Official Protocol Title:	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).
NCT number:	NCT01749514
Document Date:	05-Jul-2016

CLINICAL STUDY PROTOCOL

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)

INVESTIGATIONAL PRODUCT:	**Luspatercept (ACE-536)**
PROTOCOL NUMBER:	**A536-03**
EudraCT NUMBER:	**2012-002523-14**
SPONSOR:	**Acceleron Pharma Inc.** **128 Sidney Street** **Cambridge, MA 02139 USA** **Tel:** PPD **Fax:**
MEDICAL MONITOR:	PPD **Vice President, Medical Research**
ORIGINAL PROTOCOL DATE:	**06-Aug-2012**
AMENDMENT 01 DATE:	**29-Oct-2012**
AMENDMENT 02 DATE:	**29-Aug-2013**
AMENDMENT 03 DATE:	**23-May-2014**
AMENDMENT 04 DATE:	**22-Jul-2015**
AMENDMENT 05 DATE:	**05-Jul-2016**

ACCELERON PHARMA SIGNATURE PAGE

Signature:  **Date:** 11 Jul 2016
DD/MMM/YYYY

Name (print): PPD

By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature: 

Date: 18.7.16
DD/MMM/YYYY

Name (print): Prof. Dr. Uwe Platzbecker

Institution Name and Address:

Universitätsklinikum Carl Gustav Carus

Medical Clinic and Polyclinic I,
Fetscherstrasse 74

01307 Dresden, Germany

By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices guidelines and agree to offer guidance throughout the study as needed.

I agree to conduct the study as outlined in the protocol. The study will be conducted in accordance to current United States Food and Drug Administration (FDA) regulations, International Conference of Harmonization (ICH) Guidelines, Good Clinical Practices (GCP), the Declaration of Helsinki, and local ethical and legal requirements.

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature: _____ **Date:** _____
DD/MMM/YYYY

Name (print): _____

Institution Name and Address:

_____

_____

_____

By my signature I have read the protocol and agree to personally supervise and conduct the study as outlined in the protocol. The study will be conducted in accordance to current United States Food and Drug Administration (FDA) regulations, International Conference of Harmonization (ICH) Guidelines, Good Clinical Practices (GCP), the Declaration of Helsinki, and local ethical and legal requirements.

PROCEDURES IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Contact Information
Acceleron Medical Monitor	PPD	Acceleron Pharma Inc. 128 Sidney Street Cambridge, MA 02139 USA Direct Line: PPD Mobile: PPD Fax: PPD PPD
Chiltern Medical Advisor	PPD	Chiltern Via M. Nizzoli, 6 Milano 20147 Italia Direct Line: PPD Mobile: PPD Fax: PPD PPD
Pharmacovigilance	Chiltern	PPD

1. PROTOCOL SYNOPSIS

Name of Sponsor/Company:	Acceleron Pharma Inc. 128 Sidney Street Cambridge, MA 02139 USA
Name of Investigational Product:	Luspatercept **(**ACE-536)
Name of Active Ingredient: ACE-536 is a recombinant fusion protein consisting of a modified form of the extracellular domain (ECD) of the human activin receptor IIB (ActRIIB) linked to the human IgG1 Fc domain.	
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).	
Study Centers: Up to 20	
Phase of Development: 2	

Objectives:

Primary:

- To evaluate the proportion of patients who have a modified erythroid response (mHI-E), defined as a hemoglobin increase of ≥ 1.5 g/dL from baseline for ≥ 14 days (in the absence of red blood cell [RBC] transfusions) in non-transfusion dependent patients, or a reduction of either ≥ 4 units or ≥ 50% of units of RBCs transfused compared to pre-treatment in transfusion dependent patients.

Secondary:

- To evaluate safety and tolerability of ACE-536
- To examine rates of erythroid, neutrophil and platelet (HI-E, HI-N and HI-P) responses (International Working Group [IWG] 2006 criteria)
- To evaluate time to mHI-E and HI-E response and duration of mHI-E and HI-E response
- To evaluate frequency of RBC transfusions in transfusion dependent patients
- To examine the pharmacokinetic (PK) profile of ACE-536
- To examine other pharmacodynamic (PD) effects (e.g., iron metabolism, erythropoietin, reticulocytes, and bone biomarkers)

Exploratory:

- To evaluate biomarkers related to the TGF-β superfamily

- Evaluation of self-reported quality of life in the expansion cohort using tools including but not limited to the Functional Assessment of Cancer Therapy-Anemia Scale (FACT-An) questionnaire

Methodology:

This is a phase 2, open-label, ascending dose study to evaluate the effects of ACE-536 on anemia in patients with low or intermediate-1 risk MDS who are not currently receiving treatment with an erythropoiesis-stimulating agent (ESA). Patients who meet the study eligibility criteria will be enrolled within 28 days of screening. Patients in all cohorts will receive ACE-536, 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 Patient Dose Modification Rules (Section 10.8.1).

Each dose escalation cohort will consist of a minimum of 3 patients. The dose level of ACE-536 for the first cohort will be 0.125 mg/kg and the dose level(s) for subsequent cohort(s) will follow a modified Fibonacci dose escalation scheme, with a maximum dose level of 0.25 mg/kg for cohort 2, 0.50 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. Once a minimum of 3 patients in a cohort have completed Study Day 29, the Safety Review Team (SRT) will review preliminary safety and hematologic response data and make recommendations to the Sponsor regarding whether or not to enroll an additional 3 patients in that cohort, enroll a new cohort at a higher or lower dose, or proceed to the expansion cohort.

Expansion cohort 1 (n= approximately 30) will be treated with ACE-536 at a starting dose level of 1.0 mg/kg. Expansion cohort 1 will consist of a minimum of 10 patients who are transfusion dependent (TD) and 10 patients who are non-transfusion dependent (NTD), if feasible.

Expansion cohort 2 will be treated with ACE-536 at a starting dose level of 1.0 mg/kg. Expansion cohort 2 will be divided into two groups designated expansion cohort 2A and 2B. The targeted accrual for each group will be 25 eligible and evaluable patients but permitted to range from 22 to 28 for administrative reasons. The maximum number of patients treated will be 56.

- Expansion cohort 2A: NTD patients with ≥ 15% ring sideroblasts in the bone marrow (RS+), less than 4 weeks of exposure to erythropoietin stimulating agents (ESAs), and serum erythropoietin (EPO) level ≤ 200 U/L at screening.
- Expansion cohort 2B: Patients with < 15% ring sideroblasts in the bone marrow (RS-) and ≤ 6 RBC units in 8 weeks prior to C1D1. This group will consist of a minimum of 10 patients who have less than 4 weeks of exposure to ESAs and 5 patients who have received ≥ 4 weeks of treatment with ESAs.

In the expansion cohorts, a patient's dose level may be titrated based on criteria listed in Section 10.8.2, Expansion Cohorts Patient Dose Titration. The maximum dose level given to a patient will not exceed the maximum dose level evaluated in the dose escalation cohorts. Patients in the expansion cohorts will be treated with up to 5 doses of ACE-536 administered once every 3 weeks.

Dose Escalation Table

Cohorts[a]	ACE-536 Dose Level[b] (mg/kg)	Number of Patients
1	0.125	3-6
2	0.25	3-6
3	0.50	3-6
4	0.75	3-6
5	1.0	3-6
6	1.33	3-6
7	1.75	3-6
Expansion 1	1.0	30
Expansion 2	1.0	up to 56
Planned Total:		**up to 128**

[a] Cohort escalation is based on SRT review and recommendation to enroll additional cohorts and/or the expansion cohorts.

[b] The ACE-536 dose level for cohort 1 is 0.125 mg/kg. The dose level indicated for all subsequent dose escalation cohorts is the maximum dose level that can be recommended by the SRT for escalation per the modified Fibonacci dose escalation scheme. Dose escalation will not exceed 1.75 mg/kg.

Maximum Number of Patients (Planned): Up to 128 patients

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

Diagnosis and Main Criteria for Eligibility

Inclusion Criteria:

1. Men or women ≥ 18 years of age.

2. Documented diagnosis of idiopathic/de novo MDS or non-proliferative chronic myelomonocytic leukemia (CMML) according to WHO criteria (white blood count [WBC] < 13,000/μL) that meets International Prognostic Scoring System (IPSS) classification (Appendix 2) of low or intermediate-1 risk disease as determined by microscopic and standard cytogenetic analyses of the bone marrow and peripheral complete blood count (CBC) obtained during screening.

3. Anemia defined as:

- Mean hemoglobin concentration < 10.0 g/dL of 2 measurements (one performed within one day prior to Cycle 1 Day 1 and the other performed 7-28 days prior to Cycle 1 Day 1, not influenced by RBC transfusion within 7 days of measurement) for non-transfusion dependent patients (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 (transfusion dependent patients are allowed in dose escalation cohorts and expansion cohort 1 only; patients with ≤ 6 units of RBCs within 8 weeks prior to Cycle 1 Day 1 may be allowed in cohort 2B).

4. Serum erythropoietin levels and prior erythropoiesis-stimulating agent (ESA) treatment:
   - Dose escalation cohorts and expansion cohort 1 patients: Serum erythropoietin level > 500 U/L, OR, if ≤ 500 U/L, patient is non-responsive, refractory, or intolerant to erythropoiesis-stimulating agents (ESAs), or ESAs are contraindicated or unavailable.
   - Expansion cohort 2 patients: If patient is RS+ (defined as having ≥ 15% ring sideroblasts in the bone marrow), has less than 4 weeks' exposure to ESAs and serum erythropoietin level ≤ 200 U/L. If a patient is RS- (defined as having < 15% ring sideroblasts in the bone marrow), prior ESA treatment and any serum erythropoietin level is allowed.
5. No alternative treatment options, per national MDS guidelines, are available and/or appropriate for the patient, at the discretion of the investigator.
6. ECOG performance status of 0, 1, or 2 (if related to anemia).
7. Adequate renal (creatinine ≤ 2 x upper limit of normal [ULN]) and hepatic (total bilirubin < 2 x ULN and AST and ALT < 3 x ULN) function.
8. Adequate transferrin saturation (≥ 15%), ferritin (≥ 50 µg/L), folate (≥ 4.5 nmol/L [≥ 2.0 µg/L]) and vitamin B12 (≥ 148 pmol/L [≥ 200 pg/mL]) during screening (supplementation and retest during screening is acceptable).
9. Females of child bearing potential (defined as sexually mature women who have not undergone hysterectomy or bilateral oophorectomy, or are not naturally postmenopausal ≥ 24 consecutive months) must have negative urine or blood pregnancy test prior to enrollment and use adequate birth control methods (abstinence, oral contraceptives, barrier method with spermicide, or surgical sterilization) during study participation and for 12 weeks following the last dose of ACE-536. Males must agree to use a latex condom during any sexual contact with females of child-bearing potential while participating in the study and for 12 weeks following the last dose of ACE-536, even if he has undergone a successful vasectomy. Patients must be counseled concerning measures to be used to prevent pregnancy and potential toxicities prior to the first dose of ACE-536.
10. Patients are able to adhere to the study visit schedule, understand and comply with all protocol requirements.
11. Patient understands and is able to provide written informed consent.

Exclusion Criteria:

1. Prior treatment with azacitidine (injectable or oral) or decitabine.
2. Treatment within 28 days prior to Cycle 1 Day 1 with:
    - Erythropoiesis stimulating agent (ESA),
    - Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF),
    - 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 is longer.
5. Major surgery within 28 days prior to Cycle 1 Day 1. Patients must have completely recovered from any previous surgery prior to Cycle 1 Day 1.
6. Platelet count < 30×10^9/L.
7. Any active infection requiring parenteral antibiotic therapy within 28 days prior to Cycle 1 Day 1 or oral antibiotics within 14 days of Cycle 1 Day 1.
8. History of stroke, deep venous thrombosis (DVT) or arterial embolism within 6 months prior to Cycle 1 Day 1.
9. Known positive for human immunodeficiency virus (HIV), active infectious hepatitis B (HBV) or active infectious hepatitis C (HCV).
10. Any malignancy other than MDS which has not been in remission and/or has required systemic therapy including radiation, chemotherapy, hormonal therapy or surgery, within the last year prior to Cycle 1 Day 1.
11. Uncontrolled hypertension, defined as systolic blood pressure (BP) ≥ 150 mm Hg or diastolic BP ≥ 100 mm Hg.
12. Pregnant or lactating females.
13. History of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the investigational drug.
14. Any other condition not specifically noted above which, in the judgment of the investigator, would preclude the patient from participating in the study.
15. Transfusion event within 7 days prior to Cycle 1 Day 1.
16. Prior treatment with sotatercept (ACE-011) or ACE-536.
17. Secondary MDS.

Investigational Product and Mode of Administration:

ACE-536 drug product will be provided as either a sterile, liquid formulation or a lyophilized powder formulation for reconstitution with water. Each single-use vial of the liquid formulation contains 25 mg of ACE-536 in a 0.5 mL Tris-buffered saline solution (50 mg/mL). Each single-use vial of the lyophilic formulation contains 50 mg ACE-536 for reconstitution with 1 mL water for injection to form a citrate-buffered solution (50 mg/mL).

ACE-536 will be administered by subcutaneous (SC) injection on Day 1 of each 21 (±2) day cycle.

Safety Evaluation and Dose Escalation:

Safety will be evaluated by the Safety Review Team (SRT), which is comprised at minimum of the coordinating investigator, medical monitor, and an independent hematologist. The role of the SRT will be described in greater detail in the SRT Charter. The SRT will review safety data when a minimum of 3 patients in a cohort have completed Study Day 29, including dose-limiting toxicities (DLTs), adverse events (AEs), serious adverse events (SAEs), laboratory results (including hematology and chemistry), vital signs, and erythroid response data. The SRT may make one or more of the following recommendations to the sponsor:

- Enroll 3 additional patients in the current cohort.
- Enroll 3 patients in a new cohort at a higher or lower dose level, not to exceed the modified Fibonacci dose escalation scheme (see Section 9.1).
- Proceed to expansion cohort 1, with a recommended starting dose level not to exceed the maximum dose level evaluated in the dose escalation cohorts.
- Postpone a decision pending collection of additional data from the current cohort.

A DLT, using the current active minor version of the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.0 (NCI-CTCAE v4.0), is defined as any of the following toxicities at any dose level occurring within 28 days of the first administered dose:

- Treatment-related serious adverse event (SAE) of Grade ≥ 3
- Treatment-related non-hematologic and non-infectious adverse event (AE) of Grade ≥ 3
- Treatment-related hematologic or infectious AE of Grade ≥ 4

SRT recommendations to escalate or reduce the dose level of ACE-536 in a subsequent cohort or to continue dosing in the current cohort will be based in part upon the following criteria:

- If a DLT occurs in 0 out of a minimum of 3 patients in a cohort within 28 days following the initial dose, dose escalation may occur.
- If a DLT occurs in 1 out of 3 patients in a cohort within 28 days following the initial dose, an additional 3 patients should be enrolled in the current cohort.
    - If a DLT occurs in 1 out of 6 patients in a cohort within 28 days following the initial dose, dose escalation may occur.

- If a DLT occurs in ≥ 2 patients in a cohort within 28 days of the initial dose, the dose level for the next cohort (if any) should not be escalated; a lower dose level may be recommended.
- If a hemoglobin increase of ≥ 2.0 g/dL occurs in ≥ 2 patients in a cohort within 28 days of the initial dose, the dose level for the next cohort (if any) should not be escalated; a lower dose level may be recommended.

In addition, during enrollment of the expansion cohorts, the SRT will review safety data periodically throughout the trial, including AEs, SAEs, laboratory results (including hematology and chemistry), vital signs, and erythroid response data.

Criteria for Evaluation

- **Safety:** All patients will be assessed for safety by monitoring adverse events, clinical laboratory tests, vital signs, ECG and physical examination.
- **Efficacy:** Patients will be assessed for erythroid response for up to 24-weeks following initiation of treatment. Erythroid response endpoints will be determined by monitoring hematologic laboratory values and RBC transfusions.

  Secondary efficacy endpoints will be assessed by examining other hematology, erythropoiesis, iron metabolism, and bone metabolism parameters.

  - Erythropoiesis parameters include serum erythropoietin levels, reticulocytes, and nucleated RBCs
  - Iron metabolism parameters include serum iron, total iron binding capacity (TIBC), transferrin, soluble transferrin receptor, ferritin, non-transferrin bound iron (NTBI), and hepcidin
  - Bone metabolism parameters include bone specific alkaline phosphatase (BSAP) and C-telopeptide of type I collagen (CTX)
- **Exploratory endpoints** will include:
  - Evaluation of biomarkers related to the TGF-β superfamily
  - Evaluation of self-reported quality of life in the expansion cohort using tools including but not limited to the FACT-An questionnaire

Statistical methods

Sample Size Calculation:

There is no formal sample size calculation for the dose escalation portion of the study. A sample size of 30 evaluable patients in the expansion cohort 1 will provide approximately 90% power with 1-sided significance level of 0.05 to differentiate an erythroid response rate of 30% from a minimal erythroid response rate of 10% based on Fisher exact test.

A sample size of 25 evaluable patients in each group of expansion cohort 2 will provide approximately 80% power with 1-sided significance level of 0.05 to differentiate an erythroid response rate of 30% from a minimal erythroid response rate of 10% based on Fisher exact test

Analysis Populations:

For all analysis populations, patients will be analyzed according to assigned cohort.

The Intent-to-Treat (ITT) Population: All patients enrolled in the study who have received at least one dose of ACE-536 (Safety Population).

Efficacy Evaluable (EE) Population: All patients who received at least one dose of ACE-536 and have 1) at least two hemoglobin assessments ≥ 14 days apart post-treatment OR, 2) at least 8 consecutive weeks of transfusion frequency data between Cycle 1 Day 1 and End of Treatment visit in transfusion dependent patients.

Safety Population: All patients who received at least 1 dose of ACE-536.

Pharmacokinetics Population: All patients who have received at least 1 dose of ACE-536 and have sufficient pharmacokinetic samples collected and assayed for PK analysis.

Efficacy/Pharmacodynamic Effects Analysis:

The **primary efficacy endpoint** is modified erythroid response (mHI-E), defined as the proportion of patients who have a hemoglobin increase of ≥ 1.5 g/dL from baseline for ≥ 14 days (in the absence of RBC transfusions) in non-transfusion dependent patients, or, a reduction of either ≥ 4 units or ≥ 50% of units of RBCs transfused over a period of 8 consecutive weeks, compared to the number of units of RBCs transfused in the 8 weeks immediately prior to Cycle 1 Day 1 in transfusion dependent patients (defined as having received ≥ 4 units of RBCs within 8 weeks prior to Cycle 1 Day 1). The erythroid response will be summarized using both a point estimate and its exact 95% confidence interval based on binomial distribution. The primary efficacy analysis will be performed using the EE population.

No direct comparison testing with concurrent or historical controls will be performed.

Baseline hemoglobin will be the average of at least two measures (not influenced by transfusion within 7 days of measurement); one measure performed within one day prior to Cycle 1 Day 1 and the other performed 7-28 days prior to Cycle 1 Day 1.

The **secondary efficacy/pharmacodynamic analysis** will be performed using the ITT and EE populations and include:

- Modified erythroid response (mHI-E), as described above for primary endpoint, performed using the ITT population.
- HI-E response rate as defined by IWG 2006 criteria (Appendix 5). Improvements must last ≥ 8 weeks. For non-transfusion dependent patients, an increase of ≥ 1.5 g/dL from pre-treatment hemoglobin. For transfused patients, a reduction by ≥ 4 units of RBCs transfused (for a hemoglobin ≤ 9.0 g/dL) during any 8-week period on study, compared with the 8-week period prior to Cycle 1 Day 1.
- Time to mHI-E and HI-E response and duration of mHI-E and HI-E response as per the IWG 2006 criteria.
- Frequency of RBC transfusion, and rate of RBC transfusion independence in transfusion dependent patients.
- Other pharmacodynamic (PD) endpoints including:

- Biomarkers for iron metabolism
- Biomarkers for bone metabolism
- Relationship of biomarkers to response
- Rates of HI-N and HI-P

The **exploratory endpoints** will include:

- Evaluation of biomarkers related to the TGF-β superfamily.
- Evaluation of self-reported quality of life in the expansion cohort using tools including but not limited to the FACT-An questionnaire

All binary endpoints will be summarized using both a point estimate and its exact confidence interval based on the binomial distribution. The time-to-event type secondary endpoints will be analyzed using Kaplan-Meier method to estimate the survival curve and median time to event and 95% confidence interval.

Safety analysis: To assess clinical safety, adverse events, vital sign measurements and clinical laboratory information will be summarized. Adverse Events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Changes from baseline for clinical laboratory values and vital signs will be summarized over time. Descriptive statistics and shift tables will be generated as appropriate.

Pharmacokinetics analysis: Non-compartmental PK parameters for ACE-536, such as maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), and area under the concentration/time curve (AUC), will be estimated. Dose proportionality may be assessed using the exposure data (e.g. C_{max}, AUC) after the first dose if sufficient dose levels are studied. Descriptive statistics will be provided for serum concentrations and PK parameters. The relationship between ACE-536 exposure and response (i.e., safety, efficacy, and biomarkers) may be explored, if appropriate.

Anti-drug antibody analysis: The results of anti-drug and neutralizing antibody testing for ACE-536 and human ActRIIB protein versus time will be presented. Exploratory analysis will be performed on the potential effect of anti-drug antibodies on ACE-536 PK and drug exposure if anti-drug antibody tests are deemed positive.

2. SCHEDULE OF EVENTS

	Screen	Treatment Period																Follow up period		
		Cycle 1				Cycle 2			Cycle 3			Cycle 4			Cycle 5			EOT[12]	Post-Treatment Follow Up	EOS[13]
		C1D1[2]	C1D8	C1D11	C1D15	C2D1[2,15]	C2D8	C2D15	C3D1[2,15]	C3D8	C3D15	C4D1[2,15]	C4D8	C4D15	C5D1[2,15]	C5D8	C5D15			
	Day -28	Day 1	Day 8 (± 1d)	Day 11 (± 1d)	Day 15 (± 1d)	Day[14] 22 (± 2d)	Day 29 (± 2d)	Day 36 (± 2d)	Day[14] 43 (± 2d)	Day 50 (± 2d)	Day 57 (± 2d)	Day[14] 64 (± 2d)	Day 71 (± 2d)	Day 78 (± 2d)	Day[14] 85 (± 2d)	Day 92 (± 2d)	Day 99 (± 2d)	Day 113 (± 7d)	Day 141 (± 7d)	Day 169 (± 7d)
Informed consent	X																			
Inclusion/Exclusion	X	X																		
Medical history	X																			
QoLQuestionnaires[18]	X														X[18]			X[19]		X
Physical examination	X	X				X			X			X			X			X		X
Vital signs[1]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ECOG Status	X								X			X						X		X
ECG (12 lead)	X					X												X		
Bone marrow aspirate/biopsy[3]	X								X[3]									X		
Serum iron studies[4]	X	X				X	X		X			X			X			X	X	X
Serum folate and B_{12}	X																			
Erythropoietin levels	X	X	X		X	X						X						X	X	X
Hematology[5]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Peripheral blood smear	X	X				X									X			X		
Serum chemistry[6]	X	X			X	X	X		X	X		X	X		X	X		X		X
Urinalysis and Urine Chemistry[7]		X				X						X						X		X
Anti-drug antibody[16]		X										X						X		X[16]
PK collection		X	X	X	X	X	X					X			X	X	X	X	X	X
PD biomarkers[8]		X				X			X			X			X			X		X
Bone biomarkers[9]		X										X						X		
Pregnancy test[10]	X	X				X			X			X			X			X		X
Evaluate transfusion frequency[11]	X	X				X			X			X[2]			X			X	X	X
Concomitant medications and AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administer ACE-536 [17]		X				X[14]			X[14]			X[14]			X[14]					

[1] **Vital signs:** Weight, heart rate, systolic and diastolic blood pressure, respiration rate and temperature (measured in degrees Celsius). Height is measured only at Screening.

[2] **Study procedures** must be done prior to administration of study drug.

[3] **Bone marrow aspirate/biopsy** including cytogenetics at screening must be performed ≤ 3 months prior to C1D1 for evaluation of patient eligibility and other PD biomarkers to be determined (e.g., GDF15, GDF8, and GDF11).

- For all patients, at the end of treatment visit, a bone marrow aspirate must be performed (a bone marrow biopsy is optional).
- Dose escalation cohorts and expansion cohort 1 patients only: a bone marrow aspirate must be performed within 21 days after C3D1 (a bone marrow biopsy is not required). Note: A bone marrow aspirate is not required within 21 days after C3D1 for expansion cohort 2 patients.
- Dose escalation cohorts and expansion cohort 1 patients only: If hemoglobin increases ≥ 2 g/dL, an optional bone marrow aspirate can be performed within 7 days of the result.

[4] **Iron Studies:** Serum iron, TIBC, transferrin, soluble transferrin receptor, NTBI, ferritin.

[5] **Hematology:** RBC, WBC with differential, hemoglobin, hematocrit, nRBC, reticulocyte count, platelet count, MCV, MCH, MCHC, and RDW. On dosing days, hemoglobin values are to be drawn and resulted (up to 1 day) prior to dosing (see Section 10.8.1, Patient Dose Modification Rules). Historical hemoglobin data will be collected for 24 weeks, where available, prior to C1D1. During the screening period, hemoglobin will be measured twice; one measure performed within one day prior to Cycle 1 Day 1 and the other performed 7-28 days prior to Cycle 1 Day 1. Neither hemoglobin measure should be influenced by transfusion within 7 days of measurement.

[6] **Chemistry**: Sodium, potassium, AST, ALT, lactate dehydrogenase (LDH), total bilirubin, direct bilirubin, alkaline phosphatase, blood urea nitrogen (BUN)/urea, creatinine, GGT, calcium, phosphorus, glucose, amylase, lipase, total protein, albumin, and uric acid.

[7] **Urinalysis by dipstick analysis (local lab):** pH, specific gravity, protein, glucose, ketones, blood, leukocyte esterase, and nitrite, with microscopic examination if indicated. **Urine Chemistry (central lab):** Microalbumin and creatinine.

[8] **PD Biomarkers:** Hepcidin, GDF15, GDF8, GDF11, and others to be determined.

[9] **Bone Biomarkers:** BSAP and CTX. Not required for expansion cohort 2 patients.

[10] **Pregnancy test:** (urine or serum) is required for female patients of child bearing potential at screening and prior to each dose of ACE-536.

[11] **Transfusion history** will be collected for 24 weeks, where available, prior to C1D1.

[12] **End of Treatment (EOT)**: Should be performed 28 days (± 7 days) after the last dose of ACE-536. Patients who discontinue treatment early should complete the end of treatment visit at the time of discontinuation and complete the post-treatment follow-up (PTFU) and EOS follow-up visits 28 days (± 7 days) and 56 days (± 7 days) after the EOT visit.

[13] **End of Study (EOS):** Should be performed 56 days (± 7 days) after the Day 113/EOT visit.

[14] **Day 85 ± 2 days** is the last possible study day that ACE-536 may be administered, regardless of the cycle.

[15] If a **dose delay** is required per the dose modification rules the patient will not be dosed. The patient will return weekly to assess hematology results and adverse events until the patient is eligible to administer the next dose of ACE-536. The patient should resume the study at the planned dosing cycle (e.g. if the patient missed a dose at C4D1, then they would resume dosing at C4D1 and not skip to C5D1). Note: study days may vary if a dose delay occurred during the treatment period.

[16] If the patient has a **positive ADA** result at their last assessment, the patient may be asked to return approximately every three months for additional testing, until a negative result is obtained or the result is considered stabilized.

[17] For the **first dose of ACE-536**, dosing should occur after a minimum of 7 days post-transfusion and a minimum of 24 hours prior to a scheduled transfusion.

[18] **Expansion cohorts** only, administration of quality of life questionnaires. Quality of life questionnaire not required for expansion cohort 2 patients at C5D1.

[19] **Quality of life questionnaires** should be completed at the EOT visit for patients that discontinue treatment early and for all expansion cohort 2 patients.

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4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ActRIIB	Activin receptor IIB
ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BFU-E	Burst forming units - erythroid
BMP	Bone morphogenetic protein
BP	Blood pressure
BSAP	Bone-specific alkaline phosphatase
BSC	Best supportive care
BUN	Blood urea nitrogen
CXDY	Cycle X Day Y
CBC	Complete blood count
CFU-E	Colony forming units – erythroid
C_{max}	Maximum concentration
CMML	Chronic myelomonocytic leukemia
CREAT	Creatinine
CRF	Case report form
CRO	Contract research organization
CTX	C-terminal type I collagen telopeptide
DLT	Dose-limiting toxicity
DVT	Deep venous thrombosis
ECD	Extracellular domain
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EE	Efficacy Evaluable
ESA	Erythropoiesis stimulating agent
EOS	End of study

Abbreviation	Definition
EPO	Erythropoietin
EOT	End of treatment
FACS	Fluorescence activated cell sorting
FACT-An	Functional Assessment of Cancer Therapy-Anemia Scale
FDA	United States Food and Drug Administration
GCP	Good clinical practices
G-CSF	Granulocyte colony-stimulating factor
GDF	Growth and differentiation factor
GGT	Gamma-glutamyl transpeptidase
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HBV	Hepatitis B virus
HCV	Hepatitis C virus
Hgb	Hemoglobin
HI-E	Erythroid response
HI-N	Neutrophil response
HI-P	Platelet response
HIV	Human immunodeficiency virus
IB	Investigator brochure
ICF	Informed consent form
ICH	International conference on harmonisation
IEC	Independent ethics committee
IgG1	Immunoglobulin G1
ITT	Intent-to-Treat
IPSS	International Prognostic Scoring System
IWG	International Working Group
IB	Investigator's brochure
IV	Intravenous
K_D	Dissociation constant
LDH	Lactate dehydrogenase
mHI-E	Modified erythroid response
MedDRA	Medical Dictionary for Regulatory Activities
MCH	Mean corpuscular hemoglobin

Abbreviation	Definition
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndromes
NCI-CTCAE	National Cancer Institute-Common terminology criteria for adverse events
nRBC	Nucleated red blood cell
NTBI	Non-transferrin bound iron
ORR	Objective response rate
PD	Pharmacodynamic
PFS	Progression free survival
PHI	Protected health information
PK	Pharmacokinetic
PTFU	Post-Treatment Follow-up
QoL	Quality of Life
RBC	Red blood cell
RDW	Red blood cell distribution width
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SRT	Safety review team
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Elimination half-life
TGF-β	Transforming growth factor beta
TIBC	Total iron binding capacity
T_{max}	Time to maximum concentration
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization

5. ETHICS

5.1. Institutional Review Board

The investigator will submit this protocol, any protocol modifications, and the patient Informed Consent Form (ICF) to be used in this study to the appropriate IEC for review and approval. A letter confirming IEC approval of the protocol and ICF as well as a statement that the IEC is organized and operates according to Good Clinical Practice (GCP) and the applicable laws and regulations, must be forwarded to the sponsor prior to the enrollment of patients into the study. A copy of the approved ICF will also be forwarded to the sponsor. Appropriate reports on the progress of the study will be made to the IEC and the sponsor by the principal investigator in accordance with applicable governmental regulations and in agreement with the policy established by the sponsor.

5.2. Ethical Conduct of the Study

The sponsor and the investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable International Conference on Harmonisation (ICH) and GCP guidelines, and must also conduct the study in accordance with local regulations.

5.3. Patient Information and Consent

Informed written consent is required from each patient prior to any testing under this protocol, including screening tests and evaluations. The ICF, as specified by the study center's IEC, must follow the Protection of Human Patients regulations listed in the Code of Federal Regulations, Title 21, Part 50. The principles of informed consent in the Declaration of Helsinki should be implemented in this clinical study and should comply with local and national regulations. The consent forms must be in a language fully comprehensible to the prospective subject. Information should be given in both oral and written form whenever possible and deemed appropriate by the IEC.

The background of the proposed study and the benefits and risks of the procedures and study must be explained to the patients. It is the responsibility of the investigator to obtain consent and to provide the patient with a copy of the signed and dated ICF. Confirmation of a patient's informed consent must also be documented in the patient's medical record prior to any testing under this protocol, including screening tests and evaluations.

All ICFs used in this study must be approved by the appropriate IEC and by the Sponsor or designee. The ICF must not be altered without the prior agreement of the relevant IEC and the Sponsor.

5.4. Patient Data Protection

Prior to any testing under this protocol, including screening tests and evaluations, patients must authorize the release and use of protected health information (PHI), as required by local law.

The patient will not be identified by name in the case report form (CRF) or in any study reports. These reports will be used for research purposes only. The Sponsor, its designee, and various government health agencies may inspect the records of this study. Every effort will be made to keep the patient's personal medical data confidential.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Acceleron Pharma is the sponsor for this trial. The sponsor will serve as the medical monitor for the study. The sponsor or designee also will manage the conduct of the trial and provide for clinical monitoring, data management, biostatistics, and report writing. Clinical monitors will monitor each study center on a periodic basis and verify source documentation for each patient. The sponsor's pharmacovigilance representative will be responsible for timely reporting of Serious Adverse Events (SAEs) to health authorities as required.

7. INTRODUCTION

ACE-536 is a recombinant fusion protein consisting of a modified form of the extracellular domain (ECD) of the human activin receptor type IIB (ActRIIB) linked to the human IgG1 Fc domain. The ActRIIB receptor and its ligands are members of the TGFβ superfamily, a group of proteins involved in the development, differentiation, and/or maturation of various tissues. No species differences have been described in the ligand-receptor interactions among members of the TGFβ family as the ligands and receptors are highly conserved across species.[1] Thus, observations from pharmacology studies of ACE-536 or its murine analog RAP-536 in animal models provide significant insight into the potential of ACE-536 to treat human disease.

Members of the TGFβ family are reported to play a role in red blood cell (RBC) development, although the specific ligands and receptors that influence the process of erythropoiesis are not completely understood. In nonclinical experiments, ACE-536 has been shown to bind with high affinity to some TGFβ ligands (e.g., GDF8, GDF11, BMP6 and activin B) but substantially less, or not at all, to others (e.g., BMP10 and activin A). The emerging body of evidence on ACE-536 suggests that its mechanism of action is distinct from that of erythropoietin (EPO), and involves acceleration of the later maturation phase of erythrocyte development.

The nonclinical pharmacology data using ACE-536/RAP-536 demonstrate that the molecule can produce a rapid and robust erythroid response in a variety of settings, and that this response is due to its influence on the differentiation of hematopoietic cell types in the later stages of erythropoiesis. In contrast, EPO is active in the early, proliferative stage of erythropoiesis. ACE-536 has shown activity in animal models of various conditions in which anemia contributes significantly to disease morbidity, including anemia associated with ineffective erythropoiesis. In a murine model of myelodysplastic syndrome (MDS), RAP-536 was shown to increase RBC and Hgb in early, mid and late stage disease; normalize myeloid: erythroid ratio; increase maturation of erythroid precursors; and decrease erythroid hyperplasia.

7.1. Overview of Target Indication

The target indication for ACE-536 is for the treatment of anemia in patients with myelodysplastic syndromes (MDS). MDS are heterogeneous diseases characterized by abnormal proliferation and differentiation of erythropoietic precursor cells in the bone marrow, resulting in peripheral cytopenias; approximately 25-30% of patients with MDS have progression to acute myeloid leukemia (AML).[2,3,4]

MDS is a hematologic neoplasm primarily of the elderly, with 86% of MDS cases diagnosed in individuals age ≥ 60 years (median age at diagnosis, 76 years). According to the SEERS data, approximately 12,000 patients are diagnosed with MDS per year in the United States and approximately 20,000 in Europe.[5] The incidence rate of MDS in Germany is 4.1 per 100,000,[6] with a median age between 68 and 73 years.[7] Looking at a subset of patients in Dusseldorf, the incidence of MDS is higher in men than women with the incidence and prevalence increasing dramatically with age.[8] With the number of people over the age of 65 expected to rise over the next four decades in developed countries such as Germany, there will likely be a correlated rise in the number of patients diagnosed with MDS.[9]

MDS classification systems have been established to address the heterogeneity of MDS. The International Prognostic Scoring System (IPSS) (Appendix 2) categorizes the different types of MDS by the number of bone marrow blasts, the number of cytopenias, and bone marrow cytogenetics to predict survival and potential progression to AML.[4] The IPSS has four risk categories: low, intermediate-1, intermediate-2, and high. Standardized response criteria for clinical trials have been established to evaluate response to the treatment. The International Working Group (IWG) criteria is an evaluation tool often used to quantify the quality of a response to treatment and for the consideration of risk based treatment goals.[10]

Therapy for MDS is based on patient age, IPSS risk category, and ECOG performance status (Appendix 3).[11] MDS can be cured by stem cell transplantation; however, most patients cannot receive the transplant due to age or limited availability of appropriate donors. Therefore, supportive care is often provided for these patients. The median survival rate for low risk MDS is 5.7 years and decreases to 3.5 years for patients with intermediate-1 risk MDS.[4,12]

Anemia is the predominant cytopenia observed in MDS and is present in 85% of MDS patients at the time of diagnosis.[13] Refractory anemia resulting from ineffective erythropoiesis is a major cause of morbidity and mortality in MDS patients.[14] Supportive care with blood transfusions, erythropoiesis stimulating agents (ESAs), and other growth factors are used to treat anemia.

Clinical studies have demonstrated that ESAs can provide clinical benefit to MDS patients by reducing the need for red blood cell transfusions. Only one third of unselected patients treated with ESAs have an erythroid response.[15,16] A significant number of MDS patients have serum erythropoietin (EPO) levels in excess of 500 U/L, indicating the anemia in MDS is not a consequence of endogenous EPO deficiency and unlikely to respond to exogenous EPO.[17] This observation suggests that impaired erythropoiesis in MDS patients occurs downstream of the steps that are regulated by EPO. Ineffective erythropoiesis leading to anemia in MDS patients appears to be associated with intramedullary apoptosis of cells during the later stages of erythrocyte development beyond those regulated by EPO.[18,19]

The azanucleosides, azacitidine (Vidaza®) and decitabine (Dacogen®), and lenalidomide (Revlimid®) have demonstrated activity in patients with MDS.[20,21] A randomized phase 3 trial comparing azacitidine with best supportive care (BSC) demonstrated hematologic improvement, delayed progression to AML or death and improved quality of life.[22] A second phase 3 trial demonstrated improved 2-year overall survival.[23] A phase 3 study comparing decitabine with BSC showed improved overall response rate (ORR) and progression-free survival (PFS).[24]

MDS represents a significant hematologic malignancy of the elderly population, contributing to serious comorbidities and increased health care use and cost. Given the high prevalence of cardiac and other comorbidities in this patient population, and the strong association between comorbidities, transfusional support, and iron overload, strategies to improve anemia and maintain adequate iron balance are critical in managing patients with MDS.[2]

7.2. Summary of Nonclinical Studies

A brief summary of key findings from pharmacology and toxicology studies is provided below. A comprehensive review of ACE-536, as well as details regarding the information summarized below, is provided in the Investigators Brocure (IB). The ACE-536 IB should be reviewed prior to initating the study.

7.2.1. Pharmacology Studies

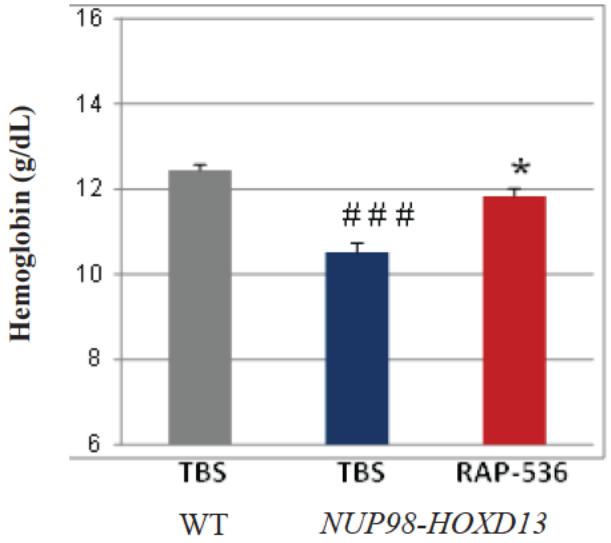
In vitro and in vivo pharmacology studies have been conducted with ACE-536 or its murine orthologue, RAP-536. The use of RAP-536 allows longer term pharmacology studies in rodents without the confounding influence of immune reactivity.

A total of 26 potential ligands within the TGFβ superfamily were assessed for their in vitro binding specificity and affinity to ACE-536 by surface plasmon resonance (Biacore). Among the ligands examined, GDF8, GDF11, BMP6 and activin B bound to ACE-536 with the highest affinities at 37°C (K_D values in the sub-nanomolar range). Further studies using a cell line reporter gene assay to assess signaling through the activin receptor demonstrate that signaling by GDF11 and GDF8 was inhibited by ACE-536.

During the course of early nonclinical pharmacology studies, an observation of a rapid, robust, and sustained increase in erythropoiesis in animals treated with ACE-536 was made. The effect of ACE-536 on bone marrow erythroid progenitor cells in mice was assessed by FACS analysis. Results demonstrate that the increase in RBC results as a consequence of a decrease of basophilic erythroblasts and a coordinate increase in subsequent, later stage polychromatic and orthochromatic erythroblasts as well as nucleated reticulocytes in both the bone marrow and spleen. Separate studies have confirmed that the increase in RBC occurs without affecting the populations of erythropoietin (EPO) responsive cells (BFU-E and CFU-E).

RAP-536 was evaluated for its ability to improve dyserythropoiesis in the *NUP98-HOXD13* mouse model of MDS.[25] Over 20 chromosomal translocations involving the NUP98 gene have been identified across a number of hematologic malignancies in humans. Among these, the NHD13 fusion gene has been reported in patients with MDS and acute myeloid leukemia (AML). The *NUP98-HOXD13* mouse model reliably recapitulates many of the features of MDS in humans, including peripheral blood cytopenias, bone marrow dysplasia, apoptosis of bone marrow progenitor cells, and progression to acute leukemia in about 60% of the mice. Development and progression of MDS in *NUP98-HOXD13* mice is relatively rapid, resulted in a shortened lifespan of ~14 months. *NUP98-HOXD13* mice were treated with RAP-536 twice weekly for 6-8 weeks beginning at 4, 8 or 10 months of age, corresponding to early-, mid- and late-stage disease. Results demonstrate significant improvement in hematologic indices following RAP-536 treatment, independent of when treatment is initiated. Figure 1 illustrates the response to RAP-536 treatment in MDS mice. Further, ACE-536 treatment led to the normalization of the M:E ratio in MDS mice.

Figure 1: Hemoglobin Response to RAP-536 Treatment in MDS Mice (n=6/Group)



$p < 0.001$ vs. wild type; *$p < 0.05$ vs. Tris-buffered Saline (TBS)

7.2.2. Toxicology Studies

Repeat-dose toxicology studies of 1 and 3 month treatment duration have been conducted with ACE-536 in Sprague-Dawley rats and cynomolgus monkeys to evaluate the toxicity of ACE-536. Recovery periods of up to 10 weeks were included as part of these studies. Findings from toxicology studies, described in more detail in the Investigator's Brochure, were different between rats and monkeys, though the expected pharmacologic effects of the drug were observed in both species.

ACE-536 exhibited favorable and predictable pharmacokinetic properties in both species. Serum concentrations of ACE-536 followed first-order absorption and first-order elimination kinetics after the first dose. The PK profiles of ACE-536 were similar among males and females, independent of dose level, and achieved peak or near peak mean serum concentrations at approximately 4 days in rats and 2-3 days in monkeys. The C_{max} and AUC were linear and approximately proportional to dose up to the highest dose levels evaluated. The serum terminal elimination half-life in rat is approximately 5 days and in monkey is 6-7 days, and clearance is independent of dose level and route of administration (SC vs IV).

Key findings identified in the 1- and 3-month rat toxicology studies included decreased heart, lung and prostate weight with no histopathology correlate, adrenal gland necrosis/congestion, and minimal liver necrosis. Mineralization of the lamina propria in the glandular portion of the stomach was only observed in the 1-month rat study. Membranoproliferative glomerulonephritis was observed histologically and immunochemistry (IHC) of kidney sections identified granular deposits containing ACE-536, rat IgG and/or complement in typical sites of histologically altered glomeruli that is suggestive of immune complex deposition. Increased BUN and creatinine were also seen. This kidney finding is believed to be associated with anti-drug antibodies and immune complex deposition; however, a direct drug mediated effect cannot be excluded.

In the three month monkey study, there was a dose dependent increase in BUN and creatinine. Histologic changes in the kidney consisted of membranoproliferative glomerulonephritis. This finding was dose dependent in both incidence and severity and was not sex dependent. At the highest dose (30 mg/kg), glomerulonephritis was accompanied by fibrosis and hemorrhage of the interstitium. The presence of immune complexes in renal tissue was demonstrated by immunohistochemistry and is suggestive of immune complex deposition; however, a direct effect of the drug cannot be excluded.

7.3. Summary of Clinical Experience

The safety, tolerability, pharmacokinetics, and pharmacodynamic effects of ACE-536 was evaluated in healthy postmenopausal women in a phase 1, randomized, double-blind, placebo-controlled, multiple ascending dose study (Study A536-02). The primary objective of the study was to evaluate the safety and tolerability of ACE-536 in this population. Secondary objectives of the study are to examine the pharmacokinetic parameters and pharmacodynamic effects of ACE-536. Preliminary data from Study A536-02 as of 05 July 2012 are summarized below.

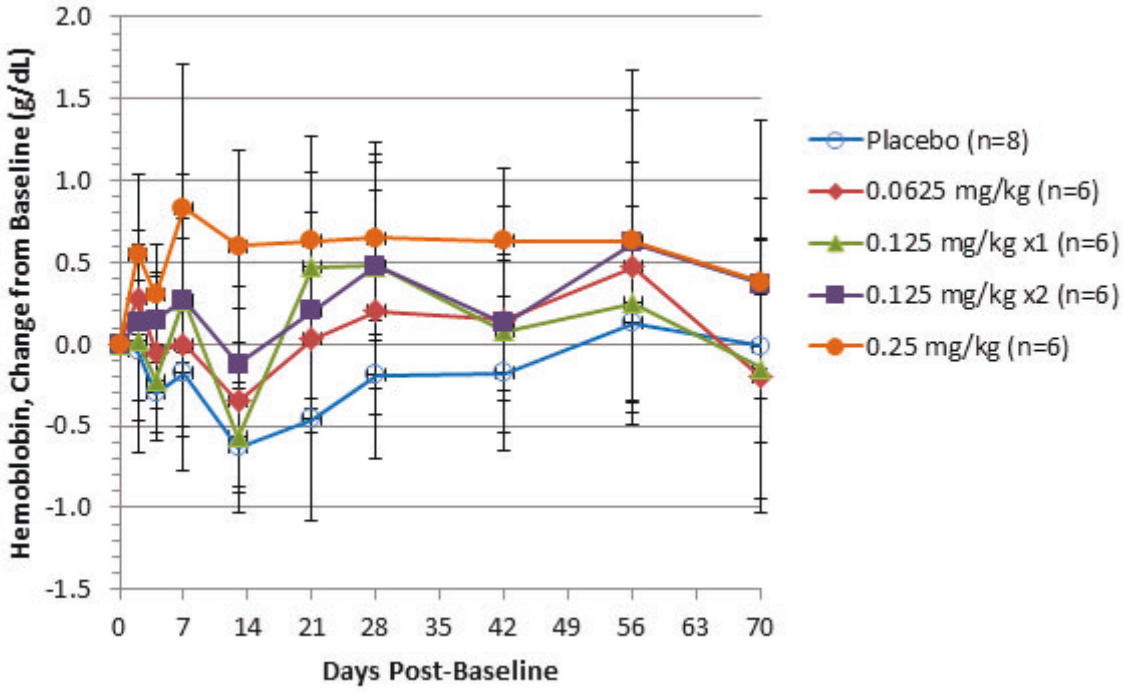
A total of 32 subjects were enrolled. The study consisted of 4 cohorts (0.0625 mg/kg x 2 doses, 0.125 mg/kg x 1 dose, 0.125 mg/kg x 2 doses, and 0.25 mg/kg x 2 doses). Subjects in each cohort were randomized and receive either ACE-536 or placebo (6 active and 2 placebo subjects per cohort). Doses were administered SC on Day 1 and Day 15. One subject in the third cohort and 5 subjects in the fourth cohort received only one dose of ACE-536.

The mean (SD) age for subjects in this study was 59.4 (5.8) years. Mean baseline hemoglobin level was 13.2 (0.6) g/dL. Preliminary analysis of PK data demonstrated that maximum ACE-536 concentration (C_{max}) and area under the curve ($AUC_{0\text{-}14d}$) after the first dose were generally dose-proportional from 0.0625 to 0.25 mg/kg. The mean time to maximum concentration (t_{max}) ranged from 7.7 to 11.7 days and the mean elimination half-life ($t_{½}$) ranged from 15.5 to 18.5 days. Pharmacokinetic results support SC dosing of ACE-536 every 3 weeks.

ACE-536 was generally safe and well-tolerated in this study of healthy postmenopausal female subjects. No serious or severe adverse events were reported. The majority of AEs were considered mild in severity. Adverse events that were considered probably or possibly related to study drug included injection site hemorrhage (3 subjects on active drug), injection site macule (2 subjects), and dry skin, hyperesthesia, muscle spasms, myalgia, generalized pruritis, and papular rash (1 subject each).

Consistent with results from the nonclinical pharmacology studies, ACE-536 administration resulted in a mean maximum increase in hemoglobin (at any timepoint during the study) of 1.3 g/dL in the 0.25 mg/kg group. The maximum hemoglobin increase from baseline at any timepoint for patients in the 0.25 mg/kg group ranged from 0.6 to 2.0 g/dL. The mean hemoglobin increase from baseline in that treatment group was at least 0.6 g/dL from Day 8 through Day 57, compared with a mean hemoglobin decrease from baseline in the placebo group of up to 0.6 g/dL through Day 43 (Figure 2).

Figure 2: Mean (±SD) Change from Baseline of Plasma Hemoglobin (g/dL) in Healthy Volunteers Treated with One or Two Doses of ACE-536



The preliminary results from this phase 1 study suggest a positive effect of 0.25 mg/kg ACE-536 on increasing hemoglobin in healthy subjects. Doses up to 0.25 mg/kg were generally safe and well-tolerated.

7.4. Potential Risks of Human Use

Increases in hematologic parameters (RBC, hemoglobin, hematocrit, reticulocytes) are expected pharmacologic effects of ACE-536 treatment. Increases in systolic and diastolic blood pressures may occur in concert with increases in hemoglobin values. Excessive or rapid increases in hemoglobin or blood pressure may occur and will be monitored. Dose modifications rules for individual subjects and dose escalation/reduction rules will be utilized to minimize risks associated with increased RBC parameters.

Adverse events observed in the Phase 1 study in healthy volunteers that were considered probably or possibly related to study drug included injection site hemorrhage, injection site macule, and dry skin, hyperesthesia, muscle spasms, myalgia, generalized pruritis, and papular rash.

Membranoproliferative glomerulonephritis was observed in both rats and monkeys, likely secondary to immune complex deposition. These findings were associated with increases in serum BUN and creatinine. The presence of immune complexes in renal tissue from monkeys treated with ACE-536 was demonstrated by immunohistochemistry.

The growth of heart and lungs was slightly reduced in rats exposed to ACE-536 as compared with control animals; these decreased heart and lung weights were reversible and there was no

corresponding histology finding. These findings were not replicated in the monkey toxicology studies; the potential for these adverse effects in humans is unknown.

Based on rat toxicology studies, treatment with ACE-536 may affect the adrenal gland. These findings were specific to the rat as they were not replicated in the monkey toxicology studies.

As with all biologics, there is the potential for anti-drug antibodies that can be associated with increased drug clearance and hypersensitivity reactions. Anti-drug antibody formation against ACE-536 as well as human ActRIIB protein will be monitored in the initial clinical studies.

Reproductive toxicity studies are currently ongoing and therefore ACE-536 should not be administered to pregnant women. Male and female subjects of childbearing potential participating in studies of ACE-536 must be willing to abstain from sexual intercourse or use adequate contraception during the treatment and for at least 12 weeks following treatment discontinuation. The effects of ACE 536 on the developing fetus are unknown. It is not known if ACE-536 is secreted in milk; therefore, ACE-536 should not be administered to nursing mothers.

It is unknown if humans will experience any of the effects of ACE-536 that were noted in the rat and monkey toxicology studies. Safety effects will be monitored closely through adverse event reporting, clinical laboratory tests, vital signs, and physical examinations.

A comprehensive review of ACE-536, as well as details regarding the information summarized above, is provided in the Investigators Brocure (IB). The ACE-536 IB should be reviewed prior to initating the study.

8. TRIAL OBJECTIVES

8.1. Primary Objective

- To evaluate the proportion of patients who have a modified erythroid response (mHI-E), defined as a hemoglobin increase of ≥ 1.5 g/dL from baseline for ≥ 14 days (in the absence of red blood cell [RBC] transfusions) in non-transfusion dependent patients, or, a reduction of either ≥ 4 units or ≥ 50% of units of RBCs transfused compared to pre-treatment in transfusion dependent patients.

8.2. Secondary Objectives

- To evaluate safety and tolerability of ACE-536
- To examine rates of erythroid, neutrophil and platelet (HI-E, HI-N and HI-P) responses (International Working Group [IWG] 2006 criteria)
- To evaluate time to mHI-E and HI-E response and duration of mHI-E and HI-E response
- To evaluate frequency of RBC transfusions in transfusion dependent patients
- To examine the pharmacokinetic (PK) profile of ACE-536
- To examine other pharmacodynamic (PD) effects (e.g., iron metabolism, erythropoietin, reticulocytes, and bone biomarkers)

8.3. Exploratory Objective

- To evaluate biomarkers related to the TGFβ superfamily
- Evaluation of self-reported quality of life in the expansion cohort using tools including but not limited to the FACT-An questionnaire

9. OVERALL STUDY DESIGN AND PLAN: DESCRIPTION

This is a phase 2, open-label, multiple ascending dose study to evaluate the effects of ACE-536 on anemia in patients with low or intermediate-1 risk MDS who are not currently receiving treatment with an erythropoiesis-stimulating agent (ESA).

9.1. Study Design

Patients who meet the study eligibility criteria will be enrolled within 28 days of screening. Patients in all cohorts will receive ACE-536, 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 Patient Dose Modification Rules (Section 10.8.1).

Each dose escalation cohort will consist of a minimum of 3 patients. The dose level of ACE-536 for the first cohort will be 0.125 mg/kg and the dose level(s) for subsequent cohort(s) will follow a modified Fibonacci dose escalation scheme with a maximum dose level of 0.25 mg/kg for cohort 2, 0.50 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. Once a minimum of 3 patients in a cohort have completed Study Day 29, the Safety Review Team (SRT) will review preliminary safety and hematologic response data and make recommendations to the Sponsor regarding whether or not to enroll an additional 3 patients in that cohort, enroll a new cohort at a higher or lower dose, or proceed to expansion cohort 1.

Expansion cohort 1 (n= approximately 30) will be treated with ACE-536 at a starting dose level of 1.0 mg/kg. Expansion cohort 1 will consist of a minimum of 10 patients who are transfusion dependent (TD) and 10 patients who are non-transfusion dependent (NTD), if feasible.

Expansion cohort 2 will be treated with ACE-536 at a starting dose level of 1.0 mg/kg. Expansion cohort 2 will be divided into two groups designated expansion cohort 2A and 2B. The targeted accrual for each group will be 25 eligible and evaluable patients but permitted to range from 22 to 28 for administrative reasons. The maximum number of patients treated will be 56.

- Expansion cohort 2A: NTD patients with ≥ 15% ring sideroblasts in the bone marrow (RS+), less than 4 weeks of exposure to erythropoietin stimulating agents (ESAs) and serum erythropoietin (EPO) level ≤ 200 U/L at screening.
- Expansion cohort 2B: Patients with < 15% ring sideroblasts in the bone marrow (RS-) and ≤ 6 RBC units in 8 weeks prior to C1D1. This group will consist of a minimum of 10 patients who have less than 4 weeks of exposure to ESAs and 5 patients who have received ≥ 4 weeks of treatment with ESAs.

In the expansion cohorts, a patient's dose level may be titrated based on criteria listed in Section 10.8.2 , Expansion Cohorts Patient Dose Titration. The maximum dose level given to a patient will not exceed the maximum dose level evaluated in the dose escalation cohorts. Patients in the expansion cohort will be treated with up to 5 doses of ACE-536 administered once every 3 weeks.

Table 2: Dose Escalation

Cohort[a]	ACE-536 Dose Level[b] (mg/kg)	Number of Patients
1	0.125	3-6
2	0.25	3-6
3	0.50	3-6
4	0.75	3-6
5	1.0	3-6
6	1.33	3-6
7	1.75	3-6
Expansion 1	1.0	30
Expansion 2	1.0	up to 56
Planned Total:		**up to 128**

[a] Cohort escalation is based on SRT review and recommendation to enroll additional cohorts and/or the expansion cohort.

[b] The ACE-536 dose level for cohort 1 is 0.125 mg/kg. The dose level indicated for all subsequent dose escalation cohorts is the maximum dose level that can be recommended by the SRT for escalation per the modified Fibonacci dose escalation scheme. Dose escalation will not exceed 1.75 mg/kg.

9.2. Discussion of Study Design

The efficacy assessment based on modified IWG criteria for erythroid response (mHI-E) was selected for this study as a variation of the accepted and widely used endpoint for the evaluation of therapies in patients with MDS, appropriate for short-term studies. This was selected as the primary endpoint due to the unknown optimal dosing interval for ACE-536 to produce a sustained response and the desire to identify the minimal safe dose level producing any erythroid response. The standard HI-E criteria for response will be evaluated as a secondary endpoint.

The initial dose level of 0.125 mg/kg is less than the maximum dose administered in the phase 1 study A536-02 of 0.25 mg/kg, which was safe and well tolerated, and produced a hemoglobin response in healthy volunteers. The safety measurements are standard for studies with investigational medications. An open-label study, conducted in a limited number of patients, with protocol-specified definitions of dose-limiting toxicity, and with protocol-specified procedures for dose escalation and reduction is considered appropriate for a proof-of-concept study in this target patient population. Dose escalation in sequential cohorts is designed to minimize the risk of excessive erythroid response and hypertension that may result from a robust response to high drug levels. Individualization of dose level in the expansion cohorts, using dose titration rules based on hemoglobin response and dose reduction rules based on safety information will maximize the proportion of patients having an erythroid response while maintaining safety.

9.3. Selection of Study Population

9.3.1. Inclusion Criteria

Eligible patients must meet **all** of the following criteria:

1. Men or women ≥ 18 years of age.
2. Documented diagnosis of idiopathic/de novo MDS or non-proliferative chronic myelomonocytic leukemia (CMML) according to WHO criteria (white blood count [WBC] < 13,000/μL) that meets IPSS classification (Appendix 2) 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 (CBC) obtained during screening.
3. Anemia defined as:
   - Mean hemoglobin concentration < 10.0 g/dL of 2 measurements (one performed within one day prior to Cycle 1 Day 1 and the other performed 7-28 days prior to Cycle 1 Day 1, not influenced by RBC transfusion within 7 days of measurement) for non-transfusion dependent patients (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 (transfusion dependent patients are allowed in dose escalation cohorts and expansion cohort 1 only; patients with ≤ 6 units of RBCs within 8 weeks prior to Cycle 1 Day 1 may be allowed in cohort 2B) .
4. Serum erythropoietin levels and prior erythropoiesis-stimulating agent (ESA) treatment:
   - Dose escalation cohorts and expansion cohort 1 patients: Serum erythropoietin level > 500 U/L, OR, if ≤ 500 U/L, patient is non-responsive, refractory, or intolerant to erythropoiesis-stimulating agents (ESAs), or ESAs are contraindicated or unavailable.
   - Expansion cohort 2 patients: If patient is RS+ (defined as having ≥ 15% ring sideroblasts in the bone marrow), has less than 4 weeks' exposure to ESAs and serum erythropoietin level ≤ 200 U/L. If a patient is RS- (defined as having < 15% ring sideroblasts in the bone marrow), prior ESA treatment and any serum erythropoietin level is allowed
5. No alternative treatment options, per national MDS guidelines, are available and/or appropriate for the patient, at the discretion of the investigator.
6. ECOG performance status of 0, 1, or 2 (if related to anemia).
7. Adequate renal (creatinine ≤ 2.0 x upper limit of normal [ULN]) and hepatic (total bilirubin < 2 x ULN and AST and ALT < 3 x ULN) function.

8. Adequate transferrin saturation (≥ 15%), ferritin (≥ 50 µg/L), folate (≥ 4.5 nmol/L [≥2.0 µg/L]) and vitamin B12 (≥ 148 pmol/L [≥ 200 pg/mL]) during screening (supplementation and retest during screening is acceptable).
9. Females of child bearing potential (defined as sexually mature women who have not undergone hysterectomy or bilateral oophorectomy, or are not naturally postmenopausal ≥ 24 consecutive months) must have negative urine or blood pregnancy test prior to enrollment and use adequate birth control methods (abstinence, oral contraceptives, barrier method with spermicide, or surgical sterilization) during study participation and for 12 weeks following the last dose of ACE-536. Males must agree to use a latex condom during any sexual contact with females of child-bearing potential while participating in the study and for 12 weeks following the last dose of ACE-536, even if he has undergone a successful vasectomy. Patients must be counseled concerning measures to be used to prevent pregnancy and potential toxicities prior to the first dose of ACE-536.
10. Patients are able to adhere to the study visit schedule, understand and comply with all protocol requirements.
11. Patient understands and is able to provide written informed consent.

9.3.2. Exclusion Criteria

Eligible patients must not meet **any** of the following criteria.

1. Prior treatment with azacitidine (injectable or oral) or decitabine.
2. Treatment within 28 days prior to Cycle 1 Day 1 with:
   - Erythropoiesis stimulating agent (ESA),
   - Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF),
   - 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 may be longer.
5. Major surgery within 28 days prior to Cycle 1 Day 1. Patients must have completely recovered from any previous surgery prior to Cycle 1 Day 1.
6. Platelet count < 30 x 10^9/L.
7. Any active infection requiring parenteral antibiotic therapy within 28 days prior to Cycle 1 Day 1 or oral antibiotics within 14 days of Cycle 1 Day 1.
8. History of stroke, deep venous thrombosis (DVT) or arterial embolism within 6 months prior to Cycle 1 Day 1.
9. Known positive for human immunodeficiency virus (HIV), active infectious hepatitis B (HBV) or active infectious hepatitis C (HCV).

10. Any malignancy other than MDS which has not been in remission and/or has required systemic therapy including radiation, chemotherapy, hormonal therapy or surgery, within the last year prior to Cycle 1 Day 1.
11. Uncontrolled hypertension defined as systolic blood pressure (BP) ≥ 150 mm Hg or diastolic BP ≥ 100 mm Hg.
12. Pregnant or lactating females.
13. History of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the investigational drug.
14. Any other condition not specifically noted above which, in the judgment of the investigator, would preclude the patient from participating in the study.
15. Transfusion event within 7 days prior to Cycle 1 Day 1.
16. Prior treatment with sotatercept (ACE-011), or ACE-536.
17. Secondary MDS.

9.4. Patient Treatment Discontinuation and Withdrawal Criteria

Patients will be informed that they have the right to discontinue treatment and/or withdraw from the study at any time for any reason without prejudice to their medical care.

A patient may be discontinued from treatment for any of the following reasons:

- Patient's request
- Patient's unwillingness or inability to comply with the protocol
- Pregnancy
- Use of prohibited medication (e.g., ESA)
- Medical reason or adverse event, at the discretion of the investigator and/or the medical monitor
- Lack of effect (e.g., worsening anemia for NTD patients as evidenced by sustained reduction in Hgb by ≥ 2 g/dL over 8 weeks or transfusion dependence), to be discussed with the medical monitor
- Disease progression (any of the following):
  - For patients with <5% blasts at baseline: ≥ 50% increase in blasts to > 5% blasts
  - For patients with 5-10% blasts at baseline: ≥ 50% increase in blasts to > 10% blasts

    (For patients with 5-10% blasts, a 2nd bone marrow sample may be collected within 4 weeks to confirm progression before discontinuing patients from treatment)
- Hypersensitivity reaction to study drug
- At the discretion of the sponsor (e.g., termination of the study or a dose level)

A patient may be withdrawn from the study for any of the following reasons:

- Patient's request
- Patient's unwillingness or inability to comply with the protocol
- Death
- Loss to follow-up
- At the discretion of the sponsor (e.g., termination of the study)

The reasons for study withdrawal and/or treatment discontinuation must be recorded in the patient's CRF. The investigator must notify the sponsor, the medical monitor and the contract research organization (CRO) immediately when a patient has been discontinued/withdrawn due to an AE. Patients who discontinue treatment early should complete the end of treatment (EOT) follow-up visit at the time of discontinuation and then complete the post-treatment follow-up (PTFU) and end of study (EOS) follow-up visits approximately 28 and 56 days later, respectively.

The investigator must notify the sponsor and the CRO when a patient has been discontinued/withdrawn for reasons unrelated to the study or study drug (e.g., withdrawn consent, lost to follow up).

10. TREATMENT OF PATIENTS

10.1. Selection and Timing of Dose for Each Patient

Once a patient is enrolled, the appropriate dose of ACE-536 will be administered as a subcutaneous injection on Cycle 1 Day 1. Subsequent doses will be administered every 3 weeks on Day 1 of the cycle. Study day 85 ± 2 days is the last possible study day that ACE-536 can be administered, regardless of the cycle. Dose reductions may be required for individual patients as outlined in the Patient Dose Modifications Rules (Section 10.8.1). If a dose delay is required, the patient will return weekly for assessment of hematology results and adverse events until the patient is eligible to receive the next dose of ACE-536. Patients will be asked to return to the clinic for three follow up visits, occurring approximately 28, 56, and 84 days after their last dose of ACE 536. If a patient has a positive anti-drug antibody (ADA) result at the last visit, the patient may be asked to return for additional ADA testing every three months, until a negative result is obtained or the result is considered to be stabilized.

10.2. Concomitant Medications

During screening and throughout the study, patients may take stable doses of medications for chronic conditions that are not specifically excluded by the protocol (see Section 9.3.1 Inclusion Criteria and Section 9.3.2 Exclusion Criteria). If a patient requires treatment with any new medications that are specifically excluded by the eligibility criteria, the patient will be discontinued from the study and should complete the end of treatment visit and enter the follow-up period of the study. The investigator should consult the medical monitor regarding any questions about whether a new medication or dosage of existing medication would require the patient to discontinue from the study. Concomitant medications will be collected beginning at study screening and will include all medications taken within 28 days prior to Cycle 1 Day 1.

10.2.1. Other Treatments for MDS

If treatment with azacitidine, decitabine, lenalidomide, ESA, or G-CSF is required during the ACE-536 treatment period, the patient should be discontinued from treatment with study drug and complete the end of treatment visit and enter the follow up period. Iron chelation therapy is allowed unless initiated within 56 days prior to C1D1.

10.2.2. RBC Transfusions

For the first dose of ACE-536, dosing should occur after a minimum of 7 days post-transfusion and prior to any scheduled transfusions. Each TD patient will have a "pre-transfusion hemoglobin threshold" for requiring transfusion, which will be calculated based on transfusion history and will be used for determining when to transfuse during the study. The baseline pre-transfusion hemoglobin threshold will be the mean of all documented pre-transfusion hemoglobin values during the 12 weeks prior to C1D1. During treatment, if the pre-transfusion hemoglobin level is increased by ≥ 1 g/dL compared to the baseline pre-transfusion hemoglobin threshold for that patient, transfusion should be delayed by a minimum of 7 days and/or the number of units transfused should be reduced by 1 or more RBC units. Patients

should not be transfused if hemoglobin is ≥ 9 g/dL unless indicated for symptoms related to anemia or other reasons at the investigator's discretion.

10.3. Treatment Compliance

ACE-536 will be administered as a SC injection at the clinical site by the study staff and will be documented in the study record. Monitoring for patient compliance with the treatment regimen is therefore unnecessary.

10.4. Randomization

This is an open-label study and a randomization scheme is not needed for this study.

10.5. Treatments Administered

Patients will continue to receive the same dose level of study drug as they were assigned at study entry unless a dose modification is required (see Section 10.8, Patient Dose Modification Rules).

10.6. Dose-Limiting Toxicity Definition

A Dose-Limiting Toxicity (DLT), using the current active minor version of the National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0 (NCI-CTCAE v4.0), is defined as any of the following toxicities, at any dose level occurring within 28 days of the first administered dose:

- Treatment-related serious adverse event (SAE) of Grade ≥ 3
- Treatment-related non-hematologic and non-infectious adverse event (AE) of Grade ≥ 3
- Treatment-related hematologic or infectious AE of Grade ≥ 4

10.7. Safety Evaluation and Dose Escalation

Safety will be evaluated by the Safety Review Team (SRT), which is comprised at minimum of the coordinating investigator, medical monitor, and an independent hematologist. The role of the SRT will be described in greater detail in the SRT Charter. The SRT will review safety data when a minimum of 3 patients in a cohort have completed Study Day 29, including dose-limiting toxicities (DLTs), adverse events (AEs), serious adverse events (SAEs), laboratory results (including hematology and chemistry), vital signs, and erythroid response data. The SRT may make one or more of the following recommendations to the sponsor:

- Enroll 3 additional patients in the current cohort.
- Enroll 3 patients in a new cohort at a higher or lower dose level, not to exceed modified Fibonacci dose escalation scheme (see Section 9.1).
- Proceed to expansion cohort 1, with a recommended starting dose level not to exceed the maximum dose level evaluated in the dose escalation cohorts.
- Postpone a decision pending collection of additional data from the current cohort.

SRT recommendations to escalate or reduce the dose level of ACE-536 in a subsequent cohort or to continue dosing in the current cohort will be based in part upon the following criteria:

- If a DLT occurs in 0 out of a minimum of 3 patients in a cohort within 28 days following the initial dose, dose escalation may occur.
- If a DLT occurs in 1 out of 3 patients in a cohort within 28 days following the initial dose, an additional 3 patients should be enrolled in the current cohort.
    - If a DLT occurs in 1 out of 6 patients in a cohort within 28 days following the initial dose, dose escalation may occur.
- If a DLT occurs in ≥ 2 patients in a cohort within 28 days of the initial dose, the dose level for the next cohort (if any) should not be escalated; a lower dose level may be recommended.
- If a hemoglobin increase of ≥ 2.0 g/dL occurs in ≥ 2 patients in a cohort within 28 days of the initial dose, the dose level for the next cohort (if any) should not be escalated; a lower dose level may be recommended.

In addition, during enrollment of the expansion cohorts, the SRT will review safety data periodically throughout the trial, including AEs, SAEs, laboratory results (including hematology and chemistry), vital signs, and erythroid response data.

10.8. Patient Dose Modification and Titration

Patients in the dose escalation cohorts have a pre-determined starting dose based on cohort number (see modified Fibonacci Dose Escalation Scheme, Section 9.1). Dose level titration (i.e., increase) is not allowed for patients in the escalation cohorts, but dose delay or reduction may be required according to Patient Dose Modification Rules (Section 10.8.1). Examples of dose level reductions for patients in dose escalation cohorts are included in Table 3 below.

All patients in the expansion cohorts will be initially treated with ACE-536 at a starting dose level of 1.0 mg/kg, which has been deemed to be safe, well tolerated, and at least minimally effective by the SRT. The expansion cohorts starting dose level and associated modifications (reductions and titrations) are in Table 3. Rules for reductions and titrations are described in Section 10.8.1 and Section 10.8.2.

Table 3: Starting Dose Levels, Dose Level Reductions (All Cohorts), and Dose Level Titrations (Expansion Cohorts Only)

2nd Dose Reduction	1st Dose Reduction	Starting Dose Level	1st Dose Titration	2nd Dose Titration
0.125 mg/kg	0.25 mg/kg	0.50 mg/kg	0.75 mg/kg	1.0 mg/kg
0.25 mg/kg	0.5 mg/kg	0.75 mg/kg	1.0 mg/kg	1.33 mg/kg
0.5 mg/kg	0.75 mg/kg	**1.0 mg/kg[a,b]**	1.33 mg/kg[a]	1.75 mg/kg[a,c]
0.75 mg/kg	1.0 mg/kg	1.33 mg/kg	1.75 mg/kg[c]	N/A
1.0 mg/kg	1.33 mg/kg	1.75 mg/kg[c]	N/A	N/A

[a] Dose titration is only applicable to patients in the expansion cohorts.

[b] Expansion cohorts starting dose level is 1.0 mg/kg

[c] Dose titration will not exceed 1.75 mg/kg, which is the maximum dose level tested in the dose escalation cohorts and determined to be safe and well tolerated by the SRT.

N/A = Not Applicable.

10.8.1. Patient Dose Modification Rules

The following dose modification rules include both pharmacodynamic and safety parameters which may require a dose delay and possibly a dose reduction. These rules should be assessed prior to dosing. If a dose delay is required the patient should have weekly visits to assess hematology results and adverse events until the patient is eligible to receive the next dose of ACE-536.

Table 4: Patient Dose Modification Rules

Observation on Dosing Day	Action	ACE-536 Dose Modification[a]
Hemoglobin ≥ 12 g/dL	Hold dose and monitor patient weekly until hemoglobin < 11 g/dL	Resume dosing once hemoglobin < 11 g/dL
Hemoglobin ≥ 2 g/dL increase from the previous dosing day (not attributable to RBC transfusion)	Continue dosing	Reduce the dose by 1 dose level[a]
Non-hematologic adverse event ≥ Grade 3, at least possibly related to study drug	Hold dose and monitor patient weekly until resolution of AE to ≤ Grade 1 or baseline	Resume dosing upon resolution of the AE to ≤ Grade 1 or baseline, and reduce the dose by 1 dose level[a,b]
White blood cell (WBC) count ≥ 13,000/µL[c]	• Dose delay until WBC < 13,000/µL and resolution of associated condition (e.g., infection) within 6 weeks • Discontinue treatment if WBC ≥ 13,000/µL persists for more than 6 weeks • Discontinue treatment if clinically significant cytomorphologic changes on bone marrow aspirate compared to baseline.	

[a] Dose level refers to dose levels listed in Table 3.
[b] Patients who require more than 2 dose reductions due to an AE should be discontinued from treatment and complete the EOT, PTFU and EOS visits.
[c] The investigator may contact the medical monitor and forward appropriate supporting documents for review and discussion prior to making decision regarding treatment discontinuation.

10.8.2. Expansion Cohorts Patient Dose Titration

For the expansion cohorts, the starting dose level to be administered on Cycle 1 Day 1 will be 1.0 mg/kg. The starting dose level with the associated dose reductions and titrations are shown in Table 3. The dose level should be titrated individually for each patient, not to exceed the maximum dose level tested of 1.75 mg/kg. Please note that all dose modification rules (i.e., dose delay and reduction rules in Section 10.8.1) supersede all dose titration rules.

For NTD patients, the dose level will be assessed for titration beginning at C3D1. Dose titration rules are as follows, using dose levels in Table 3.

- If hemoglobin increase from baseline is < 1.5 g/dL throughout the previous two cycles at a single dose level, the dose level should be increased by 1 dose level.

- If hemoglobin increase from baseline is ≥ 1.5 g/dL but not sustained for at least two consecutive study measurements during the previous two cycles at a single dose level, the dose level should be increased by 1 dose level.
- If hemoglobin increase from baseline is ≥ 1.5 g/dL (not influenced by RBC transfusion) on two or more consecutive study measurements during the previous two cycles, the dose level should remain unchanged.

For TD patients, the dose level will be assessed for titration beginning at C3D1. Dose titration rule is as follows, using dose levels in Table 3.

- Rate of transfusion is the number of units of RBCs transfused over a defined period of time. If no decrease from baseline in the rate of transfusion over the previous two cycles, the dose should be increased by 1 dose level.

The SRT will meet periodically to monitor overall safety and erythroid response data for the expansion cohorts.

10.9. Other Considerations for Dose Modification, Delay or Discontinuation

For individual patients judged by the investigator to be at an unacceptable risk, but who do not meet the protocol-defined conditions for a dose modification or interruption, the investigator should consult with the medical monitor to decide whether to continue dosing at the same dose level, reduce the dose level, delay the patient's dose, or discontinue the patient's treatment with ACE-536.

11. STUDY PROCEDURES

Please refer to Section 2, Schedule of Events for the schedule of procedures required for each visit.

11.1. Written Informed Consent

Patients will be required to sign an IEC approved ICF prior to any study related procedures, including screening evaluations.

11.2. Clinical Laboratory Tests

The following laboratory assessments will be performed at the clinical site's local laboratory according to the laboratory collection recommendations. The sponsor may request additional safety tests be performed based on ongoing data review during the study.

- Hematology: RBC, WBC with differential, hemoglobin, hematocrit, reticulocyte count, platelet count, MCV, MCH, MCHC, and RDW.
- Serum chemistry: Sodium, potassium, AST, ALT, lactate dehydrogenase (LDH), total bilirubin, direct bilirubin, alkaline phosphatase, blood urea nitrogen (BUN)/urea, creatinine, GGT, calcium, phosphorus, glucose, amylase, lipase, total protein, albumin, and uric acid.
- Urinalysis by dipstick analysis: pH, specific gravity, protein, glucose, ketones, blood, leukocyte esterase, and nitrite, with microscopic examination if indicated.
- Pregnancy test: women of child bearing potential must have a negative pregnancy test at screening and prior to administration of ACE-536 on each dosing day.
- Screening visit only: serum folate and B_{12}

The following laboratory assessments will be performed at the central laboratory according to the laboratory collection recommendations. The sponsor may request additional safety tests be performed based on ongoing data review during the study.

- Iron studies: Serum iron, TIBC, transferrin, soluble transferrin receptor, ferritin, NTBI and hepcidin.
- Nucleated RBC
- Erythropoietin levels
- Peripheral blood smear
- Urine microalbumin and creatinine
- Bone Biomarkers: serum BSAP and CTX (not collected for expansion cohort 2 patients).

11.3. Other Safety Assessments

- Physical examination
- Vital signs: weight, heart rate, systolic and diastolic blood pressure, respiration rate and temperature (measured in degrees Celsius). Height is measured only at screening.
- ECOG Status
- 12-lead ECG
- Anti-drug antibody testing
- The occurrence of a new malignancy or premalignant lesion will be monitored as an event of interest and should be included as part of the assessment of adverse events throughout the course of the study. Investigators are to report the development of any new malignancy or premalignant lesion as a serious adverse event, regardless of causal relationship to study drug, occurring at any time for the duration of the study, from the time of signing the ICF up to and including 3 months of follow up.

11.4. Pharmacokinetic and Pharmacodynamic Assessments

11.4.1. Pharmacokinetic Assessments

PK assessment of ACE-536 concentrations will be performed periodically as outlined in Section 2, (Schedule of Events). Blood samples should be drawn and processed on-site for serum collection at the time points specified. Additional details regarding PK collection and processing can be found in the Laboratory Manual.

11.4.2. Pharmacodynamic Evaluations

Pharmacodynamic assessments including hematologic laboratory assessments and transfusion information will be used to determine erythroid response to ACE-536.

Bone marrow biopsy and bone marrow aspirates will be performed for histology, cytogenetics, and morphology. Additional analyses may be included, such as flow cytometry to explore erythroid lineage markers and molecular testing to explore MDS-related genetic mutations.

Blood biomarkers for iron metabolism will include serum iron, TIBC, transferrin, soluble transferrin receptor, ferritin, NTBI, and hepcidin.

Biomarkers related to the TGFβ superfamily and/or iron metabolism, such as GDF15, GDF8, GDF11, and others may be tested in blood and/or bone marrow samples, to be determined.

The relationship of biomarkers to erythroid response may be investigated.

The sponsor may request additional biomarkers for exploratory research purposes only.

12. STUDY SCHEDULE

Please refer to Section 2, Schedule of Events for the schedule of procedures required for each visit. Note that all windows on visits should be determined relative to the date of the previous dose of ACE-536.

12.1. Screening

- Signature of the current IEC approved ICF should occur prior to initiation of any study-specific screening procedures.
- All screening procedures should occur within 28 days prior to Cycle 1 Day 1.
- Bone marrow aspirate and biopsy including cytogenetics must be performed within 3 months prior to Cycle 1 Day 1 for evaluation of patient eligibility.
- Historical hemoglobin and transfusion history will be collected for 24 weeks prior to Cycle 1 Day 1.
- Baseline hemoglobin will be calculated as the average of two measurements; one performed within one day prior to Cycle 1 Day 1, and the other performed 7-28 days prior to Cycle 1 Day 1. Neither hemoglobin measure should be influenced by transfusion within 7 days of measurement.
- Pregnancy test (urine or serum) is required of female patients of child bearing potential only.
- Concomitant medications taken within 28 days prior to Cycle 1 Day 1 will be documented in the CRF.
- Screen failure information will be maintained to document specific information, including but not limited to, reason for failure.
- For expansion cohort patients only, administration of quality of life questionnaires.

12.2. Dosing Days and Interim Visits

- All screening procedure results required to confirm eligibility must be obtained and reviewed prior to study drug administration. Patient eligibility must be confirmed from these results.
- For any RBC transfusions received during the study, the hemoglobin value just prior to transfusion should be collected.
- A patient will be considered enrolled into the study once a multi-digit patient identification number has been assigned to the patient. After assignment of the patient identification number and the completion of the required procedures, study drug administration may occur. Note that the patient dose must be calculated based on the patient's weight on the day of dosing.
- Negative pregnancy test (urine or serum) is required of female patients of child bearing potential prior to administration of ACE-536 on each dosing day.

- All study procedures on each dosing day must be done prior to administration of study drug.
- For the first dose of ACE-536, dosing should occur after a minimum of 7 days post-transfusion and a minimum of 24 hours prior to a scheduled transfusion. Patients should be observed for a minimum of 30 minutes following treatment with ACE-536.
- If a dose delay is required per the dose modification rules (Section 10.8.1), the patient will not be dosed. The patient will return weekly for assessment of hematology results and adverse events until the patient is eligible to receive the next dose of ACE-536. The patient should resume the study at the planned dosing cycle (e.g. if the patient missed a dose at C4D1, then they would resume dosing at C4D1 and not skip to C5D1).
- The hematology results can be collected up to 24 hours prior to the dosing day. For Cycle 1 Day 1, the hemoglobin should be available to confirm eligibility within one day prior.
- For dose escalation cohort and expansion cohort 1 patients, a bone marrow aspirate must be performed within 21 days after C3D1 (a bone marrow biopsy is not required). Note: a bone marrow aspirate is not required within 21 days after C3D1 for expansion cohort 2 patients.
- Any non-serious AEs that occur prior to dosing in cycle 1 should be recorded in the Medical History section of the CRF.
- All AEs that occur after dosing in Cycle 1 should be recorded in the AE page of the CRF.
- On subsequent dosing days, all AEs and abnormal findings that might require modification of dosing (see Section 10.8.1) should be reviewed prior to dosing to ensure that the patient is still eligible to receive additional doses of ACE-536.

12.3. Day 85

- Day 85 ± 2 days is the last possible study day that ACE-536 may be administered, regardless of the cycle.
- For expansion cohort 1 patients only, administration of quality of life questionnaires. Not required for expansion cohort 2 patients.

12.4. End of Treatment Visit

- The end of treatment visit should occur approximately 28 days after the last dose of ACE-536.
- Patients who discontinue treatment early should complete the end of treatment visit at the time of discontinuation.
- Patients who discontinue treatment early and all expansion cohort 2 patients should complete the quality of life questionnaires at the end of treatment visit.

- A bone marrow aspirate must be performed at the end of treatment visit (a bone marrow biopsy is optional).

12.5. Post-Treatment Follow Up Visit

- The post-treatment follow up visit should occur approximately 28 days after the end of treatment visit.

12.6. End of Study Visit

- The end of study visit should occur approximately 56 days after the end of treatment visit.
- Patients who discontinue treatment early should complete the end of study visit approximately 56 days after the end of treatment visit.
- For expansion cohorts patients only, administration of quality of life questionnaires.
- If a patient has a positive anti-drug antibody (ADA) result at the last visit, the patient may be asked to return for additional ADA testing every three months, until a negative result is obtained or the result is considered to be stabilized.

12.7. Termination of Study

The sponsor may terminate this study or discontinue a cohort, after consultation with the investigator(s), or at any time, for safety or administrative reasons. The sponsor will terminate the study if the occurrence of SAEs or other findings suggests unacceptable risk to the health of the patients.

13. STUDY DRUG MATERIALS AND MANAGEMENT

13.1. Study Drug

ACE-536 is a recombinant fusion protein consisting of a modified form of the extracellular domain (ECD) of the human activin receptor IIB (ActRIIB) linked to the human IgG1 Fc domain.

13.2. Study Drug Packaging and Labeling

ACE-536 drug product will be provided as either a sterile, liquid formulation or a lyophilized powder formulation for reconstitution with water. Each single-use vial of the liquid formulation contains 25 mg of ACE-536 in a 0.5 mL Tris-buffered saline solution (50 mg/mL).

Each single-use vial of the lyophilic formulation contains 50 mg ACE-536 for reconstitution with 1 mL water for injection to form a citrate-buffered solution (50 mg/mL).

13.3. Study Drug Storage

ACE-536 liquid formulation is stored frozen at ≤ -65˚C until use.

ACE-536 lyophilized powder formulation is stored between 2 - 8˚C until use.

13.4. Study Drug Preparation

Please refer to the study drug handling guideline, provided under separate cover, for detailed ACE-536 drug handling, administration, and storage instructions.

13.5. Administration

ACE-536 will be administered by SC injection. Multiple injections may be required to administer the appropriate dose at higher dose levels; however, no more than 4 injections will be administered per dose. The maximum volume per SC injection should not exceed 1.2 mL. Patients should be observed for a minimum of 30 minutes following treatment with ACE-536.

13.6. Study Drug Accountability

Accountability for ACE-536 is the responsibility of the investigator. Investigational clinical supplies must be received by a designated person at the clinical site and kept in a secured location. The clinical site must maintain accurate records demonstrating dates and amounts of ACE-536 received, to whom it was dispensed (patient-by-patient accounting), and accounts of any ACE-536 accidentally or deliberately destroyed or returned.

Unless otherwise notified, all vials of ACE-536, both used and unused, must be saved for drug accountability purposes. The used vials may be discarded, per the institution's standard practice, after drug accountability assessment has been completed by the clinical monitor. At the end of the study, the sponsor will provide direction for the outcome of all unused vials. Following the sponsor's instructions, the investigator must either return all unused vials of ACE-536 to the sponsor or destroy them at the clinical site. In either case, the outcome must be documented on the drug accountability log.

13.7. Study Drug Handling and Disposal

Please refer to the study drug handling guide, provided under separate cover, for detailed ACE-536 drug handling, administration, storage, and disposal instructions.

14. ASSESSMENT OF SAFETY

14.1. Adverse Event Definitions

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a study drug, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug whether or not it is considered related to the study drug.

Abnormal laboratory and other abnormal investigational findings (e.g. physical exam, ECG) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are otherwise considered clinically relevant by the investigator. In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself. In case of a fatality, the cause of death is considered as the AE, and the death is considered as its outcome.

Unexpected Adverse Events

An unexpected AE is an AE that is not described in nature or severity in the Investigator's Brochure.

Events Not to Be Considered as Adverse Events

Pre-existing medical conditions/signs/symptoms present before the Screening period that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions, and are not to be considered AEs. Anticipated day-to-day fluctuations of pre-existing conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening need not be considered adverse events.

Serious Adverse Event

A serious adverse event (SAE) is any AE, occurring at any dose level/regimen and regardless of causality that:

- Results in death.
- Is life-threatening: Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form).
- Requires inpatient hospitalization or prolongation of existing hospitalization; however, a hospitalization for an elective procedure will not be considered a SAE.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is an important medical event: an important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the

patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting per regulations, any suspected transmission of an infectious agent via a medical product is by default a suspected, unexpected serious adverse reaction (SUSAR) and should be reported in an expedited manner as described in Section 14.7.

Events Not to Be Considered as Serious Adverse Events

Elective hospitalizations to administer or to simplify study treatment or procedures are not considered SAEs.

Adverse Events of Special Interest

Events of new malignancy and premalignant lesions (excluding benign tumors or benign neoplasia) are to be reported as described in Section 14.7 within 24 hours of the investigator's knowledge of the event by fax, or other appropriate method, using the SAE Report Form, and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and subject's source documents. Documentation of the diagnosed malignancy must be provided at the time of reporting as a serious adverse event (e.g., any confirmatory histology or cytology results, X-rays, CT scans, etc.).

Malignancies or cancerous tumors are lesions capable of invading into adjacent tissues, and may be capable of spreading to distant tissues. A benign tumor has none of those properties.

Malignancy or cancer is characterized by anaplasia, invasiveness, and metastasis. For MDS studies, these also include progression to high/very high risk of MDS, myeloproliferation (e.g., clinically significant increases in blasts), progression to AML, etc.

Premalignant or precancerous lesions refer to a state of disordered morphology of cells that is associated with an increased risk of cancer. If left untreated, these conditions may lead to cancer. Such conditions are usually either dysplasia or benign neoplasia (and the dividing line between those is sometimes blurry). Sometimes the term "precancer" is used to describe carcinoma in situ, which is a noninvasive cancer that has not progressed to an aggressive, invasive stage. Not all carcinoma in situ will progress to invasive disease.

Premalignant lesions are morphologically atypical tissue which appears abnormal under microscopic examination and in which cancer is more likely to occur than in its apparently normal counterpart.

14.2. Pregnancy and In Utero Drug Exposure

The investigator will attempt to collect pregnancy information if a female patient or a male patient's female partner becomes pregnant while the patient is participating in this study. The pregnancy information will be recorded on the appropriate form and must be submitted to the Sponsor within 2 weeks of learning of the pregnancy. The patient or partner will be followed for the outcome of the pregnancy. Information on the status of the mother and child will be

forwarded to the Sponsor or designee. Generally, follow up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

14.3. Severity

Investigators must evaluate the severity/intensity of AEs according to the current active minor version of the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.0 (NCI-CTCAE v4.0), preferentially using the graded scales. If there is a change in severity of an adverse event, it must be recorded as a separate event. If a particular AE's severity/intensity is not specifically graded, the investigator should apply the general guidelines for determination of Grade 1 through Grade 5 as listed in the NCI-CTCAE v4.0 cover page (as shown below), using their best medical judgment:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

14.4. Relationship to Study Drug

Investigators must also assess the causal relationship of each AE to ACE-536. Factors for the assessment of causal relationship include, but are not limited to, temporal relationship between the AE and the administration of ACE-536, known side effects of ACE-536, medical history, concomitant therapy, course of the underlying disease and pertinent study procedures.

Probable: A causal relationship is clinically/biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of ACE-536 and there is a reasonable response on withdrawal.

Possible: A causal relationship is clinically/biologically plausible and there is a plausible time sequence between onset of the AE and administration of ACE-536.

Unlikely: A causal relationship is improbable and another documented cause of the AE is most plausible.

Unrelated: A causal relationship can be definitively excluded and another documented cause of the AE is most plausible.

14.5. Documentation and Methods of Reporting of Adverse Events by Investigator

It is the responsibility of the Investigator to document all adverse events that occur during the study. Patients will be evaluated and questioned generally for AEs during the course of the study, starting at the signing of the informed consent. The Investigator must report in detail all adverse signs and symptoms which are either volunteered by subjects or observed during or following the course of investigational product administration on the appropriate CRF page. All non-serious AEs occurring after signing of the ICF until a patient is dosed on Cycle 1 Day 1 are to be documented on the medical history CRF. All AEs and SAEs occurring after the Cycle 1 Day 1 dose through 84 days after the last study drug administration (End of Study visit) are to be reported and documented on the AE CRF.

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded on the AE CRF. Any clinically relevant changes in laboratory assessments, or other clinical findings as described in Section 14.1, are considered AEs and must be recorded on the AE CRF. AEs are to be followed for resolution as described in Section 14.6.

It is important that each AE report include a description of the event, duration (onset and resolution dates), severity, relationship with ACE-536, any other potential causal factors, any treatment given or other action taken (including dose modification or discontinuation of ACE-536) and outcome. In addition, serious AEs (SAEs) should be identified and the appropriate seriousness criteria documented. AEs categorized as SAEs must also be documented using an SAE Report Form as described in Section 14.5.1.

Specific guidance can be found in the CRF Completion Guidelines provided by the Sponsor or designee.

14.5.1. Documentation of Serious Adverse Events

All SAEs that occur after the first study drug administration on Cycle 1 Day 1 until 84 days after the last study drug administration (End of Study visit) are to be documented on the AE CRF. SAEs should not be reported for patients who are considered screen failures unless the event is deemed due to a protocol required procedure.

For all SAEs, an SAE form must be completed with as much information as possible and submitted within the time frame described in Section 14.7 (Notification about Serious Adverse Events).

When new significant information is obtained as well as when the outcome of an event is known, the investigator should record the information on a new SAE form. If the patient was hospitalized, a copy of the discharge summary must be included as part of the patient medical file. In all instances, the investigator should follow up with patients until the outcome of the SAE is known.

14.6. Reporting Period and Monitoring of Patients with Adverse Events

As described in Section 14.5, all AEs must be recorded in the CRF up until the end of the treatment period. All patients who took at least one dose of study drug, whether they completed the treatment period or not, should complete the end of treatment procedures.

All AEs will be followed until clinical database lock (or resolution if it occurs before database lock). All SAEs will undergo active follow up until resolved or the event becomes chronic or stable. Follow up data for SAEs obtained after clinical database lock will be incorporated into the ACE-536 safety database.

14.7. Notification about Serious Adverse Events

If an SAE occurs during the reporting period, the investigator must immediately, within a maximum 24 hours after becoming aware of the event, inform the sponsor via the CRO by telephone, fax, or e-mail.

All written reports should be transmitted using the study specific SAE Report Form, which must be completed by the investigator following specific completion instructions. Names, addresses, telephone and fax numbers for SAE reporting are located on the SAE Report Form and in the completion instructions provided in the Study Manual. When an SAE (or follow up information) is reported by telephone, a written report must be sent immediately thereafter by fax or e-mail. Reporting procedures and timelines for follow up information are the same as for the initially reported SAE.

Relevant pages from the CRF may be provided in parallel (e.g., medical history, concomitant therapy). In all cases, the information provided in the SAE Report Form must be consistent with the data that are recorded in the corresponding sections of the CRF.

The investigator/reporter must respond to any request for follow up information or to any question the Sponsor or designee may have on the AE within the same timelines as described for initial reports. This is necessary to permit a prompt assessment of the event by the Sponsor and (as applicable) to allow the Sponsor to meet regulatory timelines associated with expedited reporting obligations.

Requests for follow up will usually be made by the responsible clinical research associate or Medical Monitor, or an Acceleron pharmacovigilance representative who may contact the investigator directly to obtain clarification on a particularly critical event.

14.7.1. Safety Reporting to Health Authorities, Independent Ethics Committees Institutional Review Boards and Investigators

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The investigator must comply with any applicable site-specific requirements related to the reporting of SAEs involving his/her patients to the IEC that approved the study.

In accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, the Sponsor will inform the investigator of "findings that could adversely affect the safety of patients, impact the conduct of the study, or alter the IEC's approval/favorable opinion to continue the study."

The Sponsor will inform the investigator of AEs that are both serious and unexpected and are considered to be related to ACE-536 ("suspected unexpected serious adverse reactions" or SUSARs). The investigator should place copies of these Safety Reports in the Investigator Site File. National regulations with regard to Safety Report notifications to investigators will be followed.

When specifically required by regulations and guidelines, the Sponsor will provide appropriate Safety Reports directly to the concerned lead IEC and will maintain records of these notifications. When direct reporting by the Sponsor is not clearly defined by national or site-specific regulations, the investigator will be responsible for promptly notifying the concerned IEC of any Safety Reports and for filing copies of all related correspondence in the Investigator Site File.

For studies covered by the European Union Clinical Trials Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs will be carried out in accordance with that Directive and with the related Detailed Guidances.

15. STATISTICS

15.1. Analysis Populations

For all analysis populations, patients will be analyzed according to assigned treatment groups.

The Intent-to-Treat Population: All patients enrolled in the study who have received at least one dose of ACE-536 (Safety Population).

Efficacy Evaluable Population: All patients who received at least one dose of ACE-536 and have 1) at least two hemoglobin assessments ≥ 14 days apart post-treatment OR 2) at least 8 consecutive weeks of transfusion frequency data between Cycle 1 Day 1 and End of Treatment visit in transfusion dependent patients.

Safety Population: All patients who received at least 1 dose of ACE-536.

Pharmacokinetics Population: All patients who have received at least 1 dose of ACE-536 and have sufficient pharmacokinetic samples collected and assayed for PK analysis.

15.2. Statistical Plan

Summary statistics will be presented for continuous/quantitative variables, by way of number of patients (n), mean, standard deviation (SD), median, minimum and maximum and by way of group frequencies and percentages for categories of qualitative variables. Percentages will be calculated using the total patients per treatment / subgroup. 95% confidence intervals (CIs) will be presented as applicable.

All patient data will be presented in separate data listings.

15.2.1. Patient Accountability and Demographics

Exposure to study drug and reasons for discontinuation of study will be tabulated, and demographics will be presented using descriptive statistics (i.e., mean, standard deviation, median, and range).

15.2.2. Primary Efficacy Analysis

The **primary efficacy endpoint** is modified erythroid response (mHI-E), defined as the proportion of patients who have a hemoglobin increase of ≥ 1.5 g/dL from baseline for ≥ 14 days (in the absence of RBC transfusions) in non-transfusion dependent patients, or, a reduction of either ≥ 4 units or ≥ 50% of units of RBCs transfused over a period of 8 consecutive weeks, compared to the number of units of RBCs transfused in the 8 weeks immediately prior to Cycle 1 Day 1 in transfusion dependent patients (defined as having received ≥ 4 units of RBCs within 8 weeks prior to Cycle 1 Day 1). The erythroid response will be summarized using both a point estimate and its exact 95% confidence interval based on binomial distribution. The primary efficacy analysis will be performed using the EE population.

No direct comparison testing with concurrent or historical controls will be performed.

Baseline hemoglobin will be the average of at least two measures (not influenced by transfusion within 7 days of measurement); one measure performed within one day prior to Cycle 1 Day 1 and the other performed 7-28 days prior to Cycle 1 Day 1.

15.2.3. Secondary Analysis

Safety analysis: To assess clinical safety, adverse events, vital sign measurements and clinical laboratory information will be summarized. Adverse Events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Changes from baseline for clinical laboratory values and vital signs will be summarized over time. Descriptive statistics and shift tables will be generated as appropriate.

Secondary efficacy/pharmacodynamic analysis of the study will be performed using the ITT and EE populations and will include:

- Modified erythroid response (mHI-E), as described above for primary endpoint, performed using the ITT population.
- HI-E response rate as defined by IWG 2006 criteria (Appendix 5). Improvements must last ≥ 8 weeks. For non-transfusion dependent patients, an increase of ≥ 1.5 g/dL from pre-treatment hemoglobin. For transfused patients, a reduction by ≥ 4 units of RBCs transfused (for a hemoglobin ≤ 9.0 g/dL) during any 8-week period on study, compared with the 8-week period prior to Cycle 1 Day 1.
- Time to mHI-E and HI-E response and duration of mHI-E and HI-E response as per the IWG 2006 criteria.
- Frequency of RBC transfusion, and rate of RBC transfusion independence in transfusion dependent patients.
- Other pharmacodynamic (PD) endpoints including:
    - Biomarkers for iron metabolism
    - Biomarkers for bone metabolism
    - Relationship of biomarkers to response
    - Rates of HI-N and HI-P

Exploratory endpoints will include:

- Evaluation of biomarkers related to the TGFβ superfamily.
- Evaluation of self-reported quality of life in the expansion cohort using tools including but not limited to the FACT-An questionnaire.

All binary endpoints will be summarized using both a point estimate and its exact confidence interval based on the binomial distribution. The time-to-event type secondary endpoints will be analyzed using Kaplan-Meier method to estimate the survival curve and median time to event and 95% confidence interval.

15.2.4. Pharmacokinetics Analysis

Pharmacokinetics analysis: Non-compartmental PK parameters for ACE-536, such as maximum plasma concentration (C_{max}), time to maximum plasma concentration (t_{max}), and area under the concentration/time curve (AUC), will be estimated. Dose proportionality may be assessed using the exposure data (e.g. C_{max}, AUC) after the first dose if sufficient dose levels are studied. Descriptive statistics will be provided for serum concentrations and PK parameters. The relationship between ACE-536 exposure and response (i.e., safety, efficacy, and biomarkers) may be explored, if appropriate.

15.2.5. Anti-drug Antibody Analysis

Anti-drug antibody analysis: The results of anti-drug and neutralizing antibody testing for ACE-536 and human ActRIIB protein versus time will be presented. Exploratory analysis will be performed on the potential effect of anti-drug antibodies on ACE-536 PK and drug exposure if anti-drug antibody tests are deemed positive.

15.3. Determination of Sample Size

There is no formal sample size calculation for the dose escalation portion of the study. A standard dose escalation design will be implemented, and up to 42 patients will be enrolled at up to 7 different dose levels to further evaluate erythroid response.

A sample size of 30 evaluable patients in expansion cohort 1 will provide approximately 90% power with 1-sided significance level of 0.05 to differentiate an erythroid response rate of 30% from a minimal erythroid response rate of 10% based on Fisher exact test.

A sample size of 25 evaluable patients in each group of expansion cohort 2 will provide approximately 80% power with 1-sided significance level of 0.05 to differentiate an erythroid response rate of 30% from a minimal erythroid response rate of 10 % based on Fisher exact test.

15.4. Interim Analysis

There are no planned interim analyses. However, safety and erythroid response data will be reviewed periodically throughout the study.

15.5. Deviation from Original Analysis Plan

A formal Statistical Analysis Plan (SAP) for the analysis and presentation of data from this study will be prepared before the database lock. Deviations from the statistical analyses outlined in this protocol will be indicated in this plan; any further modifications will be noted in the final clinical study report.

16. SOURCE DOCUMENTATION AND INVESTIGATOR FILES

16.1. Study Monitoring

The clinical monitor will arrange to visit the clinical sites at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the clinical sites and their facilities. During these visits, CRFs and other data related to the study will be reviewed and any discrepancies or omissions will be resolved. The clinical monitor will be given access to study–relevant source documents (including medical records) for purposes of source data verification.

16.2. Audits and Inspections

The investigators and clinical sites will permit trial-related monitoring, audits, IEC review, and regulatory inspections as requested by FDA or other health authorities and the sponsor or designee. In addition to CRFs, the clinical site will permit direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed ICFs, etc.). During and/or after completion of the study, quality assurance officers named by the sponsor or the regulatory authorities may wish to perform on-site audits. The investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

17. QUALITY CONTROL AND QUALITY ASSURANCE

17.1. Data Quality Control and Quality Assurance

17.1.1. Investigator Responsibility

The investigator is responsible for ensuring the study is conducted according to the protocol, Code of Federal Regulations, GCP, and applicable regulatory requirements. The investigator's responsibilities are outlined in these documents and must include the responsibility to obtain a signed informed consent prior to patient participation in the study.

17.1.2. Protocol Modifications

The investigator should not modify the protocol without agreement from the sponsor and prior review or approval by the IEC, unless an emergency situation requires protocol modification to ensure the safety of patients. Any deviations from the protocol should be documented by the investigator or designee.

18. CONFIDENTIALITY

To maintain patient privacy, all CRFs, study drug accountability records, study reports and communications will identify the patient by the assigned patient identification number. The investigator will grant clinical monitor(s) and auditor(s) from the sponsor or designee and regulatory authorities' access to the patient's original medical records for verification of data gathered on the CRFs and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available. The patient's medical information will only be released to the extent permitted by the applicable laws and regulations.

All information regarding the investigational product supplied by the sponsor to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the sponsor. It is understood that there is an obligation to provide the sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other investigators, corporate partners, or consultants as required.

19. PUBLICATION POLICY

All information concerning ACE-536 is considered confidential and shall remain the sole property of the sponsor. The investigator(s) agree to use this information only in conducting the study and shall not use it for any other purposes without the sponsor's written approval. The investigator(s) agree not to disclose the sponsor's confidential information to anyone except to persons involved in the study that need such information to assist in conducting the study, and then only on like terms of confidentiality and non-use.

It is understood by the investigator(s) that the information developed from this clinical study will be used by the sponsor in connection with the development of ACE-536, and therefore may be disclosed as required to regulatory agencies. To allow for the use of the information derived from clinical studies, it is understood that there is an obligation to provide the sponsor with complete test results and all data developed in the study.

No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between the sponsor and the investigator(s).

20. PROTOCOL AMENDMENTS

Protocol amendments that impact patient safety, change the scope of the investigation, or affect the scientific quality of the study must be approved by the IEC and submitted to the appropriate regulatory authorities before implementation.

In the event that the protocol needs to be modified immediately to eliminate an apparent hazard to a patient, the sponsor will implement the protocol change and subsequently amend the protocol and notify the regulatory authorities and/or the IEC, as appropriate.

21. DATA HANDLING AND RECORDKEEPING

21.1. Case Report Form Completion

CRFs will be completed for each enrolled patient. It is the investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the patient's CRF. Source documentation supporting the CRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, AEs, and patient status.

Investigators will maintain copies of the CRFs at the clinical site. For patients who discontinue or terminate from the study, the CRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate CRF.

21.2. Retention of Records

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product, or according to applicable regulatory requirements. If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The sponsor must be notified in writing if a custodial change occurs.

22. STUDY FINANCE AND INSURANCE

22.1. Study Finance

The costs necessary to perform the study will be agreed with each Investigator and will be documented in a separate financial agreement that will be signed by the Investigator and Acceleron Pharma Inc. or designee, prior to the study commencing.

Participants may be reimbursed for study-related travel.

22.2. Insurance

The Sponsor has insurance coverage for study related ACE-536 induced injury and other liabilities incurred during clinical studies which will provide compensation for any study related injury according to the guidelines set out by the Association of the British Pharmaceutical Industry (ABPI), namely “Clinical Studies Compensation for Medicine Induced Injury.

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24. APPENDICES

24.1. Appendix 1: WHO Classification and Criteria for the Myelodysplastic Syndromes[26]

Disease	Blood findings	Bone marrow findings
Refractory cytopenia with unilineage dysplasia (RCUD): (refractory anemia [RA]; refractory neutropenia [RN]; refractory thrombocytopenia [RT])	Unicytopenia or bicytopenia[a] No or rare blasts (< 1%)[b]	Unilineage dysplasia: ≥ 10% of the cells in one myeloid lineage < 5% blasts < 15% of erythroid precursors are ring sideroblasts
Refractory anemia with ring sideroblasts (RARS)	Anemia No blasts	≥ 15% of erythroid precursors are ring sideroblasts Erythroid dysplasia only < 5% blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenia(s) No or rare blasts (< 1%)[b] No Auer rods < 1 x10^9/L monocytes	Dysplasia in ≥ 10% of the cells in ≥ 2 myeloid lineages (neutrophil and/or erythroid precursors and/or megakaryocytes) < 5% blasts in marrow No Auer rods ± 15% ring sideroblasts
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenia(s) < 5% blasts[b] No Auer rods < 1 x10^9/L monocytes	Unilineage or multilineage dysplasia 5%-9% blasts[b] No Auer rods
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenia(s) 5%-19% blasts[c] Auer rods ±[c] < 1 x10^9/L monocytes	Unilineage or multilineage dysplasia 10%-19% blasts[c] Auer rods ±[c]

Disease	Blood findings	Bone marrow findings
Myelodysplastic syndrome-unclassified (MDS-U)	Cytopenias < 1% blasts[b]	Unequivocal dysplasia in < 10% of cells in one or more myeloid lineages when accompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS < 5% blasts
MDS associated with isolated del(5q)	Anemia Usually normal or increased platelet count No or rare blasts (< 1%)	Normal to increased megakaryocytes with hypolobated nuclei < 5% blasts Isolated del(5q) cytogenetic abnormality No Auer rods

[a] Bicytopenia may occasionally be observed. Cases with pancytopenia should be classified as MDS-U.
[b] If the marrow myeloblast percentage is < 5% but there are 2% to 4% myeloblasts in the blood, the diagnostic classification is RAEB-1. Cases of RCUD and RCMD with 1% myeloblasts in the blood should be classified as MDS-U.
[c] Cases with Auer rods and < 5% myeloblasts in the blood and less than 10% in the marrow should be classified as RAEB-2. Although the finding of 5% to 19% blasts in the blood is, in itself, diagnostic of RAEB-2, cases of RAEB-2 may have < 5% blasts in the blood if they have Auer rods or 10% to 19% blasts in the marrow or both. Similarly, cases of RAEB-2 may have < 10% blasts in the marrow but may be diagnosed by the other 2 findings, Auer rod+ and/or 5% to 19% blasts in the blood.

24.2. Appendix 2: International Prognostic Scoring System (IPSS) for Myelodysplastic Syndromes (MDS)[4]

	IPSS Scoring Value				
Prognostic Variable	**0**	**0.5**	**1.0**	**1.5**	**2.0**
Bone Marrow Blasts (%)	< 5	5-10	—	11-20	21-30
Karyotype[a]	Good	Intermediate	Poor		
Cytopenias[b]	0-1	2-3			

[a] Good = normal, –Y, del(5q), del(20q); Intermediate = other abnormalities;
Poor = complex (≥ 3 abnormalities) or chromosome 7 anomalies
[b] Neutrophils < 1800/μL, hemoglobin < 10 g/dL, platelets < 100,000/μL.

	IPSS Classification			
Risk Group	**Low**	**Int-1**	**Int-2**	**High**
Score	0	0.5 - 1.0	1.5 - 2.0	≥ 2.5

24.3. Appendix 3: ECOG Performance Status[27]

The ECOG scale is used to assess a patient's quality of life in an evaluation by a health professional of the daily activities and how the activities are affected by the disease of the patient.

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

24.4. Appendix 4: International Working Group (IWG) Criteria - Erythroid Response Evaluation[10]

Hematologic Improvement (HI)[a]	Response Criteria (Responses must last at least 8 weeks)
Erythroid response (Hi-E) (pretreatment Hgb < 11 g/dL)	Hgb increase of ≥ 1.5 g/dL for patients not transfused; or, as defined by having received less than 4 units of RBCs within 8 weeks of Cycle 1 Day 1 Reduction by ≥ 4 units of RBCs transfused (for a Hgb ≤ 9.0 g/dL) during any 8-week period on study, compared with the 8-week period prior to study day 1
Platelet response (HI-P) (pretreatment, < 100 x10^9/L)	Absolute increase of ≥ 30 x 10^9/L for patients starting with > 20 x 10^9/L platelets Increase from < 20 x 10^9/L to > 20 x 10^9/L and by at least 100%
Neutrophil response (HI-N) (pretreatment, < 1.0 x10^9/L)	At least 100% increase and an absolute increase > 0.5 x 10^9/L

[a] Pre-treatment counts are averages of at least 2 measurements (not influenced by transfusions) ≥ 1 week apart within 28 days prior to Day 1.

Hgb indicates hemoglobin; RBC: red blood cell; HI: hematologic improvement.

24.5. Appendix 5: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0

See http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE