Supplemental Material

Data S1.

Supplemental Methods

Inclusion Criteria

Each patient had to satisfy all the following criteria to have been enrolled in the study:

Provision of written informed consent prior to any study-specific procedure.

Men and nonpregnant, nonlactating women. Women had to have been either:

Naturally postmenopausal defined as ≥1 year without menses and:

- ≥55 years, or
- <55 years with follicle-stimulating hormone ≥40.0 IU/L; or

Surgically sterile including hysterectomy, bilateral oophorectomy, and/or tubal ligation; or

Women of childbearing potential willing to use 2 acceptable methods of birth control (unless they agreed to follow the definition of true abstinence). The minimal requirement for adequate contraception was to start on day 1, continuing during the study period and for at least 30 days after the last dose of investigational medical product. Acceptable methods of birth control included:

- Oral, implanted, topical, or injectable birth control medications
- Placement of an intrauterine device with or without hormones
- Barrier methods including condom or occlusive cap with spermicidal foam or spermicidal jelly
- Vasectomized male partner who was the sole partner for this patient
- True abstinence: When this was in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods], declaration of abstinence for the duration of a trial, and withdrawal were not acceptable methods of contraception.)

There were no protocol-specific birth control requirements for men with partners who were able to become pregnant.

Age ≥18 years or legal age of majority depending on regional law, whichever was greater at week –5 (visit S1).

Fasting (minimum of 10 hours) calculated LDL-C at week –5 (visit S1)

- Primary prevention ≥130 mg/dL (3.4 mmol/L)
- Secondary prevention and/or heterozygous HeFH ≥100 mg/dL (2.6 mmol/L)
- All patients must have had fasting LDL-C ≥70 mg/dL (1.8 mmol/L) at week –1 (visit S3).

In the case of PCSK9 inhibitor use, the patient must have received 3 stable doses. It was important that lipid values were measured at PCSK9 inhibitor trough levels. Therefore, study visits were to have been scheduled in accord with the patient's PCSK9 inhibitor injection regimen so that measurement of lipid values for all visits occurred between scheduled PCSK9 inhibitor injections and <48 hours before the next scheduled PCSK9 inhibitor injection. Patients who discontinued investigational or commercial PCSK9 inhibitor must have had their last dose at least 4 months prior to screening visit S1.

Requiring statin therapy for the purpose of primary or secondary prevention of CV events.

Primary prevention patients must as a minimum have had a history of requiring lipid-modifying therapy (LMT) based on local guidelines (for example, American College of Cardiology/American Heart Association guidelines, European Society of Cardiology/European Atherosclerosis Society guidelines, Canadian Cardiovascular Society guidelines).

Secondary prevention and/or HeFH patients must have included those with a history of:

- HeFH, defined by genotyping or by clinical assessment using either the World Health Organization (WHO) criteria/Dutch Lipid Clinical Network Criteria with a

score that was >8 points or the Simon Broome Register Diagnostic Criteria with an assessment of “Definite HeFH” and/or

- Coronary artery disease, defined by:
  - Myocardial infarction (MI) (either ST-elevation MI or non-ST-elevation MI) occurring greater than 90 days prior to screening (week –5 visit S1), or
  - Percutaneous coronary or surgical coronary revascularization, occurring greater than 90 days prior to screening (week –5 visit S1), or
  - Angiographic stenosis of >50% in a least 1 major coronary artery (native or graft vessel), as documented by selective coronary angiography or computed tomography angiography (CTA), or
- Symptomatic peripheral arterial disease, defined by:
  - Peripheral vascular disease with symptoms of claudication or resting limb ischemia with either ankle brachial index ≤0.9 performed by a vascular lab or angiogram (including CTA) showing ≥50% stenosis, or
  - Peripheral arterial revascularization (surgical or percutaneous), occurring greater than 90 days prior to screening (week –5, visit S1), or
  - Abdominal aortic aneurysm confirmed by imaging or aortic aneurysm repair, occurring greater than 90 days prior to screening (week –5, visit S1), or
  - Lower extremity amputation due to peripheral vascular disease, occurring greater than 90 days prior to screening (week –5, visit S1), or
- Cerebrovascular atherosclerotic disease defined by:
  - Ischemic stroke occurring greater than 90 days prior to screening (week –5 visit S1), or

- Carotid endarterectomy, carotid stenting, or more than 70% stenosis in a carotid artery determined by carotid ultrasound or angiogram, occurring greater than 90 days prior to screening (week –5 visit S1).

Patient-reported statin intolerance defined as an inability to tolerate 2 or more statins, 1 at a low dose, due to an adverse safety effect that started or increased during statin therapy and resolved or improved when statin therapy was discontinued.

Low-dose statin therapy was defined as an average daily dose of rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg.

Patients tolerating very-low-dose statin therapy (an average daily dose of rosuvastatin <5 mg, atorvastatin <10 mg, simvastatin <10 mg, lovastatin <20 mg, pravastatin <40 mg, fluvastatin <40 mg, or pitavastatin <2 mg) were considered intolerant to that low-dose statin. Patients could continue taking very-low-dose statin therapy throughout the study provided that it was stable (used for at least 4 weeks prior to screening S1) and taken at a consistent time each day.

Written confirmation by both patient and principal investigator that the patient was statin intolerant as defined above and aware of the benefit of statin use to reduce the risk of MACE including CV death.

<u>Exclusion Criteria</u>

Patients who met any of the following criteria were not eligible:

1. Total fasting (minimum of 10 hours) TG ≥500 mg/dL (5.6 mmol/L at week –5 (visit S1).

   Note: A single repeat of fasting (minimum of 10 hours) of TG may have been completed prior to initiation of the single-blind run-in period. For those patients who had a repeat TG, the repeat value was used to determine eligibility.

2. Renal dysfunction or a glomerulonephropathy, including estimated glomerular filtration rate (eGFR; using central laboratory determined Modification of Diet in Renal Disease formula) <30 mL/min/1.73 m^2 at week –5 (visit S1).

   Note: A single repeat of eGFR may have been completed between visits S1 and S2. For those patients who had a repeat eGFR, the repeat value was used to determine eligibility.
3. Body mass index (BMI) ≥50 kg/m^2.
4. Recent (within 3 months prior to the screening visit [week –5 (visit S1)] or between screening and randomization visits) MI, unstable angina leading to hospitalization, uncontrolled, symptomatic cardiac arrhythmia (or medication for an arrhythmia that was started or dose changed within 3 months of screening), coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), carotid surgery or stenting, cerebrovascular accident, transient ischemic attack (TIA), endovascular procedure or surgical intervention for peripheral vascular disease or plans to undergo a major surgical or interventional procedure (eg, PCI, CABG, carotid or peripheral revascularization). Patients with implantable pacemakers or automatic implantable cardioverter defibrillators may have been considered if deemed by the investigator to be stable for the previous 3 months.
5. Uncontrolled hypertension, defined as sitting systolic blood pressure (SBP) ≥160 mmHg and/or diastolic blood pressure (DBP) ≥100 mmHg measured according to local standards.

   Note: At the discretion of the investigator, the time between Visits S1 and S2 could be extended by 4 weeks for adjustments in blood pressure (BP) medications and/or additional assessment of BP, with the repeat assessment value used to determine eligibility. Alternatively, patients could be rescreened if BP status had changed.

6. Hemoglobin A1C (HbA_{1C}) ≥10% at week –5 (visit S1).
7. Uncontrolled hypothyroidism, including thyroid-stimulating hormone >1.5 × the upper limit of normal (ULN) at week –5 (visit S1). Patients stabilized on thyroid replacement therapy for at least 6 weeks prior to randomization were allowed.
8. Liver disease or dysfunction, including:

   Positive serology for hepatitis B surface antigen and/or hepatitis C antibodies at week –5 (visit S1).

   Alanine aminotransferase (ALT) ≥2 × ULN, aspartate aminotransferase (AST) ≥2 × ULN, and/or total bilirubin (TB) ≥1.2 × ULN at week –5 (visit S1). If TB ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin was obtained and if consistent with Gilbert's disease or if the patient had a history of Gilbert's disease, the patient could be enrolled in the study.

   Note: At the discretion of the investigator, a single repeat of ALT, AST, and/or TB may have been completed prior to randomization. For those patients who had a repeat ALT and/or AST, the repeat value was used to determine eligibility. Also, if test for hepatitis C antibody was positive, but optional reflexive test for hepatitis C ribonucleic acid (RNA) was negative, the patient could be enrolled.
9. Gastrointestinal conditions or procedures (including weight loss surgery [eg, Lap-Band or gastric bypass]) that could have affected drug absorption.
10. Hematologic or coagulation disorders or a hemoglobin level <10 g/dL at week –5 (visit S1).
11. Persistent poor compliance or lack of tolerance with single-blind, placebo (ie, ingesting <80% average of planned doses) assessed at the T1 visit prior to randomization.

12. Active malignancy, including those requiring surgery, chemotherapy, and/or radiation in the past 5 years. Nonmetastatic basal or squamous cell carcinoma of the skin and cervical carcinoma in situ were allowed.
13. Unexplained creatine kinase (CK) >3 × ULN at screening up to randomization (ie, not associated with recent trauma or physically strenuous activity). Patients with an explained CK elevation must have had single repeat CK ≤3 × ULN prior to randomization.
14. History within the last 2 years of drug, alcohol, amphetamine and derivatives, or cocaine abuse. Patients taking amphetamine derivatives for medical reasons such as attention deficit disorder or taking prescription opioids or other medications for chronic pain that have been stable, without evidence of abuse, and prescribed by and under the care of a health care practitioner could be enrolled after evaluation by the investigator.
15. Blood donation, participation in a clinical study with multiple blood draws, major trauma, blood transfusion, or major surgery with or without blood loss within 30 days prior to randomization.
16. Use of any experimental or investigational drugs within 30 days.
17. Previous enrollment in an Esperion bempedoic acid clinical study.
18. Use of, or a plan to initiate, these prohibited therapies/supplements during the study:
    Mipomersen (had to have been stopped at least 6 months prior to week –5 [visit S1]),
    Lomitapide or apheresis therapy (must have been stopped at least 3 months prior to week –5 [visit S1]),
    Red yeast rice extract and berberine-containing products must have been stopped at least 2 weeks prior to week –5 [visit S1]),
    Use of an investigational cholesterol ester transfer protein (CETP-I) within the last 2 years (except evacetrapib within the last 3 months).

Statins were prohibited at average daily doses of rosuvastatin ≥5 mg, atorvastatin ≥10 mg, simvastatin ≥10 mg, lovastatin ≥20 mg, pravastatin ≥40 mg, fluvastatin ≥40 mg, or pitavastatin ≥2 mg.

Note: Patients could have been on any available LMT with the exception of the exclusions listed above as long as they had been stable on oral medications for 4 weeks prior to screening visit S1 and were taken at a consistent time each day.

19. Planned initiation or changes to the following drugs:

    Hormone replacement (6 weeks prior to randomization)

    Thyroid replacement (6 weeks prior to randomization)

    Diabetes medications (4 weeks prior to randomization)

    Obesity medication (4 weeks prior to randomization)

    PCSK9 inhibitors: Patients who were currently on a stable commercially available PCSK9 inhibitor (alirocumab or evolocumab) must have had at least 3 doses prior to visit S1. Patients who were previously on a PCSK9 inhibitor (either investigational or commercial), must have waited at least 4 months after last dose prior to screening (week –5, visit S1).

20. A medical or situational (ie, geographical) finding that in the investigator's opinion may have compromised the patient's safety or ability to complete the study.
21. An employee or contractor of the facility conducting the study, or a family member of the principal investigator, coinvestigator, or sponsor.
22. Pregnant, breastfeeding, or intending to become pregnant within 30 days after last dose of IMP.
23. Patients who had enrolled in a study of an experimental small interfering RNA (siRNA) inhibitor of PCSK9 were excluded.

24. In patients taking very low-dose statins, gemfibrozil was excluded per the co-administration prescribing instructions.