Pharmacokinetics and Exposure–Response of Luspatercept in Patients With β-Thalassemia: Preliminary Results From Phase 2 Studies

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INTRODUCTION
- A phase 1 trial established the production of a full-length chimaeric 2-stage erythrocyte differentiation, leading to ineffective erythropoiesis and anemia.
- Luspatercept (ACE-536) is a novel recombinant β3 integrin receptor that acts as a ligand to block linchpins of late-stage erythropoiesis in the TGF-β superfamily.
- Luspatercept has been shown to ameliorate ineffective erythropoiesis in a murine model of β-thalassemia.

METHODS
- Study Design
  - Pharmacokinetics, safety, and efficacy data were collected from two phase 2 studies (base and extension: NCT01749540 and NCT02268409) of luspatercept for the treatment of anemia in patients with β-thalassemia.
- Patients were categorized by transfusion burden at baseline:
  - NTD (non-transfusion-dependent): ≥ 1 g/dL increase in Hb
  - TD (transfusion-dependent): < 1 g/dL increase in Hb

OBJECTIVE
- To characterize the pharmacokinetics of luspatercept and to explore the exposure-response relationship for efficacy, and safety in patients with β-thalassemia.
- To establish the appropriate starting dose and dose-ranging in the phase 3 studies of luspatercept in β-thalassemia.

RESULTS
- INTRODUCTION
  - Phase 3 Starting Dose and Target AUC: Exposure–response modeling and pharmacokinetic simulation support a phase 3 starting dose of 1.0 mg/kg, with intra-patient dose escalation up to 1.25 mg/kg dependent upon patient response.
  - A phase 3 study of luspatercept for the treatment of moderately transfusion-dependent adults with β-thalassemia is ongoing (the BELIEVE study; ClinicalTrials.gov identifier: NCT03036042).

CONCLUSIONS
- Higher luspatercept serum exposure correlated with greater erythroid response.
- Exposure-response modeling and pharmacokinetic simulation support a phase 3 starting dose of 1.0 mg/kg, with intra-patient dose escalation up to 1.25 mg/kg dependent upon patient response.

REFERENCES

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DISCLOSURES