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APPLICATION NUMBER:

761136Orig2s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	3/31/2020
Cross-Discipline Team Leader	Donna Przepiorka, MD, PhD
NDA/BLA #	**BLA 761136 Original-2**
Applicant	Celgene Corporation
Date of Submission	4/4/2019
PDUFA Goal Date	4/4/2020
Proprietary Name	Reblozyl
Proper Name	Luspatercept-aamt
Dosage Form(s)	Injection, lyophilized (25 mg, 75 mg)
Recommendation on Regulatory Action	Approval
Recommended Indication	(b) (4) Limitations of Use: REBLOZYL is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.
Recommended Dosing Regimen	• Start REBLOZYL at 1.0 mg/kg once every 3 weeks as a subcutaneous injection. • If the patient is not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose, increase the dose to 1.33 mg/kg. • If the patient is not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1.33 mg/kg dose, increase the dose to 1.75 mg/kg. • Do not increase the REBLOZYL dose beyond the maximum of 1.75 mg/kg per dose.

Additional Reviews Consulted	**Discipline Reviewer(s)**
OBP (9/4/2019)	S. Johnson, PhD; Y. An, PhD
Pharmacology/Toxicology (12/31/2019)	M. Manning, PhD; H. Saber, PhD
Clinical Pharmacology (12/23/2019)	Lili Pan, PhD; Liang Li, PhD; Lian Ma, PhD; Guoxiang Shen, PhD.
Statistical (12/23/2019)	Weishi Yuan, PhD; Yu-Te Wu, PhD; Thomas E. Gwise, Ph.D.
Clinical (12/31/2019)	E. Dianne Pulte, MD
Regulatory Project Manager (DHP)	Rosa Lee-Alonzo
Deputy Director for Labeling (DHP)	Virginia E. Kwitkowski, MS, ACNP-BC
Deputy Director for Safety (DHP)	Rosanna Setse, MD, PhD
COA Consult (10/9/2019)	Selena Daniels, PharmD
DMPP (2/13/2020)	Susan Redwood, MPH, BSN
DBRUP Consult (9/18/2019)	Jacqueline Cunkelman MD, MPH; Suresh Kaul, MD, MPH
DNP Consult (9/5/2019)	David A Hosford MD PhD
PFDD (OOD) Consult (10/23/2019)	Vishal Bhatnagar, MD
OPDP (2/18/2020)	Rebecca Falter, PharmD
OSI (9/6/2019)	Anthony Orencia MD, FACP; Min Lu, MD, MPH
OSE/DMEPA (1/13/2020)	Nicole Iverson, PharmD, BCPS; Hina Mehta, PharmD

1. Benefit-Risk Assessment

BLA 761136 was submitted under 351(a) for luspatercept-aamt, an erythroid maturation agent. Original-1 was approved on 11/8/2019 for the treatment of anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions. 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 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.

Approval is recommended for the indication (b) (4)

Evidence of clinical benefit came from Study ACE-536-MDS-001 (Study MDS-001), a randomized, double-blind, placebo-controlled trial in patients with anemia requiring RBC transfusions in the setting of lower-risk MDS with ringed sideroblasts (RS). Eligible patients were refractory to or intolerant of erythropoiesis stimulating agents (ESA) (or had an erythropoietin level > 200 U/L), and required 2 or more RBC units / 8 weeks for a minimum of 16 weeks immediately prior to randomization with no 56-day period free of transfusions during that time. The study participants were randomized 2:1 to luspatercept-aamt or placebo subcutaneously every 3 weeks. The patients in both study arms also received best supportive care, including RBC transfusions, at the discretion of the investigator.

The primary endpoint of the study was the proportion of patients who were RBC transfusion-free over any consecutive 56-day period (8 weeks) (RBC-TI-8) within Weeks 1 - 24 of the study (e.g., the TI period started and ended within Weeks 1 - 24). Key secondary endpoints included the proportions of patients RBC transfusion-free over any consecutive 84-day period (12 weeks) (TI-12) within Weeks 1 - 24 and within Weeks 1 - 48 of the study. The study was sized to have 90% power to detect a 20 percentage-point difference between study arms in Weeks 1 - 24 RBC-TI-8. There were 229 patients randomized to luspatercept-aamt (n=153) or placebo (n=76). The results showed a significant difference in Weeks 1 - 24 RBC-TI-8 (24.5%; $p < 0.001$), Weeks 1 - 24 RBC-TI-12 (20.0%; $p = 0.0002$) and Weeks 1 - 48 RBC-TI-12 (21.4%; $p = 0.0003$) in favor of luspatercept-aamt.

Despite the statistical significance for the comparisons of RBC-TI between arms, the absolute response rates within Weeks 1 - 24 were rather low, 37.9% RBC-TI-8 and 28.1% RBC-TI-12. Additionally, the treatment effect was not consistent across subpopulations by baseline transfusion burden. For patients with a high transfusion burden, defined as ≥ 6 units / 8 weeks, the RBC-TI-8 within Weeks 1 - 24 was very low in both the luspatercept-aamt and placebo arms

(9.1% and 3.0%), suggesting a lack of treatment effect for this subpopulation. FDA also sought corroborating evidence from patient-reported outcomes (PRO); a consistent trend for improved global health status, reduced fatigue or reduced dyspnea with luspatercept-aamt treatment in comparison to placebo was not observed.

It is not unusual to require more than one trial for assessment of a supportive care drug, and a positive outcome in an additional randomized trial would address some of the uncertainty raised by the inconsistent treatment effect observed in Study MDS-001. However, in view of the lack of approved agents for second-line treatment in this population, and the much better treatment effect seen in the lower transfusion burden subgroup (risk difference 36.9%), the results would seem a sufficient demonstration of effectiveness for that subgroup at least.

It was also noted that Study MDS-001 accrued a small number of patients with MDS/MPN-RS-T, a rare overlap syndrome. Although the number of those patients is quite small in the lower transfusion burden subgroup (12 on luspatercept-aamt and 7 on placebo), a difference in achieving RBC-TI-8 was detectable (risk difference 46.4%). Given the rarity of MDS/MPN-RS-T, it is unlikely that a large randomized trial in this disease could be conducted, and the results for patients this disease in Study MDS-001, supported by the results in the much larger group of patients with MDS-RS would warrant extending approval to patients with ESA-refractory anemia of MDS/MPN-RS-T.

The safety profile of luspatercept-aamt in this patient population is similar to that reported for patients with beta-thalassemia, except for a higher likelihood for renal injury and fatigue. Although the most common adverse reactions (fatigue, dizziness, diarrhea and dyspnea) were usually low grade, the nature of these adverse reactions could impact the activities of daily living in an elderly population. A greater concern was that 2.1% of patients treated with luspatercept-aamt developed a fatal adverse reaction. The fatal adverse reactions must be considered carefully when weighing the risks and benefits of this supportive care drug. In the benefit risk assessment, this likelihood for adverse reactions that might impair activities of daily living in addition to the potential for fatal adverse reactions lowers enthusiasm for approval in the subgroup with higher transfusion burden anemia where the treatment effect was only 6%.

Additionally, nonclinical studies identified renal injury (specifically membranoproliferative glomerulonephritis) and development of malignancies as additional risks. Due to the lack of adequate testing and follow-up in the clinical trial, it is difficult to asses the true incidences of these risks. Additional study of safety in long-term use is warranted, especially monitoring for renal injury, progression to AML and occurrence of second malignancies, and this can be accomplished in part with a postmarket requirement to continue safety follow-up for patients on Study MDS-001. Enhanced pharmacovigilance would be suitable to obtain a better assessment of the risk of renal injury in the real world.

Therefore, with adequate instructions for dosing, monitoring and dose modifications in place in labeling, the RBC-TI-8 benefit with luspatercept-aamt appears to outweigh the risks (b) (4)

(b) (4)

The limitation of use statement that luspatercept-aamt is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia applies to this indication as well.

Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Lower-risk MDS-RS and MDS/MPN-RS-T are chronic diseases. • Anemia is a frequent manifestation of MDS-RS and MDS/MPN-RS-T and is associated with substantial symptom burden.	The anemia of MDS-RS and MDS/MPN-RS-T can be debilitating and needs to be addressed.
Current Treatment Options	• The first-line standard-of-care for anemia of lower-risk MDS is ESAs. • Azacitidine is approved for treatment of MDS, but it has attendant toxicities. • There are no drugs approved for treatment of anemia of MDS failing ESAs.	There is a need for an effective agent to treat anemia of MDS-RS and MDS/MPN-RS-T.
Benefit	• Study ACE-536-MDS-001 was a randomized, blinded trial comparing luspatercept-aamt (n=153) to placebo (n-76) for treatment of anemia failing an ESA in patients with lower-risk MDS-RS. • In the ITT analysis of RBC-TI-8, the primary endpoint, the risk difference was 24.6% (95% CI, 14.5, 34.6). • There was no treatment effect noted in the higher transfusion burden subgroup. • In the lower transfusion burden subgroup, RBC-TI-8 was achieved by 56.3% of patients with MDS-RS and by 75.0% of patients with MDS/MPN-RS-T. • Most responses lasted less than one year, but there were rare long-lasting responses.	The results show that luspatercept-aamt is active in patients with lower transfusion burden anemia, but there is substantial uncertainty regarding its potential benefit in patients with high transfusion burden anemia.
Risks and Risk Management	• Common (>10%) all-grade adverse reactions included fatigue, musculoskeletal pain, dizziness, diarrhea, nausea, hypersensitivity reactions, hypertension, headache, upper respiratory tract infection, bronchitis, and urinary tract infection. • Grade $\geq$ 2 renal impairment and transaminase elevation occurred in > 10% of patients. • Fatal adverse reactions (2.1%) included renal failure, sudden death, SIRS and general health deterioration. • Risks during the clinical trial required frequent monitoring of hemoglobin and dose modification.	The overall short-term safety profile of luspatercept-aamt is acceptable for patients with lower transfusion burden anemia. Additional longer-term follow-up is needed to assess long-term toxicities, including renal injury, progression to AML and second primary malignancies.

2. Background

2.1 Product Information

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:	Antianemic
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:	Erythroid maturation agent
Mechanism of Action:	Binds and neutralizes several endogenous TGF-β superfamily ligands, resulting in diminished Smad2/3 signaling and promotion of erythroid maturation through differentiation of late-stage erythroid precursors.

2.2 Therapeutic Context

At the present time, lenalidomide is the only drug approved for treatment of patients with transfusion-dependent anemia due to lower-risk MDS, although the indication is limited to those with deletion 5q. The approval of lenalidomide was based on a dose-ranging trial that included 148 patients.[1] RBC-TI-8, the primary endpoint, was achieved by 99/148 (67%; 95% CI: 59, 74), and the median duration of response was 44 weeks (range, 0 to > 67 weeks). In a subsequent randomized double-blind trial[2] of lenalidomide vs placebo for patients with transfusion-dependent anemia due to lower-risk MDS with deletion 5q, superiority to placebo was demonstrated based on achievement of the primary endpoint of transfusion independence for 26 or more weeks (TI-26). Approximately 52% of the patients had prior ESA use. RBC-TI-26 was achieved by 55% (95% CI:43, 67) on the 10 mg lenalidomide dose arm vs 6% (95% CI: 2, 15) on placebo. It is acknowledged that lenalidomide is a disease-modifying drug for treatment of lower-risk MDS with deletion 5q.

There are no ESAs or erythroid maturation agents approved for treatment of patients with transfusion-dependent anemia due to lower-risk MDS or for MDS-RS. The goal of treatment is

[1] Lenalidomide US Prescribing Information dated December 27, 2005. Accessed from https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
[2] Fenaux P et al. (2011) A randomized Phase 3 study of lenalidomide versus placebo in RBC transfusion-dependent patients with low-/intermediate 1-risk myelodysplastic syndromes with del5q. Blood 118:3765-3766.

to relieve the symptoms of anemia. ESAs are standard of care for first-line therapy. Lenalidomide and immunosuppressive drugs have been used off-label for patients failing ESAs (discussed extensively Clinical Review Section 2.2). Azacitidine is approved for treatment of MDS in general, but due to the attendant toxicities, hypomethylating agents are generally reserved for patients with multiple cytopenias requiring cytoreductive therapy. Allogeneic hematopoietic stem cell transplantation is the only curative therapy.

MDS/MPN-RS-T is a rare subset of the overlap syndromes.[3] Morphologically it shares the presence of ring sideroblasts with MDS-RS, but it has a distinct molecular profile. The recommended approach to treatment of MDS/MPN-RS-T with isolated anemia is similar to that for MDS.[4]

2.3 Regulatory Background

The clinical development of luspatercept-aamt in the US was conducted under IND (b) (4) and IND 112562. On 3/18/2018, Orphan Designation was granted for treatment of myelodysplastic syndromes, and on 12/3/2015, Fast Track Designation was granted for treatment of anemia in persons with IPSS-R lower risk (very low, low or intermediate risk) myelodysplastic syndrome (MDS).

On 6/26/2015, FDA granted a waiver from the requirement of a formal nonclinical study of carcinogenicity from luspatercept-aamt. There were multiple communications between FDA and the Applicant with regard to the occurrences of AML in the clinical trials of luspatercept-aamt and the risk mitigation strategies. On the basis of available nonclinical (see Section 4) and clinical data, on 11/29/2016 FDA advised the Applicant that patients treated on clinical trials of luspatercept-aamt should be observed for development of malignancies for at least 5 years after treatment.

During the course of development of luspatercept-aamt for treatment of anemia in patients with MDS, FDA provided advice to the Applicant in six formal interactions, including a type B pre-IND meeting (6/16/2010), Type B pre-Phase 3 meeting (7/29/2015), a Type B pre-BLA meeting on 10/4/2018, and written responses issued on 11/29/2016, 3/1/2018 and 5/25/2018. Key advice provided during the formal and ad hoc communications included:

- A placebo control would be acceptable if patients who required cytoreductive therapy, such as those with multiple cytopenias, were excluded from the trial.

- Hematological improvement (HI-E) was not accepted as an endpoint for regulatory purposes.

[3] Broseus J et al. (2012) Clinical features and course of refractory anemia with ring sideroblasts associated with marked thrombocytosis. Haematol 97:1036-1041.
[4] Patnaik MM et al. (2019) Refractory anemia with ring sideroblasts (RARS) and RARS with thrombocytosis: "2019 Update on Diagnosis, Risk-stratification, and Management." Am J Hematol. 94:475–488.

- Whether transfusion independence for 8 weeks (TI-8) was a meaningful endpoint would be a review issue. Risk difference rather than odds ratio should be used for the analysis of TI-8.

- Key secondary endpoints that may support labelling claims should measure different manifestations of the disease and should not be redundant in concept with the primary endpoint or any other key secondary endpoint.

On 11/8/2019, FDA approved luspatercept-aamt for the treatment of anemia in adult patients with beta thalassemia who require regular red blood cell (RBC) transfusions, with a limitation of use stating that luspatercept-aamt is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia. Luspatercept-aamt is not known to be marketed in any other country.

3. Product Quality

There was no new product quality information in the Original-2 submission. The Applicant claimed a categorical exclusion from the requirement for an environmental assessment, and the claim was accepted based on 21 CFR 25.15(d) under the provisions of 21 CFR 25.31 (b and c).

4. Nonclinical Pharmacology/Toxicology

The nonclinical data were reviewed under the Original-1 application. There were two observations in the nonclinical review considered especially pertinent to the intended population for the Original-2 application:

- *Renal injury*: Nonclinical examination of the effect of luspatercept on kidney function in cynomolgus monkeys showed up to a 2-fold increase in creatinine compared to control animals. Pathology showed drug-related membranoproliferative glomerulonephritis (MPGN) and interstitial hemorrhage and fibrosis. MPGN was observed at exposures ≥ 0.6 times the exposure at the maximal recommended human dose of luspatercept.

  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. These findings were observed at doses ≥ 0.05 the maximum recommended human dose of luspatercept.

- *Risk of Malignancy*: Nonclinical data included one toxicology study demonstrating an increased risk of hematologic malignancies in juvenile rats. The juvenile rat study involved administration of subcutaneous doses of luspatercept every 2 weeks starting on postnatal day 7 for a total of 7 doses followed by an 18-week recovery period. Hematologic malignancies (granulocytic leukemia, lymphocytic leukemia, malignant lymphoma) were observed at the high-dose level. This study was not designed to assess carcinogenicity. It should be noted that some rats were documented to have died of indeterminate cause, and not all rats were

evaluated for malignancies. One incident of disseminated pleomorphic lymphoma was observed at the high-dose level in the 3-month study in adult rats.

A nonclinical pharmacology study demonstrated a trend towards greater tumor growth in the Lewis lung carcinoma mouse model. Mice were injected with murine carcinoma cells and received luspatercept at 1 mg/kg or 10 mg/kg, erythropoietin, or vehicle weekly for one month. Tumor volume was measured via calipers, IVIS, and weight on necropsy. No difference in tumor size was observed by measurement with calipers. IVIS measurement showed increased tumor size for the luspatercept 1 mg/kg dose but not the 10 mg/kg dose. Increased tumor weight was observed in the luspatercept-treated mice, but the difference was not statistically significant.

The Nonclinical Pharmacology/Toxicology Reviewer did not conclude that the issues identified above in themselves were sufficient to preclude approval of the Original-2 application, and the clinical implications of the nonclinical findings are discussed further in Section 5.4 and 8.1. The Nonclinical Pharmacology/Toxicology Reviewer did recommend revisions to the label in concert with the change in exposure ratios based on the higher recommended dose proposed in the Original-2 application.

5. Clinical Pharmacology

The Applicant submitted one early phase trial (A536-03), an extension study (A536-05), one confirmatory trial (ACE-536-MDS-001), and multiple pharmacometrics reports applicable to the clinical pharmacology of luspatercept-aamt in the intended population. Except where indicated, the following information is taken from the Clinical Pharmacology Review.

5.1 Pharmacokinetics

The pharmacokinetics evaluation in patients with MDS showed:

- Following subcutaneous administration of luspatercept-aamt 1.0 mg/kg, the geometric mean Cmax (6.44 mcg/mL) was reached at day 5.55.

- The accumulation ratio was approximately 1.5-fold. Steady-state exposure was reached after 3 doses every 3 weeks. The apparent volume of distribution was 9.8 L.

- Luspatercept serum exposure (AUCss and Cmax) increased approximately dose-proportionally with doses from 0.125 to 1.75 mg/kg.

- Following multiple SC doses of 1.0 mg/kg, 1.33 mg/kg and 1.75 mg/kg every 3 weeks, the steady-state geometric mean Cmaxs were 9.29 mcg/mL, 12.4 mcg/mL and 16.3 mcg/mL, respectively; and the steady-state AUC was 148 day·mcg/mL, 196 day·mcg/mL and 258 day·mcg/mL, respectively.

- The apparent clearance was 0.52 L/day. The terminal phase half-life was 13 days.

- With regard to specific populations, population PK analysis suggested that no dose modification is needed by age, sex, race, mild or moderate renal impairment, mild-to-severe hepatic impairment, or baseline disease characteristics.

- Based on the biological nature of luspatercept-aamt, drug-drug interactions were not expected and no drug-drug interaction studies were conducted.

5.2 Pharmacodynamics

In patients with low transfusion burden (< 4 RBC units / 8 weeks prior to study), the mean hemoglobin increased within 7 days of start of luspatercept-aamt and the change in hemoglobin from baseline was dose-dependent, being higher with luspatercept-aamt doses of 0.75 - 1.75 mg/kg than with doses of 0.125-0.5 mg/kg. The greatest hemoglobin increase occurred after the first dose, approximately 1 g/dL at doses of 0.75 - 1.75 mg/kg. Additional smaller increases were observed after subsequent doses. Hemoglobin levels returned to baseline approximately 6 to 8 weeks following the last administration of luspatercept-aamt.

5.3 Immunogenicity

The Immunogenicity Reviewer found that the screening, confirmatory and neutralizing anti-drug antibody (ADA) assays were validated adequately. The Clinical Pharmacology Reviewer found that the sampling schedule for ADAs was acceptable and reported that for the patients with MDS:

- Treatment-emergent ADA were detected in 23/260 (8.9%) of patients treated with luspatercept-aamt and in 3/76 (4.0%) of those treated with placebo.

- Treatment emergent neutralizing ADA were detected in 9/260 (3.5%) of patients treated with luspatercept-aamt and in 2/76 (2.6%) of those treated with placebo.

- Luspatercept Ctrough was numerically lower (3.23 mcg/mL vs 4.11 mcg/mL) in patients with ADA in comparison to those without ADA.

- Luspatercept Ctrough was numerically lower (2.59 mcg/mL vs 4.11 mcg/mL) in patients with neutralizing ADA in comparison to those without ADA.

- Given the small number of patients who developed neutralizing ADA, statistical comparisons of safety and efficacy outcomes by ADA development would not be meaningful.

5.4 Dose Considerations

The analysis of data to assess the proposed luspatercept-aamt dose and schedule showed:

- The apparent CL/F and Vd/F of luspatercept-aamt increased with increasing body weight in patients with MDS (46 to 124 kg). Simulations demonstrated that weight-based dosing was optimal to minimize variability in exposure between patients.

- Based on the Tmax and t1/2, administration every 3 weeks was expected to maintain the steady-state Ctrough above the Kd of luspatercept binding to GDF11 and the IC50 of luspatercept to inhibit signaling through GDF11 in in-vitro assays.

- The starting dose of 1 mg/kg was consistent with the observed minimum effective dose for pharmacodynamics in the dose-escalation trial.

- The exposure-efficacy analysis was confounded by the dose-titration design.

- The exposure-safety analysis showed a generally flat relationship between luspatercept exposure and the probability of Grade ≥ 3 treatment-emergent adverse events through Week 6 and a modestly positive relationship after Week 6.

- Patients on Studies A536-03 and ACE-MDS-001 were followed for progression to higher-risk MDS, progression to AML, or development of a secondary primary malignancy. Dose-neoplasm analysis showed no clear relationship between the incidence rate of disease progression or second primary malignancy and the luspatercept dose or exposure.

The Clinical Pharmacology Reviewer concluded that the proposed titration-to-response dosing regimen using 1.0 to 1.33 to 1.75 mg/kg was acceptable. The BLA was considered approvable from a Clinical Pharmacology perspective.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical - Efficacy

7.1 Issues Related to the Clinical Development Program

The indication proposed for luspatercept-aamt by the Applicant is "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."

The Applicant submitted efficacy and/or safety data from 3 clinical trials of luspatercept for treatment of anemia in patients with myeloid neoplasms (outlined in Appendix 14.1). The clinical trials used in the analysis of efficacy are listed in the table below:

Table 1: Clinical Trials That Contributed to the Assessment of Efficacy

Trial	Design	Population	Contribution
ACE-536-MDS-001 Phase 3	Randomized, placebo-controlled • Luspatercept-aamt vs placebo	Transfusion-dependent anemia in patients with lower-risk MDS with ring sideroblasts	Basis for efficacy
A536-03 Phase 1/2	Dose-escalation, dose-expansion • Luspatercept-aamt alone	Anemia in patients with MDS or CMML	Dose selection

Source: FDA analysis; see Appendix 14.1 for details of the study designs
Abbreviations: CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndromes

The Applicant submitted results for one randomized trial, ACE-536-MDS-001 (MDS-001), to serve as the primary basis of efficacy. FDA frequently requires multiple trials to establish efficacy, especially for a supportive care drug. At a Type B meeting on 7/29/2015, FDA indicated that whether a one randomized trial with additional data from a single-arm trial was adequate would be a review issue.

Except where indicated, the following information is taken from the Statistical and Clinical Reviews.

7.2 Issues Related to the Design of Study ACE-536-MDS-001

Study MDS-001 was a randomized, double-blind, placebo-controlled trial in patients with anemia requiring RBC transfusions in the setting of lower-risk MDS with ringed sideroblasts (RS). Eligible patient were adults with the following key disease-related eligibility requirements:

- Diagnosis of MDS with $\geq$ 15% ringed sideroblasts (or $\geq$ 5% with an SF3B1 mutation)
- Very low, low or intermediate risk by IPSS-R (patients with 5q- were excluded)
- Refractory to or intolerant of prior ESA treatment, or erythropoietin level > 200 U/L
- Required 2 or more RBC units / 8 weeks for a minimum of 16 weeks immediately prior to randomization and with no 56-period free of transfusions during that time.
- Hgb $\leq$ 10 g/dL prior to transfusions
- White blood cell count < 13 Gi/L, neutrophils $\geq$ 0.5 Gi/L, and platelets $\geq$ 50 Gi/L
- No prior disease-modifying agents for MDS

The study participants were randomized 2:1 to luspatercept-aamt or blinded placebo subcutaneously every 3 weeks. Randomization was stratified by baseline transfusion burden (< vs $\geq$ 6 U RBC over 8 weeks) and IPSS-R at baseline (very low/low vs intermediate). The

luspatercept-aamt regimen, titrating 1 mg/kg -> 1.33 mg/kg -> 1.75 mg/kg based on response, was based on the findings in the Study A536-03 that hemoglobin increases and achievement of transfusion independence were observed with starting doses $\geq$ 0.75 mg/kg, no safety issues were identified using doses up to 1.75 mg/kg, and activity and safety of the titration scheme were confirmed in an expansion cohort. The patients in both study arms also received best supportive care, including RBC transfusions, at the discretion of the investigator.

The primary endpoint of the study was the proportion of patients who were RBC transfusion-free over any consecutive 56-day period (8 weeks) (TI-8) within Weeks 1 - 24 of the study (e.g., the TI period *started and ended within* Weeks 1 - 24). Risk difference was used to quantitate the treatment effect. The study was sized to have 90% power to detect a 20 percentage-point difference in Weeks 1 - 24 RBC-TI-8 (30% vs 10%) between luspatercept-aamt and placebo with a one-sided alpha of 0.025. Key secondary endpoints included the proportions of patients RBC transfusion-free over any consecutive 84-day period (12 weeks) (RBC-TI-12) within Weeks 1 - 24 and within Weeks 1 - 48 of the study. There were 16 additional secondary and 4 additional exploratory endpoints. Type 1 error was controlled only the for key secondary endpoints. The final analysis was to be conducted in the ITT population when all patients had completed at least 48 weeks of treatment or discontinued earlier.

The major issue identified in the study design was the endpoint of RBC-TI-8. The meaningfulness of such a short duration of response is unclear when the disease itself has a rather protracted course. Resolution of the concern would require corroborating evidence of activity on additional measures that might be meaningful to the patient, such as longer durations being transfusion-free or with reduced symptoms.

The Applicant also planned analyses of reduction in RBC transfusions over Weeks 9-24, HI-E lasting at least 8 weeks, and hemoglobin increase $\geq$ 1 g/dL lasting at least 8 weeks as additional efficacy measures. The meaningfulness of mean reduction in transfusions or in achieving a specific percentage transfusion reduction short of 100% (i.e., less than transfusion independence) has not been established. Additionally, due to the lack of standardization of the interval between last prestudy transfusion and study start as well as the wide variability in baseline hemoglobin accepted for eligibility, any analysis of hemoglobin increase would not be credible. As such, at this time, the alternative measures as defined in the protocol would not be considered reliable measures of clinical benefit for the intended population.

Lastly, placebo for use in this study was not provided by the Applicant. Instead, a designated individual at the clinical site, such as the pharmacist, was unblinded, and the protocol instructed this individual to prepare a syringe of 0.9% sodium chloride for injection (a clear and colorless solution) for placebo to be dispensed in a blinded manner. However, luspatercept-aamt prepared for administration may be slightly yellow or slightly opalescent, and these characteristics may result in unmasking. Unmasking the blinded study drug may result in bias with regard to giving or withholding transfusions based on knowing the treatment, and how this potential bias was mitigated was not addressed by the study design.

7.3 Issues Related to the Conduct of Study ACE-536-MDS-001

There were 229 patients randomized 2:1 to luspatercept-aamt (n=153) or placebo (n=76). The demographics of study participants are shown in Appendix 14.2. Table 2 shows the key baseline disease characteristics of the randomized patients.

Table 2: ACE-536-MDS-001: Key Baseline Disease Characteristics

Demographic Parameters	**Luspatercept-aamt** (N=153)	**Placebo** (N=76)
WHO 2016 Classification		
MDS-RS	135 (88%)	65 (86%)
MDS/MPN-RS-T	14 (9%)	9 (12%)
Other	4 (3%)	2 (3%)
Baseline transfusion burden		
< 4 units/8 weeks	46 (30%)	20 (26%)
≥ 4 to < 6 units/8 weeks	41 (27%)	23 (30%)
≥ 6 units/8 weeks	66 (43%)	33 (43%)
Baseline hemoglobin (FDA adjudicated)		
< 7.5 gm/dl	17 (11%)	5 (7%)
7.5-8.5 gm/dl	36 (24%)	23 (30%)
> 8.5-10 gm/dl	75 (49%)	41 (54%)
> 10 gm/dl	25 (16%)	7 (9%)
Cytopenias		
Platelets < 100 Gi/L	8 (5%)	6 (8%)
Neutrophils < 1 Gi/L	15 (10%)	10 (13%)
Prior ESA duration		
< 6 months	48 (31%)	20 (27%)
6 - 12 months	34 (22%)	9 (12%)
> 12 - 24 months	35 (23%)	21 (28%)
> 24 months	31(20%)	20 (26%)
None	5 (3%)	6 (8%)
IPSS-R category		
Very low risk	18 (12%)	6 (8%)
Low risk	109 (71%)	57 (75%)
Intermediate risk	25 (16%)	13 (17%)
High risk	1 (<1%)	0
ESA status		
ESA refractory	144 (97%)	69 (99%)
ESA Intolerant	4 (3%)	1 (1%)
Baseline erythropoietin		
< 200 U/L	88 (58%)	50 (66%)
200-500 U/L	43 (28%)	15 (20%)
> 500 U/L	21 (14%)	11 (15%)

Source: Adapted from Clinical Review Table 4 and Statistical Review Table 11

Both the demographics and the baseline disease characteristics of the randomized population appeared to be balanced across arms. It was noted, however, that only 87% of the randomized patients had MDS-RS; 10% had MDS/MPN-RS-T. As MDS-RS and MDS/MPN-RS-T are considered distinct disorders, it would be necessary to confirm efficacy in each. Key demographics and baseline characteristics by diagnosis are shown in Appendix 14.3.

Only 2% of the study participants were considered to be ESA-intolerant at baseline. The number of patients who were ESA-intolerant is too small to assess efficacy. (b) (4) Additionally, only 6% of patients had severe thrombocytopenia and 11% had severe neutropenia at baseline. Although cytoreductive therapy rather than growth factor therapy is generally considered for treatment of patients with multiple cytopenias, the study description in labeling should describe the paucity of patients with thrombocytopenia and neutropenia in the study to allow healthcare providers to understand the lack of efficacy data for luspatercept-aamt in this subgroup in case they are considering using this as an alternative to cytoreductive therapy.

7.4 Issues Related to the Analysis of Efficacy

The primary objective of the study was to demonstrate an improvement in achievement of transfusion independence using luspatercept-aamt. Table 3 shows the results of the primary analyses of the primary and key secondary endpoints.

Table 3: Study ACE-526-MDS-001 - Primary Efficacy Analysis

Endpoint	**Luspatercept-aamt (N=153) n, % (95% CI)**	**Placebo (N=76) n, % (95% CI)**	**Risk Difference (95% CI)**	**p-value**
Primary Endpoint				
TI-8 within Weeks 1-24	58 (37.9) (30.2, 46.1)	10 (13.2) (6.5, 22.9)	24.6 (14.5, 34.6)	<0.0001
Key Secondary Endpoints				
TI-12 within Weeks 1-24	43 (28.1) (21.1, 35.9)	6 (7.9) (3.0, 16.4)	20.0 (10.9, 29.1)	0.0002
TI-12 within Weeks 1-48*	51 (33.3) (25.9, 41.4)	9 (11.8) (5.6, 21.3)	21.4 (11.2, 31.5)	0.0003

Source: Adapted from the Statistical Review Tables 4 and 5
*The median (range) duration of treatment was 49 weeks (6 to 114 weeks) on the REBLOZYL arm and 24 weeks (7 to 89 weeks) on the placebo arm.

Additionally, the median duration of the RBC-TI-8 response was 30.6 weeks (95% CI: 20,6, 40.6) on the luspatercept-aamt arm and 13.6 weeks (95% CI: 9.1, 54.9) on the placebo arm. The Statistical Reviewer concluded that the study results demonstrated a higher response rate with luspatercept-aamt than with placebo, but "though the primary and key secondary endpoints showed statistically significant improvement of luspatercept over placebo, the absolute response rates were rather low and the effect may not be clinically meaningful."

Additional sensitivity analyses were performed to test the robustness of the efficacy results. These analyses demonstrated:

- The treatment effect was not substantially different using a modified definition of RBC-TI-8 *starting during* Week 1-24 (rather than *occurring within* Weeks 1-24), with a risk difference of 29.3% (95% CI: 18.4, 40.2) (Clinical Review Table 8).

- The rate of achievement of RBC-TI-8 on the luspatercept-aamt arm did not vary substantially during different follow-up time intervals, being 37.9% during Weeks 1-24, 35.3% during Weeks 24-48, and 30.7% during Weeks 48-72 (Statistical Review Table 6).

- The rate of achievement of TI starting during Weeks 1-24 on the luspatercept-aamt arm decreased numerically as the target duration of TI increased, being 42.5% for RBC-TI-8, 32.7% for RBC-TI-12, 27.5% for RBC-TI-16 (Clinical Review Table 8), and 15.7% for RBC-TI-48 (Response to Information Request received 12/17/2019).

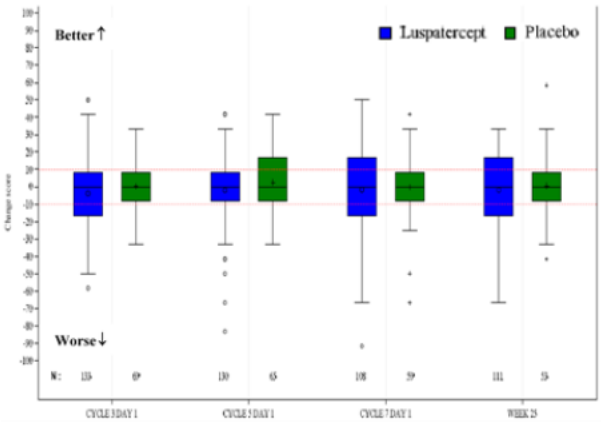
These additional analyses support the robustness of the results of the primary analysis and confirm that the treatment effect for luspatercept-aamt is rather modest.

As indicated in the description of the study design above, the Applicant prespecified multiple additional secondary and exploratory endpoints. As stated previously, increases in hemoglobin or percentage reduction in transfusions are not accepted measures of clinical benefit for treatment of anemia in patients with MDS at this time, and these endpoints were not considered further. The Statistical Reviewer did assess the data for overall survival and concluded that the results were not robust due to the short follow-up (Statistical Review Figure 3).

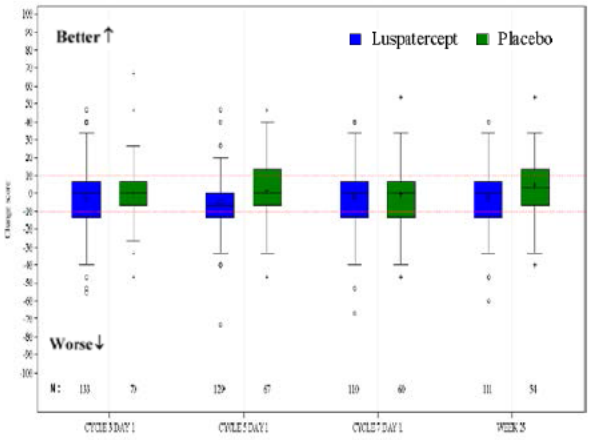
To further assess the meaningfulness of the treatment effect for RBC-TI-8, FDA also sought corroborating evidence from patient-reported outcomes. In Study MDS-001, patients were asked to complete the EORTC QLQ-C30 questionnaire at baseline, on Day 1 of every other 21 day treatment cycle, and at the Week 25 visit. The Statistical Reviewer found the data to be sufficiently complete to allow review, but there were no prespecified hypotheses for testing, so results are only descriptive. FDA focused on the global health status, physical functioning, fatigue and dyspnea domains, as these were considered most relevant for a treatment of anemia. Figure 1 shows the population mean and quartiles for change in global health status, physical functioning, fatigue and dyspnea domain scores. The population metrics appeared largely unimproved in the luspatercept-aamt arm over time.

Figure 1: Study ACE-536-MDS-001: EORTC QLQ-C30 Population Mean Change from Baseline

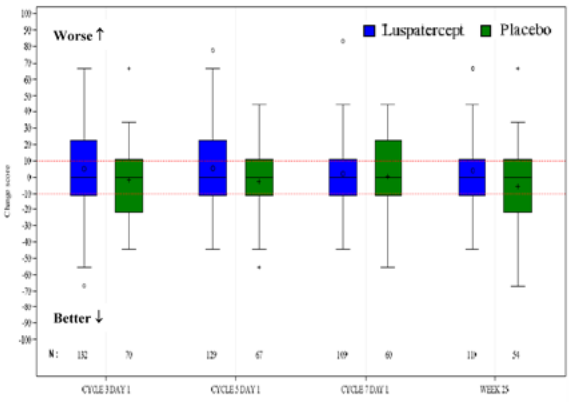
(a) Global Health Status



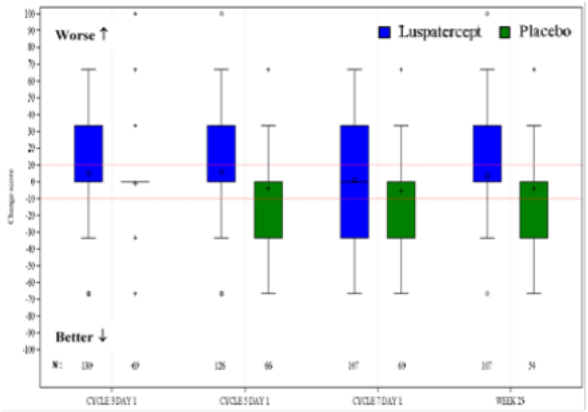
(b) Physical Functioning



(b) Fatigue



(b) Dyspnea



Source: ACE-536-MDS-001 Clinical Study Report Figure 15

The observation that a small subgroup of patients in the luspatercept-aamt arm of Study MDS-001 achieved exceptional responses raised a question as to whether the treatment effect was consistent across subpopulations. As seen in Table 4, a treatment effect was detectable only in the subgroups with a baseline RBC transfusion burden < 6 units / 8 weeks.

Table 4: Study ACE-526-MDS-001 - RBC-TI-8 by Baseline Transfusion Burden

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

Source: Adapted from the Statistical Review Table 11 and Clinical Review Table 9

Of note is the observation that a proportion of patients in the placebo group achieved RBC-TI-8. As noted by the Clinical Reviewer, a substantial number of patients had a hemoglobin of 10 gm/dL or more at treatment start (Clinical Review Table 4), and given the estimated mean remaining lifespan or T_{50} of 39-58 days and the estimated mean remaining lifespan of 110-120 days for transfused RBCs,[5] there is potential for RBC-TI-8 (duration 56 days) to have been observed solely on the basis of the high hemoglobin at treatment start. In theory, the bias from this factor should have been obviated by the randomization process, and although it might still affect the absolute RBC-TI-8 rate, it should not impact quantitation of the treatment effect. Indeed, the risk difference is similar for the two subgroups (< 4 units / 8 weeks and ≥ 4 to < 6 units / 8 weeks) where a treatment effect could be detected, even though the RBC-TI-8 rate in the placebo group is different.

Lastly, the Applicant also assessed the impact of treatment with luspatercept-aamt on variant allele frequency (VAF) for SF3B1, the most common mutation in the study population. They reported no difference in change in VAF between study arms and no difference in change in VAF between RBC-TI-8 responders vs nonresponders (Study Report ACE-536-MDS-001-TD-Mut-001 finalized 1/28/2019). These results are consistent with the assertion that luspatercept-aamt is not a disease-modifying drug.

[5] Kuruvilla DJ, et al. (2014) Mean remaining lifespan: A new clinically relevant parameter to assess the quality of transfused red blood cells. Transfusion 54: 2724-2729; Luten M, et al (2008) Survival of red blood cells after transfusion: a comparison between red cells concentrates of different storage periods. Transfusion 48: 1478-1485; Mock DM, et al. (2011) Red blood cell (RBC) survival determined in humans using RBCs labeled at multiple biotin densities. Transfusion 51: 1047-1057.

7.5 Efficacy Issues Related to the Recommended Dose

In Study MDS-001, the Applicant tested the luspatercept-aamt regimen of 1 mg/kg -> 1.33 mg/kg -> 1.75 mg/kg titrating to response. The Applicant claimed a trend for a positive exposure-efficacy relationship, but the Clinical Pharmacology Reviewer could not confirm this conclusion due to confounding by the dose titration design. The actual maximal dose level were 1 mg/kg, 1.33 mg/kg and 1.75 mg/kg for 18%, 18% and 63% on the luspatercept-aamt arm and 7%, 9% and 84% on the placebo arm, respectively, confirming use of the full titration range in the investigational arm and supporting dosing up to 1.75 mg/kg for efficacy.

The Applicant proposed instructions for use to treat patients through at least 3 doses (9 weeks) at the 1.75 mg/kg level before concluding lack of efficacy. FDA identified seven patients on the luspatercept-aamt arm who achieved first RBC-TI-8 after escalation to 1.75 mg/kg; the median time to RBC-TI-8 was 45 days (range, 26-71 days) after the escalation. This supports the proposed 9 weeks at the 1.75 mg/kg level before concluding lack of efficacy.

7.6 Efficacy Conclusions

The Statistical Reviewer concluded that Study MDS-001 was positive on the basis of the analyses of the primary and key secondary transfusion independence endpoints, RBC-TI-8 and RBC-TI-12. Of note, the absolute values of these endpoints was rather low for a supportive care drug, 37.9% and 28.1%, respectively, with the treatment effect for luspatercept-aamt only 20 to 25 percentage points in comparison to placebo. Moreover, a prespecified subgroup analysis showed the loss of treatment effect in patients with high transfusion burden. Additionally, key PRO outcomes were not supportive of the treatment effect. Taken together, these results leave substantial uncertainty about the clinical benefit of treatment with luspatercept-aamt in patients with anemia due to MDS with ring sideroblasts; such uncertainty generally warrants a second trial for corroboration.

However, when considering only the lower transfusion burden subgroup (< 6 RBC unit / 8 weeks as prespecified in the protocol), the magnitude of the treatment effect is more credible. Table 5 shows the results for the primary endpoint, RBC-TI-8, median time to response start, median observed duration of response and the incidences of longer duration response in the lower transfusion burden subgroup by diagnosis (MDS-RS and MDS/MPN-RS-T).

Table 5: Study ACE-526-MDS-001 - Outcomes by Diagnosis in Patients Requiring 2 - 5 RBC Units / 8 Weeks at Baseline

Outcome	Luspatercept-aamt (95% CI)	Placebo (95% CI)	Risk Difference (95% CI)
MDS-RS			
RBC-TI-8 occurring within Weeks 1-24	40 / 71 (56.3%) (44.0, 68.1)	7 / 36 (19.4%) (8.2, 36.0)	36.9 (20.0, 54.2)
Median time to TI start (range)	1 day (1-106)	22 days (1-100)	-
Median observed duration of TI (range)	30.2 weeks (8.1-171.9+)	12 weeks (9.1-66.4+)	-
RBC-TI-12 occurring within Weeks 1-24	31 / 71 (43.7%)	3 / 36 (8.3%)	-
RBC-TI-48 starting within Weeks 1-24	16 / 71 (22.5%)	1 / 36 (2.8%)	-
MDS/MPN-RS-T			
RBC-TI-8 occurring within Weeks 1-24	9 / 12 (75.0) (42.8, 94.5)	2 / 7 (28.6) (3.7, 71.0)	46.4 (5.0, 87.9)
Median time to TI start (range)	1 day (1-43)	1 day, 23 days	-
Median observed duration of TI (range)	18.9 weeks (8.7+ - 131.9)	12.2 weeks, 22.3 weeks	-
RBC-TI-12 occurring within Weeks 1-24	5 / 12 (41.7%)	2 / 7 (28.6%)	-
RBC-TI-48 starting within Weeks 1-24	2 / 12 (16.7%)	0 / 7 (0%)	-

Source: CDTL analysis; data from Safety Update files dated 11/1/2019 and Response to Information Request 12/19/2019
Abbreviations: +, on-going response; CI, confidence interval; RBC-TI-8, RBC transfusion-free for at least 8 weeks; RBC-TI-12, RBC transfusion-free for at least 12 weeks; RBC-TI-48, RBC transfusion-free for at least 48 weeks;

Although the treatment effect in this subgroup is still not as high as might be desired for a supportive care drug, if the risks do not outweigh the benefit, such a treatment might be a reasonable to consider prior to use of more toxic cytoreductive therapies for patients who have a low transfusion burden. In summary, the data would support the indication:

(b) (4)

8. Clinical - Safety

8.1 Pre-established Safety Risks

Luspatercept-aamt reported acts by sequestering TGF-beta superfamily ligands. Since these ligands are involved in numerous cellular processes, it was not possible to predict class safety risks based on mechanism of action. As discussed in Section 4, the main risks identified in

nonclinical studies were renal injury and development of malignancies. With regard to prior human data, the current US Prescribing Information for luspatercept-aamt for treatment of anemia in patients with beta-thalassemia includes warnings for thrombosis, hypertension and embryo-fetal toxicity. Thrombosis did not emerge as a particular interest in the MDS population, and the risk of embryo-fetal toxicity is not considered to differ in the MDS population, so these two risks will not be discussed further. The most common (>10%) adverse reactions in patients with beta thalassemia were headache, bone pain, arthralgia, fatigue, cough, abdominal pain, diarrhea and dizziness.

8.2 Safety Database

Safety data were available for 345 adults with MDS or other myeloid neoplasms treated on Studies MDS-001 and A536-03/05. The safety population included 269 patients treated with luspatercept-aamt and 76 treated with placebo. In the dose-escalation study, there were only 3 patients treated in the cohorts using less than the recommended starting dose, so the available data would not be sufficient for a detailed dose-toxicity analysis. FDA utilized 2 main cohorts for review of safety:

- The *pooled safety cohort* consisted of all 242 patients treated with luspatercept-aamt using the recommended dose-schedule on Studies MDS-001 and A536-03/05. The median time on treatment was 50.4 weeks (range, 3 – 221 weeks); 67% of patients were exposed for 6 months or longer and 49% were exposed for greater than one year. The Applicant flagged events within 42 days of treatment end as treatment-emergent, presumably due to the long half-life of the drug.

- The *randomized cohort* consisted of 153 patients treated with luspatercept-aamt and 76 patients treated with placebo on Study MDS-001. Due to the drop-out rate in only the control arm after the Week 25 study visit, comparative analyses are limited to Weeks 1 - 24 on study, and events through day 21 of the last cycle were considered treatment-emergent.

Table 6 shows the characteristics of patients in the safety population. The Clinical Reviewer cited the low number of non-Caucasian patients, but it was also noted that race was not identified for a substantial proportion of the population.

Table 6: Pooled Safety Population Characteristics

	Luspatercept-aamt (n=242)	
Sex		
Male	153	(63%)
Female	89	(37%)
Age group		
< 65 years	50	(21%)
65-74 years	103	(43%)
≥ 75 years	89	(37%)
Age		
Median (range) (years)	72 (30, 95)	
Race		
White	196	(81%)
Other race	2	(<1%)
Not provided	44	(18%)
Baseline Performance Status		
ECOG 0	106	(44%)
ECOG 1	126	(52%)
ECOG 2	10	(4%)
Renal Impairment		
Normal	74	(31%)
Mild	100	(41%)
Moderate	67	(28%)
Severe	1	(<1%)
Hepatic Impairment		
Normal	130	(54%)
Mild impairment	90	(37%)
Moderate impairment	20	(8%)
Severe impairment	1	(<1%)
Missing	1	(<1%)
Anti-drug antibodies		
Negative	202	(83%)
Preexisting	13	(5%)
Treatment-emergent	18	(7%)
Missing	9	(4%)
Baseline IPSS-R		
Very Low	23	(10%)
Low	162	(67%)
Intermediate	48	(20%)
High	8	(3%)
Very High	1	(<1%)

Source: CDTL analysis

8.2 Issues Related to Major Safety Events

Among the 242 patients treated with luspatercept-aamt, the incidences of adverse reaction-related discontinuations (4.5%) and dose reductions (2.9%) were low. Seventeen patients had a treatment-emergent adverse event with a fatal outcome. FDA identified 5 (2.1%) deaths as adverse reactions (Table 7)

Table 7: Pooled Safety Population - Fatal Adverse Event Adjudication

Subject	Study Day	Sponsor's Reported Cause of Death (Considered Unrelated)	FDA-Adjudicated Adverse Reaction as Root Cause of Death
A536-03-(b) (6)	469	Sudden death	Sudden death
CGNACE536MDS001-(b) (6)	116	Renal failure	Renal failure
CGNACE536MDS001-(b) (6)	127	Sepsis	SIRS
CGNACE536MDS001-(b) (6)	135	Multiple organ dysfunction syndrome	Renal failure
CGNACE536MDS001-(b) (6)	606	General physical health deterioration	General physical health deterioration

Source: CDTL analysis

A536-03-(b) (6) - The patient was a 64 year-old man with MDS-RS. Past medical history included type 2 diabetes mellitus, psoriatic arthropathy, peripheral sensory neuropathy, edema, conduction disorder, congestive cardiomyopathy, hypertension, arthritis bacterial, and arthralgia. His treatment course was marked by several dose delays and/or dose reductions due to hemoglobin >11 gm/dL or rise in hemoglobin > 2 gm/dL. The last dose of luspatercept-aamt was given on Day 450 (dose reduced to 0.5 mg/kg due to rapid rise in hemoglobin). The patient was found dead on Day 469. Review of available laboratory data and vital signs prior the death showed no substantial abnormalities. There was no autopsy. Given the multiple occurrences of rapidly rising hemoglobin, and with the last dose less than 3 weeks from death, it was concluded the death was at least possibly related to luspatercept-aamt.

CGNACE536MDS001-(b) (6) - The patient was a 79 year-old woman with MDS-RS with an ongoing history of asthenia, cardiac failure, dyslipidemia, hypertension, postmenopause, and pulmonary arterial hypertension. The last dose of study drug was given on Day 86. The subsequent course was marked by an admission for noncardiac chest pain on Day 97; treatment interruption for Grade 2 edema, Grade 3 asthenia and Grade 1 creatinine on Day 106; elevated transaminases and bilirubin on Day 111, rising to Grade 3 ALT, Grade 2 bilirubin and Grade 2 creatinine. While hospitalized, the patient developed Grade 4 renal failure and generalized edema. Supportive care was provided but dialysis was not performed. The patient died Day 116 with renal failure. No autopsy was performed. Given the lack of clear alternative etiology of the renal failure, co-occurrence of other adverse reactions, and the onset proximate to dosing, the death was at least possibly related to luspatercept-aamt.

CGNACE536MDS001-(b) (6) - The patient was an 86 year-old woman with MDS-RS with an on-going history of depression, dyslipidemia, hypertension, postmenopause, and pain. On Day 53, the patient was hospitalized with Grade 1 diarrhea, Grade 2 "abdominal infection,"

confusion, fever and general deterioration. All blood culture were negative. The event resolved on Day 56. The last dose of study drug was given on Day 106. The patient was hospitalized on Day 126 for Grade 4 sepsis with somnolence, dyspnea, asthenia, edema and lactic acidosis. All cultures were negative. The neutrophil count was reported as 4.16 Gi/L. Antibiotics were administered. The patient died on Day 127. No autopsy was performed. Although the investigator identified the etiology as sepsis, with a normal neutrophil count in the absence of positive cultures, this case could also be due to drug-related systemic inflammatory response syndrome (SIRS), and therefore the death was at least possibly related to luspatercept-aamt.

CGNACE536MDS001-(b) (6) - The patient was a 77 year-old man with MDS-RS with a history of gastroesophageal reflux disease, cardiac failure congestive, diabetes mellitus and hypovitaminosis. On-going medications included metformin. The creatinine was elevated to Grade 2 at baseline. On Day 64, the patient developed elevated bilirubin, elevated AST and ALT worsening to Grade 3, Grade 3 fatigue, and Grade 3 elevated creatinine. Study drug was withdrawn. The last dose was given on Day 107. On Day 120, the patient was additionally found to have Grade 4 pancreatitis and lactic acidosis. Metformin was discontinued. Supportive care was administered, and the pancreatitis resolved, but the patient developed acute pulmonary failure with on-going renal failure and hyperbilirubinemia. The patient died on Day 135. In this case, the root cause of death appears to be the worsening renal function which may have contributed to metformin toxicity and the subsequent multiorgan failure. Therefore, the death was at least possibly related to luspatercept-aamt.

CGNACE536MDS001-(b) (6) - The patient was a 79 year-old man with MDS/MPN-RS-T with a history of hypothyroidism, Type 1 diabetes mellitus, muscular weakness and erythema multiforme. At study start, he had a ECOG performance status of 0. The treatment course was marked by recurrent episodes of confusion and lethargy, an episode of dyspnea, hypoxia, and dizziness on Day 372, pneumonia on Day 415, and squamous cell carcinoma of the skin (excised). The last dose of luspatercept-aamt was given on Day 547. On Day 566, the patient was hospitalized with Grade 3 asthenia. The hemoglobin was 7.8 gm/dL. He was transfused but did not improve and died on Day 606. The Applicant reported no evidence of progression to higher-risk MDS or to AML. In the absence of an alternative cause, the death was considered at least possibly related to luspatercept-aamt.

On review of these five cases, there is no single adverse reaction predominating. The root causes appear related to rapidly rising hemoglobin, renal injury, SIRS and progressive asthenia. At least two patients were taking metformin, but given how commonly this drug is used in this population, that may be coincidental. Other than withdrawing treatment, no additional single mitigation strategy would be likely to prevent these deaths.

8.3 Issues Related to Common Adverse Reactions

Using grouped terms (Appendix 14.4), the most common (≥10%) all-grade adverse reactions in the pooled safety cohort included fatigue, musculoskeletal pain, dizziness, diarrhea, nausea,

hypersensitivity reactions, hypertension, headache, upper respiratory tract infection, bronchitis, and urinary tract infection. The most common (≥2%) Grade ≥ 3 adverse reactions included fatigue, hypertension, syncope and musculoskeletal pain. Selected laboratory abnormalities that changed from Grade 0-1 at baseline to Grade ≥ 2 at any time during the studies in at least 10% of patients included creatinine clearance decreased, total bilirubin increased, and alanine aminotransferase increased.

Table 8 shows the most common adverse reactions for patients treated with luspatercept-aamt or placebo through the first 8 cycles in the Study MDS-001. Adverse reactions were identified by occurrence in at least 5% of treated patients with a difference between arms of at least 2%.

Table 8: Study ACE-536-MDS-001 - Common Adverse Reactions Through Cycle 8

Adverse Reaction [a]	Luspatercept-aamt (N=153)		Placebo (N=76)	
	All Grades n (%)	Grade 3 n (%)	All Grades n (%)	Grade 3 n (%)
Fatigue	63 (41)	11 (7)	17 (22)	2 (3)
Musculoskeletal pain	30 (20)	3 (2)	11 (14)	0 (0)
Dizziness/vertigo	28 (18)	1 (<1)	5 (7)	1 (1)
Nausea	25 (16)	1 (<1)	8 (11)	0 (0)
Diarrhea	25 (16)	0 (0)	7 (9)	0 (0)
Headache	21 (14)	0 (0)	5 (7)	0 (0)
Dyspnea	20 (13)	2 (1)	4 (5)	1 (1)
Hypersensitivity reactions	15 (10)	1 (<1)	5 (7)	0 (0)
Renal impairment	12 (8)	3 (2)	3 (4)	0 (0)
Tachycardia	12 (8)	0 (0)	1 (1)	0 (0)
Syncope / presyncope	8 (5)	5 (3)	0 (0)	0 (0)
Injection site reactions	10 (7)	0 (0)	3 (4)	0 (0)
Upper respiratory tract infection	10 (7)	1 (<1)	2 (3)	0 (0)
Influenza / influenza like illness	9 (6)	0 (0)	2 (3)	0 (0)

Source: CDTL analysis
[a] Includes grouped terms.

In a Response to Information Request received 12/17/2019, the Applicant provided an analysis of the hazard rate of fatigue over time, showing an approximate 4-fold increase over placebo at the start of treatment that fell over near placebo levels after 105 days. Similarly, there was approximately a 3-fold increase in dyspnea over placebo, and the risk fell by day 63. The Applicant noted, however, that the analysis consider only first events, and the results did not consider events that persisted or recurred over time.

Shifts from Grades 0-1 to Grades 2-4 abnormalities for selected laboratory tests during the first 8 cycles in Study MDS-001 are shown in Table 9.

Table 9: Study ACE-536-MDS-001 - Selected Grades 2-4 Treatment-Emergent Laboratory Abnormalities

Parameter	Luspatercept-aamt		Placebo	
	N[a]	n (%)	N[a]	n (%)
ALT elevated	151	13 (9)	74	5 (7)
AST elevated	152	6 (4)	76	0 (0)
Total bilirubin elevated	140	17 (12)	66	3 (5)
Creatinine clearance reduced	113	30 (27)	62	13 (21)

Source: CDTL analysis
[a] Number of patients at Grades 0-1 at baseline.
ALT = alanine aminotransferase; AST = aspartate aminotransferase.

8.4 Additional Safety Issues

Patient-Reported Outcomes

The Clinical Reviewer focused on the QLQ-C30 global quality of life, fatigue and dyspnea domains. She noted that worsening global quality of life was reported at various timepoints for 22-27% of patients on luspatercept and for 15-20% of patients on placebo, worsening fatigue was reported by 31-40% on luspatercept-aamt and 21-32% on placebo, and worsening dyspnea was reported by 23-27% on luspatercept-aamt and 11-15% on placebo.

Renal Injury

Due to the nonclinical findings (Section 4), the risk of renal injury was a concern. The nonclinical findings identified MPGN and nephrotic syndrome specifically as potential risks of treatment with luspatercept-aamt. Drugs have been reported as the etiology of 7% to 14% of cases of membranous nephropathy.[6] The time to onset of drug-induced membranous nephropathies is unclear. A definitive analysis of the risks MPGN and nephrotic syndrome in patients treated with luspatercept-aamt was not possible, since the necessary tests for screening (i.e. 24 hour urine protein, frequent urinalyses, etc.) were not performed, so only indirect evidence could be assessed.

As shown in the comparative analysis in Table 9 above, the creatinine clearance was reduced to Grades 2-4 levels through Cycle 8 in slightly more patients on the luspatercept-aamt arm (27% vs 21%), but only 1% of patients on either arm had a Grades 3-4 abnormality. The Applicant reported no change in urinary albumin-creatinine ratio in the patients on Study MDS-001, but they also indicated that there were substantial confounders, such as from comorbidities and concomitant medications (Integrated Summary of Safety Section 5.5.8.4). For reductions in estimated creatinine clearance in the pooled safety cohort with longer follow-up, 36% shifted from Grades 0-1 to Grades 2-4, and 5% shifted to Grades 3-4. In the absence of a control arm in

[6] Hogan JJ et al. Drug-induce glomerular disease: Immune-mediated injusry. Clin J Am Soc Nephrol 2015; 10:1300-1310.

the long-term follow-up, there is not sufficient information to assess the risk of renal injury with long-term use of luspatercept-aamt.

Risk of Malignancy

The current US Prescribing Information for erythropoiesis-stimulating agents (ESAs) include boxed warnings regarding shortened overall survival and/or increased the risk of tumor progression or recurrence in clinical studies of patients with breast, non-small cell lung, head and neck, lymphoid and cervical cancers. Although the mechanism of action of luspatercept-aamt is very different from that of the approved ESAs, FDA also assessed the risks of MDS progression and development of second primary malignancies in the luspatercept-aamt safety population.

Progression of MDS: Progression to AML is a risk for patients with MDS. For patients with low or intermediate risk MDS, the median time to 25% AML evolution is 3.2 to 10.8 years and not calculable for those with very low risk disease. The expected rate of progression of MDS from lower risk to higher risk disease is less well defined. As shown in the Clinical Review Figure 17, the rate progression to higher-risk MDS or AML was nearly 20% at 4 years for patients on Study A536-03/05, but there was no clinically meaningful difference in progression when comparing the treatment arms in Study MDS-001. The assessment, however, was confounded by lack of planned prospective disease assessments. potential bias from selective reporting of AML, and incomplete follow-up.

Second Primary Malignancy: As shown in the Clinical Review Figure 16, the cumulative incidence of second primary malignancies was nearly 30% at 4 years for patients on Study A536-03/05, but there was no clinically meaningful difference in second primary malignancy when comparing the treatment arms in Study MDS-001. Again, however, the assessment was confounded by incomplete follow-up.

Anti-Drug Antibodies (ADA)

In Study MDS-001, 18 patients in the luspatercept arm developed ADA. When comparing ADA+ vs ADA- patients, the Clinical Reviewer reported a > 10% increase in injection site reactions, upper respiratory tract infections, diarrhea and influenza, and a > 10% decrease in fatigue in patients who were ADA+ (Clinical Review Table 38), but the small numbers of patients precluded meaningful conclusions.

Dose Cap

According to Protocol ACE-536-MDS-001, the dose of luspatercept-aamt was to be capped at 168 mg (Protocol Section 7.2.1.1). (b) (4)
There was not a sufficient number of patients treated without a cap to determine if capping impaired response or if not capping posed additional safety risks.

8.5 Safety Conclusions

The safety profile of luspatercept-aamt in this patient population is similar to that reported for patients with thalassemia, except for a higher likelihood for renal injury and fatigue. The fatal adverse reactions must be considered carefully when weighing the risks and benefits of this supportive care drug. Additionally, although the most common adverse reactions (fatigue, dizziness, diarrhea and dyspnea) were usually low grade, the nature of these adverse reactions could impact the activities of daily living in an elderly population. Due to the lack of adequate testing and follow-up, additional study of safety in long-term use is warranted, especially monitoring for renal injury, progression to AML and occurrence of second malignancies. This can be accomplished in part with a postmarket requirement to continue safety follow-up for patients on Study MDS-001, and enhanced pharmacovigilance would be suitable to obtain a better assessment of the risk of renal injury in the real world.

9. Advisory Committee Meeting

This application was not discussed by an Advisory Committee.

10. Pediatrics

Luspatercept-aamt has orphan designation for treatment of MDS and is therefore exempt from the requirement for pediatric studies under the Pediatric Research Equity Act (PREA). This application included no data from children with MDS treated with luspatercet-aamt. Based on findings in juvenile animals, luspatercept-aamt is not recommended for use in pediatric patients

11. Other Relevant Regulatory Issues

Three clinical sites were selected for inspection: Dr. Katja Sockel in Germany (Study A536-03 Site 301 and Study ACE-536-MDS-001 Site 104), Dr. Ghulam Mufti in London, U.K. (Study A536-MDS-001 Site 500) and Dr. Pierre Fenaux in France (Study A536-MDS-001 Site 200). Inspection of the Applicant's records was also conducted. The inspection review identified no significant deficiencies and concluded that the data submitted are considered to be reliable to support review of the requested indication.

12. Labeling

12.1 Prescribing Information

How to communicate the lack of achievement of transfusion independence in the high transfusion burden subgroup was discussed extensively. Simply displaying the subgroup results in Section 14 might be considered inadequate, since it does not convey the adverse risk benefit profile in Highlights or other key sections of the Prescribing Information. A limitation of use statement was also considered, but the labeling reviewers advised a preference to state the

intended population clearly in the indication statement instead. The recommendation below reflects this last approach.

Recommendations for Significant Labeling Changes

Section	Recommended Labeling
1	Revise the indication (b) (4)
2	Revise to describe the recommended dosages separately for the two indications.
6	Add a summary of adverse reactions in the safety population and limit the tabulated comparison to the first 8 cycles in Study MDS-001
14	Limit the displayed data to the results of the ITT analysis and the results in the intended population by diagnosis.

12.2 Patient Labeling

Revised to be consistent with the final recommended labeling.

13. Postmarketing Recommendations

13.1 Risk Evaluation and Management Strategies (REMS)

It was concluded that a REMS is not needed to ensure that the benefits of luspatercept-aamt outweigh its risks in the intended population.

13.2 Postmarketing Requirements (PMRs) and Commitments (PMCs)

PMR -1

Characterize the long-term safety of luspatercept-aamt in patients with myelodysplastic syndromes with ring sideroblasts (MDS-RS) or myelodysplastic syndromes/myeloproliferative neoplasm with RS and thrombocytosis (MDS/MPN-RS-T). Complete Study ACE-536-MDS-001 with at least 5 years of follow-up for enrolled subjects. Submit datasets with the final clinical study report. In the final clinical study report, include subgroup analyses of transformation to higher-risk MDS or acute myeloid leukemia and of time to development of second primary malignancies by disease and by baseline transfusion burden

14. Appendices

Appendix 14.1: Listing of Clinical Trials Relevant to this NDA

Trial*	Trial Design	Luspatercept-aamt Dose and Schedule	Population	Endpoints	Countries / Centers
Pivotal Study					
ACE-536-MDS-001	Multicenter, Phase 3, randomized, blinded, placebo controlled trial (2:1 randomization stratified by baseline transfusion burden and IPSS-R category)	Every 3 weeks titrated to response using 1 -> 1.33 -> 1.75 mg/kg	Adults with anemia requiring ≥ 2 U RBC/8 weeks and failing ESA with lower-risk MDS and ≥ 15% sideroblasts (229 patients randomized)	1°: TI-8 through Week 24 Key 2°: TI-12 through Week 24 and through Week 48	65 sites in the US (11) and ex-US (54)
Studies with Supporting Efficacy and Safety Data					
A536-03	Multicenter, single-arm, multiple ascending-dose study with a multiple-cohort expansion phase	Every 3 weeks using 0.125 to 1.75 mg/kg in the escalation phase, and titrated to response using 1 -> 1.33 -> 1.75 mg/kg in the expansion cohorts, for up to 5 doses	Adults with anemia and lower-risk MDS or CMML (Escalation: 27 patients; Expansion: 89 patients)	mHI-E LTB: ≥ 1.5 g/dL HGB increase lasting ≥ 14 days HTB: ≥ 4 U or ≥ 50% transfusion reduction lasting ≥ 8 weeks	12 sites in Germany
A536-05	Multicenter, single-arm extension study	Based on dose during prior study	Treated on prior study with luspatercept-aamt (75 patients treated)	-	11 sites in Germany

Source: CDTL analysis
Abbreviations: CMML, chronic myelomonocytic leukemia; ESA, erythropoiesis stimulating agent; HTB, high transfusion burden; IPSS-R, Revised International Prognostic Scoring System; LTB, low transfusion burden; MDS, myelodysplastic syndromes; mHI-E, modified hematological improvement-erythroid response; RBC, red blood cell; TI-8, transfusion independence lasting ≥ 8 weeks; TI-12, transfusion independence last ≥ 12 weeks; U, units.

Appendix 14.2: ACE-536-MDS-001: Demographic Characteristics of the Randomized Population

Demographic Parameters	**Luspatercept-aamt** (N=153)	**Placebo** (N=76)
Sex		
Male	94 (61%)	50 (66%)
Female	59 (39%)	26 (34%)
Age group		
< 65 years	29 (19%)	16 (21%)
65-74	72 (47%)	29 (38%)
≥ 75 years	52 (34%)	31 (41%)
Age		
Median (Min, max) (years)	71 (40, 95)	72 (26, 91)
Baseline Performance Status		
ECOG 0	54 (35%)	33 (43%)
ECOG 1	91 (59%)	32 (42%)
ECOG 2	8 (5%)	11 (14%)
Race		
White	107 (70%)	51 (67%)
Other race	2 (1%)	1 (1%)
Not provided	44 (29%)	24 (32%)
Ethnicity		
Hispanic	3 (2%)	4 (5%)
Non-Hispanic/not provided	150 (98%)	72 95%)
Geographic region		
EU	122 (80%)	57 (75%)
North America	31 (20%)	19 (25%)

Source: Clinical Review Table 3

Appendix 14.3: ACE-536-MDS-001: Key Demographic and Baseline Disease Characteristics by Diagnosis for Patients with Baseline Transfusion Burden < 6 Units/8 Weeks

	MDS-RS		MDS/MPN-RS-T	
	Luspatercept (n=71)	**Placebo (n=36)**	**Luspatercept (n=12)**	**Placebo (n=7)**
Sex				
Male	36 (51%)	23 (64%)	4 (33%)	4 (57%)
Female	35 (49%)	13 (36%)	8 (67%)	3 (43%)
Age group				
< 65 years	17 (24%)	3 (8%)	2 (17%)	4 (57%)
65-74	28 (39%)	14 (39%)	6 (50%)	2 (29%)
≥ 75 years	26 (37%)	19 (53%)	4 (33%)	1 (14%)
Age				
Median (Min, max) (years)	71 (42, 95)	76 (43, 91)	71 (56, 83)	64 (26, 76)
Race				
White	51 (72%)	27 (75%)	7 (58%)	2 (29%)
Other race	0 (0%)	1 (3%)	1 (8%)	0 (0%)
Not provided	20 (28%)	8 (22%)	4 (33%)	5 (71%)
Baseline Performance Status				
ECOG 0	27 (38%)	17 (47%)	2 (17%)	2 (29%)
ECOG 1	41 (58%)	14 (39%)	10 (83%)	4 (57%)
ECOG 2	3 (4%)	5 (14%)	0 (0%)	1 (14%)
Baseline transfusion burden				
< 4 units/8 weeks	38 (54%)	16 (44%)	6 (50%)	4 (57%)
≥ 4 to < 6 units/ 8 weeks	33 (46%)	20 (56%)	6 (50%)	3 (43%)
Baseline erythropoietin				
< 200 U/L	43 (61%)	28 (78%)	7 (58%)	7 (100%)
200-500 U/L	18 (25%)	5 (14%)	5 (42%)	0 (0%)
> 500 U/L	9 (13%)	3 (8%)	0 (0%)	0 (0%)
Prior ESA duration				
< 6 months	20 (28%)	11 (31%	1 (8%)	3 (43%)
6 - 12 months	19 (27%)	4 (11%)	4 (33%)	0 (0%)
>12 - 24 months	16 (23%)	8 (22%)	3 (25%)	1 (14%)
> 24 months	15 (21%)	12 (33%)	3 (25%)	2 (29%)
Missing	1 (1%)	1 (3%)	1 (8%)	1 (14%)

Source: CDTL analysis

Appendix 14.4: Grouped Terms Used for the Safety Analyses

Adverse Reaction	Basis for Grouping
Abdominal pain	HLT Gastrointestinal and abdominal pains (excl oral and throat)
Confusion	HLT Confusion and disorientation
Cough	HLT Coughing and associated symptoms
Diarrhea	HLT Diarrhoea (excl infective)
Dizziness	Broad SMQ Vestibular disorders
Dyspnea	HLT Breathing abnormalities
Edema	HLT Oedema NEC
Fatigue	HLT Asthenic conditions
Headache	HLT Headache NEC
Hemorrhage	SMQ haemorrhage terms (excl labs)
Hypersensitivity reactions	Narrow SMQ Hypersensitivity and Narrow SMQ Anaphylactic reaction
Hypertension	Narrow SMQ Hypertension
Influenza	PTs Influenza, and Influenza-like illness
Injection site reactions	HLT Injection site reactions
Kidney injury	HLT Renal failure and impairment; HLT Renal function analyses
Liver test abnormalities	HLT Liver function analyses
Musculoskeletal pain	HLT Musculoskeletal and connective tissue pain and discomfort
Nausea/vomiting	HLT Nausea and vomiting symptoms
Syncope	PTs Syncope, Presyncope, and Loss of consciousness
Tachyarrhythmias	PTs Tachycardia, Atrial fibrillation, Atrial tachycardia, Sinus tachycardia, and Supraventricular tachycardia
Thromboembolic events	Narrow SMQ Embolic and thrombotic events
Viral infection	HLGT Viral infectious disorders

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