HemaSphere

EHA EUROPEAN HEMATOLOGY ASSOCIATION

(S104) ENERGIZE: A GLOBAL PHASE 3 STUDY OF MITAPIVAT DEMONSTRATING EFFICACY AND SAFETY IN ADULTS WITH ALPHA- OR BETA-NON–TRANSFUSION-DEPENDENT THALASSEMIA

Topic: 27. Thalassemias

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Background:

In thalassemia, ATP production in erythroid progenitor cells is insufficient to meet the increased demand of oxidative stress resulting from unpaired globin chain precipitation, hemichrome formation, and ensuing cellular damage; this leads to ineffective erythropoiesis (IE) and chronic hemolytic anemia. Guidelines for non–transfusion-dependent thalassemia (NTDT) recommend raising hemoglobin (Hb) by ≥1 g/dL to reduce morbidities attributed to IE and anemia. No oral disease-modifying therapies are approved for the treatment of β-thalassemia, and no agents are approved for α-thalassemia. Mitapivat is a first-in-class, oral, allosteric activator of pyruvate kinase that increases ATP production. Mitapivat may decrease metabolic stress, addressing the underlying pathophysiology across the full range of thalassemias, with the potential to reduce complications and improve health-related quality of life (HRQoL).

Aims:

To assess the efficacy and safety of mitapivat vs placebo in adults with α- or β-NTDT in ENERGIZE (NCT04770753), a phase 3, double-blind, randomized, placebo-controlled, global trial.

Methods:

Adults (≥18 years) with α- or β-NTDT and baseline (BL) Hb ≤10 g/dL were randomized 2:1 to mitapivat 100 mg twice daily or placebo for 24 weeks (wks). NTDT was defined as ≤5 red blood cell (RBC) units transfused 24 wks before randomization and no RBC transfusions ≤8 wks before informed consent or during screening. The primary endpoint was Hb response (defined as ≥1.0 g/dL increase in average Hb concentration over Wks 12–24 compared with BL). Key secondary endpoints were changes from BL in average Hb concentration and Functional Assessment of Chronic Illness Therapy–Fatigue Scale (FACIT-Fatigue) score over Wks 12–24. Safety and markers of hemolysis and erythropoiesis were among the secondary

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endpoints.

Results:

194 patients (pts) were randomized (mitapivat N=130; placebo N=64); 94.8% completed the 24-wk trial. Mean age was 41.2 years, mean BL Hb was 8.3 g/dL, 86.6% received no transfusions in the 24 wks before randomization, and 32.0% had α-NTDT. BL characteristics were similar between treatment arms.

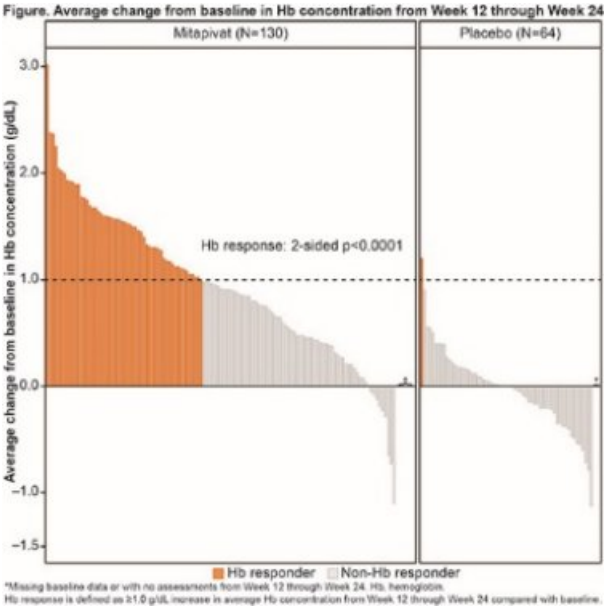
Mitapivat demonstrated statistically significant improvements vs placebo for Hb response (42.3% vs 1.6%, respectively; 2-sided p<0.0001 [Figure]), and for changes from BL in Wks 12–24 average Hb (least-squares mean [LSM] difference (95% CI): 0.96 g/dL (0.78, 1.15); 2-sided p<0.0001) and Wks 12–24 average FACIT-Fatigue score (LSM difference (95% CI): 3.40 (1.21, 5.59); 2-sided p<0.0026). Results favored mitapivat across all prespecified subgroups. Improvements in several markers of hemolysis and erythropoiesis were also observed, consistent with the proposed mechanism of mitapivat.

The proportion of pts with treatment-emergent adverse events (TEAEs) of any grade was similar across treatment arms (mitapivat 82.9%; placebo 79.4%). The most common TEAEs (≥10% of pts) with mitapivat were headache, initial insomnia, nausea, and upper respiratory tract infection. Among mitapivat-treated pts, 6.2% had serious TEAEs (none considered treatment related) and 3.1% had TEAEs leading to treatment discontinuation; none occurred with placebo.

Summary/Conclusion:

Mitapivat significantly increased Hb and improved fatigue vs placebo; improvements were observed across all prespecified subgroups. Mitapivat was generally well tolerated with a low treatment discontinuation rate. These data are the first proof of efficacy of a disease-modifying therapy across the full range of NTDT (α- and β-thalassemia). Mitapivat may represent a new oral treatment option addressing both pathophysiology and HRQoL in thalassemia.

Figure. Average change from baseline in Hb concentration from Week 12 through Week 24



*Missing baseline data or with no assessments from Week 12 through Week 24. Hb, hemoglobin.
Hb response is defined as ≥1.0 g/dL increase in average Hb concentration from Week 12 through Week 24 compared with baseline.

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