2. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company: Acceleron Pharma</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
Volume:
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: A Phase 2, Open-Label, Ascending Dose Study of ACE-536 for the Treatment of Anemia in Patients With Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS)</td></tr>
<tr><td colspan="3">Principal Coordinating Investigator: Dr. Uwe Platzbecker
Other 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. Stefan Wirths, Dr. Thomas Illmer, and Dr. Gerda Silling, Dr. Haifa Al-Ali</td></tr>
<tr><td colspan="3">Study site(s) and countries: Thirteen study centers in 1 country (Germany) participated in the study, of which 1 center only screened subjects (Site 311 [Dr. Stefan Wirths])</td></tr>
<tr><td colspan="3">Publications (reference): None</td></tr>
<tr><td colspan="2">Studied period (weeks): ~28
Date first subject enrolled: 21 January 2013
Date last subject completed: 22 October 2018</td><td>Phase of development: 2</td></tr>
<tr><td colspan="3">Trial registry number(s): NCT01749514
ClinicalTrials.gov identifier: NCT01749514
EudraCT number: 2012-002523-14</td></tr>
<tr><td colspan="3">Objectives
Primary:
To evaluate the proportion of subjects who have a modified erythroid response, defined as (1) a hemoglobin (Hgb) increase of ≥ 1.5 g/dL from baseline for ≥ 14 days (in the absence of red blood cell [RBC] transfusions) in low transfusion burden (LTB) subjects or (2) reduction of either ≥ 4 units or ≥ 50% of units of RBCs transfused compared to pretreatment in high transfusion burden (HTB) subjects.
Secondary:
To evaluate the safety and tolerability of luspatercept
To examine rates of erythroid, neutrophil, and platelet responses by International Working Group 2006 criteria in MDS
To evaluate time to and duration of modified erythroid response and erythroid response
To evaluate frequency of RBC transfusions in HTB subjects
To examine the pharmacokinetic profile of luspatercept</td></tr>
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- To examine other pharmacodynamic effects (eg, iron metabolism, erythropoietin [EPO], reticulocytes, and bone biomarkers)

Methodology: Subjects who met the study eligibility criteria were enrolled within 28 days of screening. Subjects in all cohorts received luspatercept, administered subcutaneously (SC), every 3 weeks for up to 5 cycles. Dose delay(s) and dose reduction(s) may be required for individual patients as outlined in the Subject Dose Modification Rules.

Each dose escalation cohort had planned enrollment of up to 3 subjects. The dose level of luspatercept for Cohort 1 was 0.125 mg/kg, and the dose level(s) for subsequent cohort(s) followed a modified Fibonacci dose escalation scheme with a maximum dose level of 0.25 mg/kg for Cohort 2, 0.5 mg/kg for Cohort 3, 0.75 mg/kg for Cohort 4, 1.0 mg/kg for Cohort 5, 1.33 mg/kg for Cohort 6, 1.75 mg/kg for Cohort 7, and a maximum dose level not to exceed 1.75 mg/kg. After a minimum of 3 subjects in a cohort had completed Study Day 29, the Safety Review Team (SRT) reviewed preliminary safety and hematologic response data and made recommendations to the Sponsor regarding whether to enroll an additional 3 subjects in that cohort, enroll a new cohort at a higher or lower dose, or proceed to Expansion Cohort 1.

Expansion Cohort 1 was treated with luspatercept at a starting dose level of 1.0 mg/kg. The planned accrual for Expansion Cohort 1 was a minimum of 10 subjects who were HTB and 10 subjects who were LTB (n = approximately 30).

Expansion Cohort 2 was treated with luspatercept at a starting dose level of 1.0 mg/kg. Expansion Cohort 2 was divided into 2 groups, designated Expansion Cohorts 2A and 2B. The planned accrual for each group was 25 eligible and evaluable subjects but permitted to range from 22 to 28 for administrative reasons. The planned maximum number of subjects treated was 56.

- Expansion Cohort 2A: LTB subjects (< 4 units of RBC transfusions within 8 weeks prior to Cycle 1 Day 1) with ≥ 15% ringed sideroblasts (RS) in the bone marrow (RS+), less than 4 weeks of exposure to erythropoiesis-stimulating agent (ESAs), and serum EPO level ≤ 200 IU/L at screening
- Expansion Cohort 2B: Subjects with < 15% RS in the bone marrow (RS-) and ≤ 6 RBC units in 8 weeks prior to Cycle 1 Day 1. This group consisted of a minimum of 10 subjects who have less than 4 weeks of exposure to ESAs and a minimum of 5 subjects who have received ≥ 4 weeks of treatment with ESAs.

Expansion cohort 3 (n= up to approximately 25) were treated with luspatercept at a starting dose level of 1.0 mg/kg. Expansion cohort 3 consisted of subjects who were: RS-, had a baseline EPO level of ≤ 500 U/L at screening, were transfused with ≤ 6 RBC units in the 8 weeks prior to C1D1, and had no prior ESA treatment.

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In the expansion cohorts, a subject's dose level may have been titrated based on criteria listed in Section 10.8.2 of the Protocol. The maximum dose level given to a subject was not to exceed the maximum dose level evaluated in the dose escalation cohorts. Subjects in the expansion cohorts were treated with up to 5 doses of luspatercept administered once every 3 weeks.

There were no planned interim analyses.

Number of subjects (planned, enrolled, and analyzed): Approximately 52 to 128 subjects were planned for the study, 116 subjects enrolled onto the study, 101 subjects completed 5 doses of treatment, and 108 subjects completed the study.

Diagnosis and main criteria for inclusion:

Key inclusion criteria were as follows:

1. Men or women ≥ 18 years of age
2. Documented diagnosis of idiopathic/de novo MDS or non-proliferative chronic myelomonocytic leukemia according to World Health Organization criteria (white blood cell count < 13,000/μL) that meets International Prognostic Scoring System classification of low or intermediate-1 risk disease as determined by the microscopic and standard cytogenetic analyses of the bone marrow and peripheral complete blood count obtained during screening.
3. Anemia defined as:
   - Mean Hgb concentration < 10.0 g/dL of 2 measurements (1 performed within 1 day prior to Cycle 1 Day 1 and the other performed 7 to 28 days prior to Cycle 1 Day 1, not influenced by RBC transfusion within 7 days of measurement) for LTB subjects (defined as having received < 4 units of RBCs within 8 weeks prior to Cycle 1 Day 1) (participation in all cohorts), OR
   - Transfusion dependent, defined as having received ≥ 4 units of RBCs within 8 weeks prior to Cycle 1 Day 1 (HTB subjects were allowed in dose escalation cohorts and Expansion Cohort 1 only; subjects with ≤ 6 units of RBCs within 8 weeks prior to Cycle 1 Day 1 may have been allowed in Cohort 2B).
4. Serum EPO levels and prior ESA treatment:
   - Dose escalation cohorts and Expansion Cohort 1 subjects: Serum EPO level > 500 U/L, OR, if ≤ 500 U/L, subject is non-responsive, refractory, or intolerant to ESAs, or ESAs are contraindicated or unavailable.
   - Expansion Cohort 2 subjects: If a subject is RS+ (defined as having ≥ 15% RS in the bone marrow), has less than 4 weeks' exposure to ESAs and serum EPO level ≤ 200 U/L. If a subject is RS- (defined as having < 15% RS in the bone marrow), prior ESA treatment and any serum EPO level is allowed.
5. No alternative treatment options, per national MDS guidelines, are available and/or appropriate for the subject, at the discretion of the investigator.

Key exclusion criteria were as follows:

1. Prior treatment with azacitidine (injectable or oral) or decitabine

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2. Treatment within 28 days prior to Cycle 1 Day 1 with the following medications:
    - ESA
    - Granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor
    - Lenalidomide
3. Iron chelation therapy if initiated within 56 days prior to Cycle 1 Day 1
4. Treatment with another investigational drug or device, or approved therapy for investigational use ≤ 28 days prior to Cycle 1 Day 1, or if the half-life of the previous product is known, within 5 times the half-life prior to Cycle 1 Day 1, whichever was longer.

Test product, dose and mode of administration: Luspatercept was administered by SC injection at 0.125, 0.25, 0.5, 0.75, 1.0, 1.33, and 1.75 mg/kg. No more than 4 injections were administered per dose. A listing of batch number(s) for the study drug used in this study is provided in Appendix 16.1.6.

Duration of treatment: The total duration of participation for a patient was approximately 28 weeks (4-week screening period, 12-week treatment period, and 12-week follow up period). If a patient had a positive anti-drug antibody (ADA) result at the last visit, the patient would have been asked to return for additional ADA testing every 3 months until a negative result was obtained or the result was considered to be stabilized.

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

Criteria for evaluation:

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

Safety: All subjects were assessed for safety by monitoring adverse events, clinical laboratory tests, vital signs, electrocardiogram (ECG), and physical examination.

Statistical methods: Unless otherwise noted, continuous data were summarized with the following descriptive statistics: number of observations, mean, standard deviation (SD), median, minimum, and maximum. Categorical data were summarized with frequencies and percentages. Percentages were calculated using the total subjects per treatment or subgroup and 95% confidence intervals were provided, as applicable.

Missing data were generally treated as missing, not imputed, unless otherwise stated. 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.

All summaries were presented by dose cohort and could also be presented by lower (0.125 to 0.5 mg/kg) or higher (0.75 to 1.75 mg/kg) dose groups, as specified. The summaries could also be presented for HTB and LTB subjects separately as specified. All summaries were descriptive. No formal hypothesis testing was planned.

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SUMMARY – CONCLUSIONS

EFFICACY RESULTS

The results in this report were based on the database lock of 01 March 2019. Forty-four (67.7%) of the 65 LTB subjects had an Hgb increase ≥ 1.5 g/dL for ≥ 14 days. All 44 of these subjects were treated with luspatercept at the higher dose levels of ≥ 0.75 mg/kg.

A reduction in RBC transfusion burden of ≥ 4 units or ≥ 50% of units during any rolling 8-week period was seen in 26 (51.0%) of the 51 HTB subjects. The majority of these 26 HTB subjects (23 [88.5%] subjects) were treated with luspatercept at dose levels of 0.75 to 1.75 mg/kg.

The majority of subjects who had an erythroid response (all values or mean values) were receiving luspatercept at dose levels of ≥ 0.75 mg/kg. The total mean (SD) time to response for LTB subjects was 21 (12.7) days, and the mean (SD) duration of response was 74 days. This was comparable to the mean (SD) time to response (16 [23.4] days) and the median duration of response (101 days) for HTB subjects. Durations of response was limited by the short treatment duration in this study (i.e., 85 days). Overall, RS+ (ring sideroblasts) subjects were more likely to exhibit an erythroid response than RS- subjects (48.5% vs. 17% respectively).

Thirty-three (41.3%) of the 80 subjects with ≥ 2 units of RBC transfusions at baseline experienced transfusion independence. In these 33 subjects, the median duration of longest RBC transfusion independence was 96 days, and the median time to first RBC transfusion independence was 1 day. In addition, the median duration of exposure to study drug in the overall safety population of 116 subjects was 105 days, with a planned duration of participation in the study for approximately 196 days. The treatment window from Cycle 1, Day 1 to end of treatment (EOT) was 113 days.

A greater percentage of RS+ subjects than RS- subjects experienced transfusion independence for ≥ 8 weeks. Twenty-three (48.9%) RS+ subjects and 10 (32.3%) RS- subjects achieved transfusion independence of ≥ 8 weeks. The median time to first RBC transfusion independence was 1 day in both RS+ and RS- subjects, with a mean (SD) time to first transfusion independence of 13 days (20.5) in RS+ subjects and a mean (SD) time to first transfusion independence of 7 days (13.7) in RS-subjects. Median duration of TI in RS+ subjects was 103 days (range 56-139 days); the median duration of TI in RS- subjects was 92 days (range 63-113 days).

Overall, HTB subjects experienced a mean (SD) change from baseline in RBC transfusion frequency of -0.60 (1.25) units over a rolling 8-week interval. Subjects in the 0.75 to 1.75 mg/kg treatment group experienced a larger mean decrease in frequency of RBC transfusions from baseline of -0.70 as compared to the negligible reductions from baseline in RBC transfusion frequency in the 0.125 to 0.5 mg/kg treatment group of -0.01.

SAFETY RESULTS

The majority of subjects (87 [75.0%]) received all 5 cycles of study drug with mean (SD) duration of exposure among all treatment groups of 97.8 (17.5) days. There were 15 (12.9%) subjects who experienced a dose delay or reduction and 51 (44.0%) subjects who experienced a dose titration over the duration of the study.

Most subjects (95 [81.9%] of 116) experienced at least 1 treatment-emergent adverse event (TEAE), the majority of which were classified as Grade 2 (40 subjects [34.5%]). Twenty (17.2%) subjects

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experienced a total of 22 serious adverse events (SAEs). Two (1.7%) subjects experienced SAEs that were considered related to study drug (general physical health deterioration and myalgia).

The most common TEAEs reported as at least possibly related by the investigator included headache (6 [5.2%] subjects overall), hypertension (6 [5.2%] subjects overall), fatigue (5 [4.3%] subjects overall), and bone pain (5 [4.3%] subjects overall). Hypertensive events were transient and not associated with end organ damage. The majority of bone pain events were low grade, transient, and resolved quickly.

During the study, 30 (25.9%) subjects experienced Grade 3 TEAEs; in 7 (6.0%) subjects, these events were considered possibly or probably related to study drug. One subject experienced a serious Grade 4 TEAE (anemia) that was not considered related to study drug. No subjects experienced a Grade 5 TEAE.

Five (5.3%) subjects experienced a TEAE that led to study drug withdrawal, including general physical health deterioration, MDS (i.e., disease progression to high risk MDS refractory anemia with excess blasts [RAEB-2]), diffuse large B cell lymphoma, transformation to AML, and dyspnea. No DLTs were reported, and no deaths occurred during the study.

Five of the 116 subjects experienced an AESI and had progression to AML, high risk MDS, or any new malignancy and premalignant lesions (excluding benign tumors or benign neoplasia). In each individual case, the subjects possessed substantial risk factors for MDS progression.

- Two subjects (305-0502 and 303-2007) progressed to AML. Subject 305-0502, whose progression to AML was originally reported as experiencing blast cell count increase, had the following risk factors for MDS progression in: age > 65; duration of MDS diagnosis between initial diagnosis and disease progression (approximately 4 years); baseline bone marrow mutations, including ASXL1, FLT3, and RAD21; and a baseline IPSS-R score of 5.5 (high). Subject 303-2007 had risk factors for disease progression including Trisomy 8, and intermediate prognostic risk factor, karyotype: 47, XX,+8[15] and 46,XX[10].
- One subject (305-1024) progressed to MDS RAEB-2. Risk factors for MDS progression in this subject included age > 65; baseline bone marrow mutations, including ASXL1; and a baseline IPSS-R score of 3.5 (intermediate).
- One subject (304-0603) progressed to myelofibrosis with the following risk factors: age > 65; baseline bone marrow mutations, including SETBP1 and SF3B1; and a baseline IPSS-R score of 2.5 (low).
- One subject (310-2005) developed a malignancy of diffuse large B cell lymphoma with the following risk factors: age > 65, gender (male), and race (white).

Twelve (10.3%) of the 116 subjects who received luspatercept were found to have treatment-emergent ADA response. By Cycle 4 Day 1, treatment-emergent ADA response was seen in eight (6.9%) subjects with a median titer value of 34.5 and increased to 10.3% with a median titer value of 46 by end of the study. Luspatercept clearance was approximately 20% higher in ADA-positive on-treatment subjects compared with ADA-negative subjects. However, this increase in clearance did not appear to be related to any change in Hgb response, as the maximum change in Hgb over any 8-week rolling period appeared to be no different between ADA-negative subjects and ADA-positive on-treatment subjects. Of the 20 subjects who experienced ADA responses, there were a small number of subjects who had very minor allergic reactions. There was no overall correlation between

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the presence of ADAs and clinically significant AEs. In addition, no PD impacts were observed in these subjects; however, PK results showed increased clearance in ADA positive subjects. Luspatercept was generally well tolerated at dose levels up to 1.75 mg/kg, and no safety concerns were raised. Based on these results, additional trials are justified to further determine safe and efficacious doses of luspatercept in patients with low or intermediate-1 risk MDS.

CONCLUSION

An Hgb increase of ≥ 1.5 g/dL for ≥ 14 days was seen in 67.7% of LTB subjects; all of whom were treated with luspatercept at dose levels of ≥ 0.75 mg/kg. Twice as many subjects achieved an increase of ≥ 1.0 g/dL versus an increase of ≥ 1.5 g/dL in Hgb during any rolling 8-week interval (32 [49.2%] versus 16 [24.6%], respectively). The maximum mean (SD) increase in Hgb, in all LTB subjects during any rolling 8-week interval, was 1.5 (0.9) g/dL (range: -0.9 to 4.2). Based on the data, it can be concluded that non-responders also showed some improvement in Hgb levels.

A reduction in RBC transfusion burden of ≥ 4 units or ≥ 50% of units during any rolling 8-week period was seen in 51.0% of HTB subjects, with the majority of subjects receiving treatment with luspatercept at dose levels of ≥ 0.75 mg/kg. Thirteen (25.5%) HTB subjects maintained RBC transfusion independence (i.e., experienced a transfusion free duration) for ≥ 8 weeks during the study, and a 45% mean reduction from baseline in RBC transfusions in HTB subjects overall was reported. Treatment with luspatercept resulted in a decreased frequency of RBC transfusions in HTB subjects in the majority of treatment groups. The mean (SD) change from baseline in RBC transfusion frequency was -0.60 (1.25) units over a rolling 8-week interval.

The total mean (SD) time to response for LTB subjects was 21 (12.7) days, and the mean (SD) duration of response was 79 (16.3) days. This was comparable to the mean (SD) time to response 16 (23.4) days and the mean (SD) duration of response (93 [24.3]) for HTB subjects. Durations of response were limited by the short treatment duration in this study (i.e., 85 days).

Overall, there was a mean EOT percentage increase from baseline in EPO levels of 220.49%. Both LTB and HTB subjects showed lower absolute EPO levels over time with luspatercept treatment in responders compared with non-responders. There were no significant differences in absolute EPO levels over time between low dose and high dose HTB subjects; however, in LTB subjects, the high dose group started from a lower baseline EPO level and had lower EPO changes over time compared with the low dose group.

Overall, luspatercept was generally well tolerated at dose levels up to 1.75 mg/kg and no significant safety concerns have been identified by the SRT during conduct of the study. There were no deaths or DLTs reported during the study. There were 20 subjects who experienced a total of 22 SAEs; however, only 2 (1.7%) subjects experienced SAEs that were considered possibly or probably related to study drug (general physical health deterioration and myalgia). Five subjects experienced TEAEs that led to study drug withdrawal (general physical health deterioration [1 subject], MDS [ie, disease progression to high risk MDS RAEB-2; 1 subject], transformation to AML [1 subject], diffuse large B cell lymphoma [1 subject], and dyspnea [1 subject]). Most subjects experienced at least 1 TEAE, but the majority were low- to mid-grade (Grade 1 to Grade 3) TEAEs and of the type expected in this subject population.

Of the 20 subjects who experienced ADA responses, there were a small number of subjects who had very minor allergic reactions. There was no overall correlation between the presence of ADAs and

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clinically significant AEs. In addition, no PD impacts were observed in these subjects; however, PK results showed increased clearance in ADA positive subjects.

No safety concerns related to luspatercept were raised with respect to vital signs, physical findings, ECGs, laboratory assessments, or any other safety assessment. Based on the analyses in this report, continued trials at the demonstrated safe and efficacious doses of luspatercept are justified.

Although the sample size of the low dose cohorts (0.125 to 0.5 mg/kg) was too small to draw significant comparisons or conclusions, observations could be made based on trends seen within the data in that small number of subjects. Based on the data from this Phase 2 study, the sponsor believes that luspatercept has demonstrated an adequate safety and efficacy profile and that further study of this investigational medicinal product is justified.

Date of the Report: 11 September 2019