

Bempedoic Acid Plus Ezetimibe Fixed-Dose Combination in Patients with Hypercholesterolemia and High CVD Risk Treated with Maximally Tolerated Statin Therapy

BACKGROUND

- Despite the development of effective therapeutic options, many patients fail to achieve adequate lowering of low-density lipoprotein (LDL) cholesterol.
- Bempedoic acid is a once-daily, oral, first-in-class adenosine triphosphate-citrate lyase (ACL) inhibitor.
- As bempedoic acid and ezetimibe both lower LDL-cholesterol by the upregulation of LDL receptor expression, an effect achieved through disparate mechanisms, there is a strong rationale for the development of a fixed-dose combination (FDC) of the two agents.

OBJECTIVE

- Evaluate the efficacy and safety of a bempedoic acid 180 mg and ezetimibe 10 mg FDC compared with placebo, ezetimibe 10 mg alone, and bempedoic acid 180 mg alone in patients with hypercholesterolemia at high CVD risk who were receiving maximally tolerated background statin therapy.

METHODS

- **Design:** Multisite, double-blind, randomized parallel trial; Duration: 12 weeks
- **Inclusion criteria:** presence of ASCVD (history of acute myocardial infarction (MI), silent MI, unstable angina, coronary revascularization procedures, clinically significant coronary heart disease (CHD), symptomatic peripheral arterial disease or cerebrovascular atherosclerotic disease) or heterozygous familial hypercholesterolemia (HeFH) with a baseline fasting LDL-cholesterol 100 mg/dL or greater; multiple CVD risk factors defined as diabetes plus one other risk factor or three CVD risk factors with a baseline fasting LDL-cholesterol 130 mg/dL or greater; receiving maximally tolerated statin
- **Exclusion criteria:** Total fasting triglycerides of 500 mg/dL or greater; body mass index (BMI) of 40 kg/m² or greater; recent cardio-vascular or cerebrovascular event or procedure (within 3 months prior to screening); other clinically relevant disease that would interfere with study participation.
- **Primary outcome measure:** The percentage change from baseline to week 12 in LDL-cholesterol.
- **Secondary outcome measures:** Percentage change from baseline to week 12 in hsCRP, non-HDL-cholesterol, total cholesterol and apolipoprotein B.
- 382 patients were randomly assigned 2:2:2:1 to treatment with:
 - BA 180 mg + EZE 10 mg FDC (n=108)
 - bempedoic acid 180 mg (n=110)
 - ezetimibe 10 mg (n=109) OR
 - placebo (n=55)
- An overall power of at least 92% was calculated for 100 patients per active treatment groups and 50 patients in the placebo arm.

- Data handling method was post hoc after data from three sites were excluded due to integrity concerns.

RESULTS

- 301 patients completed the study: 86 in BA group, 88 in BA + EZE group, 86 in EZE group, 41 in placebo group.
- **Primary outcome measure:** LDL-cholesterol lowering with BA + EZE FDC was significantly greater than that for the placebo, ezetimibe, or bempedoic acid groups ($P < 0.001$ for all comparisons) with BA + EZ FDC providing a reduction of 36.2%.
- **Secondary outcome measures:** BA + EZE FDC reduced hsCRP by 35.1% compared with an increase of 21.6% in the placebo group ($P < 0.001$) and a reduction of 8.2% in the ezetimibe group ($P = 0.002$). BA + EZE FDC reduced non-HDL cholesterol, total cholesterol and apolipoprotein B more than placebo ($P < 0.001$), ezetimibe ($P < 0.003$) or bempedoic acid ($P < 0.001$).
- **Author's conclusion:** The addition of BA + EZE FDC to maximally tolerated statin therapy provides significant atherogenic lipid lowering compared with either agent alone or placebo.

STRENGTHS

- Random assignment stratified by CVD risk category and baseline intensity to make groups more equivalent
- Prohibited use of other lipid-lowering therapies that could have skewed results

LIMITATIONS

- Short study duration
- High dropout rate/site exclusions
- Exclusion criteria too stringent
- Slight imbalances in baseline demographics among treatment groups
- Nonpharmacological treatments (diet, exercise) were not taken into account

CONCLUSION

- The addition of BA + EZE FDC to maximally tolerated statins can help patients achieve LDL-cholesterol goals.
- Although an effective therapy, it may not be cost effective when CV benefits have not yet been studied as only the brand name is available in pharmacies.
- Future studies with a longer duration are needed to assess CVD outcomes.

Reference: Ballantyne CM, Laufs U, Ray KK, et al. Bempedoic acid plus ezetimibe fixed-dose combination in patients with hypercholesterolemia and high CVD risk treated with maximally tolerated statin therapy. *Eur J Prev Cardiol.* 2020;27(6):593-603.

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