INTRODUCTION

Patients with end-stage kidney disease (ESKD) suffer reduced quality of life, primarily caused by decreased renal function. Erythropoiesis-stimulating agents (ESAs) effectively increase hemoglobin (Hb) levels in patients with ESKD, but they are associated with increased risks of cardiovascular disease (CVD) and mortality. The US Food and Drug Administration has required manufacturer risk management plans for ESAs to address these risks.

Although these risks are linked to a poor cardiovascular outcome in ESKD patients, CVDs do not readily occur at the targeted Hb range (10–12 g/dL).

Sotatercept (ACE-011), an SHH agonist that promotes late-stage erythropoiesis and acts during late-stage erythropoiesis to increase the production of mature erythrocytes, is being investigated for the treatment of renal anemia. In this study, we assessed the safety, tolerability, and efficacy of sotatercept in ESKD subjects with renal anemia.

METHODS

Study Design and Administration

A total of 35 subjects were randomized and received ≥1 dose of study medication and comprise the full safety population. Subjects were randomized to placebo or one of three dose levels of sotatercept: 0.3 mg/kg, 0.5 mg/kg, and 0.7 mg/kg. Treatment was administered subcutaneously, as 7-day dosing cycles. The study comprised a 7-day treatment phase, a 7-day follow-up phase, and a 183-day observation period. The treatment phase was followed by a 7-day treatment-free period.

RESULTS

Subjects

A total of 35 subjects entered the study; 21 completed the study, and 14 withdrew prematurely (9 due to AEs, 5 due to protocol-off deviations). The target population comprised patients on hemodialysis, peritoneal dialysis, or home hemodialysis with a predialysis Hb level of 8–12 g/dL and a target Hb level of 10–12 g/dL. Subjects had a mean age of 59.2 years, and 80% were men.

Efficacy

Subjects entered the study with a mean baseline Hb level of 8.9 ± 1.5 g/dL and a mean Hb increase of 0.9 ± 0.6 g/dL following ESA washout. The target Hb range (10–12 g/dL) was maintained for 10%, 19%, 27%, and 32% of all possible dose cycles. The median time to achieve the target Hb range was 5.3 months. The proportion of subjects with an Hb increase ≥1 g/dL and an Hb ≥10 g/dL at the end of each dose cycle was 7%, 17%, 27%, 32%, and 36%.

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The mean change from baseline in serum erythropoietin (EPO) levels (IAA) during the study was –0.1 ± 3.0 IU/L, –2.4 ± 0.5 IU/L, –2.3 ± 0.8 IU/L, and –2.1 ± 0.3 IU/L for the placebo, 0.3 mg/kg, 0.5 mg/kg, and 0.7 mg/kg groups, respectively. This was an expected finding due to increased endogenous EPO synthesis, as a consequence of increased erythropoiesis.

Safety

The most frequent adverse events (AEs) were injection-site reactions, pain, hypertension, and anemia. The most frequent laboratory abnormalities were increases in serum creatinine, calcium, and phosphorus levels. There were no dose-dependent changes in home blood pressure (BP) measurements. Ten subjects had AEs of hypocalcemia.

CONCLUSIONS

Sotatercept 0.3 mg/kg displayed lower and less consistent serum Hb concentrations (range: –2.0 to –11.0 IU/L) that was not observed in other dose groups. This is an expected finding due to increased endogenous EPO synthesis, as a consequence of increased erythropoiesis.

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