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

Kenneth T Kim, MD[1], **Niels G Borgstein, MD**[2], **Yijun Yang**[2], **Eric Haltom**[2], **Louisa Mook**[2], **Michelle D Ababa, MD**[1], **Sandeep K Reddy, MD**[3] and **Matthew Leigh Sherman, MD**[2], (1)West Coast Clinical Trials, 5630 Cerritos Ave., Cypress, CA 90630, (2)Acceleron Pharma, 149 Sidney Street, Cambridge, MA 02139, (3)Suite 207, 3801 Katella Ave., Los Alamitos, CA 90720

ACE-011 is a soluble fusion protein consisting of the extracellular domain of activin receptor IIA linked to the Fc portion of human IgG1 and is a potent activin antagonist. ACE-011 is currently in clinical development for the treatment of bone loss in a variety of disease indications. In addition to its effect on bone forming cells, activin is also known as erythroid differentiation factor (EDF) and has been reported to have proerythrocytic effects and induced terminal differentiation of red blood cells (RBC). In preclinical studies, ACE-011 administration to mice and cynomolgus monkeys is associated with increases in erythropoiesis.

A randomized, double-blind, placebo-controlled, multiple-dose, dose-escalation study was conducted in healthy postmenopausal women to evaluate the safety, tolerability and pharmacodynamics of ACE-011 in 4 cohorts of 10 subjects (8 active: 2 placebo). Subjects were to receive 4 monthly doses of ACE-011 at 0.1, 0.3, 1.0 and 2.0 mg/kg or placebo by subcutaneous (SC) route of administration and followed up for 3 months. Safety evaluations were conducted on each cohort prior to dose escalation.

A total of 31 subjects received at least one dose of ACE-011 or placebo; 9 subjects in cohort 1 (0.1 mg/kg) received all 4 doses, 10 subjects in cohort 2 (0.3 mg/kg) received 3 doses and 9 subjects in cohort 3 (1 mg/kg) received 2 doses of either ACE-011 or placebo. A dose and time dependent increase in hemoglobin values was observed in all treatment groups; these elevations were statistically significant in the 0.3 and 1.0 mg/kg cohorts. A maximum tolerated dose level was determined to be 1 mg/kg after one subject experienced progressive and persistent hypertension that was attributed to a rapid and significant rise in hemoglobin levels approximately 1 week following her second dose of ACE-011. Increases in hemoglobin and hematocrit represent the dose limiting pharmacodynamic effects of ACE-011, and further dose escalation to the 2 mg/kg dose was suspended. These effects were seen in the red cell lineage; no significant effects on white blood cells or platelets were observed. JAK2 kinase activity was measured in 3 subjects with elevated hemoglobin levels after ACE-011 treatment and was negative.

Preliminary analysis of the data, 29 days after the administration of the first dose, is shown below.

Δ Hemoglobin (g/dL) **from baseline**	**Placebo** (n=7)	**0.1 mg/kg** (n=8)	**0.3 mg/kg** (n=8)	**1 mg/kg** (n=8)
Day 8 Mean (SD) Median Min, Max	0.171 (0.399) 0.3 -0.3, 0.7	0.675 (0.403) 0.65 0.20, 1.2	0.85 (0.563)* 0.75 0.2, 1.6	1.213 (0.506)** 1.25 0.4, 2.0
Day 15 Mean (SD) Median Min, Max	-0.35 (0.695) -0.55 -1.1, 0.8	0.425 (0.413) 0.6 -0.3, 0.9	0.438 (0.912)* 0.3 -0.6, 2.4	1.75 (0.685)** 1.5 0.9, 3.1
Day 29 Mean (SD) Median Min, Max	0.34 (0.207) 0.4 0, 0.5	0.613 (0.323) 0.7 -0.1, 1.0	1.212 (0.909)* 1.15 0.1, 2.8	2.675 (0.997)** 2.45 1.7, 4.4

* $p<0.05$, ** $p<0.01$ compared to placebo

In one of the subjects with a history of chronic anemia, as a result of iron deficiency, the hemoglobin level increased by almost 2 g/dL from a baseline value of 8.4 g/dL following the first SC dose of 1 mg/kg ACE-011, and reached a level of 11 g/dL within 3 weeks after the second dose of ACE-011.

ACE-011 was generally well tolerated, except for the case described above with uncontrolled hypertension at the 1 mg/kg dose level. The majority of the non-hematological treatment-emergent adverse events were mild in severity and not related to study drug. A dose-dependent decrease in serum FSH levels, a biological marker of activin inhibition, was also observed in postmenopausal subjects following treatment with ACE-011.

These data indicate that ACE-011 is associated with increases in hemoglobin and hematocrit levels in both healthy volunteers as well as in a subject with iron deficiency anemia and may be a potential novel agent for the treatment of patients with impaired erythropoiesis.

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Submitter's E-mail Address: nborgstein@acceleronpharma.com
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