IMPROVEMENTS IN HEMOGLOBIN, QUALITY OF LIFE, AND SIX-MINUTE-WALK DISTANCE IN ADULTS WITH B-THALASSEMIA TREATED WITH LUSPATERCEPT: LONG-TERM PHASE 2 STUDY

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Background

Serious hematologic conditions such as β-thalassemia are associated with an erythroid maturation defect leading to anemia and other clinical sequelae. Luspatercept (ACE-536) is being developed as an erythroid-maturation agent (EMA) for treatment of β-thalassemia. Luspatercept binds to select TGF-β superfamily ligands, reducing aberrant Smad2/3 signaling and promoting late-stage erythroid maturation and increased hemoglobin (Hgb); it has corrected the effects of ineffective erythropoiesis in a mouse model of thalassemia (Suragani R, Blood, 2014), and increased Hgb and was well tolerated in a phase 1 study in healthy volunteers (Attie K, Am J Hematol, 2014).

Aims

This ongoing, phase 2, multicenter, open-label study followed by a long-term extension (ext) evaluates the effects of luspatercept in patients (pts) with either transfusion-dependent (TD) or non-transfusion dependent (NTD) β-thalassemia. Key endpoints include Hgb increase, pt-reported quality-of-life (QoL) and assessment of functional improvement in 6-minute walk distance (6MWD) in NTD pts, and reductions in RBC transfusion burden in TD pts.

Methods

Inclusion: age ≥18 yr and either NTD (<4 RBC U/8 weeks prior to first dose with baseline Hgb <10 g/dL) or TD (≥4 RBC U/8 weeks prior to first dose, confirmed over 6 months). Pts treated every 3 weeks subcutaneously for up to 5 doses (titration up to 1.25 mg/kg) in the base study were then eligible for treatment up to 5 additional years (base completed NCT01749540; ext ongoing NCT02268409).

Results

Data (as of 31Aug2017) were available for 63 pts treated at dose levels ≥0.6 mg/kg. 31 NTD, 32 TD; median (range) age (yr) was 38 (20-62); 67% had prior splenectomy. For NTD pts, at baseline, median (range) Hgb (g/dL) was 8.5 (6.5-9.8); mean (SD) liver iron concentration (LIC, mg/g dw) was 5.1 (3.6). For TD pts, at baseline, median (range) transfusion burden was 8 U/12 weeks (4-18 U); mean (SD) LIC (mg/g dw) was 4.7 (4.7).

22/31 (71%) NTD pts achieved mean Hgb increase of ≥1.0 g/dL and 17/31 (55%) achieved an even greater increase of ≥1.5 g/dL in mean Hgb over any 12-week period compared to baseline. Increases in mean Hgb over a 12-week period correlated positively with improvement in both a pt-reported QoL questionnaire (FACIT-F) and with improvements in 6MWD at weeks 16 and 48. At week 48, a statistically significant improvement from baseline in mean (SD) 6MWD was seen in NTD pts (n=9), 484 (121) vs 408 (68) meters, p=0.02.

22/32 (69%) TD pts achieved ≥33% reduction in transfusion burden over any 12-week interval compared to baseline. 12/29 (41%) achieved ≥33% reduction in transfusion burden over a fixed 12-week interval (weeks 13-24) compared to baseline, and 12/29 (41%) continued to have a response at a fixed interval of weeks 37-48 on study.

Luspatercept was generally well tolerated, with no related serious adverse events and few grade 3 related AEs: bone pain (n=3), asthenia (n=2), and headache (n=1). The most frequent related AEs (≥10%) were bone pain, headache, myalgia, arthralgia, musculoskeletal pain, asthenia, injection site pain, and back pain.

Conclusion

In this phase 2 open-label study, long-term luspatercept treatment in pts with β-thalassemia was generally safe and

well tolerated up to 2 years. Clinically relevant measures of luspatercept efficacy were observed in both NTD pts (increased Hgb levels and improved QoL) and TD pts (decreased transfusion burden).

Session topic: 28. Thalassemias

Keyword(s): Erythroid differentiation, Erythropoieisis, TGF-, Thalassemia