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RESEARCH**

APPLICATION NUMBER:

761136Orig2s000

CLINICAL REVIEW(S)

Clinical Review
 Elizabeth Pulte
 BLA 761136 Original 2
 REBOLZYL (luspatercept-aamt)

CLINICAL REVIEW

Application Type	Original
Application Number(s)	BLA 761136 Ori-2
Priority or Standard	Standard
Submit Date(s)	4/4/19
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Division/Office	OHOP/DHP
Reviewer Name(s)	Elizabeth Pulte, MD
Review Completion Date	12/31/19
Established/Proper Name	Luspatercept-aamt
(Proposed) Trade Name	REBOLOZYL
Applicant	Celgene Corporation
Dosage Form(s)	Injection, lyophilized (25 mg, 75 mg)
Applicant Proposed Dosing Regimen(s)	1.0 mg/kg every 3 weeks, increase to 1.33 mg/kg or 1.75 mg/kg if inadequate response
Applicant Proposed Indication(s)/Population(s)	For the treatment of adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS)-associated anemia who have ring sideroblasts and require red blood cell (RBC) transfusions. Limitations of Use: REBLOZYL is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.
Recommendation on Regulatory Action	Complete response
Recommended Indication(s)/Population(s) (if applicable)	

Table of Contents

Glossary	8
1. Executive Summary	10
1.1. Product Introduction	10
1.2. Conclusions on the Substantial Evidence of Effectiveness	11
1.3. Benefit-Risk Assessment	12
1.4. Patient Experience Data	17
2. Therapeutic Context	17
2.1. Analysis of Condition	18
2.2. Analysis of Current Treatment Options	18
3. Regulatory Background	24
3.1. U.S. Regulatory Actions and Marketing History	24
3.2. Summary of Presubmission/Submission Regulatory Activity	24
3.3. Foreign Regulatory Actions and Marketing History	24
4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety	25
4.1. Office of Scientific Investigations (OSI)	25
4.2. Product Quality	25
4.3. Clinical Microbiology	25
4.4. Nonclinical Pharmacology/Toxicology	25
4.5. Clinical Pharmacology	26
4.6. Devices and Companion Diagnostic Issues	27
4.7. Consumer Study Reviews	27
5. Sources of Clinical Data and Review Strategy	28
5.1. Table of Clinical Studies	28
5.2. Review Strategy	29
6. Review of Relevant Individual Trials Used to Support Efficacy	29
6.1. MDS-001	29
6.1.1. Study Design	29

6.1.2. Study Results	37
6.2. A536-03.....	62
6.2.1. Study Design	62
6.2.2. Study Results	67
7. Integrated Review of Effectiveness.....	72
7.1. Assessment of Efficacy Across Trials.....	72
7.1.1. Primary Endpoints	72
7.1.2. Secondary and Other Endpoints	73
7.1.3. Subpopulations	74
7.1.4. Dose and Dose-Response	75
7.1.5. Onset, Duration, and Durability of Efficacy Effects.....	75
7.2. Additional Efficacy Considerations.....	75
7.2.1. Considerations on Benefit in the Postmarket Setting.....	75
7.2.2. Other Relevant Benefits.....	76
7.3. Integrated Assessment of Effectiveness	76
8. Review of Safety.....	77
8.1. Safety Review Approach	77
8.2. Review of the Safety Database	78
8.2.1. Overall Exposure.....	78
8.2.2. Relevant characteristics of the safety population:	79
8.2.3. Adequacy of the safety database:	80
8.3. Adequacy of Applicant's Clinical Safety Assessments	80
8.3.1. Issues Regarding Data Integrity and Submission Quality.....	80
8.3.2. Categorization of Adverse Events.....	81
8.3.3. Routine Clinical Tests.....	82
8.4. Safety Results.....	82
8.4.1. Deaths.....	82
8.4.2. Serious Adverse Events.....	85
8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects.....	87
8.4.4. Significant Adverse Events.....	88

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions	88
8.4.6. Laboratory Findings	93
8.4.7. Vital Signs	95
8.4.8. Electrocardiograms (ECGs)	97
8.4.9. QT	97
8.4.10. Immunogenicity	97
8.5. Analysis of Submission-Specific Safety Issues	99
8.6. Safety Analyses by Demographic Subgroups	112
8.7. Specific Safety Studies/Clinical Trials	115
8.8. Additional Safety Explorations	115
8.8.1. Human Carcinogenicity or Tumor Development	115
8.8.2. Human Reproduction and Pregnancy	115
8.8.3. Pediatrics and Assessment of Effects on Growth	115
8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound	115
8.9. Safety in the Postmarket Setting	115
8.9.1. Safety Concerns Identified Through Postmarket Experience	115
8.9.2. Expectations on Safety in the Postmarket Setting	116
8.9.3. Additional Safety Issues From Other Disciplines	116
8.10. Integrated Assessment of Safety	116
9. Advisory Committee Meeting and Other External Consultations	118
10. Labeling Recommendations	118
10.1. Prescription Drug Labeling	118
10.2. Nonprescription Drug Labeling	118
11. Risk Evaluation and Mitigation Strategies (REMS)	118
12. Postmarketing Requirements and Commitments	118
13. Appendices	119
13.1. References	119
13.2. Financial Disclosure	121

Table of Tables

Table 1: Currently available treatments for MDS.....	20
Table 2: Clinical studies used in the evaluation process.....	28
Table 3: Demographic characteristics of patients on MDS-001 by study arm.....	40
Table 4: Baseline disease characteristics of patients on MDS-001 by study arm.....	42
Table 5: Rate of use of selected medication classes	44
Table 6: Rate of TI-8 by study arm.....	46
Table 7: Rate of TI-12 in weeks 1-24 and 1-48 by study arm.....	47
Table 8. Study MDS-001: RBC TI Difference Using Alternative Endpoint Definitions.....	48
Table 9: Frequency of achievement of TI-8 in the primary analysis period by baseline transfusion requirement and study arm.....	51
Table 10: Response by baseline hemoglobin level.....	52
Table 11: Response by selected demographic and disease factors.....	53
Table 12: Response by selected disease and demographic factors.....	54
Table 13: Study MDS-001: EORTC QLQ-C30 Completion Rate.....	56
Table 14: Health care resource utilization rates by study arm and resource type.....	59
Table 15: Erythropoietin at baseline and post-baseline changes in patients treated on the luspatercept arm.....	61
Table 16: Erythropoietin at baseline and post-baseline changes in patients treated on the placebo arm.....	62
Table 17: Erythropoietin, Responders on luspatercept arm only.....	62
Table 18: Demographic characteristics for patients on trial A536-03.....	68
Table 19: Disease and other pertinent characteristics for patients on trial A536-03.....	69
Table 20: Drug exposure in safety database.....	79
Table 21: Demographic characteristics of the safety population by treatment and dose.....	79
Table 22: Grouped terms used for analysis of adverse events.....	81
Table 23: Deaths reported on study A536-05 with brief narrative of the event.....	82
Table 24: Study MDS-001: Causes of Deaths through Week 25.....	83
Table 25: Deaths on trial MDS-001.....	84
Table 26: Serious adverse events observed in study MDS-001 in the first 8 cycles of treatment by study arm.....	85
Table 27: Adverse events of grade 3 and higher observed in study ACE-536-MDS-001 in the first 8 cycles of treatment by study arm.....	86
Table 28: Adverse events observed in study MDS-001 in the first 8 cycles of treatment by study arm.....	89
Table 29: Adverse events observed in study ACE-536-MDS-001 in cycles 1-8 versus extension cycles.....	90
Table 30: Adverse events observed in study A536-03 in patients treated with a dose of 1 mg/kg or higher.....	92

Table 31: Number and percentage of patients on trial MDS-001 experiencing shifts in hepatic enzyme values from 0-1 to 2-4 by study arm.....	94
Table 32: Patients experiencing increase in direct or indirect bilirubin by study arm at any time during the study.....	94
Table 33: Number and percentage of patients on trial MDS-001 experiencing shifts in creatinine clearance and selected electrolyte values from 0-1 to 2-4 by study arm.....	95
Table 34: Number and percentage of patients on trial MDS-001 experiencing shifts in hematologic values from 0-1 to 2-4 by study arm.....	95
Table 35: Blood pressure outliers by treatment arm.....	96
Table 36: Blood pressure outliers within the first 25 weeks of therapy by treatment arm.....	96
Table 37: Blood pressure outliers after the first 25 weeks of therapy by treatment arm.....	96
Table 38: Adverse events observed in the luspatercept arm of study MDS-001 by incidence of ADA.....	98
Table 39: Incidence and duration of fatigue in patients treated on MDS-001 by arm and cycle.....	99
Table 40: Median duration and outcome of events of fatigue in patients on trial MDS-001 by study arm and cycle number. Total number of events shown.	100
Table 41: Subjects with transaminases ≥ 3 x ULN, bilirubin of ≥ 1.5 x ULN, and normal alkaline phosphatase at any time during treatment with luspatercept	102
Table 42: Neoplasms observed (patients) with use of luspatercept versus placebo in patients with MDS.....	106
Table 43: Incidence of MDS progression or AML transformation by treatment.....	109
Table 44: Duration of treatment, time to event, and total lifetime dos by trial and treatment arm.....	111
Table 45: Adverse events observed in the luspatercept arm of study MDS-001 in the first 8 cycles of treatment for women versus men	112
Table 46: Adverse events observed in the luspatercept arm of study MDS-001 in the first 8 cycles of treatment by study arm by patient age	114

Table of Figures

Figure 1: Potential treatment algorithm for MDS.....	19
Figure 2: Schema for the trial ACE-536-MDS-001.....	30
Figure 3: Example of files with status “current” in the ISS Analysis Dataset Legacy folder.....	45
Figure 4: Graphic representation of transfusion events and response for subset of patients.....	46
Figure 5: Change in hemoglobin in patients treated on MDS-001 by (A) arm an (B) response to therapy within the luspatercept arm. Adapted from Sponsor’s analysis.....	49
Figure 6: Median change in hemoglobin by study arm and response.....	50
Figure 7: Improved (A) and worsened (B) global quality of life by study arm and cycle.....	57
Figure 8: Change in global QoL over time for patients receiving luspatercept who responded to therapy (at least TI-8) during the primary phase of treatment.....	57
Figure 9: Improved (A) and worsened (B) fatigue by arm and cycle number.....	58
Figure 10: Changes in fatigue over time for patients on the luspatercept arm who responded to therapy.....	58
Figure 11: Improved (A) and worsened (B) dyspnea by arm and cycle number.....	59
Figure 12: Changes in ferritin by arm and study visit.....	60
Figure 13: Median change in hemoglobin in low transfusion burden patients receiving luspatercept.....	71
Figure 14: Study MDS-001: Cumulative Incidence of Viral Infections during Weeks 1 – 24.....	101
Figure 15: Cumulative incidence of SPM by study and arm adapted from Sponsor’s analysis....	107
Figure 16: Cumulative incidence of SPM by study and arm, FDA analysis.....	108
Figure 17: Cumulative incidence of AML/MDS by study and arm.....	110

Glossary

AC	advisory committee
AE	adverse event
AML	acute myeloid leukemia
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HMA	hypomethylating agents
ICH	International Council for Harmonization
IND	Investigational New Drug Application
IPSS	International Prognostic Scoring System
IPSS-R	Revised International Prognostic Scoring System
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat

Clinical Review
Elizabeth Pulte
BLA 761136 Original 2
REBOLZYL (Iuspatercept-aamt)

MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MPGN	membranoproliferative glomerulonephritis
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
QoL	quality of life
RBC	red blood cell
RBC-TI	red blood cell transfusion independence
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
SPM	second primary malignancy
TEAE	treatment emergent adverse event
TI-8	transfusion independence for at least 8 weeks
TI-12	transfusion independence for at least 12 weeks
TI-16	transfusion independence for at least 16 weeks

1. Executive Summary

1.1. Product Introduction

Proposed Trade Name:	Reblozyl®
Established Name:	Luspatercept-aamt
Also Known As:	ACE-536
Molecular Weight:	76 kDaltons
Dosage Forms:	Injection, lyophilized (25 mg, 75 mg)
Therapeutic Class:	Erythroid maturation agent
Chemical Class:	Recombinant protein
Structure:	Fusion protein comprised of a modified extracellular domain of the human activin receptor type IIB linked to a human IgG1 Fc domain
Pharmacologic Class:	Therapeutic protein
Mechanism of Action:	Unknown

Luspatercept-aamt is approved under BLA 761136 for use in β -thalassemia patients requiring transfusion. BLA 761136 Original-2 was submitted for the proposed indication of treatment of adult patients with very low- to intermediate-risk myelodysplastic syndromes (MDS)-associated anemia who have ring sideroblasts and require red blood cell (RBC) transfusions with a limitation of use stating that it is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia. The proposed dose for patients with anemia associated with MDS is 1.0 mg/kg once every 3 weeks by subcutaneous (SC) injection with increases to 1.33 mg/kg and 1.75 mg/kg sequentially after 2 doses each if the patient is not red blood cell (RBC) transfusion-free.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Transient transfusion independence was obtained in a minority of patients after treatment with luspatercept. However, use of luspatercept was associated with a lower quality of life. In addition, the endpoint of transfusion independence is somewhat subjective in that the decision to transfuse is a clinical decision and therefore can be influenced by conscious or unconscious bias. Furthermore, the protocol created risk of inadvertent unblinding, increasing the risk of unequal use of transfusion. The baseline hemoglobin was defined in a manner inconsistent with prior experience and produced a falsely low baseline, casting doubt on the

degree of hemoglobin increase associated with use of luspatercept. Luspatercept was associated with a substantial risk of adverse events, including fatigue, dyspnea, hepatotoxicity, renal toxicity, gastrointestinal adverse events, infections, bleeding, malignancy, and fatal adverse events.

Recommendation: complete response letter.

Comments for the CR letter are as follows:

Clinical/Statistical:

1. You did not provide substantial evidence of effectiveness of luspatercept in the treatment of adults with anemia associated with MDS with ringed sideroblasts and require RBC transfusions. Issues leading to this conclusion included:
 - The blinding in trial ACE-536-MDS-001 (MDS-001) is inadequate, increasing the risk of bias in a trial that uses an endpoint which may be manipulated due to conscious or unconscious bias. Specifically, the production of the placebo control syringe on site and the lack of specific instructions to mask the product increase the risk of accidental unblinding unacceptably.
 - The effect size of the primary endpoint of transfusion independence for 8 weeks (TI-8) in trial MDS-001 was small with a TI-8 being obtained in only about 38% of subjects with a differential response compared to placebo of about 25%, i.e. only about one quarter of the subjects exposed to luspatercept had any apparent benefit, assuming that fulfillment of the primary objective represents a benefit to the patient.
 - The duration of response for patients on the luspatercept arm of MDS-001 was short, with about half of those who achieved TI-8 losing response before 16 weeks. The significance of a TI-8 in the context of lower risk MDS, a condition with a life expectancy measurable in years, is not clear.
 - Patient reported outcome (PRO) data showed no improvement in quality of life for patients who received luspatercept or who responded to luspatercept. Thus, the benefit of decreased transfusion requirement was not correlated with any improvement in quality of life for patients.

To address these issues, submit the results of a trial of luspatercept therapy designed to ensure adequate blinding while testing for a treatment effect that provides a demonstrable benefit to the patient.

2. The risks associated with use of luspatercept therapy as evidenced from the data submitted from the clinical development program are not outweighed by the benefit of luspatercept therapy. Specifically, the following adverse events must be addressed and

strategies to mitigate the risk implemented:

- Fatigue is a major and persistent adverse event seen in both MDS-001 and the phase 2 trial A536-03.
- Hepatotoxicity was observed in trial MDS-001 and A536-03. A risk mitigation strategy to reduce the risk of severe or fatal hepatotoxicity is required.
- Renal toxicity was observed in both non-clinical findings and in both clinical trials. The non-clinical results showed a risk of membranoproliferative glomerulonephritis (MPGN) at clinically relevant doses. The risk is incompletely characterized due to lack of 24-hour urine collection for protein and creatinine and renal biopsies for patients with findings consistent with MPGN. A more complete characterization of the risk of renal toxicity including MPGN is needed.
- A numerically higher rate of progression to higher risk MDS and transformation to AML was consistently observed in the luspatercept arm of MDS-001 compared to placebo and in the phase 2 trial compared to either arm of MDS-001. The risk is incompletely assessed due to lack of pre-planned assessment of IPSS-R score during the study, which may lead to failure to identify progression, and due to lack of long term follow up. Given that luspatercept is intended as a supportive care drug, not a treatment for the underlying condition, this must be addressed prior to approval.
- A numerically higher rate of second primary malignancy (SPM) was observed in the luspatercept arm of MDS-001 and in the phase 2 trial. The risk of SPM must be fully characterized prior to approval.
- Although no correlation between luspatercept dose and malignancy was observed, an increased risk was observed with longer total lifetime dose of luspatercept. The risk of malignancy (progression or SPM) by total lifetime exposure must be characterized.

1.3. Benefit-Risk Assessment

The primary efficacy trial, MDS-001, technically met the primary objective, demonstrating increased rate of transfusion independence for 8 weeks. However, there is substantial concern that the trial may have been inadvertently partially or completely unblinded and that the reduction in transfusion may be at least partially driven by an artificially low threshold for transfusion and unconscious bias due to accidental unblinding. In addition, the effect size and duration of response were small, even assuming no issues with blinding or trial design. The decrease in transfusion burden was accompanied by an increase in quality of life issues, including reduced global quality of life, increased dyspnea, and increased fatigue. Finally, subgroup analysis demonstrated that the effect was indistinguishable from placebo for

Clinical Review
Elizabeth Pulte
BLA 761136 Original 2
REBOLZYL (luspatercept-aamt)

numerous populations, including people with high transfusion burden, patients with high baseline erythropoietin, and patients with low platelets.

Luspatercept use was associated with substantial risks, including an increased risk of fatigue, dyspnea, dizziness, syncope/presyncope, renal insufficiency, hepatotoxicity, infection, diarrhea, and malignancy. These risks, particularly the risks of renal insufficiency and malignancy, were inadequately monitored during the trial and therefore are incompletely characterized. Deaths in the first 8 cycles were more common in patients treated with luspatercept, with frequent proximate causes or contributors to death being renal failure and infection.

Overall, the benefit-risk assessment for luspatercept in the setting of lower risk MDS is negative.

Benefit-Risk Integrated Assessment

Use of luspatercept was associated with a higher rate of 8-week transfusion independence (TI-8) in patients with anemia associated with lower risk MDS. The effect was robust, with an identifiable, albeit smaller, effect still observed at 12 and 16 weeks. However, there were several concerns about the significance of this result. First, the effect was limited to patients with a baseline transfusion burden of ≤ 6 units per 8 weeks, with no effect seen in patients with higher baseline transfusion requirements. Second, patients with a low transfusion burden (< 4 units/8 weeks) had a high probability of achieving TI-8 in the placebo arm as well, suggesting that some of the responses seen were due to either variation in the underlying disease or issues with the trial design. Third, there were concerns about the trial design and the possibility of accidental unblinding due to the specification that the placebo be prepared on site and no requirement that the syringe be masked. Fourth, subgroup analysis demonstrated that, in addition to the issues relating to baseline transfusion burden mentioned above, patients with lower platelet counts or higher erythropoietin did not have an apparent benefit from therapy. Fifth, patient reported outcomes (PRO) and adverse event reporting suggested that the increase in TI-8 was accompanied by a decrease in global health and increase in the key symptoms of fatigue and dyspnea. Sixth, no evidence of secondary benefit, i.e. decrease in hospitalization or emergency department visits, was demonstrated. Finally, the response rate relative to placebo and duration of response are considerably less than those observed for approved agents. The clinical benefit of a transfusion free period of 8 weeks for a condition with a life expectancy measurable in years is not clear.

A number of significant adverse events were observed with use of luspatercept. Fatigue and dyspnea were common adverse events, which correlated well with the finding of higher incidence of worsening of these events on the PRO reports. Fatigue occurred throughout the treatment period and about half of events documented were not resolved at the time of data cut off. Thus, the patients receiving luspatercept experienced more of the types of adverse events that transfusion is expected to alleviate, negating any advantage that the small increase in hemoglobin may have given them. Hepatotoxicity, including at least one Hy's law case, was observed. Renal toxicity, including fatal renal failure and persistent renal impairment, was observed. An increase in viral infections and infections with no pathogen specified was observed with use of luspatercept along with an increase in the use of systemic antibiotics. A numeric increase in the risk of progression and second primary malignancy was observed, although the significance of this finding is unclear since it is confounded by lack of formal long-term assessment of MDS progression and an imbalance in the rate of mortality due to causes other than MDS.

Overall, the benefits of use of luspatercept are minor. Although the primary endpoint of the trial was met, issues with blinding and unorthodox definition of baseline hemoglobin call the result into question. The lack of correlation with any evidence of better health or quality of life for patients makes the reduction in transfusion rate of dubious importance at best. In addition, the response rates and duration of response were

both short, even putting the best possible interpretation on the data and giving the product the benefit of every possible doubt. Conversely, the risks are real and significant, including a possible risk of increased progression, risk of organ toxicity, and increase in the symptoms that transfusion is meant to alleviate. In summary, the use of luspatercept was associated with transient benefit and significant risk, making the benefit/risk assessment negative.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• MDS is a chronic, incurable condition with no curative treatment options except HSCT • Lower risk MDS has a long life expectancy and treatment is typically aimed at reducing symptom burden • Transfusion dependence 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	• Hypomethylating agents (HMA) have been demonstrated to produce responses, reduce transfusion burden, and improve quality of life in patients with MDS. Longer survival has been seen in some, but not all, studies. Transfusion independence rates are generally higher for HMA and with longer duration than that reported for luspatercept. • There are no approved treatment options for the treatment of transfusion dependent anemia in MDS in the US, except for lenalidomide in the setting of 5q- MDS. However, erythropoietin stimulating agents are approved in the EU and are used off label routinely in the US. The response rate to ESA is higher and duration longer than that reported for luspatercept.	The current treatment options for treating anemia in the context of MDS are inadequate and further options are needed. However, any new treatments must be demonstrated to be effective and safe. Approval of a drug that does not provide clinical benefit and adequate safety does not serve the patients' or public's best interest.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• A minority of patients experienced transient transfusion independence and marginal increase in hemoglobin, but they did not report improvement and often reported worsening in symptoms that would be expected to correlate with improved hemoglobin. • The duration of response was short for most patients. • No decrease in health care utilization was observed, suggesting that any decrease in health care resources utilized during transfusion was negated by the increased need for treatment of adverse events.	Due to the lack of correlation with any clinically meaningful outcome, the increase in transfusion independence cannot be considered to be a meaningful clinical benefit.
Risk and Risk Management	• Significant hepatotoxicity was observed, including at least one Hy's law case. • Renal toxicity was observed, including fatal cases. The full extent of the toxicity cannot be characterized due to the Sponsor's failure to perform the tests necessary to make definitive diagnoses. • Fatigue was extremely common in the luspatercept arm and observed throughout the study. • Major increases in incidence of other adverse events including dyspnea, dizziness, syncope/presyncope, diarrhea, hypertension, confusion, and viral infection were observed. • The rates of MDS progression and second primary malignancy were numerically higher in patients treated with luspatercept compared to placebo.	The overall risk profile of luspatercept is significant. Concerning renal and hepatic toxicities were observed. Fatigue, including severe and long lasting fatigue was observed throughout the study. There appears to be an increase in the risk of both progression to higher risk disease and second primary malignancies. Given that luspatercept is intended as a supportive care drug, not a treatment for the underlying illness, these findings are extremely concerning and strongly argue against approval.

1.4. Patient Experience Data

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

☐	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
x	Clinical outcome assessment (COA) data, such as	6.1.2 Study results
	x Patient reported outcome (PRO)	6.1.2
	☐ Observer reported outcome (ObsRO)	
	☐ Clinician reported outcome (ClinRO)	
	☐ Performance outcome (PerfO)	
	☐ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐ Patient-focused drug development or other stakeholder meeting summary reports	
	☐ Observational survey studies designed to capture patient experience data	
	☐ Natural history studies	
	☐ Patient preference studies (e.g., submitted studies or scientific publications)	
	☐ Other: (Please specify)	
	☐ Patient experience data that were not submitted in the application, but were considered in this review:	
	☐ Input informed from participation in meetings with patient stakeholders	
	☐ Patient-focused drug development or other stakeholder meeting summary reports	
	☐ Observational survey studies designed to capture patient experience data	
	☐ Other: (Please specify)	
	☐ Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Myelodysplastic syndrome (MDS) is the general name given to a group of hematologic conditions characterized by anemia with or without other cytopenias, dysplasia, and ineffective hematopoiesis. There is an increased risk of progression to acute myeloid leukemia (AML) for MDS, although the risk varies by stage and clinical features of the disease. The international prognostic scoring system (IPSS) and revised international prognostic scoring system (IPSS-R) are widely used to stratify the risk of morbidity, mortality, and progression to AML for patients with MDS based on bone marrow blast percentage, cytogenetic prognostic group, and degree of cytopenias. Patients with IPSS low and intermediate-1 disease have median survival rates of 5.7 and 3.5 years, respectively. When the IPSS-R system is used, patients with very low risk, low risk, and intermediate risk disease have median survival times of 8.8, 5.3, and 3.0 years, respectively, with a time to evolution to AML in 25% of patients of 10.8 and 3.2 years, respectively, for low and intermediate risk disease (rate could not be determined for very low risk disease¹.)

An older method of describing the variation within MDS is the FAB classification, which classifies MDS morphologically into refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEBT) and chronic myelomonocytic leukemia (CMML). Patients with RARS often have a relatively good prognosis, although progression to a more aggressive form of the disease or more severe cytopenias is expected. Recently, splicesomal mutations in the gene SF3B1 have been associated with RARS. RARS is classically considered to have a relatively good prognosis. However, a recent meta-analysis examining survival in patients with MDS with and without the SF3B1 mutation found similar overall survival and lower leukemia-free survival in patients with SF3B1 mutations, although variation was observed depending on region with longer OS seen for patients with SF3B1 mutations in Asia as compared to Europe or North America².

2.2. Analysis of Current Treatment Options

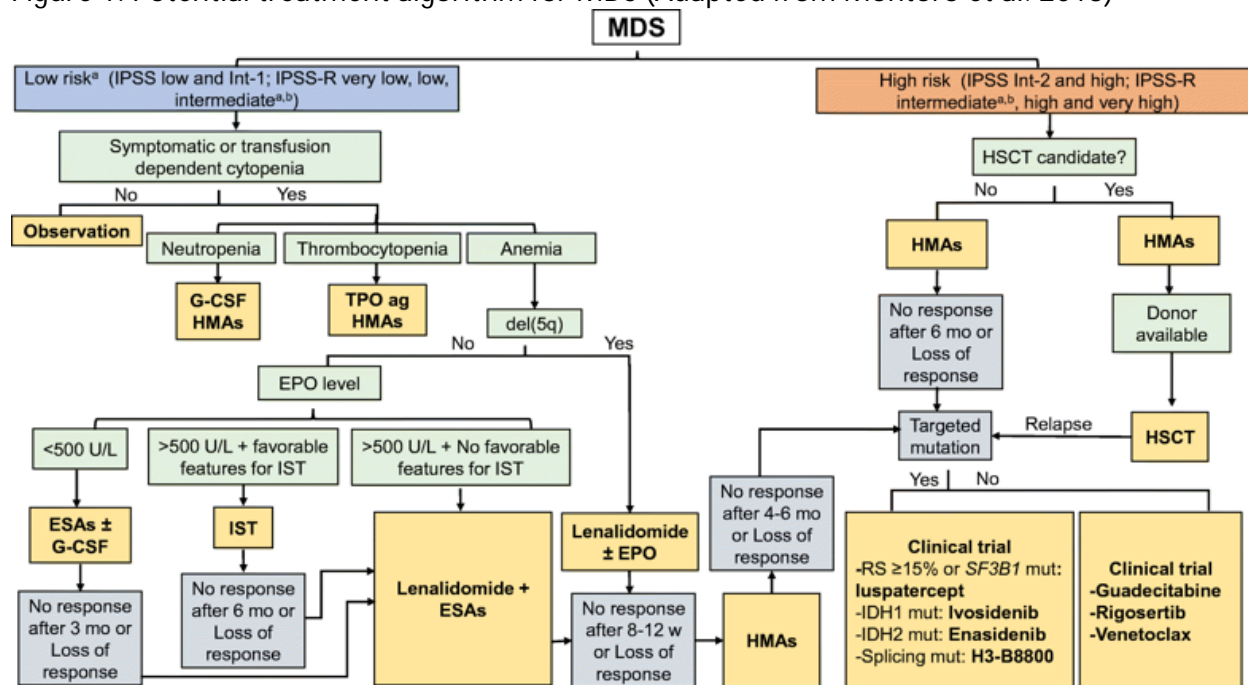
Currently, treatment options for patients with lower risk myelodysplastic syndrome are limited. Lower risk MDS is typically defined to include IPSS-R very low, low, and intermediate risk disease, although the inclusion of intermediate risk disease in this category is controversial and some intermediate risk disease may be treated as higher risk. In the older IPSS system, low and intermediate-1 risk disease were generally considered to be lower risk disease.

Since survival is generally high and risk of transformation to AML low in this population, treatment often focuses on amelioration of symptoms. Anemia is a defining characteristic of

MDS and anemia and anemia related symptoms (i.e. fatigue, dyspnea, increased risk of comorbid issues such as cardiac disease) are frequently the initial focus of treatment in lower risk disease.

Currently, recommended treatment for lower risk MDS varies depending on disease and patient characteristics. The initial recommendation varies depending on disease characteristics (i.e. presence of 5q-) and patient characteristics (i.e. erythropoietin level). The figure below shows one treatment algorithm for lower risk MDS based on patient and disease characteristics³. Note that a number of the recommended treatment options represent off label use of medications approved for other indications. This review will focus on treatment of anemia in lower risk MDS since this is the indication for luspatercept being sought by the Sponsor.

Figure 1: Potential treatment algorithm for MDS (Adapted from Montoro et al. 2018)



At this time, there are four medications approved for the treatment of MDS: the hypomethylating agents (HMAs), azacitidine and decitabine, lenalidomide, and imatinib. The evidence leading to their approval will be discussed below. Off label use of erythropoiesis stimulating agents (ESAs), other hematopoietic stimulating agents, immunosuppressive therapy, and approved agents in non-approved situations and the evidence for use of these agents in MDS will be discussed as well to provide context. Finally, the benefits and risks of

transfusion, including the effect of transfusion on patient reported quality of life, will be briefly discussed. Unless otherwise stated, red blood cell transfusion independence (RBC-TI) will be defined as no RBC transfusions for at least 8 consecutive weeks. However, it should be noted that the value of an 8 week transfusion free period in the context of lower risk MDS has been questioned by experts in the field⁴.

Approved agents

The table below describes currently available treatment options for MDS. The use of each agent and the limitations of use will be discussed below.

Table 1: Currently available treatments for MDS

Lenalidomide	Transfusion-dependent low or intermediate-1 risk MDS associated with deletion 5q with or without other cytogenetic abnormalities
Azacitidine	MDS subtypes RA, RARS, RAEB, RAEBT, CMML
Decitabine	MDS (any subtype) in the intermediate-1, intermediate-2, or high risk IPSS groups
Imatinib	MDS/MPD associated with PDGFR gene rearrangements

Hypomethylating agents

Two HMAs, azacitidine and decitabine, are approved for use in MDS. Azacitidine is approved for use in MDS regardless of IPSS score⁵. Decitabine is approved for use in untreated and previously treated MDS with IPSS scores of intermediate-1 or higher⁶. Both agents have been used in clinical trials and practice for lower risk disease, although this use is off label for decitabine.

The approval of azacitidine was based on a higher overall response rate and overall survival compared to conventional care (including supportive care only). RBC-TI was evaluated in one trial considered in the approval, although it should be noted that higher risk patients made up 87% of the trial participants. Of the patients who were RBC transfusion dependent at baseline, 45% achieved RBC-TI versus 11.4% on conventional care and the median duration of RBC-TI was 13.0 months (i.e. approximately 52 weeks).

A meta-analysis of azacitidine in lower-risk MDS⁷ which included primarily patients who were ESA refractory and non-del5q- showed an overall RBC-TI rate of 54% for those patients for whom data were available. However, data were missing for a large number of patients and there was considerable heterogeneity among the trials. Using a random-effects model, the pooled estimate of RBC-TI was 38.9% overall and 40.5% for the ESA refractory subgroup. Higher

probability of response was associated with planned administration of at least 6 cycles of azacitidine in a multivariate analysis. Information on duration of RBC-TI was not provided. Of note, this meta-analysis was published in 2018 and submitted initially for publication in 2017 and thus does not include more recently published trials. More recent trials include a single arm study of a five-day regimen of azacitidine which demonstrated RBC-TI in 48% of subjects (10/21 with initial RBC transfusion dependence)⁸.

Relatively little information is available on the use of decitabine in patients with lower risk MDS. The approval for decitabine in MDS is limited to patients with intermediate-1 or higher disease and was based on overall response rate. One phase 2 study comparing low dose azacitidine to low dose decitabine (dosing for 3 days every 4 weeks) showed that 28% of patients treated with decitabine and 18% of those treated with azacitidine achieved RBC-TI⁹. Information on duration of RBC-TI was not provided.

A population level evaluation of RBC-TI in patients with lower risk MDS receiving hypomethylating agents demonstrated that approximately 33% of transfusion dependent patients achieved RBC-TI after treatment with HMAs and that higher transfusion burden prior to starting treatment (≥ 3 units/8 weeks) was associated with lower probability of achieving RBC-TI¹⁰. Of note, this study was carried out using the SEER-Medicare database and thus was largely limited to patients age 65 and older.

Lenalidomide

Lenalidomide is approved for use in transfusion dependent patients with MDS associated with 5q- with or without other cytogenetic abnormalities. The approval was based on a single arm study enrolling patients who were RBC transfusion dependent to lenalidomide at 10 mg daily or 21/28 days. RBC-TI was seen in 67% of patients with a median duration of 44 weeks¹¹. Quality of life (QoL) or patient reported outcomes (PRO) were not included in the approval. However, a study examining QoL in patients receiving lenalidomide for MDS¹² with 5q- found an increase in physical and social domains of health related QoL measures among those patients who achieved an increase in hemoglobin of at least 2 gm/dl. Fatigue was decreased significantly only at one timepoint examined (24 weeks) and was not significantly changed at other timepoints. There were issues with missing data for later timepoints which may confound the interpretation. Overall survival was similar between the two arms, but there were few events in either arm. Use of lenalidomide in non-5q- MDS will be discussed in the section on non-approved agents used in practice, below.

Imatinib

Imatinib was approved for use in myelodysplastic/myeloproliferative diseases MDS/MPD associated with platelet-derived growth factor (PDGFR) gene re-arrangements as determined with an FDA-approved test. The approval was based on a phase 2 open-label study evaluating the efficacy of imatinib in patients with life-threatening diseases with Abl, Kit, or PDGFR protein kinases¹³. The study included 7 subjects with MDS/MPD. An additional 24 patients from published cases reports were considered in the approval. Of these patients, 16 had PDGFR gene rearrangements, all of whom responded hematologically and 12 out of 14 evaluable responded cytogenetically. Transfusion information was not explicitly included in the approval.

Off-label use

ESA

ESAs are frequently used off label in patients with lower risk MDS who have symptomatic anemia or transfusion requirements. Favorable prognostic factors for response to ESAs are low transfusion requirement, baseline serum erythropoietin level of <500, and lower IPSS score¹⁴⁻¹⁶. A review of the use of ESAs in lower risk MDS concludes that there is generally evidence of clinical benefit in terms of increase in hemoglobin and reduction in transfusion requirement in patients treated with ESAs¹⁷. One randomized study of darbepoetin versus placebo demonstrated a decreased rate of transfusion among patients receiving darbepoetin, although a RBC-TI rate was not provided¹⁸.

Quality of life measures have been reported in a few studies. In the study mentioned above, there was a non-significant trend towards improved QoL in patients receiving darbepoetin. Another study examining epoetin- α versus placebo in MDS reported a "different" QoL score in patients who responded to epoetin- α versus placebo at 24 weeks¹⁹, although no further details (including the sign of the difference) were reported. Finally, a better QoL was reported in patients who had a hematologic response to ESAs in a third, non-controlled study, indicating that in general a hematologic response was associated with improvement in QoL²⁰.

Lenalidomide

Lenalidomide is approved for use in MDS with 5q deletion, but also sometimes used off label for non-5q- MDS. A phase 3 trial of lenalidomide versus placebo in patients with ESA refractory transfusion dependent non-5q-²¹ found a RBC-TI rate of 26.9% versus 2.5% in placebo with a median duration of response of 30.9 weeks. Overall, no significant difference was observed in

QoL scores between placebo and lenalidomide, although there was an improvement in QoL scores for patients who achieved RBC-TI.

Immunosuppression

A variety of immunosuppressive agents are used to treat selected patients with lower risk MDS based on evidence of T-cell hyperactivity in some patients with MDS. A multi-center retrospective study of patients treated with immunosuppressive therapy found a RBC-TI rate of 30% overall²². It should be noted that RBC-TI was defined as 6 weeks with no RBC transfusions and hemoglobin of at least 8 gm/dl in this study. However, the median duration of TI was 19.9 months. Interestingly, there was a trend towards lower probability of achieving RBC-TI in patients with SF3B1 mutations, although the difference was not statistically significant.

Transfusion

Transfusion is used to improve hemoglobin in patients with MDS and symptomatic anemia. It is associated with several well described risks, including hypersensitivity, infection, and iron overload. In addition, transfusion is time consuming and inconvenient. However, a recent study demonstrated that RBC transfusion was associated with an increase in quality of life in patients with chronic anemia²³, indicating that the risks and inconveniences do not outweigh the clinical benefit to appropriate patients.

Analysis

The number of approved treatment options for lower risk MDS is limited. Use of off label treatment provides further potential treatment options, but the efficacy and safety of treatment with non-approved agents has not been established.

The efficacy of various treatment options varies considerably depending on the situation and underlying disease characteristics. Lenalidomide has demonstrated an ability to produce durable RBC-TI in patients with del 5q MDS with at least some evidence of improved QoL in patients who respond to treatment. Azacitidine has a demonstrated rate of RBC-TI of roughly 35-45% with duration of response generally >10 months.

RBC-TI rates for therapies used off label are generally lower and with more variability in their quality, with most off-label therapies having lower RBC-TI rates or shorter durations of RBC-TI.

Of note, although information on QoL is incomplete and only minimally available for some agents, improved QoL is generally associated with improved hemoglobin in both approved and

off label treatments for MDS and other conditions associated with chronic anemia. In addition, RBC transfusion has been demonstrated to improve QoL in patients with chronic anemia²³.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Luspatercept is currently marketed in the US for treatment of adults with β -thalassemia who require regular red blood cell transfusions. It is not currently marketed in the US and has never been previously marketed in the US for treatment of anemia in MDS. The presubmission regulatory history is summarized below.

3.2. Summary of Presubmission/Submission Regulatory Activity

Note: the summary below is limited to events relevant to the MDS indication. See review of the application for use of luspatercept in β -thalassemia for details of regulatory history regarding this indication.

- 16 Jun 2010: A type B pre-IND meeting was held with the initial Sponsor (Acceleron Pharma)
- 14 Jul 2011 IND 112562 became active under Acceleron
- 7 Nov 2011 Full clinical hold placed on IND 112562 due to CMC issues
- 15 Feb 2012 Full hold removed
- 29 Jun 2012 and 26 Sep 2012 Fast track requests denied due to lack of adequate evidence of clinical activity in the treatment of the conditions for which the designation was requested (MDS and β -thalassemia)
- 18 Mar 2013 Orphan designation for MDS granted
- 3 Apr 2015 IND transferred to Celgene
- 29 Jul 2015 A type B pre-phase 3 meeting held to discuss the clinical development program with respect to use of luspatercept in treatment of anemia due to very low to intermediate risk MDS with ring sideroblasts
- 03 Dec 2015 fast track status for treatment of anemia in persons with IPSS-R lower risk (very low, low, intermediate risk) myelodysplastic syndrome granted
- 05 Sep 2018 A type B pre-BLA CMC meeting held
- 04 Oct 2018 A type B pre-BLA meeting was held to discuss the luspatercept clinical developmental programs for MDS and β -thalassemia to support a BLA submission

3.3. Foreign Regulatory Actions and Marketing History

Luspatercept has been submitted to the EMA for approval for use in β -thalassemia and MDS.

At the time of writing, no decision had been announced.

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

4.1. Office of Scientific Investigations (OSI)

No significant issues were identified by the OSI.

4.2. Product Quality

No significant issues were identified by product quality.

4.3. Clinical Microbiology

NA

4.4. Nonclinical Pharmacology/Toxicology

Toxicology studies in rats and monkeys demonstrated renal adverse events at clinically meaningful doses. Specifically, membranoproliferative glomerulonephritis (MPGN) was observed in both rats and cynomolgus monkeys at exposures of ≥ 0.4 and ≥ 0.6 times the maximal recommended clinical dose of luspatercept, respectively. In addition, in a rat renal injury model, exacerbation of renal toxicity (urinary kidney injury biomarkers and glomerular and tubulointerstitial findings) were observed at doses of ≥ 0.05 times the maximum recommended human dose. Thus, renal injury is observed at doses under, sometimes far under, those to which patients would be expected to be exposed. Despite these data, no 24 hour urine collection, biopsies, or other specific renal monitoring beyond routine chemistries and urinalysis was planned or implemented.

There were no dedicated carcinogenicity studies performed. However, three hematologic malignancies were observed in a juvenile rat toxicology study, including one granulocytic leukemia, one lymphocytic leukemia, and one malignant lymphoma, and one premature death due to disseminated pleomorphic lymphoma was observed in a toxicology study in adult rats. It should be noted that not all rats in the juvenile toxicology study mentioned above underwent necropsy, so there may have been additional tumors that were missed. A mouse Lewis lung carcinoma model showed a trend towards increased tumor size with administration of luspatercept, but the differences were not statistically significant. Follow up studies with larger numbers of animals to clarify the issue were not performed.

Clinical Review
Elizabeth Pulte
BLA 761136 Original 2
REBOLZYL (luspatercept-aamt)

Reproductive studies demonstrated adverse effects on reproduction in rabbits and rats, including reduced average number of implantations and viable embryos, decreased number of live births, reduced fetal weight, increase in skeletal variations and malformations, and reduced maternal food consumption during gestation in rabbits.

Reviewer's comment: Luspatercept is purported to work via binding to TGF- β ligands, with high binding affinity to growth differentiation factor 11 (GDF11), GDF8, bone morphogenic protein 6 (BMP6), and activin B. The action is claimed to be independent of erythropoietin. A recent publication has cast doubt on the role of GDF11 in hematopoiesis²⁴, leading to the conclusion that the true mechanism of action, if any, is unknown.

The non-clinical findings are concerning for risk of renal toxicity, in particular glomerular abnormalities, malignancy, and effects on the developing embryo or fetus. No dedicated carcinogenicity studies were conducted, but hematologic malignancies were observed incidentally in toxicology studies.

4.5. Clinical Pharmacology

The clinical pharmacology review concluded that the proposed luspatercept starting dose and dose titration scheme is supported by PK, efficacy, and safety findings overall. This conclusion was based on the following findings:

- In the phase 2 study, higher response rates were observed at doses ≥ 0.8 mg/kg
- Doses up to 1.75 mg/kg were tolerated in patients with MDS with an MTD not reached on the phase 2 study at doses up to 1.75 mg/kg.

However, the review also notes that an apparent positive exposure-dependent trend observed for RBC-T18 during the first 15 weeks for patients treated with disease of at least 1 mg/kg was not statistically significant. The reviewer notes that the exposure-efficacy analysis was confounded by the dose titration design in which titration was based on individual subjects' responses.

The review noted that steady state was reached after three doses given every three weeks.

The majority of patients (59%) had dose increases up to 1.75 mg/kg, with more non-responders than responders requiring dose increase to the maximum dose.

The clinical pharmacology report noted that anti-drug antibodies (ADA) were reported in 23/260 patients tested (8.9%) including neutralizing antibodies being reported in 10/260 patients (3.8%). Serum concentration tended to decrease in the presence of neutralizing antibodies but there was no discernible effect on efficacy or safety reported.

Clinical Review
Elizabeth Pulte
BLA 761136 Original 2
REBOLZYL (luspatercept-aamt)

An analysis of the risk of MDS progression/transformation to AML and SPM events versus dose was performed. No clear dose/risk relationship was observed, but patients who experienced malignancy were noted to have had a higher overall exposure to luspatercept. However, it should be noted that the range was broad and the significance of the difference in median overall exposure is not completely characterized.

Reviewer's notes: The clinical pharmacology review in general supports the Sponsor's proposed dosing plan. However, there are several unresolved issues associated with the clinical pharmacologic findings including:

- *The dose-response findings for doses of ≥ 0.8 mg/kg are confounded by the intra-patient dose escalation used.*
- *The Sponsor proposes a dose increase if a response is not obtained after two doses in a drug that does not reach steady state until after three doses. This may result in unnecessary dose increases.*
- *The effect of ADA is incompletely characterized. Given the small number of patients with ADA and the low probability of achieving a response, the findings are near anecdotal level.*

4.6. Devices and Companion Diagnostic Issues

NA-no companion diagnostic device planned

4.7. Consumer Study Reviews

NA

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 2: Clinical studies used in the evaluation process

Trial Identity	Trial Design	Regimen	Study Endpoints	No. of patients enrolled (treated)	Study Population
Controlled Studies to Support Efficacy and Safety					
ACE-536-MDS-001	Randomized phase 3	1 mg/kg	RBC-TI ≥8 weeks	229 (229: IP: 153, placebo 76)	Low, very low, intermediate MDS with RS
A536-03	Phase 2, single arm, dose escalation	0.125 mg/kg-1.75 mg/kg	↑ Hgb ≥1.5 g/dl ↓ RBCTR	107 (107)*	MDS
Studies to Support Safety					
A536-02	Ascending dose, placebo	0.0625 mg/kg-0.25 mg/kg x2	Safety	32 (IP: 24, placebo: 8)	Healthy post-menopausal
A536-05	Open-label, extension	0.5-1.75 mg/kg	Evaluate long term safety	70 (70)*	MDS
Studies supporting other indications (Thalassemia)					
ACE-536-β-thal-001	Phase 3, randomized	1.0 mg/kg -1.25 mg/kg q3w	≥33% ↓ RBCTR	336 (332)	β-thalassemia, TD
A536-04	Phase 2 ascending dose	0.2-1.25 mg/kg	↑ Hgb ≥1.5 g/dl ≥20% ↓ RBCTR	64 (64)	β-thalassemia
A536-06	Open label, extension	0.8-1.25 mg/kg	Evaluate LT safety	51 (51)	β-thalassemia

*An additional 9 subjects were reported in the 3 month safety update. No efficacy information is available for these patients but safety data are available and included in the safety analysis. Of these patients, five enrolled in the extension trial.

Abbreviations: Hgb: hemoglobin; IP: investigational product; RBCTR: red blood cell transfusion requirement; RS: ring sideroblasts; TD: transfusion dependent

5.2. Review Strategy

The primary efficacy analysis was based on trial MDS-001. Issues considered in the review included the rate of transfusion independence at 8, 12, and 16 weeks, duration of response, hematologic improvement, and PRO data submitted in support of the treatment effect. The phase 2 study A536-03 provided supporting evidence to examine whether effects could be observed across more than one trial.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. ACE-536-MDS-001 A phase 3, double-blind, randomized study to compare the efficacy and safety of luspatercept (ACE-536) versus placebo for the treatment of anemia due to IPSS-R very low, low, or intermediate risk myelodysplastic syndrome in subjects with ring sideroblasts who require red blood cell transfusions

6.1.1. Study Design

Overview and Objective

The primary objective for trial ACE-536-MDS-001, also called the MEDALIST trial, ClinicalTrials.gov identified NCT02631070, hereafter abbreviated MDS-001, was to evaluate RBC transfusion independence of luspatercept compared to placebo for the treatment of anemia due to IPSS-R very low, low, or intermediate risk MDS in patients with ring sideroblasts who require RBC transfusions.

Secondary objectives included:

- To assess the safety and tolerability of luspatercept compared to placebo
- To evaluate the effect of luspatercept on reduction in RBC transfusions, increase in hemoglobin, duration of RBC-TI, improvement in HRQoL, increase in neutrophils, increase in platelets, decrease in serum ferritin, decrease in ICT use, and time to RBC-TI compared to placebo.
- To evaluate population PK and exposure-response relationships for luspatercept in MDS subjects

Trial Design

The trial was a Phase 3, double-blind, randomized, placebo-controlled, multicenter study to

determine the efficacy and safety of luspatercept (ACE-536) versus placebo for the treatment of anemia due to IPSS-R very low, low, or intermediate risk MDS in subjects with ring sideroblasts who require RBC transfusions.

Eligible subjects were randomized at a 2:1 ratio to either:

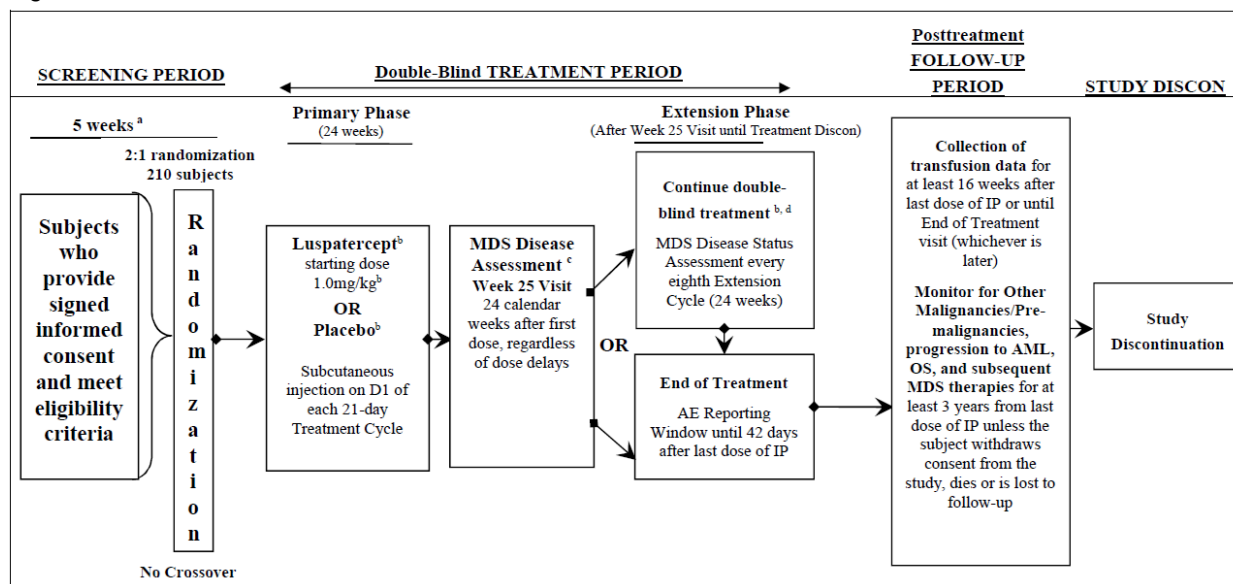
- Experimental Arm - Luspatercept (ACE-536): Starting dose of 1.0 mg/kg subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle) OR
- Control Arm: Placebo (volume equivalent to experimental arm) subcutaneous injection every 3 weeks (administered on Day 1 of each 21-day treatment cycle).

After randomization, no crossover between the treatment arms was permitted at any point during the study. Best supportive care could be used in combination with study treatment in both arms when clinically indicated per investigator discretion.

Randomization was stratified by:

- RBC Transfusion burden at baseline (mean of the two consecutive 8-week periods immediately prior to randomization):
 - ≥ 6 RBC units/8 weeks vs.
 - < 6 RBC units/8 weeks
- IPSS-R at baseline:
 - Very low, low vs.
 - Intermediate.

Figure 2: Schema for the trial ACE-536-MDS-001



AE = adverse event; AML = acute myeloid leukemia; D1 = Day 1; Discon = discontinuation; Hgb = hemoglobin; IP = investigational

Clinical Review
Elizabeth Pulte
BLA 761136 Original 2
REBOLZYL (luspatercept-aamt)

product; IWG = International Working Group; MDS = myelodysplastic syndromes; OS = overall survival.

a Historical documentation of RBC transfusion dependence should have been available (RBC units transfused and pretransfusion Hgb values) for at least 16 weeks prior to randomization.

b Dose may have been titrated up to a maximum of 1.75 mg/kg (Section 9.4.5.1.1).

c After completion of the Week 25 Visit MDS disease assessment by the investigator, subjects who experienced clinical benefit and had not experienced disease progression per IWG-MDS criteria for altering natural history of MDS (Cheson, 2006; Appendix E of the study protocol in Appendix 16.1.1), may have continued double-blind treatment with IP beyond the Week 25 Visit in the Extension Phase of the Treatment Period until they met the protocol discontinuation criteria (Section 9.3.3).

d The MDS disease assessment was to be repeated by the investigator at Extension Cycle 8, Day 1 and Day 1 of every eighth Extension Cycle thereafter (ie, Extension Cycle 8, 16, 24+, etc, or every 24 weeks in the event of dose delays) until the subject was discontinued from treatment. For subjects to continue double-blind treatment in the Extension Phase of the Treatment Period, each MDS disease assessment (criteria detailed in Section 9.5.1.1.1) had to confirm continued clinical benefit and absence of disease progression per IWG-MDS criteria for altering natural history of MDS (Cheson, 2006; Appendix E of the study protocol in Appendix 16.1.1).

Reviewer's note: The trial is described as a double-blind trial. However, the Sponsor did not provide the placebo, but rather placebo was supplied by the individual site. This opens the possibility of unmasking due to small differences in the appearance of the syringe or stopper, printing of the label, or even the time required for the preparation of the product.

In addition, the investigational product is described as "clear to slightly opalescent" and thus the active product could be differentiated from the placebo visually. Masking procedures are not defined, the only instruction with respect to syringe preparation was a statement that "The individual site's designated individuals will prepare the placebo syringe to match the active syringe." Thus, the masking may vary from site to site and whether it is sufficient to prevent accidental unblinding is largely unknown.

Finally, luspatercept is prepared (b) (4) Prior studies have suggested that citrate causes more stinging at the injection site than saline²⁵, leading to a further risk of accidental unblinding. Taken together, this information makes it highly likely to virtually certain that unblinding occurred at one or more sites.

It is important to note that there is no positive evidence of intentional unblinding. No evidence of misconduct was found on site inspection.

The study was divided into the Screening Period, a double-blind Treatment Period (Primary Phase and Extension Phase) and a Post-treatment Follow-up Period.

In the Primary Phase of the Treatment Period (Weeks 1-24), subjects received investigational product (IP) through at least the first 24 calendar weeks unless the subject experienced unacceptable toxicities, withdrew consent, or met any other discontinuation criteria.

The Week 25 Visit was the MDS Disease Assessment, which was completed after the end of 24 calendar weeks after the date of first dose, regardless of dose delays. Based on the outcome of the Week 25 Visit MDS Disease Assessment, subjects were either discontinued from treatment with IP and entered the Posttreatment Follow-up Period or continued double-blind treatment with IP in the Extension Phase of the Treatment Period. In order for subjects to remain on

CDER Clinical Review Template

Version date: September 6, 2017 for all NDAs and BLAs

Clinical Review
Elizabeth Pulte
BLA 761136 Original 2
REBOLZYL (luspatercept-aamt)

double-blind treatment beyond the first 24 calendar weeks, the following criteria must have been confirmed upon the completion of the MDS Disease Assessment by the investigator at the Week 25 Visit:

- Evidence of clinical benefit (e.g., decrease in RBC transfusion requirement compared to baseline requirement or hemoglobin increase compared to baseline) AND
- Absence of disease progression per IWG criteria for altering natural history of MDS.

Subjects who met the criteria for remaining on double-blind treatment with IP in the Extension Phase were permitted to continue dosing on Day 1 of each 21-day treatment cycle until the subject experienced unacceptable toxicities, disease progression per IWG criteria, withdrew consent, or met any other discontinuation criteria. MDS Disease Assessment were repeated by the investigator at Extension Cycle 8, Day 1 and Day 1 of every eighth Extension cycle thereafter (i.e., Extension Cycle 8, 16, 24+, or every 24 weeks in the event of dose delays) until the subject is discontinued from IP.

In the posttreatment follow-up period, all subjects discontinued from protocol-prescribed therapy for any reason would be followed for adverse event (AE)/serious adverse event (SAE) reporting for a period of 42 days after the last dose of IP, as well as for SAEs made known to the Investigator at any time thereafter that are suspected of being related to IP. For subjects who did not complete the Primary Treatment Phase or participate in the Extension Phase or subjects who terminated the Extension Phase with less than 1-year of anti-drug antibody (ADA) monitoring, ADA and pharmacokinetic (PK) samples were collected at End of Treatment (EOT) and then every 12 weeks for up to 1 year from the first dose in the Primary Treatment Phase. Transfusion data collection continued up until 16 weeks from the date of last dose of IP or the EOT Visit (whichever is later).

Continuation of monitoring for progression to AML and other malignancies/pre-malignancies occurred in the Posttreatment Follow-up Period along with collection of information related to subsequent MDS therapies, and overall survival for at least 3 years from the date of last dose of IP unless the subject withdrew consent from the study, died, or was lost to follow-up.

The expected duration of the study was approximately 6 years with approximately 2 years of enrollment, approximately 1 additional year of blinded luspatercept or placebo treatment after the last subject is randomized, and at least an additional 3 years to complete the posttreatment follow-up period.

Transfusion was permitted during the study at the discretion of the investigator for symptoms of anemia or comorbidity. In addition, each subject had a "pre-transfusion hemoglobin threshold" at which transfusion would be required. This value was defined as the mean of all documented pre-transfusion hemoglobin values in the 16 weeks preceding the first dose of

luspatercept.

Reviewer's comments: The criteria for transfusion are somewhat subjective and the investigator's decision of whether a given symptom or clinical scenario justifies transfusion may be influenced by their perception of whether the patient is receiving the study drug versus placebo. In addition, there were no planned assessments for MDS progression or transformation after completion of treatment.

Key inclusion and exclusion criteria:

Key inclusion criteria

- Adult subjects with diagnosis of MDS who:
 - Meet the IPSS-R classification of very low-, low-, or intermediate-risk disease
 - Ring sideroblasts of $\geq 15\%$ of erythroid precursors in marrow or $\geq 5\%$ if SF3B1 mutation present
 - $< 5\%$ blasts in marrow
 - Peripheral WBC count $< 13\text{K}/\mu\text{L}$
- Refractory to, intolerant of, or ineligible for prior ESA treatment defined as any of the following:
 - Nonresponse or response no longer maintained on prior ESA containing regimen at erythropoietin dose of $\geq 40,000$ IU/week for at least 8 doses or darbepoetin- α ≥ 500 microg q3w at least 4 doses or equivalent
 - Documentation of discontinuation of prior ESA-containing regimen due to intolerance or AE
 - Low chance of response to ESA based on endogenous erythropoietin level of > 200 U/L
- RBC transfusion requirement of ≥ 2 units/8 weeks of packed RBCs confirmed for a minimum of 16 weeks immediately preceding randomization
- Hemoglobin levels within 7 days prior to administration of RBC transfusion of ≤ 10 g/dl for RBC transfusion to be counted towards meeting eligibility; RBC transfusions for elective surgery or when hemoglobin > 10 g/dl do not qualify towards eligibility requirement
- No consecutive 56-day period that was RBC transfusion free during the 16 weeks preceding randomization

Key exclusion criteria

- Prior therapy with disease modifying agents including immunomodulatory agents, HMA, or immunosuppressive therapy
- Prior treatment with luspatercept or sotatercept

Clinical Review
Elizabeth Pulte
BLA 761136 Original 2
REBOLZYL (luspatercept-aamt)

- Del(5q)
- Secondary MDS (i.e. MDS known to have arisen from chemical injury, chemotherapy, or radiotherapy)
- Known clinically significant anemia due to vitamin deficiency, hemolytic anemia, or GI bleeding
- Prior hematopoietic stem cell transplantation (HSCT)
- Uncontrolled hypertension
- Cytopenias defined as ANC <500/ μ L or platelets <50K/ μ L
- Inadequate organ function defined as any of the following:
 - GFR or creatinine clearance <40 ml/min
 - AST/ALT $\geq$ 3.0 x ULN
 - TB $\geq$ 2.0 x ULN unless attributed to ineffective erythropoiesis or Gilbert

Reviewer's comment: The inclusion and exclusion criteria limit enrollment of patients with cytopenias. Thus, the available safety and efficacy data are relevant only to a minority of patients with MDS (i.e. those with ringed sideroblasts and no more than moderate cytopenias.) Of note, no upper limit on platelet count was established, allowing patients with MDS/MPN-RS-T to enroll.

Study Endpoints

Primary endpoint:

- RBC-TI $\geq$ 8 weeks: Proportion of patients who were RBC transfusion free over any consecutive 56-day period in weeks 1-24

Secondary endpoints:

- RBC-TI $\geq$ 12 weeks: Proportion of patients who were RBC transfusion free over any consecutive 84-day period in weeks 1-24 or weeks 1-48
- RBC-TI $\geq$ 8 weeks: Proportion of patients who were RBC transfusion free over any consecutive 56-day period in weeks 1-48
- Reduction in RBC units transfused over 16 weeks: Mean change in total RBC units transfused over a fixed 16 week period, weeks 9-24 or 33-48
- mHI-E per IWG: Proportion of patients who achieved a modified erythroid hematologic improvement (mHI-E) over any consecutive 56-day period in weeks 1-24 or weeks 1-48
- Mean Hgb $\geq$ 1.0 g/dl: Proportion of subjects who achieved mHI-E over any consecutive 56-day period in weeks 1-24 or weeks 1-48
- Duration of RBC-TI: Maximum duration of RBC-TI for subjects who achieved RBC-TI of $\geq$ 8 weeks in weeks 1-24 and week 1 through EOT
- HRQoL: Change in EORTC QLQ-C30 score in weeks 1-48 or baseline through EOT

- HI-N per IWG: Proportion of subjects who achieved hematologic improvement for neutrophils (HI-N) over any consecutive 56-day period weeks 1-24 or weeks 1-48
- HI-P per IWG: Proportion of subjects who achieved hematologic improvement for platelets (HI-P) over any consecutive 56-day period weeks 1-24 or weeks 1-48
- Mean decrease in serum ferritin: Change in serum ferritin in weeks 9-24 or weeks 33-48
- Mean decrease in ICT use: Change in mean daily dose of iron chelation therapy (ICT) in weeks 9-24 or 33-48
- Progression to AML: Number and percentage of subjects progressing to AML; time to AML progression from randomization through at least 3 years post-last dose or weeks 1-48
- Overall Survival (OS): Time from date of randomization to death due to any cause in weeks 1-48 and randomization through at least 3 years post last dose
- Safety: Type, frequency, severity of AEs, and relationship of AEs to luspatercept/placebo in screening through 42 days post last dose, weeks 1-48
- Population PK Model: A population PK model that described the PK exposure data of luspatercept and associated variability from randomization through 1 year post-first dose
- Exposure-response relationship: Exposure-response relationship for primary efficacy endpoint, AEs of interest, and selected secondary endpoints from randomization through 1 year post-first dose
- ADAs: Frequency of ADAs and the effect on efficacy or safety or PK from randomization through 1 year post-first dose

Exploratory endpoints:

- TGF- β superfamily biomarkers and other exploratory markers: Evaluation of biomarkers related to the TGF- β superfamily with response to treatment with luspatercept and other exploratory markers to further understand the mechanism of action of luspatercept
- MDS-associated molecular mutations: Evaluation of the prognostic value of MDS-associated gene mutations in both treatment groups as well as evaluating the impact of these mutations on clinical benefit with luspatercept
- HRU: Evaluation of HRU associated with IP during study
- HRQoL: Change in QoL-E scores

Statistical Analysis Plan

Subjects were randomized to receive luspatercept or placebo at a 2:1 ratio by an IRT. Randomization was stratified by baseline RBC transfusion burden (≥ 6 or < 6 RBC units/8 weeks) and baseline IPSS-R risk category (very low and low, or intermediate).

Clinical Review
Elizabeth Pulte
BLA 761136 Original 2
REBOLZYL (luspatercept-aamt)

Assuming a response rate of 0.30 in the luspatercept arm and a response rate of 0.10 in the placebo arm, a total sample size of 210 (140 in the luspatercept arm, and 70 in the placebo arm) would have 90% power to detect the difference, based on an one-sided alpha of 0.025, test statistics on difference of proportions using pooled estimate of variance and 10% dropout rate.

The primary and secondary analyses were based on the ITT population. The Cochran–Mantel–Haenszel (CMH) test was used to test the difference between the 2 response rates at a 1-sided significance level of 0.025 with randomization factors as strata.

A sequential gate-keeping approach was used to control the overall type I error rate in multiplicity. Two endpoints, the primary efficacy endpoint of RBC transfusion independence (RBC-TI) $\geq$ 8 weeks and the key secondary endpoint of RBC-TI $\geq$ 12 weeks (week 1-48 & week 1-24), were tested sequentially in the pre-specified order. The primary efficacy endpoint will be tested first at the one-sided 0.025 significance level. The test for the RBC-TI $\geq$ 12 weeks analysis (first tested for week 1-48, then week 1-24) can only be made if superiority of luspatercept is demonstrated for the primary efficacy endpoint, RBC-TI $\geq$ 8 weeks, at the one-sided 0.025 significance level.

An interim analysis for futility on the primary and key secondary endpoint were to be performed when approximately 105 subjects completed the Primary Phase of the Treatment Period (first 24 weeks of double-blind treatment) or discontinued before reaching 24 weeks of double-blind treatment (50% information for primary endpoint). There was no plan to claim luspatercept superiority at the interim analysis.

The health-related quality of life was measured by the EORTC QLQ-C30 and QoLE questionnaires. Changes from baseline in overall score and sub-scores were analyzed and compared between treatment groups using repeated measures of Analysis of Variance ANCOVA using the screening scores and stratification factors as covariates.

Protocol Amendments

There were two global amendments and three country specific amendments, none of which pertained to the US.

Protocol amendment 1

- Modified inclusion criteria related to contraception to align with the definition of highly effective methods as per Clinical Trial Facilitation Group guidelines
- Added monitoring of other malignancies/premalignant conditions as important medical events
- Added site guidance regarding collection of transfusion data

Clinical Review
Elizabeth Pulte
BLA 761136 Original 2
REBOLZYL (luspatercept-aamt)

- Added testing of other exploratory markers
- Included dose modifications and discontinuation criteria regarding leukocyte increase and disease progression per IWG-MDS criteria
- Accounted for update to WHO classification system and included FAB classification system for baseline MDS diagnosis
- Extended collection of transfusion data after IP discontinuation to 16 weeks after last dose or EOT visit (whichever was later)
- Updated inclusion criterion on baseline hemoglobin and transfusion requirements to include upper pretransfusion hemoglobin threshold of 10 g/dl
- Clarified exclusion criterion to allow participation for patients with Gilbert syndrome and TB >2 x ULN
- Revised exclusion criterion to exclude patients with significant cardiac dysfunction based on echo or MUGA within 6 months
- Revised exclusion criterion regarding permitted medications to allow enrollment of subjects who received a prior subtherapeutic course of an HMA or lenalidomide
- Updated exclusion criterion regarding prior ESAs to reflect that required washout window was decreased from 6 to 4 weeks
- Updated to align with IB edition 8
- Added information related to risk/benefit assessment
- Revised eligibility criteria to allow use of experimental agents prior to randomization
- Other minor corrections/clarifications

Protocol amendment 2:

- Removal of "progression to AML or high/very high risk category MDS per IPSS-R" from the dose modification and treatment discontinuation criteria
- Modification of dose modification criteria related to leukocytosis
- Clarified that post-treatment ADA and PK sampling to be performed for all subjects
- Updated timing of week 25 visit procedures and MDS disease assessments
- Extended posttreatment follow-up from at least 2 years to at least 3 years
- Minor corrections/clarifications

6.1.2. Study Results

Compliance with Good Clinical Practices

The study was conducted under a US Investigational New Drug application, in accordance with ICH guidelines for good clinical practice (GCP), the principles expressed in the Declaration of Helsinki, and consistent with the CFR, Title 21. The study protocols and informed consent documents were reviewed by local IRB/IEC as required by regulations prior to implementation at practicing institutions.

CDER Clinical Review Template

Version date: September 6, 2017 for all NDAs and BLAs

37

Clinical Review
Elizabeth Pulte
BLA 761136 Original 2
REBOLZYL (luspatercept-aamt)

Financial Disclosure

Financial arrangements between the Sponsor to Investigators were reported for two investigators at two sites. (b) (6) reported receiving approximately (b) (4) from the Sponsor (b) (4). (b) (6) reported the following payments: \$18,400 in 2016 for educational talks (b) (6) \$9600 in consulting fees in 2017, and \$3300 in 2018 for an educational talk on MDS therapies at a Celgene event (b) (6). (b) (6) notes that he is (b) (6) paid directly to the institution rather to him personally.

Steps taken to minimize bias include blinding of the trial (although see section 6.1.1 trial design for concerns with regards to blinding) and use of multiple investigational sites to minimize the influence of any single site on the study outcome. Neither investigator enrolled (b) (6) % of the total number of patients on the trial, although it should be noted that (b) (6) was a high enrolling site.

Patient Disposition

Of the 290 subjects screened for MDS-001, 229 were randomized, 153 to luspatercept and 76 to placebo. Of the 61 screen failures, 40 did not meet the inclusion criteria and 19 met one or more exclusion criteria. Of those who failed to meet the inclusion criteria, the most common failure was inclusion criterion 3 (documented diagnosis of lower risk MDS with ring sideroblasts), occurring in 32 subjects. Three subjects failed to meet the RBC transfusion documentation requirement. No other inclusion criterion was a cause of screen failure in more than 1 subject. Reasons for screen failure due to meeting exclusion criteria were more varied, with 6 subjects meeting criterion 12 (eGFR or creatinine clearance <40 ml/min), 4 criterion 3 (MDS associated with del 5q), 3 criterion 14 (total bilirubin $\geq 2 \times$ ULN), and 2 each criteria 1, 8, and 20 (prior therapy with disease modifying agent, treatment within 5 weeks with restricted agents, and uncontrolled infection, respectively). No other criteria were met by more than one subject.

The majority of patients completed 24 weeks of treatment in the primary phase of the study, with slightly fewer patients in the luspatercept arm completing the initial treatment phase (83.7% versus 89.5%). A higher proportion of the patients on the luspatercept arm entered the extension phase (51.0% versus 15.8%). As of the data cut off for the 3-month safety update, 48 subjects, all on the luspatercept arm, continued to receive treatment.

Among patients receiving placebo, the most common reason for discontinuation was lack of efficacy (50/76 subjects), followed by other and withdrawal by patient (10 each). Adverse events and disease progression were the reason for withdrawal for 4 and 2 subjects,

CDER Clinical Review Template

Version date: September 6, 2017 for all NDAs and BLAs

respectively. Among those who withdrew for patient request or other reasons, being found to be on the placebo arm after unblinding was cited as a reason for withdrawal for 6 subjects and evidence of lack of efficacy (i.e. no improvement in transfusion rate, lack of response) was cited as part of the decision in 4 cases. Forty-six out of 76 subjects continue to be followed on the study. Reasons for discontinuation for the other 30 include death (18), patient request (10), and other (2).

Among the 105 subjects receiving luspatercept who discontinued treatment, the most common reason was lack of efficacy (63), followed by withdrawal by subject (16), adverse event (15), progressive disease (5), other (4), and protocol violation (2). Among discontinuations for withdrawal by subject, adverse events were mentioned as part of the decision by two subjects and perceived lack of efficacy by three. Fifty-four subjects discontinued trial participation, with reasons for discontinuation including death (27), withdrawal by subject (20), lost to follow up (4), and other (3).

Reviewer's comments: Adverse events were reported as the reason for withdrawal from treatment for 10% of subjects receiving luspatercept versus 5% of those receiving placebo. Withdrawal from treatment during the first 24 weeks was more common in the luspatercept arm. Taken together, these two findings suggest that early intolerance of treatment was an issue for the study medication.

Withdrawal from trial participation (and therefore from long term follow-up) were roughly similar between the two arms.

Protocol Violations/Deviations

Protocol deviations and violations were very common in study MDS-001, with the Sponsor reporting 2446 protocol deviations or violations in 232 subjects, including 40 protocol violations in 40 individual patients.

Protocol deviations, defined by the Sponsor as unplanned deviations from the approved protocol that did not result in harm to the study subjects or affect the data integrity, were extremely common, with one or more events occurring in 98% of patients on the luspatercept arm and 95% of patients on the placebo arm. The most common deviation was missing visit or assessment, occurring in 93% of subjects in each arm. IP issues were more common among subjects in the luspatercept arm (58% versus 45%). Other common issues included out of window visit or assessment, occurring in 40% and 41% of subjects in the luspatercept and placebo arms, respectively, and informed consent issues, occurring in 49% and 43% of subjects.

Protocol violations occurred in 24 (16%) and 7 (9%) of subjects in the luspatercept and placebo arms, respectively. The most common protocol violations included entered study but did not meet entry criteria (9 and 3 subjects) and GCP issues (8 and 3 subjects). Investigational product

issues (6), failure to withdraw after meeting withdrawal criteria (2), and concomitant medication or procedure (1) issues were seen in the luspatercept arm only and missing visit or assessment/procedure (1) was seen in the placebo arm only.

Demographic Characteristics

The treatment arms were generally well balanced between the luspatercept and placebo arms. However, small differences in the demographics of each arm were observed. Relatively more men were enrolled in the placebo arm, compared to the luspatercept arm. Although median age was similar between the arms, the placebo arm had a larger percentage of both younger and older patients (i.e. <65 or ≥75 years of age). Similarly, patients on the luspatercept arm were more likely to have an ECOG score of 1 compared to the placebo arm. The vast majority of subjects were identified as white and non-Hispanic. All subjects were treated in Europe or North America.

The vast majority of patients in either arm had at least one medical history term in addition to MDS (152/153 in the luspatercept arm and 75/76 in the placebo arm.) Patients on the luspatercept arm were more likely (>10% difference) to have terms in the psychiatric and social circumstances system organ class (SOC) and to a lesser degree (5-10% difference) in the vascular disorders SOC. Conversely, patients in the placebo arm were more likely (5-10% difference) to have events in the musculoskeletal and connective tissues disorders, surgical and medical procedures, cardiac disorders, general disorders and administrative site conditions, infections and infestations, and hepatobiliary disorders SOC.

Table 3: Demographic characteristics of patients on MDS-001 by study arm

Demographic Parameters	Luspatercept (N=153)	Placebo (N=76)	Total (N=229)
Sex			
Male	94 (61%)	50 (66%)	144 (63%)
Female	59 (39%)	26 (34%)	85 (37%)
Age group			
< 65 years	29 (19%)	16 (21%)	45 (20%)
65-74	72 (47%)	29 (38%)	101 (44%)
≥ 75 years	52 (34%)	31 (41%)	83 (36%)
≥80 years	17 (11%)	14 (18%)	31 (14%)
Age			
Median (Min, max)	71 (40, 95)	72 (26, 91)	71 (26, 95)
Baseline Performance Status			
ECOG 0	54 (35%)	33 (43%)	87 (40%)

Table 3: Demographic characteristics of patients on MDS-001 by study arm

Demographic Parameters	Luspatercept (N=153)	Placebo (N=76)	Total (N=229)
ECOG 1	91 (59%)	32 (42%)	123 (54%)
ECOG 2	8 (5%)	11 (14%)	19 (8%)
Race			
White	107 (70%)	51 (67%)	158 (69%)
Other race	2 (1%)	1 (1%)	3 (1%)
Not provided	44 (29%)	24 (32%)	68 (30%)
Ethnicity			
Hispanic	3 (2%)	4 (5%)	7 (3%)
Non-Hispanic/not provided	150 (98%)	72 (95%)	222 (97%)
Geographic region			
EU	122 (80%)	57 (75%)	179 (78%)
North America	31 (20%)	19 (25%)	50 (22%)

Reviewer's note: *Virtually no non-white subjects and few Hispanic subjects were enrolled in this trial. Thus, the safety and efficacy of luspatercept in the setting of MDS in any patient population other than non-Hispanic whites cannot be assessed.*

Several minor imbalances in patient and disease characteristics were observed between the study arm. In general, these differences (i.e. lower percentage of women, higher baseline percentage of patients with lower transfusion requirement) may bias the study towards higher apparent efficacy as lower response rates were seen in women and patients with higher baseline transfusion requirements.

More patients over age 80 enrolled on the placebo arm compared to the luspatercept arm. This is of potential importance to the interpretation of survival data, since older patients have a higher baseline risk of death. For example, the expected 10-year survival per the Charlson comorbidity index decreases from 77% at 70-79 year old to 53% in an 80+ year old, assuming no other comorbid conditions. Thus, the baseline risk of death due to unrelated causes is unbalanced between the two arms due to a relative excess of older patients in the placebo arm.

Other Baseline Characteristics

The study was stratified by baseline transfusion (≤ 6 units/8 weeks versus >6 units/8 weeks) and IPSS-R score (very low or low versus intermediate). Other baseline characteristics of potential interest included baseline hemoglobin, WHO 2016 classification, baseline platelet count, prior

ESA use, and baseline erythropoietin level (table 4).

The Sponsor defined baseline hemoglobin as the mean of all documented pre-transfusion hemoglobin values during the 16 weeks prior to the first dose of study medication. Because transfusion was allowed between the time of consent and start of therapy, many patients had higher hemoglobin levels at the start of therapy (cycle 1 day 1). The FDA used the cycle 1 day 1 value as the baseline value for its analyses as this value is reflective of the actual hemoglobin at start of study and thus would reduce the risk that observed changes in hemoglobin were due to pre-treatment transfusion rather than to drug effect. The percentage of patients in various hemoglobin groups by each definition is listed in the table below.

Table 4: Baseline disease characteristics of patients on MDS-001 by study arm

Demographic Parameters	Luspatercept (N=153)	Placebo (N=76)	Total (N=229)
WHO 2016 Classification			
MDS/MPN-RS-T	14 (9%)	9 (12%)	23 (10%)
MDS-RS-MLD	129 (84%)	62 (82%)	191 (83%)
MDS-RS-SLD	6 (4%)	3 (4%)	9 (4%)
Other	4 (3%)	2 (3%)	6 (3%)
Baseline transfusion			
≤6 units/8 weeks	75 (49%)	30 (40%)	105 (46%)
>6 units/8 weeks	78 (51%)	46 (61%)	124 (54%)
Baseline hemoglobin ¹			
<7.5 gm/dl	57 (37%)	25 (33%)	82 (36%)
7.5-8.5 gm/dl	69 (45%)	41 (54%)	110 (48%)
>8.5-10 gm/dl	26 (17%)	10 (13%)	26 (16%)
10+ gm/dl	1 (<1%)	0	1 (<1%)
Baseline hemoglobin ²			
<7.5 gm/dl	17 (11%)	5 (7%)	22 (10%)
7.5-8.5 gm/dl	36 (24%)	23 (30%)	59 (26%)
>8.5-10 gm/dl	75 (49%)	41 (54%)	116 (51%)
10+ gm/dl	25 (16%)	7 (9%)	32 (14%)
Platelet count (x10 ⁹ /L)			
<100	8 (5%)	6 (8%)	14 (6%)
≥100 K to 400	128 (84%)	61 (80%)	189 (83%)
>400	17 (11%)	9 (12%)	26 (11%)

Table 4: Baseline disease characteristics of patients on MDS-001 by study arm

Demographic Parameters	Luspatercept (N=153)	Placebo (N=76)	Total (N=229)
Prior ESA duration			
<6 months	48 (31%)	20 (27%)	68 (30%)
6-12	34 (22%)	9 (12%)	43 (19%)
>12-24	35 (23%)	21 (28%)	56 (24%)
>24 months	31(20%)	20 (26%)	51 (22%)
IPSS-R category			
Very low risk	18 (12%)	6 (8%)	24 (10%)
Low risk	109 (71%)	57 (75%)	166 (72%)
Intermediate risk	25 (16%)	13 (17%)	38 (17%)
High risk	1 (<1%)	0	1 (<1%)
ESA status			
ESA refractory	144 (97%)	69 (99%)	213 (93%)
ESA Intolerant	4 (3%)	1 (1%)	5 (2%)
Baseline erythropoietin* (IU/L)			
<100	51 (33%)	31 (41%)	83 (36%)
100-<200	37 (24%)	19 (25%)	56 (25%)
200-500	43 (28%)	15 (20%)	58 (25%)
>500	21 (14%)	11 (15%)	32 (14%)

¹Sponsor's definition

²FDA definition (hemoglobin on cycle 1 day 1)

*Data missing for one subject in the luspatercept arm

Reviewer's comments: A substantial number of subjects enrolled did not have refractory anemia with ring sideroblasts, but rather MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T). This entity was adopted under the 2016 WHO guidelines and thus was not identified as a separate entity at the time the trial began enrolling.

Although the majority of patients were identified as being ESA refractory rather than ESA intolerant, baseline erythropoietin levels of <200 were common. The basis for declaring a patient to be "ESA refractory" is somewhat unclear. The protocol states that the subject must have "documentation of non-response or response that was no longer maintained to prior ESA-containing regimen," but does not provide a specific definition of "non-response".

Of note, 32 subjects entered the study with a hemoglobin of >10 gm/dl and thus not in need of transfusion at the start of study. This makes any transfusion independence response which

starts on cycle 1 day 1 difficult to interpret.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment was administered by the investigational staff and compliance documented in the case report forms.

Most patients received at least one concomitant medication during therapy (151/153 in the luspatercept arm and 72/76 in the placebo arm.) Medications more commonly used (>10% difference) among patients receiving luspatercept included antibacterials for systemic use, agents acting on the renin-angiotensin system, and drugs for obstructive airway disease. See table, below, for further details of differences in prescription rates between the study arms.

Table 5: Rate of use of selected medication classes by study arm with risk difference >5 between arms (adapted from Sponsor's analysis)

Medication class	Luspatercept	Placebo	RD
Antibacterials for systemic use	80 (52%)	27 (36%)	16.8
Drugs for acid-related disorders	70 (46%)	26 (34%)	11.6
Diuretics	56 (37%)	21 (28%)	9.0
Agents acting on the renin-angiotensin system	47 (31%)	14 (18%)	12.3
Psycholeptics	45 (29%)	15 (20%)	9.7
Drugs used in diabetes	36 (23%)	12 (16%)	7.7
Psychoanaleptics	35 (23%)	11 (15%)	8.4
Drugs for obstructive airway disease	29 (19%)	6 (8%)	11.1
Calcium channel blockers	19 (12%)	4 (5%)	7.1
Thyroid therapy	18 (12%)	5 (7%)	5.2
Drugs for functional gastrointestinal disorders	16 (11%)	3 (4%)	6.6
Corticosteroids, dermatological preparations	16 (11%)	2 (3%)	7.9

No rescue medications other than transfusion, discussed in the efficacy section, are relevant. Twenty-three (15%) of patients on the luspatercept arm and 22 (29%) in the placebo arm reported subsequent treatment of their MDS, with therapies utilized including azacitidine, epoetin, lenalidomide, and daratumumab.

Reviewer's comments: Patients on the luspatercept arm were more likely to have baseline psychiatric and social issues, which may explain the higher incidence of use of psychiatric medications. However, the higher need for antibacterials, anti-hypertensives, and drugs for gastrointestinal issues was not explained by differences in baseline patient characteristics and may be related to higher rates of TEAE including infection, hypertension, and nausea, vomiting, and diarrhea. Thyroid hormone levels were not routinely checked during the study, but the increase in use of thyroid therapy and finding of increased risk of fatigue (see below) may

indicate a potential issue.

Data Quality and Integrity

Several data quality issues were identified during the course of the review as noted below:

- The data files initially submitted to support the quality of life findings were unreadable. The Sponsor submitted readable files in response to an inquiry by the Agency.
- The Analysis Dataset Legacy folders and Analysis Data Definition folders initially submitted for MDS-001 and the integrated summary of safety contained multiple duplicates of file names that were each identified as the current version (see figure 3, below, for an example). Multiple IRs to the Sponsor and a telecon were required to resolve this issue initially. It recurred after data from a data sweep performed in November, 2019 were added.
- Files were initially submitted without data cut-off information.

Figure 3: Example of files with status current in the ISS Analysis Dataset Legacy folder.

1	Section	File Name	Submitted In	Life Cycle Status	Size (KB)
2	Analysis Dataset Legacy	adae.xpt	0001 (1) 04/04/2019 C	Current	11,045.20
3	Analysis Dataset Legacy	adae.xpt	0015 (17) 07/03/2019	Current	14,252.70
4	Analysis Dataset Legacy	adcm.xpt	0001 (1) 04/04/2019 C	Current	15,007.30
5	Analysis Dataset Legacy	adcm.xpt	0015 (17) 07/03/2019	Current	18,656.60
6	Analysis Dataset Legacy	adex.xpt	0001 (1) 04/04/2019 C	Current	1,070.90
7	Analysis Dataset Legacy	adex.xpt	0015 (17) 07/03/2019	Current	1,276.00
8	Analysis Dataset Legacy	adlb.xpt	0001 (1) 04/04/2019 C	Current	2,810.50
9	Analysis Dataset Legacy	adlb.xpt	0015 (17) 07/03/2019	Current	3,342.00
10	Analysis Dataset Legacy	admh.xpt	0001 (1) 04/04/2019 C	Current	5,769.10
11	Analysis Dataset Legacy	admh.xpt	0015 (17) 07/03/2019	Current	5,898.60
12	Analysis Dataset Legacy	adsl.xpt	0001 (1) 04/04/2019 C	Current	820.5
13	Analysis Dataset Legacy	adsl.xpt	0015 (17) 07/03/2019	Current	1,308.80
14	Analysis Dataset Legacy	advx.xpt	0001 (1) 04/04/2019 C	Current	472.4
15	Analysis Dataset Legacy	advx.xpt	0015 (17) 07/03/2019	Current	549.9

Reviewer's comments: Although the issues involving data quality were ultimately resolved, the issues complicated review of the submission.

Efficacy Results – Primary Endpoint

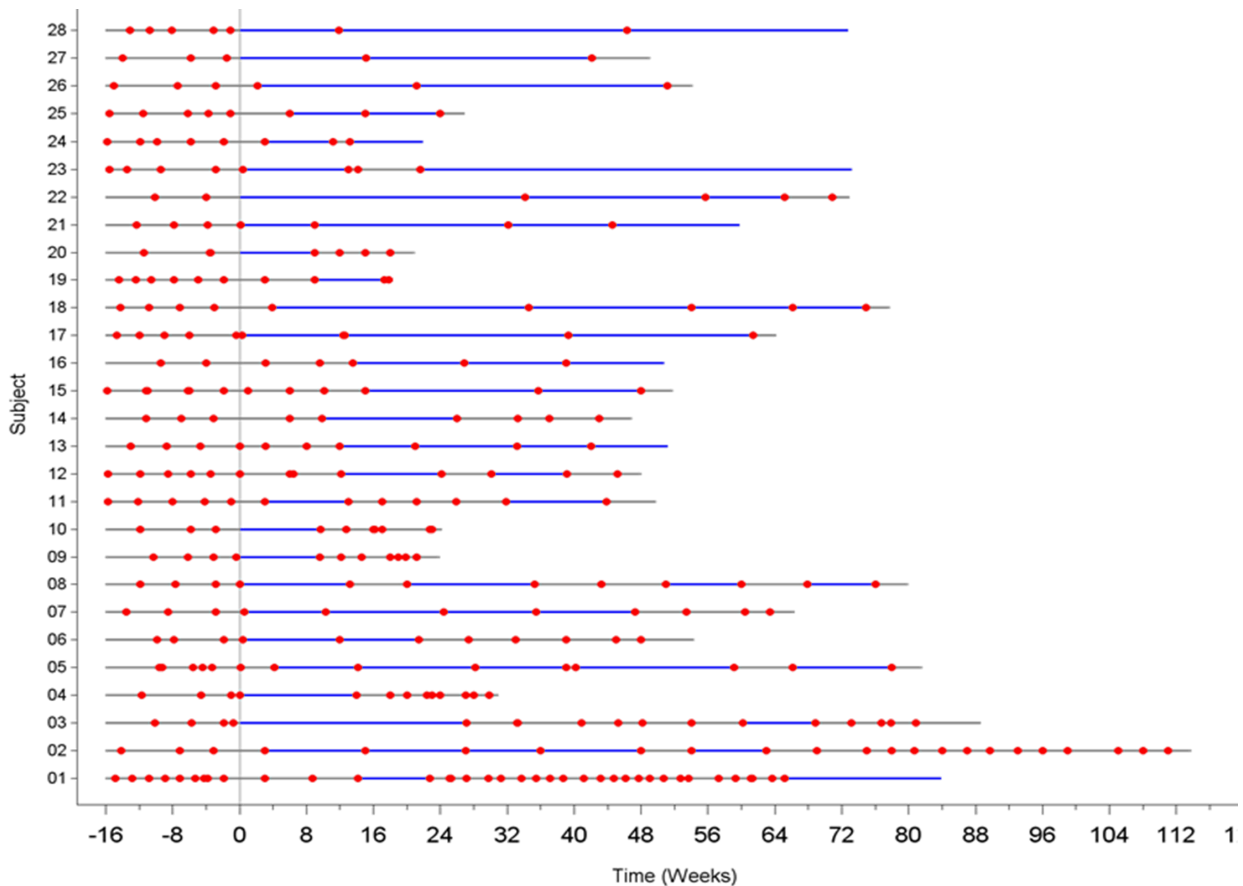
As noted in the table below, the study met its primary objective of increased TI-8 occurring within the first 24 weeks of the study. A modest overall improvement in TI-8 with a risk difference of 24.6% was observed between the two arms, with a highly significant p-value.

Table 6: Rate of TI-8 by study arm

Parameter	Luspatercept (N = 153)	Placebo (N = 76)
RBC-TI ≥ 8 weeks from Week 1 to Week 24		
Number of Responders	58	10
Response Rate (%) (95% CI)	37.91 (30.20, 46.10)	13.16 (6.49, 22.87)
Difference (%) (95% CI)	24.56 (14.48, 34.64)	
p-value	< 0.0001	

The Sponsor provided a graphic showing transfusion events and time in response (TI-8 or better) for responders in each arm. This graphic is reproduced in part below:

Figure 4: Graphic representation of transfusion events and response for subset of patients experiencing response on the luspatercept arm of MDS-001 (adapted from Sponsor's analysis)



The figure demonstrates several points of interest. First, a notable number of subjects received transfusions immediately prior to the start of study. Second, although some responses were

prolonged, a pattern of multiple short responses separated by transfusion events, was common, i.e. patients 11, 12, 24.

Reviewer's comments: The trial met its primary endpoint of increased TI-8. However, as is clear from the representative figure above, a large number of the responses were transient. As noted elsewhere, the life expectancy of a transfused red blood cell is 50-60 days. Thus, it is unclear whether the drug or transfusion is responsible for the shorter transfusion free periods.

Efficacy Results – Secondary and other relevant endpoints

Transfusion independence for at least 12 weeks (TI-12) within the first 24 weeks of the study was a key secondary endpoint for the study and TI-12 at any time in the first 48 weeks was a secondary endpoint of interest. The Sponsor's analyses for these endpoints was confirmed by the FDA and demonstrated a statistically significant increase in TI-12, both in the first 24 weeks and in the first 48 weeks (see table 7, below.) Of note, the difference in TI-12 rate between placebo and active drug was smaller than the difference in the TI-8 rate.

Table 7: Rate of TI-12 in weeks 1-24 and 1-48 by study arm

Endpoint	Luspatercept (N = 153)	Placebo (N = 76)
RBC-TI ≥ 12 weeks from Week 1 to Week 24		
Number of Responders	43	6
Response Rate (%) (95% CI)	28.10 (21.14, 35.93)	7.89 (2.95, 16.40)
Difference (%) (95% CI)	20.00 (10.92, 29.08)	
p-value	0.0002	
RBC-TI ≥ 12 weeks from Week 1 to Week 48		
Number of Responders	51	9
Response Rate (%) (95% CI)	33.33 (25.93, 41.40)	11.84 (5.56, 21.29)
Difference (%) (95% CI)	21.37 (11.23, 31.51)	
p-value	0.0003	

The FDA proposed two additional analyses to test the robustness of the effect. First, transfusion independence lasting 16 weeks (TI-16) was examined, then TI-8, TI-12, and TI-16 where the event began in the first 24 weeks but ended at any time were examined.

Table 8. Study MDS-001: RBC TI Difference Using Alternative Endpoint Definitions

Outcome	Number of Responders (ORR)		ORR Difference (95% CI)
	Luspatercept (N=153)	Placebo (N=76)	
TI-8 within Weeks 1 - 24 ^a	58 (37.9%)	10 (13.2%)	24.6% (14.5, 34.6)
TI-12 within Weeks 1 - 24 ^b	43 (28.1%)	6 (7.9%)	20.0% (10.9, 29.1)
TI-16 within Weeks 1 - 24 ^c	29 (19.0%)	3 (4.0%)	15.0% (7.4, 22.6)
TI-8 starting Weeks 1 - 24 ^c	65 (42.5%)	10 (13.2%)	29.3% (18.4, 40.2)
TI-12 starting Weeks 1 - 24 ^c	50 (32.7%)	7 (9.2%)	23.5% (13.6, 33.3)
TI-16 starting Weeks 1 - 24 ^c	42 (27.5%)	4 (5.3%)	22.2% (13.5, 30.9)

^a Primary endpoint

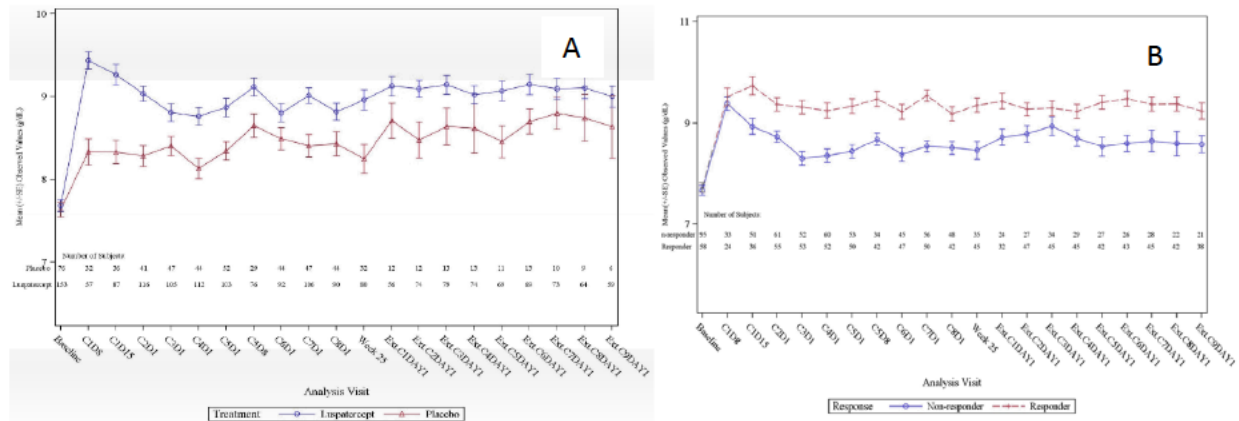
^b Key secondary endpoint

^c FDA alternative analysis

Reviewer's comments: The increase in transfusion independence appears to be robust. However, the effect becomes numerically smaller as the period of transfusion independence required to be considered a response is increased. The effect size for patients with TI-16 is only 15% for events occurring in the first 24 weeks and 22% for events starting in the first 24 weeks but ending at any time. Of note, many patients receiving placebo dropped out of the study after the first 24 weeks and thus potential TI in the placebo arm that started in week 24 but did not end until later may not have been recorded, possibly artificially inflating the apparent effect size for transfusion independence starting in weeks 1-24 but ending at any time.

Modified hemoglobin improvement (mHI) was a prespecified secondary endpoint of the trial. The Sponsor's analysis concluded that a meaningful increase in hemoglobin could be observed in the luspatercept arm based on their assessment of the change in hemoglobin from baseline to any post-baseline value. The Sponsor's analysis of hemoglobin increase by arm and by TI-8 response is shown in figure 5, below.

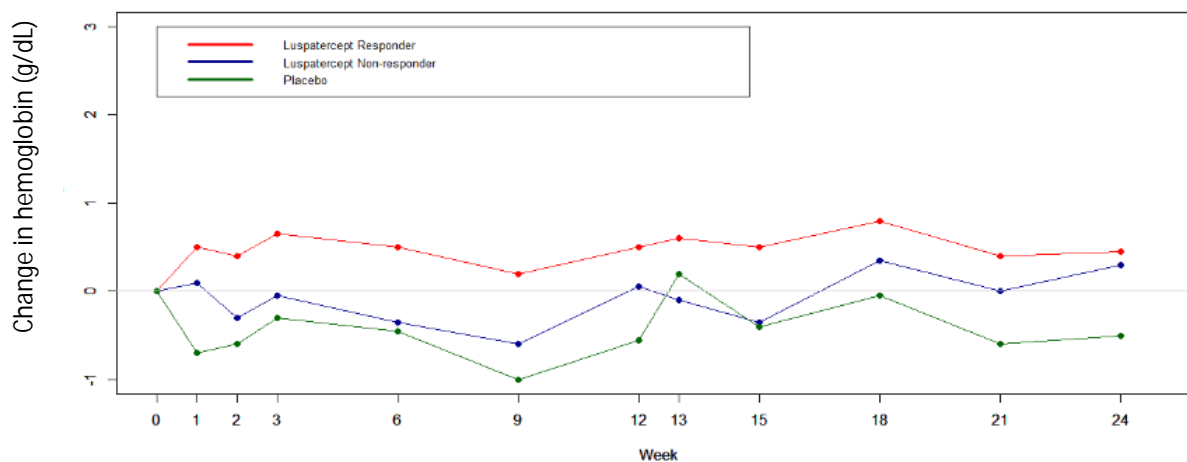
Figure 5: Change in hemoglobin in patients treated on MDS-001 by (A) arm and (B) response to therapy within the luspatercept arm. Adapted from the Sponsor’s analysis.



It should be noted that the figures provided by the Sponsor did not take recent transfusion or lack thereof into account when determining hemoglobin level at a given timepoint. In addition, the baseline hemoglobin used is the mean of all pre-transfusion hemoglobin levels in the 16 weeks prior to start of the study and therefore may not reflect the hemoglobin level at the time of the start of the study.

Because of this issue and the issues mentioned above concerning the definition of baseline hemoglobin, the FDA performed a separate analysis examining median change in hemoglobin in the trial. For this analysis, any hemoglobin level that was checked within 2 weeks of a transfusion was considered to be confounded by the transfusion and not included in the analysis. The baseline hemoglobin used was per the FDA definition of hemoglobin on day 1 of cycle 1. In order to give the best chance of highlighting the best potential change in hemoglobin, the analysis examined patients who were considered responders to luspatercept based on observation of TI-8 separately from those who were considered non-responders.

Figure 6: Median change in hemoglobin by response and arm (FDA analysis)



A small increase in hemoglobin was seen in patients who were considered responders to luspatercept, with a median increase by week 24 of less than 1 g/dl. No change or a small decrease in hemoglobin was observed for patients who were considered non-responders and for those who received placebo. Similar results were observed for mean change in hemoglobin. Although the overall change was small, it was persistent throughout the first 24 weeks of the study.

Reviewer's comments: The apparent effect of luspatercept on hemoglobin varied depending on the baseline used. Per the Sponsor's analysis, an increase of >1 g/dl was observed in patients who were treated with luspatercept with a more sustained effect in patients who were considered responders. Per the FDA analysis, a small increase in hemoglobin in patients who had not been transfused within 14 days was observed for patients receiving luspatercept who had a response. The highest median change was about 1 gm/dL, although larger changes were seen in a few individuals. Most of the apparent effect occurred in the first cycle, although serum levels of luspatercept did not reach steady state until the 3rd to 4th cycle.

The Sponsor presented additional data describing an unplanned analysis examining percentage of patients who experienced a 50% or greater reduction in transfusion burden for 8, 16, or 24 weeks during the study. This information will not be discussed further here for the following reasons:

- This is an unplanned post-hoc analysis of the data with no prespecified statistical plan
- There is no precedent for the use of reduction in transfusion burden as a basis for approval in the context of anemia resulting from MDS
- The reduction in transfusion burden may be confounded by the same issues that were

mentioned above with regards to the transfusion independence measurements, i.e. possible unblinding, risk of unconscious bias, etc.

- No temporal cut off (i.e. first 24 weeks) was used. Since most patients on the placebo arm discontinued after week 25, this artificially inflates the purported effect of luspatercept considerably
- The Sponsor made no attempt to correlate reduction in transfusion burden with any even potentially clinically meaningful endpoint.

Reviewer's comments: No importance should be placed on the Sponsor's late introduction of a post-hoc analysis of an unproven endpoint of no known clinical benefit.

Subpopulation Analysis

Subpopulation analyses were performed for a variety of demographic and disease characteristic subpopulations. All subpopulation analyses refer to the probability of achievement of the primary efficacy result of TI-8 in the first 24 weeks of treatment.

The effect of baseline transfusion requirement on ability to achieve a TI-8 was evaluated (table 9, below). A prespecified analysis for TI-8 by baseline transfusion requirement was performed by the Sponsor and verified by the FDA. The FDA analysis expressed differences between arms as an effect difference, rather than an odds ratio as per the Sponsor's analysis. Confidence intervals were calculated using an unstratified CMH test.

Patients who had a baseline transfusion requirement of <4 units/8 weeks were likely to have a response, regardless of study arm, with a response rate of 80.4% in the luspatercept arm and 40.4% in the placebo arm. Conversely, patients with a baseline transfusion requirement of ≥6 units/8 weeks were unlikely to achieve a TI-8 regardless of arm, with a rate of 9.1% in the luspatercept arm and of 3.0% in the placebo arm and a 95% confidence interval that included zero (-15.5 to 27.2).

Table 9: Frequency of achievement of TI-8 in the primary analysis period by baseline transfusion requirement and study arm.

	Responders / N		ORR (95% CI)		ORR Difference (95% CI)
	Luspatercept	Placebo	Luspatercept	Placebo	
< 4 units	37 / 46	8 / 20	80.4 (66.1, 90.6)	40.0 (19.1, 63.9)	40.4 (14.5, 63.9)
≥ 4 and < 6 units	15 / 41	1 / 23	36.6 (22.1, 53.1)	4.3 (0.1, 21.9)	32.2 (6.8, 55.0)
≥ 6 units	6 / 66	1 / 33	9.1 (3.4, 18.7)	3.0 (0.1, 15.8)	6.1 (-15.5, 27.2)

Reviewer's comment: Patients with a low baseline transfusion requirement were likely to achieve at least a TI-8 regardless of study arm. This suggests that part of the ability of these

patients to achieve a response was related to changing transfusion requirement due to disease variability or to a different standard for transfusion threshold being applied during the study compared to in general practice. The rate of TI-8 for patients with a high transfusion burden did not vary statistically by study arm, despite the fact that these patients made up the largest single cohort in terms of transfusion requirement. This suggests that luspatercept is ineffective for patients with a high transfusion burden.

The effect of baseline hemoglobin on transfusion requirement was considered of potential interest as well. A pre-specified analysis was performed by the Sponsor and verified by the FDA using the Sponsor's definition of baseline hemoglobin. A second, post-hoc analysis was performed using the FDA's definition of baseline hemoglobin. Using this definition, 25 patients in the luspatercept arm and 7 in the placebo arm had a baseline hemoglobin of ≥ 10 g/dl and therefore no immediate transfusion requirement.

In general, the response difference was greater for patients with lower baseline hemoglobin by either definition, with confidence intervals overlapping zero for patients with hemoglobin ≥ 10 g/dl by the FDA definition or >8.5 g/dl by the Sponsor's definition. Interestingly, a larger apparent effect size was observed for lower hemoglobin levels using the FDA's definition (table 10).

Table 10: Response by baseline hemoglobin level

	Responders / N		ORR (95% CI)		ORR difference (95% CI)
	Luspatercept	Placebo	Luspatercept	Placebo	
Hemoglobin ¹ (g/dl)					
Hemoglobin <7.5	18 / 57	1 / 25	31.6 (19.9, 45.2)	4.0 (0.1, 20.4)	27.6 (4.0, 49.2)
Hemoglobin 7.5-8.5	32 / 69	7 / 41	46.4 (34.3, 58.8)	17.1 (7.2, 32.1)	29.3 (10.2, 46.9)
Hemoglobin 8.5-10	7 / 26	2 / 10	26.9 (11.6, 47.8)	20.0 (2.5, 55.6)	6.9 (-29.2, 42.5)
Hemoglobin ≥ 10	1 / 1	0		0	NA
Hemoglobin ² (g/dl)					
Hemoglobin <7.5	6 / 17	0 / 5	35.3 (14.2, 61.7)	0.0 (0.0, 52.2)	35.3 (-15.9, 77.8)
Hemoglobin 7.5-8.5	16 / 36	3 / 23	44.4 (27.9, 61.9)	13.0 (2.8, 33.6)	31.4 (5.2, 54.3)
Hemoglobin 8.5-10	26 / 75	6 / 41	34.7 (24.0, 46.5)	14.6 (5.6, 29.2)	20.0 (1.0, 38.0)
Hemoglobin ≥ 10	10 / 25	1 / 7	40.0 (21.1, 61.3)	14.3 (0.4, 57.9)	25.7 (-17.1, 64.5)

¹Sponsor's definition

²FDA definition (hemoglobin on cycle 1 day 1)

Other demographic and disease variables of interest were evaluated in a pre-planned analysis, as noted in table 11 below. Of note, larger differences in response were noted for younger patients, men, and patients with higher baseline performance status. The 95% confidence interval overlapped zero for women, patients with ECOG performance status of 0 or 2, and

those with erythropoietin ≥ 400 IU/L.

Table 11: Response by selected demographic and disease factors

	Responders / N		ORR (95% CI)		ORR difference
	Luspatercept	Placebo	Luspatercept	Placebo	
Age group					
Age < 65 years	17 / 29	3 / 16	58.6 (38.9, 76.5)	18.8 (4.0, 45.6)	39.9 (9.1, 65.6)
Age ≥ 65 years	41 / 124	7 / 60	33.1 (24.9, 42.1)	11.7 (4.8, 22.6)	21.4 (5.9, 36.2)
Gender					
Male	32 / 94	4 / 50	34.0 (24.6, 44.5)	8.0 (2.2, 19.2)	26.0 (9.0, 42.0)
Female	26 / 59	6 / 26	44.1 (31.2, 57.6)	23.1 (9.0, 43.6)	21.0 (-2.0, 42.7)
Race					
White	40 / 107	8 / 51	37.4 (28.2, 47.3)	15.7 (7.0, 28.6)	21.3 (5.0, 37.5)
Other race/Not reported	18 / 46	2 / 25	39.1 (25.1, 54.6)	8.0 (1.0, 26.0)	31.1 (6.9, 53.0)
Performance status					
ECOG 0	17 / 54	5 / 33	31.5 (19.5, 45.6)	15.2 (5.1, 31.9)	16.3 (-5.4, 37.1)
ECOG 1	38 / 91	4 / 32	41.8 (31.5, 52.6)	12.5 (3.5, 29.0)	29.3 (9.2, 48.0)
ECOG 2	3 / 8	1 / 11	37.5 (8.5, 75.5)	9.1 (0.2, 41.3)	28.4 (-17.8, 67.1)
Baseline platelet count ($\times 10^9/L$)					
<100	2/8	1/6	25.0 (3.2, 65.1)	16.7 (0.4, 64.1)	8.3 (-43.4, 57.7)
100-400	42/128	8/61	32.8 (24.8, 41.7)	13.1 (5.8, 24.2)	19.7 (4.4, 34.4)
≥ 400	14/17	1/9	82.4 (56.6, 96.2)	11.1 (0.3, 48.2)	71.2 (31.8, 92.5)
Baseline erythropoietin (IU/L)					
Erythropoietin <100	23 / 51	7 / 31	45.1 (31.1, 59.7)	22.6 (9.6, 41.1)	22.5 (0.1, 43.2)
Erythropoietin 100-400	29 / 75	3 / 32	38.7 (27.6, 50.6)	9.4 (2.0, 25.0)	29.3 (8.9, 48.3)
Erythropoietin ≥ 400	5 / 26	0 / 13	19.2 (6.6, 39.4)	0.0 (0.0, 24.7)	19.2 (-15.9, 51.4)

Reviewer's note: Older patients and women had lower response rates and less differential in response compared to younger patients and men. Very few non-white patients were enrolled so the effect of race on efficacy and safety of luspatercept should be considered to be unknown, particularly given that there were very few patients with a confirmed race other than white. Patients with an ECOG performance status of zero who received luspatercept were less likely to have a response compared to those with a PS of 1-2. The point estimate for response increased with platelet count, although the confidence intervals were large.

The confidence intervals showed no statistical difference between luspatercept and placebo for women, patients with performance status of 0 or 2, baseline platelet count of $<100 \times 10^9/L$, and high erythropoietin. However, the study was not powered to show differences between subpopulations and therefore the statistical differences should be interpreted with caution. Overall, these results suggest that any benefit luspatercept may have in terms of transfusion

reduction is limited to a small subpopulation.

Finally, an unplanned subpopulation analysis was performed on two further populations. First, a subpopulation analysis of effect by erythropoietin level dividing baseline erythropoietin into ≤ 500 IU/L and > 500 IU/L was performed to determine whether luspatercept showed promise for the treatment of patients with very high baseline erythropoietin levels who are unlikely to respond to ESAs. Second, an analysis by 2016 WHO classification was performed to examine the effect of each histology on the efficacy of luspatercept. The effect size was smaller for both arms among patients with high erythropoietin levels, with the confidence interval overlapping zero for patients with erythropoietin levels of > 500 IU/L. Patients with MDS/MPN-RS-T were more likely to achieve a TI-8, regardless of study arm, and the point estimate of the difference between the arms was greater, although, possibly due to the small number of patients enrolled, the confidence interval overlapped zero. Because practice standards may vary by location, an unplanned analysis of response by geographic location (North America versus Europe) was performed. Response rates on both arms were higher and the difference between arms was higher in North America compared to Europe.

Table 12: Response by selected disease and demographic factors

	Responders / N		ORR (95% CI)		ORR Difference (95% CI)
	Luspatercept	Placebo	Luspatercept	Placebo	
Baseline Erythropoietin (IU/L)					
≤ 500	54 / 131	10 / 65	41.2 (32.7, 50.2)	15.4 (7.6, 26.5)	25.8 (11.3, 40.0)
> 500	3 / 21	0 / 11	14.3 (3.0, 36.3)	0.0 (0.0, 28.5)	14.3 (-22.6, 48.3)
MDS WHO 2016 Diagnosis					
RS-T	9 / 14	2 / 9	64.3 (35.1, 87.2)	22.2 (2.8, 60.0)	42.1 (-1.2, 74.7)
RS MLD/SLD	46 / 135	8 / 65	34.1 (26.1, 42.7)	12.3 (5.5, 22.8)	21.8 (7.1, 35.9)
Not RS	3 / 4	0 / 2	75.0 (19.4, 99.4)	0.0 (0.0, 84.2)	75.0 (-22.9, 99.4)
Geographic location					
North America	17 / 31	4 / 19	54.8 (36.0, 72.7)	21.1 (6.1, 45.6)	33.7 (5.1, 58.4)
Europe	41 / 122	6 / 57	33.6 (25.3, 42.7)	10.5 (4.0, 21.5)	23.1 (7.4, 38.0)

Reviewer's comments: As noted above, patients with high erythropoietin levels were unlikely to achieve a response. The data hint at the possibility that patients with MDS/MPN-RS-T may be more likely to respond compared to other histologies, but the number of cases is small and the analysis is not pre-planned and thus should be considered exploratory only. The difference in response rate by location is of interest since it may suggest that differences in practice affected the results. In particular, practitioners in North America appear more willing to allow longer delays in transfusion, leading to a higher rate of response in both arms. Again, the case numbers are small and the significance of this finding uncertain.

Dose/Dose Response

Patients on study MDS-001 were dose increased after inadequate response to two doses at a given dose level, starting at 1.0 mg/kg and increasing up to 1.75 mg/kg.

The clinical pharmacology review contains a complete evaluation of dose and dose response. Key findings are related to the appropriateness of the proposed dosing regimen are summarized below:

- An increase in the response rate was observed when examining the efficacy of doses of <0.8 mg/kg versus ≥ 0.8 mg/kg.
- Dose increases were triggered by lack of response after two doses at a given dose level, although steady state was reached only after the third dose at a given dose level.
- The relationship between dose and response at doses of 1.0-1.75 mg/kg was unclear. A linear trend towards greater responses at higher doses was observed, but the trend was not statistically significant.

Reviewer's comments: The starting dose of 1.0 mg/kg appears reasonably well supported by the available evidence. However, the proposed dose increases are less well supported given the lack of clear evidence of improvement in response at doses of >1.0 mg/kg. In particular, since dose increases were permitted before steady state serum concentrations were achieved, the importance of the dose increase in the achievement of any response after dose increase is difficult to assess.

Durability of Response

Duration of response for RBC-TI was defined as the longest duration of response for subjects who achieved at least a TI-8 during the primary analysis period (weeks 1-24) or in weeks 1-48. The median duration of response for patients who achieved TI-8 in weeks 1-24 was 30.6 weeks in the Iuspaterecept arm and 13.6 weeks in the placebo arm. No major difference in duration of response was reported for analysis in weeks 1-48 versus 1-24.

Persistence of Effect

Refer to section on durability of response, above.

Additional Analyses Conducted on the Individual Trial

Quality of Life measurement using PRO data

Quality of life was examined using the EORTC QLQ-C30 and QoL-E instruments. There were no prespecified hypotheses regarding comparison of the health-related quality of life (HRQoL) assessments. Therefore, all results are considered exploratory and descriptive. Key results for

the EORTC QLQ-C30 instrument were included in the final CSR and further results were added in a separate report.

Patients were asked to fill out the EORTC QLQ-C30 on day 1 of cycles 1, 3, 5, and 7 and week 25. A patient was considered compliant if at least half of the questions were answered at a given assessment visit. Compliance rates were generally high and similar between the two arms, with the exception of a compliance rate of 89% in the luspatercept arm and 79% in the placebo arm at 25 weeks (table 13). It should be noted that the recall period for the PRO instrument was one week and it was administered on day 1 of each cycle. Thus, changes in quality of life due to adverse events related to luspatercept may not be accurately assessed due to the recall period corresponding to the time period of lowest plasma drug level.

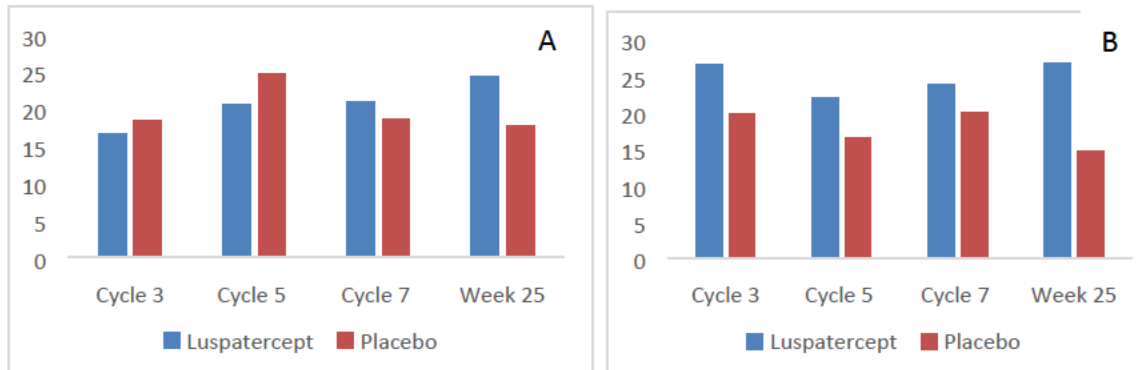
This review will concentrate on results for global quality of life and for the symptoms of fatigue and dyspnea as these are the most relevant to patients requiring treatment for anemia in the setting of MDS.

Table 13. Study MDS-001: EORTC QLQ-C30 Completion Rate

Study Visit	Completion Rate Based on Randomized Population n/N (%)		Completion Rate Based on On-Study Population n/N (%)	
	Luspatercept	Placebo	Luspatercept	Placebo
Cycle 1 Day 1	150/153 (98%)	76/76 (100%)	150/153 (98%)	76/76 (100%)
Cycle 3 Day 1	137/153 (90%)	70/76 (92%)	137/151 (91%)	70/76 (92%)
Cycle 5 Day 1	133/153 (87%)	67/76 (88%)	133/146 (91%)	67/73 (92%)
Cycle 7 Day 1	112/153 (73%)	60/76 (79%)	112/134 (84%)	60/70 (86%)
Week 25	113/153 (74%)	54/76 (71%)	113/127 (89%)	54/68 (79%)

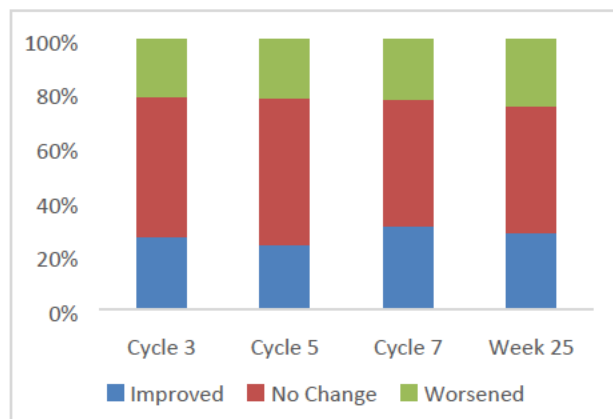
Between 17% and 24% of patients on the luspatercept arm and 18-25% of those on the placebo arm reported improved global quality of life during the primary phase of the study (figure 7). No clear temporal trend was observed. Worsening of global quality of life was reported in 22-27% of patients receiving luspatercept and 15-20% of patients receiving placebo. No clear temporal trend was observed, but patients receiving luspatercept were more likely than those receiving placebo to report worsened quality of life throughout the first 25 weeks of the study.

Figure 7: Improved (A) and worsened (B) global quality of life by study arm and cycle.



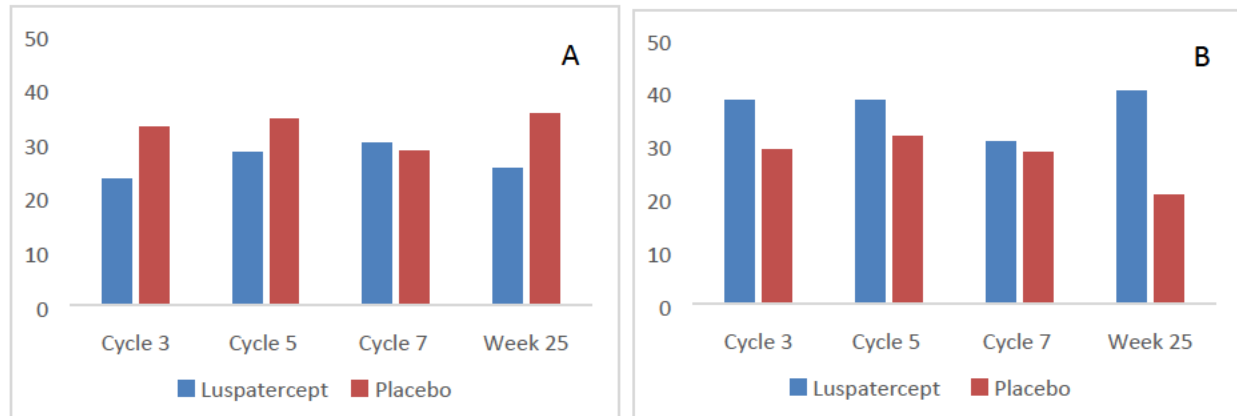
When only patients who responded to treatment in the luspatercept arm were included, the results were numerically slightly better, with about as many patients reporting improvement versus worsening of global quality of life. However, there was no evidence of improved QoL in patients receiving luspatercept, even after restricting to patients who experienced a response by trial criteria, demonstrating that the lack of improvement in global QoL could not be attributed entirely to a lack of response to therapy (figure 8.)

Figure 8: Change in global QoL over time for patients receiving luspatercept who responded to therapy (at least TI-8) during the primary phase of treatment.



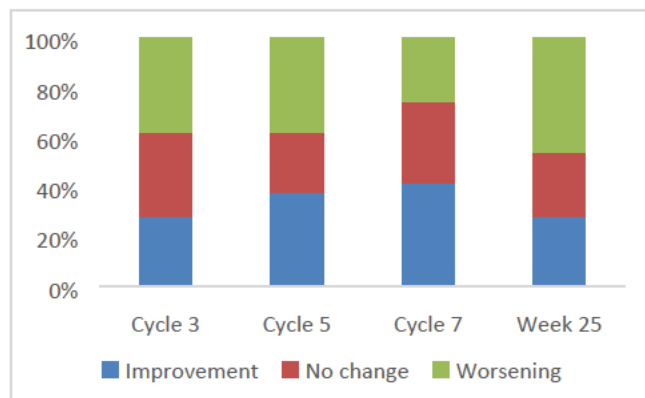
When fatigue was examined, a similar result was seen, with 23-30% patients receiving luspatercept and 29%-35% of those receiving placebo reporting improved fatigue. Worsening fatigue was reported by 31-40% of those receiving luspatercept and 21-32% of those receiving placebo.

Figure 9: Improved (A) and worsened (B) fatigue by arm and cycle number.



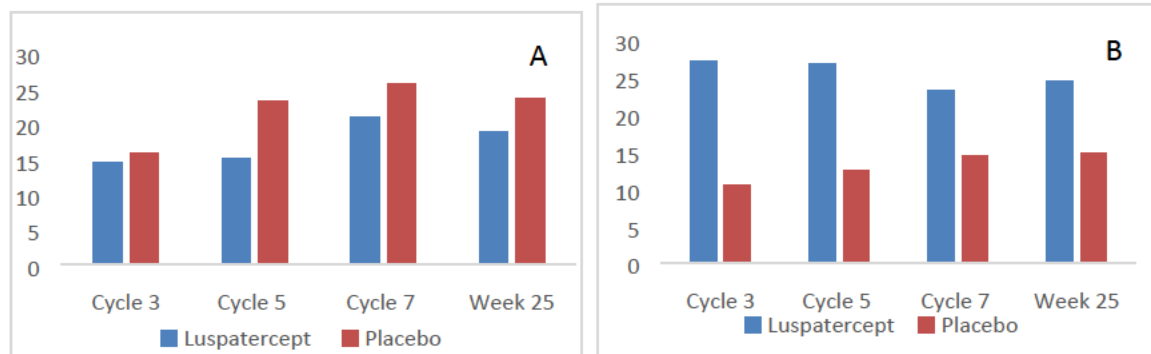
Patients who were considered responders showed a similar lack of improvement in quality of life. For example, in week 25, twenty-three patients who responded reported worsening fatigue versus 14 reporting improvement and 13 reporting no change in fatigue compared to baseline levels (figure 10).

Figure 10: Changes in fatigue over time for patients on the luspatercept arm who responded to therapy.



Similarly, 15-21% of those receiving luspatercept and 16-24% of those receiving placebo reported improved dyspnea during cycle 3 to week 25 of the study and 23-27% of those receiving luspatercept and 11-15% of those receiving placebo reported worsening.

Figure 11: Improved (A) and worsened (B) dyspnea by arm and cycle number.



Reviewer’s comments: *The PRO data do not show improvement in global quality of life or severity of key symptoms among patients receiving luspatercept. In general, patients receiving luspatercept were more likely to report worsening in quality of life and less likely to report improvement compared to those receiving placebo. It should be noted that the survey was given at the start of each cycle, at the time when the blood level of luspatercept was at its lowest, and that the recall period for the survey was 1 week, i.e. patients were asked to recall their symptoms and quality of life in the past week. Thus, the instrument is likely to underestimate the extent of disability caused by the medication. Although the analyses were exploratory and no alpha was allocated to them, the trends are extremely clear. The PRO analysis does not support a clinically significant treatment effect of luspatercept in patients with anemia related to MDS.*

Health Care Utilization

Health care utilization was documented by examining office visits, ED visits, and hospitalizations in patients on study MDS-001. Patients in the placebo arm were more likely to require an office visit compared to patients on the luspatercept arm, with office visits being documented in 66% of patients receiving luspatercept and 71% of those receiving placebo. However, patients receiving luspatercept were numerically more likely to require ED visits compared to those receiving placebo, with 33% of those on luspatercept versus 26% of those receiving placebo requiring an ED visit. In addition, among patients who required an ED visit, the number of visits per patient required was higher in the luspatercept arm, at an average of 1.76 visits/patient versus 1.3 visits/patient in the placebo arm. Rates of hospitalization were similar between the two arms.

Table 14: Health care resource utilization rates by study arm and resource type

	Luspatercept (visits/patients (%))	Placebo (visits/patients (%))
Number of office visits	477/101 (66%)	265/54 (71%)

Table 14: Health care resource utilization rates by study arm and resource type

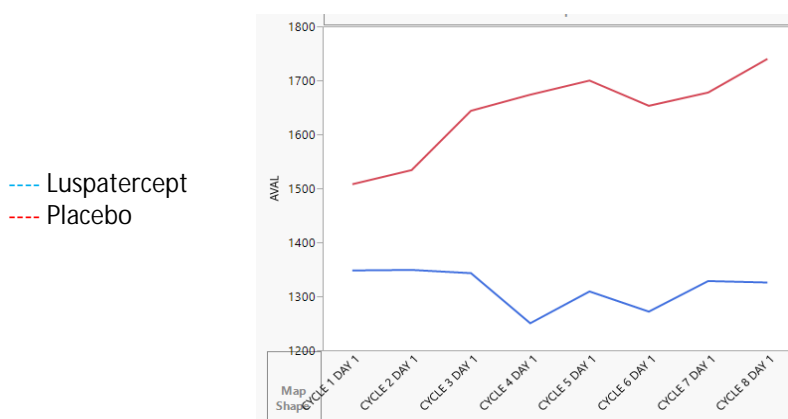
	Luspatercept (visits/patients (%))	Placebo (visits/patients (%))
Number of ED visits	88/50 (33%)	26/20 (26%)
Number of hospitalizations	73/43 (28%)	39/24 (32%)

Reviewer's comment: No clear pattern of increased or decreased health care utilization was associated with use of luspatercept. Use of the drug does not appear to reduce the need for medical intervention in patients with very low to intermediate risk MDS, suggesting that any reduced need for visits for transfusion was balanced by an increased need for treatment of adverse events.

Changes in Total Body Iron

Baseline ferritin was slightly lower in patients receiving luspatercept versus placebo, with a mean ferritin of 1348 in the luspatercept arm versus 1508 in the placebo arm. Mean ferritin trended up in the placebo arm in weeks 1-24, whereas it was stable in the luspatercept arm (see figure 12, below.) Among patients receiving luspatercept who continued on the study for at least 8 cycles past the first 24 weeks, mean ferritin was roughly stable over time, although an increase in ferritin was seen at the last recorded visit. It should be noted that ferritin did not normalize in either arm, but remained very elevated in both arms and throughout the study. As noted above, no MRI for liver iron or liver biopsies for iron content were reported and thus the significance of the changes in ferritin are uncertain.

Figure 12: Changes in ferritin by arm and study visit



Of note, per the concomitant medications file, five patients on the luspatercept arm and one on the placebo arm received IV or oral iron during the course of the study. Conversely, iron

chelating agents were given during the course of the study to 75 (49%) patients receiving luspatercept and 37 (49%) receiving placebo. The effect of iron and iron chelating agents on the above results is uncertain but felt to be likely to be minor.

Reviewer's comments: There appears to be a stabilization in ferritin among patients receiving luspatercept compared to a continued increase in those receiving placebo, consistent with fewer transfusions. However, the role of iron administration and chelation during the study may confound the data and the significance of the changes in ferritin is uncertain in the absence of any confirmatory evidence of lower liver or cardiac iron.

The gold standard tests for total body iron content, liver MRI or biopsy, were not performed. Ferritin alone may not adequately reflect total body iron stores. One study of cardiac and hepatic siderosis in MDS and other causes of transfusion dependent anemia found that ferritin underestimated liver iron concentration in 1.4% of patients with MDS and overestimated liver iron concentration in 10.1% of patients with MDS²⁶. The effect of luspatercept treatment on the risk of over- or underestimation of liver iron is unknown. Thus, any conclusions about the effect of luspatercept on iron overload based on serum ferritin measurements alone are necessarily tentative.

Erythropoietin levels

Baseline and post-baseline erythropoietin levels were measured in trial MDS-001. Patients who received luspatercept were more likely to have a post-baseline shift to higher levels of erythropoietin compared to those who received placebo. However, patients who experienced a response were not apparently more likely to have an increase in erythropoietin compared to the overall cohort of patients receiving luspatercept.

Table 15: Erythropoietin at baseline and post-baseline changes in patients treated on the luspatercept arm

		<i>post-baseline</i>		
		<100	100-500	>500
	<100 (N=69)	17 (25%)	44 (64%)	8 (12%)
<i>baseline</i>	100-500 (N=69)	0	24 (35%)	45 (65%)
	>500 (N=15)	0	1 (7%)	14 (93%)

Table 16: Erythropoietin at baseline and post-baseline changes in patients treated on the placebo arm

		<i>post-baseline</i>		
		<100	100-500	>500
<i>baseline</i>	<100 (N=34)	26 (76%)	8 (24%)	0
	100-500 (N=32)	2 (6%)	22 (69%)	8 (25%)
	>500 (N=9)	0	4 (44%)	5 (56%)

Table 17: Erythropoietin, Responders on luspatercept arm only

		<i>post-baseline</i>		
<i>(IU/L)</i>		<100	100-500	>500
<i>baseline</i>	<100 (N=30)	9 (30%)	20 (67%)	1 (3%)
	100-500 (N=26)	0	13 (50%)	13 (50%)
	>500 (N=2)	0	1 (50%)	1 (50%)

Reviewer’s comments: *Patients who received luspatercept were more likely to have an increase in erythropoietin after treatment compared to those who received placebo. The significance of this finding is uncertain, although it is concerning for several reasons. First, elevated erythropoietin levels are correlated with poorer response to therapy with ESA. Thus, patients who receive luspatercept may be less likely to respond to treatment with ESAs in the future. Although the current trial involved only subjects who were resistant or intolerant to ESAs and the proposed indication is for patients who are resistant to treatment with ESAs, this finding suggests that any consideration of movement of luspatercept to an earlier line of therapy should be undertaken only with caution. In addition, prior work has established that some tumors have erythropoietin receptors on their surface, possibly indicating a mechanism of action by which SPM may occur.*

6.2 A536-03: A phase 2, open-label, ascending dose study of ACE-536 for the treatment of anemia in patients with low or intermediate-1 risk myelodysplastic syndrome

Trial Design

Overall design

Single arm, open label, dose escalation and dose expansion study of ACE-536 in patients with anemia associated with low or intermediate-1 risk MDS who were not previously treated with an ESA. Dosing cohorts planned from 0.125 mg/kg to up to 1.75 mg/kg every 3 weeks with expansion cohorts starting at dose level 1.0 mg/kg every 3 weeks.

Clinical Review
Elizabeth Pulte
BLA 761136 Original 2
REBOLZYL (luspatercept-aamt)

Expansion cohorts were as follows:

- Cohort 1: Consisted of patients with high or low transfusion burden with at least 10 in each group
- Cohort 2a: Consisted of patients with ringed sideroblasts, low transfusion burden (<4 units within 8 weeks prior to cycle 1), less than 4 weeks ESA exposure, and serum erythropoietin of ≤ 200 IU/L
- Cohort 2b: Subjects with <15% RS in marrow, ≤ 6 RBC units in 8 weeks prior to cycle 1 day 1

Study endpoints:

Primary endpoints:

- Primary efficacy endpoint defined as proportion of subjects who had modified erythroid response defined as
 - Hgb increase of ≥ 1.5 g/dl from baseline for ≥ 14 days in the absence of transfusion or
 - Reduction of either ≥ 4 units or $\geq 50\%$ of units of RBCs transfused over period of 8 consecutive weeks compared to number transfused in 8 weeks immediately prior to cycle 1 day 1

Secondary endpoints:

- Safety analyses including assessment of clinical safety, AEs, VS measurements, and clinical laboratory information
- Efficacy/PD analysis including:
 - Modified erythroid response
 - Erythroid response as defined by IWG 2006 criteria
 - Time to and duration of modified erythroid response and erythroid response
 - Frequency of RBC transfusion and rate of RBC transfusion independence
- Other PD endpoints including
 - Biomarkers for iron metabolism
 - Biomarkers for bone metabolism
 - Relationship of biomarkers to response
 - Neutrophil and platelet response rates

Exploratory endpoints:

- Evaluation of biomarkers related to TGF-beta superfamily
- Evaluation of self-reported QoL

Key inclusion and exclusion criteria:

Key eligibility criteria

- Adults with MDS with WBC <13K, low or intermediate-1 risk disease
- Anemia defined as follows:
 - Hgb <10 g/dl on two measurements not influenced by RBC transfusion within 7 days of measurement for LTB subjects (all cohorts) or
 - Transfusion dependent, having received ≥ 4 units within 8 weeks prior to cycle 1 day 1 for expansion cohort 1 or ≤ 6 units RBCS within 8 weeks for cohort 2B
- Erythropoietin levels and prior ESA as follows:
 - Dose escalation and dose expansion cohort 1: erythropoietin level >500 IU/L or non-responsive, refractory, or intolerant to ESA or ESA contraindicated or unavailable
 - Expansion cohort 2: If RS+, <4 weeks exposure to ESA and serum erythropoietin ≤ 200 IU/L; if RS- then any prior erythropoietin level and ESA treatment allowed
- No alternative treatment options available or appropriate
- Adequate organ function defined as:
 - Creatinine ≤ 2 x ULN
 - AST/ALT <3 x ULN
 - TB <2 x ULN
- Adequate vitamin and iron levels

Key exclusion criteria

- Prior azacytidine or decitabine
- Treatment with ESA, G-CSF or lenalidomide within 28 days of cycle 1 day 1
- Iron chelation initiated within 56 days prior to cycle 1 day 1
- Treatment with another investigational drug or device or approved therapy for investigational use within 28 days of cycle 1 day 1 or within 5 times the half-life, if known, whichever is longer
- Platelet count <30 x 10⁹/L
- Known HIV, hepatitis B or C, history of VTE or ATE, uncontrolled hypertension, other concurrent illness that may preclude subject from participating
- Secondary MDS
- Prior treatment with sotatercept or luspatercept

Reviewer's note: The duration of follow up for study A536-03 was initially 8 weeks, increased to 12 weeks in the first amendment of the trial protocol. No criteria for RBC transfusion was prespecified in the trial. However, the protocol provided guidance recommending transfusion for hemoglobin of <8 or at the discretion of the investigator if symptoms or anemia or comorbidities were present.

Statistical Analysis Plan

Patients were assessed for erythroid response for up to 24-weeks following initiation of treatment. Erythroid response endpoints will be determined by monitoring hematologic laboratory values and RBC transfusions. Secondary efficacy endpoints were assessed by examining other hematology, erythropoiesis, iron metabolism, and bone metabolism parameters.

The maximum number of patients to be enrolled in the study was 128. There was no formal sample size calculation for the dose escalation portion of the study. A sample size of 30 evaluable patients in the expansion cohort 1 would provide approximately 90% power with 1-sided significance level of 0.05 to differentiate an erythroid response rate of 30% from a minimal erythroid response rate of 10% based on Fisher exact test. A sample size of 25 evaluable patients in each group of expansion cohort 2 will provide approximately 80% power with 1-sided significance level of 0.05 to differentiate an erythroid response rate of 30% from a minimal erythroid response rate of 10% based on Fisher exact test.

The primary efficacy analysis was performed on the ITT population. All efficacy summaries were presented by dose cohort for LTB and HTB patients separately. No formal hypothesis testing was planned. Summaries were also generated for following group of patients:

- Patients in the expansion cohorts 1, 2A, and 2B
- All patients in the ITT population
- Lower dose group includes patients on 0.125, 0.25 and 0.5 mg/kg dose cohorts
- Higher dose group includes patients on 0.75 mg/kg and above
- Higher dose patients who meet expansion cohort 2A criteria
- Higher dose patients who meet expansion cohort 2B criteria

The primary endpoint, a modified erythroid response, was summarized using a point estimate of response rate with exact 95% confidence interval (CI) based on binomial distribution for LTB and HTB patients separately. The complete hemoglobin measurements and RBC transfusion records were listed for each patient.

Secondary endpoints were analyzed similar to the primary endpoint.

Protocol Amendments

Amendment 1

- Dose escalation cohort populations changed from 6 to a minimum of 3 subjects
- Dose escalation levels revised to reflect starting dose of 0.125 mg/kg

- Clarified that maximum dose level for a subject will not exceed maximum dose level evaluated in the dose escalation cohorts
- Follow up increased from 8 to 12 weeks for a total duration of 28 weeks of study participation
- Limitations on serum erythropoietin level and lack of available therapy added to inclusion criteria
- Inclusion criteria regarding informed consent clarified
- Exclusion criterion related to restrictions on conditions not related to the underlying condition modified
- Safety review team language added to state that if a DLT occurs in 0/3 subjects, dose escalation may occur, if DLT occurs in 1/3 subjects, a further 3 should be enrolled and dose escalated only if DLT occurs in 1/6 after additional enrollment
- Dose limiting toxicity definition modified to include non-infectious AEs of grade 3+ and infectious AEs of 4+
- Additional chemistries added
- Dose modification for hemoglobin rules modified from ≥ 13 g/dl to ≥ 12 g/dl

Amendment 2

- Evaluation of self-reported QoL added in the expansion cohort
- Two additional dose escalation cohorts (1.33 mg/kg and 1.75 mg/kg) added
- Maximum dose changed to 1.75 mg/kg
- Exclusion criteria added for transfusion within 7 days prior to cycle 1 day 1
- Exclusion criteria added for prior treatment with sotatercept or luspatercept
- Specified that hemoglobin levels should be collected just prior to transfusion during the study
- Additional follow up visit added between end of treatment and end of study
- Definition of DLT changed from any treatment related SAE to any treatment, related SAE grade 3 or higher
- ITT definition changed to maintain consistency with safety population

Amendment 3

- Clarified that all subjects must use birth control up to 12 weeks following last dose of luspatercept
- Updated language providing objective measures for determining RBC transfusion requirements
- Dose modification rules updated to restrict dose reductions to dose levels tested in dose escalation cohorts and determined to be safe
- Dose modification rules updated to replace 25% dose reduction with defined dose levels that were reviewed by safety review team in the dose escalation phase

Clinical Review
Elizabeth Pulte
BLA 761136 Original 2
REBOLZYL (Iuspatercept-aamt)

- Dose titration rules updated to limit dose titrations to levels tested in the escalation cohorts
- Rules for titration in the expansion phase updated to define titration for both HTB and LTB subjects

Amendment 4

- Included the ability to use QoL tools other than FACT-An questionnaire
- Added expansion cohort 2 and increased planned enrollment
- Details of lyophilized powder formulation added
- Inclusion criteria updated
- Study drug administration revised to limit number of injections per dose to 4 and volume increased to accommodate higher doses

Amendment 5

- Number of centers increased
- Definitions of expansion cohorts 2A and 2B expanded
- Removed restriction requiring 24 hours between RBC transfusion and dosing
- Additional dose modification rule added for $WBC \geq 13 \times 10^9/L$, which required dose delay until $WBC < 13 \times 10^9/L$ and resolution of associated syndromes and discontinuation if cytomorphologic changes on marrow compared to baseline

STUDY RESULTS

Compliance with Good Clinical Practices

The study was conducted in accordance with Good Clinical Practice guidelines as described in the International Council for Harmonization (ICH) E6 guidelines and in accordance with the ethical principles outlined in the Declaration of Helsinki. The study was approved by an IEC prior to commencement.

Financial Disclosure

No disclosable financial arrangements with the Sponsor were reported for this trial.

Data Quality and Integrity

Data were provided as legacy datasets. In general, data quality appeared to be acceptable. The last subject last visit for trial A536-03 was reported to be 9 August 2017 and the report is dated 12 September 2018. Also see review of data quality and integrity issues in the ISS data files noted in the assessment of MDS-001, above.

Patient Disposition

Overall, 101 of the 107 subjects enrolled completed the protocol as planned. Seventy-five transitioned to study A536-05 after completion of the initial protocol, including five of the 9 who were included only in the safety analysis. Of the 6 who did not complete the protocol as planned, one discontinued at Sponsor's discretion due to being found not to be eligible for the protocol, two due to withdrawal by subject, and three due to other reasons including worsening of general condition, no response, and care transferred to another hospital.

Protocol Violations/Deviations

A total of 74 protocol deviations occurred in 66 subjects. Of these, 30 were deviations related to entry criteria. Of the non-entry criteria issues, the most common was dose not modified according to preset criteria (16 subjects) and study treatment deviations (9 subjects).

Demographic Characteristics

The total number of patients reported as being treated on trial A536-03 was 116. However, 9 of these patients apparently enrolled after the completion of the primary efficacy analysis and no efficacy data were included for them. Results for these patients will be included in the safety analysis only. Of the patients treated and with efficacy results available, 92 were treated at the recommended dose of 1.0 mg/kg. Demographic characteristics of patients treated in this cohort were similar to those of patients on the overall study.

Transfusion burden was evaluated as being in one of two categories: low transfusion burden for patients requiring ≤ 4 units of packed RBC per 8 weeks versus high transfusion burden requiring > 4 units per 8 weeks. The primary objective of the study varied by transfusion burden (see below). In addition, only 57% of all patients and 52% in the 1.0 mg/kg cohort had ring sideroblasts. Thus, the data from the phase 2 study are considered supportive only.

Table 18: Demographic characteristics for patients on trial A536-03

Demographic Parameters	Total (N=116)	Dose 1.0 mg/kg (N=92)
Sex		
Male	72 (62%)	62 (67%)
Female	44 (38%)	30 (33%)
Age group		
< 65 years	29 (25%)	21 (23%)

Table 18: Demographic characteristics for patients on trial A536-03

Demographic Parameters	Total (N=116)	Dose 1.0 mg/kg (N=92)
65-74	44 (38%)	33 (36%)
≥ 75 years	43 (37%)	38 (41%)
Median age (Min, Max)		
	72 (27, 90)	73 (30, 90)
Baseline Performance Status*		
ECOG 0	60 (52%)	53 (58%)
ECOG 1	53 (46%)	37 (40%)
ECOG 2	2 (2%)	2 (2%)
Race		
White	116 (100%)	92 (100%)
Geographic location		
EU	116 (100%)	92 (100%)

*No data available for one subject in the 0.25 mg/kg cohort

Table 19: Disease and other pertinent characteristics for patients on trial A536-03

Demographic Parameters	Total (N=116)	1.0 mg/kg (N=92)
Baseline transfusion		
≤4 units/8 weeks	65 (56%)	58 (63%)
>4 units/8 weeks	51 (44%)	34 (37%)
Platelet count (x10⁹/L)		
<100	21 (18%)	19 (21%)
≥100 to 400	83 (72%)	65 (71%)
>400	12 (10%)	8 (9%)
Prior ESA therapy		
Yes	51 (44%)	38 (41%)
No	65 (56%)	54 (59%)
IPSS-R category		
Very low risk	5 (4%)	5 (5%)

Table 19: Disease and other pertinent characteristics for patients on trial A536-03

Demographic Parameters	Total (N=116)	1.0 mg/kg (N=92)
Low risk	67 (58%)	53 (58%)
Intermediate risk	34 (29%)	25 (27%)
High or very high	10 (9%)	9 (10%)
Ring sideroblasts		
Yes	66 (57%)	48 (52%)
No or unknown	50 (43%)	44 (48%)

Reviewer's comments: Note that 9 patients entered the protocol after the initial CSR and efficacy data files completed. These patients will be included in the safety review, but not the efficacy review. The population, treatment, and follow up of the phase 2 study were substantially different from those of trial MDS-001. In particular, the population treated in the phase 2 study was not limited to patients with ring sideroblasts or lower risk MDS. This limits the conclusions that can be drawn from a review of efficacy in this study and it will be used primarily to examine safety.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Use of prior medications was observed in 87% of subjects, with the most commonly used medications including proton pump inhibitors, aspirin, statins, and thyroid supplementation. Nineteen subjects had received prior treatment for MDS other than ESAs including lenalidomide in 10 subjects and 50 had received prior treatment with ESAs.

The vast majority (94%) of subjects received concomitant medications. Of note, the most commonly used concomitant medications were similar to the most common prior medications, with the exception of ramipril, which was used concomitantly in 23 subjects but not commonly used prior to the start of the study. In addition, pantoprazole was used prior to the study by 31 subjects and concomitantly by 37 subjects.

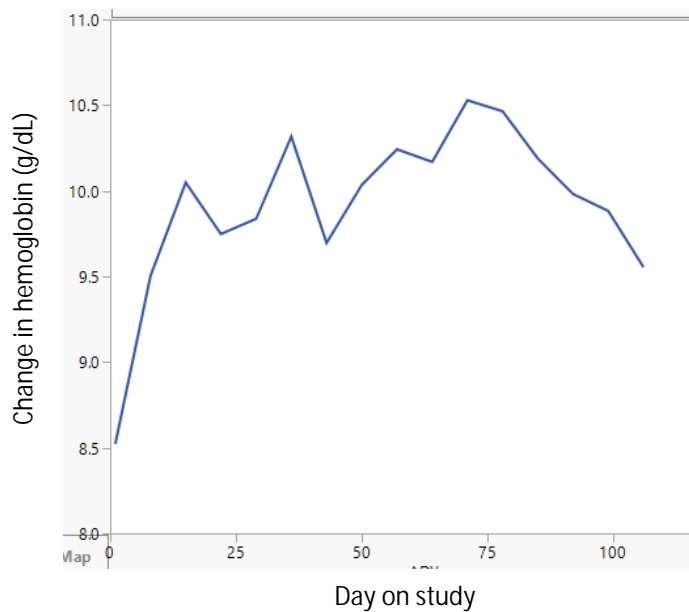
Reviewer's comments: Anti-hypertensives and proton pump inhibitors were commonly used concomitant medications in the luspatercept arm of the controlled trial. These results support the suggestion that luspatercept results in an increased risk of hypertension and gastrointestinal upset.

Efficacy Results – Primary Endpoint

As noted above, the efficacy endpoints used in this study were different from those used in the controlled trial, limiting the extent to which the information can contribute to the review.

The primary efficacy endpoint for patients with low transfusion burden was increase in hemoglobin of at least 1.5 g/dL. Individual hemoglobin values varied considerably, with net change in hemoglobin compared to baseline value ranging from -2.48 g/dL to +5.3 g/dL. When hemoglobin values occurring within 14 days of a documented transfusion were eliminated, 41 patients (77%) achieved an increase in hemoglobin of at least 1.5 g/dL. The median change in hemoglobin at any time on study for all patients was 1.4, excluding values obtained within 14 days of transfusion and values obtained >8 weeks after end of treatment. Changes over time are shown in figure 13, below. The majority of the increase in hemoglobin occurred in the first 15 days of treatment, although some increase could be observed in later time periods.

Figure 13: Median change in hemoglobin in low transfusion burden patients receiving luspatercept excluding values obtained within 14 days of transfusion*



*For clarity, only values obtained weekly (i.e. 1, 8, 15, etc) are included.

Per the Sponsor's analysis, 24 out of 47 (51%) of the high transfusion burden subjects experienced a decrease in transfusion burden of ≥ 4 units or $\geq 50\%$.

Reviewer's comments: The data from the phase 2 trial are difficult to interpret in context and considered supportive only. The median change in hemoglobin in the low transfusion burden

group was <1.5 g/dL; however, the majority of individual patients did achieve an increase in hemoglobin of at least 1.5 g/dL. It is interesting to note that the main apparent effect of luspatercept occurs in the first cycle whereas the pharmacokinetic data suggest that the drug reaches steady state after the third cycle.

Reduction in transfusion burden is not an endpoint that has previously been used for approval of supportive medications in MDS and thus no further analysis or comment will be made on the Sponsor's finding of reduced transfusion burden.

Efficacy Results – Secondary and Other Relevant Endpoints

Per the Sponsor's report, 12 out of the 47 (26%, 95% CI 14-40%) high transfusion burden subjects treated experienced a TI-8. Two of these patients were treated at lower doses than used in the phase 3 trial, including one treated at 0.125 mg/kg and one at 0.75 mg/kg. Of the 37 patients treated at a dose of 1.0 mg/kg or higher, 10 (27%) experienced TI-8.

Subpopulations

Due to the small sample size among patients receiving the recommended dose and endpoints of uncertain significance, subpopulation analysis was not undertaken.

Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

No PRO data were included in the submission for this study.

Additional Analyses Conducted on the Individual Trial

No additional analyses were conducted on this trial.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

The primary endpoints, treatment plan, and study populations varied between the two studies, making cross study comparison difficult. The primary endpoints of decreased transfusion burden or increased hemoglobin used in the phase 2 trial have not been demonstrated to produce meaningful clinical benefit to the patient and therefore are not adequate endpoints for

approval.

The primary endpoint of MDS-001 was TI-8 in the first 24 weeks of treatment. This can be reasonably compared to the secondary endpoint of TI-8 in the phase 2 trial. The point estimate of TI-8 for MDS-001 was higher at 38% compared to 26% seen in the phase 2 trial, but the confidence intervals for the two values overlap. Thus, there appears to be an effect observed across trials.

However, several issues complicate the interpretation of these data. First, the prespecified hemoglobin values used in each trial (hemoglobin of <8 or mean of the pre-transfusion hemoglobin values prior to start of the study) may be lower than the threshold at which the investigator might have considered transfusion off protocol, especially given the high probability of comorbidities in this patient population and the risk of changing clinical status. Conversely, the necessary allowance for transfusion when clinically required introduces the risk of bias, especially in a single arm trial or where there is risk of accidental unblinding.

These issues make the finding of transfusion independence a difficult endpoint to interpret.

In addition, expert opinion has expressed doubts as to the value of an 8 week transfusion free period⁴, especially for patients with a low baseline transfusion burden.

7.1.2. Secondary and Other Endpoints

Longer periods of transfusion independence were not evaluated in trial A536-03. When transfusion independence for up to 16 weeks was evaluated in MDS-001, an effect of luspatercept continued to be observed, but the point estimate of the effect decreased to 19% of subjects. When patients who had a response starting in weeks 1-24 but ending at any time were included in the analysis, the point estimate increased to 27.5%. Thus, the effect is robust, but only a minority of patients will achieve a more than transient benefit.

Increases in hemoglobin were observed in both the phase 2 trial and the phase 3 trial. Among patients treated with the recommended dose of luspatercept who had a low transfusion burden on the phase 2 trial, the majority of patients did achieve an increase in hemoglobin of at least 1.5 g/dL. In the phase 3 trial, the Sponsor's analysis showed an increase in hemoglobin of >1 g/dL among patients who received luspatercept with a sustained response among those who had a TI-8 response and a rapid decrease among those who did not. The FDA's analysis showed a smaller increase of <1 g/dL among patients who received luspatercept and experienced a response only, with no difference in hemoglobin observed between luspatercept non-responders and placebo.

The two major differences in the analysis methods were related to the baseline hemoglobin used and the decision of whether to include post-transfusion hemoglobin values. The Sponsor's

analysis used as baseline hemoglobin the mean of all documented pretransfusion hemoglobin values during the 16 weeks prior to dose 1. This definition has the advantage of avoiding confounding by transfusion, but the disadvantage of establishing a baseline that may not be relevant to the hemoglobin observed at day 1 of treatment and therefore inflating the apparent effect of the investigational product on hemoglobin. Conversely, the FDA's definition avoids the latter risk at the expense of increasing the former. An examination of the last pretransfusion value available demonstrated that said value was, for most patients, so remote from the start of the study as to be not representative of the hemoglobin value at the start of the study and thus an evaluation using last pre-transfusion hemoglobin was not practical.

The majority of the increase in hemoglobin observed in either study occurred in the first 8-15 days after administration of the first dose. This is unexpected, given that the steady state concentration is not reached until after the third dose and raises concern about confounding. However, nonclinical findings also showed that the majority of the increase in hemoglobin observed in monkeys occurred in the first 29 days of treatment. Since the increase in non-clinical studies clearly occurred in the absence of transfusion, it seems reasonable to conclude that an increase in hemoglobin early in treatment is biologically plausible.

Taken together, the evidence suggests that luspatercept use is associated with an increase in hemoglobin in patients who respond, but the extent of the hemoglobin increase is uncertain and variable from patient to patient.

7.1.3. Subpopulations

Subpopulation analysis indicated lower efficacy with confidence intervals overlapping zero for patients with higher baseline hemoglobin, female gender, ECOG performance status of 0 or 2, high baseline transfusion burden, low platelet count, and high erythropoietin levels. The trial was not powered to detect differences in efficacy between subpopulations, so the results should not be overinterpreted. However, the data are particularly concerning for several populations.

First, the point estimate and risk difference compared to placebo are both very low for patients with high transfusion burden. This, combined with the confidence interval overlapping zero, suggests that the efficacy in this population is quite low.

Second the point estimates for efficacy trend down as erythropoietin increases, going from 45.1% for patients with erythropoietin of <100 IU/L to 19.2% for patients with erythropoietin of 400 IU/L or higher. This trend along with the overlapping confidence intervals provide evidence that the efficacy is lower in patients with a higher erythropoietin level.

A similar trend was observed for platelet count, with higher platelet counts being associated with higher efficacy and a confidence interval overlapping zero for patients with the lowest

platelet count.

Overall, the bulk of the evidence supports that luspatercept has less or no efficacy in patients with high transfusion burden, low platelets, or high erythropoietin. The effect of gender and performance status on efficacy cannot be determined using the available data.

7.1.4. Dose and Dose-Response

Patients treated with a dose of at least 1 mg/kg were more likely to experience a response compared to those who were treated at lower doses. However, there was no clear increase in response in doses higher than 1 mg/kg. As noted above, the analysis of dose-response was confounded by early intra-patient dose escalation in MDS-001. The decision to dose escalate prior to the attainment of steady state serum concentration further complicates the evaluation of dose response and the need to dose escalate. Overall, no definite conclusion on the value of dose increase above 1.0 mg/kg can be drawn.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

The median duration of TI-8 was 30.6 weeks for patients on the luspatercept arm of the controlled trial. Duration of response was not discussed in the phase 2 trial. No continued effect on hemoglobin or transfusion requirement after discontinuation of treatment is expected and therefore this aspect will not be further discussed.

The apparent onset of effect, particularly in MDS-001 was within one week of administration: The largest increase in hemoglobin was observed in both low transfusion burden patients in the phase 2 trial and in the luspatercept arm of trial MDS-001 occurred between cycle 1 day 1 and cycle 1 day 8. The reason for this is not clear since the drug does not reach steady state until cycle 4. However, as noted above, similar findings were observed in non-clinical studies, which, along with the consistency of the finding between studies, provides some reassurance that this is a real effect and not an epiphenomenon due to some issue in one or more of the studies.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Patients on the above trials were monitored carefully for changes in hemoglobin and transfusion timing was adjusted in response to changes in hemoglobin. Although the increase in hemoglobin observed was modest, there was significant individual variation and increases may be high in some patients. In addition, it is not yet clear whether higher hemoglobin values are associated with an increased risk of adverse events, as has been noted in patients treated with ESAs. Thus, there is considerable risk in the postmarket setting that patients may experience insufficient monitoring resulting in excessive elevation of hemoglobin and possible increased risk of adverse events such as thrombosis, hypertension, or issues, especially if patients are not

treated per label recommendations.

7.2.2. Other Relevant Benefits

As noted in the review of trial MDS-001, above, the PRO data show a trend towards worsening in quality of life for many patients treated with luspatercept, including higher rates of reporting of worsening of key symptoms of fatigue and dyspnea and worsening of global health compared to placebo. In addition, the one week recall period of the PRO instrument may underestimate the full effect of the product on quality of life. Subgroup analysis restricting to only patients who experienced a TI-8 response did not demonstrate evidence of improved QoL in this patient population. Overall, the PRO data do not support a treatment effect.

7.3. Integrated Assessment of Effectiveness

The overall efficacy assessment does not clearly demonstrate a clinically meaningful benefit to patients with use of luspatercept in lower risk MDS. An increase in TI-8 was observed in a minority of patients, but this increase did not correlate with improved QoL or other benefit to the patient.

At least some of the apparent treatment effect may be explained by partial unblinding due to differences in the physical appearance of the placebo and luspatercept and to the decision to have the placebo produced on site rather than provided by the Sponsor. In addition, 13% of patients receiving placebo experienced a TI-8, suggesting that some of the effect was due to either fluctuations in the underlying disease or to differences in transfusion threshold used in the trial versus that used off study. Finally, the life expectancy of RBC in the circulation after transfusion is about 50-60 days²⁷. Thus, a large percentage of the apparent effect, especially in the early part of the trial, may be due to good pre-trial transfusion. This suspicion is supported by the notable increase in hemoglobin at cycle 1 day 1 compared to the baseline used by the Sponsor.

The claim that luspatercept increases hemoglobin is uncertain. The Sponsor's analysis of MDS-001 shows an increase in hemoglobin of >1 g/dL in patients who received luspatercept and were considered responders. However, when the cycle 1 day 1 value for hemoglobin is used as the baseline and values measured within 14 days of a transfusion were not included in the analysis, the apparent treatment effect is greatly reduced, with a median increase of <1 gram per deciliter observed. The phase 2 study showed a median increase of between 1 and 1.5 g/dl among patients with low transfusion burden who received a dose of 1 mg/kg of luspatercept. Individual responses varied greatly and a trend towards reduced hemoglobin was observed by the end of the study. In summary, the minority of patients who respond to treatment with luspatercept appear to have an increase in hemoglobin, but the exact amount of increase that might be expected is uncertain.

The PRO data demonstrated that patients who received luspatercept were more likely than those who received placebo to feel worse during their treatment. Key symptoms of anemia of fatigue and dyspnea were clearly numerically worse in patients treated with luspatercept. Although these findings were exploratory, they do not support a treatment effect. At best, luspatercept may be said to increase the lab value for hemoglobin without producing any of the positive effects expected with reduction of anemia. Parallels may reasonably be drawn with the results observed for the anti-arrhythmic drugs flecainide and ecainide²⁸ or to torcetrapib²⁹, all of which succeeded in their primary objective of improving an ECG or lab value but leading to deleterious effects on the patient.

Finally, interpreting the data in the best possible light, i.e. making the assumption that there were no undocumented unblinding incidents, that the transfusion free periods were due to drug effect and not to prior transfusion, and that the PRO data were unduly pessimistic, the best possible statement that can be made with respect to efficacy is that the effect size was 24.6 percentage points compared to placebo and the median duration of response was 30.6 weeks. Currently available therapy generally provides a better probability of response and longer duration of response. Lower risk MDS has a life expectancy measured in years and the value of a transient decrease in transfusion requirement in this population is unclear.

8. Review of Safety

8.1. Safety Review Approach

Data for the safety review are derived from trials MDS-001, A536-03, and A536-05.

The phase 3 study MDS-001 provided safety data at the recommended dose levels that can be directly compared to data from patients receiving placebo. For the comparison with placebo, analysis will be restricted to the first 24 weeks of treatment, as the median length of treatment for placebo treated patients was 24 weeks with a longer median treatment for luspatercept, potentially confounding the data. A separate analysis comparing subjects treated with luspatercept before and after 24 weeks will be performed.

The phase 1 and 2 study A536-03 and extension study A536-05 provide additional safety data for patients treated with luspatercept at doses from 0.125 mg/kg to 1.75 mg/kg. The data from the extension trial provides additional information concerning safety and rare events, including, most critically, late events that may not be apparent in the first 24 or 48 weeks after treatment is started. This is of particular importance for the evaluation of risk of malignancy.

The safety of luspatercept was previously reviewed in the context of treatment of β -thalassemia. Major safety issues leading to warnings and precautions being listed in the label

include thrombosis/thromboembolism and hypertension. In addition, commonly occurring adverse reactions noted in the label include headache, bone pain, arthralgia, fatigue, cough, abdominal pain, diarrhea, and dizziness. In addition, abnormalities in hepatic enzymes were noted in patients receiving luspatercept for β -thalassemia. Finally, one case of AML was reported in a patient receiving luspatercept for β -thalassemia

Thrombosis and thromboembolism were observed in 8 out of 223 patients (4%) with β -thalassemia treated on the trial that led to approval for this indication. Events included deep venous thrombosis, pulmonary embolism, portal vein thrombosis, and ischemic strokes. Thrombosis and thromboembolism were considered events of interest in the safety analysis of the MDS-001 trial. It should be noted that patients with MDS may be at lower baseline risk of thrombosis compared with those with β -thalassemia, especially those who have undergone splenectomy, and thus a lower risk might be expected in the MDS population.

Hypertension was reported in 61 out of 571 (11%) of luspatercept treated patients across all clinical studies including reports of grade 3-4 hypertension. We approached the evaluation of hypertension in several ways. First, the rate of hypertension identified as an adverse event was examined. Second, the rate of increased systolic or diastolic blood pressure in patients with a normal baseline was examined. Finally, changes in the use of anti-hypertensives during the study was examined.

Changes in liver function were examined by evaluation of both reports of adverse events of hepatotoxicity and examination of the frequency of change in hepatic enzymes from normal (CTCAE grade 0-1) to abnormal (CTCAE grade 2-4).

Progression of MDS, transformation to AML, and SPM were considered events of interest in this review. These events will be examined in detail in the review.

Other common AEs identified in the label were considered AEs of potential interest during the safety evaluation.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

A total of 269 subjects received luspatercept for the treatment of anemia in MDS in trials A536-03, A536-05, and MDS-001. The recommended starting dose identified in A536-03 was 1 mg/kg every 3 weeks and this was used as the starting dose for trial MDS-001, with dose escalation up to 1.75 mg/kg every 3 weeks allowed and dose decreases to 0.8 mg/kg or 0.6 mg/kg allowed for toxicity.

Table 20: Drug exposure in safety database

Clinical Trial Groups	Luspatercept-all patients	Luspatercept-recommended dose	Placebo
MDS-001	153	153	76
A536-03	116	92	0

8.2.2. Relevant characteristics of the safety population:

The safety database consisted of patients enrolled on either trial MDS-001 or A536-03/05. A total of 269 patients were exposed to luspatercept at any dose. Of these, 245 were exposed at the recommended starting dose of 1.0 mg/kg.

In general, the baseline demographics were similar between arms and between those treated at the recommended dose and those treated at other doses of luspatercept (table 21). Men dominated all treatment groups, but there were relatively more women in the luspatercept treatment groups. Median age was similar between groups, although, as noted above, there were more patients in the extremes of age in the placebo group. More patients were intermediate or higher IPSS-R score in the luspatercept treatment groups compared to placebo due to differences in study entry criteria in MDS-001 versus the phase 2 trial. However, higher risk disease was observed only in a small number of patients in the luspatercept groups. The majority of patients had documented ring sideroblasts, although almost 20% in the luspatercept arm did not, compared to none in the placebo group. The majority of patients in all arms were non-Hispanic white. Race was not documented for a substantial number of patients, but since the geographic location of most of those without documented race was France, a white majority country, most of those who are listed as unknown can be safely assumed to be white.

Table 21: Demographic characteristics of the safety population by treatment and dose

	Luspatercept (all)	Luspatercept (recommended dose)	Placebo
Total number	269	245	76
Gender			
Male	166 (62%)	156 (64%)	50 (66%)
Female	103 (38%)	89 (36%)	26 (34%)
Age (years)			
Median (range)	72 (27, 95)	72 (30, 95)	72 (26, 91)
IPSS-R score			
Very low	23 (9%)	23 (9%)	6 (8%)
Low	176 (65%)	162 (66%)	57 (75%)

Table 21: Demographic characteristics of the safety population by treatment and dose

	Luspatercept (all)	Luspatercept (recommended dose)	Placebo
Intermediate	59 (22%)	50 (20%)	13 (17%)
High or very high	11 (4%)	10 (4%)	0
Ring Sideroblasts?			
Yes	219 (81%)	201 (82%)	76 (100%)
No/Unknown	50 (19%)	44 (18%)	0
Race			
White	223 (83%)	199 (81%)	51 (67%)
Other	2 (1%)	2 (1%)	1 (1%)
Unknown	44 (16%)	44 (18%)	24 (32%)
Ethnicity			
Hispanic	3 (1%)	3 (1%)	4 (5%)
Other	266 (99%)	242 (99%)	74 (95%)

8.2.3. Adequacy of the safety database:

Reviewer's comment: The size of the safety database is adequate to provide estimates of common adverse reactions that may be observed with the use of luspatercept. However, key demographic populations were missing. In particular, the population of both MDS-001 and A536-03 was almost entirely racially white and ethnically non-Hispanic and thus the safety in patients of minority ethnic or racial backgrounds with MDS cannot be determined from these trials. Second, follow up in the non-randomized trial was short, with long-term follow up available only for a subset of patients who enrolled on the extension trial. This may confound analysis of the frequency of late events. In addition, follow up for MDS-001 is limited to three years and thus data regarding potential long-term toxicities are inadequate and additional information may be needed to confirm the long-term safety for luspatercept. This is of particular importance for assessing the risk of malignancy, which may occur years after a toxic exposure. All patients were over age 18 and thus no conclusions can be drawn regarding safety in the pediatric population from the available data. Finally, key tests needed to confirm or definitively rule out certain conditions were not performed (see below).

Patients receiving luspatercept were slightly more likely to have intermediate or higher risk disease. No patients on placebo and 11 on luspatercept had high or very high risk disease. These patients were excluded from analysis of progression and transformation risk.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There were several initial issues with the data files, including duplicate files of a given type labelled "current" and unreadable QoL files. After several information requests and a phone call to the Applicant, files which were readable and well organized were submitted. Further correction was required after submission of additional safety data from a data sweep in July, 2019 were provided. See section on data quality and integrity in the efficacy section of the review of MDS-001 (page 45) for further details.

8.3.2. Categorization of Adverse Events

Grouped terms were used to identify treatment emergent adverse reactions of interest. Because the median time of treatment varied between the Iuspaterecept and control arms, a comparison of the frequency of TEAE was restricted to the first 24 weeks (8 cycles) of treatment. Grouped terms are as defined in the table below.

Table 22: Grouped terms used for analysis of adverse events

Adverse reaction	MedDRA terms
Dizziness	Broad SMQ Vestibular disorders
Hemorrhage	Narrow SMQ haemorrhage terms (excl laboratory terms)
Edema	HLT Edema, NEC
Fatigue	HLT asthenic conditions
Diarrhea	HLT diarrhea (excl infective)
Renal failure	HLT Renal failure and impairment
Musculoskeletal pain	HLT Musculoskeletal and connective tissue pain and discomfort
Dyspnea	HLT Breathing abnormalities
Infections, NOS	HLGT infection pathogen unspecified
Viral infections	HLGT Viral infectious disorders
Headache	HLT Headache NEC
Tachyarrhythmias	PT tachycardia, atrial fibrillation, atrial tachycardia, sinus tachycardia, supraventricular tachycardia
VTE	Narrow SMQ embolic and thrombotic events
Nausea/vomiting	HLT Nausea and vomiting symptoms
Confusion	HLT Confusion and disorientation
Liver abnormalities	HLT Liver function analyses
Fall	PT Fall
Injection site reactions	HLT Injection site reactions
Hypersensitivity reactions	Narrow SMQ hypersensitivity and Narrow SMO anaphylactic reaction
Syncope/presyncope	PT presyncope, syncope, loss of consciousness
Influenza	PT Influenza, influenza-like illness
Hypertension	Narrow SMQ Hypertension

Table 22: Grouped terms used for analysis of adverse events

Adverse reaction	MedDRA terms
Cough	HLT coughing
Abdominal pain	HLT gastrointestinal and abdominal pain
UTI	PT urinary tract infection
URI	PT upper respiratory tract infection
Bronchitis	PT bronchitis
Anemia	HLT Anemia NEC
Disturbances in consciousness	HLT Disturbances in consciousness NEC

8.3.3. Routine Clinical Tests

Routine clinical tests required by the protocol included regular monitoring of physical exam, including vital signs and performance status, ECG monitoring, and routine labs including complete blood count with differential, blood chemistries, iron studies with ferritin, and erythropoietin. Bone marrow biopsies were monitored regularly including evaluation for cytogenetic changes. It should be noted that 24 hour urine collection for protein and creatinine and kidney biopsies for suspicious findings were not performed.

8.4. Safety Results

8.4.1. Deaths

No deaths were reported for study A536-03. The following deaths were reported in patients on the extension study, A536-05. As noted above, follow up for A536-03 was short (12 weeks after treatment discontinuation), but 75/116 patients treated enrolled on the extension study and thus data on long term outcomes, including deaths, for these patients are available.

Table23: Deaths reported on study A536-05 with brief narrative of the event.

ID#	Brief narrative
(b) (6)	69 y/o F with MDS died after completion of treatment. No further details available.
(b) (6)	70 y/o F with MDS died of infection in cycle 39. No focus of infection was identified, and all cultures were negative. Tumor lysis syndrome and leukostasis were reported as concurring events at time of death but no change in diagnosis (CMML) reported.
(b) (6)	83 y/o F died after completing treatment. The cause of death is not stated, but it is noted that the patient experienced colitis and general health deterioration on study.

Table23: Deaths reported on study A536-05 with brief narrative of the event.

ID#	Brief narrative
(b) (6)	68 y/o M with low risk MDS died of decompensated aortic stenosis, PNA, and renal failure on day 204 of study.
	81 y/o M died of acute cardiac failure during cycle 13 (day 531). The death occurred in the setting of transformation to AML.
	75 y/o M died of adenocarcinoma of the liver in cycle 21 (day 703).
	79 y/o M died of sepsis during cycle 69 (day 1440).
	67 y/o M with low risk MDS enrolled on A536-03. He progressed to AML and died of complications. The Sponsor notes that the patient had 3 mutations associated with risk of progression.
	64 y/o M died of sudden death during cycle 7 (day 469).
	78 y/o M died after discontinuing therapy for lack of efficacy. No details on cause of death available.
	73 M with intermediate risk MDS presented day 266 of treatment with general physical health deterioration which worsened to grade 5.
	79 y/o M died after completion of treatment, no further details available.

Reviewer's note: Due to the lack of long term follow up for patients on A536-03 who did not enroll on A536-05, information concerning deaths and survival are necessarily incomplete. Thus, the true rate of death within the first several years after start of treatment is indeterminant. However, deaths due to MDS were noted as was at least one death related to carcinoma of the liver. In addition, renal insufficiency appears to have contributed to at least one death.

There were 45 deaths reported on the controlled trial including 27 in the luspatercept arm and 18 on the placebo arm. The overall death rate was similar or slightly higher in the placebo arm. However, deaths were more common in the first 24 weeks on the luspatercept arm, with 6 deaths occurring in the first 24 weeks on the luspatercept arm compared to 2 on the placebo arm (table 24). Of the deaths on the luspatercept arm, one was due to progression. Given the controversy surrounding the risk of progression with treatment with luspatercept and the early occurrence, this was not considered to be a treatment related death. The other five were considered at least possibly related to the treatment. For three of the deaths, infection was the proximate cause or a major contributor to death. For the other two, renal injury was the proximate cause or major contributor to death.

Table 24: Study MDS-001: Causes of Deaths through Week 25

	Luspatercept (N=153)	Placebo (N=76)
Deaths	6 (3.9%)	2 (2.6%)

Table 24: Study MDS-001: Causes of Deaths through Week 25

	Luspatercept (N=153)	Placebo (N=76)
Root cause of death		
Progression to AML	1	0
Adverse drug reaction	5	1
Infection	(3)	(1)
Renal injury	(2)	-
Other	0	1
Complication of hip fracture	-	(1)

A total of 27 deaths on study were reported for the luspatercept arm of the controlled trial. Of these, six occurred in the first 8 cycles of therapy and seven within 30 days of the last dose of luspatercept. The proximate causes of death are listed in table 25, below. Of note, several patients for whom the proximate cause of death was infectious had suffered relapse prior to death. Cause of death was unknown for a single patient in the luspatercept arm. MDS and AML were prominent causes of death in the luspatercept arm, but not the placebo arm. Other neoplasms were the cause of death for two subjects on the luspatercept arm as well.

A total of 18 deaths were reported among patients on the placebo arm of the controlled trial. Of these, two occurred during the first 8 cycles of treatment and three within 30 days of end of treatment. Cause of death was unknown for eight of the patients. Of those with a known cause of death, infection for four, and a variety of causes including cardiac failure, cerebrovascular accident, general health deterioration, hepatic encephalopathy, hepatic failure, and respiratory failure in six subjects.

Table 25: Deaths by treatment arm and timing of death (within or not within 30 days of last treatment) for patients on MDS-001

Cause of death	Luspatercept (N=153)		Placebo (N=76)	
	Total	Within 30 days	Total	Within 30 days
All	27 (18%)	7 (5%)	18 (24%)	3 (4%)
MDS/AML	4 (3%)	1 (<1%)	0	0
Infectious	6 (4%)	3 (2%)	5 (7%)	2 (3%)
Other neoplasm	2 (1%)	0	0	0
Unknown	1 (<1%)	0	8 (11%)	0
Other	14 (9%)	3 (2%)	5 (7%)	1 (1%)

Reviewer's comments: *In summary, luspatercept use was not clearly associated with an increased risk of death during the time period examined. However, there were substantial concerns about the risk of early death related to infection and renal injury. The cause of death*

was unknown for a large number of patients on the placebo arm and only one on the luspatercept arm, limiting the interpretability of the data.

One possible reason for the higher rate of mortality in the placebo arm is a higher risk of death due to irrelevant causes. Unfortunately, a formal Charlson comorbidity score was not calculated for participants, but, apart from age, most of the comorbidities associated with an increased risk of death per the Charlson criteria were exclusion criteria (i.e. HIV, active malignancy other than MDS, severe liver, kidney, or cardiac dysfunction) or limited (i.e. history of myocardial infarction was allowed, but only if it occurred >6 months before start of the study). Thus, it is likely that age represents one of, possibly the only, major Charlson Comorbidity Index criterion apart from MDS in patients on this trial and thus can be used as a proxy for overall score. As noted above, the placebo arm of the study contained more patients age 80 or older and thus at higher baseline risk of death, than the luspatercept arm.

Age at death was higher for patients in the placebo arm compared to the luspatercept arm, with the mean age (range) at death for patients in the luspatercept arm being 74.6 (60-86) versus 79 (64-91) in the placebo arm. Fourteen patients in the luspatercept arm (50% of deaths, 9% of trial participants assigned luspatercept) were under age 75 at death versus 3 in the placebo arm (17% of deaths, 4% of trial participants assigned to placebo). Thus, the baseline risk of death and rate of death due to irrelevant factors appears unbalanced. In conclusion, the effect of luspatercept on mortality is difficult to assess given the available data.

It should also be noted that only four deaths due to progression of MDS or transformation to AML have been observed thus far whereas progression or transformation has been observed in a total of 10 subjects. Given the poor prognosis of AML with pre-existing MDS, it is likely that further deaths from AML may be expected within a relatively short time period.

8.4.2. Serious Adverse Events

Events listed as serious adverse events (SAE) were rare in the trial MDS-001 in either arm of treatment (table 26). Infection was a relatively common issue, occurring in 9% of patients on the luspatercept arm versus 8% on the placebo arm. Other issues with a risk difference (RD) for SAE of >1% included dyspnea, hemorrhage, anemia, renal failure, syncope/presyncope, and disturbances in consciousness (higher in luspatercept) and viral infections (higher in placebo.)

Table 26: Serious adverse events observed in study MDS-001 in the first 8 cycles of treatment by study arm

Adverse reaction	Luspatercept (N=153)	Placebo (N=76)	RD
Hemorrhage	3 (2%)	0	2.0
Anemia	2 (1%)	0	1.3

Table 26: Serious adverse events observed in study MDS-001 in the first 8 cycles of treatment by study arm

Adverse reaction	Luspatercept (N=153)	Placebo (N=76)	RD
Disturbances in consciousness	2 (1%)	0	1.3
Dyspnea	2(1%)	0	1.3
Renal failure	2 (1%)	0	1.3
Syncope/presyncope	2 (1%)	0	1.3
Confusion	1 (<1%)	0	0.7
Tachyarrhythmias	1 (<1%)	0	0.7
URI	1 (<1%)	0	0.7
Fall	3 (2%)	1 (1%)	0.6
Infections, pathogen unspecified	13 (9%)	6 (8%)	0.6
VTE	2 (1%)	1 (1%)	0
UTI	1 (<1%)	1 (1%)	-0.7
Viral infections	0	1 (1%)	-1.3

Because evaluation of events considered by the Sponsor to be SAE may not provide complete information concerning risk of severe toxicity, an additional analysis examining the rate of grade 3 or higher events was performed. Fatigue of grade 3 and higher was more frequent in the luspatercept arm, with a risk difference of 4.6 percentage points. Other conditions with a risk difference of ≥ 2 with higher rates in patients receiving luspatercept included fall, syncope/presyncope, musculoskeletal pain, hemorrhage, liver abnormalities, renal failure, confusion, and disturbances in consciousness. Grade 3 or higher events with a risk difference of at least 2 and higher in placebo included hypertension and UTI.

Table 27: Adverse events of grade 3 and higher observed in study MDS-001 in the first 8 cycles of treatment by study arm

Adverse reaction	Luspatercept (N=153)	Placebo (N=76)	RD
Fatigue	11 (7%)	2 (3%)	4.6
Fall	6 (4%)	0	3.9
Syncope/presyncope	5 (3%)	0	3.3
Confusion	3 (2%)	0	2.0
Disturbances in consciousness	3 (2%)	0	2.0
Hemorrhage	3 (2%)	0	2.0
Liver abnormalities	3 (2%)	0	2.0
Musculoskeletal pain	3 (2%)	0	2.0

Table 27: Adverse events of grade 3 and higher observed in study MDS-001 in the first 8 cycles of treatment by study arm

Adverse reaction	Luspatercept (N=153)	Placebo (N=76)	RD
Renal failure	3 (2%)	0	2.0
Infections, pathogen unspecified	12 (8%)	5 (7%)	1.3
Hypersensitivity reactions	2 (1%)	0	1.3
Nausea/vomiting	1 (<1%)	0	0.7
URI	1 (<1%)	0	0.7
Anemia	9 (6%)	4 (5%)	0.6
Dyspnea	2 (1%)	1 (1%)	0
Viral infections	1 (<1%)	1 (1%)	-0.7
VTE	1 (<1%)	1 (1%)	-0.7
Hypertension	3 (2%)	3 (4%)	-2.0
UTI	1 (<1%)	2 (3%)	-2.0

Reviewer's comments: Events considered serious by the Sponsor's criteria were relatively rare, with a risk difference of 2 or more seen only for hemorrhage. However, there were more events of grade 3 or higher that were not necessarily considered as SAEs, including a number with RD of ≥ 2 . Grade 3 or higher events of fatigue were notably more common in the luspatercept arm compared to the placebo arm. In addition, grade 3 and higher syncope/presyncope and falls were concerningly common in the luspatercept arm. The risk differences observed for most other events were based on small numbers, making them difficult to interpret in isolation, although see further discussion in section 8.4.5 and below. In addition, the presence of grade 3 and higher events of hepatotoxicity and renal insufficiency are concerning as even rare events may indicate unacceptable risk of organ toxicity.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Adverse events were listed as the primary reason for treatment discontinuation for 14 subjects, including 10 (6.5%) in the luspatercept arm and 4 (5.3%) in the placebo arm. AE leading to treatment discontinuation in the luspatercept arm included two events each of sepsis, transaminase increase, and fatigue and one event each of chronic kidney disease, headache, memory impairment, myalgia, Parkinson's disease, pulmonary fibrosis, renal failure, and hemorrhagic shock. Events leading to treatment discontinuation in the placebo arm included one each of thrombocytosis, general health deterioration, respiratory failure, and arthralgia. In addition, 11 subjects had adverse events with the outcome of "drug withdrawn" listed in the adverse events dataset but were not identified as having treatment discontinued due to drug withdrawal in the ADSL dataset. Of these, 6 had treatment withdrawn due to development of AML or MDS progression and were considered to have drug withdrawal for progression rather

than adverse events. One suffered a fatal motor vehicle accident. The remaining four had drug withdrawal after a post-procedural complication, colon adenoma, cerebral hemorrhage, and asthenia.

8.4.4. Significant Adverse Events

See section 8.5 for analysis of adverse events of special interest.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Treatment emergent adverse events (TEAE) were observed in 150 (98%) of patients on luspatercept arm and 70 (92%) on the placebo arm. A wide variety of TEAE were observed more commonly in the first 24 weeks of the study among patients receiving luspatercept. Events of special interest will be discussed in further detail in section 8.5

As noted in the table below, several symptoms commonly associated with MDS including fatigue, dizziness, dyspnea, and syncope/presyncope, were more common among patients receiving luspatercept compared to those receiving placebo, with risk differences as high as +16.8 percentage points for fatigue.

Infectious issues including influenza and influenza-like illness, infection without identified pathogen, viral infections, UTI, and URI were more common among patients receiving luspatercept. Interestingly, identified fungal and bacterial infections were not more common.

Gastrointestinal issues including nausea, vomiting, diarrhea, and abdominal pain were observed more frequently in the luspatercept arm. The reason for this finding is unclear since luspatercept is not an oral drug and there is no obvious mechanism of action for GI events. However, the finding is consistent across several studies and is therefore likely to be an adverse drug reaction.

Hypertension is noted to be slightly lower in the luspatercept arm compared to the placebo. However, see results in the vital signs section as there were events of blood pressure outside the normal range documented under vital signs that were not captured as adverse events. When all shifts in blood pressure from less than normal (systolic <140 and diastolic <90) to higher than normal were considered, more events occurred in the luspatercept arm (see vital signs section, below). In addition, use of concomitant medications for the treatment of hypertension was more common in the luspatercept arm compared to the placebo arm.

Injection site reactions, including pain and irritation at the site of injection, were more common in the luspatercept arm. This is of potential significance since the excipients in the luspatercept preparation may have led to patient unblinding.

Tachyarrhythmias were observed more commonly in the luspatercept arm, with the majority of the difference being due to atrial arrhythmias.

Hemorrhage, including severe hemorrhage, was noted more frequently in the luspatercept arm.

Table 28: Adverse events observed in study MDS-001 in the first 8 cycles of treatment by study arm

Adverse reaction	Luspatercept (N=153)	Placebo (N=76)	RD
Fatigue	62 (41%)	18 (24%)	16.8
Dizziness	28 (18%)	5 (7%)	11.7
Diarrhea	24 (16%)	6 (8%)	7.8
Dyspnea	20 (13%)	4 (5%)	7.8
Tachyarrhythmias	12 (8%)	1 (1%)	6.5
Hypersensitivity reactions	15 (10%)	5 (7%)	6.3
Viral infections	18 (12%)	4 (5%)	6.2
Headache	21 (14%)	5 (7%)	6.1
Nausea/vomiting	25 (16%)	8 (11%)	5.8
Renal failure	10 (7%)	1 (1%)	5.2
Musculoskeletal pain	30 (20%)	11 (15%)	5.1
Syncope/presyncope	8 (5%)	0	4.6
Confusion	7 (5%)	0	4.6
Infections, NOS	45 (29%)	18 (25%)	4.4
Injection site reactions	10 (7%)	2 (3%)	3.9
URI	10 (7%)	2 (3%)	3.9
Hemorrhage	14 (9%)	5 (7%)	3.6
Disturbances in consciousness	7 (5%)	1 (1%)	3.3
Influenza	4 (3%)	0	2.6
Abdominal pain	12 (8%)	5 (7%)	1.2
Liver abnormalities	11 (7%)	4 (5%)	1.9
Cough	20 (13%)	9 (12%)	1.3
Bronchitis	4 (3%)	1 (1%)	1.3
VTE	4 (3%)	1 (1%)	1.3
UTI	7 (5%)	3 (4%)	0.7
Fall	11 (7%)	5 (7%)	0.6
Anemia	10 (7%)	5 (7%)	-0.1
Hypertension	9 (6%)	6 (8%)	-2.0
Edema	18 (12%)	11 (15%)	-2.7

Reviewer's comments: Overall, the adverse event profile of luspatercept is considerable, given that it is intended as a supportive care medication and does not make any claims to altering the course of the underlying disease. Several of the adverse events, including fatigue, dizziness, dyspnea, confusion, presyncope/syncope, and falls, may be seen in association with anemia and transfusions are frequently given to prevent these symptoms. The value of a drug that increases hemoglobin while not only failing to relieve these adverse events but actually worsening them is questionable.

Infectious issues appear to be more common among patients receiving luspatercept. No increase in neutropenia was observed in patients treated with luspatercept versus placebo (see lab results, below), but lack of neutropenia does not guarantee lack of immunosuppression, i.e. steroids increase neutrophil count but are associated with immunosuppression. Indeed, an increase in use of steroids was observed in the luspatercept arm and an increased need for steroids may partially explain the results, although it is unlikely to be the only factor involved.

Similarly, the rate of hemorrhage, including severe hemorrhage, is higher in the luspatercept arm without any difference in platelet count being observed between the arms. Coagulation parameters and platelet function were not examined during the study, so the role of these factors cannot be assessed. In addition, the increased risk might be related to effects on vascular endothelium.

The increase in GI events is puzzling given that this is not an oral drug and may be related to an increased need for other supportive care drugs (i.e. proton pump inhibitors, inhaled steroids) in at least some cases. Alternatively, luspatercept may have an undescribed effect on the gastrointestinal system.

Injection site reactions were more common among patients receiving luspatercept. This may be related to characteristics of luspatercept or of the excipients compared to saline.

Because some events of interest may not be observed until later in the treatment and the issue of whether the incidence of TEAE decreases over time is of interest, an analysis of events in the luspatercept arm occurring after cycle 8 was performed. For the extension cycles, the denominator used is the number of subjects who received at least one dose of treatment in any extension cycle.

Table 29: Adverse events observed in study ACE-536-MDS-001 in cycles 1-8 versus extension cycles

Adverse reaction	Cycles 1-8 N=153	Extension cycles N=100
Fatigue	62 (41%)	34 (34%)

Table 29: Adverse events observed in study ACE-536-MDS-001 in cycles 1-8 versus extension cycles

Adverse reaction	Cycles 1-8 N=153	Extension cycles N=100
Infections, pathogen not specified	45 (29%)	51 (51%)
Musculoskeletal pain	30 (20%)	24 (24%)
Dizziness	28 (18%)	21 (21%)
Diarrhea	24 (16%)	26 (26%)
Nausea/vomiting	25 (16%)	20 (20%)
Headache	21 (14%)	7 (7%)
Cough	20 (13%)	19 (19%)
Dyspnea	20 (13%)	14 (14%)
Viral infections	18 (12%)	16 (16%)
Edema	18 (12%)	22 (22%)
Hypersensitivity reactions	15 (10%)	10 (10%)
Hemorrhage	14 (9%)	15 (15%)
Abdominal pain	12 (8%)	6 (6%)
Tachyarrhythmias	12 (8%)	7 (7%)
Fall	11 (7%)	15 (15%)
Anemia	10 (7%)	10 (10%)
Injection site reactions	10 (7%)	1 (1%)
URI	10 (7%)	12 (12%)
Liver abnormalities	11 (7%)	8 (8%)
Renal failure	10 (7%)	4 (4%)
Disturbances in consciousness	7 (5%)	8 (8%)
Hypertension	9 (6%)	8 (8%)
Syncope/presyncope	8 (5%)	6 (6%)
Confusion	7 (5%)	3 (3%)
UTI	7 (5%)	12 (12%)
Influenza	4 (3%)	9 (9%)
Bronchitis	4 (3%)	15 (15%)
VTE	4 (3%)	2 (2%)

Reviewer's comments: Although the incidence of some events was lower in the extension cycles as compared to the first 8 cycles of treatment, in general, patients continued to experience new events at a high frequency, as well as potentially continuing to suffer from AE that began in the first 8 cycles. Given that patients who continue treatment in the extension cycles represent the

“best case” patients, i.e. those who are willing to continue treatment, this finding is of some concern.

The only AE for which an unequivocal decrease in incidence was observed were fatigue, headache, and injection site reactions. It should be noted that the incidence of fatigue continued to be high at 34% and that many patients who experienced fatigue earlier had not had resolution of their fatigue. Thus, fatigue continued to be a major issue in later cycles, despite the decrease in absolute number of new events observed.

Infectious issues appear to be more common later in treatment with luspatercept with over half of patients experiencing infections with the pathogen not identified. In addition, more viral infections, URI, UTI, influenza, and bronchitis were observed in later cycles compared to earlier.

Based on the non-clinical data, there was concern about the possibility of renal events. In particular, drug induced membranoproliferative glomerulonephritis (MPGN) occurring later in the course of treatment. Renal impairment and failure were seen in only 4 patients after cycles 1-8. However, renal impairment occurring in the first 8 cycles was documented to be ongoing in 5 out of the 10 subjects who experienced it (one event was fatal). In addition, MPGN may not be initially associated with renal failure but may present with other symptoms, i.e. edema or hypertension. Edema was very commonly in patients receiving luspatercept in extension cycles, with 22% of subjects developing new edema during that time period. Hypertension was also reported more frequently than in the first 24 weeks, agreeing with the results from the vital sign assessment. See section 8.5 for further discussion of this issue.

The incidence of TEAE occurring in patients treated with the recommended dose of luspatercept in the phase 2 trial was examined. In this population, infection without identified pathogen was seen most commonly, at 49% of subjects. Viral infection, hemorrhage, hypertension, and fatigue were commonly observed as well.

Table 30: Adverse events observed in study A536-03 in patients treated with a dose of 1 mg/kg or higher

Adverse reaction	Luspatercept (N=101)
Infections, pathogen not specified	49 (49%)
Viral infections	29 (29%)
Hemorrhage	23 (23%)
Hypertension	23 (23%)
Fatigue	17 (17%)
Edema	16 (16%)
Dyspnea	16 (16%)

Table 30: Adverse events observed in study A536-03 in patients treated with a dose of 1 mg/kg or higher

Adverse reaction	Luspatercept (N=101)
Musculoskeletal pain	15 (15%)
URI	15 (15%)
UTI	15 (15%)
Diarrhea	14 (14%)
Hypersensitivity reactions	14 (14%)
Cough	13 (13%)
Thrombosis	13 (13%)
Dizziness	12 (12%)
Bronchitis	10 (10%)
Fall	9 (9%)
Headache	9 (9%)
Nausea/vomiting	8 (8%)
Tachyarrhythmias	8 (8%)
Abdominal pain	7 (7%)
Anemia	7 (7%)
Renal failure	7 (7%)
Injection site reactions	6 (6%)
Syncope/presyncope	6 (6%)
Liver abnormalities	5 (5%)
Disturbances of consciousness	5 (5%)
Influenza and influenza-like illness	2 (2%)
Confusion	1 (1%)

Reviewer's comments: In general, the TEAE findings in study A536-03 were similar to those seen in the controlled trial. The higher rate of infections observed in the phase 2 trial may be due to better supportive care being built into the later controlled trial due to early experience or may be due to differences in the patient population. Interestingly, fatigue is less commonly reported in the phase 2 trial, possibly due to shorter treatment duration.

8.4.6. Laboratory Findings

Routine laboratory evaluations were performed on trial MDS-001, including complete blood count (CBC) with differential, routine chemistries, and urinalysis as well as erythropoietin and iron studies. Results for erythropoietin and ferritin are described under the efficacy findings, section 6.1.2. Unless otherwise specified, the values shown are for events occurring in weeks 1-

24 of the study.

More patients in the luspatercept arm experienced increases in transaminases and bilirubin, with results being especially marked for bilirubin. No increases in alkaline phosphatase were observed, suggesting that cholestasis was not the mechanism of action for the increases observed.

Table 31: Number and percentage of patients on trial MDS-001 experiencing shifts in hepatic enzyme values from 0-1 to 2-4 in weeks 1-24 by study arm

Parameter	Luspatercept	Placebo	RD
Albumin	2 (1%)	0	+1.3
Alkaline phosphatase	0	0	0
AST	6 (4%)	0	+4.0
ALT	14 (9%)	4 (5%)	+3.9
Bilirubin elevated	17 (11%)	2 (3%)	+8.5

An increase in bilirubin may be due to hemolysis or liver function. In order to distinguish which of these was the major issue in patients on the study, an analysis of changes in direct and indirect bilirubin was undertaken. Specific CTCAE grades are not available for direct or indirect bilirubin, so the table shows any shift from $\leq$ ULN to $>$ ULN or from $1-\leq 2$ x ULN to >2 x ULN. Although the risk of increase in either direct or indirect bilirubin was higher for the luspatercept arm, the effect was more prominent for direct bilirubin, suggesting that liver abnormalities are a more common reason for increased bilirubin in patients receiving luspatercept than hemolysis.

Table 32: Patients experiencing increase in direct or indirect bilirubin by study arm at any time during the study

Parameter	Luspatercept	Placebo	RD
Direct bilirubin	27/152 (17.8%)	6/75 (8%)	+9.8
Indirect bilirubin	36/152 (23.7%)	14/75 (18.7%)	+5.0

Changes in renal function and possible accompanying electrolyte abnormalities are of concern with the use of the investigational product. A small increase in the risk of shift in creatinine clearance from grade 0-1 to 2-4 was observed in the luspatercept arm in the first 24 weeks of the study, with a risk difference of +1.6, consistent with the risk of renal failure and insufficiency observed in the adverse reactions evaluation. In addition, shifts in values were observed for glucose (increase), potassium (increase), sodium (decrease), and urate (increase).

Table 33: Number and percentage of patients on trial MDS-001 experiencing shifts in creatinine clearance and selected electrolyte values from 0-1 to 2-4 in weeks 1-24 by study arm

Parameter	Luspatercept	Placebo	RD
Creatinine clearance	29 (19%)	13 (17%)	+1.6
Glucose (increase)	34 (22%)	11 (14%)	+7.8
Potassium (increase)	5 (3%)	0	+3.3
Sodium (decrease)	3 (2%)	1 (1%)	+1.3
Urate (increase)	31 (20%)	5 (7%)	+13.7

Changes in hematologic parameters were observed in both arms. Decreased hemoglobin was more common in the luspatercept arm. Decreases in platelet count were roughly similar between the two arms. Decreases in white blood count, lymphocytes, and neutrophils were more common in the placebo arm, whereas increased lymphocyte count was more common in the luspatercept arm.

Table 34: Number and percentage of patients on trial MDS-001 experiencing shifts in hematologic values from 0-1 to 2-4 in weeks 1-24 by study arm

Parameter	Luspatercept	Placebo	RD
Hemoglobin (decreased)	21 (14%)	7 (9%)	+4.5
Platelets (decreased)	5 (3%)	3 (4%)	-0.7
WBC (decreased)	17 (11%)	16 (21%)	-9.9
Lymphocytes (decreased)	21 (14%)	18 (24%)	-10.0
Lymphocytes (increased)	2 (1%)	0	+1.3
Neutrophils (decreased)	9 (6%)	12 (16%)	-9.9

Reviewer's comments: The changes in hepatic enzyme values are consistent with the finding of increased hepatic toxicity and Hy's law cases described in section 8.5. Changes in electrolytes are consistent with the observed renal toxicity. Shifts in hemoglobin from grade 0-1 to grade 2-4 were more common in the luspatercept arm, possibly supporting the hypothesis that unblinding led to variability in treatment decisions. Interestingly, the platelet count was not different between the two arms, despite a higher rate of bleeding observed in the luspatercept arm (see review of TEAE). Unfortunately, coagulation and platelet function studies are not available to correlate with this finding. Total WBC, lymphocytes, and neutrophils were all more frequently decreased in the luspatercept arm compared to the placebo arm. This is in contrast to the finding of increased risk of infection noted above. The reasons for this are unclear. This finding could suggest a steroid-like demarginalization and immunosuppression effect or even be related to concomitant treatment with steroid preparations.

8.4.7. Vital Signs

An evaluation of blood pressure outliers demonstrated a higher number of patients with normal blood pressure at baseline experiencing hypertension in the luspatercept arm compared to the placebo arm, with 21.2% of subjects in the luspatercept arm and 10.5% in the placebo arm having documented diastolic hypertension and 36.6% in the luspatercept arm and 26.3% in the placebo arm having documented hypertension at any time during treatment.

Table 35: Blood pressure outliers by treatment arm

	DBP $\geq$ 90 mmHg	SBP $\geq$ 140 mmHg
Luspatercept (N=153)	33 (21.2%)	56 (36.6%)
Placebo (N=76)	8 (10.5%)	20 (26.3%)

The differences in frequency of events was lower when only the first 25 weeks of treatment were considered, with diastolic hypertension being comparable between arms during this time period but continued increase in the percentage of patients experiencing systolic hypertension, at 32% for luspatercept versus 25% for placebo.

Table 36: Blood pressure outliers within the first 25 weeks of therapy by treatment arm

	DBP $\geq$ 90 mmHg	SBP $\geq$ 140 mmHg
Luspatercept	17 (11.1%)	49 (32.0%)
Placebo	8 (10.5%)	19 (25.0%)

Because non-clinical findings suggested that late hypertension associated with renal insufficiency and possible MPGN may be an issue, hypertensive events later in treatment were examined as well. Because of high drop out rates, the denominator used for calculating percentage of patients with events was the number of patients with any measurement of blood pressure after the 175th day of therapy. This may slightly underestimate the percentage of patients with diastolic hypertension since some patients had documented systolic blood pressures only, but it avoids inflating the risk. Hypertension continued to be observed in the luspatercept arm in later time periods, with 18% and 28% of patients experiencing diastolic and systolic hypertension, respectively, at any time after the first 25 weeks of the study.

Table 37: Blood pressure outliers after the first 25 weeks of therapy by treatment arm

	DBP $\geq$ 90 mmHg	SBP $\geq$ 140 mmHg
Luspatercept (N=129)	23 (18%)	36 (28%)
Placebo (N=53)	1 (2%)	4 (8%)

Reviewer's notes: Hypertension has been noted as an adverse event in prior trials using luspatercept in β -thalassemia. The data from trial MDS-001 demonstrate a persistent risk of hypertension throughout treatment with luspatercept. In addition, use of concomitant medications for hypertension was higher in the luspatercept arm compared to the placebo arm,

suggesting that the late events observed represent breakthrough cases that occur despite treatment with effective anti-hypertensives.

8.4.8. Electrocardiograms (ECGs)

Overall ECG findings were judged to have clinically significant abnormalities in 10 subjects, including 8 receiving luspatercept and 2 receiving placebo. Of these, 7 had ECGs with baseline abnormalities of clinical significance. Two had normal baseline ECGs and one had baseline abnormalities that were not considered clinically significant. Each of the three patients with change in ECG to clinically significant abnormalities was on the luspatercept arm. Events documented included AV block (2 subjects) and atrial fibrillation (1 subject). It should be noted that tachyarrhythmias, primarily supraventricular, were identified as a more frequent TEAE (see adverse events description, above).

8.4.9. QT

QTcF elevations were observed in 11 subjects on the trial MDS-001. Of these, 5 were observed on screening ECGs. Of the remaining 6, four occurred in patients receiving luspatercept, 2 in patients receiving placebo. A consult was made to the interdisciplinary review team for QT studies. See their review for a complete analysis of QT interval changes with treatment with luspatercept. They found no major changes in QT interval in patients receiving luspatercept and a low pretest probability given that luspatercept is a biological product and unlikely to directly interact with the cardiac ion channel.

In summary, there appears to be little risk of QTc prolongation with treatment with luspatercept.

8.4.10. Immunogenicity

Anti-drug antibodies (ADA) were observed in 23 subjects on the study MDS-001, including 18 in the luspatercept arm and 5 in the placebo arm, of which 10 were neutralizing antibodies. Seven subjects in the luspatercept arm and 2 in the placebo arm had pre-existing ADA. Of the 11 TEADA in the luspatercept arm and 3 in the placebo arm, 5 in the luspatercept arm and 2 in the placebo arm were neutralizing antibodies.

The incidence of TEAE in patients receiving luspatercept who had ADA versus those who did not was examined as noted below. Because ADA may develop at any time during treatment, AE were determined for the full treatment period. Numbers of cases were too small to examine incidence with neutralizing antibodies versus non-neutralizing antibodies or treatment emergent versus pre-existing antibodies.

The small number of patients with ADA complicates interpretation of differences in incidence, since a single patient represents about 6% of ADA+ cases. Thus, only differences of 10 or more will be considered of potential interest. Differences of >10 with more cases observed in the ADA negative population were observed for hypersensitivity reactions and fatigue (table 38). Differences of >10 with more cases observed in the ADA+ population were seen for injection site reactions, URI, diarrhea, and influenza.

Table 38: Adverse events observed in the luspatercept arm of study MDS-001 by incidence of ADA

Adverse reaction	ADA- (N=135)	ADA+ (N=18)	RD
Hypersensitivity reactions	27 (20%)	1 (6%)	14.4
Fatigue	79 (59%)	8 (44%)	14.1
Edema	34 (27%)	3 (17%)	8.5
Abdominal pain	19 (14%)	1 (6%)	8.5
Bronchitis	18 (13%)	1 (6%)	7.7
Infections, pathogen not specified	69 (51%)	8 (44%)	6.7
Anemia	16 (12%)	1 (6%)	6.3
VTE	7 (5%)	0	5.2
Syncope/presyncope	14 (10%)	1 (6%)	4.8
Disturbances in consciousness	13 (10%)	1 (6%)	4.0
Renal failure	12 (9%)	1 (6%)	3.3
Dizziness	42 (31%)	5 (28%)	3.3
Tachyarrhythmias	18 (13%)	2 (12%)	2.1
Headache	25 (19%)	3 (17%)	1.8
Confusion	9 (7%)	1 (6%)	1.1
Fall	23 (17%)	3 (17%)	0.3
Musculoskeletal pain	45 (33%)	6 (33%)	0
Dyspnea	28 (21%)	4 (22%)	-1.5
UTI	18 (13%)	3 (17%)	-3.4
Nausea/vomiting	31 (23%)	5 (28%)	-4.8
Liver abnormalities	16 (12%)	3 (17%)	-4.8
Hemorrhage	28 (21%)	5 (28%)	-7.1
Hypertension	13 (10%)	3 (17%)	-7.1
Viral infections	27 (20)	5 (28)	-7.8
Cough	32 (24%)	6 (33%)	-9.6
Injection site reactions	8 (6%)	3 (17%)	-10.8
URI	15 (11%)	4 (22%)	-11.1
Diarrhea	36 (27%)	7 (39%)	-12.2

Table 38: Adverse events observed in the luspatercept arm of study MDS-001 by incidence of ADA

Adverse reaction	ADA- (N=135)	ADA+ (N=18)	RD
Influenza	14 (11%)	5 (28%)	-17.4

Reviewer's comments: Overall, there did not appear to be a major difference in adverse reactions in patients who developed anti-drug antibodies versus those who did not. The case numbers for patients with ADA precluded analysis by pre-existing antibodies versus treatment emergent or neutralizing versus non-neutralizing. A higher risk of some inflammatory/infectious issues was observed for patients with ADA (influenza, URI, injection site reactions), but the significance of this is uncertain since other immune/infectious issues were unchanged (UTI, infection pathogen not specified, viral illness). The lower incidence of fatigue may be related to lower drug levels.

8.5. Analysis of Submission-Specific Safety Issues

Fatigue

As noted above, fatigue was more common among patients receiving luspatercept compared to those receiving placebo. Overall, fatigue was observed in 86 subjects (56%) on the luspatercept arm versus 22 (29%) on the placebo arm (table 39). When only events occurring in the first 8 cycles were included, fatigue was observed in 62 (41%) of subjects receiving luspatercept and 18 (24%) of those receiving placebo.

The incidence of events was highest in both luspatercept and placebo arms in the first 4 cycles of treatment. However, the incidence of fatigue remained higher in the luspatercept arm versus the placebo arm during later time periods. The median duration of fatigue was similar to slightly longer in the luspatercept group at 22 days versus 20 days in the placebo arm (table 40). In addition, in about half of patients in both arms the event of fatigue was considered unresolved at the time of data cut-off, with 53 patients (35%) in the luspatercept arm and 12 (16%) in the placebo arm experiencing unresolved fatigue at any time point during the study. This indicates that many events of fatigue were long lasting, with no direct evidence that the fatigue would resolve at any time.

Table 39: Incidence of fatigue in patients treated on MDS-001 by arm and cycle

	Cycles	Luspatercept	Placebo
Number of patients experiencing event		87 (57%)	22 (29%)
Incidence Cycles 1-8		62 (41%)	18 (24%)
Cycle	1-4	52 (34%)	11 (14%)

Table 39: Incidence of fatigue in patients treated on MDS-001 by arm and cycle

	Cycles	Luspatercept	Placebo
	5-8	21 (14%)	8 (11%)
	Later cycles	16 (10%)	5 (7%)
Number of patients with unresolved events		53 (35%)	12 (16%)

Table 40: Median duration and outcome of events of fatigue in patients on trial MDS-001 by study arm and cycle number. Total number of events shown.

		Luspatercept	Placebo
Number of events	All events	150	26
	Cycles 1-4	69	12
	Cycles 5-8	27	9
	Later cycles	54	5
Median duration (range)	All events	22 (1, 532)	20 (2, 336)
	Cycles 1-4	21 (1, 187)	18.5 (3, 119)
	Cycles 5-8	45 (7, 279)	48 (2, 336)
	Later cycles	22 (1, 532)	12 (3, 20)
Outcome	Resolved	77	11
	Not resolved	73	15
	Resolved, C1-4	36	5
	Not resolved C1-4	33	7
	Resolved C5-8	14	3
	Not resolved C5-8	13	6
	Resolved later cycles	28	3
	Not resolved later cycles	26	2

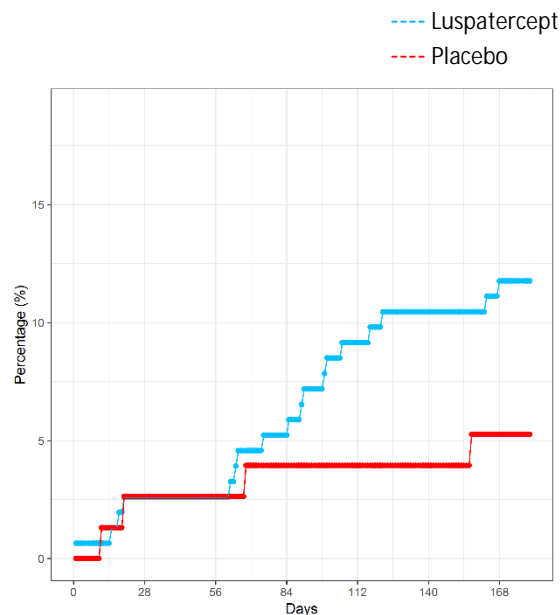
Reviewer's comments: Fatigue, including severe fatigue, was much more common in the luspatercept arm compared to the placebo arm, with increased incidence of fatigue being observed at every time point examined. Duration of fatigue was marginally longer in the luspatercept arm. In addition, events of fatigue occurring in cycles 5-8 tended to be longer lasting compared to those occurring earlier. Although some events were transient, many cases were long lasting or had not resolved at the time of data cut-off. Thus, it is likely that the apparent decrease in incidence of fatigue in later cycles is due to more patients already experiencing fatigue and thus not receiving a new diagnosis of treatment emergent fatigue rather than to relief of the symptom. This correlates with the PRO data that demonstrated increased fatigue compared to baseline at all time points measured (see PRO data above).

Infection

Three deaths related to infection occurred in the luspatercept arm during Weeks 1 - 24. During the first 8 cycles on Study MDA-001, the luspatercept arm had a higher incidence of viral infections (12% vs 5%) and infection pathogen not specified (29% vs 25%) than the placebo arm. Within the category of viral infections, influenza and influenza-like illness were more common among patients receiving luspatercept (6% vs 3%). Within the broad category of infection without specified pathogen, upper respiratory infections, bronchitis, and urinary tract infections were more commonly seen in the luspatercept arm.

The difference in the rate of viral infections predominated after 3 cycles of therapy (Figure 14).

Figure 14. Study MDS-001: Cumulative Incidence of Viral Infections during Weeks 1 - 24



Source: FDA analysis

Patients receiving luspatercept were more likely to require antibacterials for systemic use (52% versus 36%), consistent with the finding of more frequent infections. Of note, the reason documented for administration of antibacterials was most frequently urinary tract infection and respiratory tract infections. Antivirals for systemic use were prescribed for a higher proportion of patients on the luspatercept arm (7% vs 3%), most frequently for HSV or VZV infection.

Hepatotoxicity

Two subjects met the laboratory criteria for Hy's law.

The first subject (b) (6) was a male patient age <65. The patient had an AST of 87 (ULN 36), ALT of 145 (ULN 43), and bilirubin of 42 (ULN 21). Concurrent alkaline phosphatase was WNL. Baseline values for this subject were WNL with the exception of a mild elevation of bilirubin at 26. The patient had elevations of transaminases throughout the study, with several values meeting the criteria for grade 2 abnormalities but none grade 3 or higher and no other values meeting the Hy's lab criteria. At the time of the values meeting Hy's law criteria, the patient had concurrent hyperglycemia, potassium, and white blood cells (primarily neutrophils). Of note, the patient was receiving luspatercept at 1.33 mg/kg at the time of the Hy's law finding and was dose reduced with improvement, but not resolution, of the liver abnormalities, which continued throughout the rest of the treatment period.

A second subject (b) (6) was a male patient age ≥75 who had a grade 3 elevation of AST on day 114 of the study. The narrative provided by the Sponsor indicates that this subject experienced cholelithiasis and pancreatitis at this time. Ultrasound showed cholelithiasis. No increase in alkaline phosphatase is documented in the laboratory findings, although increased amylase and lipase are documented in the narrative. Treatment was discontinued due to these findings shortly thereafter. This case is considered ambiguous because of the finding of cholelithiasis, but not fully ruled out as a Hy's law case due to the lack of definitive findings of cholestasis.

Several other subjects had concurrent elevations in transaminases and bilirubin that did not meet Hy's law criteria, but appeared during treatment in the absence of baseline abnormalities of > grade 1 (see table 41, below).

Table 41: Subjects with transaminases ≥3 x ULN, bilirubin of ≥1.5 x ULN, and normal alkaline phosphatase at any time during treatment with luspatercept

Subject number	Cycles	AST (U/L)	ALT (U/L)	Bilirubin (umol/L)
(b) (6)	Ext cycle 2	79	149	37
	Ext cycle 11	87	145	43
	Ext cycle 13	53	140	33
	Ext cycle 17	131	165	31
	Day 114	466	328	31*

*The value documented in the laboratory data is 31, with ULN of 21. However, the narrative documents a value of 6 mg/dl, ULN 1.19.

Shift tables showing changes in transaminase levels demonstrate more frequent and severe

shifts in transaminases in subjects treated with luspatercept compared to placebo during the first 8 cycles (25 weeks) of treatment (see table 31, lab results). In addition, seven patients had shifts from grade 1 to 2 (3), 0 to 2 (2), or 0 to 3 (1) during the course of the study, measured at times other than the routine labs during the first 8 cycles. All but one of these (subject (b) (6) discussed above) occurred after the first 25 weeks of treatment, thus the risk cannot be directly compared to the risk with use of placebo.

Reviewer's comments: A larger percent of subjects on the luspatercept arm experienced shifts to higher values for AST compared to the placebo arm. In addition, several patients experienced increases in transaminases and bilirubin which were consistent with an increased risk for liver damage, including two who met laboratory criteria for Hy's law, although a possible secondary etiology was observed in one subject. However, in the absence of definite documentation of cholestasis, this case should be considered as a potential Hy's law case, since cholelithiasis may have been an incidental finding, not related to the liver abnormalities. Many of the cases of increased liver enzymes occurred after the first eight cycles, raising the possibility that liver toxicity may be predominantly a late event.

Renal toxicity

The role of TGF- β superfamily members in renal disease is complex. GDF11 has been demonstrated to increase kidney fibrosis and renal dysfunction³⁰. However, GDF11 expression was shown to increase kidney regeneration after ischemic-reperfusion injury in a mouse model, acting via Smad2,³¹ suggesting that blockade of GDF11 may result in worsening of renal damage after ischemic injury. Interestingly, Smad2 and Smad3 appear to have antagonistic effects on renal fibrosis³². Thus, it is not clear a priori what effect luspatercept would be likely to have on renal function, but there would appear to be some risk of renal toxicity with its use.

Nonclinical examination of the effect of luspatercept on kidney function in cynomolgus monkeys showed an up to 2-fold increase in creatinine compared to control animals. Pathology showed drug-related MPGN and interstitial hemorrhage and fibrosis in rats and cynomolgus monkeys at ≥ 0.4 and ≥ 0.6 times the exposure at the maximal recommended clinical dose of luspatercept, respectively. In a renal injury model in Sprague Dawley rats, exacerbation of urinary kidney injury biomarkers and glomerular and tubulointerstitial findings were observed compared to sham-operated and vehicle-treated animals at doses of ≥ 0.05 times the maximum recommended human dose. Thus, the non-clinical findings suggested a high risk of renal issues at clinical or subclinical doses.

Renal injury occurred more frequently on the luspatercept arm (10 patients or 7% in the luspatercept arm vs 1 patient or 1% in the placebo arm) in the first 24 weeks on Study MDS-001. Of the 10 patients in the luspatercept arm with renal failure in the first 24 weeks, the event was considered ongoing in 5 patients. An additional 4 patients experienced renal injury in

later cycles. Laboratory analysis showed decrease in creatinine clearance in 29 patients (19%) in the first 24 weeks of treatment and 36 patients (24%) at any time during the study.

Nephrotic syndrome related to MPGN may be potential risks of treatment with luspatercept. Unfortunately, a definitive analysis of these risks is not possible, since the necessary tests (i.e. 24-hour urine protein) were not performed, so only indirect evidence could be assessed. Patients with MPGN may present with findings of erythrocytes and RBC casts in the urine, proteinuria (potentially up to the nephrotic range), and renal insufficiency. Of the patients treated on Study MDS-001, 12 (8%) on the luspatercept arm and 3 (4%) on the placebo arm had a new finding of RBC in the urine or increased RBC in the urine associated with new or increased proteinuria during treatment. Five (3%) subjects on the luspatercept arm and none on the placebo arm had new or increased RBC in the urine, proteinuria > 0.35 g/L, and decreased creatinine clearance, which was considered potentially consistent with MPGN.

Signs and symptoms of nephrotic syndrome were not observed prominently in the first 8 cycles of treatment, with the exception of fatigue and hypertension, which are nonspecific. However, nephrotic syndrome would be expected to be a late complication and may not be observed in the first 24 weeks. In order to assess the risk of nephrotic syndrome, an analysis of risk of signs and symptoms of nephrotic syndrome in the entire treatment period was performed. Proteinuria into the full nephrotic range (> 3 g/L) was observed in only a single patient, who had nephrotic range proteinuria at baseline. Eight (5%) patients on the luspatercept arm and 1 (1%) on the placebo arm had increases in urine protein to > 1 g/L with baseline values of < 1 g/L. Edema was observed in 37 (24%) subjects on the luspatercept arm and 13 (17%) on the placebo arm at any time during the study. Of note, both edema and hypertension were more common in the luspatercept arm later in treatment compared to earlier (see section 8.4.5).

Reviewer's comments: Luspatercept was associated with a decrease in creatinine clearance and an increased risk of renal toxicities in patients receiving it for treatment of MDS. No definitive cases of MPGN were observed, but this is due to the Sponsor's failure to require biopsies for patients with findings consistent with MPGN, despite a known risk based on non-clinical data. At least five patients on the luspatercept arm and none on the placebo arm had findings and symptoms consistent with drug induced MPGN and the more cautious interpretation would be to consider these likely cases.

Hypertension

Hypertension was identified as a TEAE in the first 8 cycles in 9 (6%) of patients in the luspatercept arm versus 6 (8%) in the placebo arm. However, increases in SBP into the hypertensive range were observed in the vital signs data in more patients in the luspatercept arm, (see vital signs evaluation) and patients on the luspatercept arm were more likely to receive antihypertensives as concomitant medications. An increase in the risk of hypertension

was observed in patients receiving luspatercept for β -thalassemia as well (see luspatercept label). Overall, the evidence suggests a risk of hypertension with luspatercept treatment across indications.

Second primary malignancies

TGF- β signaling plays a complex role in tumor initiation and progression³³, at least in part via the Smad pathway. Luspatercept acts via the TGF- β pathway, with high affinity binding to GDF11, GDF8, BMP6, and activin B and inhibits signaling through Smad2/3.

In addition, non-clinical data included one study demonstrating an increased risk of hematologic malignancies in juvenile and adult rats. Another study demonstrated a trend towards greater tumor growth in mice in a Lewis lung carcinoma model. Thus, there is reason to suspect that luspatercept administration may alter the risk of malignancy, either directly or via immune alterations.

An analysis of the risk of malignancy in patients on the MDS-001 study was performed. Because malignancies may appear after the end of therapy and patients were followed for risk of transformation and second primary malignancy for 3 years following completion of treatment, the analysis was not limited to the first 24 weeks or treatment emergent events only. The Sponsor provided an update to the safety information for trial MDS-001 based on a data sweep conducted 1 July 2019. This information is used to calculate the number of cases and risk for the controlled trial while the overall risk is calculated based on the 1 January 2019 update, since the phase 2 trial was not included in the 1 July data sweep.

A total of 33 events of non-MDS neoplasms were observed in the controlled trial, including 19 occurring in 13 patients (8.5%) in the luspatercept arm and 4 occurring in 3 patients (3.9%) in the placebo arm. Of these, 11 occurring in 7 patients (4.6%) in the luspatercept arm and 1 occurring in one patient (1.3%) on the control arm were malignant. The majority of malignant events were non-melanoma skin cancers.

In addition, 30 events in 26 patients were observed in in the neoplasms SOC the non-randomized trials A536-03 and -05. All events occurred in patients receiving a dose of at least 1.0 mg/kg. These included 13 events of progression to higher risk MDS or transformation to AML. Skin neoplasms including 3 basal cell carcinoma, 2 squamous cell carcinoma, and one skin papilloma were observed. Two cases of myelofibrosis in two unique patients and one case of CMML were reported. Further malignant neoplasms included bronchial carcinoma, hepatic cancer, DLBCL, NSCLC, prostate cancer, and renal cell carcinoma. Finally, benign neoplasms including benign bone neoplasm and lipoma were reported.

Table 42: Neoplasms observed (patients) with use of luspatercept versus placebo in patients with MDS

Neoplasm category	Luspatercept (all)*	Luspatercept (MDS-001)**	Placebo**
Any neoplasm***	33 (25)	19 (13)	4 (3)
Benign skin	3 (3)	2 (2)	3 (2)
Malignant skin	9 (8)	7 (5)	0
Other benign	10 (6)	6 (4)	0
Other malignant	11 (9)	4 (2)	1 (1)

*Based on 1 January 2019 update

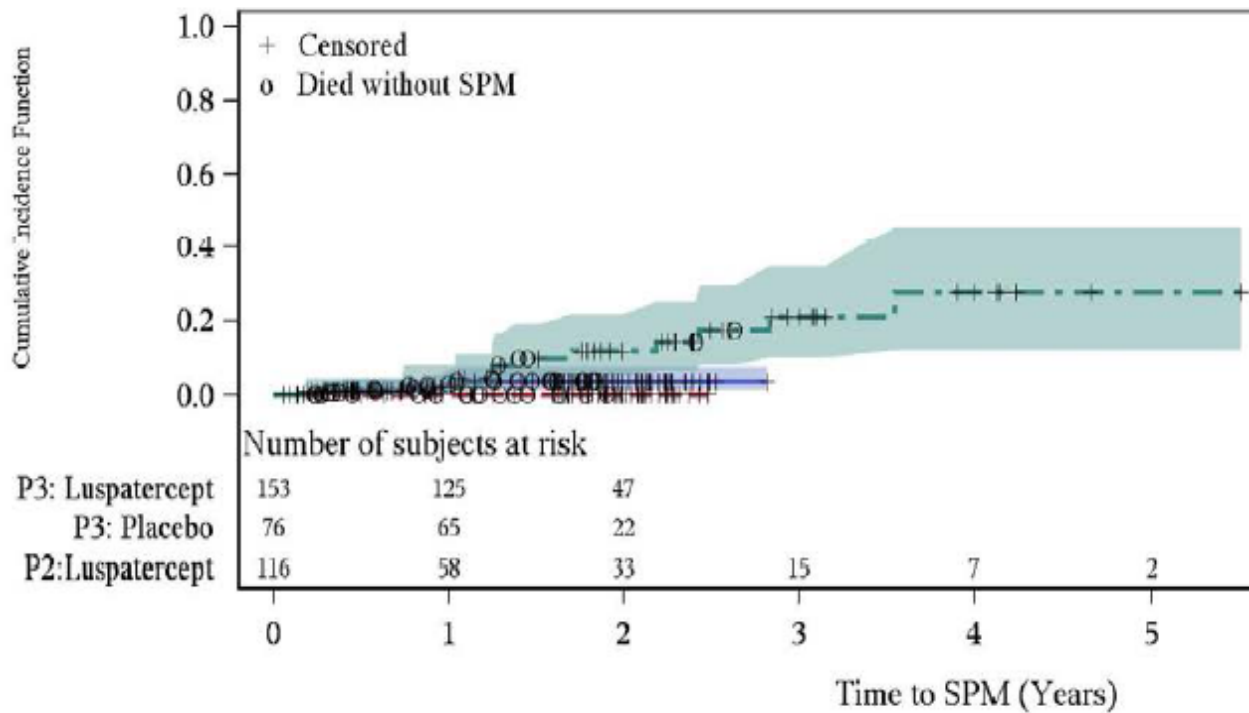
**Based on 1 July 2019 update

***Excludes MDS progression/transformation to AML

Neoplasms were observed, although more rarely, with use of luspatercept in other conditions. In the randomized trial for use of luspatercept in β -thalassemia, 13 events (11 patients) in the neoplasm SOC were reported in the luspatercept arm, including one case of AML and one hepatocellular carcinoma, compared to two events, both benign, in the placebo arm, and eight events, all benign, in the phase 2 trial in β -thalassemia. It should be noted that the β -thalassemia population is, in general, younger than the MDS population.

Another way of examining the risk of SPM is using cumulative incidence curves, with death as a competing risk. The Sponsor provided the figure below using this method. The Sponsor provided confidence intervals as well as point estimates of incidence. Although MDS-001 was not powered to determine a difference in SPM rate between arms and no analysis of difference between trials was planned, it is notable that the confidence intervals for SPM risk between the luspatercept arm and the control arm do not overlap.

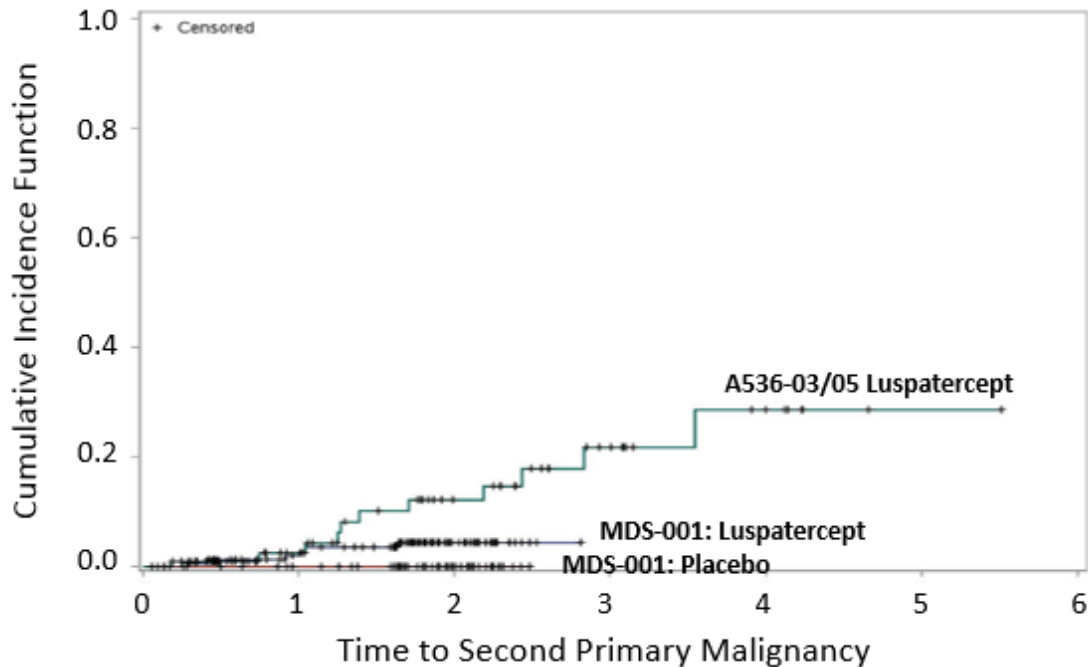
Figure 15: Cumulative incidence of SPM by study and arm adapted from Sponsor’s analysis. The green line represents events on trials A536-03/005, the blue events on the luspatercept arm of MDS-001, and the red events on the placebo arm of MDS-001.



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The FDA repeated the above analysis. Of note, the Sponsor incorrectly omitted one subject from the analysis. The subject had a history of bladder cancer which was considered in remission and therefore not an exclusion at the time of enrollment. The subject experienced a relapse of his bladder cancer during the trial and was included in the FDA’s analysis. The results are essentially similar, with a numerically higher rate of SPM again being observed with use of luspatercept compared to placebo in both studies.

Figure 16: Cumulative incidence of SPM by study and arm, FDA analysis



Reviewer's comments: A high rate of SPM was observed in patients receiving luspatercept in both the phase 2 trial and in the phase 3 trial, with an increased risk observed in the phase 3 trial compared to placebo. The higher rate observed is consistent throughout the study, with differences observable as soon as one year after the start of the study. Although the trial was not powered to see statistical differences in the risk of SPM and the analysis is post-hoc, it is notable that the 95% confidence intervals calculated by the Sponsor did not overlap.

The reason for the difference in rate of SPM between the luspatercept arm of MDS-001 and the phase 2 study is unclear. However, it should be noted that patients for whom data is available on the phase 2 study enrolled in the extension trial and thus had ongoing use of luspatercept while patients on trial MDS-001 were followed after completion of treatment. Thus, it is possible that the lower rate observed in the luspatercept arm of trial MDS-001 is related to lower lifetime exposure.

Several caveats should be considered when interpreting the data. First, the rate of mortality due to incidental or unknown cause was higher in the placebo arm, complicating the interpretation of the competing risk curves. Second, the data are immature, especially data from MDS-001, given the potential for SPM to develop years or decades after the initial insult. Third, patients in the phase 2 trial who did not choose to enroll in the extension study were not followed long term so their survival and SPM rate cannot be fully determined. Finally, cross study comparisons such as those between the phase 2 trial and MDS-001 can be difficult to interpret.

Overall, the bulk of the evidence supports a finding of increased risk of SPM in patients receiving luspatercept. The literature supports a biologically plausible mechanism of action of carcinogenesis. Despite the absence of dedicated carcinogenicity studies, the non-clinical data demonstrate findings suspicious for carcinogenesis. An increased risk was observed on both the phase 2 study and the luspatercept arm of the controlled trial. An increased risk of malignancy was observed in trials examining use of luspatercept in other conditions, including in younger patients receiving it for β -thalassemia. Finally, the competing risk curves show a small, but persistent difference in the rate of malignancy. Given that luspatercept is intended as a supportive care drug, this is a major finding and should be taken into account when considering the approvability of the drug.

Disease progression and transformation to AML

Per the most recent data sweep performed in July, 2019, 10 patients (6.5%) had progressed or transformed on the luspatercept arm versus 4 (5.3%) on the placebo arm (see table 43 below). However, a further transformation in a patient on the luspatercept arm was reported in a recent 15-day safety report, bringing the total to 11 (7.2%). In addition, 13 cases of progression or transformation were observed in study A536-05.

Table 43: Incidence of MDS progression or AML transformation by treatment

	Luspatercept (all)	Luspatercept (controlled trial)*	Placebo
MDS progression/AML	23	10 (6.5%)	4 (5.3%)

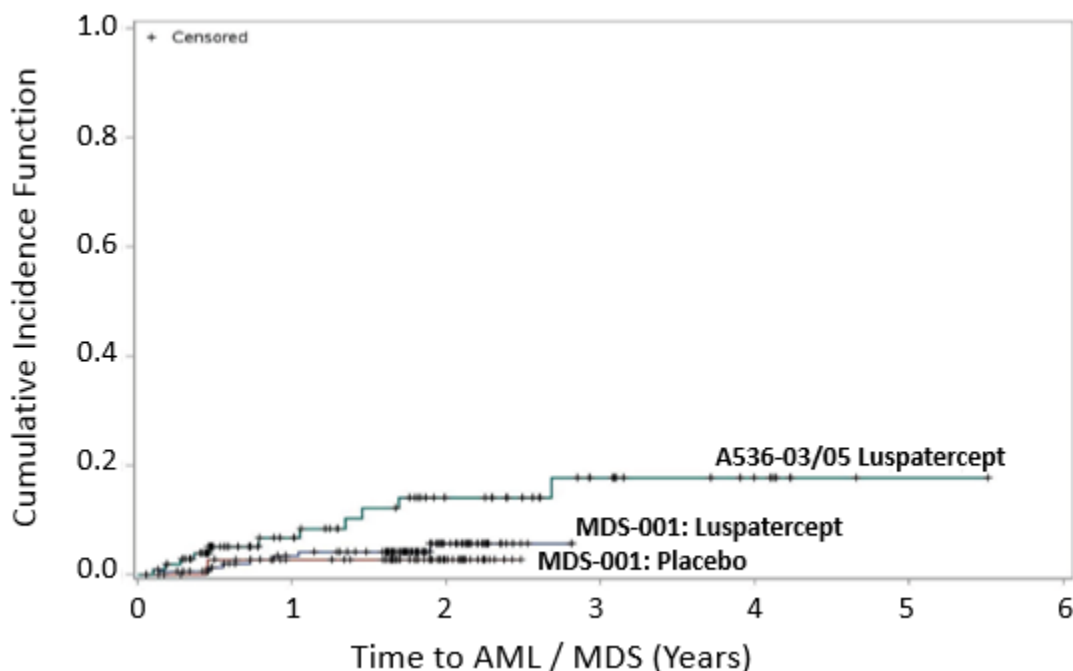
*An additional case of AML occurring in November, 2019 was reported to IND 112562 as a safety event.

As noted above, a probable case of AML was observed in the β -thalassemia trial. The diagnosis is not considered confirmed because of lack of cytogenetic changes consistent with AML. However, the only cytogenetic analysis was performed after induction chemotherapy was given, making the lack of classic cytogenetic changes of less significance. Certainly, the investigator considered this a case of confirmed AML since induction chemotherapy was given. A case of MPN blast phase/AML was reported to the IND as an event in the ongoing study of luspatercept in myelofibrosis as well. This case was reported only incidentally in a safety report of a patient who experienced a humerus fracture and thus it is possible that other transformations to blast phase have occurred but not been reported.

Another way of examining risk is to examine the cumulative incidence of progression using death as a competing risk. Competing risk curves are shown in figure 17 below. The risk of progression or transformation observed was higher in the phase 2 trial compared to the controlled trial and, within the controlled trial, the risk was higher at all time points after the

first year for the luspatercept arm versus the placebo arm. (Note that the curve below does not include the transformation reported to the IND mentioned above and that patients with high or very high risk MDS at baseline in the phase 2 study were excluded from the analysis.)

Figure 17: Cumulative incidence of AML/MDS by study and arm*



*Does not include an additional event occurring in November, 2019 as noted above.

The difference in SPM and progression/transformation rate between the luspatercept arm of the controlled trial and the phase 2 trial is of interest. One potential difference between the trials is treatment duration. As noted, patients on the phase 2 trial only continued to be followed if they enrolled in the extension trial. These patients therefore may have received a higher cumulative dose of luspatercept compared to patients on the controlled trial. Total time on therapy was longer for patients who experienced an event on the phase 2 trial compared to either patients who experienced an event or who did not experience an event on the luspatercept arm of the controlled trial. Finally, median total lifetime dose of the study drug was higher for patients on the phase 2 trial compared to the luspatercept arm of the controlled trial (table 44 below; also see clinical pharmacology review).

An additional finding of interest is that the time to event is longer for patients in the placebo arm who experienced events, particularly compared to those in the luspatercept arm on the controlled trial. Notably, the median time to event on the luspatercept arm was only 57 days longer than the duration of treatment, whereas the time to event was 315 days longer for patients on the placebo arm.

Table 44: Duration of treatment, time to event, and total lifetime dose by trial and treatment arm.

	Phase 2 trial	MDS-001 luspatercept	MDS-001 placebo
Duration of treatment (days)			
Patients with event	526 (1, 1494)	322 (423, 918)	148 (106, 150)
Patients without event	86 (1, 1528)	364 (21, 1184)	148 (51, 701)
Time to event (days)	623 (162, 807)	379 (50, 918)	463 (26, 1295)
Lifetime dose (mg/kg)	23.3 (1.3, 115.2)	12.6 (2.0, 89.7)	5 (0.6, 8.8)

Reviewer's comments: MDS carries an inherent risk of transformation to AML and progression to higher risk disease over time is expected. Thus, some background risk of AML and higher risk MDS is expected in any trial in MDS.

The data provided by the Sponsor demonstrate a small but persistent elevation in the risk of progression or transformation in the luspatercept arm compared to the control arm. The differences were not considered statistically significant, but since the trial was not powered to determine a difference in progression/transformation rate, the lack of statistical significance is meaningless. In addition, events (SPM and progression/transformation) were more likely to occur on or shortly after stopping treatment in patients receiving luspatercept while they generally occurred >6 months after treatment in patients receiving placebo. However, it should be noted that malignancy may occur at any time after exposure to a carcinogen and the timing, while suggestive, is not definitive.

The greater risk of events seen in patients on the phase 2 trial may be related to longer exposure, with patients in the phase 2 study who had an event receiving a median of >200 days more treatment compared to patients in the controlled study. Thus, greater lifetime exposure may explain the higher rate of events in the phase 2 trial.

Several caveats to these data should be noted. First, patients who participated in trial A536-03 were not followed for survival or progression after their initial treatment unless they enrolled on trial A536-05. Thus, the total incidence and rate of progression cannot be accurately calculated. Second, none of the studies included a requirement for formal evaluation for progression at any given timepoint, but relied on clinical observation to determine when to perform a bone marrow examination to evaluate a possible relapse. Thus, progression, especially from intermediate to high risk, could be underestimated as there may not be obvious changes in the peripheral blood counts in these patients and biopsies were not performed. It should be noted that leukocytosis, possibly representing not yet diagnosed progression, was reported in 5 patients on the luspatercept arm versus one on the placebo arm. Third, there is an imbalance in the rate of death from irrelevant causes between the two arms, making evaluation of the competing risk

curves difficult and again likely underestimating the risk of progression due to luspatercept. Finally, the data are very immature. In general, malignancies are late events and may occur 10 years or more after the inciting exposure. Thus, the short follow up almost certainly results in an underestimation of the risk.

Data from the controlled trial MDS-001 are not mature with respect to carcinogenicity risk. Despite this, a greater risk of neoplasms and in particular malignant neoplasms including MDS progression and transformation was observed in the luspatercept arm compared to the placebo arm. These results are possibly confounded by the finding of higher non-progression mortality in the placebo arm.

Overall, as with SPM, the bulk of the evidence, including a plausible mechanism of action, non-clinical findings, and clinical findings, including the occurrence of AML in patients treated with luspatercept for other indications, suggests an increased risk of MDS progression/transformation to AML with use of luspatercept. At minimum, an increased risk of progression/transformation cannot be ruled out based on the available data. Given that luspatercept is intended strictly as a supportive care drug with no claim of potential utility in treating the underlying disease, this represents a major safety issue and substantially alters the benefit/risk calculation.

8.6. Safety Analyses by Demographic Subgroups

Subgroup analyses were performed using age (<75 vs ≥75) and gender (women versus men) as demographic subgroups of interest. Typically, a subgroup analysis by race would be undertaken, but this is not possible due to the lack of non-white participants.

Overall, women experienced more TEAE than men with treatment with luspatercept (table 45). Events of nausea and vomiting, musculoskeletal pain, urinary tract infections, anemia, presyncope/syncope, and hypersensitivity occurred more often in women with a risk difference of ≥5. Conversely, dizziness occurred more frequently in men, with a risk difference of 7.7. Fatigue was very common in people of either gender, but the risk difference between genders was relatively low at 3.0.

Table 45: Adverse events observed in the luspatercept arm of study MDS-001 in the first 8 cycles of treatment for women versus men

Adverse reaction	Women (N=59)	Men (N=94)	RD
Nausea/vomiting	17 (29%)	8 (9%)	20.3
Musculoskeletal pain	16 (27%)	14 (15%)	12.2
UTI	6 (10%)	1 (1%)	9.1

Table 45: Adverse events observed in the luspatercept arm of study MDS-001 in the first 8 cycles of treatment for women versus men

Adverse reaction	Women (N=59)	Men (N=94)	RD
Anemia	6 (10%)	4 (4%)	5.9
Syncope/presyncope	5 (8%)	3 (3%)	5.3
Hypersensitivity reactions	8 (14%)	8 (9%)	5.0
Influenza	5 (8%)	4 (4%)	4.2
Infections, pathogen not specified	23 (39%)	33 (35%)	3.9
Disturbances in consciousness	4 (7%)	3 (3%)	3.6
Injection site reactions	5 (8%)	5 (5%)	3.2
URI	5 (8%)	5 (5%)	3.2
Fatigue	25 (42%)	37 (39%)	3.0
Edema	8 (14%)	10 (11%)	2.9
Viral infections	8 (14%)	10 (11%)	2.9
Headache	9 (15%)	12 (13%)	2.5
Diarrhea	10 (17%)	14 (15%)	2.1
Liver abnormalities	5 (8%)	6 (6%)	2.1
Hemorrhage	6 (10%)	8 (9%)	1.7
Hypertension	4 (7%)	5 (5%)	1.5
Abdominal pain	5 (8%)	7 (7%)	1.0
Cough	8 (14%)	12 (13%)	0.8
Dyspnea	8 (14%)	12 (13%)	0.8
Bronchitis	1 (2%)	3 (3%)	-1.5
VTE	1 (2%)	3 (3%)	-1.5
Confusion	2 (3%)	5 (5%)	-1.9
Tachyarrhythmias	4 (7%)	9 (10%)	-2.8
Fall	3 (5%)	8 (9%)	-3.4
Renal failure	2 (3%)	7 (7%)	-4.1
Dizziness	8 (14%)	20 (21%)	-7.7

The types of adverse events observed varied with age (Table 46). Patients age <75 were more likely to experience infections with pathogen not specified, nausea or vomiting, injection site reactions, tachyarrhythmias, UTI, headache, and viral infections whereas older patients were more likely to experience confusion, dyspnea, anemia, and fatigue. Fatigue in particular was very common in older patients, occurring in half of patients age 75 or older during the first 8 cycles of treatment. Concerningly, 10% of older patients experienced falls and 8% experienced

confusion during treatment.

Table 46: Adverse events observed in the luspatercept arm of study MDS-001 in the first 8 cycles of treatment by study arm by patient age

Adverse reaction	<75 years (N=101)	≥75 years (N=52)	RD
Infections, pathogen not specified	36 (36%)	9 (17%)	18.3
Nausea/vomiting	19 (19%)	6 (12%)	7.3
Injection site reactions	9 (9%)	1 (2%)	7.0
Tachyarrhythmias	11 (11%)	2 (4%)	7.0
UTI	7 (7%)	0	6.9
Headache	16 (16%)	5 (10%)	6.2
Viral infections	14 (14%)	4 (8%)	6.2
Hypersensitivity reactions	12 (12%)	4 (8%)	4.2
Musculoskeletal pain	21 (21%)	9 (17%)	3.5
Diarrhea	17 (17%)	7 (13%)	3.4
Hypertension	7 (7%)	2 (4%)	3.1
Dizziness	19 (19%)	9 (17%)	1.5
URI	7 (7%)	3 (6%)	1.2
Disturbances in consciousness	5 (5%)	2 (4%)	1.1
Bronchitis	3 (3%)	1 (2%)	1.0
Edema	12 (12%)	6 (12%)	0.3
Influenza	6 (6%)	3 (6%)	0.2
Syncope/presyncope	5 (5%)	3 (6%)	-0.8
Liver abnormalities	7 (7%)	4 (8%)	-0.8
VTE	2 (2%)	2 (4%)	-1.9
Renal failure	5 (5%)	4 (8%)	-2.7
Abdominal pain	7 (7%)	5 (10%)	-2.7
Cough	12 (12%)	8 (15%)	-3.5
Hemorrhage	8 (8%)	6 (12%)	-3.6
Fall	6 (6%)	5 (10%)	-3.7
Confusion	3 (3%)	4 (8%)	-4.8
Dyspnea	11 (11%)	9 (17%)	-6.4
Anemia	4 (4%)	6 (12%)	-7.6
Fatigue	36 (36%)	26 (50%)	-14.4

Reviewer's comments: The incidence and type of TEAE varied between genders and in older versus younger patients. Overall, women were more likely to experience adverse events

compared to men, with especially high rates of nausea/vomiting, musculoskeletal pain, and urinary tract infections occurring in women. This is of potential concern since women also appear to have less benefit from use of luspatercept (see subpopulation analysis of efficacy, above.)

Older patients were more likely than younger to experience fatigue and dyspnea, as well as potentially disabling or deadly events such as confusion and falls. Subpopulation analysis did not reveal any need to restrict use of luspatercept by demographic group, but did demonstrate potential concerns about the safety in older patients and the benefit-risk ratio in women.

8.7. Specific Safety Studies/Clinical Trials

No trials addressing specific safety concerns were undertaken.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

See non-clinical review and section 8.3.8, for details regarding human carcinogenicity and tumor development/progression risk associated with luspatercept.

8.8.2. Human Reproduction and Pregnancy

The reproductive and pregnancy risk of luspatercept has not been examined clinically. Also see non-clinical review for further information.

8.8.3. Pediatrics and Assessment of Effects on Growth

No clinical studies in pediatric patients have been completed. See review of non-clinical data for further information.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Luspatercept has a low potential for abuse. No evidence of withdrawal or rebound has been identified.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Luspatercept was approved for use in β -thalassemia requiring transfusion in November, 2019. No postmarketing safety concerns have been identified at the time of writing (December, 2019).

8.9.2. Expectations on Safety in the Postmarket Setting

There is a substantial risk that patients receiving luspatercept with less extensive monitoring in the postmarketing setting will experience severe and irreversible or fatal renal insufficiency or hepatic toxicity. An increase in progression of MDS and transformation to AML may be detectable on the population level if this drug becomes standard of care for treatment of lower risk MDS.

8.9.3. Additional Safety Issues From Other Disciplines

None.

8.10. Integrated Assessment of Safety

The review reveals several safety concerns with respect to use of luspatercept in the setting of lower risk MDS.

First, the review confirms the greater incidence of fatigue and dyspnea suggested by the PRO data. Indeed, the adverse events data suggest that the PRO data under-represent the risk of fatigue and dyspnea. An analysis of fatigue by cycle indicated that events occur throughout treatment and may be persistent and severe. Fatigue is the most common grade 3 or higher AE reported in the study.

Patients receiving luspatercept had an increased risk of dizziness, syncope or presyncope, and falls as well. The underlying mechanism for these issues is unclear, as luspatercept use was associated with both cardiac events (tachyarrhythmias) and neurologic events (confusion, disturbance of consciousness) that might result in symptoms of dizziness and syncope. Given that patients with MDS are often older and that both falls and bleeding were increased in the luspatercept arm as well, the increased risk of syncopal events is of concern.

Despite no evidence of a decrease in white blood cell counts, patients receiving luspatercept were more likely to experience infections, particularly infections with pathogen not identified and viral infections, compared to placebo. Respiratory infections (bronchitis, URI, influenza) and urinary tract infections appeared to account for the bulk of the infectious events. The concomitant medication data demonstrate increased use of antibiotics in the luspatercept arm, supporting the AE findings.

Gastrointestinal symptoms including diarrhea, nausea, vomiting, and abdominal pain, were common adverse events in patients receiving luspatercept. The etiology of these events is unclear given that luspatercept is not an oral drug. An effect of alterations in TGF- β signaling in the digestive tract or off target effect may be postulated, but there is no direct evidence to support this or other hypotheses at this time.

Issues previously identified in the review of luspatercept for use in the setting of β -thalassemia, including hypertension and thrombosis, were observed in this review as well, although neither of these events was seen as prominently as in the thalassemia population. Hypertension appeared to be more common later in treatment and not all cases identified in the vital signs report appeared to be documented in the adverse events reporting. Patients receiving luspatercept were more likely to receive anti-hypertensives, suggesting that the vital signs findings represented persistent hypertension, not a transient elevation.

Hepatic insufficiency was observed more commonly among patients receiving luspatercept, with a higher apparent risk in women compared to men. In addition, two cases meeting laboratory values for Hy's law were observed. One case was confounded and considered possibly related to cholelithiasis, but no secondary cause of the abnormalities could be found in the other case. In addition, the abnormal values decreased, but did not resolve, after decrease in the dose of luspatercept, suggesting a causal relationship.

Renal insufficiency, including fatal renal failure, was observed in the luspatercept arm of the study MDS-001 than in the placebo arm and renal events, including fatal events, were observed in the phase 2 trial. Although definitive testing for MPGN was not performed, patients with finding and symptom clusters suspicious for drug induced MPGN were identified in the luspatercept arm but not in the placebo arm. Due to the lack of availability of the gold standard tests for MPGN and short follow up, the risk of renal events, particularly MPGN, is incompletely characterized.

Malignancy, both MDS progression/transformation and SPM, is of concern. Patients on the phase 2 trial and on the luspatercept arm of trial MDS-001 had numerically higher rates of MDS progression and SPM. The rate of MDS progression and SPM was higher on the phase 2 trial as compared to the luspatercept arm of the controlled trial, possibly due to longer term exposure and higher cumulative exposure to luspatercept. The trial was not powered for evaluation of progression or SPM risk, but the finding of a persistent increase in events in both studies compared to placebo strongly argues that the risk for progression and SPM due to luspatercept is real and likely to result in adverse outcomes if the drug is approved.

The Sponsor has repeatedly pointed to the lack of increased mortality as evidence of the safety of luspatercept. Although this argument should be considered, there are several reasons why it should not be taken at face value.

First, the patient populations differed, with the placebo arm containing more patients age 80 or older, i.e. more patients with an increased baseline risk of death due to causes unrelated to the MDS. Second, many of the patients who experienced progression or transformation on either arm of the study (but who are more likely to be in the luspatercept arm) were alive at last

contact. Although this is a tribute to the quality of care patients received on the study, it is not evidence of the safety of luspatercept. Finally, the follow up time is short and the risk of mortality due to issues such as renal impairment is still unknown.

In summary, there are substantial risks associated with the use of luspatercept, including risk of persistent or recurrent fatigue and dyspnea, risk of hepatotoxicity, risk of renal insufficiency, and risk of malignancy. The risks of renal insufficiency and malignancy are incompletely characterized. The risk profile might be considered acceptable for a disease altering drug, especially if some clear benefit in terms of survival or response was observed. However, it is difficult to justify for a supportive care drug, especially given that the most common adverse events (fatigue, dyspnea, dizziness) are symptoms that transfusion is meant to decrease. Even in the absence of major organ damage or carcinogenicity, the majority of patients receiving luspatercept appear to feel worse than when receiving transfusions or other standard of care treatment for their anemia. Thus, no benefit to the patient is evident.

9. Advisory Committee Meeting and Other External Consultations

This application was not discussed at an advisory committee meeting.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

NA-Complete response recommended.

10.2. Nonprescription Drug Labeling

NA

11. Risk Evaluation and Mitigation Strategies (REMS)

NA-complete response recommended.

12. Postmarketing Requirements and Commitments

NA-complete response recommended

13. Appendices

13.1. References

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13.2. Financial Disclosure

Financial disclosure information was provided for studies ACE-536-MDS-001 and A536-03. Two investigators on study ACE-536-MDS-001 disclosed financial relationships with the Sponsor (b) (6)

(b) (6)
reports receiving approximately \$31,300 for a variety of talks and consulting. All reported payments were for work related to MDS (i.e. educational talks on MDS), but not directly related to the study or Luspatercept.

No financial interests or arrangements were reported for study A536-03/A536-05. Disclosure statements were not provided by 8 investigators on this study, including one site PI. The sponsor (Acceleron) reports making due diligence attempts to obtain financial information from these investigators.

Covered Clinical Study (Name and/or Number): ACE-536-MDS-001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>450</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>2</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: <u>0</u> Significant payments of other sorts: <u>£400,000</u> (b) (6); <u>\$31,300</u> (b) (6) Proprietary interest in the product tested held by investigator: <u>0</u>		

Clinical Review
 Elizabeth Pulte
 BLA 761136 Original 2
 REBOLZYL (Iuspaterecept-aamt)

Significant equity interest held by investigator in SO Sponsor of covered study: <u>Celgene</u>		
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>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

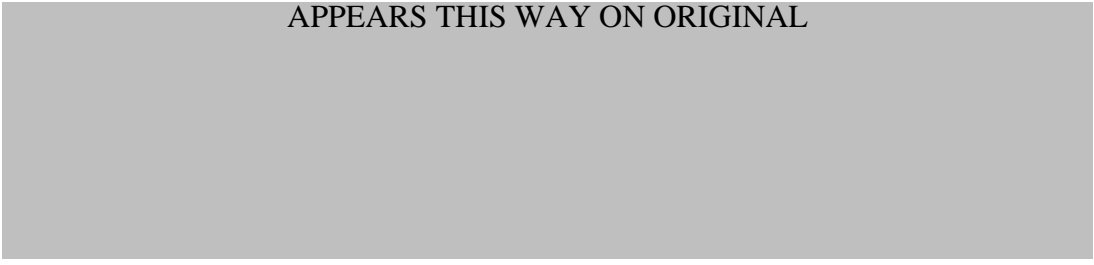
Covered Clinical Study (Name and/or Number): A536-03/A536-05

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>79</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: <u>0</u> Significant payments of other sorts: <u>0</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in SO Sponsor of covered study: <u>Accelaron</u>		
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	Yes ☒	No ☐ (Request information

Clinical Review
Elizabeth Pulte
BLA 761136 Original 2
REBOLZYL (Iuspatercept-aamt)

minimize potential bias provided:		from Applicant)

APPEARS THIS WAY ON ORIGINAL



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

/s/

ELIZABETH D PULTE
12/31/2019 03:13:13 PM

DONNA PRZEPIORKA
12/31/2019 03:15:03 PM
The TL comments are incorporated in the CDTL review.