Official Protocol Title:	An Open-Label Extension Study to Evaluate the Long-Term Effects of ACE-536 for the Treatment of Anemia in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS) Previously Enrolled in Study A536-03
NCT number:	NCT02268383
Document Date:	29-Mar-2019

CLINICAL STUDY PROTOCOL

An Open-Label Extension Study to Evaluate the Long-Term Effects of ACE-536 for the Treatment of Anemia in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS) Previously Enrolled in Study A536-03

INVESTIGATIONAL PRODUCT:	**Luspatercept (ACE-536)**
PROTOCOL NUMBER:	**A536-05**
EUDRACT NUMBER:	**2014-001280-13**
SPONSOR:	**Acceleron Pharma Inc.** **128 Sidney Street** **Cambridge, MA 02139 USA** **Tel:** PPD **Fax:** PPD
MEDICAL MONITOR:	PPD **Vice President, Medical Research**
ORIGINAL PROTOCOL DATE:	**16-April-2014**
AMENDMENT 01 DATE:	**22-July-2015**
AMENDMENT 02 DATE:	**05-Jul-2016**
AMENDMENT 03 DATE:	**05-Jul-2017**
AMENDMENT 04 DATE:	**06-Mar-2018**
AMENDMENT 05 DATE:	**29-Mar-2019**

ACCELERON PHARMA SIGNATURE PAGE

Signature: PPD

Date: 02-APR-2019
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:** _____
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 Council 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 Council 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 PPD
Chiltern Medical Advisor	PPD	Chiltern Via M. Nizzoli, 6 Milano 20147 Italia 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: ACE-536
Name of Active Ingredient: Luspatercept (ACE-536)
Title of Study: An Open-Label Extension Study to Evaluate the Long-Term Effects of ACE-536 for the Treatment of Anemia in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS) Previously Enrolled in Study A536-03
Study Centers: Up to 20
Phase of development: 2
Objectives: **Primary:** • To evaluate the long-term safety and tolerability of ACE-536 in patients with low or intermediate-1 risk MDS who were previously enrolled in study A536-03. **Secondary:** • To evaluate erythroid response (modified HI-E from International Working Group [IWG] 2006 criteria[1]), defined as proportion of patients with: o A mean hemoglobin (Hgb) increase ≥ 1.5 g/dL over an 8-week period as compared to baseline, not influenced by red blood cell (RBC) transfusion, in non-transfusion dependent (NTD) patients. o A decrease of ≥ 4 units or ≥ 50% of units of RBCs transfused over a period of 8 weeks, relative to the 8 weeks immediately prior to Day 1, in transfusion dependent (TD) patients. • To evaluate rates of erythroid, neutrophil and platelet (HI-E, HI-N and HI-P) responses (IWG 2006 criteria) • To evaluate the rate of RBC transfusion independence lasting ≥ 8 weeks in TD patients • To evaluate time to HI-E response and duration of HI-E response (modified and non-modified IWG 2006 criteria) • To evaluate the mean change in RBC transfusion burden in TD patients and mean change in hemoglobin levels in NTD patients • To evaluate the pharmacokinetic (PK) profile of ACE-536 • To evaluate other pharmacodynamic (PD) effects (e.g., iron overload/metabolism, erythropoietin (EPO), and reticulocytes)

Exploratory:

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

Study Design:

This open-label extension study will evaluate the safety, tolerability, and PD effects of up to 60 months of ACE-536 treatment in patients with low or intermediate-1 risk MDS previously treated with ACE-536 for up to 3 months in study A536-03.

The base study A536-03 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). A total of up to 153 patients may be enrolled in the base study A536-03 and may be eligible for study A536-05.

Consenting patients that meet the A536-05 eligibility criteria may immediately roll over from A536-03 to study A536-05. These patients will forego the Post-treatment Follow-up (PTFU) and End of Study (EOS) visit of A536-03 to begin study A536-05. For these patients, C1D1 of A536-05 may take place 28 (± 7) days after the last dose administered in study A536-03, which may coincide with the patient's A536-03 End of Treatment (EOT) visit. These patients will be considered "patients without treatment interruption." Patients enrolled in expansion cohorts 2 and 3 in Study A536-03 must meet the "patients without treatment interruption" criteria to be considered for the A536-05 study, unless otherwise prospectively approved by the sponsor.

Patients who complete the EOS visit for the base study A536-03 prior to C1D1 of A536-05 are considered "patients with treatment interruption." These patients will have a 28-day screening period to allow them to be re-assessed for eligibility by meeting additional inclusion criteria, as defined in Section 9.2.

Patients who have completed the EOT visit for the base study A536-03 but have not reached the EOS visit (i.e., patients in the follow-up period for A536-03), may still participate, but should be treated as patients with treatment interruption and should not begin study A536-05 C1D1 until they have completed their A536-03 EOS visit so that new baseline assessments can be measured.

For patients without treatment interruption, transfusion status (NTD or TD) will carry-over from the base study A536-03. For patients with treatment interruption, transfusion status will be reassessed prior to C1D1 of study A536-05. Transfusion status for all patients is defined as follows for all patients:

- NTD patients are defined as patients who require a transfusion of < 4 units of RBCs in the 8 weeks prior to C1D1
- TD patients are defined as patients who require a transfusion of ≥ 4 units of RBCs in the 8 weeks prior to C1D1

Each TD patient will have a defined "pre-transfusion hemoglobin threshold" 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 of base study A536-03 for patients without treatment interruption, or prior to C1D1 of study A536-05 for patients with

treatment interruption. 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.

Patients will participate in the extension study A536-05 for approximately 8 years, including a 28-day screening period, a 60-month treatment period, and a 3-year follow-up period.

The Safety Review Team (SRT) established for study A536-03 will review safety and PD data periodically throughout study A536-05.

Starting Dose Level:

A patient without treatment interruption may continue to be dosed with ACE-536 at the same dose level administered at their last dose in study A536-03, unless a dose reduction is required based upon patient dose modification rules from study A536-05.

All patients with treatment interruption will be initially treated with ACE-536 at an assigned 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 based on data from the base study A536-03. Examples of possible starting dose levels with respective dose levels for modification (reductions and titrations) are shown in the table below for reference.

Possible Starting Dose Levels with Dose Level Modifications (Reductions and Titrations)

3rd Dose Reduction	2nd Dose Reduction	1st Dose Reduction	Starting Dose Level	1st Dose Titration	2nd Dose Titration	3rd Dose Titration
	0.125 mg/kg	0.25 mg/kg	**0.50 mg/kg**	0.75 mg/kg	1.0 mg/kg	1.33 mg/kg
0.125 mg/kg	0.25 mg/kg	0.5 mg/kg	**0.75 mg/kg**	1.0 mg/kg	1.33 mg/kg	1.75 mg/kg
0.25 mg/kg	0.5 mg/kg	0.75 mg/kg	**1.0 mg/kg**	1.33 mg/kg	1.75 mg/kg	
0.5 mg/kg	0.75 mg/kg	1.0 mg/kg	**1.33 mg/kg**	1.75 mg/kg		
0.75 mg/kg	1.0 mg/kg	1.33 mg/kg	**1.75 mg/kg**			

- Starting dose level for patients with treatment interruption is 1.0 mg/kg.
- Starting dose level for patients without treatment interruption will be last dose level administered in study A536-03 unless a dose reduction is required based upon patient dose modification rules from study A536-05.
- Patients may be titrated up and down dose levels as required per protocol to meet dose modification and titration rules.
- Patients who require more than 2 dose reductions due to an AE should be discontinued from treatment and complete the EOT, PTFU, LTFU and EOS visits.
- The maximum dose titration will not exceed 1.75 mg/kg.

Individual Dose Modification:

The following dose modification rules include parameters which may indicate when a dose delay and/or dose reduction is required. These rules should be assessed prior to each dosing. If a dose delay is required, the patient should have visits every 1 - 3 weeks to assess hematology results and adverse events (AE) until the patient is eligible to receive the next dose of ACE-536.

Observation on Dosing Day	Action	ACE-536 Dose Modification
Hemoglobin ≥ 12 g/dL	Hold dose and monitor patient 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
Non-hematologic AE ≥ Grade 3, at least possibly related to study drug	Hold dose and monitor patient 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]
≥50% increase in white blood cell count (WBC) compared to pre-dose WBC of previous treatment cycle and above upper limit of normal in the absence of an associated condition (e.g., infection or concomitant corticosteroid use)[b]	Dose delay; recheck CBC, including WBC at least weekly during dose delay.	Treatment may be resumed if WBC values are below upper limit of normal within 2 weeks
	If WBC remains above upper limit of normal for ≥ 2 consecutive weeks in absence of an associated condition (e.g., infection or concomitant corticosteroid use); continue dose delay and collect bone marrow/peripheral blood samples to assess MDS disease status.	Treatment may be resumed if: • Absence of disease progression per IWG response criteria for altering natural history of MDS[1] AND • WBC values return below upper limit of normal Discontinue treatment if: • Disease progression per IWG response criteria for altering natural history of MDS[1] OR • WBC remain above upper limit of normal
Presence of ≥ 1% blasts in peripheral blood	Dose interruption; immediately prepare peripheral blood smear for cytomorphology assessment.	If cytomorphology assessment confirms ≥ 1% blasts in the peripheral blood; discontinue treatment If cytomorphology assessment determines < 1% peripheral blasts are present, repeat hematology assessment. • If presence of < 1% blasts in peripheral blood, treatment can be resumed at next scheduled dosing cycle. • If presence of ≥ 1% blasts in peripheral blood; discontinue treatment

[a] Patients who require more than 2 dose reductions due to an AE should be discontinued from treatment and complete the EOT, PTFU, LTFU, and EOS visits.

[b] The investigator may contact the medical monitor and forward appropriate supporting documents for review and discussion prior to making decision regarding treatment discontinuation.

Individual Dose Titration for NTD Patients:

For NTD patients (with or without interruption), after C1D1, the dose level will be assessed for titration every cycle starting at C3D1 (e.g., C3D1, C4D1, C5D1, etc.). The dose level should be titrated individually for each patient not to exceed the maximum dose level evaluated in the base study A536-03 as follows:

- If hemoglobin increase from baseline is < 1.5 g/dL throughout the previous two cycles at the same dose level, the dose level will be increased by 1 dose level (unless dose modification is required).
- 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 the same dose level, the dose level will be increased by approximately 1 dose level (unless dose modification required).
- If hemoglobin increase from baseline is ≥ 1.5 g/dL (not influenced by RBC transfusion) as measured by two or more consecutive study measurements during the previous two cycles at the same dose level, the dose level will be unchanged (unless dose modification is required).

Baseline hemoglobin to assess titration will be the average of two or more measurements performed during the screening period for base study A536-03 (for patients without treatment interruption) or study A536-05 (for patients with treatment interruption).

Individual Dose Titration for TD Patients:

For all TD patients (with and without treatment interruption), the dose level will be assessed for titration every cycle starting at Cycle 3 Day 1 (e.g., C3D1, C4D1, C5D1, etc.). The dose level should be titrated individually for each patient not to exceed the maximum dose level evaluated in the base study A536-03 as follows:

- If patient has ≥ 1 transfusion event during the previous 2 cycles at the same dose level, the dose will be increased by 1 dose level (unless a dose modification is required).

Number of patients: A planned total of up to 153 patients who enrolled in the base study A536-03 may be eligible for the extension study A536-05.

Inclusion Criteria:

All patients must meet the following criteria:

1. Completion of the treatment period in the base study A536-03.
2. 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 dosing with ACE-536.

3. Patient is able to adhere to the study visit schedule, understand and comply with all protocol requirements.
4. Patient understands and is able to provide written informed consent.

Patients with treatment interruption (defined as patients who complete their A536-03 EOS visit) must also meet the following criteria:

5. Documented diagnosis of idiopathic/de novo MDS or non-proliferative chronic myelomonocytic leukemia (CMML) according to the World Health Organization (WHO) criteria[2] (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;
6. 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), for NTD patients (defined as having received < 4 units of RBCs within 8 weeks prior to Cycle 1 Day 1), OR
   - Transfusion Dependent (TD), defined as having received ≥ 4 units of RBCs within 8 weeks prior to Cycle 1 Day 1.
7. Platelet count ≥ 30 x 10^9/L.
8. ECOG performance status of 0, 1, or 2 (if related to anemia).
9. Adequate renal (creatinine ≤ 2.0 x upper limit of normal [ULN]) and hepatic (total bilirubin < 2 x ULN and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3 x ULN) function.

Exclusion Criteria:

All patients must not meet any of the following criteria:

1. Discontinuation/withdrawal from the base study A536-03 (due to patient request, patient unwillingness or inability to comply with the protocol, pregnancy, use of prohibited medication [e.g. azacitidine], medical reason or AE, disease progression, persistent increase in white blood cell count (WBC), presence of ≥ 1% blasts in peripheral blood, hypersensitivity reaction to the study drug, at the discretion of the sponsor, or loss to follow-up) prior to completion of the treatment period.
2. Prior treatment with azacitidine (injectable or oral) or decitabine.
3. Treatment within 28 days prior to Cycle 1 Day 1 with:
   - ESA,
   - Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF),
   - Lenalidomide.
4. For patients with treatment interruption only: Iron chelation therapy if initiated within 56 days prior to Cycle 1 Day 1.

5. Treatment with another investigational drug (including sotatercept [ACE-011]) or device, or approved therapy for investigational use ≤ 28 days prior to Cycle 1 Day 1, or if the half-life of the previous investigational product is known, within 5 times the half-life prior to Cycle 1 Day 1, whichever is longer.
6. 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.
7. Known positive for human immunodeficiency virus (HIV), active infectious hepatitis B (HBV) or active infectious hepatitis C (HCV).
8. Uncontrolled hypertension defined as systolic blood pressure (SBP) ≥ 150 mm Hg or diastolic blood pressure (DBP) ≥ 100 mm Hg.
9. Pregnant or lactating females.
10. History of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the investigational drug.
11. Any other condition not specifically noted above which, in the judgment of the investigator, would preclude the patient from participating in the study.

Investigational product, dosage 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 may contain either 25 mg, 50 mg, or 75 mg ACE-536 for reconstitution with 0.5 mL, 1 mL, or 1.5 mL water, respectively, to form a citrate-buffered solution (50 mg/mL) for injection.

ACE-536 will be administered by SC injection on Day 1 of each cycle.

Criteria for Evaluation:

Safety Assessments:

- All patients will be assessed for safety by monitoring AEs, clinical laboratory tests, vital signs, ECG, anti-drug antibody (ADA) testing, ECOG status, and physical examination.

Efficacy Assessments:

- Patients will be assessed for erythroid response over approximately 63 months following initiation of treatment. Erythroid response endpoints will be determined by monitoring hematologic laboratory values and RBC transfusions.
- Other secondary efficacy endpoints will be assessed by examining erythropoiesis, iron overload, and iron metabolism:
    - Erythropoiesis parameters include serum EPO levels, reticulocytes, nucleated RBCs and soluble transferrin receptor
    - Iron overload/metabolism parameters include serum iron, total iron binding capacity (TIBC), transferrin, soluble transferrin receptor, ferritin, and hepcidin

PK Assessments:

- Blood samples will be drawn to evaluate PK parameters.

Exploratory Assessments:

- Biomarkers related to the TGF-β superfamily

Patient-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 study although up to 153 patients may participate from the base study A536-03 study.

Analysis Populations:

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

Efficacy Evaluable (EE) Population: All patients who received at least one dose of ACE-536 and have 1) at least four hemoglobin assessments over an 8-week period post-treatment in NTD patients OR, 2) at least 8 consecutive weeks of transfusion frequency data between Cycle 1 Day 1 and EOT visit in TD patients.

Pharmacokinetics Population: All patients who received at least 1 dose of ACE-536 during Study A536-05 and have sufficient serum ACE-536 values for PK analysis.

Primary Endpoint Analysis:

Safety analysis: To assess clinical safety, AEs, vital sign measurements and clinical laboratory information will be summarized. AEs 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.

Efficacy/Pharmacodynamic Effects Analysis of Secondary Endpoints:

All efficacy analyses will be performed for the EE and mITT populations.

Efficacy will be evaluated by determining the proportion of patients who have a modified HI-E erythroid response rate based upon the IWG 2006 criteria (Appendix 5), defined as 1) A mean hemoglobin increase ≥ 1.5 g/dL over an 8-week period as compared to baseline, not influenced by RBC transfusion in NTD patients or 2) A decrease of ≥ 4 units or ≥ 50% of units of RBCs transfused over a period of 8 weeks, relative to the number of units of RBCs transfused in the 8 weeks immediately prior to Cycle 1 Day 1 in TD patients.

Baseline hemoglobin will be the average of two or more measures (not influenced by RBC transfusion) performed during the screening period for study A536-03 (for patients without interruption) or study A536-05 (for patients with interruption).

Baseline units of RBCs transfused will be the 8-week period prior to study A536-03 (for patients without interruption) or study A536-05 (for patients with interruption).

The erythroid response will be summarized using both a point estimate and its exact 95% confidence interval based on binomial distribution.

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

Analysis of other Secondary efficacy/pharmacodynamic endpoints will include:

- Time to HI-E response and duration of HI-E response as per the IWG 2006 criteria and modified IWG 2006 criteria.
- Mean RBC transfusion burden
- Rate of RBC transfusion-free period lasting ≥ 8 weeks in TD patients.
- Mean hemoglobin level change in NTD patients
- Other PD endpoints including:
    - Biomarkers for iron overload/metabolism
    - Relationship of biomarkers to response
    - Rates of HI-N and HI-P

The **exploratory endpoints** will include:

- Biomarkers related to the TGF-β superfamily.
- Patient-reported quality of life 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.

2. SCHEDULE OF EVENTS

	Screening[1]	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9
		C1D1[2]	C2D1[2]	C3D1[2]	C4D1[2]	C5D1[2]	C6D1[2]	C7D1[2]	C8D1[2]	C9D1[2]
Informed consent	X[1]									
Inclusion/Exclusion	X	X[2]								
Medical history[3]	X									
QoL Questionnaires [4]		X				X				X
Physical examination	X	X				X				X
Vital signs[5]	X	X	X	X	X	X	X	X	X	X
ECOG Status	X	X		X		X		X		X
ECG (12 lead)[6]		X								
Bone marrow aspirate[7]	X	X[7]								X[7]
Serum iron studies[8]		X				X				X
Erythropoietin levels		X				X				X
Hematology[9]	X	X	X	X	X	X	X	X	X	X
Peripheral blood smear		X				X				X
Serum chemistry[10]	X	X		X		X		X		X
Urinalysis and Urine Chemistry[11]	X	X				X				X
Anti-Drug Antibody[12]		X				X				X
PK collection		X				X				X
PD biomarkers[13]		X				X				X
Pregnancy test[14]	X	X	X	X	X	X	X	X	X	X
Evaluate transfusion frequency[15]	X	X	X	X	X	X	X	X	X	X
Administer ACE-536		X	X	X	X	X	X	X	X	X
Concomitant medications and AEs	Collected Continuously									

	Cycle 10 C10D1[2]	Cycle 11 C11D1[2]	Cycle 12 C12D1[2]	Cycle 13 C13D1[2]	Cycle 14 C14D1[2]	Cycle 15 C15D1[2]	Cycles 16 - 87[2,16]	EOT[17]	PTFU[18]	LTFU[19]	EOS[20]
Informed consent							**Repeat Cycles 12-15 eighteen times: visits are 21 ±5 days apart unless a dose delay is required.**				
Inclusion/Exclusion											
Medical history[3]											
QoL Questionnaire[4]				(X)[4]				X			
Physical examination				X				X			
Vital signs[5]	X	X	X	X	X	X		X			
ECOG Status		X		X		X		X			
ECG (12 lead)[6]								X			
Bone marrow aspirate[7]				(X)[7]				X[7]			
Serum iron studies[8]				X				X	X		
Erythropoietin levels				X				X	X		
Hematology[9]	X	X	X	X	X	X		X	X		
Peripheral blood smear				X				X			
Serum chemistry[10]		X		X		X		X			
Urinalysis and Urine Chemistry[11]				X				X			
Anti-Drug Antibody[12]				X				X[12]			
PK Collection				X				X			
PD biomarkers[13]				X				X			
Pregnancy test[14]	X	X	X	X	X	X		X			
Evaluate transfusion frequency[15]	X	X	X	X	X	X		X	X		
Administer ACE-536[2]	X	X	X	X	X	X					
Monitoring for AEs of special interest[21] (Refer to Section 14.1 for details)	After signing ICF and until at least 3 years post last dose of IP or until death, loss to follow up, withdrawal of consent for further data collection.										
Survival follow-up[21]										X	X
Concomitant medications and AEs	Collected Continuously										

[1] **Screening procedures:** Other than informed consent, procedures listed as part of the 28-day screening period are only applicable to patients with treatment interruption. Patients with treatment interruption will need to qualify per the additional inclusion criteria listed in Section 9.2.1. For patients without treatment interruption, C1D1 may coincide with EOT visit of the base study A536-03. Procedures that are required to confirm eligibility for patients without treatment interruption can be performed at the base study A536-03 EOT visit and used to confirm eligibility prior to dosing on C1D1 of study A536-05.

[2] **Study procedures** must be done prior to administration of study drug. For patients without treatment interruption, C1D1 procedures shaded grey may be conducted as part of the EOT visit for study A536-03 and may not need to be repeated for study A536-05. All screening and Cycle 1 Day 1 procedure results required to confirm eligibility must be obtained and reviewed prior to study drug administration in A536-05.
Visit schedule: Each dosing visit (cycles 1-87) will be 21 days (±5 days) from the previous dosing visit, unless a dose delay is required. If a dose delay is required per the dose modification rules (Section 10.8), the patient will not be dosed. The patient will return every 1-3 weeks for assessment of hematology results and AEs until the patient is eligible to receive the next dose of ACE-536 and start the next cycle. 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).
Dosing: The patient dose must be calculated based on the patient's weight on the day of dosing. Dose modification rules and titration rules must be reviewed and implemented prior to dosing as required per protocol (see Section 10.8 and Section 10.9). A dose titration cannot occur until C3D1.

[3] **Medical History:** Medical history for patients with treatment interruption will include medical events occurring after EOS visit in study A536-03 and prior to C1D1 for study A536-05. Medical history for patients without treatment interruption will be taken from study A536-03.

[4] **Quality of life questionnaires** are only required on C1D1, C5D1, C9D1, C13D1, C17D1, C25D1, C33D1, C41D1, C49D1, C57D1, C65D1, C73D1, C81D1, EOT, and EOS.

[5] **Vital signs** will include weight, heart rate, and systolic and diastolic blood pressure.

[6] **ECG:** May be collected within 28 days prior to C1D1.

[7] **Bone marrow aspirate:** Patients with treatment interruption must have a bone marrow aspirate including cytogenetics performed ≤ 3 months prior to C1D1 for evaluation of eligibility per inclusion criteria Section 9.2.1. A bone marrow aspirate will not be performed on C1D1 for patients without treatment interruption. A bone marrow aspirate must be performed within 21 days after C9D1, C17D1, C25D1, C41D1, C57D1, and C73D1 for all patients. At the EOT visit, a bone marrow aspirate is required for all patients, unless performed < 3 months following a previous bone marrow aspirate and not clinically indicated. Refer to the Laboratory Manual for processing and shipping instructions.

[8] **Serum Iron Studies:** May include serum iron, TIBC, transferrin, soluble transferrin receptor, ferritin.

[9] **Hematology:** RBC, WBC with differential, hemoglobin, hematocrit, nucleated red blood cells (nRBC), reticulocyte count, platelet count, peripheral blasts, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and red blood cell distribution width (RDW). On dosing days, hemoglobin values may be drawn and resulted (up to 1 day) prior to dosing (see Section 10.8, Individual Dose Modification Rules).

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

[11] **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):** urine chemistries include but are not limited to: microalbumin and creatinine.

[12] 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.

[13] **PD Biomarkers:** May include hepcidin, GDF15, GDF8, GDF11, Activin A and others to be determined.

[14] **Pregnancy test:** (urine or serum) is required for female patients of child bearing potential only.

[15] **Transfusion Frequency:** Transfusion history will be collected from the EOS visit in the base study A536-03 through the C1D1 visit of A536-05 as available for patients with treatment interruption up to 24 weeks. TD patients will have a defined "pre-transfusion hemoglobin threshold" for requiring transfusion during the study 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 of base study A536-03 (for TD patients without treatment interruption) or study A536-05 (for TD patients with treatment interruption). 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.

16 **Cycles 16 through 87:** Patients may complete up to 87 Cycles. The last dose of ACE-536 may not be administered after 87 cycles or 1825 calendar days from C1D1, whichever occurs first.

17 **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 EOT visit at the time of discontinuation, followed by PTFU, LTFU, and EOS visits.

18 **Post-Treatment Follow-Up (PTFU):** Patients will complete the PTFU visit 2 months (± 7 days) after the last dose of ACE-536

19 **Long-Term Follow-Up (LTFU)**: Patients will complete LTFU visits every 3 months (± 7 days) after the last dose of ACE-536 for 3 years after the last dose of ACE-536.

20 **End of Study (EOS):** Should be performed 3 years after the last dose of ACE-536.

21 Long-Term Post-Treatment Follow-Up for overall survival (OS), progression to AML, other malignancies/pre-malignancies (please refer to Section 14.1 for details) may be conducted by record review (including public records if allowed by local regulations) and/or telephone contact with the patient, family, or the patient's treating physician. The investigator must make every effort to obtain information regarding the patient's survival status before determining the patient is lost to follow-up.

3. TABLE OF CONTENTS

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
BMP	Bone morphogenetic protein
BSC	Best supportive care
BUN	Blood urea nitrogen
CXDY	Cycle X Day Y
CBC	Complete blood count
C_{max}	Maximum concentration
CMML	Chronic myelomonocytic leukemia
CRF	Case report form
CRO	Contract research organization
DBP	Diastolic blood pressure
ECD	Extracellular domain
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EE	Efficacy Evaluable
ESA	Erythropoiesis stimulating agent
EOS	End of study
EPO	Erythropoietin
EOT	End of treatment
FACT-An	Functional Assessment of Cancer Therapy-Anemia Scale
FDA	United States Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good clinical practices
G-CSF	Granulocyte colony-stimulating factor
GDF	Growth and differentiation factor
GGT	Gamma-glutamyl transpeptidase

Abbreviation	Definition
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's brochure
ICF	Informed consent form
ICH	International conference on harmonisation
IEC	Independent ethics committee
IgG1	Immunoglobulin G1
mITT	Modified Intent-to-Treat
IPSS	International Prognostic Scoring System
IWG	International Working Group
IV	Intravenous
K_D	Dissociation constant
LDH	Lactate dehydrogenase
LTFU	Long-term follow-up
MedDRA	Medical Dictionary for Regulatory Activities
MCH	Mean corpuscular hemoglobin
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
NTD	Non-transfusion dependent
ORR	Overall response rate
PD	Pharmacodynamic
PFS	Progression free survival
PHI	Protected health information
PK	Pharmacokinetic

Abbreviation	Definition
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
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard deviation
SRT	Safety review team
SUSAR	Suspected unexpected serious adverse reaction
$T_{1/2}$	Elimination half-life
TD	Transfusion dependent
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 Council 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.[3] 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 (erythropoiesis). 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 completely independent from that of erythropoietin (EPO), and involves stimulation of the later, maturation phase of erythroblast differentiation and maturation in the bone marrow.

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).[4,5,6]

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.[7] The incidence rate of MDS in Germany is 4.1 per 100,000,[8] with a median age between 68 and 73 years.[9] Looking at a subset of patients in Düsseldorf, the incidence of MDS is higher in men than women with the incidence and prevalence increasing dramatically with age.[10] 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.[11]

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.[6] 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.[1]

Therapy for MDS is based on patient age, IPSS risk category, and ECOG performance status (Appendix 4).[12] 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.[6,13]

Anemia is the predominant cytopenia observed in MDS and is present in 85% of MDS patients at the time of diagnosis.[14] Refractory anemia resulting from ineffective erythropoiesis is a major cause of morbidity and mortality in MDS patients.[15] 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 RBC transfusions. Only one third of unselected patients treated with ESAs have an erythroid response.[16,17] A significant number of MDS patients have serum 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.[18] 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.[19,20]

The azanucleosides, azacitidine (Vidaza®) and decitabine (Dacogen®), and lenalidomide (Revlimid®) have demonstrated activity in patients with MDS.[21,22] 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.[23] A second phase 3 trial demonstrated improved 2-year overall survival.[24] A phase 3 study comparing decitabine with BSC showed improved overall response rate (ORR) and progression-free survival (PFS).[25]

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.[4]

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 Investigator's Brochure (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 ortholog, RAP-536. The RAP-536 molecule has the same ECD as ACE-536, but contains a murine IgG Fc domain in place of the human IgG Fc. The RAP-536 ortholog is substantially less immunogenic in rodent species and therefore permitted the conduct of longer term pharmacology studies in rodents without the confounding influence of immune reactivity.

ACE-536 has been shown to have significant effects on erythropoiesis. Evidence suggests that it binds ligands that normally act to modulate the differentiation of late-stage erythroid precursors (normoblasts). Because ACE-536 affects late-stage erythrocyte precursor populations, its action is distinct from that of EPO. Unlike EPO, ACE-536 is not a growth-promoting cytokine.

Studies of ACE-536 in normal animals across several species (mice, rats, and cynomolgus monkeys) demonstrated an erythroid response that was rapid in onset, robust, and sustained. These effects were also demonstrated in a variety of animal models of anemia, including anemia associated with kidney failure, acute blood loss, and chemotherapy.

RAP-536 was shown to significantly improve hematologic parameters, including increased hemoglobin concentrations, and to correct ineffective erythropoiesis and anemia in mouse models of MDS and β-thalassemia, both target indications for ACE-536. This is consistent with its proposed mechanism of action of driving the late stages of erythroid differentiation that is downstream and distinct from EPO.

Additional information regarding pharmacological effects of ACE-536 is summarized in the current version of the ACE-536 IB.

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. In addition, the main phase of a repeat-dose toxicology study of 6 months treatment duration in cynomolgus monkeys is complete. Findings from toxicology studies are described in more detail in the IB.

7.3. Summary of Clinical Experience

The safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) 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 PK parameters and PD effects of ACE-536.

A total of 32 subjects were enrolled. Eligible subjects were healthy, postmenopausal women, 45-75 years old. The anticipated PD effect was an increase in plasma hemoglobin level. Screening and baseline hemoglobin values had to be between 11.0 and 14.5 g/dL, inclusive, to mitigate the risk of substantial excursions above the normal range. Sequential cohorts of 8 subjects each were randomized to receive either ACE-536 (n=6) or placebo (n=2) administered as a SC injection on Day 1 and Day 15. Each subject was to be followed for 112 days (16 weeks) after receiving their last dose of ACE-536 or placebo. The following dose levels were evaluated: 0.0625, 0.125, and 0.25 mg/kg.

ACE-536 administered every 2 weeks by subcutaneous (SC) injection for one or two doses at dose levels of 0.0625, 0.125 or 0.25 mg/kg was generally safe and well-tolerated in healthy postmenopausal female subjects. No serious or severe adverse events (AE) were reported. The majority of AEs were considered mild in severity. AEs that were considered at least possibly drug-related across ACE-536 dose groups included injection site hemorrhage (3 subjects), injection site macule (2 subjects), and dry skin, macule, hyperesthesia, muscle spasms, myalgia, generalized pruritus, and papular rash (1 subject each). Injection site pain was reported in one placebo-treated subject.

PK results indicated mean area under the concentration-time curve (AUC) and maximum concentration (C_{max}) values increased in a dose-proportional manner with ACE-536 dose level; mean time to maximum concentration (T_{max}) ranged from 7.0 to 9.8 days, and mean $T_{½}$ ranged from 14.9 to 16.2 days after the first dose. These PK results support intermittent SC dosing of ACE-536 in future studies, e.g., every 3 weeks.

PD assessments for hematological markers showed increases in hemoglobin levels at the 0.125 mg/kg dose level and more consistently at the 0.25 mg/kg dose level. Small increases in reticulocyte count and EPO levels were also observed at the two higher dose levels of ACE-536 investigated. A small decrease in serum follicle-stimulating hormone (FSH) levels was observed at 0.25 mg/kg. These data support further studies of ACE-536 in conditions associated with ineffective erythropoiesis and anemia.

Two phase 2 studies with ACE-536 are ongoing. Study A536-03 is entitled, “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 A536-04 is entitled “A Phase 2, Open-Label, Ascending Dose Study to Evaluate the Effects of ACE-536 in Patients with ß-Thalassemia”. Preliminary results from these studies and additional information regarding the completed Phase 1 study can be found in the current version of the IB.

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 patients and dose escalation/reduction rules will be utilized to minimize risks associated with increased RBC parameters.

AEs observed in the Phase 1 study in healthy volunteers and the ongoing phase 2 studies that were considered probably or possibly related to study drug included injection site reactions

(hemorrhage, pruritus, rash), skin rash, hyperesthesia, muscle spasms, myalgia, pruritus, and hyperkalemia

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

Repeat dose toxicology studies of 1 and 3 month duration have been conducted with ACE-536 in Sprague-Dawley rats and cynomolgus monkeys to evaluate the toxicity of ACE-536. In addition, a repeat-dose toxicology study of 6 months treatment duration in cynomolgus monkeys is ongoing. Reproductive toxicity studies are currently ongoing and therefore ACE-536 should not be administered to pregnant or nursing women. Male and female patients of childbearing potential participating in studies of ACE-536 must be willing to abstain from sexual intercourse or use adequate contraception during study participation and for at least 12 weeks following treatment discontinuation. Please refer to the IB for additional information regarding findings from toxicology studies. 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 AE 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 IB. The ACE-536 IB should be reviewed prior to initating the study.

8. TRIAL OBJECTIVES

8.1. Primary Objective

- To evaluate the long-term safety and tolerability of ACE-536 in patients with low or intermediate-1 risk MDS who were previously enrolled in study A536-03.

8.2. Secondary Objectives

- To evaluate erythroid response (modified HI-E from IWG 2006 criteria), defined as proportion of patients with:
  - A mean hemoglobin (Hgb) increase ≥ 1.5 g/dL over an 8-week period as compared to baseline, not influenced by RBC transfusion, in non-transfusion dependent (NTD) patients.
  - A decrease of ≥ 4 units or ≥ 50% of units of RBCs transfused over a period of 8 weeks, relative to the 8 weeks immediately prior to Day 1, in transfusion dependent (TD) patients.
- To evaluate rates of erythroid, neutrophil and platelet (HI-E, HI-N and HI-P) responses (IWG 2006 criteria)
- To evaluate the rate of RBC transfusion independence lasting ≥ 8 weeks in TD patients
- To evaluate time to HI-E response and duration of HI-E response (modified and non-modified IWG 2006 criteria)
- To evaluate the mean change in RBC transfusion burden in TD patients and mean change in hemoglobin levels in NTD patients
- To evaluate the PK profile of ACE-536
- To evaluate other PD effects (e.g., iron overload/metabolism, EPO, and reticulocytes)

8.3. Exploratory Objective

- To examine biomarkers related to the TGF-β superfamily
- To examine self-reported quality of life 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, extension study to evaluate the safety, tolerability, and PD effects of up to 60 months of ACE-536 treatment and 3 years of follow-up in patients with low or intermediate-1 risk MDS previously treated with ACE-536 for up to 3 months in the base study A536-03.

9.1. Study Design

Patients in all cohorts will receive ACE-536, administered subcutaneously (SC), every 3 weeks for up to 87 cycles or up to 1825 days, whichever occurs first. Dose titration(s), delay(s) and dose reduction(s) may be required for individual patients as outlined in the Individual Dose Modification Rules (Section 10.8).

The base study A536-03 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 ESA. A total of up to 153 patients may be enrolled in the base study A536-03 and may be eligible for study A536-05.

Consenting patients that meet the A536-05 eligibility criteria may immediately roll over from A536-03 to study A536-05. These patients will forego the Post-treatment Follow-up (PTFU) and End of Study (EOS) visit of A536-03 to begin study A536-05. For these patients, C1D1 of A536-05 may take place 28 (± 7) days after the last dose administered in the base study A536-03, which may coincide with the patient's A536-03 End of Treatment (EOT) visit. These patients will be considered "patients without treatment interruption." Patients enrolled in expansion cohorts 2 and 3 in Study A536-03 must meet the "patients without treatment interruption" criteria to be considered for the A536-05 study, unless otherwise prospectively approved by the sponsor.

Patients who complete the EOS visit for the base study A536-03 prior to C1D1 of A536-05 are considered "patients with treatment interruption." These patients will have a 28-day screening period to allow them to be re-assessed for eligibility by meeting additional inclusion criteria, as defined in Section 9.2.

Patients who have completed the EOT visit for the base study A536-03 but have not reached the EOS visit (i.e. patients in the follow-up period for A536-03), may still participate, but should be treated as patients with treatment interruption and should not begin study A536-05 C1D1 until they have completed their A536-03 EOS visit so that new baseline assessments can be measured.

For patients without treatment interruption, transfusion status (NTD or TD) will carry-over from the base study A536-03. For patients with treatment interruption, transfusion status will be reassessed prior to C1D1 of study A536-05. Transfusion status for all patients is defined as follows for all patients:

- NTD patients are defined as patients who require a transfusion of < 4 units of RBCs in the 8 weeks prior to C1D1
- TD patients are defined as patients who require a transfusion of ≥ 4 units of RBCs in the 8 weeks prior to C1D1

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 of base study A536-03 for patients without treatment interruption, or prior to C1D1 of study A536-05 for patients with treatment interruption. 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.

Patients will participate in the extension study A536-05 for approximately 8 years, including a 28-day screening period, a 60-month treatment period and a 3-year follow-up period.

The SRT established for study A536-03 will review safety and PD data periodically throughout study A536-05.

9.2. Selection of Study Population

9.2.1. Inclusion Criteria

All patients must meet the following criteria:

1. Completion of the treatment period in the base study A536-03.
2. 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 dosing with ACE-536.
3. Patient is able to adhere to the study visit schedule, understand and comply with all protocol requirements.
4. Patient understands and is able to provide written informed consent.

Patients with treatment interruption (defined as patients who completed the A536-03 EOS visit) must also meet the following criteria:

5. Documented diagnosis of idiopathic/de novo MDS or non-proliferative chronic myelomonocytic leukemia (CMML) according to WHO criteria16 (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;
6. 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) for NTD patients (defined as having received < 4 units of RBCs within 8 weeks prior to Cycle 1 Day 1), OR
- Transfusion Dependent (TD), defined as having received ≥ 4 units of RBCs within 8 weeks prior to Cycle 1 Day 1.

7. Platelet count (≥ 30 x 10^9/L).
8. ECOG performance status of 0, 1, or 2 (if related to anemia).
9. Adequate renal (creatinine ≤ 2.0 x upper limit of normal [ULN]) and hepatic (total bilirubin < 2 x ULN and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) < 3 x ULN) function.

9.2.2. Exclusion Criteria

All patients must not meet the following criteria:

1. Discontinuation/withdrawal from the base study A536-03 (due to patient request, patient unwillingness or inability to comply with the protocol, pregnancy, use of prohibited medication [e.g. azacitidine], medical reason or AE, disease progression, persistent increase in white blood cell (WBC) count, presence of ≥ 1% blasts in peripheral blood, hypersensitivity reaction to the study drug, at the discretion of the sponsor, or loss to follow-up) prior to completion of the treatment period.
2. Prior treatment with azacitidine (injectable or oral) or decitabine.
3. 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.
4. For patients with treatment interruption only: Iron chelation therapy if initiated within 56 days prior to Cycle 1 Day 1.
5. Treatment with another investigational drug (including sotatercept [ACE-011]) or device, or approved therapy for investigational use ≤ 28 days prior to Cycle 1 Day 1, or if the half-life of the previous investigational product is known, within 5 times the half-life prior to Cycle 1 Day 1, whichever is longer.
6. 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.
7. Known positive for human immunodeficiency virus (HIV), active infectious hepatitis B (HBV) or active infectious hepatitis C (HCV).
8. Uncontrolled hypertension defined as systolic blood pressure (SBP) ≥ 150 mm Hg or diastolic blood pressure (DBP) ≥ 100 mm Hg.
9. Pregnant or lactating females.

10. History of severe allergic or anaphylactic reactions or hypersensitivity to recombinant proteins or excipients in the investigational drug.
11. Any other condition not specifically noted above which, in the judgment of the investigator, would preclude the patient from participating in the study.

9.3. 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 AE, 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 (per IWG criteria for altering natural history of MDS[1]):
  - For patients with 5-10% blasts, a second bone marrow sample should be collected within 4 weeks for clinical assessment (e.g., cytomorphology, cytogenetics) to confirm progression before discontinuing patients from treatment.
- Persistent increase in white blood cell (WBC) count as per Individual Dose Modifications Section 10.8
- Presence of ≥ 1% blasts in peripheral blood as per Individual Dose Modifications Section 10.8
- 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 EOT follow-up visit at the time of discontinuation, then complete the PTFU visit 2 months ± 7 days after the last dose of ACE-536, the LTFU visits every 3 months, and finally the EOS visit 3 years after the last dose of ACE-536.

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 SC injection on Cycle 1 Day 1. Subsequent doses will be administered every 3 weeks on Day 1 of the cycle for up to 87 cycles. The last dose of ACE-536 may not be administered after 87 cycles or 1825 calendar days from C1D1, whichever occurs first. Dose reductions may be required for individual patients as outlined in the Individual Dose Modifications Rules (Section 10.8). If a dose delay is required, the patient will return every 1-3 weeks for assessment of hematology results and AEs until the patient is eligible to receive the next dose of ACE-536. Patients will be asked to return to the clinic for follow-up visits, the first occurring approximately 28 days after the last dose of ACE-536 and then approximately every 3 months from then on, until 3 years after the last dose of ACE-536. If a patient has a positive 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 9.2). 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 EOT 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. For patients with treatment interruption, concomitant medications will be collected beginning at study screening and will include all medications taken within 28 days prior to Cycle 1 Day 1. For patients without treatment interruption, concomitant medication will be collected beginning at C1D1.

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 EOT visit and enter the follow-up period. Iron chelation therapy is allowed for patients without treatment interruption. For patients with treatment interruption, iron chelation therapy is allowed unless initiated within 56 days prior to C1D1. If iron chelation therapy is required during study treatment, patient should follow standard of care for management of iron chelation therapy.

10.2.2. RBC Transfusions

Concurrent treatment for anemia with blood transfusions is allowed, at the discretion of the investigator, for low hemoglobin levels, symptoms associated with anemia (e.g., hemodynamic or pulmonary compromise requiring treatment) or comorbidity.

For any RBC transfusions (NTD or TD patients) received during the study, collect hemoglobin values just prior to transfusion.

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 of base study A536-03 for patients without treatment interruption, or prior to C1D1 of study A536-05 for patients with treatment interruption. 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

A patient participating in the extension Study A536-05 without treatment interruption may continue to be dosed with ACE-536 at the same dose level administered at their last dose in the base study A536-03 (see Section 10.7, Starting Dose Level). All patients with treatment interruption (defined as patients who have completed their EOS visit for study A536-03) will be initially treated with ACE-536 at an assigned starting dose level of 1.0 mg/kg, which has been determined to be safe and well tolerated by the Safety Review Team (SRT) based on data from the base study A536-03.

10.6. Safety Review Team

Safety will be evaluated by the 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 periodically throughout the trial, including AEs, SAEs, laboratory results (including hematology and chemistry), vital signs, and erythroid response data.

10.7. Starting Dose Level

A patient without treatment interruption may continue to be dosed with ACE-536 at the same dose level administered at their last dose in study A536-03, unless a dose reduction is required based upon patient dose modification rules from study A536-05. All patients with treatment interruption will be initially treated with ACE-536 at an assigned 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 based on data from study A536-03. Examples of possible starting dose levels with respective dose levels for modification (reductions and titrations) are shown in the table below for reference.

Possible Starting Dose Levels with Dose Level Modifications (Reductions and Titrations)

3rd Dose Reduction	2nd Dose Reduction	1st Dose Reduction	Starting Dose Level	1st Dose Titration	2nd Dose Titration	3rd Dose Titration
	0.125 mg/kg	0.25 mg/kg	**0.50 mg/kg**	0.75 mg/kg	1.0 mg/kg	1.33 mg/kg
0.125 mg/kg	0.25 mg/kg	0.5 mg/kg	**0.75 mg/kg**	1.0 mg/kg	1.33 mg/kg	1.75 mg/kg
0.25 mg/kg	0.5 mg/kg	0.75 mg/kg	**1.0 mg/kg**	1.33 mg/kg	1.75 mg/kg	
0.5 mg/kg	0.75 mg/kg	1.0 mg/kg	**1.33 mg/kg**	1.75 mg/kg		
0.75 mg/kg	1.0 mg/kg	1.33 mg/kg	**1.75 mg/kg**			

- Starting dose level for patients with treatment interruption is 1.0 mg/kg.
- Starting dose level for patients without treatment interruption will be last dose level administered in study A536-03unless a dose reduction is required based upon patient dose modification rules from study A536-05.
- Patients may be titrated up and down dose levels as required per protocol to meet dose modification and titration rules.
- 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.
- The maximum dose titration will not exceed 1.75 mg/kg.

10.8. Individual Dose Modification Rules

The following dose modification rules include parameters which may indicate when a dose delay and/or dose reduction is required. These rules should be assessed prior to each dosing. If a dose delay is required the patient should have visits every 1-3 weeks to assess hematology results and AEs until the patient is eligible to receive the next dose of ACE-536.

Observation on Dosing Day	Action	ACE-536 Dose Modification
Hemoglobin ≥ 12 g/dL	Hold dose and monitor patient 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
Non-hematologic AE ≥ Grade 3, at least possibly related to study drug	Hold dose and monitor patient 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]
≥ 50% increase in white blood cell count (WBC) compared to pre-dose WBC of previous treatment cycle and above upper limit of normal in the absence of an associated condition (e.g., infection or concomitant corticosteroid use)[b]	Dose delay; recheck CBC, including WBC at least weekly during dose delay.	Treatment may be resumed if WBC values are below upper limit of normal within 2 weeks
	If WBC remains above upper limit of normal for ≥ 2 consecutive weeks in absence of an associated condition (eg, infection or concomitant corticosteroid use); continue dose delay and collect bone marrow/peripheral blood samples to assess MDS disease status.	Treatment may be resumed if: • Absence of disease progression per IWG response criteria for altering natural history of MDS[1] AND • WBC values return below upper limit of normal Discontinue treatment if: • Disease progression per IWG response criteria for altering natural history of MDS[1] OR • WBC remain above upper limit of normal
Presence of ≥ 1% blasts in peripheral blood (based on local laboratory hematology sample)	Dose interruption; immediately prepare peripheral blood smear for cytomorphology assessment.	If cytomorphology assessment confirms ≥ 1% blasts in the peripheral blood; discontinue treatment If cytomorphology assessment determines < 1% peripheral blasts

Observation on Dosing Day	Action	ACE-536 Dose Modification
		are present, repeat hematology assessment. • If presence of < 1% blasts in peripheral blood, treatment can be resumed at next scheduled dosing cycle. • If presence of ≥ 1% blasts in peripheral blood; discontinue treatment

[a] Patients who require more than 2 dose reductions due to an AE should be discontinued from treatment and complete the EOT, PTFU, LTFU, and EOS visits.

[b] The investigator may contact the medical monitor and forward appropriate supporting documents for review and discussion prior to making decision regarding treatment discontinuation.

10.9. Individual Dose Titration

10.9.1. Individual Dose Titration for NTD Patients

For NTD patients (with or without interruption), after C1D1, the dose level will be assessed for titration every cycle starting at C3D1) (e.g., C3D1, C4D1, C5D1, etc.). The dose level should be titrated individually for each patient not to exceed the maximum dose level evaluated in the base study A536-03 as follows:

- If hemoglobin increase from baseline is < 1.5 g/dL throughout the previous two cycles at the same dose level, the dose level will be increased by 1 dose level (unless dose modification is required).
- 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 the same dose level, the dose level will be increased by approximately 1 dose level (unless dose modification required).
- If hemoglobin increase from baseline is ≥ 1.5 g/dL (not influenced by RBC transfusion) as measured by two or more consecutive study measurements during the previous two cycles at the same dose level, the dose level will be unchanged (unless dose modification is required).

Baseline hemoglobin to assess titration will be the average of two or more measurements performed during the screening period for base study A536-03 (for patients without treatment interruption) or study A536-05 (for patients with treatment interruption).

10.9.2. Individual Dose Titration for TD Patients

For all TD patients (with and without treatment interruption), the dose level will be assessed for titration every cycle starting at Cycle 3 Day 1 (e.g., C3D1, C4D1, C5D1, etc.). The dose level should be titrated individually for each patient not to exceed the maximum dose level evaluated in the base study A536-03 as follows:

- If patient has ≥ 1 transfusion event during the previous 2 cycles at the same dose level, the dose will be increased by 1 dose level (unless a dose modification is required).

10.10. 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.

Patient treatment interruption for site administrative reasons will be allowed between Cycles 17 and 18 and between Cycles 35 and 36 upon discussion with the sponsor.

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, peripheral blasts, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), and red blood cell width (RDW).
- Serum chemistry: Sodium, potassium, AST, ALT, lactate dehydrogenase (LDH), total bilirubin, direct bilirubin, alkaline phosphatase, blood urea nitrogen (BUN)/urea, creatinine, gamma- glutamyl transpeptidase (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 for women of child bearing potential only

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, and hepcidin.
- nRBC
- EPO levels
- Peripheral blood smear
- Urine Chemistry: Microalbumin and creatinine.

11.3. Other Safety Assessments

- Physical examination
- Vital signs: weight, heart rate, systolic and diastolic blood pressure
- ECOG Status
- 12-lead ECG
- ADA 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 years 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 relevant Laboratory Manual.

11.4.2. Pharmacodynamic Evaluations

- PD assessments including hematologic laboratory assessments and transfusion information will be used to determine erythroid response to ACE-536.
- Bone marrow aspirates will be performed for histology, cytogenetics, and morphology. Additional analyses may be included, such as flow cytometry and/or molecular testing.
- Blood biomarkers for iron metabolism will include serum iron, TIBC, transferrin, soluble transferrin receptor, ferritin, 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

- The screening period is only applicable to patients with treatment interruption (defined as patients who completed the EOS visit for the base study A536-03).
- Signature of the current IEC approved ICF should occur prior to initiation of any study-specific screening procedures.
- All screening procedures, except for a bone marrow aspirate, should occur within 28 days prior to Cycle 1 Day 1.
- Patients with treatment interruption must have a bone marrow aspirate including cytogenetics within 3 months prior to Cycle 1 Day 1 for evaluation of patient eligibility per the additional inclusion criteria listed in Section 9.2.1.
- Qualification is required per the additional inclusion criteria listed in Section 9.2.1.
- Historical hemoglobin and transfusion history will be collected for up to 24 weeks, where available, prior to Cycle 1 Day 1 of A536-05. Patients without treatment interruption will be evaluated for secondary endpoints based on historical hemoglobin and transfusion history collected for up to 24 weeks, where available, prior to Cycle 1 Day 1 of A536-03.
- Pregnancy test (urine or serum) is required of female patients of child bearing potential during the screening period.
- Concomitant medications taken within 28 days prior to Cycle 1 Day 1 will be documented in the CRF.
- A medical history will be collected at screening and will include medical events occurring after EOS visit in study A536-03 and prior to C1D1 for study A536-05. Medical history for patients without treatment interruption will be taken from study A536-03.
- Screen failure information will be maintained to document specific information, including but not limited to, reason for failure.

12.2. Dosing Days and Interim Visits

- All screening and Cycle 1 Day 1 procedure results required to confirm eligibility must be obtained and reviewed prior to study drug administration in A536-05. 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.
- Note that the patient dose must be calculated based on the patient's weight on the day of dosing.

- All study procedures on each dosing day must be done prior to administration of study drug.
- If a dose delay is required per the dose modification rules (Section 10.8), the patient will not be dosed. The patient will return every 1-3 weeks for assessment of hematology results and AEs 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 patients with treatment interruption, the hemoglobin should be available to confirm eligibility within one day prior.
- A bone marrow aspirate must be performed within 21 days after C9D1, C17D1, C25D1, C41D1, C57D1, and C73D1.
- A pregnancy test (urine or serum) is required prior to ACE-536 administration on all dosing days for female patients of childbearing potential.
- For patients with treatment interruption, 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) should be reviewed prior to dosing to ensure that the patient is still eligible to receive additional doses of ACE-536.

12.3. End of Treatment Visit

- The EOT visit should occur approximately 28 days after the last dose of ACE-536.
- Patients who discontinue treatment early should complete the EOT visit at the time of discontinuation.
- A bone marrow aspirate is required at the EOT visit unless performed < 3 months following a previous bone marrow aspirate and not clinically indicated.

12.4. Post-Treatment Follow-Up Visit

- The PTFU visit should occur approximately 2 months after the last dose of ACE-536.

12.5. Long-Term Follow-Up Visits

- LTFU visits should occur approximately every 3 months for 3 years after the last dose of ACE-536.

12.6. End of Study Visit

- The EOS visit should occur approximately 3 years after the last dose of ACE-536.

- Patients who discontinue treatment early should complete the EOS visit approximately 3 years after the EOT visit.
- If a patient has a positive 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 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 may contain either 25 mg, 50 mg, or 75 mg ACE-536 for reconstitution with 0.5 mL, 1 mL, or 1.5 mL water, respectively, to form a citrate-buffered solution (50 mg/mL) for injection.

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.

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 guideline 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 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 IB.

Events Not to Be Considered as Adverse Events

Pre-existing medical conditions/signs/symptoms present before the Screening period (from study A536-03 for patients without treatment interruption; from study A536-05 for patients with treatment interruption) 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 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 (per IPSS-R[26], Appendix 3), 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 AE, 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 AEs 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 patients or observed during or following the course of investigational product administration on the appropriate CRF page. For patients without treatment interruption, any AE ongoing at the time of EOT in A536-03 needs to be re-entered as an AE in A536-05. For patients with treatment interruption, all non-serious AEs occurring after signing of the ICF until a patient is dosed on C1D1 are to be documented on the medical history CRF. All AEs and SAEs occurring after the Cycle 1 Day 1 dose until approximately 2 months after the last study drug administration (PTFU 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 approximately 2 months after the last study drug administration (PTFUS 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 approximately 2 months after the last study drug administration (PTFU visit). All patients who took at least one dose of study drug, whether they completed the treatment period or not, should complete the EOT, PTFU, LTFU, and EOS visits.

All unresolved AEs will be followed until clinical database lock (or resolution if it occurs before database lock). All unresolved 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 for the Investigator Site File. 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 (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 modified Intent-to-Treat Population (mITT): All patients enrolled in the study who received at least one dose of ACE-536.

Efficacy Evaluable (EE) Population: All patients who received at least one dose of ACE-536 and have 1) at least four hemoglobin assessments over an 8-week period post-treatment in NTD patients OR, 2) at least 8 consecutive weeks of transfusion frequency data between Cycle 1 Day 1 and EOT visit in TD patients.

Pharmacokinetics Population: All patients who received at least 1 dose of ACE-536 during Study A536-05 and have sufficient serum ACE-536 values 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, SD, median, and range).

15.2.2. Primary Endpoint Analysis

Safety analysis: To assess clinical safety, AEs, vital sign measurements and clinical laboratory information will be summarized. AEs 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.

15.2.3. Secondary Analysis

Efficacy/Pharmacodynamic Effects Analysis of Secondary Endpoints:
All efficacy analyses will be performed for the EE and mITT populations.

Efficacy will be evaluated by determining the proportion of patients who have a modified HI-E erythroid response rate based upon the IWG 2006 criteria (Appendix 5), defined as 1) A mean hemoglobin increase ≥ 1.5 g/dL over an 8-week period as compared to baseline, not influenced by RBC transfusion in NTD patients or 2) A decrease of ≥ 4 units or ≥ 50% of units of RBCs transfused over a period of 8 weeks, relative to the number of units of RBCs transfused in the 8 weeks immediately prior to Cycle 1 Day 1 in TD patients.

Baseline hemoglobin will be the average of two or more measures (not influenced by RBC transfusion) performed during the screening period for study A536-03 (for patients without interruption) or study A536-05 (for patients with interruption).

Baseline units of RBCs transfused will be the 8-week period prior to study A536-03 (for patients without interruption) or study A536-05 (for patients with interruption).

The erythroid response will be summarized using both a point estimate and its exact 95% confidence interval based on binomial distribution.

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

Analysis of other secondary efficacy/pharmacodynamic endpoints will include:

- Time to HI-E response and duration of HI-E response as per the IWG 2006 criteria and modified IWG criteria.
- Mean RBC transfusion burden
- Rate of RBC transfusion-free period lasting ≥ 8 weeks in TD patients.
- Mean hemoglobin level change in NTD patients
- Other PD endpoints including:
  - Biomarkers for iron overload/metabolism
  - Relationship of biomarkers to response
  - Rates of HI-E, HI-N and HI-P

Exploratory endpoints will include:

- Biomarkers related to the TGFβ superfamily.
- Patient-reported quality of life 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 C_{max}, T_{max}, and 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 ADAs on ACE-536 PK and drug exposure if ADA tests are deemed positive.

15.3. Determination of Sample Size

There is no formal sample size calculation for the study although up to 153 patients may participate from the A536-03 study.

15.4. Interim Analysis

Safety and erythroid response data will be reviewed periodically throughout the study. A formal interim analysis of the safety and efficacy data will be performed to support registration filings, as needed throughout the study conduct.

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[2]

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]
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)[6]

	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: Revised International Prognostic Scoring System (IPSS-R) for Myelodysplastic Syndromes (MDS)[26]

	IPSS-R Scoring Value						
Prognostic Variable	**0**	**0.5**	**1**	**1.5**	**2**	**3**	**4**
Cytogenetics[a]	Very good	—	Good	—	Intermediate	Poor	Very poor
Bone Marrow Blasts (%)	≤ 2	—	> 2 - < 5	—	5 - 10	> 10	—
Hemoglobin (g/dL)	≥ 10	—	8 - <10	< 8	—	—	—
Platelets (x 10^9/L)	≥ 100	50 - <100	< 50	—	—	—	—
Absolute Neutrophil Count (ANC; x 10^9/L)	≥ 0.8	< 0.8	—	—	—	—	—

— indicates not applicable
[a] Very good = -Y, del(11q); Good = Normal, del(5q), del(12p), del(20q), double including del(5q); Intermediate – del(7q), +8, +19, i(17q), any other single or double independent clones; Poor = -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities; Very poor = complex: > 3 abnormalities

Risk Category	**Risk Score**
Very low	≤ 1.5
Low	> 1.5 - 3
Intermediate	> 3 - 4.5
High	> 4.5 - 6
Very high	> 6

24.4. Appendix 4: 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

24.5. Appendix 5: International Working Group (IWG) Criteria - Erythroid Response Evaluation[1]

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.

24.6. Appendix 6: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0

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

24.7. Appendix 7: International Working Group Response Criteria for Myelodysplastic Syndromes[28]

Table 3. Proposed modified International Working Group response criteria for altering natural history of MDS[7]

Category	Response criteria (responses must last at least 4 wk)
Complete remission	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines*
	Persistent dysplasia will be noted*†
	Peripheral blood‡
	Hgb ≥ 11 g/dL
	Platelets ≥ 100 × 10^9/L
	Neutrophils ≥ 1.0 × 10^9/L†
	Blasts 0%
Partial remission	All CR criteria if abnormal before treatment except:
	Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5%
	Cellularity and morphology not relevant
Marrow CR†	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment†
	Peripheral blood: if HI responses, they will be noted in addition to marrow CR†
Stable disease	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following:
	Return to pretreatment bone marrow blast percentage
	Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets
	Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence
Cytogenetic response	Complete
	Disappearance of the chromosomal abnormality without appearance of new ones
	Partial
	At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with:
	Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts
	5%-10% blasts: ≥ 50% increase to > 10% blasts
	10%-20% blasts: ≥ 50% increase to > 20% blasts
	20%-30% blasts: ≥ 50% increase to > 30% blasts
	Any of the following:
	At least 50% decrement from maximum remission/response in granulocytes or platelets
	Reduction in Hgb by ≥ 2 g/dL
	Transfusion dependence
Survival	Endpoints:
	Overall: death from any cause
	Event free: failure or death from any cause
	PFS: disease progression or death from MDS
	DFS: time to relapse
	Cause-specific death: death related to MDS

Deletions to IWG response criteria are not shown.

To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

MDS indicates myelodysplastic syndromes; Hgb, hemoglobin; CR, complete remission; HI, hematologic improvement; PR, partial remission; FAB, French-American-British; AML, acute myeloid leukemia; PFS, progression-free survival; DFS, disease-free survival.

*Dysplastic changes should consider the normal range of dysplastic changes (modification).[41]

†Modification to IWG response criteria.

‡In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.