tools for prognostication in MDS are the International Prognosis Scoring System (IPSS) or revised version (IPSS-R), although a newer version incorporating molecular features (IPSS-M) was recently proposed.[1,2,6] Both the IPSS and IPSS-R risk stratify patients with newly diagnosed MDS into risk categories based on blast percentage, number of cytopenias, and cytogenetic profile. For lower-risk MDS (conventionally defined as MDS with a risk score in the low or intermediate-1 range for IPSS, or in the very low, low, or intermediate range for IPSS-R), median survival has been reported to range from 2 to >10 years, depending on a number of clinical factors such as age.[1,2] Most patients with lower-risk MDS are affected by anemia and anemia-related symptoms, which may negatively impact health-related quality of life.[3] Anemia and transfusion dependence have also been reported to correlate with shorter survival in patients with MDS.[4]

2.2 Standard of Clinical Care

Historically, erythropoiesis stimulating agents (ESA) have been considered first-line therapy for transfusion-dependent anemia in lower-risk MDS, though none are FDA approved for this indication and therefore their use in this setting is considered off-label. However, in August 2023, luspatercept was approved for treatment of anemia in ESA-naïve patients with IPSS-R very low- to intermediate-risk MDS who may require regular RBC transfusions. In the pivotal COMMANDS trial which led to the approval of luspatercept for this indication, the primary endpoint was red blood cell transfusion independence (RBC-TI) for at least 12 weeks with a concurrent mean hemoglobin increase of at least 1.5 g/dL (weeks 1-24). The response rate based on this composite endpoint was 67% in the luspatercept group versus 46% in the epoetin alfa group, though the difference in response rate was primarily driven by the ringed sideroblast-positive subgroup.[7,8] Therefore, both ESA and luspatercept are now considered frontline options.

Luspatercept was also previously approved for the treatment of anemia failing an ESA and requiring 2+ RBC units/8 weeks in patients with IPSS-R very low- to intermediate-risk MDS with ringed sideroblasts (MDS-RS) or myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T), based on an 8-week RBC-TI rate of 38% in the pivotal MEDALIST trial.[9] Currently, it remains an option in the second line or later setting after ESA failure.

Other therapeutic options include lenalidomide and hypomethylating agents. Lenalidomide is approved for the treatment of transfusion-dependent anemia in IPSS low- or intermediate-1 risk MDS with

deletion 5q (del5q), and was associated with an 8-week RBC-TI rate of 67% in the pivotal study.[10] Lenalidomide is sometimes used off-label in patients without del5q who are ineligible for or refractory to ESA as well, though the reported 8-week RBC-TI rate for these patients is lower, around 27%.[11]

Hypomethylating agents (azacitidine, decitabine, and decitabine-cedazuridine) are also options, though often reserved for higher-risk MDS or refractory LR-MDS in clinical practice. Azacitidine is broadly approved for MDS including CMML and was associated with an 8-week RBC-TI rate of 45% in the pivotal AZA-001 study.[12] Decitabine and decitabine-cedazuridine are also broadly approved for MDS including CMML; the latter was associated with a 49% RBC and platelet transfusion independence rate among patients who were transfusion dependent at baseline in the pivotal study.[13,14]

2.3 Pertinent Drug Development and Regulatory History

Imetelstat is a covalently-lipidated 13-mer oligonucleotide that acts as a competitive inhibitor of the enzyme telomerase. Shorter telomere length and high telomerase activity have been reported to be poor prognostic features in lower-risk MDS,[15-17] suggesting that telomerase may be a relevant therapeutic target for this population.

The key regulatory history for imetelstat is as follows:

- On May 11, 2005, the original IND 072072 for imetelstat was submitted, intended for use in patients with advanced hematological and solid tumor malignancies.
- 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 advisory committee meeting.

The proposed indication is 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).

3 Study 63935937MDS3001 (MDS3001)

3.1 Efficacy Summary

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.

Eligible patients were adults with the following key disease-related eligibility requirements:

- Diagnosis of MDS according to the World Health Organization (WHO) 2016 criteria
- Low or intermediate-1 risk by IPSS

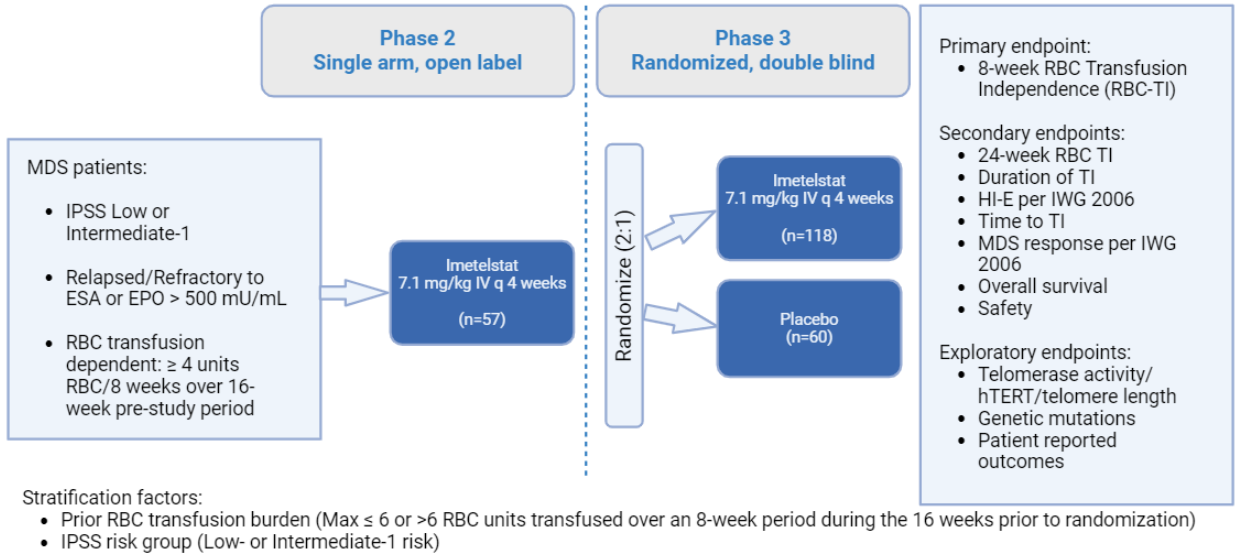
- RBC transfusion dependent, defined as requiring at least 4 RBC units transfused over an 8-week period during the 16 weeks prior to randomization; pre-transfusion Hgb was required to be ≤ 9.0 g/dL to count towards the 4 units total
- Relapsed or refractory to ESA treatment, or erythropoietin level > 500 mU/mL
- Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L independent of growth factor support
- Platelets ≥ 75 x 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

The details of the Phase 3 study design are provided in the Applicant's Briefing Document and summarized in Figure 1. 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).

Figure 1. Design schema of MDS3001



Source: FDA's rendering based on the Applicant's Summary of Clinical Efficacy in MDS

Key demographic and baseline disease characteristics of the patients enrolled in Study MDS3001 are shown in Table 1.

Table 1. Key demographic and baseline disease characteristics for Study MDS3001

Parameter	Imetelstat (Phase 2) N=57	Imetelstat (Phase 3) N=118	Placebo (Phase 3) N=60
Sex			
Male	32 (56.1%)	71 (60.2%)	40 (66.7%)
Female	25 (43.9%)	47 (39.8%)	20 (33.3%)
Age			
Median in years (min, max)	71.0 (46, 83)	71.5 (44, 87)	73.0 (39, 85)
Region			
North America	12 (21.1%)	13 (11.0%)	12 (20.0%)
European Union	37 (64.9%)	80 (67.8%)	38 (63.3%)
Rest of world	8 (14.0%)	25 (21.2%)	10 (16.7%)
IPSS category			
Low	36 (63.2%)	80 (67.8%)	40 (66.7%)
Intermediate-1	21 (36.8%)	38 (32.2%)	20 (33.3%)
Prior therapies			
ESA	51 (89.5%)	108 (91.5%)	52 (86.7%)
Luspatercept	5 (8.8%)	7 (5.9%)	4 (6.7%)
HMA	8 (14.0%)	0	1 (<1%)
Lenalidomide	12 (21.1%)	1 (<1%)	0
RBC transfusion burden per 8 weeks			
Median RBC units (min, max)	7.0 (4, 14)	6.0 (4, 33)	6.0 (4, 13)
Median baseline blood counts			
Neutrophils (cells/L)	2.9×10^9	2.6×10^9	2.7×10^9
Hemoglobin (g/dL)	7.8	7.9	7.8
Platelets (cells/L)	251×10^9	230×10^9	239×10^9

Source: Study MDS3001 Phase 2 and Phase 3 Clinical Study Report

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.

Key secondary endpoints included 24-week RBC-TI, duration of 8-week RBC-TI, and rate of hematologic improvement per IWG 2006 criteria. Other secondary endpoints included rates of complete remission (CR), partial remission (PR), or marrow complete remission (mCR); overall survival (OS); progression-free survival (PFS); 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.

The Applicant seeks to use the difference in 8-week RBC-TI (39.8% imetelstat versus 15.0% placebo; p= <0.001) and the difference in 24-week RBC-TI (28.0% imetelstat versus 3.3% placebo, p = <0.001) in the

Phase 3 trial, and similar 8-week and 24-week RBC-TI rates with imetelstat observed in the Phase 2 trial (37% and 25% respectively for all subjects; 42% and 32% respectively in the target population), as evidence of effectiveness for imetelstat.

3.2 Efficacy Issues

FDA acknowledges that the results of Study MDS3001-Phase 3 met the statistical goals for the primary endpoint of 8-week RBC-TI and key secondary endpoint of 24-week RBC-TI, but the following issues in the study design and efficacy results were identified:

- It is not clear that the magnitude and durability of RBC-TI outweighs the risks of treatment with imetelstat for patients with lower-risk MDS.
- The HI-E, CR, PR, and OS results are not supportive of a disease-modifying treatment effect.
- The patient-reported outcomes are not supportive of a treatment effect.

3.2.1 Magnitude and Durability of RBC Transfusion Independence

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.[18] 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) and at least 1 year (1-year RBC-TI). As shown in Table 2, the point estimate of the response rate decreased as the target duration of RBC-TI increased, being only 13.6% for 1-year RBC-TI at the time of the primary analysis, with a lower bound of the confidence interval of only 8.0%. In an updated analysis with data cutoff of 13 October 2023, the rate of 1-year RBC-TI was only slightly higher at 17.8% (95% CI 11.4, 25.9) for imetelstat versus 1.7% (95% CI 0, 8.9) for placebo.

Table 2. MDS3001-Phase 3: Primary analysis of rate of RBC-TI by Study Arm

Outcome	Imetelstat (N=118)	Placebo (N=60)
8-week RBC-TI[a], n (%) (95% CI)	47 (39.8) (30.9, 49.3)	9 (15.0) (7.1, 26.6)
24-week RBC-TI[b], n (%) (95% CI)	33 (28.0) (20.1, 37.0)	2 (3.3) (12.6, 34.2)
1-year RBC-TI[c], n (%) (95% CI)	16 (13.6) (8.0, 21.1)	1 (1.7) (0, 8.9)

[a] Primary endpoint
[b] Key secondary endpoint
[c] Additional endpoint evaluated by the Applicant post-hoc
Source: Study MDS3001 Phase 3 Clinical Study Report
Data cutoff 13 October 2022

Additionally, the Applicant reported 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. 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 3, 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) for placebo, which was only a 1.1 week difference. This minimal difference in the median duration of the longest RBC-TI interval 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 3. 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)** **Placebo (N=60)**	5.0 (4.0, 7.7) 3.9 (3.6, 4.0)
8-week RBC-TI responders	**Imetelstat (N=47)** **Placebo (N=9)**	51.6 (26.9, 83.9) 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

3.2.2 High proportion of hematologic improvement-erythroid (HI-E) in the placebo arm

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.

In the Phase 3 trial, there was no significant difference in the proportion of subjects who achieved an HI-E response per IWG 2006 criteria, 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. 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.

3.2.3 Lack of CR or PR benefit

Complete remission (CR) and partial remission (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 ≤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 ≥100 x 10^9/L, neutrophils ≥1.0 x 10^9/L, and blasts 0%. PR is defined as all CR criteria if abnormal before treatment except bone marrow blasts decreased by ≥50% over pretreatment but still >5%. In both cases, response must last at least 4 weeks.

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.

3.2.4 Lack of evidence of improvement in 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).[11] 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.

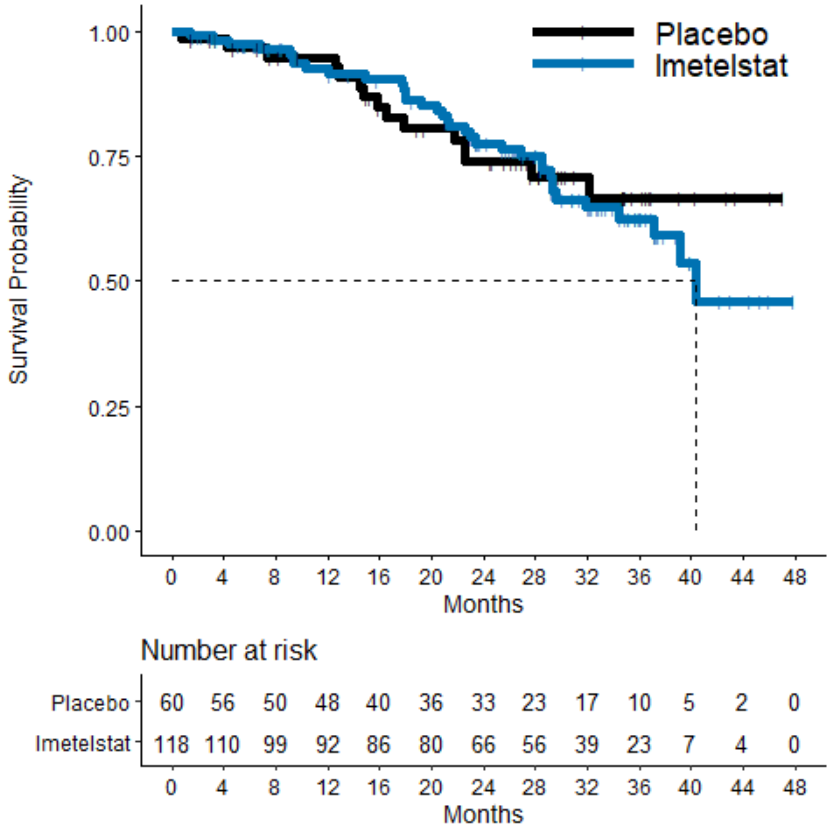
In Study MDS3001, OS was included as a secondary endpoint, but no formal hypothesis testing was planned. Of note, no other trial has demonstrated an OS advantage in lower-risk MDS with transfusion-dependent anemia. The OS results at the time of the primary efficacy analysis and the most recent planned analysis are summarized in Table 4 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 hazard ratio between the imetelstat and placebo arms was 0.98 (95% CI: 0.53, 1.82) (Table 4 and Figure 2). 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).

Table 4. 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)	1.07 (0.46, 2.48)	
5 January 2024	Deaths, n (%)	35 (29.7%)	15 (25.0%)
	Hazard Ratio (95% CI)	0.98 (0.53, 1.82)	

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

Figure 2. MDS3001-Phase 3: Kaplan-Meier Plot of Overall Survival (ITT Set) at Updated Analysis



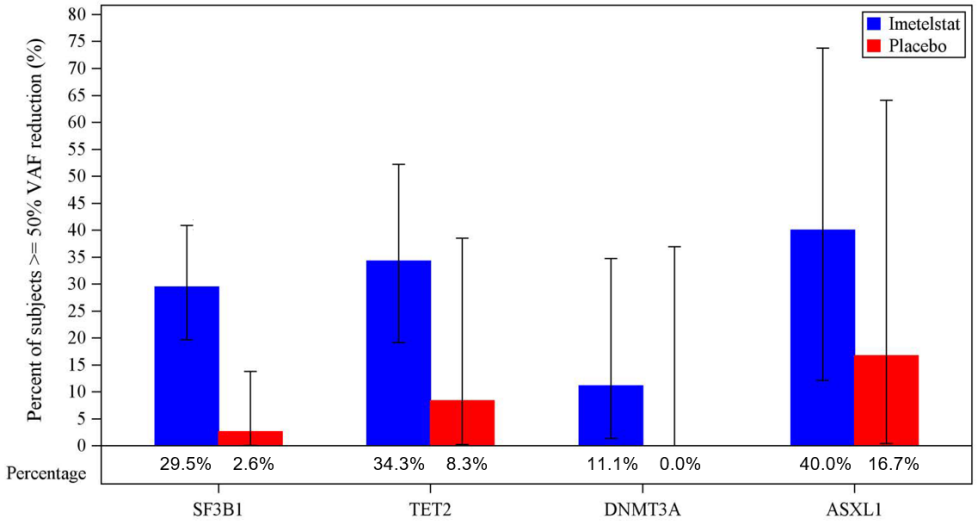
Source: FDA analysis using ADTTEEF dataset
Data cutoff 5 January 2024

Unlike growth factors such as ESAs which artificially raise blood cell counts, 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.

3.2.5 Reduction in mutational burden

The Applicant reported 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 sideroblast subtype, with a trend toward VAF reduction in other mutations such as TET2, DNMT3A, and ASXL1, as shown in Figure 3.

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



		SF3B1	TET2	DNMT3A	ASXL1
Number of Patients with ≥50% VAF reduction/Total Evaluable	Imetelstat	23/78 (29.5%)	12/35 (34.3%)	2/18 (11.1%)	4/10 (40.0%)
	Placebo	1/38 (2.6%)	1/12 (8.3%)	0/8 (0.0%)	1/6 (16.7%)

Source: Study MDS3001 Phase 3 Clinical Study Report
Data cutoff 13 October 2022

However, 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 (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 ≥ 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.

3.2.6 Lack of improvement in patient-reported outcomes

Patient-generated disease symptom information was collected in MDS3001 using the FACT-Anemia and QUALMS 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.

Of note, 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.

In order to support a marketing application, transfusion independence data should 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.

3.2.7 Lack of evidence of reduction in medical resource utilization

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 5, though the total number of medical encounters per patient was comparable between arms.

Table 5. 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)	97 (0.8/patient)	51 (0.9/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.

3.2.8 Uncertainty regarding applicability to the US population

In order to qualify for FDA marketing approval, an application should provide evidence of applicability to the United States (US) population and US medical practice (21 CFR 314.106). However, the vast majority of subjects in Study MDS3001 (93%) were enrolled at non-US sites and the primary efficacy result varied greatly between the US and non-US sites. As shown in Table 6, 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 6. 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 (%)	1/8 (12.5%)	0/5 (0%)	12.5%
95% CI	(0.3%, 52.7%)	(0%, 52.2%)	(-42.5%, 53.3%)
Non-United States			
8-week RBC-TI (%)	46/110 (41.8%)	9/55 (16.4%)	25.5%
95% CI	(32.5%, 51.6%)	(7.8%, 28.8%)	(9.6%, 38.2%)

Source: Applicant's Response to FDA Information Request dated 2 October 2023

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.

3.2.9 Summary of Efficacy Results and Issues

- 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). Similar results were observed in the Phase 2 trial (37% and 25% respectively for all subjects; 42% and 32% respectively in the target population).
- A statistically significant treatment effect was not observed on endpoints reflective of a disease-modifying effect, including HI-E (63.6% vs. 51.7%), CR or PR (0% vs. 0%), and OS (HR=0.98 [95% CI: 0.53, 1.82] at most recent data cut).
- More subjects achieved ≥ 50% VAF reduction in mutation burden on the imetelstat arm compared to the placebo arm, although these findings are limited by the exploratory methodological approach. Furthermore, the clinical significance of a ≥ 50% VAF reduction in mutation burden is unclear.
- 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). Overall, the patient-reported outcomes collected in Study MDS3001-Phase 3 did not reflect an improvement in fatigue or other anemia-related symptoms.
- Residual uncertainties remain about how the observed efficacy of imetelstat might translate to clinical practice.
    - Only 13 patients were enrolled in the US, with RBC-TI rates of 12.5% (1/8) in the imetelstat arm and 0% (0/5) in the placebo arm.
    - 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 analysis excludes protocol-mandated procedures such as transfusions.

3.3 Safety Summary

The overall treatment emergent adverse event (TEAE) profiles of imetelstat and placebo are presented in Table 7. A greater number of grade 3-4 TEAE, serious adverse events (SAE), and events leading to dose modification, including dose interruption, decrease, and discontinuation, were observed in the imetelstat arm of the study.

Table 7. MDS3001-Phase 3: Overall safety profile of imetelstat versus placebo

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
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 using ADAE dataset
Data cutoff 13 October 2022

Overall, patients who received imetelstat experienced more grade 3+ TEAE, TEAE leading to treatment modification, and SAE. Much of the difference was due to higher rates of cytopenias in the imetelstat arm. However, when thrombocytopenia and neutropenia were excluded from the analysis, the rate of grade 3-4 events continued to be higher in the imetelstat arm.

Common TEAE and grade 3+ TEAE are described in Table 8. TEAE occurring more commonly in patients receiving imetelstat included infections, fatigue, arthralgia/myalgia, anemia, hemorrhage, hepatic disorders, and headache. Common laboratory abnormalities are listed in Table 9. Cytopenias, including decreased platelets, decreased neutrophils, and decreased leukocytes were seen more commonly in patients on the imetelstat arms of the study, with grade 3-4 events also being more common in the imetelstat arm. In addition, transaminases and alkaline phosphatase elevations were seen more commonly in the imetelstat arm, although grade 3-4 events were rare in either arm.

Table 8. MDS3001-Phase 3: Common TEAE and grade 3-4 TEAE, excluding lab-based AEs, by study arm

Adverse Event	Imetelstat N=118 (%)		Placebo N=59 (%)		Risk Difference	Risk Difference
	All Grade	Grade 3-4	All Grade	Grade 3-4	All Grade	Grade 3-4
Infections[a]	42	11	34	14	+9	-3
Fatigue[b]	29	0	22	1.7	+7	-1.7
Arthralgia/myalgia[b]	25	2.5	17	5	+8	-2.5
Anemia[c]	20	20	10	7	+10	+13
Hemorrhage[d]	21	2.5	12	1.7	+9	+0.8
Hepatic disorders[b]	14	3.4	10	1.7	+4	+1.7
Headache	13	0.8	5	0	+8	+0.8
Diarrhea	12	0.8	12	1.7	0	-0.8
Peripheral edema	11	0	14	0	-3	0
Dyspnea	9	0.8	9	0	0	+0.8
Constipation	8	0	12	0	-4	0
Syncope	6	1.7	1.7	0	+4	+1.7
Iron overload[b]	6	1.7	14	5	-8	-3.4
Fractures[b]	5	3.4	1.7	1.7	+3	+1.7
Arterial occlusive events[b]	3.4	0	15	5	-12	-5
Cardiac failure[b]	3.4	3.4	5	1.7	-1.7	+1.7

Events with an absolute risk difference of >2.5 are included.

[a] SOC Infections and infestations

[b] Includes multiple adverse reaction terms

[c] HLT anemia NEC

[d] Broad SMQ

Source: FDA analysis using ADAE dataset

Data cutoff 13 October 2022

Table 9. MDS3001-Phase 3: Common Laboratory Abnormalities.

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	96	65	34	8	+62	+57
Leukocytes decreased	94	53	58	1.7	+36	+51
Neutrophils decreased	92	71	47	7	+45	+6.4
Hemoglobin decreased	64	64	64	64	0	0
Chemistry						
Creatinine increased	77	0	75	0	+2	0
Alkaline phosphatase increased	49	0	14	0	+35	0
Aspartate aminotransferase increased	48	0.8	22	1.7	+26	-0.8
Alanine aminotransferase increased	40	3.4	37	5	+3	-1.6
Bilirubin increased	39	0.8	39	1.7	0	-0.8

Abnormalities occurring in >30% 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 13 October 2022

Overall, 19 (16%) of patients in the imetelstat arm and 8 (14%) in the placebo arm died by the time of data cutoff for the initial submission (13 October 2022). One death within 30 days of last dose of medication was observed in each study arm. In the imetelstat arm, one fatal event of sepsis was observed during treatment, and in the placebo arm, one fatal event due to aortic stenosis was observed. The fatal adverse reaction on the imetelstat arm was a 72 year old man with IPSS low risk MDS who was documented to have grade 3 neutropenia and thrombocytopenia on day 619 of treatment. He received treatment on that day, which was noted to be a protocol violation. Twenty-one days later (study day 644), he developed grade 4 sepsis and died of septic shock, respiratory failure, pneumonia, and cardiac ischemia on day 649, 30 days after the last dose of study medication. In addition, two patients died of complications of infections that began less than 30 days prior to the end of treatment, although the deaths occurred more than 30 days after the last dose of study medication, suggesting that the neutropenia and related increased risk of infection observed with use of imetelstat have consequences that persist after the end of treatment.

3.4 Safety Issues

FDA identified several safety issues regarding the use of imetelstat in patients with lower risk MDS:

- The rates of neutropenia and thrombocytopenia, including grade 3-4 neutropenia and thrombocytopenia, were higher in patients receiving imetelstat compared to placebo, with risk differences of >50 percentage points between the two arms.
- Patients on the imetelstat arm were more likely to require myeloid growth factor support or platelet transfusion and despite increased supportive care experienced higher rates of infections and hemorrhagic events compared to those on the placebo arm, indicating that the neutropenia and thrombocytopenia observed resulted in clinical consequences.

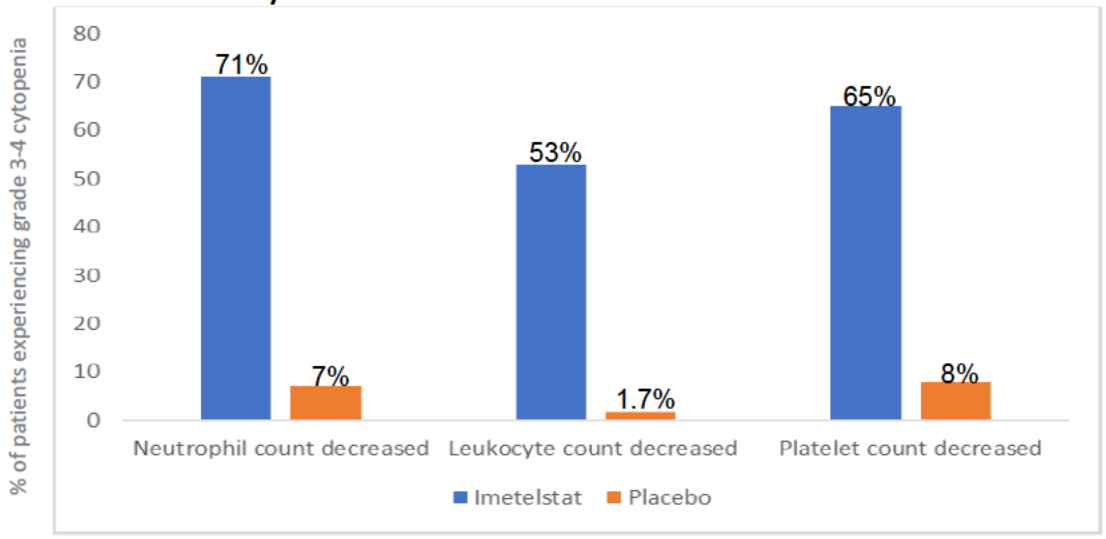
- Other adverse reactions, including hepatic toxicity, fatigue, arthralgia/myalgia, and fractures, were observed more frequently on the imetelstat arm.
- Patients who received imetelstat were more likely to require treatment modification, including treatment discontinuation, due to cytopenias compared to those who received placebo.
- There has been inadequate dose exploration in the setting of lower risk MDS, and the appropriate dose of imetelstat may not be identified.

3.4.1 Cytopenias

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 4). Laboratory values will be used to discuss the rate of cytopenias unless otherwise specified.

Figure 4. MDS3001-Phase 3: Grade 3-4 cytopenias, percent of patients with at least one decrease in the relevant laboratory value



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 10, the median duration of individual events of Grade 3-4 neutropenia and thrombocytopenia was just under two weeks in the imetelstat arm (Table 10). 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.

Table 10: 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)	1.4 (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 include 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.

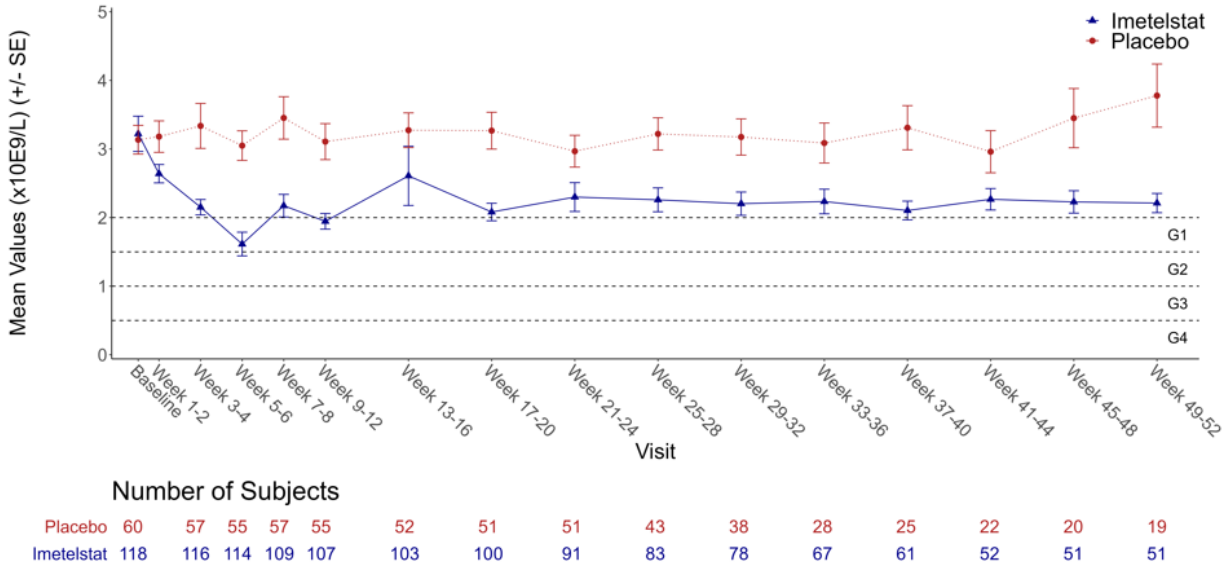
Source: Applicant's response to information request dated 21 December 2023

Data cutoff 13 October 2022

3.4.1.1 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 5. 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 5. MDS3001-Phase 3: Mean neutrophil count over time in first 52 weeks of 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 11, 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 11. 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 12). 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 12. MDS3001-Phase 3: Neutrophil count decrease 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

Dose modification for neutropenia was required more frequently in patients receiving imetelstat compared to placebo (Table 13). 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 13: Dose modification for neutropenia by study arm

	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

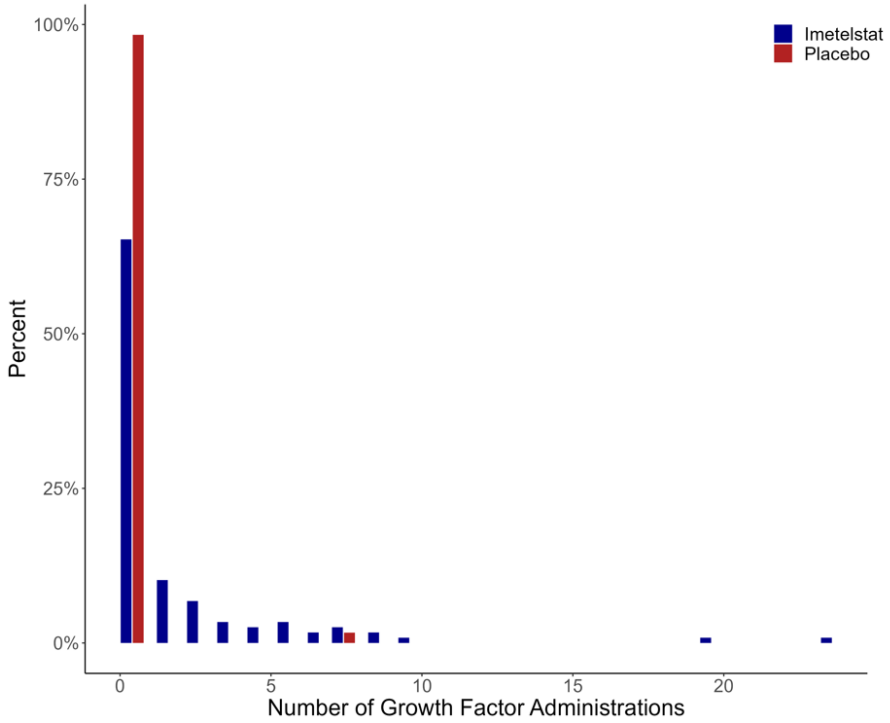
More patients receiving imetelstat required myeloid growth factor support, with 42 (36%) of patients on the imetelstat arm requiring myeloid growth factor support at any time after start of therapy versus two patients in the placebo arm Table 14 and Figure 6. Among patients who received growth factor 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 14. Rate of myeloid growth factor use by study arm

	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 6. MDS3001-Phase 3: Histogram of patients requiring myeloid growth factor support by study arm



Source: FDA analysis using ADCM dataset
Data cutoff 13 October 2022

The rates of infection in patients in each arm of the study is shown below in Table 15. The rate of events of infections was higher in the imetelstat arm compared to placebo by 8.5 percentage points. Both bacterial and viral infections were more common in the imetelstat arm, although the difference was small for bacterial infections. Five cases of sepsis, including one fatal case, were seen in the imetelstat arm while none were observed in the placebo arm. Common specific infections included COVID-19, upper respiratory tract infections (URI), pneumonia, urinary tract infections (UTI), and sepsis. All of these except for pneumonia were seen more frequently in the imetelstat arm.

Table 15. MDS3001-Phase 3: Infectious events by study arm

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	5.1	+6.9	-3.4
UTI	9	1.7	5	0	+3.4	+1.7
URI†	7.6	0	6.8	0	+0.8	0
Pneumonia†	5.1	3.4	5.1	3.4	0	0
Sepsis†	4.2	4.2	0	0	+4.2	+4.2

*SOC Infections and infestations
**HLGT
†Grouped term
Source: FDA analysis using ADAE 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 16). 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 16. MDS3001-Phase 3: Use of anti-infective agents by study arm

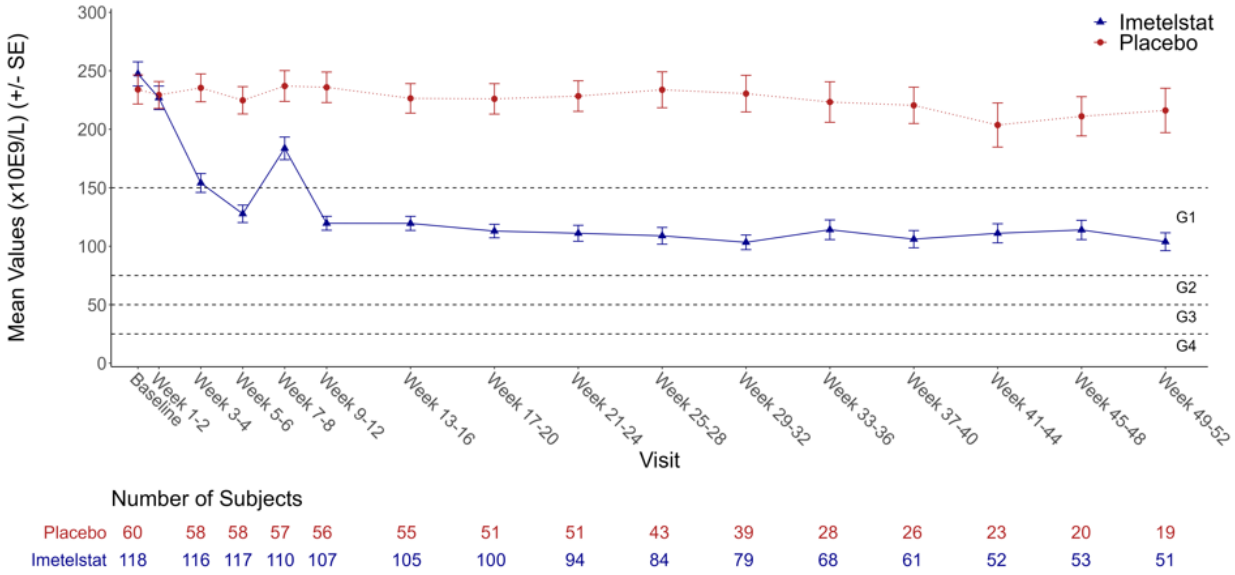
	Imetelstat N=118 (%)	Placebo N=59 (%)
Any anti-infective	64	59
Any except vaccines	42	34
Antibiotics	36	32
Anti-virals	10	5

Source: FDA analysis using ADCM dataset
Data cutoff date 13 October 2022

3.4.1.2 Thrombocytopenia

Thrombocytopenia was frequently observed in patients treated with imetelstat (Figure 7). 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 7. 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 17).

Table 17. MDS3001-Phase 3: Platelet count decrease by grade and study arm

	Imetelstat N=118	**Placebo N=59**
Any grade worsening	113 (96%)	27 (46%)
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

Dose modifications for thrombocytopenia were required more frequently in the imetelstat arm compared to the placebo arm (Table 18). 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 18: Frequency of dose modification for thrombocytopenia 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

Changes in platelet count by cycle and study arm are described in Table 19. 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 19. MDS3001-Phase 3: Platelet count decrease 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

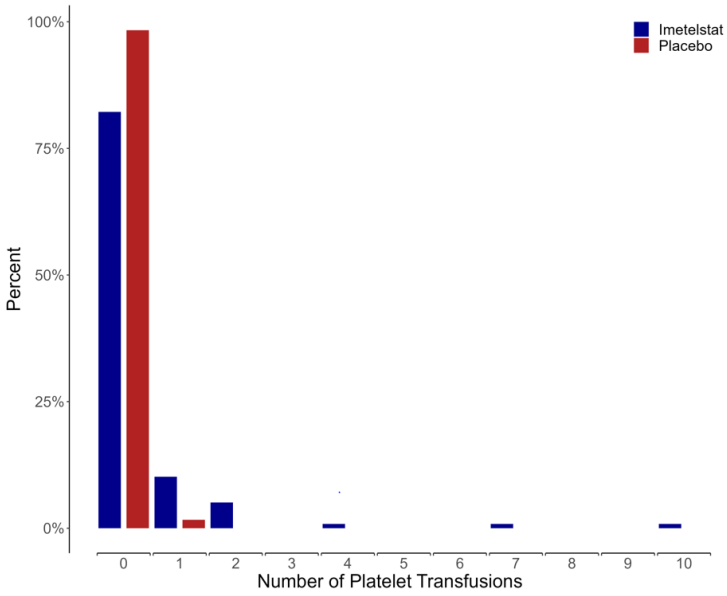
Platelet transfusions were given more frequently in patients on the imetelstat arm as shown in Table 20 and Figure 8, with 21 (18%) patients in the imetelstat arm and 1 (2%) in the placebo arm receiving at least one platelet transfusion. In addition, patients on the imetelstat arm required up to 10 separate transfusions whereas the patient on the placebo arm received platelets only once.

Table 20. Rate of platelet transfusions 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 8. MDS3001-Phase 3: Histogram of platelet transfusion requirements by study arm



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 21). 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 21. MDS3001-Phase 3: Hemorrhage events by study arm

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

In summary, platelet decreases were observed in over 90% of patients receiving imetelstat. 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.

3.4.2 Hepatic toxicity

Treatment emergent adverse events of hepatic toxicity were observed more frequently in the imetelstat arm compared to the placebo arm (Table 22). Most events were low grade, with <5% of events of either hepatic toxicity or transaminase increased being grade 3 or higher.

Table 22. MDS3001-Phase 3: Hepatotoxicity adverse reactions by study arm

Adverse event	Imetelstat (N=118)		Placebo (N=59)	
	All grades	Grade 3-4	All grade	Grade 3-4
Hepatic toxicity*	17 (14%)	4 (3.4%)	7 (12%)	1 (1.7%)
Transaminase increase**	20 (17%)	5 (4.2%)	4 (7%)	2 (3.4%)

*Includes PT hyperbilirubinemia, hepatic cirrhosis, hepatic steatosis, bilirubin conjugated increased, hepatitis, hepatomegaly, hepatoxicity
**Includes alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyl transferase increased
Source: FDA analysis using ADAE dataset
Data cutoff 13 October 2022

Laboratory values of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin were collected on patients being treated on MDS3001-Phase 3. Both transaminases were elevated more commonly in the imetelstat arm, with the largest difference being in AST (Table 23). Most events were no more than grade 2 and no grade 4 events were seen.

One method of determining the probability that a drug is hepatotoxic is by use of Hy's law. Criteria for Hy's law cases are the presence of transaminase elevations of at least three times the upper limit of normal with simultaneous increase in bilirubin to at least two times the upper limit of normal in the absence of cholestasis (no elevation in alkaline phosphatase) and with no other identifiable reason for the abnormalities.[19] Two events meeting the laboratory definition of Hy's law cases were observed in the imetelstat arm. 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 deferiprox simultaneously. The abnormalities resolved when both medications were stopped and recurred after restarting first imetelstat then deferiprox. The

Applicant attributed the abnormalities to deferiprox, but the timing of the dechallenge and rechallenge events makes attribution difficult.

Table 23. MDS3001-Phase 3: Increased transaminases and bilirubin by study arm

Adverse event	Imetelstat (N=118)		Placebo (N=59)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
ALT	47 (40%)	4 (3.4%)	22 (37%)	4 (5%)
AST	57 (48%)	1 (0.8%)	13 (22%)	1 (1.7%)
Bilirubin	46 (39%)	1 (0.8)	23 (39%)	1 (1.7%)

Values represent number of grades of increase any time after start of treatment compared to baseline.
Source: FDA analysis using ADAE dataset
Data cutoff 13 October 2022

3.4.3 Fractures

An increased risk of fractures was observed in patients receiving imetelstat compared to those receiving placebo, with events in the custom grouped term of fractures (including femur fracture, hand fracture, hip fracture, humerus fracture, lumbar vertebral fracture, and thoracic vertebral fracture) occurring in 6 (5%) of patients in the imetelstat arm and 1 (1.7%) patient in the placebo arm (risk difference +3.4). Grade 3 or higher events occurred in 4 (3.4%) of patients in the imetelstat arm and 1.7% in the placebo arm. Although not directly comparable, it is notable that 6 (11%) of patients on the phase 2 portion of MDS3001 experienced fractures, including femur fracture (4 events), spinal compression fracture, wrist fracture, hip fracture, radius fracture, thoracic vertebral fracture, skull fracture, and rib fracture. Finally, fractures were documented in 61 patients (8%) who received imetelstat as monotherapy or as part of combination therapy at any dose and in a variety of hematologic and solid tumors, including 47 (8%) who received imetelstat as monotherapy at any dose and 20 (10%) who received imetelstat monotherapy at a dose of 7.1 mg/kg. The reasons for this finding are unknown. Hypocalcemia was reported in one patient on the phase 2 portion of the study and one patient on the placebo arm of the phase 3 portion. Vitamin D deficiency was reported in one patient each on the phase 2 portion and the imetelstat arm of the phase 3 portion of the study, however, vitamin D was not routinely measured during the study. Laboratory measurement of calcium levels were not provided and therefore, changes in calcium levels cannot be determined apart from hypocalcemia documented in the laboratory findings.

Although the AE of “fall” is not more common in patients receiving imetelstat (1.7% in each arm), syncope and associated events (presyncope, syncope, fall) were more commonly observed in the imetelstat arm (see Section 3.4.4 below). The higher rate of syncope and pre-syncope might help explain the difference in rate of fractures, although there was not a strong association between syncopal events and fractures.

In summary, a rate of fractures between 5% and 11% was observed in patients receiving imetelstat across a variety of studies, including both monotherapy and combination therapy and at varying doses. The consistency of this finding suggests a potential causal connection, although the specific mechanism of action cannot be determined with currently available data.

3.4.4 Other clinician-reported adverse events

A number of adverse events may adversely affect how patients feel and function even when the events are relatively low grade, especially if the duration of events is long or events recur. Examples of events in

this category include myalgia, arthralgia, other pain (e.g., headaches), fatigue/malaise, pruritus, or mild to moderate gastrointestinal events.

No increase in GI events including diarrhea, constipation, or abdominal pain were observed. However, a higher rate of arthralgia/myalgia, headache, pruritus, and fatigue were observed in patients who receiving imetelstat compared to placebo in the phase 3 portion of study MDS3001 (Table 24).

Table 24. MDS3001-Phase 3: Rate of symptomatic adverse events with an incidence of ≥5% and occurring more commonly in the imetelstat arm

Event	Imetelstat N=118 (%)		Placebo N=59 (%)		Risk difference	
	All Grade	Grade 3-4	All Grade	Grade 3-4	All Grade	Grade 3-4
Fatigue*	29	0	22	1.7	+6.8	-1.7
Myalgia/arthralgia*	25	2.5	19	5	+6.8	-2.5
Headache	13	0.8	5	0	+7.6	+0.8
Syncope*	6	1.7	1.7	0	+4.2	+1.7
Pruritus	6	0	1.7	0	+4.2	0
Fractures*	5	3.4	1.7	1.7	+3.4	+1.7

* Includes multiple preferred terms as follows:
Fatigue: fatigue, malaise, asthenia
Arthralgia/myalgia: back pain, bone pain, arthralgia, myalgia, neck pain, pain, non-cardiac chest pain, musculoskeletal pain, pain in jaw, pelvic pain, pain in extremity
Syncope: Fall, pre-syncope, syncope
Fractures: hand fracture, hip fracture, lumbar vertebral spine fracture, femur fracture, humerus fracture
Source: FDA analysis using ADAE dataset.
Data cutoff 13 October 2022

In summary, adverse events of fatigue, headache, arthralgia/myalgia, and pruritus were more common in patients receiving imetelstat versus placebo. These adverse reactions may adversely affect how patients feel and function even when low grade and affect the overall benefit-risk profile of imetelstat.

3.4.5 Inadequate dose exploration and high dose modifications in MDS

3.4.5.1 Dose modifications in patients in Study MDS3001

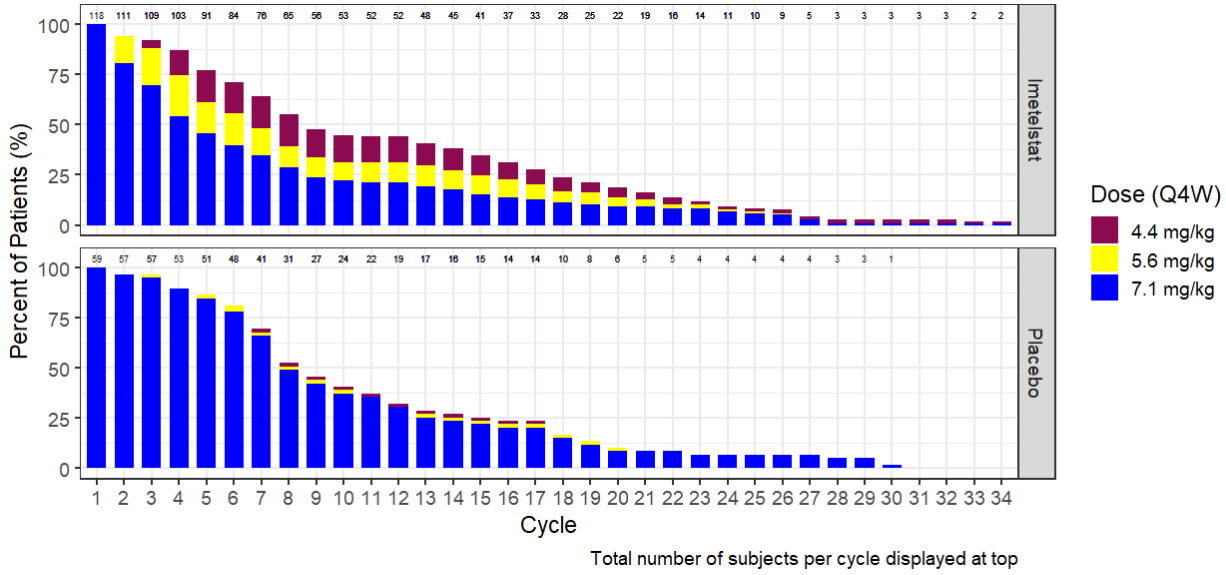
There was a high rate of dose modifications with imetelstat compared to placebo in Study MDS3001, as shown in Table 25 and Figure 9.

Table 25. 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 9. 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; Table 13, Section 3.4.1.1) or thrombocytopenia (27 patients; Table 18, Section 3.4.1.2). 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).

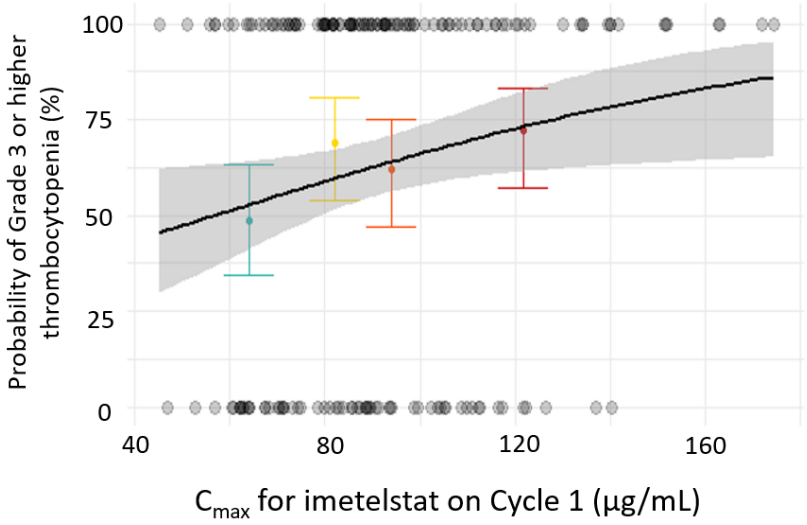
3.4.5.2 Dose exploration across the drug development program

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.

3.4.5.3 Exposure-response relationships between imetelstat and Grade 3-4 Thrombocytopenia

In Study MDS3001, higher maximum plasma concentrations of imetelstat (Cmax) correlated with a higher probability of Grade 3-4 thrombocytopenia, as shown Figure 10, which supports the observation of higher rates of thrombocytopenia with imetelstat (Section 3.3). This finding suggests that the starting dose and regimen of imetelstat may be too high, and may be further optimized.

Figure 10. 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

Although there was also a positive exposure-response relationship between the average plasma concentration of imetelstat (Cavg) 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.

4 Benefit-Risk Assessment

4.1 Potential benefits vs. potential risks

The potential benefits of imetelstat must be weighed carefully against the potential risks. As shown in Table 26, the potential benefits of imetelstat include a 25% higher chance of achieving an 8-week or 24-week RBC-TI period over placebo. However, this is in the context of requiring monthly infusion visits for imetelstat, no clear evidence of a CR/PR or OS benefit, and no clear improvement in PROs.

Table 26. MDS3001-Phase 3: Potential benefits of imetelstat

	Imetelstat (N=118)	Placebo (N=60)	Difference
8-week RBC-TI	40%	15%	+25%
24-week RBC-TI	28%	3%	+25%

Source: Table 2

The potential risks of imetelstat include a high risk of neutropenia and thrombocytopenia, including more Grade ≥3 events. Patients on imetelstat are also more likely to require myeloid growth factor or platelet transfusion while on treatment and have downstream consequences of cytopenias, such as infections and hemorrhage, as shown in Table 27.

Table 27. MDS3001-Phase 3: Potential risks of imetelstat

	Imetelstat (N=118)	Placebo (N=59)	Difference
Grade 3-4 neutropenia*	**71%**	**7%**	**+64%**
Myeloid growth factor requirement	36%	3%	+33%
Infection (any grade)	47%	34%	+13%
Grade 3-4 thrombocytopenia*	**65%**	**8%**	**+57%**
Platelet transfusion requirement	18%	2%	+16%
Bleeding (any grade)	22%	12%	+10%

*Based on local laboratory data

Source: Figure 4, Figure 6, Figure 8, Table 8

4.2 Cytopenias by response status

Furthermore, many patients experienced worsening Grade ≥3 thrombocytopenia and neutropenia regardless of 8-week RBC-TI response status, as shown in Table 28. It is important to note that 70% of patients who did not achieve a response had Grade 3+ neutropenia and 69% of patients who did not achieve a response had Grade 3+ thrombocytopenia while on treatment with imetelstat. Therefore, there is a large subset of patients who have clinically significant cytopenias with no benefit. Many subjects also required intervention for cytopenias, such as myeloid growth factor or platelet transfusion, during the course of treatment *regardless of response status*, as shown in Table 29.

Table 28. MDS3001-Phase 3: Worsening ≥ Grade 3 neutropenia and thrombocytopenia on treatment, according to 8-week RBC-TI responder status

	Imetelstat		Placebo	
	Responders (N=47)	**Non-responders (N=71)**	**Responders (N=9)**	**Non-responders (N=51)**
Subjects with worsening ≥ Grade 3 neutropenia	72%	70%	0	8%
Subjects with worsening ≥ Grade 3 thrombocytopenia	60%	69%	11%	8%

Source: FDA analysis based on information from Applicant's response to FDA Information Request dated 22 January 2024

Table 29. MDS3001-Phase 3: Myeloid growth factor and platelet transfusion requirement on treatment, according to 8-week RBC-TI responder status

	Imetelstat		Placebo	
	Responders (N=47)	**Non-responders (N=71)**	**Responders (N=9)**	**Non-responders (N=51)**
Subjects requiring myeloid growth factor	40%	31%	0	2%
Subjects requiring platelet transfusion	11%	23%	0	2%

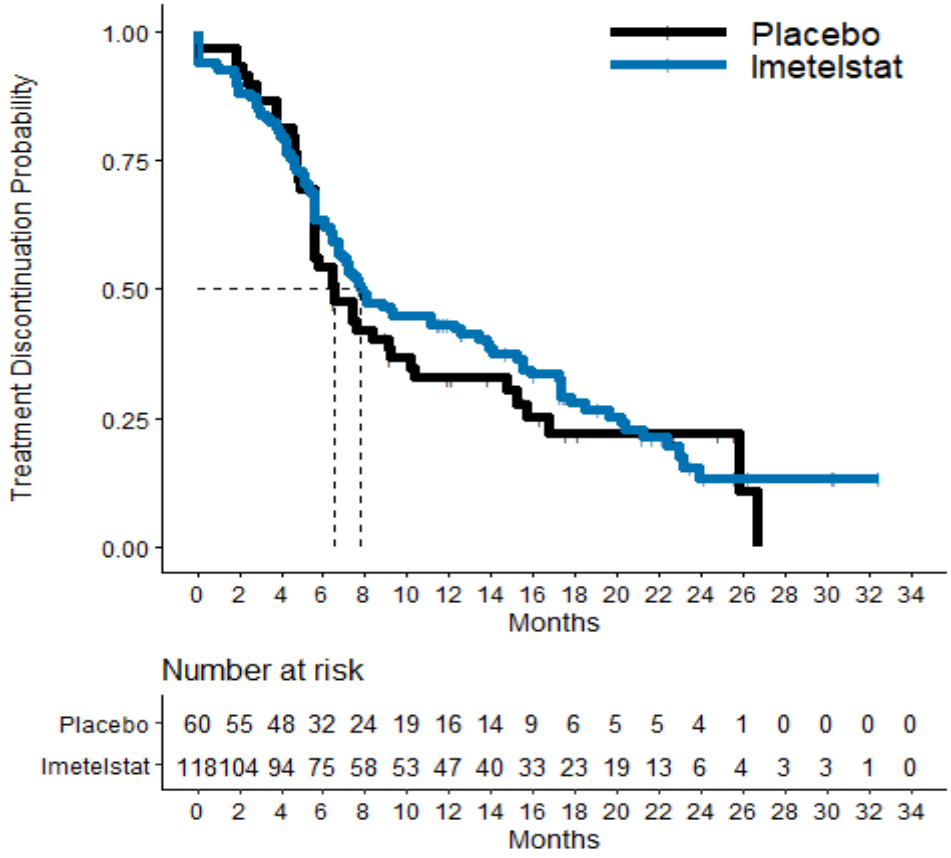
Source: Applicant's response to FDA Information Requests dated 21 December 2023 and 9 January 2024

4.3 Additional risks and uncertainties

4.3.1 Duration of treatment

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 11, and the median duration of treatment was only 8 cycles for patients treated with imetelstat, the same as placebo.

Figure 11. 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

4.3.2 Fatigue

Additional risks of imetelstat treatment include a higher risk of fractures, arthralgias/myalgias, and possibly fatigue. Regarding fatigue, it should be noted that although patient-reported 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). 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 30.

Table 30. 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

5 Summary and Conclusions

The Applicant is seeking approval of imetelstat (proposed trade name RYTELO) 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).

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 other secondary endpoints reflective of a disease-modifying effect, including HI-E (63.6% vs. 51.7%), CR or PR (0% vs. 0%), 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. As shown in Table 1 above, 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. As noted in Table 27, 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, and it is not clear that the risks of treatment with imetelstat are outweighed by the potential benefit for the intended population. FDA requests discussion of whether the benefits of imetelstat outweigh the risks in patients with lower-risk MDS with transfusion dependent anemia who have not responded to, or have lost response to, or are ineligible for ESA.

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