2. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Acceleron Pharma Inc.</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
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Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
Luspatercept</td></tr>
<tr><td>Name of Active Ingredient: ACE-536</td></tr>
<tr><td colspan="3">Title of Study: An Open-Label Extension Study to Evaluate the Long-Term Effects of ACE-536 for the Treatment of Anemia in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS) Previously Enrolled in Study A536-03</td></tr>
<tr><td colspan="3">Coordinating Principal Investigator: Dr Uwe Platzbecker
Principal Investigators: Dr Katharina Götze, Dr Aristoteles Giagounidis, Dr Jörg Chromik (former Principal Investigator Dr Oliver Ottmann), Dr Karin Mayer, Dr Markus Radsak, Dr Ulrich Germing, Dr Philipp Kiewe, Dr Thomas Wolff, Dr Thomas Illmer, and Dr Gerda Silling</td></tr>
<tr><td colspan="3">Study site(s) and countries: Twelve study centers in 1 country (Germany) participated in the study</td></tr>
<tr><td colspan="3">Publications (reference): None</td></tr>
<tr><td colspan="2">Studied period: Up to 96 months
Date first subject first visit: 09 October 2014
Date of data cutoff: 19 March 2020</td><td>Phase of development: 2</td></tr>
<tr><td colspan="3">Objectives:
Primary:
• To evaluate the long-term safety and tolerability of luspatercept in subjects with low or intermediate-1 risk MDS who were previously enrolled in Study A536-03
Secondary:
• To evaluate erythroid response (modified hematologic improvement-erythroid response [HI-E] from International Working Group [IWG] 2006 criteria), defined as the proportion of subjects with:
o A mean hemoglobin (Hgb) increase ≥ 1.5 g/dL over an 8-week period as compared to baseline, not influenced by RBC transfusion in low transfusion burden (LTB) subjects.
o A decrease of ≥ 4 units or ≥ 50% of units of red blood cells (RBCs) transfused over a period of 8 weeks, relative to the number of units of RBCs transfused in the 8 weeks immediately prior to Cycle 1 Day 1 (C1D1) in high transfusion burden (HTB) subjects
• To evaluate rates of erythroid, neutrophil, and platelet (HI-E, hematologic improvement-neutrophil response [HI-N], and hematologic improvement-platelet response [HI-P]) responses (IWG 2006 criteria)
• To evaluate the rate of RBC transfusion independence lasting ≥ 8 weeks in HTB subjects
• To evaluate time to HI-E response and duration of HI-E response (modified and non-modified IWG 2006 criteria)
• To evaluate the mean change in RBC transfusion burden in HTB subjects and the mean change in Hgb levels in LTB subjects
• To evaluate the pharmacokinetic profile of luspatercept</td></tr>
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- To evaluate other pharmacodynamic (PD) effects (e.g., iron overload/metabolism, erythropoietin [EPO], and reticulocytes)

Exploratory:

- To examine biomarkers related to the transforming growth factor beta superfamily
- To examine self-reported quality using tools including but not limited to the Functional Assessment of Cancer Therapy-Anemia Scale (FACT-An) questionnaire

Methodology: Consenting subjects who met the Study A536-05 eligibility criteria immediately rolled over from Study A536-03 to Study A536-05 following the last luspatercept dose. These subjects did not undergo the Post-treatment Follow-up (PTFU) and End of Study (EOS) visit in Study A536-03 but instead were initiated immediately into the extension study (A536-05). For these subjects, C1D1 of Study A536-05 took place 28 (± 7) days after the last dose administered in Study A536 03, which coincided with the subject's A536-03 End of Treatment (EOT) visit. These subjects were considered "subjects without treatment interruption." Those subjects who completed the EOS visit for Study A536-03 prior to C1D1 of A536-05 were considered "subjects with treatment interruption" and were reassessed for eligibility by meeting additional inclusion criteria in a 28-day screening period.

A subject without treatment interruption continued to be dosed with luspatercept at the same dose level administered as their last dose in Study A536-03 (unless a dose reduction was required based upon subject dose modification rules from Study A536-05). All subjects with treatment interruption were initially treated with luspatercept at a starting dose level of 1.0 mg/kg.

Subjects could participate in the extension Study A536-05 for up to 96 months, including a 28-day (1 month) screening period, a 60-month treatment period, and a 3-year follow-up period.

Number of subjects (planned, enrolled, and analyzed): A total of 75 of 116 subjects enrolled in Study A536-03 continued on to the extension Study A536-05. Sixty-seven (89.3%) of these subjects rolled over directly into Study A536-05, and 8 (10.7%) subjects had a treatment interruption between Study A536-03 and Study A536-05 (subjects who completed the Study A536-03 EOS visit prior to C1D1 of A536-05). All subjects had discontinued treatment in Study A536-05, 14 (18.7%) subjects had completed the study (these subjects could have discontinued treatment but then completed the follow-up visits, which would have resulted in completing the study, despite not having completed treatment), and 61 (81.3%) subjects had discontinued the study.

Diagnosis and main criteria for inclusion:

Key inclusion criteria were as follows:

1. Completion of the treatment period in the base study A536-03.

All subjects with treatment interruption were also required to meet the following criteria:

2. Documented diagnosis of idiopathic/de novo MDS or non-proliferative chronic myelomonocytic leukemia according to World Health Organization criteria 16 (white blood cell count < 13,000/μL) that meets International Prognostic Scoring System classification of low or intermediate-1 risk disease as determined by microscopic and standard cytogenetic analyses of the bone marrow and peripheral complete blood count obtained during screening.
3. Anemia defined as:

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- Mean Hgb concentration < 10.0 g/dL of 2 measurements (one performed within 1 day prior to C1D1 and the other performed 7 to 28 days prior to C1D1) for LTB subjects (defined as having received < 4 units of RBCs within 8 weeks prior to C1D1), OR
- Transfusion dependent, defined as having received ≥ 4 units of RBCs within 8 weeks prior to C1D1.

Key exclusion criteria were as follows:

4. Prior treatment with azacitidine (injectable or oral) or decitabine.
5. Treatment within 28 days prior to C1D1 with:
   - Erythropoiesis-stimulating agent
   - Granulocyte colony-stimulating factor and granulocyte-macrophage colony stimulating factor
   - Lenalidomide
6. For subjects with treatment interruption only: iron chelation therapy if initiated within 56 days prior to C1D1.
7. Known positive for human immunodeficiency virus, active infectious hepatitis B, or active infectious hepatitis C.

Test product, dose and mode of administration: Luspatercept was administered by subcutaneous injection at 0.5, 0.75, 1.0, 1.33, or 1.75 mg/kg on C1D1. No more than 4 injections were administered per dose. Subsequent doses will be administered every 3 weeks on Day 1 of the cycle for up to 87 cycles. The last dose of luspatercept may not be administered after 87 cycles or 1825 calendar days from C1D1, whichever occurs first. Subjects received the dose level of luspatercept that they were assigned at study entry unless a dose modification was required. The batch numbers for the study drug used in this study are provided in Appendix 16.1.6.

Duration of treatment: This open-label extension study evaluated the effects of up to 60 months of luspatercept treatment in subjects with low or intermediate-1 risk MDS previously enrolled and treated with luspatercept for up to 3 months in Study A536-03.

Reference therapy, dose, and mode of administration: Not applicable.

Criteria for evaluation:

Efficacy: No formal hypothesis testing was planned. For each subject, all efficacy endpoints were derived based on an analysis cutoff day, defined as the last dose + 56 days (PTFU) or the last date from transfusion record data, whichever was earlier.

Safety: The safety endpoints included treatment-emergent adverse events (TEAEs), changes in laboratory tests, vital signs, and electrocardiograms.

Statistical methods: Unless otherwise noted, continuous data were summarized with the following descriptive statistics: number of observations, mean, standard deviation (SD), minimum, median, and maximum. Categorical data were summarized with frequencies and percentages (%). In cases where missing data caused percentages not to sum to 100, a missing data row was provided. Percentages used column totals as the denominator unless otherwise indicated. For time-to-event variables, the Kaplan-Meier curves were presented if the number of subjects was greater than 5.

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All study data were included in study data listings. Missing data were generally treated as missing, and not imputed, unless otherwise stated.

The summaries were also presented for LTB and HTB subjects separately, as specified. All summaries were descriptive. No formal hypothesis testing was planned.

CONCLUSIONS:

Efficacy conclusions were as follows:

- Forty (80.0%) of the 50 LTB subjects had a mean Hgb increase of ≥ 1.5 g/dL over a rolling 8-week interval in the absence of RBC transfusion, including 37 (78.7%) of the 47 direct rollover LTB subjects and 3 interrupted LTB subjects.
- The majority (21 [84.0%]) of the 25 HTB subjects had a reduction of ≥ 4 units or ≥ 50% reduction in RBC transfusion burden during a rolling 8-week interval in the study, including 17 (85.0%) of 20 direct rollover HTB subjects and 4 (80%) of 5 interrupted HTB subjects. In HTB subjects, the mean reduction in transfusion burden was 4.4 units over 8 weeks.
- A total of 61 (81.3%) subjects had an erythroid response (modified HI-E; as defined by a mean Hgb increase of ≥ 1.5 g/dL over an 8-week period as compared to baseline, not influenced by RBC transfusion in LTB subjects and a decrease of ≥ 4 units or ≥ 50% of units of RBCs transfused over a period of 8 weeks, relative to the number of units of RBCs transfused in the 8 weeks immediately prior to C1D1, in HTB subjects).
- Overall, 60 (80.0%) subjects had an erythroid response (HI-E; as defined by mean Hgb values with an increase of ≥ 1.5 g/dL from baseline during any rolling 8-week interval in the absence of transfusion (in which rolling 8-week starts and ends at a Hgb measurement date with duration ≥ 8 weeks) and mean Hgb values with an increase of ≥ 1.5 g/dL from baseline during any rolling 8-week in the absence of transfusion in LTB subjects and a reduction of ≥ 4 units of RBC transfusions over any rolling 8-week window on treatment compared to baseline in HTB subjects), with a mean (SD) time to first erythroid response of 14 (22.5) days. The Kaplan Meier estimate for median duration of erythroid response was 723 days.
- In LTB subjects, when assessing response (defined as an Hgb increase of ≥ 1.5 g/dL from baseline during any rolling 8-week interval in the absence of transfusion), the mean (SD) time to first response was 15 (22.7) days, and the Kaplan-Meier estimate for the median duration of response was not estimated.
- In HTB subjects, when assessing response (defined as a reduction by ≥ 4 units of RBC transfusions during any rolling 8-week interval on treatment compared to baseline), the mean (SD) time to first response was 13 (22.6) days, and the Kaplan-Meier estimate for the median duration of response was 352 days.
- The majority (27 [64.3%]) of 42 subjects with ≥ 2 units of RBC transfusions at baseline experienced red blood cell transfusion independence (RBC-TI), defined as at least 8 weeks

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without a transfusion. The Kaplan-Meier estimate for median duration of RBC independence in these 27 subjects was 464 days.

- In HTB subjects, the frequency of RBC transfusions decreased, with a mean (SD) change from baseline of 1.10 (1.40) transfusions over an 8-week interval.
- Subjects generally experienced clinically non-significant increases in platelets on luspatercept therapy as assessed by utilizing mean platelet values at baseline and over time.
- A small number of subjects had a neutrophil response associated with luspatercept treatment. The clinical utility of such a finding is not immediately apparent without further validation.
- The change from baseline over time for several iron parameters, including serum iron, total iron binding capacity (TIBC), transferrin, and hepcidin, was evaluated, with none of these parameters achieving clinically important changes from baseline in subjects administered with luspatercept. The mean (SD) change in transferrin and TIBC from baseline to EOT was statistically significant in HI-E non-responders. There was no statistically significant difference between responders and non-responders in mean change from baseline in iron, TIBC, and transferrin values at EOT.
- Overall, mean soluble transferrin receptor and reticulocytes values increased initially and then trended down toward baseline over time. A statistically significant increase in reticulocytes from baseline to C5D1 was observed. Similarly, in HTB subjects, there was an increase in mean observed EPO values initially, which then trended down toward baseline over time. In LTB subjects, the mean serum EPO change increase from baseline was greater in HI-E non responders than in HI-E responders.
- Overall, changes from baseline in total bilirubin, direct bilirubin, and LDH were not clinically significant, with small mean percentage changes from baseline and values remaining largely within normal ranges. Thus, there does not appear to be an association between luspatercept treatment and increased hemolysis.
- In HTB subjects, pretransfusion Hgb levels decreased slightly, with a mean (SD) postbaseline change from baseline of -0.09 (1.02) g/dL. In addition, mean (SD) postbaseline changes from baseline also indicated small decreases in pretransfusion Hgb levels in both HI-E responders (-0.11 [1.12] g/dL) and HI-E non-responders (-0.02 [0.57] g/dL).
- Overall, the mean changes from baseline in total score and across subscales of the FACT-An scale were small, with transient increases and decreases from baseline. Mean changes from baseline to each visit of the Functional Assessment of Chronic Illness Therapy: Fatigue subscale were small, with transient increases and decreases from baseline.
- Bone marrow aspiration data were sparse, and there were no clinically meaningful trends in mean changes from baseline.

Safety conclusions were as follows:

- Almost half of the subjects (46 [61.3%]) had received 17 or more cycles of luspatercept. Mean duration of study drug exposure was 732.8 days. All subjects had discontinued treatment, 14 (18.7%) subjects had completed the study (these subjects discontinued treatment but completed the follow-up visits), and 61 (81.3%) subjects had discontinued the study.
- All subjects experienced at least 1 TEAE. The highest proportion of subjects experienced TEAEs that were Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 (38 [50.7%] subjects).
- Fifty-six (74.7%) subjects experienced Grade 3 and 4 TEAEs. There were 13 deaths during the study. Seven deaths due to serious adverse events (SAEs) occurred within 56 days after the last treatment (sepsis, infection, aortic stenosis, cardiac failure [2 subjects], general physical health deterioration, and sudden death). All were not related to study drug except for general physical health deterioration and sudden death, which were considered as unlikely related to study drug. Six deaths occurred during survival follow-up (due to unknown reasons [4 subjects], transformation to acute myeloid leukemia [AML], and adenocarcinoma).
- Fifty-eight (77.3%) subjects experienced an SAE; 48 (64.0%) subjects experienced an SAE of Grade 3 and 4. Two SAEs in 1 subject were considered related to study drug (muscular weakness and musculoskeletal pain).
- Twenty-three (30.7%) subjects experienced TEAEs leading to study treatment discontinuation. The most commonly reported TEAEs that led to treatment discontinuation were MDS (i.e., disease progression to high-risk MDS; 5 [6.7%] subjects) and transformation to AML (4 [5.3%] subjects). No organ-specific pattern of TEAEs leading to study treatment discontinuation could be identified.
- The most frequently reported TEAEs overall, regardless of causality, include viral upper respiratory tract infection (25 [33.3%] subjects); hypertension (23 [30.7%] subjects); and diarrhoea, fatigue, and urinary tract infection (17 [22.7%] subjects each).
- The most common TEAEs considered by the investigator to be related to the study drug were hypertension (5 [6.7%] subjects); headache, arthralgia, and fatigue (4 [5.3%] subjects each); and peripheral edema and bone pain (3 [4.0%] subjects each). Peripheral edema was not considered as an adverse drug reaction because the 3 subjects had underlying conditions and concomitant disease (risk factors: hypertension, iron overload, obesity, and hepatic steatosis). Episodes of hypertension that were considered by the investigator to be related to the study drug were transient and not associated with end organ damage. No organ-specific pattern of related TEAEs could be identified.
- Twenty-six TEAEs of malignancies and premalignant disorders were reported in 22 subjects (11 TEAEs of solid tumors, 6 TEAEs of MDS [i.e., disease progression to high-risk MDS], 5 TEAEs of transformation to AML, and 1 TEAE of myelofibrosis, actinic keratosis, leukostasis syndrome, and tumor lysis syndrome each). None of these were considered by the investigator to be related to the study drug. There were 5 cases of progression to AML in this study, all in subjects who possessed multiple risk factors delineated previously for MDS transformation.
- Three subjects were confirmed to have treatment-emergent anti-drug antibody during the study. One event of conjunctivitis captured in the search criteria special medical query

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(SMQ) Hypersensitivity (broad) was observed. The event was nonserious and not related to study the drug. There were no other adverse events associated with hypersensitivity prior to or at the time of onset of conjunctivitis. The event was considered resolved after treatment with dexpanthenol and Euphrasia officinalis.

- Luspatercept was generally well tolerated, and no study drug-related safety concerns were identified.

DISCUSSION AND OVERALL CONCLUSIONS

This Phase 2 open-label extension study evaluated the safety, tolerability, and PD effects of up to 60 months of luspatercept treatment and 3 years of follow-up in subjects with low or intermediate-1 risk MDS previously treated with luspatercept for up to 3 months in the base study, Study A536-03.

A total of 75 of 116 subjects enrolled in Study A536-03 continued on to the extension Study A536-05. Sixty-seven (89.3%) of these subjects rolled over directly into Study A536-05, and 8 (10.7%) subjects had a treatment interruption between Study A536-03 and Study A536-05 (subjects who completed the Study A536-03 EOS visit prior to C1D1 of A536-05).

Overall, the efficacy demonstrated in Study A536-03 continued during longer-term luspatercept treatment in Study A536-05. An Hgb increase of ≥ 1.5 g/dL over a rolling 8-week interval was seen in 40 (80.0%) of the 50 LTB subjects, including 37 (78.7%) of 47 direct rollover LTB subjects and 3 (100%) of 3 interrupted LTB subjects. In HTB subjects, the mean reduction in transfusion burden was 4.4 units over 8 weeks. Twenty-one (84.0%) of the 25 HTB subjects had a reduction of ≥ 4 units or ≥ 50% reduction in RBC transfusion burden during a rolling 8-week interval in the study, including 17 (85.0%) of 20 direct rollover HTB subjects and 4 (80%) of 5 interrupted HTB subjects. The frequency of RBC transfusions events decreased in HTB subjects, with a mean (SD) change from baseline of 1.10 (1.40) transfusions over an 8-week interval. The majority (27 [64.3%]) of 42 subjects with ≥ 2 units of RBC transfusions at baseline experienced RBC-TI, defined as at least 8 weeks without a transfusion.

When assessing erythroid response (modified HI-E; as defined by a mean Hgb increase of ≥ 1.5 g/dL over an 8-week period as compared to baseline, not influenced by RBC transfusion in LTB subjects and a decrease of ≥ 4 units or ≥ 50% of units of RBCs transfused over a period of 8 weeks, relative to the number of units of RBCs transfused in the 8 weeks immediately prior to C1D1 in HTB subjects), 61 (81.3%) subjects had an erythroid response (modified HI-E).

When assessing erythroid response (HI-E; as defined by mean Hgb values with an increase of ≥ 1.5 g/dL from baseline during any rolling 8-week interval in the absence of transfusion (in which rolling 8-week starts and ends at a Hgb measurement date with duration ≥8 weeks) and mean Hgb values with an increase of ≥ 1.5 g/dL from baseline during any rolling 8-week interval in the absence of transfusion in LTB subjects and a reduction of ≥ 4 units of RBC transfusions during any rolling 8-week window on treatment compared to baseline in HTB subjects), 60 (80.0%) subjects had an erythroid response (HI E), with a mean (SD) time to first erythroid response of 14 (22.5) days. The Kaplan Meier estimate for median duration of erythroid response was 486 days.

Subjects generally experienced clinically non-significant increases in platelets on luspatercept therapy assessed by utilizing mean platelet values at baseline and over time. A small number of subjects had a neutrophil response associated with luspatercept treatment. Overall, soluble transferrin receptor as well as reticulocytes and absolute reticulocytes values increased initially then trended down toward baseline.

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Mean serum ferritin levels were mostly stable during treatment, with decreases observed initially in the HI-E responders. Increases in EPO levels were observed initially, which trended down over time with luspatercept treatment, and the increase was less in responders compared with non-responders in LTB subjects.

Overall, luspatercept was generally well tolerated; no significant safety concerns were identified by the SRT during the study, and no new safety concerns were identified during longer-term luspatercept use compared with Study A536-03. There were 13 deaths during the study. Seven deaths due to SAEs occurred within 56 days after the last treatment (sepsis, infection, aortic stenosis, cardiac failure [2 subjects], general physical health deterioration, and sudden death), and 6 deaths occurred during survival follow up (due to unknown reasons [4 subjects], transformation to AML, and adenocarcinoma). A total of 58 (77.3%) subjects experienced an SAE, of which 2 SAEs in 1 subject were considered related to study drug (muscular weakness and musculoskeletal pain). There were 5 cases of progression to AML in this study, all in subjects who possessed multiple risk factors delineated previously for MDS transformation.

All subjects experienced at least 1 TEAE, the highest proportion of which were severe and of the type expected in this subject population. The most common TEAEs considered by the investigator to be related to the study drug were hypertension (5 [6.7%] subjects); headache, arthralgia, and fatigue (4 [5.3%] subjects each); and peripheral edema and bone pain (3 [4.0%] subjects each). Seven (9.3%) subjects experienced a CTCAE Grade 3 or 4 TEAE that was determined to be related to the study drug.

Twenty-three (30.7%) experienced TEAEs that led to treatment withdrawal including MDS (i.e., disease progression to high-risk MDS; 5 subjects) and transformation to AML (4 subjects). Twenty-six TEAEs of malignancies and premalignant disorders were reported in 22 subjects, of which 11 TEAEs were deemed by the investigator to be unlikely related to luspatercept and 15 TEAEs were deemed not related to luspatercept (11 TEAEs of solid tumors, 6 TEAEs of MDS [i.e., disease progression to high-risk MDS], 5 TEAEs of transformation to AML, and 1 TEAE of myelofibrosis, leukostasis syndrome, tumor lysis syndrome, and actinic keratosis each). No organ specific pattern of related TEAEs has been identified; the malignant/premalignant TEAEs were deemed not related to study drug by the investigator. No safety concerns were raised with respect to vital signs, physical findings, ECGs, laboratory assessments, or any other safety assessment.

Date of the report: 1*5 September 2020*