Long-term safety and efficacy of bempedoic acid in patients at high risk of atherosclerotic cardiovascular disease: results from the CLEAR Harmony open-label extension study

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Background: Bempedoic acid (BA) is an oral first-in-class, ATP-citrate lyase inhibitor that lowers low-density lipoprotein cholesterol (LDL-C) levels in adults with hypercholesterolemia. In the phase 3 CLEAR Harmony study (NCT02666664, n=2230), BA 180 mg for 52 weeks significantly lowered LDL-C at week 12 compared with placebo and was maintained for 52 weeks in hypercholesterolemic patients with atherosclerotic cardiovascular disease (ASCVD) and/or heterozygous familial hypercholesterolemia (HeFH) on stable, maximally tolerated statins.

Purpose: To report long-term safety, tolerability, and efficacy of BA from the CLEAR Harmony open-label extension (OLE) study (NCT03067441).

Methods: After completing the 52-week placebo-controlled CLEAR Harmony study, patients immediately entered the OLE and received BA for 78 weeks, followed by a 4-week washout period; the potential cumulative exposure to BA was 2.5 years. The primary endpoint was long-term safety of BA in the OLE.

Results: A total of 1462 patients enrolled in the OLE (BA n=970; placebo n=492 from CLEAR Harmony). At OLE baseline, mean (SD) age was 66.9 (8.7) years, 73.9% were male, 96.3% had ASCVD, 3.7% had HeFH with or without ASCVD, and all were receiving statins (93.5% moderate or high intensity). At baseline of CLEAR Harmony, patients had mean (SD) LDL-C of 102.9 (29.9) mg/dL (BA) and 99.0 (24.2) mg/dL (placebo). The majority of OLE patients (86.2%, n=1260) completed 78 weeks of BA treatment. At week 12 and 78 of OLE treatment, respectively, mean LDL-C lowering from CLEAR Harmony baseline was −14.9% and −14.4%. A total of 1143 patients (78.2%) reported a treatment-emergent adverse event (TEAE), and 299 (20.5%) reported a serious TEAE. TEAEs of special interest, determined by the therapeutic area or prior observations in preclinical or early clinical studies, occurred at similar rates as CLEAR Harmony (creatine kinase elevations, 1.8%; gout, 2.6%; hepatic enzyme elevations, 2.0%; hypoglycemia, 1.2%; muscular disorders, 8.5%; neurocognitive disorders, 0.9%; new onset/worsening diabetes mellitus, 5.5%; renal disorders, 2.8%) with biochemical changes that were stable over the course of the study and approached baseline levels after treatment discontinuation. Overall, 114 patients (7.8%) reported a TEAE leading to discontinuation of BA (most common: myalgia [0.6%], muscle spasm [0.5%]).

Conclusion: Durable lipid lowering was observed through 78 weeks of BA treatment and patient adherence to BA therapy was high (86.2%). Overall safety during the OLE was similar to results reported in the 52-week-long CLEAR Harmony study and the overall BA phase 3 clinical program, with no new safety findings.