Efficacy and safety of bempedoic acid in association with anti-PCSK9 and ezetimibe in statin-intolerant patients: a randomized crossover trial

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Promoter of the study

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Background

Statin intolerance occurs in up to 15-20% of treated patients, appearing as muscle aches, pains, weakness, cramps, or because of abnormalities in serum markers of liver or muscle function.[1, 2] These conditions are associated with treatment discontinuation, increased low-density lipoprotein cholesterol (LDL-C) value and higher risk of cardiovascular events.[2]

The combined use of Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors with ezetimibe is commonly performed in these patients, and has been associated with an estimated LDL-C reduction of 65-70%.[3-5] This drug combination may be insufficient to reach the LDL-C target in high- and very-high-risk patients with statin intolerance, also considering the goals recommended by the current international guidelines.[6] Also, PCSK9 inhibitor dosage escalations frequently fail to achieve the target. Doubling the dosage of alirocumab from 75 mg to 150 mg, when administrated as monotherapy, determines a further reduction of only 3,6% of LDL-C serum level.[5, 7] The full dose of Evolocumab (420 mg every two weeks), was approved only in the setting of homozygous familiar hypercholesterolemia.[8]

Bempedoic acid is an oral, once-daily prodrug, metabolized in the liver to an active inhibitor of ATP-citrate lyase, blocking cholesterol synthesis upstream of 3-hydroxy-3-methylglutaryl-coenzyme A reductase and thereby increasing hepatic expression of the LDL receptor and decreasing circulating LDL-C levels.[9]

The CLEAR (Cholesterol Lowering via Bempedoic acid, an ACL-Inhibiting Regimen) Harmony trial demonstrated that bempedoic acid in addition to maximally tolerated statin therapy did not lead to a higher incidence of adverse events compared to placebo and significantly lowered LDL-C levels.[10] In the CLEAR Serenity study, bempedoic acid showed a safe and effective profile compared with placebo in patients with statin intolerance.[11] In the CLEAR Tranquility, it provided an oral therapeutic option complementary to ezetimibe in patients intolerant to high-dose statins who required additional LDL-C lowering.[12]

Rational

PCSK9 is a secreted glycoprotein which modulates the circulating levels of LDL-C through downregulation of the expression of low density lipoprotein receptor (LDL-R). PCSK9 synthesis is transcriptionally regulated by the intracellular cholesterol pool.[13]

Statins decrease hepatic intracellular cholesterol and induce the nuclear translocation of sterol-regulatory element binding protein-2 (SREBP-2), which increase PCSK9 expression as well as its circulating levels.[14-16] The synergistic effect of PCSK9 inhibitors when combined with statins has been previously demonstrated and has been associated with an additional mean reduction of LDL-C of -14.2%.[4, 17-20] Conversely, PCSK9 inhibitors up-titration reduced the mean LDL-C level of only 3% in most of the patient not receiving statins.[5, 7]

Bempedoic acid, by regulating the same metabolic pathway of statin, might increase the expression of PCSK9 and exert a synergistic effects with PCSK9 inhibitors. Bempedoic acid reduces cholesterol synthesis through inhibition of ATP-citrate lyase, an enzyme upstream from 3-hydroxy-3-methylglutaryl-coenzyme A determining an increased expression of SREBP-2 and PCSK9 in mice.[9, 21] Moreover Bempedoic acid has been demonstrated to increase the expression of mRNA encoding PCSK9 of about 1.5 fold in human hepatocytes.[21] Hence, bempedoic acid mimic the biological effect of statins in terms of overexpression and increased hepatocellular secretion of PCSK9, and might enhance the effect of PCSK-9 in term of LDL-C reduction.

The synergistic effect of bempedoic acid plus PCSK9 inhibitors has been investigated by one phase 2 trial (NCT03193047), which showed a statistical superiority of bempedoic acid plus evolocumab strategy versus placebo plus evolocumab in terms of percent change in LDL-C up to 2 months.[22] To date, no randomized phase 3 clinical trial have evaluated the effect of bempedoic acid in association with anti-PCSK9 and ezetimibe in statin-intolerant patients not attaining the recommended LDL-C target.

We hypothesized that the association of bempedoic acid with PCSK9 inhibitors and ezetimibe may be safe and effective in reducing LDL-C in statin-intolerant patients.

Study design

This is an investigator-initiated, phase 4, open-label, multicentre, 2-way crossover trial. The study will enlist statin-intolerant patients at high-risk and very high-risk of cardiovascular events, not reaching the LDL-C goal recommended by the 2019 ESC/EAS Guidelines for management of dyslipidaemias based on their individual risk estimate (Tables 1 and 2).[6] The patients enrolled have to be intolerant to statin and have not changed their hypolipidemic therapy within 6 weeks prior recruitment.

The study design is depicted in Figure 1. Eligible participants as per the inclusion criteria will be randomized with 1:1 allocation ratio, without restrictions, into two treatment sequences of 12 weeks, respectively, separated by a washout period of 4 weeks.

Being the inclusion criteria of this study highly selective, the rationale behind the crossover design is the lower sample size needed, and the shorter times to complete the enrolment. Furthermore, since the patients will serve as their own controls, the influence by confounders will be reduced. Being the primary endpoint of this study result of laboratory measurements, we assumed the absence of any carryover effect after the washout period of 4 weeks. Moreover, we assumed the absence of any period effect on the study endpoint.

The phase 1 will start at week 0 (P_1-0)and stop at week 12 (P_1-12); the phase 2 will start at week 16 (P_2-0), after the washout period, and stop at week 28 (P_2-12).

The two study treatments will be:

- PCSK9 inhibitors (Evolocumab 140 mg or Alirocumab 75 mg or Alirocumab 150 mg) plus Ezetimibe 10 mg plus Bempedoic acid (Treatment A)
- PCSK9 inhibitors (Evolocumab 140 mg or Alirocumab 75 mg or Alirocumab 150 mg) plus Ezetimibe 10 mg (Treatment B)

All patients will be randomly assigned to a Treatment A-Treament B (AB Group) sequence or to a Treatment B-Treatment A (BA Group) sequence.

We will record laboratory and clinical variables at study visits scheduled for weeks 0, 4, 12, 16, 20, 28. Blood samples will be collected and stored at each visit by the participating centres, and analysed by a central core laboratory (University of Salerno).

At the end of the study, the decision to continue or not treatment with bempedoic acid, as well as any other therapeutic decision, will be left to the treating physician.

Inclusion Criteria:

- High- or very-high-risk patients (Table 1) who do not reach the recommended LDL-C target (Table 2) despite lipid-lowering pharmacological therapy for primary or secondary prevention (≤70 mg/dl in high-risk patients, ≤55 mg/dl in very-high-risk patients and ≤40 mg/dl in patients with 2 major cardiovascular events within 2 years)[6]
- Patients treated with PCSK9 inhibitors plus ezetimibe for at least 12 weeks
- Patients with statin intolerance, defined as inability to tolerate at least two statins, one at the lowest starting daily dose and another at any daily dose, either due to objectionable symptoms (real or perceived) or abnormal laboratory analysis, temporally related to statin treatment, reversible upon statin discontinuation, reproducible by rechallenge (restarting medication), and excluding other known factors)
- Age ≥18 years

Exclusion Criteria:

- Fasting blood triglycerides greater than or equal to 500 mg/dL
- Body Mass Index (BMI) greater than or equal to 50 kg/m2
- Severe chronic kidney disease (GFR< 30 ml/min) or glomerular nephropathy
- Recent history (<4 weeks) of clinically significant cardiovascular disease or planning to undergo a major surgical or interventional procedure

- Statin assumption (including low/medium dose and low/medium intensity statins)
- Uncontrolled hypertension
- Uncontrolled hypothyroidism or hyperthyroidism
- Liver disease or dysfunction (Child-Pugh B)
- Gastrointestinal conditions or procedures that could affect drug absorption
- Active malignancy
- Unexplained creatine kinase elevations >3 times the upper limit of normal
- Lipid-modifying therapies prohibited: mipomersen within 6 months of screening, lomitapide, or apheresis within 3 months of screening, inhibitor cholestrerol ester transfer protein inhibitors within 2 years of screening (with the exception of evacetrapib, which must have been discontinued ≥3 months prior to screening); and red yeast rice extract and berberine-containing products within 2 weeks of screening
- Participation in other studies
- Unavailable to sign informed consent

Primary endpoint

- The primary endpoint is the mean percentage change in LDL-C after 12 weeks of treatment

Secondary endpoints

Beside the safety and the efficacy in reducing LDL-C, secondary objectives of this study are the evaluation of PCSK9 serum levels, lipid and inflammatory profile, and glucose metabolism parameters in statin-intolerant patients treated with bempedoic acid, PCSK9 inhibitors and ezetimibe. Indeed, no previous studies have evaluated changes of PCSK9 serum levels in humans during treatment with bempedoic acid, especially in absence of statin. This information would increase

current knowledge on the mechanisms of action and may corroborate the hypothesis of a synergistic effect of bempedoic acid and PCSK9 inhibitors.

Insulin resistance (IR) is a leading mechanism in the pathophysiology of type 2 diabetes mellitus, hypertension, dyslipidaemia, atherosclerotic vascular disease, and has been associated with the risk of coronary heart disease and stroke.[23] A recent meta-analysis of five studies and 3,629 patients showed that the use of bempedoic acid significantly reduces the risk of new onset or worsening diabetes.[24] No previous studies have investigated about the effects of bempedoic acid on insulin resistance in human, especially in patients not treated with statins, which may act as a potential confounder. IR, sensitivity and beta cell function can be non-invasively measured by using the homeostasis model assessment (HOMA) calculations based on fasting glucose, fasting insulin, and/or C-peptide levels.[25, 26]

On this basis, the following secondary endpoints will be considered for this study:

- The mean absolute change from baseline to week 12 in low-density lipoprotein cholesterol
- Percentage of patients reaching the recommended LDL-C target
- Changes in plasmatic levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C), non-HDL cholesterol, lipoprotein(a), apolipoprotein B, fasting glucose, glycated haemoglobin (HbA1c), fasting insulinemia, homeostatic model assessment (HOMA) index, high-sensitivity C-reactive protein (hs-CRP) after 12 weeks of treatment
- Changes in PCSK9 serum levels before starting the treatment and after 12 weeks of treatment
- Number of participants with abnormal uric acid level, abnormal AST/ALT level, ALT or AST >3x ULN, and/or unexplained creatine kinase (CK) >3x ULN
- The number and type of adverse events
- MACE, rehospitalization and death at 12 and 28 weeks

Visit schedule and assessments

Subjects considered eligible for this study will be included if they meet all inclusion criteria and none of the exclusion criteria, after signing the informed consent. The study protocol assessments will be done according to the schedule of assessments reported in Table 3.

Blood samples for protocol assessments will be collected and send to the central laboratory. Unscheduled visits for safety evaluation will be permitted for the entire duration of the study.

Study measures

- Subject demographics and medical history: year of birth, age, and sex.
- Cardiovascular risk factors: hypertension, diabetes, and tobacco use.
- Comorbidities: heterozygous familial hypercholesterolemia, atherosclerotic cardiovascular disease (ASCVD), prior myocardial infarction, prior percutaneous coronary intervention, prior coronary artery bypass graft, and heart failure.
- Height (cm), weight (kg), and BMI (kg/m^2).
- Lipid-lowering drugs: fibrates, nicotinic acid, bile acid sequestrant, and others.
- Concomitant pharmacological therapy.
- Serum levels of LDL-C, total cholesterol, HDL-C, non-HDL-C, triglicerides, lp(a), APO-B, fasting glucose, fasting insulinemia, HbA1c, hsCRP, PCSK9, creatinine, uric acid, ALT, AST, and CK
- Clinical events: rehospitalization and death.

Sample size

A sample size of 130 randomized patients was expected to provide a 95% power to detect a difference of 15% in the percent change from baseline to week 12 in LDL-C between treatments. This calculation was based on a two-tailed t test for matched pairs at the 5% level of significance, and a common standard deviation of 25, with a potential dropout rate of 10%.

Statistical Analysis

All participants who will receive at least one dose of each intervention will be included in the study analysis. An intention-to-treat analysis will be performed.

Comparisons between Treatment A vs Treatment B will be made within patients. A within patient comparison takes into account the correlation between measurements for each participant because they act as their own control, therefore measurements are not independent. The value of measurement on treatment A minus measurement on treatment B separately for each participant will be evaluated. Participant baseline and follow-up data will be analysed using descriptive statistics. For the primary and secondary outcome measures, continuous variables will be analysed using paired samples t test.[27] The effect estimates will be expressed in mean difference and standard error. Categorical variables will be analysed using Mainland-Gart test.[28] A p value of <0.05 will be considered as statistically significant.

Statistical analyses will be carried out using RStudio software (RStudio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA URL http://www.rstudio.com/.)

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TABLE 1. Cardiovascular risk categories

VERY HIGH RISK	People with any of the following: ➢ Documented ASCVD, either clinical or unequivocal on imaging. ➢ Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. ➢ Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound. ➢ DM with target organ damage[a], or at least three major risk factors, or early onset of T1DM of long duration (>20 years) ➢ Severe CKD (eGFR <30 mL/min/1.73 m2) ➢ A calculated SCORE ≥ 10% for 10-year risk of fatal CVD ➢ FH with ASCVD or with another major risk factor
HIGH RISK	People with: ➢ Markedly elevated single risk factors, in particular TC>8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥ 180/110 mmHg. ➢ Patients with FH without other major risk factors. ➢ Patients with DM without target organ damage[a], with DM duration ≥ 10 years or another additional risk factor ➢ Moderate CKD (eGFR 30-59 mL/min/1.73 m2) ➢ A calculated SCORE ≥ 5% and <10% for 10-year risk of fatal CVD

ASCVD, atherosclerotic cardiovascular disease; ACS, acute coronary syndrome; BP, blood pressure; CABG, coronary artery bypass graft surgery; CKD, chronic kidney disease; CT, computed tomography; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; FH, familial hypercholesterolaemia; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention; SCORE, Systematic Coronary Risk Estimation; T1DM, type 1 DM; TC, total cholesterol; TIA, transient ischaemic attack.

[a] Target organ damage is defined as microalbuminuria, retinopathy, or neuropathy.

TABLE 2. Treatment goals for low-density lipoprotein cholesterol

CARDIOVASCULAR RISK	LDL-C TARGET
VERY HIGH	• Reduction of ≥ 50% from baseline and an LDL-C goal: <1.4 mmol/L (<55 mg/dL) • For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin-based therapy, an LDL-C goal: <1.0 mmol/L (<40 mg/dL)
HIGH	• Reduction of ≥ 50% from baseline and an LDL-C goal: <1.8 mmol/L (<70 mg/dL)

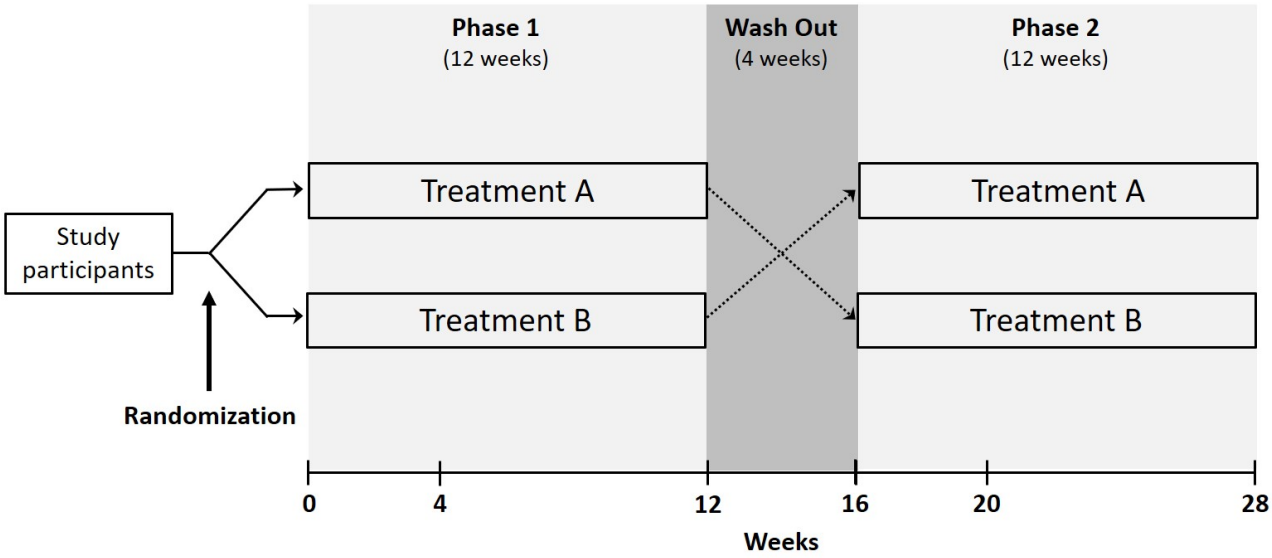
ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol.

TABLE 3. Schedule of assessments

		Phase 1			Phase 2		
	Screening and randomization	**P_1-0** (0 weeks)	**P_1-4** (4 weeks)	**P_1-12** (12 weeks)	**P_2-0** (16 weeks)	**P_2-4** (20 weeks)	**P_2-12** (28 weeks)
Inclusion and exclusion criteria	R	-	-	-	-	-	-
Informed consent	R	-	-	-	-	-	-
Demographics	-	R	-	-	-	-	-
Height	-	R	-	-	-	-	-
Weight	-	R	-	-	R	-	-
Medical history	-	R	-	-	-	-	-
Lipid-lowering drugs	-	R	-	-	-	-	-
Concomitant medications	-	R	-	-	-	-	-
Blood for LDL-C	-	R	R	R	R	R	R
Blood for PCSK9		R	R	R	R	R	R
Blood for creatinine	-	R	-	R	R	-	R
Blood for total cholesterol, HDL-C, non-HDL-C, triglicerides, lp(a), APO-B, fasting glucose, fasting insulinemia, HbA1c, hsCRP	-	R	-	R	R	-	R
Blood for uric acid, ALT, AST, and CK	-	R	R	R	R	R	R
Clinical events	-	R	R	R	R	R	R

APO-B, apolipoprotein B; HbA1C, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; OxPL, oxidized phospholipids; PCSK9, Proprotein Convertase Subtilisin/Kexin type 9; R, required.

FIGURE 1. Study design



Treatment A: PCSK9 inhibitors + Ezetimibe + Bempedoic acid
Treatment B: PCSK9 inhibitors + Ezetimibe