

ACE-011, a Soluble Activin Receptor Type IIA IgG-Fc Fusion Protein, Increases Hemoglobin and Hematocrit Levels in Postmenopausal Healthy Women

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Introduction

- ACE-011 is a soluble fusion protein consisting of the extracellular domain of activin receptor type IIA (ActRIIA) linked to the Fc protein of human IgG1. ACE-011 binds with high affinity to activin and inhibits signaling through the ActRIIA receptor
- Activin signaling through the ActRIIA receptor regulates bone metabolism, red blood cell formation and reproductive tissue including breast
- Activin is known as erythroid differentiation factor (EDF) and is able to cause the premature differentiation of red blood cell precursors.
- In preclinical studies, ACE-011 administration to mice and cynomolgus monkeys is associated with increases in erythropoiesis

Study Design

- A randomized, double-blind, placebo-controlled, multiple-dose, dose-escalation study
- Four cohorts of 10 subjects (8 active: 2 placebo) were to receive 4 monthly doses of ACE-011 at 0.1, 0.3, 1.0, or 2.0 mg/kg or placebo by SC injection and followed for 3 months. Safety review were conducted on each cohort prior to dose escalation

Results

- 31 postmenopausal women, age ranging from 49 to 81 yrs: 7 subjects received placebo, 8 subjects received ACE-011 at 0.1 mg/kg (4 doses), 8 subjects received ACE-011 at 0.3 mg/kg (3 doses), and 8 subjects received ACE-011 1.0 mg/kg (2 doses)

Safety and Tolerability

- All 31 subjects were evaluable for safety and tolerability
- Commonly reported adverse events were headache, paresthesia, dizziness, and fatigue
- In the 1.0 mg/kg group, adverse events related to elevations of hematologic laboratory measures (hemoglobin, hematocrit and RBC) were noted. No erythroid lineage AEs were reported in the 0.1 or 0.3 mg/kg treatment groups
- One subject in the 1.0 mg/kg dose group experienced an SAE of persistent and progressive hypertension that was attributed to a rapid and significant rise in hemoglobin levels. This was considered dose limiting for this healthy population and resulted in the discontinuation of further study drug administration for all subjects. ACE-011 was well tolerated in all other subjects.

ACE-011 Increases Hemoglobin

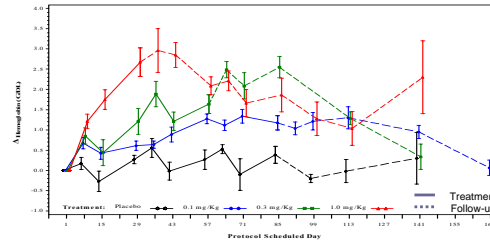


Figure 1a. Change in Hemoglobin (g/dL) vs. time

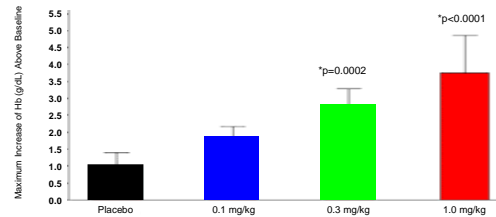


Figure 1b. Maximum increase in hemoglobin (g/dL) above baseline (p-values based on comparison to placebo group)

ACE-011 Increases Red Blood Cells

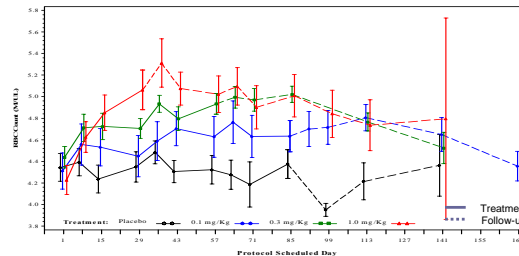


Figure 2. Red blood cells (M/uL) vs. time

Other Hematologic Results

- No clinically significant changes in WBC count, platelets, or reticulocytes were observed
- In a chronic anemic subject (baseline hemoglobin of 8.4 g/dL), within the first week following her first dose of 1 mg/kg ACE-011, hemoglobin increased to 9.6 g/dL and to as high as 11.0 g/dL within 3 weeks following her second dose of ACE-011. Hgb levels remained above baseline at the end of the study (9.8 g/dL). This subject did not have other obvious attributable causes for polycythemia
- 3 subjects with elevated hemoglobin levels were analyzed for JAK2 mutation and all tested negative

By blocking terminal red blood cell differentiation, ACE-011 allows for continued proliferation of red cell progenitors and ultimately, the production of greater numbers of mature red cells

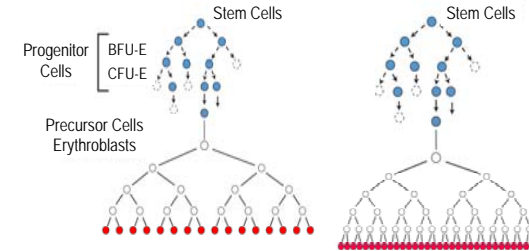


Figure 3. Proposed mechanism of ACE-011 driven increases in red blood cells

Conclusions

- ACE-011 increased hemoglobin, hematocrit and RBC levels in a dose-dependent manner in healthy postmenopausal women
- ACE-011 increased hemoglobin levels in a subject with chronic iron deficient anemia
- These data demonstrate that ACE-011 is a novel agent with potential for the treatment of patients with impaired erythropoiesis