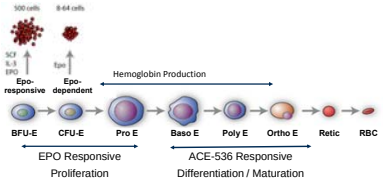
ACE-536 Increases Hemoglobin in Healthy Postmenopausal Women: A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study

Kenneth M. Attie[1], Ingrid E. Boyd[1], Dawn M. Wilson[1], Mark Allison[2], Matthew L. Sherman[1]
[1]Acceleron Pharma, Inc., Cambridge, MA; [2]Celerion, Tempe, AZ

Introduction

ACE-536 is a recombinant fusion protein consisting of a modified form of the extracellular domain of the human type IIB activin receptor linked to the human IgG1 Fc domain. ACE-536 acts as a ligand trap for members of the TGF-β superfamily involved in erythropoiesis.

ACE-536 promotes late-stage erythrocyte precursor cell differentiation by inhibiting specific TGF-β family ligands that control terminal differentiation. Studies of ACE-536 in several species demonstrated a rapid and robust red blood cell (RBC) response. ACE-536 also significantly improved hematologic parameters in mouse models of diseases with ineffective erythropoiesis, such as myelodysplastic syndromes (MDS) and β-thalassemia. This study is the first human clinical trial of ACE-536.



Methods

- This was a single-center, randomized, double-blind, placebo-controlled, multiple ascending dose study to evaluate the safety, tolerability, PK, and pharmacodynamic (PD) effects of ACE-536 in healthy, postmenopausal women (age 45-75 yr)
- The primary objective of the study was to evaluate safety and tolerability; secondary objectives included PK and PD effects
- Inclusion criteria included hemoglobin (Hgb) 11.0-14.5 g/dL, FSH >40 IU/L, and BMI 20-32 kg/m^2
- Sequential cohorts of 8 subjects each were randomized to receive either ACE-536 (n=6) or placebo (n=2) SC on Days 1 and 15
- ACE-536 dose levels tested prior to halting dose escalation (per protocol due to Hgb increase ≥ 1.5 g/dL in ≥ 2/6 subjects) were 0.0625, 0.125 and 0.25 mg/kg
- Per protocol individual dose-skipping rules for the Day 15 dose included Hgb increase ≥ 1.0 g/dL, increased BP, or ≥ grade 3 adverse event (AE)
- For Days 1-57, subjects were assessed for safety by monitoring AEs, clinical laboratory tests, ECG, vital signs and physical examination; Longer-term follow up visits occurred on Study Days 71 and 127

Demographics

- 32 subjects were enrolled, with mean (SD) age 59.4 (5.8) yr (Table 1)
- Mean (SD) baseline hemoglobin was 13.2 (0.6) g/dL

Table 1. Demographics and Baseline Characteristics.

Characteristic Mean (SD)	Placebo (N=8)	ACE-536 Treatment (mg/kg) 0.0625 (N=6)	0.125 x1 dose (N=6)	0.125 x2 doses (N=6)	0.25 (N=6)	Overall (N=32)
Age (yr)	58.6 (4.7)	59.3 (7.5)	57.7 (5.8)	60.5 (2.6)	61.0 (8.7)	59.4 (5.8)
Race, Ethnicity, n (%)						
Native American	1 (13%)	1 (17%)	0 (0%)	0 (0%)	0 (0%)	2 (6%)
Black	1 (13%)	1 (17%)	0 (0%)	0 (0%)	0 (0%)	2 (6%)
White, Non-Hispanic	4 (50%)	4 (67%)	3 (50%)	6(100%)	4(67%)	21(66%)
White, Hispanic	2 (25%)	0 (0%)	3 (50%)	0 (0%)	2 (33%)	7 (22%)
Weight (kg)	65.3 (7.5)	71.3 (3.4)	70.5 (7.8)	68.8 (10.6)	69.2 (9.6)	68.8 (7.9)
BMI (kg/m^2)	24.4 (2.3)	27.3 (3.3)	26.9 (2.9)	24.9 (3.0)	27.2 (2.9)	26.1 (3.0)
Hemoglobin (g/dL)	13.1 (0.6)	13.2 (0.6)	13.3 (0.3)	13.1 (0.9)	13.3 (0.7)	13.2 (0.6)

Pharmacokinetics

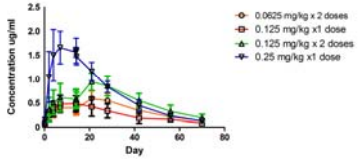
- Mean time to C_{max} (T_{max}) was 7.8-11.2 days and mean $T_{½}$ was 14.9-18.2 days and did not vary significantly with dose (Table 2)
- ACE-536 demonstrated dose-dependent increases for AUC_{0-14} and 1st dose Cmax (Figure 1)

Table 2. Pharmacokinetic Parameters for ACE-536 (Non-compartmental Analysis).

ACE-536 (mg/kg) Mean (SD)	0.0625 (n=6)	0.125 x1 Dose (n=6)	0.125 x2 Doses (n=6)	0.25 (n=6)
AUC_{0-14}, hr*µg/mL	4.7 (1.1)	6.5 (2.1)	6.1 (2.3)	19.6 (4.3)
C_{max}, 1st dose, µg/mL	0.43 (0.10)	0.58 (0.27)	0.56 (0.17)	1.78 (0.29)
T_{max}, 1st dose, days	10.0 (4.5)	11.0 (3.7)	11.2 (3.8)	7.8 (3.7)
$T_{1/2}$, days*	18.2 (2.8)	16.2 (2.2)	17.9 (3.1)	14.9 (1.6)
CL/F, mL/day/kg*	9.1 (2.9)	7.1 (3.8)	10.7 (2.4)	4.6 (0.5)
V_z/F, mL/kg*	230.3 (43.4)	159.2 (71.1)	258.4 (84.1)	98.9 (17.2)

* Uses last dose administered

Figure 1. Mean (±SD) ACE-536 Concentration Following 1 or 2 SC Doses.



Pharmacodynamic Effects

- The mean maximum hemoglobin increase from baseline at any timepoint in the 0.25 mg/kg group (n=6) was 1.3 g/dL (p<0.01 vs placebo [n=8]); 5/6 subjects in the 0.25 mg/kg group received a single dose of ACE-536
- The proportion of subjects with a hemoglobin increase ≥1.0 g/dL showed a dose-dependent increase (Figure 2)
- Mean hemoglobin levels increased in the 0.25 mg/kg group by at least 0.6 g/dL from Day 8 through Day 57, and decreased in the placebo group by up to 0.6 g/dL through Day 43 (Figure 3)
- A slight increase in mean reticulocyte count (Figure 4) was seen in groups treated with higher doses of ACE-536 as compared with the placebo group

Figure 2. Proportion of Subjects (%) with Hemoglobin Increase ≥1.0 g/dL.

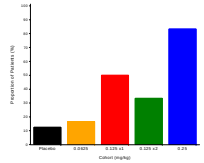


Figure 3. Mean (+SE) Change in Hemoglobin (g/dL).

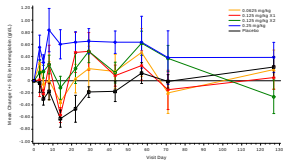
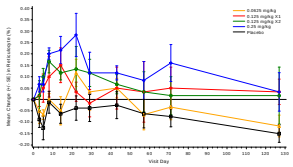


Figure 4. Mean (+SE) Change in Reticulocytes (%RBC).



Safety

- ACE-536 at doses up to 0.25 mg/kg SC generally well tolerated
- There were no serious or severe adverse events; 7/24 (29%) reported AEs at least possibly related to administration of study drug (Table 3)
- No clinically significant changes in laboratory measures, vital signs, physical exam, or ECG were observed, and no anti-drug Abs were detected

Table 3. Treatment-Related Adverse Events by Dose Group (No. of Subjects [%]).

Preferred Term	Placebo (N=8)	ACE-536 Treatment (mg/kg) 0.0625 (N=6)	0.125 x1 dose (N=6)	0.125 x2 doses (N=6)	0.25 (N=6)	Overall (N=32)
Injection site haemorrhage	0 (0%)	1 (17%)	1 (17%)	0 (0%)	1 (17%)	3 (9%)
Injection site macule	0 (0%)	0 (0%)	0 (0%)	1 (17%)	1 (17%)	2 (6%)
Injection site pain	1 (13%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Muscle spasms	0 (0%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	1 (3%)
Myalgia	0 (0%)	1 (17%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Hyperaesthesia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	1 (3%)
Dry Skin	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	1 (3%)
Macule	0 (0%)	0 (0%)	0 (0%)	1 (17%)	0 (0%)	1 (3%)
Pruritus, generalized	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	1 (3%)
Rash, papular	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (17%)	1 (3%)

Summary/Conclusions

- The results from this first-in-human clinical study show that ACE-536 is associated with a robust and sustained increase in hemoglobin levels in healthy subjects after one or two doses of 0.25 mg/kg SC
- Dose levels up to 0.25 mg/kg were generally safe and well-tolerated
- The PK profiles support SC dosing of ACE-536 once every 3 weeks
- These data support further evaluation of ACE-536 in diseases characterized by ineffective erythropoiesis and anemia; Phase 2 studies are ongoing in patients with MDS and β-thalassemia

Acknowledgments

- Acceleron: Christopher Rovaldi, Ty McClure, Amelia Pearsall, Ravi Kumar
- Independent consultants: Dan Waldon (PK); Angie Aldridge (CRA)
- Clinical laboratories: Celerion, ICON
- **Disclosure:** All authors were full-time employees of Acceleron Pharma or Celerion at the time of the study.

ACCELERON