21 March 2024
EMA/287504/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nustendi

International non-proprietary name: Bempedoic acid / Ezetimibe

Procedure No. EMEA/H/C/004959/II/0035

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

ACC	American College of Cardiology
ACL	Adenosine triphosphate citrate lyase
ACSVL1	Very long-chain acyl-CoA synthetase 1
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AHA	American Heart Association
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
BMI	Body mass index
BPH	Benign prostatic hyperplasia
BUN	Blood urea nitrogen
CEC	Clinical events committee
CHD	Coronary heart disease
CI	Confidence interval
CK	Creatine kinase
CLEAR	Cholesterol Lowering via Bempedoic Acid, an ATP citrate lyase Inhibiting Regimen
CoA	Coenzyme A
COVID-19	Coronavirus disease 2019
CRF	Case report form
CSR	Clinical study report
CTT	Cholesterol Treatment Trialists
CV	Cardiovascular
CVD	Cardiovascular disease
CVOT	Cardiovascular outcome(s) trial
DC	Diabetes committee
EAIR	Exposure-adjusted incidence rate
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate

EMA	European Medicines Agency
EOP2	End-of-Phase 2
ERA	Environmental risk assessment
ETC-1002	Analyte of bempedoic acid measured in plasma, urine, or feces
EU	European Union
FAS	Full analysis set
FCMP	Fixed combination medicinal product
FDA	Food and Drug Administration
HbA1c	Haemoglobin, type A1C
HeFH	Heterozygous familial hypercholesterolemia
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
HR	Hazard ratio
hsCRP	High-sensitivity C-reactive protein
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ILEP	International Lipid Expert Panel
IMP	Investigational medicinal product
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LLN	Lower limit of normal
LMT	Lipid-modifying therapy
LS	Least square
LSM	Least square mean
MAA	Marketing authorization application
MACE	Major adverse cardiovascular event
MACE-3	3-component major adverse cardiovascular event
MACE-4	4-component major adverse cardiovascular event
MACE-5	5-component major adverse cardiovascular event
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
NDA	New drug application
NHBLI	National Heart, Lung, and Blood Institute
non-HDL-C	Non-high-density lipoprotein cholesterol
NODM	New onset diabetes mellitus

NPC1L1	Niemann-Pick C1-Like 1
OAT	Organic anion transporter
PAD	Peripheral artery disease
PCR	Polymerase chain reaction
PCSK9	Proprotein convertase subtilisin kexin type 9
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PI	product information
PPS	Per-protocol analysis set
QD	Once daily
SA	Scientific advice
SAE	Serious adverse event
SAS	Safety analysis set
SD	Standard deviation
SMQ	Standardized MedDRA Query
SOC	System organ class
STP	Sewage treatment plant
ULN	Upper limit of normal
US	United States
vs	Versus
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Daiichi Sankyo Europe GmbH submitted to the European Medicines Agency on 27 June 2023 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adults with established or at high risk for atherosclerotic cardiovascular disease to reduce cardiovascular risk for NUSTENDI, based on results from Study 1002-043, known as the CLEAR [Cholesterol Lowering via Bempedoic Acid, an ATP citrate lyase (ACL) Inhibiting Regimen] Outcomes Trial; this is a Phase 3, randomized, double-blind, placebo-controlled study to assess the effects of bempedoic acid (ETC-1002) on the occurrence of major cardiovascular events in patients with, or at high risk for, cardiovascular disease who are statin intolerant; As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.0 of the RMP has also been submitted. As part of the application the MAH is requesting a 1-year extension of the market protection.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0334/2017 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication. On 02 January 2024, the MAH withdrew their claim for additional marketing protection.

Scientific advice

The MAH received Scientific Advice (SA) from the CHMP on 26 May 2016 (EMEA/H/SA/3294/1/2016/SME/II) and on 31 May 2018 (EMEA/H/SA/3294/1/FU/1/2018/SME/II). The CHMP overall agreed with the design and objectives of the study conducted to support this submission.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Patrick Vrijlandt Co-Rapporteur: Alar Irs

Timetable	Actual dates
Submission date	27 June 2023
Start of procedure:	12 August 2023
CHMP Rapporteur Assessment Report	10 October 2023
PRAC Rapporteur Assessment Report	13 October 2023
PRAC members comments	18 October 2023
CHMP Co-Rapporteur Assessment	19 October 2023
Updated PRAC Rapporteur Assessment Report	19 October 2023
PRAC Outcome	26 October 2023
CHMP members comments	n/a
Updated CHMP Rapporteur(s) (Joint) Assessment Report	2 November 2023
Request for supplementary information (RSI)	9 November 2023
PRAC Rapporteur Assessment Report	29 January 2024
PRAC members comments	30 January 2024
Updated PRAC Rapporteur Assessment Report	1 February 2024
CHMP Rapporteur Assessment Report	8 February 2024
PRAC Outcome	8 February 2024
CHMP members comments	12 February 2024
Updated CHMP Rapporteur Assessment Report	16 February 2024
Request for supplementary information (RSI)	22 February 2024
PRAC Rapporteur Assessment Report	4 March 2024
CHMP Rapporteur Assessment Report	7 March 2024
PRAC members comments	12 March 2024
CHMP members comments	12 March 2024
Updated PRAC Rapporteur Assessment Report	15 March 2024
Updated CHMP Rapporteur Assessment Report	15 March 2024
Opinion	21 March 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

The applicant submitted a variation procedure for Nustendi (bempedoic acid and ezetimibe 180/10 mg) with an extension of a therapeutic indication for adults with established or at high risk for atherosclerotic cardiovascular disease (CVD) to reduce the cardiovascular risk. The variation is primarily based on efficacy and safety results from **Study 1002-043**, known as the **CLEAR Outcomes** trial, a multi-centre randomised, double-blind, placebo-controlled, event-driven trial. This study was designed to evaluate whether long-term treatment with bempedoic acid reduces the risk of major adverse cardiovascular events (MACE) in patients with CVD, or at high risk for CVD, with a fasting screening LDL-C ≥100 mg/dL (2.6 mmol/L) while taking stable and optimized background LDL-C-modifying therapies and with a history of statin intolerance.

The data have been submitted to support the addition of this new therapeutic indication for Nustendi. The requested variation proposed amendments in section 4.1, 4.8 and 5.1 to the SmPC. The PL is proposed to be updated accordingly.

The newly proposed therapeutic indication was initially:

"Cardiovascular disease

Nustendi is indicated in adults with established or at high risk for atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

- *in combination with a statin with or without other lipid-lowering therapies in patients previously treated with a statin and ezetimibe or,*
- *alone or in combination with other lipid-lowering therapies in patients who are either statin-intolerant, or for whom a statin is contraindicated, and previously treated with ezetimibe alone,*
- *in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without statin.*

For study results with respect to effects on LDL-C, cardiovascular events and populations studied see section 5.1."

During the assessment, the following therapeutic indication was eventually agreed by the CHMP:

"Cardiovascular disease

Nustendi is indicated in adults with established or at high risk for atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

- *in patients on a maximum tolerated dose of a statin and not adequately controlled with additional ezetimibe treatment or,*
- *in patients who are either statin-intolerant, or for whom a statin is contraindicated, and not adequately controlled with ezetimibe treatment or,*
- *in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets.*

For study results with respect to effects on LDL-C, cardiovascular events and populations studied see section 5.1."

2.1.2. About the product

Bempedoic acid is an oral, first-in class, small molecule that inhibits adenosine triphosphate-citrate lyase (ACL), an enzyme upstream of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the target of statins, in the cholesterol biosynthesis pathway, resulting in decreased hepatic cholesterol synthesis, an increase in low-density lipoprotein (LDL)-receptors, and reduction in circulating LDL-C.

Ezetimibe's molecular target is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and phytosterols. Ezetimibe localizes at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in LDL receptors, resulting in clearance of cholesterol from the blood.

Bempedoic acid and ezetimibe both reduce LDL-C in the blood indirectly through increasing the expression of LDL receptors, but by different, complementary mechanisms.

In the European Union (EU) and United Kingdom (UK), bempedoic acid and bempedoic acid with ezetimibe (Nilemdo® and Nustendi®, respectively) are registered since 2020.

The current therapeutic indication of Nustendi (bempedoic acid and ezetimibe 180/10 mg) is worded as follows in section 4.1 of the SmPC:

"*Nustendi is indicated in adults with primary hypercholesterolaemia (heterozygous familial and nonfamilial) or mixed dyslipidaemia, as an adjunct to diet:*

- *in combination with a statin in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin in addition to ezetimibe (see sections 4.2, 4.3, and 4.4),*
- *alone in patients who are either statin-intolerant or for whom a statin is contraindicated, and are unable to reach LDL-C goals with ezetimibe alone,*
- *in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without statin."*

The recommended dose of Nustendi is one film-coated tablet of 180 mg/10 mg taken once daily.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

During the CHMP Scientific Advice (SA; EMEA/H/SA/3294/1/2016/SME/II and EMEA/H/SA/3294/1/FU/1/2018/SME/II), the CHMP/SAWP overall agreed with the design and objectives of the study conducted to support this submission.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

This Environmental Risk Assessment (ERA), conducted according to EMEA/CHMP/SWP/4447/00 corr 2 dated June 1, 2006, concerns the product Nustendi (bempedoic acid/ezetimibe fixed dose combination).

Nustendi has received centralized marketing authorization from the EMA on 27 March 2020 (EMEA/H/C/004959).

Nustendi is indicated in adults with primary hypercholesterolaemia (heterozygous familial and nonfamilial) or mixed dyslipidaemia, as an adjunct to diet:

• in combination with a statin in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin in addition to ezetimibe,

• alone in patients who are either statin-intolerant or for whom a statin is contraindicated, and are unable to reach LDL-C goals with ezetimibe alone,

• in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without statin.

In agreement with Council Directive 2001/83/EC, as amended, separate Environmental Risk Assessments have been submitted for bempedoic acid and ezetimibe, the two active ingredients contained in Nustendi. As the $PEC_{surfacewater}$ for both active substances exceeded the action limit, both ERAs contained the results of (and plans for) Phase II ERA studies. All ERA studies in both ERAs have been completed and the assessments were accepted by the EMA.

In the present Type II variation application, the Marketing Authorization Holder is requesting an extension of the therapeutic indication of Nustendi. The proposed new indication at the time of the initial submission was:

Hypercholesterolaemia and mixed dyslipidaemia

Nustendi is indicated in adults with primary hypercholesterolaemia (heterozygous familial and nonfamilial) or mixed dyslipidaemia, as an adjunct to diet:

• in combination with a statin in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin in addition to ezetimibe,

• alone in patients who are either statin-intolerant or for whom a statin is contraindicated, and are unable to reach LDL-C goals with ezetimibe alone,

• in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without statin.

Cardiovascular disease

Nustendi is indicated in adults with established or at high risk for atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

• in combination with a statin with or without other lipid-lowering therapies in patients previously treated with a statin and ezetimibe or,

• alone or in combination with other lipid-lowering therapies in patients who are either statinintolerant, or for whom a statin is contraindicated, and previously treated with ezetimibe alone, in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without statin.

Although only a marginal impact is expected, the widened indication of Nustendi could potentially lead to an increased use of the product in the European Union.

However, as the action limit for $PEC_{surfacewater}$ of both active substances contained in Nustendi was already exceeded at the time of submission of the previous ERAs, and the respective Phase II ERA studies have been executed and completed, a potential increased use of Nustendi based in the widened indication will not have an impact on the risk to the environment.

All ERA studies for both active substances, as agreed with the CHMP, have been completed and the assessments were accepted by the CHMP. The existing Environmental Risk Assessment remains unchanged.

In conclusion, in agreement with European guidance, no further ERA studies are submitted for the requested Type II variation (extension of indication) of Nustendi.

2.2.2. Discussion on non-clinical aspects

No further non-clinical data have been submitted for this variation. A justification has been submitted for the absence of further ERA studies. At the time of the initial MAA for the fixed dose combination of bempedoic acid and ezetimibe, an ERA was provided. It was concluded that the PEC_{sw} exceeded the action limit for both active substances and therefore, Phase IIA assessments were performed. A risk to the sewage treatment plant (STP), surface water, groundwater, sediment and terrestrial compartment was not anticipated based on the prescribed use of bempedoic acid and ezetimibe as fixed dose combination. The current indication extension does not affect the outcome of the initial ERA. It is therefore agreed that no further studies are required and the initial conclusions of the ERA are still valid.

2.2.3. Conclusion on the non-clinical aspects

Based on the updated data submitted in this application, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of bempedoic acid and ezetimibe.

Considering the above data, bempedoic acid and ezetimibe are not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4. Clinical efficacy

2.4.1. Main study

CLEAR Outcomes (Study 1002-043)

Methods

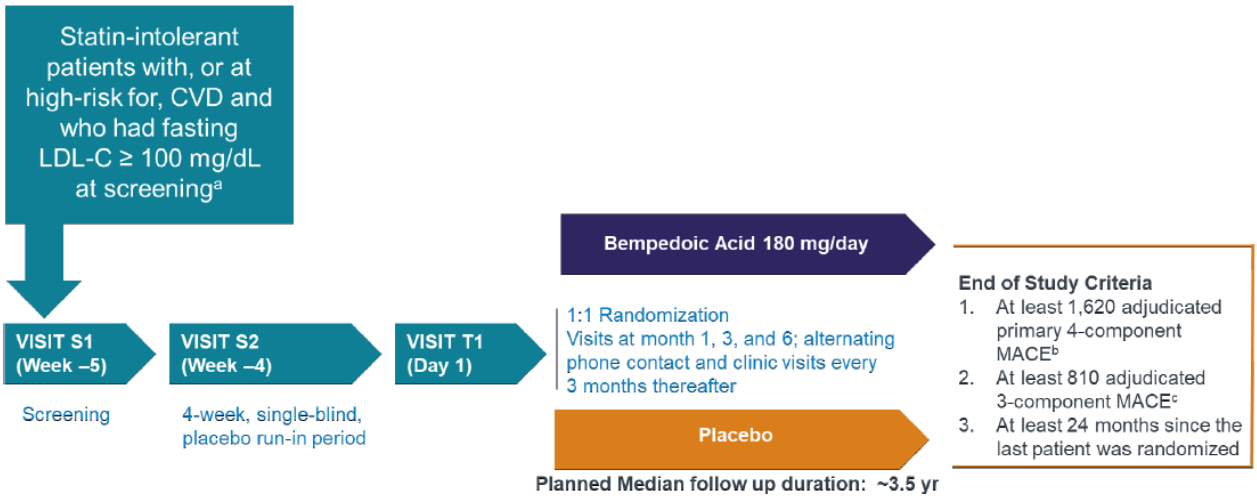
Study design

The CLEAR Outcomes trial was a phase 3, randomized, double-blind, placebo-controlled study initiated in 2016.

The trial consisted of:

- an approximate 1-week screening period,
- a 4-week, single-blind, placebo run-in period,
- and a double-blind, randomized, placebo-controlled treatment period that continued until study stopping criteria were met (Figure 1).

Figure 1: Study Design



CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; MACE = major adverse cardiovascular event; S = Screening Visit; T = Treatment Visit. a Enrollment of high-risk patients without a history of atherosclerotic CVD was capped at 30%. b Including CV death, nonfatal MI, nonfatal stroke, or coronary revascularization. c Including CV death, nonfatal MI, or nonfatal stroke.

On Day 1 (Treatment Visit 1), patients meeting eligibility criteria were randomized 1:1 to receive double-blind bempedoic acid 180 mg or matching placebo QD by mouth. Randomized patients returned for clinic visits at Months 1, 3 and 6 (Treatment Visits 2, 3, and 4, respectively). Following Month 6, patients were contacted every 3 months (alternating phone visits and clinic visits) for the remainder of the study. The final visit was onsite with a follow-up phone call approximately 30 days later.

The study continued until the following 3 conditions were met: 1) at least 1620 patients experienced a positively adjudicated primary MACE-4 endpoint consisting of nonfatal MI, nonfatal stroke, coronary revascularization, or CV death, 2) at least 810 patients experienced a positively adjudicated MACE-3

(nonfatal MI, nonfatal stroke, or CV death), and 3) 24 months (2 years) had elapsed since the last patient was randomized.

Study participants

Main inclusion/exclusion criteria

Patients who met all of the inclusion criteria and none of the exclusion criteria were eligible for enrollment in this study. Patients qualified for the study if they had a history of or were at high risk for CVD as described under Inclusion Criteria #7.

Inclusion Criteria

Eligible patients must have met the criteria listed below to be eligible for the study.

- Provision of signed informed consent prior to any study-specific procedure.
- Patient-reported statin intolerance due to an adverse safety effect that started or increased during statin therapy and resolved or improved when statin therapy was discontinued resulting in an inability to tolerate:
  - 2 or more statins at any dose, or
  - 1 statin at any dose and unwilling to attempt a second statin or advised by a physician to not attempt a second statin.

    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 to be intolerant to low dose statin. Patients were allowed to continue taking very low dose statin therapy throughout the study provided that it was stable (used for at least 4 weeks prior to screening) and well tolerated.
- Written confirmation by both patient and investigator that the patient was statin intolerant as defined above, aware of the benefit of statin use to reduce the risk of MACE including death, and also aware that many other patients who are unable to tolerate a statin are able to tolerate a different statin or dose.
- Age ≥18 years or legal age of majority based on regional law, whichever was greater, and ≤85 years at Week -5 (Visit S1).
- Men and nonpregnant, nonlactating women. Women must have been one of the following:
  - Naturally postmenopausal defined as ≥1 year without menses and:
    - ≥55 years, or
    - <55 years with follicle-stimulating hormone (FSH) ≥40.0 IU/L, or
  - Surgically sterile including history of hysterectomy, bilateral oophorectomy, and/or tubal ligation, or
  - Women of childbearing potential willing to use an acceptable method(s) of birth control during the study and for 30 days after the end of treatment, including:
    - oral, topical, injectable, or implantable 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 is the sole partner for this patient,
- true abstinence that is 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 the study or withdrawal are not acceptable methods of true abstinence).

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

- Fasting LDL-C ≥100 mg/dL (2.6 mmol/L) at Week -5 (Visit S1) while taking stable (4 weeks prior to Visit S1) and optimized background LDL-C-lowering therapies that may have included very low dose statin (see definition above), ezetimibe, niacin, bile acid resins, fibrates, and/or PCSK9 inhibitors.

  Note: A single repeat of LDL-C may have been completed prior to initiation of the single-blind Run–in Period. For those patients who had a repeat LDL-C, the repeat value was used to determine eligibility.

- History of, or at high risk for, CVD including documented evidence of one or more of the following:
  - Documented history of CVD (ie, secondary prevention)
    - Coronary artery disease, defined by:
      - MI (either ST-elevation MI or non-ST-elevation MI) occurring greater than 90 days prior to screening, or
      - Percutaneous coronary or surgical coronary revascularization, occurring greater than 90 days prior to screening, 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 PAD, defined by:
      - Peripheral vascular disease with symptoms of claudication or resting limb ischemia with either ankle brachial index <0.9 or angiogram (including CTA) showing ≥50% stenosis (ankle brachial index measured after a period of rest and with the patient in the supine position using a Doppler device), or
      - Peripheral arterial revascularization (surgical or percutaneous), occurring greater than 90 days prior to screening, or abdominal aortic aneurysm confirmed by imaging or aortic aneurysm repair, occurring greater than 90 days prior to screening, or
      - Lower extremity amputation due to peripheral vascular disease, occurring greater than 90 days prior to screening, or
    - Cerebrovascular atherosclerotic disease defined by:
      - Ischemic stroke occurring greater than 90 days prior to screening, or
      - Carotid endarterectomy, carotid stenting, or more than 70% stenosis in a carotid artery determined by carotid ultrasound or angiogram (Note: If stenosis assessed by carotid ultrasound was reported as ranging between 60%-79%, patient may have qualified only if internal carotid artery peak systolic velocity was >230 cm/sec), occurring greater than 90 days prior to screening, or
  - High risk for a CVD event (ie, high-risk primary prevention)

- Reynolds Risk score >30% or a Systematic COronary Risk Evaluation (SCORE) Risk score >7.5% over 10 years (see Protocol, Appendix 3 and Appendix 4 for additional details; Appendix 16.1.1), or
- Coronary artery calcium score >400 Agatston units at any time in the past, or
- Patients with type 1 or type 2 diabetes, aged >65 years (women) or >60 years (men).

Exclusion Criteria

Patients who met any exclusion criteria below were not eligible to enroll in the study.

- Total fasting TG >500 mg/dL (5.6 mmol/L) at Week -5 (Visit S1).

  Note: A single repeat 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.

- Renal dysfunction or a glomerulonephropathy defined as either nephritic or nephrotic syndrome, including estimated glomerular filtration rate (eGFR; using central laboratory determined Modification of Diet in Renal Disease [MDRD] formula) <30 mL/min/1.73 m2 at Week -5 (Visit S1).

  Note: A single repeat of eGFR may have been completed prior to randomization. For those patients who had a repeat eGFR, the repeat value was used to determine eligibility.

- Forms of CVD that included any of the following:
  - Recent (within 90 days prior to or during screening) acute CVD events including, but not only transient ischemic attack (TIA), MI, coronary revascularization, peripheral arterial revascularization, ischemic stroke, carotid endarterectomy, carotid stenting,
  - Recent (within 90 days of screening) unstable or symptomatic cardiac arrhythmia (including any associated medication changes). Patients with stable well controlled atrial arrhythmias were allowed to participate in the study.
  - Patients with implantable pacemakers or automatic implantable cardioverter defibrillators may have been considered if deemed by the Investigator to be stable for greater than 90 days prior to screening,
  - New York Heart Association Functional Classification Class IV heart failure,
  - Uncontrolled hypertension, defined as mean sitting systolic blood pressure (SBP) ≥180 mmHg and/or diastolic blood pressure (DBP) ≥110 mmHg,

    Note: At the discretion of the Investigator, BP medications could have been adjusted and/or additional assessment of BP may have been completed prior to randomization, with the repeat assessment value used to determine eligibility. Alternatively, patients could have been rescreened if BP status had changed.
  - Planned coronary revascularization (patient may have rescreened 3 months post-procedure).
- HbA1C ≥10% at Week -5 (Visit S1).
- Uncontrolled hypothyroidism, including thyroid-stimulating hormone (TSH) >1.5 × the upper limit of normal (ULN) at Week -5 (Visit S1). Note: At the discretion of the Investigator, thyroid replacement therapy could have been adjusted and/or additional measurement of TSH may have been completed prior to randomization, with the repeat TSH value used to determine eligibility.

- Liver disease or dysfunction, including:
    - Positive serology for hepatitis B surface antigen (HBsAg) and/or hepatitis C antibodies (HCV-AB) at Week -4 (Visit S2), or
    - Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≥2.0 × ULN at Week -5 (Visit S1).

    Note: At the discretion of the Investigator, a single repeat of ALT and/or AST 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 RNA was negative, patient could have been enrolled.
- Gastrointestinal conditions or procedures (including weight loss surgery, eg, Lap-Band® or gastric bypass) that may have affected drug absorption.
- Hematologic or coagulation disorders or a haemoglobin (Hgb) level <10 g/dL at Week -5 (Visit S1).
- 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.
- Unexplained creatine kinase (CK) >3 × ULN at Week -5 (Visit S1) (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.
- History within the last 2 years of drug, alcohol, amphetamine and derivatives, or cocaine abuse. Patients with amphetamine derivatives prescribed by and under the care of a health care practitioner could have been enrolled after evaluation by the Investigator.
- Blood transfusion for any reason within 30 days prior to randomization.
- Use of any experimental or investigational drugs within 30 days prior to screening or 5 half-lives, whichever was longer.
- Randomization into another Phase 3 bempedoic acid clinical study.
- Use of, or a plan to initiate, these prohibited therapies/supplements during the study:
    - Mipomersen (must 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 (must be stopped at least 2 weeks prior to Week -5 [Visit S1]),
    - Statins are prohibited at average daily doses of rosuvastatin ≥5 mg, atorvastatin ≥10 mg, simvastatin ≥10 mg, lovastatin ≥20 mg, pravastatin ≥40 mg, Fluvastatin ≥40mg, or pitavastatin ≥2 mg.
- Planned initiation or dose adjustments of these allowed drugs prior to screening and during the clinical trial (stable use of these drugs was permitted):
    - Statins were allowed only 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 (must have been stable at least 4 weeks prior to Week -5 [Visit S1]),

    - Other lipid-regulating drugs or supplements (must have been stable at least 4 weeks prior to Week -5 [Visit S1]),
    - PCSK9 inhibitors (must be stable at least 12 weeks prior to Week -5 [Visit S1]).
- Lack of adherence (ie, less than 80% of planned doses) with IMP (single-blind placebo) during the Run-in Period.
- Lack of tolerance with IMP (single-blind placebo) during the Run-in Period.
- 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.
- An employee or contractor of the facility conducting the study, or a family member of the Principal Investigator, Co-Investigator, or Sponsor.
- Pregnant, breastfeeding, or intending to become pregnant within 30 days after study completion or last dose of IMP.

Treatments

The patients received bempedoic acid 180 mg or placebo, as study treatment.

Starting on Day 1, patients were randomized 1:1 to receive double-blind bempedoic acid 180 mg or matching placebo orally QD until their EOS visit. Patients were to ingest IMP orally QD at a similar time with or without food.

Objectives

Primary Objective

The primary objective was to evaluate whether administration of bempedoic acid 180 mg/day versus placebo reduced the risk of a MACE in patients with, or at high risk for, CVD who were statin intolerant. This was assessed with a composite primary efficacy endpoint that included time to first occurrence of CV death, nonfatal myocardial infarction (MI), nonfatal stroke, or coronary revascularization.

Secondary Objectives

- To evaluate whether long-term treatment with bempedoic acid 180 mg/day versus placebo reduced the risk of other clinical endpoints of CV morbidity and mortality and all-cause mortality.
- To evaluate the effect of long-term treatment with bempedoic acid 180 mg/day versus placebo on LDL-C and hsCRP.
- To evaluate the long-term safety and tolerability of bempedoic acid 180 mg/day compared to placebo.
- To evaluate the 12-month efficacy of treatment with bempedoic acid 180 mg/day versus placebo on absolute change in HbA1C in the Inadequately Controlled Diabetes Efficacy Population (patients with type 2 diabetes mellitus and having an HbA1C of 7% or greater at baseline).
- To evaluate whether long-term treatment with bempedoic acid 180 mg/day versus placebo reduced the risk of new-onset diabetes.

Tertiary Objective

- To evaluate the effect of long-term treatment with bempedoic acid 180 mg/day versus placebo on non-HDL-C, TC, high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), HbA1C, and fasting glucose.

Outcomes/endpoints

Primary Endpoint

The primary efficacy endpoint for this study was the time to first occurrence of a MACE-4 as adjudicated by the Clinical Events Committee, where MACE-4 is defined as the composite endpoint of CV death, nonfatal MI, nonfatal stroke, or coronary revascularization.

Secondary Efficacy Time-to-Event Endpoints

Key secondary efficacy time-to-event endpoints are listed below.

- Time to first occurrence of the composite endpoint of CV death, nonfatal MI, or nonfatal stroke (3-component MACE [MACE-3])
- Time to first occurrence of (fatal + nonfatal) MI
- Time to first occurrence of coronary revascularization
- Time to first occurrence of (fatal + nonfatal) stroke
- Time to CV death
- Time to all-cause mortality

Additional secondary efficacy time-to-event endpoints are listed below.

- Time to first occurrence of the composite endpoint of all-cause mortality, nonfatal MI, nonfatal stroke, or coronary revascularization
- Time to first occurrent of 5-component composite endpoint of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina (MACE-5)
- Time to first occurrence of nonfatal MI
- Time to fatal MI
- Time to first occurrence of nonfatal stroke
- Time to fatal stroke
- Time to first occurrence of (fatal + nonfatal) hemorrhagic stroke
- Time to first occurrence of (fatal + nonfatal) nonhemorrhagic stroke
- Time to hospitalization for unstable angina
- Time to first occurrence of new-onset type 2 diabetes mellitus

Secondary Efficacy Lipid and Biomarker Endpoints

- Percent change from baseline to Month 6 in LDL-C
- Percent change from baseline to Month 6 in hsCRP
- Change from baseline to Month 12 in HbA1C in patients with inadequately controlled type 2 diabetes mellitus

Tertiary Efficacy Lipid and Other Biomarker Endpoints

- Absolute change and percent change from baseline to Months 3, 6, 12, 24, then every 6 months through the end-of-study in LDL-C
- Absolute change and percent change from baseline to Months 3, 6, 12, 24, then every 6 months through the end of study in non-HDL-C, TC, HDL-C, and TG
- Percent change from baseline to Month 12 and at the end of study in hsCRP
- Change from baseline to Month 3, 6, 12, then every 6 months through the end of study in HbA1C
- Change from baseline to Month 3, 6, 12, then every 6 months through the end of study in fasting glucose

Safety Endpoints

Safety endpoints included AEs, AEs of special interest (AESI), vital signs (eg, heart rate, weight, blood pressure [BP]), and clinical laboratory measures.

Sample size

This event-driven study was designed to provide at least 90% power to detect an approximate 15% relative risk reduction in HR corresponding to the primary composite MACE-4 endpoint (CV death, nonfatal MI, nonfatal stroke, or coronary revascularization) at an overall study significance level (alpha) of 0.05.

A statistical relationship between on-treatment LDL-C differences between the bempedoic acid and ezetimibe group and the placebo group and CV event risk reduction was used to derive the postulated treatment effect of 15%. Assuming a 3.59% annual event rate in the placebo group, a minimum of 1620 primary composite MACE-4 events were needed.

The average follow-up duration for all patients was estimated to be approximately 42 months (~3.5 years), with an enrolment phase of approximately 33 months, a minimum follow-up duration of 24 months (2 years), and a lost-to-follow-up rate of 1% per year. Based on these assumptions, approximately 14,000 patients (approximately 7000 in the bempedoic acid and ezetimibe group and 7000 in the placebo group) were to be randomized into the study to achieve 1620 patients experiencing a positively adjudicated primary endpoint event.

It was expected that at least 50% of the 1620 patients experiencing a positively adjudicated primary MACE-4 (810 patients) would experience a positively adjudicated MACE-3 (CV death, nonfatal MI, or nonfatal stroke). Therefore, the study would stop when at least 1620 patients experienced a positively adjudicated primary MACE-4 endpoint, with 810 patients experiencing a positively adjudicated MACE-3, and a minimum of 24 months (2 years) had elapsed since the last patient was randomized.

Randomisation and blinding (masking)

Patients who satisfied all entry criteria were randomized to blinded IMP on Day 1 (Visit T1). Patients were randomized 1:1 to bempedoic acid or matching placebo using an interactive web response system (IWRS).

It was a double blind study.

Statistical methods

The following populations were defined for analysis purposes:

- The Full Analysis Set (FAS), also known as the intention-to-treat analysis set, included all randomized patients and re-randomized patients. Patients in the FAS were included in their assigned treatment group.
- The Safety Analysis Set (SAS) included all patients in the FAS who received at least 1 dose of double-blind IMP. Patients in the SAS were included in the treatment group that they actually received.
- The Per-protocol Analysis Set (PPS) is a subset of the FAS that excluded patients with selected major protocol deviations. The PPS has the same treatment group assignment as the FAS and was used for sensitivity analyses of the primary and key secondary efficacy endpoints.

Analyses of diabetes and related biomarkers were conducted based on the baseline glycaemic status defined below.

Status	Definition
Diabetes	Met 1 or more of the following criteria at baseline captured by information recorded prior to Day 1: • Medical history or adverse events indicating diabetes as defined by in the Diabetes Committee Charter (Appendix 16.1.13) • Prior glucose-lowering medication as defined in the Diabetes Committee Charter[a] (Appendix 16.1.13) • HbA_{1C} measurement ≥6.5% • Two or more measurements of fasting glucose ≥126 mg/dL (7.0 mmol/L)
Inadequately Controlled Diabetes	With diabetes and a HbA_{1C} of 7% or greater at baseline.
No Diabetes	Not meeting any of the criteria for diabetes at baseline.
Prediabetes	No diabetes at baseline and with: • HbA_{1C} measurement of ≥5.7% and <6.5%, OR • 1 or more measurements of fasting glucose ≥100 mg/dL (5.6 mmol/L), but not more than 1 value of fasting glucose ≥126 mg/dL (7.0 mmol/L)
Normoglycemia	No diabetes and not meeting the criteria for prediabetes at baseline.

HbA1C = haemoglobin A1c. a If prior medication was the only criteria met for diagnosis of diabetes, a query was sent to the Investigator for confirmation.

Efficacy Analyses

The primary and key secondary efficacy endpoints were tested sequentially in the order below in a gate-keeping testing procedure to control the study-wise type I error rate at 5%. Each endpoint was tested at a 2-sided significance level of 0.05 and tested only if the previous endpoint achieved statistical significance.

- Time to first occurrence of MACE (CV death, nonfatal MI, nonfatal stroke, or coronary revascularization; MACE-4; primary endpoint).
- Time to first occurrence of the composite endpoint of CV death, nonfatal MI, or nonfatal stroke (MACE-3).

- Time to first occurrence of fatal or nonfatal MI
- Time to first occurrence of coronary revascularization
- Time to first occurrence of fatal or nonfatal stroke
- Time to CV death
- Time to all-cause mortality

Any MACE endpoints that occurred during the study were submitted for adjudication; positively adjudicated MACE per the CEC were included in efficacy analyses. The primary efficacy endpoint was analyzed in the FAS using a Cox Proportional Hazards model with treatment as a factor. The hazard ratio (HR) and its 95% confidence interval (CI) and p-value from the log-rank test were provided.

If none of the MACE-4 events was observed, the patient was censored as described in the statistical analysis plan (SAP). Multiple imputation and tipping point analyses were performed as sensitivity analyses to account for potential bias due to censoring.

Secondary time-to-event endpoints were analyzed in a manner analogous to that used for the primary efficacy analysis, using a Cox Proportional Hazards model. The time to occurrence of new onset type 2 diabetes mellitus during the study was analyzed by a Cox Proportional Hazards model among patients who did not have diabetes at baseline.

Pre-specified sensitivity analyses of the MACE-4 and MACE-3 endpoint included analysis based on the PPS, an on-treatment analysis, assessment of impact from cross-in adjunctive lipid-modifying therapy, and subgroup analyses.

Cross-in lipid-modifying therapy was defined as:

- any statin not used at baseline and started after randomization, or any increase in intensity of a background statin during the course of the study, that is continued for 90 days or more;
- non-statin oral lipid-modifying therapy (LMT) not used at baseline (same preferred name), started after randomization, and continued for 90 days or more; or
- PCSK9 inhibitors not used at baseline and started after randomization, or with an increase in intensity from baseline if used at baseline (for alirocumab), and continued for 90 days or more if a monoclonal antibody; or at least 1 dose of siRNA after randomization, and before the End of Study visit.

In addition, the incidence rate as number of events per 100 person years, along with the total number of person years and difference in incidence rate between groups with 95% CIs were provided for the primary endpoint and key secondary endpoints.

Percent change from baseline in LDL-C and absolute change from baseline in HbA1C were analyzed using ANCOVA, with treatment group as a factor and the relevant baseline as a covariate. For each analysis, the least squares mean (LSM) and standard error (SE) were provided for each treatment group, along with the placebo-corrected LSM, its 95% CI, and associated p-value.

For hsCRP, a nonparametric (Wilcoxon rank sum test) analysis with Hodges Lehmann estimates and CI was performed.

Safety Analyses

Descriptive summaries were produced for all safety endpoints. All AEs were coded by system organ class (SOC) and preferred term (PT) using MedDRA Version 23.1. The summarization of adverse events included only treatment emergent adverse events (TEAEs), defined as AEs that began or worsened after

randomization and the first dose of double-blind IMP and through the end of the study, including the Follow-up Period.

Results

Participant flow

Patient disposition is summarized in Table 1 (screened patients) and Table 2 (FAS).

A total of 2037 (29.1%) patients in the bempedoic acid group and 2209 (31.7%) patients in the placebo group did not complete IMP, primarily due to patient decision (13.7% and 16.4%, respectively) or AE (11.3% and 10.7%, respectively). Overall, 125 (0.9%) patients did not complete study treatment due to being lost-to-follow-up. Overall, 2% of patients did not complete study treatment due to the COVID-19 pandemic (2.2% in the bempedoic acid group, 1.8% in placebo group), primarily as a result of patient decision (1.8% in the bempedoic acid group, 1.4% in placebo group).

Table 1: patient disposition (all screened patients).

Disposition	Bempedoic Acid n (%)	Placebo n (%)	Total n (%)
Total patients screened	-	-	22,084
Screen failure	-	-	8068 (36.5)
Inclusion/exclusion criteria	-	-	7187 (32.5)
Consent withdrawn	-	-	636 (2.9)
Other	-	-	109 (0.5)
Adverse event	-	-	51 (0.2)
Physician decision	-	-	43 (0.2)
Protocol deviation	-	-	34 (0.2)
Death	-	-	8 (<0.1)
Study terminated by Sponsor or Investigator	-	-	0
Site 18705 patients randomized – excluded from FAS[a]	18	28	46
All patients randomized excluding Site 18705	6992	6978	13,970

FAS = Full Analysis Set. Note: The denominator for percentage is the number of randomized patients, except for those who failed screening and the corresponding reason (where the percentage is based on the total patients screened). Primary reason will also include due to the pandemic counts. a Patients from site 18705 were excluded due to data irregularities and possible falsified data.

Table 2: Patient disposition (full analysis set).

Disposition	Bempedoic Acid (N = 6992) n (%)	Placebo (N = 6978) n (%)	Total (N = 13,970) n (%)
All patients randomized	6992	6978	13,970
Study treatment (IMP) disposition			
Never started treatment	2 (<0.1)	3 (<0.1)	5 (<0.1)
Completed	4953 (70.8)	4766 (68.3)	9719 (69.6)
Alive at EOT	4699 (67.2)	4496 (64.4)	9195 (65.8)
Died during study	254 (3.6)	270 (3.9)	524 (3.8)

Patients with Baseline Ezetimibe Use

From all patients, a total of 1612 patients were on baseline ezetimibe use. Of those, 803 patients were randomized to bempedoic acid and 809 patients were randomized to placebo. See further details in table 3 below.

Table 3: Patient disposition on patients with Baseline Ezetimibe Use (full analysis set).

	Statistic	Bempedoic Acid (N=803)	Placebo (N=809)	Total (N=1612)
All Patients Randomized	n	803	809	1612
Study Medication Disposition				
Never Started a Treatment	n (%)	0	0	0
Completed	n (%)	563 (70.1)	535 (66.1)	1098 (68.1)
Alive at the end of treatment	n (%)	537 (66.9)	511 (63.2)	1048 (65.0)
Died during the study	n (%)	26 (3.2)	24 (3.0)	50 (3.1)
Did not Complete	n (%)	240 (29.9)	274 (33.9)	514 (31.9)

Protocol deviations

Protocol deviation disposition was consistent between treatment groups. The majority of patients had a major protocol deviation (57.2% overall), most commonly related to laboratory assessment criteria (26.6% overall), informed consent (12.6% overall), and concomitant medication criteria (12.9% overall).

Table 4: Major (key) protocol deviations (full analysis set).

Protocol Deviation Category Subcategory	**Bempedoic Acid (N = 6992) n (%)**	**Placebo (N = 6978) n (%)**	**Total (N = 13,970) n (%)**
Patients with major protocol deviations	3892 (55.7)	4101 (58.8)	7993 (57.2)
Laboratory Assessment Criteria	1842 (26.3)	1878 (26.9)	3720 (26.6)
Informed Consent	859 (12.3)	902 (12.9)	1761 (12.6)
Concomitant Medication Criteria	760 (10.9)	1046 (15.0)	1806 (12.9)
Visit Schedule Criteria	638 (9.1)	653 (9.4)	1291 (9.2)
Study Procedures Criteria	595 (8.5)	575 (8.2)	1170 (8.4)
Eligibility and Entry Criteria	495 (7.1)	442 (6.3)	937 (6.7)
IMP Compliance	206 (2.9)	190 (2.7)	396 (2.8)
Other	201 (2.9)	252 (3.6)	453 (3.2)
Serious Adverse Event Criteria	115 (1.6)	140 (2.0)	255 (1.8)
Source Document Criteria	57 (0.8)	72 (1.0)	129 (0.9)
Administrative Criteria	17 (0.2)	18 (0.3)	35 (0.3)
Randomization Criteria	8 (0.1)	17 (0.2)	25 (0.2)

IMP = investigational medicinal product. Note: Protocol deviations were reviewed prior to database lock and classified based on clinical review. Note: Percentages may add up to more than 100% because a patient may have had more than one deviation.

Approximately 30% of patients in both treatment groups had protocol deviations related to the COVID-19 pandemic. The majority of COVID-19-related deviations were minor (27% in each group) and were primarily related to visit schedule criteria (25% in each group). Approximately 25% of patients in both groups did not have one or more study procedures performed due to the pandemic.

Baseline data

Overall, demographic and baseline characteristics of the patient population in CLEAR Outcomes were balanced between treatments groups and reflective of a global population whose health risk factors included elevated LDL-C and who were predisposed to experiencing a CV event (see Table 5).

Patients with Baseline Ezetimibe Use

Further, demographic and baseline characteristics patients with baseline ezetimibe use were generally consistent with the overall population, with the exception of there being a higher percentage of males (59.6%), a higher percentage of patients located in Western Europe (24.6%), and a lower percentage in Eastern Europe (33.9%) in the group with baseline ezetimibe use.

Table 5: Demographic baseline characteristics (Full Analysis Set).

Characteristic	Bempedoic Acid (N = 6992)	Placebo (N = 6978)	Overall (N = 13,970)
Age (years)			
Mean (SD)	65.5 (9.05)	65.5 (8.89)	65.5 (8.97)
Median (Min, Max)	66.0 (21, 92)	66.0 (22, 92)	66.0 (21, 92)
Age Category, n (%)			
<65 years	2859 (40.9)	2907 (41.7)	5766 (41.3)
≥65 to <75 years	3070 (43.9)	3027 (43.4)	6097 (43.6)
≥75 years	1063 (15.2)	1044 (15.0)	2107 (15.1)
Sex, n (%)			
Male	3631 (51.9)	3599 (51.6)	7230 (51.8)
Female	3361 (48.1)	3379 (48.4)	6740 (48.2)
Race, n (%)			
White	6397 (91.5)	6335 (90.8)	12,732 (91.1)
American/Mexican Indian or Alaska Native	240 (3.4)	247 (3.5)	487 (3.5)
Black or African American	156 (2.2)	172 (2.5)	328 (2.3)
Asian	130 (1.9)	136 (1.9)	266 (1.9)
Multiple	48 (0.7)	70 (1.0)	118 (0.8)
Native Hawaiian or Other Pacific Islander	20 (0.3)	17 (0.2)	37 (0.3)
Other	1 (<0.1)	1 (<0.1)	2 (<0.1)
Ethnicity, n (%)			
Not Hispanic or Latino	5802 (83.0)	5835 (83.6)	11,637 (83.3)
Hispanic or Latino	1190 (17.0)	1143 (16.4)	2333 (16.7)
Region, n (%)			
Central and Eastern Europe	3408 (48.7)	3307 (47.4)	6715 (48.1)
North America (US and Canada)	1503 (21.5)	1515 (21.7)	3018 (21.6)
Latin America	902 (12.9)	876 (12.6)	1778 (12.7)
Western Europe	786 (11.2)	829 (11.9)	1615 (11.6)
Other (Rest of World)	393 (5.6)	451 (6.5)	844 (6.0)

Max = maximum; Min = minimum; SD = standard deviation; US = United States.

Table 6: Medical History and Concomitant Illness (Full Analysis Set).

Parameter	Bempedoic Acid (N = 6692) n (%)	Placebo (N = 6978) n (%)	Total (N = 13,970) n (%)
History of hypertension			
Yes	5944 (85.0)	5932 (85.0)	11,876 (85.0)
No	1048 (15.0)	1046 (15.0)	2094 (15.0)
Tobacco use			
Never used	3361 (48.1)	3288 (47.1)	6649 (47.6)
Former user	2114 (30.2)	2164 (31.0)	4278 (30.6)
Current user	1517 (21.7)	1526 (21.9)	3043 (21.8)
Alcohol consumption			
Non-drinker	3745 (53.6)	3697 (53.0)	7442 (53.3)
Former drinker	401 (5.7)	454 (6.5)	855 (6.1)
Current drinker	2846 (40.7)	2827 (40.5)	5673 (40.6)
eGFR (mL/min/1.73 m^2)			
≥90	1216 (17.4)	1233 (17.7)	2449 (17.5)
60 to <90	4322 (61.8)	4282 (61.4)	8604 (61.6)
30 to <60	1437 (20.6)	1444 (20.7)	2881 (20.6)
≥30	17 (0.2)	18 (0.3)	35 (0.3)
Missing	0	1 (<0.1)	1 (<0.1)
Chronic kidney disease history			
Yes	488 (7.0)	442 (6.3)	930 (6.7)
No	6504 (93.0)	6536 (93.7)	13,040 (93.3)
BMI (kg/m^2)			
Mean (SD)	29.87 (5.197)	29.97 (5.246)	29.92 (5.222)
Median	29.30	29.30	29.30
Min, Max	16.1, 80.7	15.1, 62.9	15.1, 80.7
BMI category (kg/m^2), n (%)			
<25	1078 (15.4)	1005 (14.4)	2083 (14.9)
25 to <30	2839 (40.6)	2869 (41.1)	5708 (40.9)
≥30	3075 (44.0)	3102 (44.5)	6177 (44.2)
Missing	0	2 (<0.1)	2 (<0.1)
Weight (kg)			
Mean (SD)	84.20 (17.074)	84.54 (17.251)	84.37 (17.163)
Median	82.60	83.30	83.00
Min, Max	39.0, 209.5	36.3, 198.0	36.3, 209.5

BMI = body mass index; eGFR = estimated glomerular filtration rate. Note: Baseline was defined as the last value prior to the first dose of IMP.

Patients with Baseline Ezetimibe Use

In patients with baseline ezetimibe use, noteworthy medical history and concomitant illness were generally similar to the FAS, with the exception of there being slightly more patients reporting former tobacco use and current alcohol use in this subgroup (42.5% and 54.5% vs 30.6% and 40.6%, respectively, in the FAS. See table 7 below.

Table 7: Demographic baseline characteristics in Patients with Baseline Ezetimibe Use (Full Analysis Set).

	Statistic	Bempedoic Acid (N=803)	Placebo (N=809)	Total (N=1612)
Age (Years)	n	803	809	1612
	Mean (SD)	65.9 (8.32)	66.2 (8.40)	66.0 (8.36)
	Median	67.0	67.0	67.0
	Q1, Q3	61.0, 72.0	61.0, 72.0	61.0, 72.0
	Min, Max	37, 86	41, 88	37, 88
Age Category				
<65 Years	n (%)	320 (39.9)	323 (39.9)	643 (39.9)
>=65 to <75 Years	n (%)	374 (46.6)	358 (44.3)	732 (45.4)
>=75 Years	n (%)	109 (13.6)	128 (15.8)	237 (14.7)
Sex				
Male	n (%)	464 (57.8)	496 (61.3)	960 (59.6)
Female	n (%)	339 (42.2)	313 (38.7)	652 (40.4)
Race				
American/Mexican Indian or Alaska Native	n (%)	13 (1.6)	6 (0.7)	19 (1.2)
Asian	n (%)	8 (1.0)	8 (1.0)	16 (1.0)
Black or African American	n (%)	14 (1.7)	12 (1.5)	26 (1.6)
Native Hawaiian or Other Pacific Islander	n (%)	2 (0.2)	1 (0.1)	3 (0.2)
White	n (%)	760 (94.6)	769 (95.1)	1529 (94.9)
Multiple	n (%)	6 (0.7)	13 (1.6)	19 (1.2)
Ethnicity				
Hispanic or Latino	n (%)	86 (10.7)	74 (9.1)	160 (9.9)
Not Hispanic or Latino	n (%)	717 (89.3)	735 (90.9)	1452 (90.1)
Region				
North America (US and Canada)	n (%)	189 (23.5)	189 (23.4)	378 (23.4)
Latin America	n (%)	74 (9.2)	64 (7.9)	138 (8.6)
Western Europe	n (%)	190 (23.7)	206 (25.5)	396 (24.6)
Eastern Europe	n (%)	280 (34.9)	267 (33.0)	547 (33.9)
Other (Rest of the World)	n (%)	70 (8.7)	83 (10.3)	153 (9.5)
Weight (kg)	n	803	809	1612
	Mean (SD)	85.51 (16.656)	86.45 (17.576)	85.98 (17.125)
	Median	84.00	86.00	85.00
	Q1, Q3	74.00, 95.50	74.00, 97.40	74.00, 96.50
	Min, Max	40.0, 156.0	41.5, 198.0	40.0, 198.0
Height (cm)	n	803	809	1612
	Mean (SD)	169.66 (9.924)	170.04 (10.366)	169.85 (10.147)
	Median	170.00	171.00	170.20
	Q1, Q3	162.60, 177.80	162.60, 178.00	162.60, 177.80
	Min, Max	144.0, 198.1	122.2, 197.0	122.2, 198.1
BMI (kg/m^2)	n	803	809	1612
	Mean (SD)	29.62 (4.763)	29.83 (5.162)	29.73 (4.967)
	Median	29.10	29.20	29.15
	Q1, Q3	26.30, 32.30	26.30, 32.70	26.30, 32.50
	Min, Max	18.3, 50.5	18.2, 61.1	18.2, 61.1
BMI category (kg/m^2)				
<25	n (%)	115 (14.3)	124 (15.3)	239 (14.8)
25 to <30	n (%)	359 (44.7)	327 (40.4)	686 (42.6)
>= 30	n (%)	329 (41.0)	358 (44.3)	687 (42.6)
Missing	n (%)	0	0	0
Heart Rate (beats per minute [bpm])	n	803	809	1612
	Mean (SD)	67.5 (10.02)	67.9 (10.20)	67.7 (10.11)
	Median	67.0	68.0	67.0
	Q1, Q3	60.0, 74.0	60.0, 74.0	60.0, 74.0
	Min, Max	42, 105	35, 108	35, 108
Key laboratory Results				
LDL-C (mg/dL)	n	803	809	1612
	Mean (SD)	133.16 (31.292)	132.57 (34.575)	132.87 (32.972)
	Median	128.00	126.50	127.00
	Q1, Q3	112.00, 151.00	110.00, 147.50	111.00, 149.00
	Min, Max	51.5, 287.0	49.0, 408.0	49.0, 408.0
LDL-C (mmol/L)	n	803	809	1612
	Mean (SD)	3.45 (0.811)	3.44 (0.898)	3.44 (0.855)
	Median	3.30	3.30	3.30
	Q1, Q3	2.90, 3.90	2.90, 3.80	2.90, 3.90
	Min, Max	1.3, 7.4	1.3, 10.6	1.3, 10.6
LDL-C category (mg/dL)				
<130	n (%)	420 (52.3)	444 (54.9)	864 (53.6)
>=130 and <160	n (%)	249 (31.0)	235 (29.0)	484 (30.0)
>=160	n (%)	134 (16.7)	130 (16.1)	264 (16.4)

CVD risk category				
Secondary prevention (Documented CVD History)	n (%)	619 (77.1)	658 (81.3)	1277 (79.2)
Coronary artery disease (CAD)	n (%)	519 (64.6)	552 (68.2)	1071 (66.4)
Symptomatic peripheral arterial disease (PAD)	n (%)	101 (12.6)	88 (10.9)	189 (11.7)
Cerebrovascular atherosclerotic disease (CeVD)	n (%)	84 (10.5)	95 (11.7)	179 (11.1)
Primary prevention (At high risk for CVD)	n (%)	184 (22.9)	151 (18.7)	335 (20.8)
History of Diabetes				
Yes	n (%)	268 (33.4)	275 (34.0)	543 (33.7)
No	n (%)	535 (66.6)	534 (66.0)	1069 (66.3)
Statin intolerance criteria				
Failed 2 or more statins	n (%)	674 (83.9)	700 (86.5)	1374 (85.2)
Failed 1 statin (Reason for not attempting 2nd statin)	n (%)	129 (16.1)	109 (13.5)	238 (14.8)
Patient refused to	n (%)	99 (12.3)	83 (10.3)	182 (11.3)
Physician advised not to	n (%)	30 (3.7)	26 (3.2)	56 (3.5)
Missing	n (%)	0	0	0
Baseline LMT				
Statin Use	n (%)	91 (11.3)	111 (13.7)	202 (12.5)
Statin + other LMT	n (%)	91 (11.3)	111 (13.7)	202 (12.5)
Other LMT without statin	n (%)	712 (88.7)	698 (86.3)	1410 (87.5)
Statin intensity				
No Statin	n (%)	712 (88.7)	698 (86.3)	1410 (87.5)
Very Low	n (%)	89 (11.1)	101 (12.5)	190 (11.8)
Low	n (%)	0	0	0
Moderate	n (%)	1 (0.1)	8 (1.0)	9 (0.6)
High	n (%)	1 (0.1)	1 (0.1)	2 (0.1)
Missing	n (%)	0	1 (0.1)	1 (0.1)
Ezetimibe use				
Yes	n (%)	803 (100.0)	809 (100.0)	1612 (100.0)
Estimated glomerular filtration rate (eGFR) (mL/min/1.73m²)				
>=90	n (%)	112 (13.9)	139 (17.2)	251 (15.6)
60 to <90	n (%)	505 (62.9)	518 (64.0)	1023 (63.5)
30 to <60	n (%)	184 (22.9)	149 (18.4)	333 (20.7)
<30	n (%)	2 (0.2)	3 (0.4)	5 (0.3)
Missing	n (%)	0	0	0
History of chronic kidney disease				
Yes	n (%)	68 (8.5)	43 (5.3)	111 (6.9)
No	n (%)	735 (91.5)	766 (94.7)	1501 (93.1)

Table 8: Baseline Laboratory Parameters (Full Analysis Set).

Parameter	Bempedoic Acid (N = 6992)	Placebo (N = 6978)	Overall (N = 13,970)
LDL-C (mg/dL), n			
Mean (SD)	139.0 (34.9)	139.0 (35.2)	139.0 (35.0)
Median	134.50	134.50	134.50
Minimum, maximum	37.0, 459.0	28.5, 417.5	28.5, 459.0
LDL-C (mmol/L), n			
Mean (SD)	3.60 (0.903)	3.60 (0.913)	3.60 (0.908)
Median	3.50	3.50	3.50
Minimum, maximum	1.0, 11.9	0.7, 10.8	0.7, 11.9
LDL-C category, n (%)			
<130 mg/dL	3074 (44.0)	3089 (44.3)	6163 (44.1)
≥130 and <160 mg/dL	2213 (31.7)	2250 (32.2)	4463 (31.9)
≥160 mg/dL	1705 (24.4)	1639 (23.5)	3344 (23.9)

Table 9: Baseline Cardiovascular Characteristics (Full Analysis Set).

Parameter	Bempedoic Acid (N = 6992) n (%)	Placebo (N = 6978) n (%)	Overall (N = 13,970) n (%)
Cardiovascular disease risk category			
Secondary prevention (documented CVD history)	4892 (70.0)	4872 (69.8)	9764 (69.9)
Coronary artery disease	3574 (73.1)	3536 (72.6)	7110 (72.8)
Percutaneous coronary or surgical coronary revascularization, occurring >90 days prior to screening	2626 (53.7)	2623 (53.8)	5249 (53.8)
MI (either ST- or non-ST-elevation MI) occurring >90-days prior to screening	2274 (46.5)	2199 (45.1)	4473 (45.8)
Angiographic stenosis of >50% in a least 1 major coronary artery (native or graft vessel), as documented by selective coronary angiography or CTA	1217 (24.9)	1214 (24.9)	2431 (24.9)
Symptomatic peripheral arterial disease	794 (16.2)	830 (17.0)	1624 (16.6)
Peripheral vascular disease with symptoms of claudication or resting limb ischemia with either ankle brachial index <0.9 or angiogram (including CTA) showing >50% stenosis	613 (12.5)	658 (13.5)	1271 (13.0)
Peripheral arterial revascularization (surgical or percutaneous), occurring >90 days prior to screening	180 (3.7)	187 (3.8)	367 (3.8)
Abdominal aortic aneurysm confirmed by imaging or aortic aneurysm repair, occurring >90 days prior to screening	78 (1.6)	68 (1.4)	146 (1.5)
Lower extremity amputation due to peripheral vascular disease, occurring >90 days prior to screening	12 (0.2)	18 (0.4)	30 (0.3)
Cerebrovascular atherosclerotic disease	1027 (21.0)	1040 (21.3)	2067 (21.2)
Ischemic stroke occurring >90 days prior to screening	825 (16.9)	836 (17.2)	1661 (17.0)
Carotid endarterectomy, carotid stenting, or >70% stenosis in a carotid artery determined by carotid ultrasound or angiogram, occurring >90 days prior to screening	250 (5.1)	250 (5.1)	500 (5.1)
Primary prevention (At high risk for CVD)	2100 (30.0)	2106 (30.2)	4206 (30.1)
Patients with type 1 or type 2 diabetes, aged >65 years (women) or >60 years (men)	1150 (54.8)	1187 (56.4)	2337 (55.6)
Reynolds Risk score >30% or a SCORE Risk score >7.5% over 10 years	868 (41.3)	922 (43.8)	1790 (42.6)
Coronary artery calcium score >400 Agatston units at any time in the past.	86 (4.1)	55 (2.6)	141 (3.4)
None	104 (5.0)	85 (4.0)	189 (4.5)

CTA = computed tomography angiography; CVD = cardiovascular disease; MI = myocardial infarction; SCORE = Systematic COronary Risk Evaluation. Note: For CVD characteristics, percent.

Patients with Baseline Ezetimibe Use

In patients with baseline ezetimibe use, slightly more patients had documented CVD history (79.2%) compared with the FAS. See table 9 above.

Table 10: Baseline Glycaemic Status and History of Diabetes (Full Analysis Set).

Parameter	Bempedoic Acid (N = 6992)	Placebo (N = 6978)	Overall (N = 13,970)
History of diabetes			
Yes	2963 (42.4)	3022 (43.3)	5985 (42.8)
No	4029 (57.6)	3956 (56.7)	7985 (57.2)
Glycemic status			
No diabetes	3848 (55.0)	3749 (53.7)	7597 (54.4)
Normoglycemic	937 (13.4)	864 (12.4)	1801 (12.9)
Prediabetes	2911 (41.6)	2885 (41.3)	5796 (41.5)
Diabetes	3144 (45.0)	3229 (46.3)	6373 (45.6)
Inadequately controlled diabetes	1356 (19.4)	1369 (19.6)	2725 (19.5)

Patients with Baseline Ezetimibe Use

In patients with baseline ezetimibe use, 64.1% of patients had a baseline glycaemic status of no diabetes, including 48.1% and 16.0% who had prediabetes and normal glycaemic control, respectively; 14.6% of patients had inadequately controlled diabetes at baseline.

Table 11: History of Statin Intolerance and Background Lipid-modifying Therapy Use (Full Analysis Set).

Symptoms	Bempedoic Acid (N = 6992) n (%)	Placebo (N = 6978) n (%)	Total (N = 13,970) n (%)
Statin intolerance criteria			
Failed 2 or more statins	5477 (78.3)	5495 (78.7)	10,972 (78.5)
Failed 1 statin	1515 (21.7)	1483 (21.3)	2998 (21.5)
Patient refused to attempt second statin	1368 (19.6)	1349 (19.3)	2717 (19.4)
Physician advised against second statin	146 (2.1)	133 (1.9)	279 (2.0)
Missing	1 (<0.1)	1 (<0.1)	2 (<0.1)
Background LMT			
Statin use	1601 (22.9)	1573 (22.5)	3174 (22.7)
Statin only	1400 (20.0)	1363 (19.5)	2763 (19.8)
Statin and other LMT	201 (2.9)	210 (3.0)	411 (2.9)
Other LMT without statin	1288 (18.4)	1291 (18.5)	2579 (18.5)
None	4103 (58.7)	4114 (59.0)	8217 (58.8)
Statin intensity			
No statin	5391 (77.1)	5405 (77.5)	10,796 (77.3)
Very low	1573 (22.5)	1538 (22.0)	3111 (22.3)
Low	3 (<0.1)	5 (0.1)	8 (0.1)
Moderate	20 (0.3)	27 (0.4)	47 (0.3)
High	3 (<0.1)	1 (<0.1)	4 (<0.1)
Missing	2 (<0.1)	2 (<0.1)	4 (<0.1)
Ezetimibe use			
Yes	803 (11.5)	809 (11.6)	1612 (11.5)
No	6189 (88.5)	6169 (88.4)	12,358 (88.5)

LMT = lipid-modifying therapy. Note: Patients who did not have documented secondary preventions for cardiovascular disease were counted as primary prevention.

Table 12: Prior Use of Statins (Safety Analysis Set).

Prior Medication	Bempedoic Acid (N = 7001) n (%)	Placebo (N = 6964) n (%)	Total (N = 13,965) n (%)
Number of patients with ≥1 prior medication	6999 (100.0)	6963 (100.0)	13,962 (100.0)
HMG COA reductase inhibitors	6999 (100.0)	6963 (100.0)	13,962 (100.0)
Atorvastatin	5364 (76.6)	5411 (77.7)	10,775 (77.2)
Rosuvastatin	3995 (57.1)	4039 (58.0)	8034 (57.5)
Simvastatin	2680 (38.3)	2679 (38.5)	5359 (38.4)
Pravastatin	1061 (15.2)	1037 (14.9)	2098 (15.0)
Fluvastatin	230 (3.3)	267 (3.8)	497 (3.6)
Pitavastatin	221 (3.2)	225 (3.2)	446 (3.2)
Lovastatin	201 (2.9)	200 (2.9)	401 (2.9)
Cerivastatin	11 (0.2)	15 (0.2)	26 (0.2)
Unknown statin	4 (0.1)	0	4 (<0.1)

HMG COA = 3-hydroxy-3-methylglutaryl coenzyme A; IMP = investigational medicinal product; WHO = World Health Organization. Note: Medications were coded using WHO dictionary version Sep2018 (Enhanced). Note: Patient were counted only once per unique Anatomic Therapeutic Class and once per unique preferred name. Note: Includes medications that started and ended prior to the first dose of IMP.

Table 13: Baseline Lipid-modifying Therapy (Full Analysis Set).

Baseline LMT	Bempedoic Acid (N = 6992) n (%)	Placebo (N = 6978) n (%)	Total (N = 13,970) n (%)
Number of patients with baseline LMT	2889 (41.3)	2864 (41.0)	5753 (41.2)
Statins	1601 (22.9)	1573 (22.5)	3174 (22.7)
Selective cholesterol absorption inhibitors (Ezetimibe)	803 (11.5)	809 (11.6)	1612 (11.5)
Other	406 (5.8)	372 (5.3)	778 (5.6)
Fibrates	371 (5.3)	393 (5.6)	764 (5.5)
PCSK9 inhibitors	35 (0.5)	50 (0.7)	85 (0.6)
Bile acid sequestrants	48 (0.7)	36 (0.5)	84 (0.6)
Niacin derivatives	33 (0.5)	50 (0.7)	83 (0.6)

LMT = lipid-modifying therapy;Note: Baseline LMT was defined as any lipid-modifying agents that were ongoing at the time of randomization. Medications were coded using WHO dictionary version Sep2018 (Enhanced).

Patients with Baseline Ezetimibe Use

In patients with baseline ezetimibe use, fewer patients were taking a statin at baseline (12.5%) compared with the FAS (22.7%). However, it should be noted that all patients in this subpopulation were taking baseline LMT by definition, while 58.8% of the FAS were not taking a baseline LMT. See table 13 above.

Table 14: History of Statin Intolerance and Background Lipid-modifying Therapy Use (Full Analysis Set)

Symptoms	Bempedoic Acid (N = 6992) n (%)	Placebo (N = 6978) n (%)	Total (N = 13,970) n (%)
Statin intolerance criteria			
Failed 2 or more statins	5477 (78.3)	5495 (78.7)	10,972 (78.5)
Failed 1 statin	1515 (21.7)	1483 (21.3)	2998 (21.5)
Patient refused to attempt second statin	1368 (19.6)	1349 (19.3)	2717 (19.4)
Physician advised against second statin	146 (2.1)	133 (1.9)	279 (2.0)
Missing	1 (<0.1)	1 (<0.1)	2 (<0.1)
Background LMT			
Statin use	1601 (22.9)	1573 (22.5)	3174 (22.7)
Statin only	1400 (20.0)	1363 (19.5)	2763 (19.8)
Statin and other LMT	201 (2.9)	210 (3.0)	411 (2.9)
Other LMT without statin	1288 (18.4)	1291 (18.5)	2579 (18.5)
None	4103 (58.7)	4114 (59.0)	8217 (58.8)
Statin intensity			
No statin	5391 (77.1)	5405 (77.5)	10,796 (77.3)
Very low	1573 (22.5)	1538 (22.0)	3111 (22.3)
Low	3 (<0.1)	5 (0.1)	8 (0.1)
Moderate	20 (0.3)	27 (0.4)	47 (0.3)
High	3 (<0.1)	1 (<0.1)	4 (<0.1)
Missing	2 (<0.1)	2 (<0.1)	4 (<0.1)
Ezetimibe use			
Yes	803 (11.5)	809 (11.6)	1612 (11.5)
No	6189 (88.5)	6169 (88.4)	12,358 (88.5)

Table 15: Important Cardiovascular-related Concomitant Medications by ATC Drug Class 4 (Full Analysis Set).

ATC 4	Bempedoic Acid (N = 7001) n (%)	Placebo (N = 6964) n (%)	Total (N = 13,965) n (%)
Platelet aggregation inhibitors excluding heparin			
Acetylsalicylic acid	3967 (56.7)	3988 (57.3)	7955 (57.0)
ACE inhibitors			
Plain	2758 (39.4)	2760 (39.6)	5518 (39.5)
With calcium channel blockers	130 (1.9)	149 (2.1)	279 (2.0)
With diuretics	272 (3.9)	277 (4.0)	549 (3.9)
Other combinations	131 (1.9)	138 (2.0)	269 (1.9)
Angiotensin II antagonists			
Plain	2177 (31.1)	2258 (32.4)	4435 (31.8)
With calcium channel blockers	75 (1.1)	85 (1.2)	160 (1.1)
With diuretics	307 (4.4)	288 (4.1)	595 (4.3)
Other combinations	90 (1.3)	90 (1.3)	180 (1.3)
Beta blocking agents			
Plain	72 (1.0)	111 (1.6)	183 (1.3)
With calcium channel blockers	4 (0.1)	9 (0.1)	13 (0.1)
Non-selective	137 (2.0)	142 (2.0)	279 (2.0)
Selective	3616 (51.6)	3587 (51.5)	7203 (51.6)
Direct thrombin inhibitors	103 (1.5)	86 (1.2)	189 (1.4)
Other antithrombotic agents	12 (0.2)	14 (0.2)	26 (0.2)

ACE = angiotensin converting enzyme; ATC = Anatomical Therapeutic Chemical; IMP = investigational medicinal product Note: Patient were counted only once per unique ATC Drug Class and once per unique preferred name within ATC Drug Class. Note: Concomitant medications were medications that started prior to and continued through first dose of IMP or started after the first dose of IMP.

Patients with Baseline Ezetimibe Use

Also in the patients on baseline ezetimibe use, 64.1% of patients had a baseline glycaemic status of no diabetes, including 48.1% and 16.0% who had prediabetes and normal glycaemic control, respectively; 14.6% of patients had inadequately controlled diabetes at baseline.

Numbers analysed

Full Analysis Set: 13,970 patients (6992 in the bempedoic acid group, 6978 in the placebo group).

Safety Analysis Set: 13,965 patients (7001 in the bempedoic acid group, 6964 in the placebo group).

Per-protocol Analysis Set: 13,820 patients (6912 in the bempedoic acid group, 6908 in the placebo group)

Note, the Full Analysis Set (FAS) included all randomized patients, excluding patients from Site 18705. Patients in the FAS were included in their assigned treatment group. Note: The Safety Analysis Set (SAS) included all patients in the FAS who received at least 1 dose of IMP. Patients in the SAS were grouped according to the actual treatment received. Five patients, 2 randomized to bempedoic acid and 3 to placebo, did not receive any treatment and were not included in the SAS; 11 patients were randomized to placebo but received ≥1 dose of bempedoic acid and were, therefore, counted in bempedoic acid group for the SAS. Note: The Per-Protocol Set was a subset of the FAS that excluded patients with selected major protocol deviations (see SAP, Section 6.4).

Outcomes and estimation

Primary efficacy endpoint - time to first occurrence of MACE-4 (CV death, nonfatal MI, nonfatal stroke, or coronary revascularization)

Study 1002-043 met its primary efficacy endpoint. Treatment with bempedoic acid resulted in a statistically significant reduction in risk of a first occurrence of a MACE-4 by 13% compared with patients who received placebo with a HR of 0.87 (95% CI: [0.79, 0.96]; p = 0.0037; Table 16).

A total of 819 (11.7%) and 927 (13.3%) patients in the bempedoic acid and placebo groups, respectively, experienced at least 1 MACE-4 during the study, representing an absolute risk reduction of 1.6%.

Review of the Kaplan Meier curve (Figure 1) shows that the risk of a MACE-4 was lower for the bempedoic acid group by Month 6. At year 4, the risk remained notably lower in the bempedoic acid group (13.5%) compared with the placebo group (15.6%), representative of an absolute reduction of 2.1%.

Suspected cases, confirmed cases, and hospitalizations for COVID-19 did not have a clinically meaningful impact on evaluation of the primary endpoint in this study as there were few patients who had a first MACE-4 that was temporally related to a COVID-19 case; 10 (0.1%) patients in the bempedoic acid group and 11 (0.2%) patients in the placebo group experienced their first MACE-4 within 14 days before or 30 days after a positive COVID polymerase chain reaction (PCR) test. A first MACE-4 was experienced within 14 days before or 30 days after a suspected COVID-19 case in 12 (0.2%) and 20 (0.3%) patients, respectively.

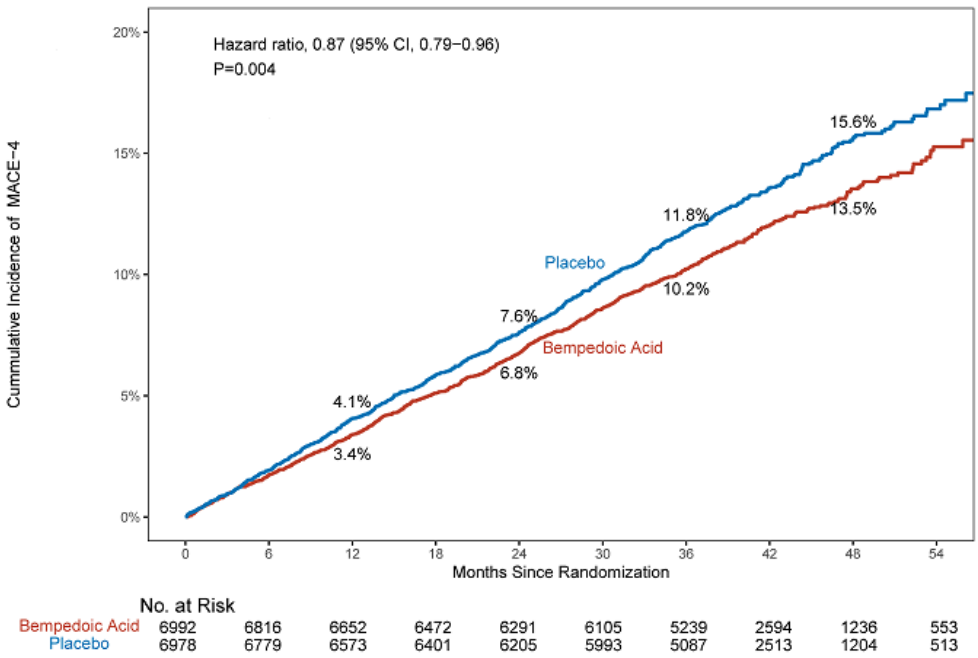
Of the MACE-4 components, significant risk reduction was noted for nonfatal-MI (HR: 0.73; 95% CI: [0.62, 0.87]; nominal p = 0.0003) and coronary revascularization (HR: 0.81; 95% CI: [0.72, 0.92]; p = 0.0013).

Table 16: Primary Endpoint: Time to First Occurrence of a MACE-4 (Full Analysis Set).

Endpoint Statistic	Bempedoic Acid (N = 6992) n (%)	Placebo (N = 6978) n (%)	Hazard Ratio (95% CI)[a]	*p*-value[b]
Primary Endpoint: MACE-4	819 (11.7)	927 (13.3)	0.87 (0.79, 0.96)	0.0037
MACE-4 Components				
Nonfatal MI	236 (3.4)	317 (4.5)	0.73 (0.62, 0.87)	0.0003[c]
Nonfatal Stroke	119 (1.7)	144 (2.1)	0.82 (0.64, 1.05)	0.1091[c]
Coronary revascularization	435 (6.2)	529 (7.6)	0.81 (0.72, 0.92)	0.0013
CV death	269 (3.8)	257 (3.7)	1.04 (0.88, 1.24)	0.6227

CI = confidence interval; CV = cardiovascular; MACE-4 = 4-component major adverse cardiovascular event; MI = myocardial infarction. a Hazard ratio and corresponding 95% CI were based on a Cox proportional hazard model fitting treatment as explanatory variable. b p-value was based on log rank test. c Nominal value. Note: MACE-4 was defined as the composite endpoint of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization. Note: the table also presents the time to first occurrence for each of the components of MACE-4; patients may be included in more than 1 category.

Figure 2: Kaplan-Meier curve for time to first occurrence of MACE-4 (full analysis set).



CI = confidence interval; MACE-4 = 4-component major adverse cardiovascular event; No = number Note: MACE-4 defined as the composite endpoint of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization.

Cardiovascular Death

Treatment with bempedoic acid did not appear to influence the risk of CV death (HR: 1.04; 95% CI: [0.88, 1.24]; p = 0.6227; Table 16). All on-study deaths were adjudicated by the CEC to determine if the death was CV or non-CV-related and further classified into sub-categories.

When there was no/very limited documentation on the cause of death a narrative was written by the investigator and the death was classified as an undetermined cause of death, which was to be contained within the category of CV death per the CEC Charter.

Overall, data from 858 patient deaths were reviewed by the CEC, including 436 (6.2%) of the 6992 patients in the bempedoic acid group and 422 (6.0%) of the 6978 patients in the placebo group (Table

17). There were a total of 530 CV deaths, including 271 (62.2%) of the 436 total deaths in the bempedoic acid group and 259 (61.4%) of the 422 total deaths in the placebo group.

There were 8 different subcategories of CV deaths which are presented in Table 17. The most common category for CV death in both treatment groups was undetermined (118 of 271 CV deaths in the bempedoic acid group, 94 of 259 CV deaths in the placebo group), followed by sudden cardiac death (83 of 271 CV deaths in the bempedoic acid group, 87 of 259 CV deaths in the placebo group) and acute myocardial infarction (29 of 271 CV deaths in the bempedoic acid group, 21 of 259 CV deaths in the placebo group).

Table 17: Summary of Positively-adjudicated Cardiovascular Deaths (Full Analysis Set).

Category	Bempedoic Acid (N = 6992) n (%)	Placebo (N = 6978) n (%)
All Deaths	436 (6.2)	422 (6.0)
All non-CV Death (non-MACE)	165 (2.4)	163 (2.3)
Cardiovascular Death (MACE)	271 (3.9)	259 (3.7)
Undetermined	118 (1.7)	94 (1.3)
Sudden cardiac death	83 (1.2)	87 (1.2)
Acute Myocardial Infarction	29 (0.4)	21 (0.3)
Stroke	19 (0.3)	17 (0.2)
Heart failure	12 (0.2)	26 (0.4)
Cardiovascular procedure	5 (0.1)	6 (0.1)
Other cardiovascular causes	4 (0.1)	8 (0.1)
Cardiovascular hemorrhage	1 (<0.1)	0

The lack of effect of bempedoic acid treatment on overall CV death (HR: 1.04; 95% CI: [0.88, 1.24]) is generally consistent with what was observed in recent CVOTs, including IMPROVE-IT (HR: 1.00; 95% CI: [0.89, 1.13]; Cannon et al., 2017), FOURIER (HR: 1.05; 95% CI: [0.88, 1.25]; Sabatine et al, 2017b), and ODYSSEY (HR: 0.88; 95% CI: [0.74-1.05; Schwartz et al, 2018]). However, the proportion of CV deaths of undetermined cause in CLEAR Outcomes was higher than expected and, given that a significant portion of the follow up time period of the trial occurred during the global COVID-19 pandemic, further investigation into the role of the pandemic on CV death incidence was conducted. The high proportion of undetermined CV deaths in CLEAR Outcomes appears to be related to the global COVID-19 pandemic and the difference in occurrence between treatment groups during the pandemic is likely due to chance.

Patients with baseline ezetimibe use

In the patients with baseline ezetimibe use, bempedoic acid reduced the risk of MACE-4 compared with placebo, with a HR of 0.94 (95% CI: [0.74, 1.20]).

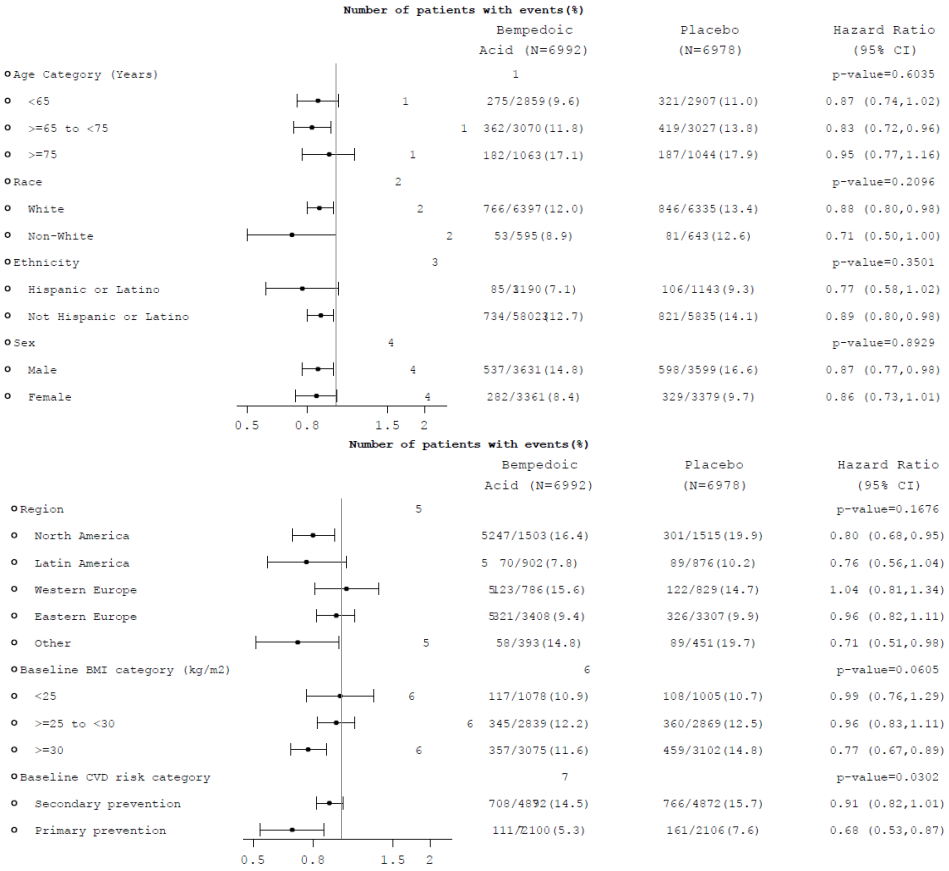
Bempedoic acid also reduced the risk of MACE-3 compared with placebo, with a HR of 0.85 (95% CI: [0.62, 1.16]) for patients with baseline ezetimibe use.

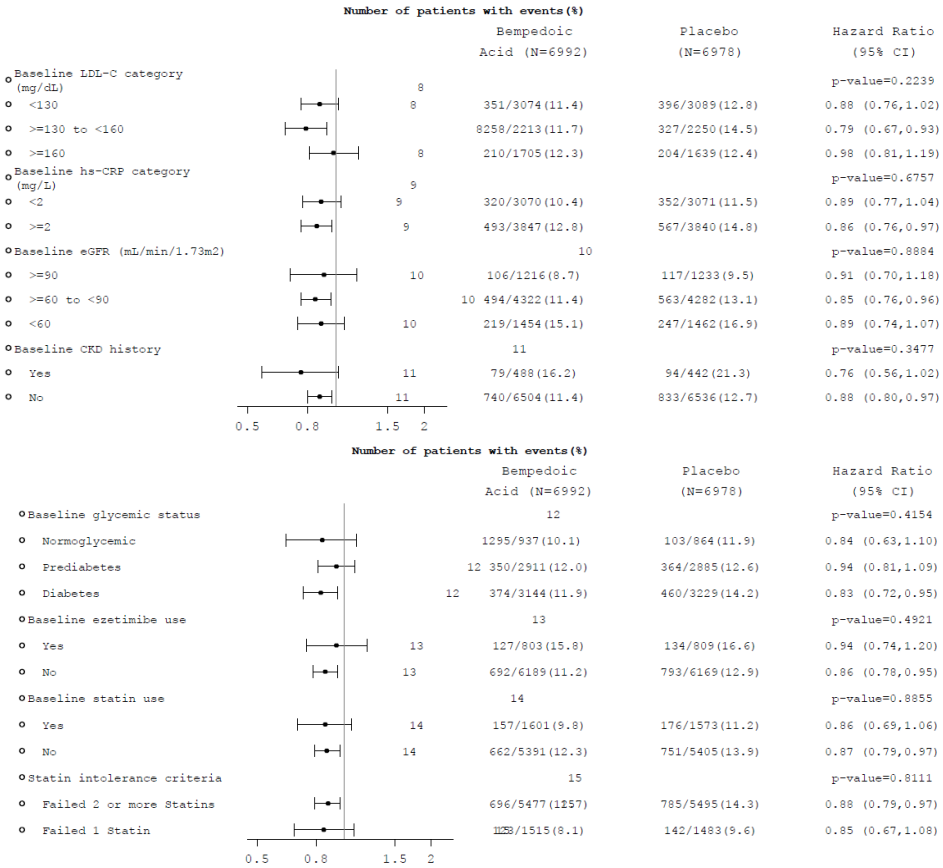
Subgroup Analyses

The results have shown consistency within the subgroups assessed and with effects observed for the overall population (see Figure 3). Among the 15 subgroup analyses, 14 subgroups showed no interaction with treatment (interaction p >0.05), including demographic subgroups, and status of with or without background statin use and with or without background ezetimibe use, among others. Cardiovascular disease risk category (primary prevention vs secondary prevention) was the only analysis with a nominally significant interaction with treatment (p = 0.0302). While some variability was observed in the

reported MACE-4 HRs by geographical region, there was a little observed difference in baseline characteristics or LDL-C reduction across regions.

Figure 3: Forest plot of Hazard Ratios (bempedoic acid vs placebo) for 4-component major adverse cardiac event by subgroup (Full Analysis Set).





Sensitivity Analyses

Overall, the results of sensitivity analyses conducted for the primary endpoint were generally consistent with the results reported for the FAS, indicating the robustness of the results (Table 18).

Table 18: Sensitivity Analysis of Primary Efficacy Endpoint.

Population	Bempedoic Acid	Placebo	Hazard Ratio (95% CI)	*p*-value
Full Analysis Set[a]	821/6992 (11.7%)	929/6978 (13.3%)	0.87 (0.79, 0.96)	0.0037
Per-protocol Set	799/6912 (11.6%)	914/6908 (13.2%)	0.86 (0.78, 0.95)	0.0021
On-treatment (PPS)	615/6912 (8.9%)	745/6908 (10.8%)	0.80 (0.72, 0.89)	0.0001
Before LMT cross-in (PPS)	745/6912 (10.8%)	831/6908 (12.0%)	0.86 (0.77, 0.94)	0.0019

CI = confidence interval; LMT = lipid modifying therapy; PPS = per-protocol set. [a] Full Analysis Set included full data from patients in Ukraine.

Total Event Analysis: Based on a total event analysis, the effect of treatment with bempedoic acid compared with placebo on the primary endpoint was greater (HR: 0.80; 95% CI: [0.72, 0.89]; p = 0.0001) compared to the analysis based on first events.

Key secondary efficacy endpoint - composite endpoint of MACE-3

Statistically significant and clinically meaningful reductions in MACE-3 (composite endpoint of nonfatal MI, nonfatal stroke, or CV death), MI (nonfatal and fatal), and coronary revascularization were observed.

The time to first occurrence of MACE-3 results was consistent with the MACE-4 results. Treatment with bempedoic acid was associated with a significant reduction in risk of MACE-3 (HR: 0.85; 95% CI: [0.76,

0.96]; p = 0.0058). MACE-3 was experienced by 8.2% and 9.5% of patients in the bempedoic acid and placebo groups, respectively. At Year 3, the cumulative risk of MACE-3 was 1.1% lower in the bempedoic acid group than the placebo group; this treatment differential increased to 2% at Year 4 (Figure 4).

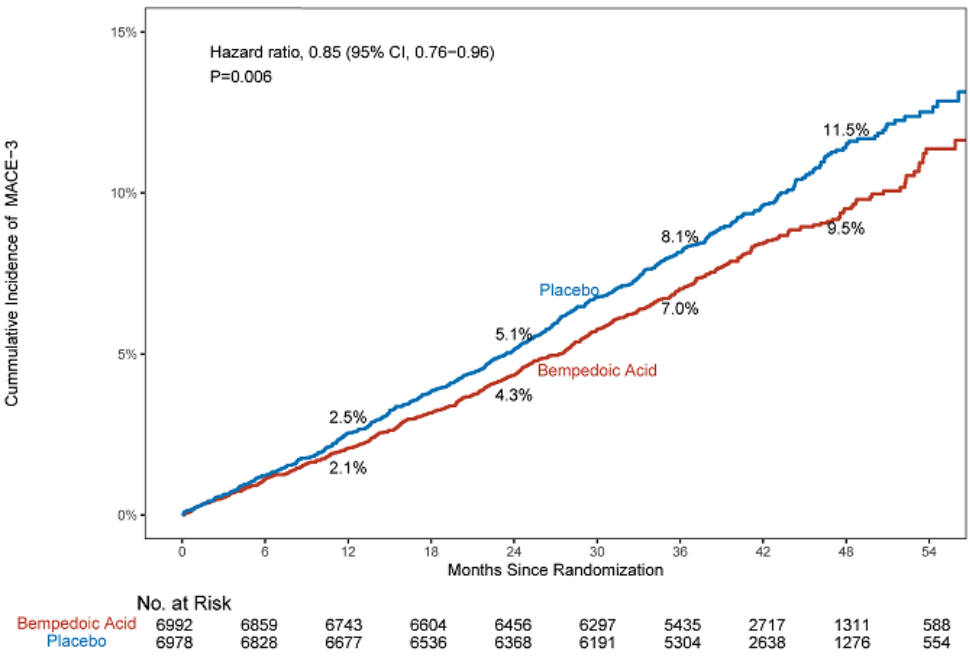
The proportion of patients who experienced nonfatal MI, CV death, and nonfatal stroke was 3.3%, 3.3%, and 1.6%, respectively, in the bempedoic acid group and 4.4%, 3.2%, and 1.9%, respectively, in the placebo group. Of all MACE-3, nonfatal MI accounted for 40.5% of events in the bempedoic acid group and 46.6% of events in the placebo group. Cardiovascular death and nonfatal stroke accounted for 40.3% and 19.1% of events in the bempedoic acid group, respectively, and 33.5% and 19.9% of events in the placebo group, respectively.

Table 19: Key Secondary Efficacy Endpoints (Full Analysis Set)

Endpoint	Bempedoic Acid (N = 6992)	Placebo (N = 6978)	Hazard Ratio (95% CI)	*p*-value
MACE-3	575 (8.2)	663 (9.5)	0.85 (0.76, 0.96)	0.0058
Fatal and nonfatal MI	261 (3.7)	334 (4.8)	0.77 (0.66, 0.91)	0.0016
Coronary revascularization	435 (6.2)	529 (7.6)	0.81 (0.72, 0.92)	0.0013
Fatal and nonfatal stroke	135 (1.9)	158 (2.3)	0.85 (0.67, 1.07)	0.1593
CV death	269 (3.8)	257 (3.7)	1.04 (0.88, 1.24)	0.6227[a]
All-cause mortality	434 (6.2)	420 (6.0)	1.03 (0.90, 1.18)	0.6608[a]

CI = confidence interval; CV = cardiovascular; MACE = major adverse cardiovascular event; MI = myocardial infarction a Nominal value. Note: 3-Component MACE is defined as the composite endpoint of nonfatal MI, nonfatal stroke, or CV death. Note: Hazard ratios and corresponding 95% CI were based on a Cox proportional hazard model fitting treatment as explanatory variable. Note: p-values were based on log rank test.

Figure 4: Kaplan-Meier Curve for Time to First Occurrence of 3-component MACE (Full Analysis Set).



CI = confidence interval; MACE = major adverse cardiovascular event; No = number Note: 3-component MACE defined as the composite endpoint of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

Patients with Baseline Ezetimibe Use

Bempedoic acid also reduced the risk of MACE-3 compared with placebo, with a HR of 0.85 (95% CI: [0.62, 1.16]) for patients with baseline ezetimibe use.

Sensitivity analyses

Sensitivity analyses conducted in the PPS overall (HR: 0.85, 95% CI: [0.76, 0.95]) and with patient data censored at the time of starting the first cross-in adjunctive LMT therapy (HR: 0.85, 95% CI: [0.76, 0.96]) were consistent with the above results. When considering only those events that occurred up to 30 days after the last dose of IMP (on-treatment analysis), the reduction in risk associated with bempedoic acid treatment increased compared with the main analysis (HR: 0.78; 95% CI: [0.69, 0.89]; p=0.0001).

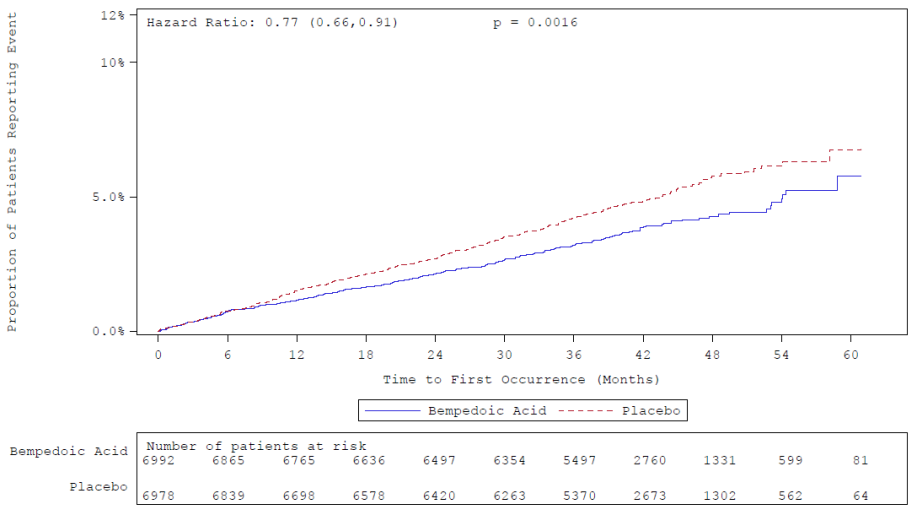
Subgroup analysis

As observed for MACE-4, results of a covariate analysis of MACE-3 confirm the robustness of the treatment effect across prespecified subgroups after adjusting for these covariates individually. Only baseline CVD risk category and BMI category had a nominal interaction with treatment (p = 0.0080 and p = 0.0202, respectively). For baseline CVD risk category, while a reduction in MACE-3 events was observed in both CVD risk categories, bempedoic acid treatment was associated with a lower estimated hazard ratio (HR: 0.61; 95% CI: [0.46, 0.80]) in patients with a baseline CVD risk category of primary prevention compared with that in secondary prevention patients (HR: 0.92; 95% CI: [0.81, 1.04]).

Key secondary efficacy endpoint - time to first occurrence of (fatal + nonfatal) MI

A total of 261 (3.7%) and 334 (4.8%) patients in the bempedoic acid and placebo groups, respectively, experienced fatal and nonfatal MI. Treatment with bempedoic acid was associated with a significant reduction in risk of fatal and nonfatal MI overall compared with placebo (HR: 0.77; 95% CI: [0.66, 0.91]; p = 0.0016). At Year 3, the cumulative probability of fatal and nonfatal MI was 1% lower in the bempedoic acid group than the placebo group; the absolute risk reduction increased to 1.5% at Year 4 (Figure 5).

Figure 5: Kaplan-Meier Curve for Time to First Occurrence of Fatal and Nonfatal Myocardial Infarction.

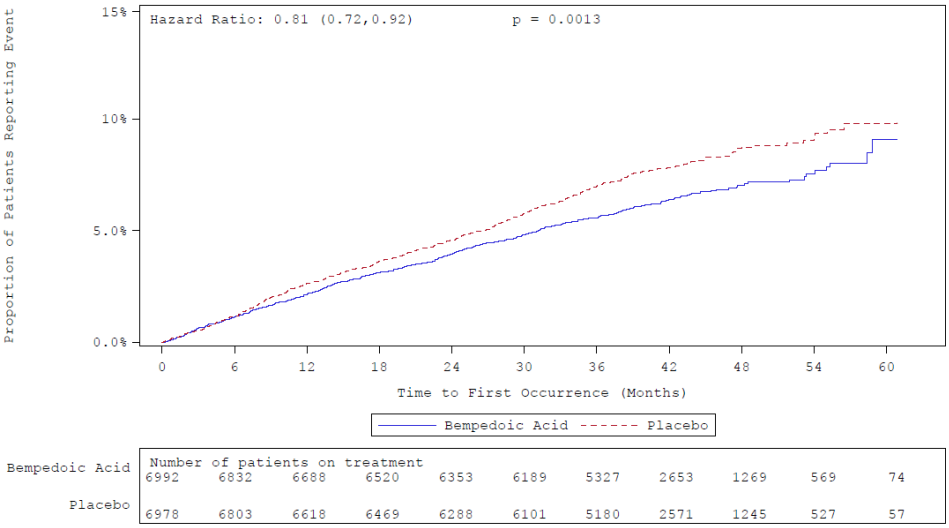


Key secondary efficacy endpoint - Time to first occurrence of coronary revascularization

A total of 435 (6.2%) and 529 (7.6%) patients in the bempedoic acid and placebo groups, respectively, required coronary revascularization. Of the patients in the bempedoic acid group requiring coronary revascularizations, 48.5% were elective (39.8% percutaneous coronary intervention [PCI], 8.7% coronary artery bypass graft [CABG]) and 51.5% were non-elective (44.8% PCI, 6.7% CABG); in the placebo group, 41.4% were elective (33.6% PCI, 7.8% CABG) and 58.6% were non-elective (50.1% PCI, 8.5% CABG).

Treatment with bempedoic acid was associated with a significant reduction in risk for coronary revascularization overall compared with placebo (HR: 0.81; 95% CI: [0.72, 0.92]; p = 0.0013). At Year 3, the cumulative probability of coronary revascularization was 1.4% lower in the bempedoic acid group

Figure 6: Kaplan-Meier Curve for Time to First Occurrence of Coronary Revascularization.



Key secondary efficacy endpoint - Time to first occurrence of (fatal + nonfatal) stroke

Occurrence of fatal and nonfatal stroke was 1.9% (135 patients) in the bempedoic acid group and 2.3% (158 patients) in the placebo groups. A numerical risk reduction was noted for fatal and nonfatal stroke; however, the reduction was not statistically significant at the 0.05 level (HR: 0.85; 95% CI: [0.67, 1.07]; p = 0.1593). The hierarchical testing was, therefore, stopped and all other p-values are reported for information only.

Key secondary efficacy endpoint - Time to CV death and all-cause mortality

Occurrence of CV death was similar in the bempedoic acid (269 patients, 3.8%) and placebo (257 patients, 3.7%) groups.

Occurrence of all-cause mortality was similar in the bempedoic acid (434 patients, 6.2%) and placebo (420 patients, 6.0%) group. No difference was noted in the risk of all-cause mortality (HR: 1.03; 95% CI: [0.90, 1.18]; p = 0.6608).

Additional secondary efficacy endpoints

The risk of occurrence of other secondary CV endpoint events is summarized in Table 20.

Table 20: Other Secondary Time-to-Event Endpoints - Cardiovascular Events and All-cause Mortality (Full Analysis Set).

Endpoint Statistic	Bempedoic Acid (N = 6992)	Placebo (N = 6978)	Hazard ratio (95% CI)[a]	*p*-value[b]
All-cause mortality, MI, stroke, or coronary revascularization	962 (13.8)	1062 (15.2)	0.89 (0.82, 0.97)	0.0100
5-component MACE[c]	831 (11.9)	952 (13.6)	0.86 (0.78, 0.94)	0.0013
Nonfatal MI	236 (3.4)	317 (4.5)	0.73 (0.62, 0.87)	0.0003
Fatal MI	29 (0.4)	21 (0.3)	1.38 (0.79, 2.42)	0.2604
Nonfatal stroke	119 (1.7)	144 (2.1)	0.82 (0.64, 1.05)	0.1091
Fatal stroke	18 (0.3)	16 (0.2)	1.12 (0.57, 2.20)	0.7383
Fatal + nonfatal hemorrhagic stroke	20 (0.3)	9 (0.1)	2.21 (1.01, 4.85)	0.0425
Fatal + nonfatal nonhemorrhagic stroke	118 (1.7)	150 (2.1)	0.78 (0.61, 0.99)	0.0437
Hospitalization for unstable angina	91 (1.3)	137 (2.0)	0.66 (0.50, 0.86)	0.0018

CI = confidence interval; MACE = major adverse cardiovascular event; MI = myocardial infarction. [a] Hazard ratio and corresponding 95% CI are based on a Cox proportional hazard model fitting treatment as explanatory variable. [b] nominal p-value was based on the log-rank test. [c] 5-component MACE was defined as the composite endpoint of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina.

- *Time to first occurrence of the composite endpoint of all-cause mortality, nonfatal MI, nonfatal stroke, or coronary revascularization*

The risk of the composite endpoint of nonfatal MI, nonfatal stroke, coronary revascularization, or death due to any cause was reduced in the bempedoic acid group compared with the placebo group (HR: 0.89; 95% CI: [0.82, 0.97]; nominal p = 0.0100).

- *Time to first occurrent of 5-component composite endpoint of CV death, nonfatal MI, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina (MACE-5)*

MACE-5 (nonfatal MI, nonfatal stroke, coronary revascularization, CV death, or hospitalization for unstable angina) (HR: 0.86; 95% CI: [0.78, 0.94]; nominal p = 0.0013),

- *Time to first occurrence of nonfatal MI*

Nonfatal MI (HR: 0.73; 95% CI: [0.62, 0.87]; nominal p = 0.0003).

As nonfatal MI and nonfatal stroke were components of the key efficacy analyses, total event analyses were conducted (Study 1002-043 CSR, Table 14.2.6). The total number of events of nonfatal MI per 100 person years was 1.1 (264 total events) in the bempedoic acid group and 1.6 (379 total events) in the placebo group. The total number of events of nonfatal stroke per 100 person years was 0.5 (127 total events) in the bempedoic acid group and 0.7 (157 total events) in the placebo group. Based on total event analysis, the effect of treatment with bempedoic acid compared with placebo on the risk of nonfatal MI (HR: 0.69; 95% CI: [0.58, 0.83]; p = 0.0001) and nonfatal stroke (HR: 0.80; 95% CI: [0.63, 1.03]; p = 0.0867) was slightly greater compared to the estimates based on first events alone. Like the analyses for MACE-4 and MACE-3, these total events data reinforce the treatment effect of bempedoic acid on these cardiovascular events.

- *Time to first occurrence of nonfatal stroke*

Fatal and nonfatal non-hemorrhagic stroke (HR: 0.78; 95% CI: [0.61, 0.99]; nominal p = 0.0437).

A higher rate of fatal and nonfatal hemorrhagic stroke was noted in the bempedoic acid group compared with the placebo group (HR: 2.21; 95% CI: [1.01, 4.85]; nominal p = 0.0425); however, the number of these events was low overall (20 patients vs 9 patients, respectively). All fatal strokes occurred at a similar frequency between treatment groups (0.3% and 0.2% in the bempedoic acid and placebo groups, respectively). As noted above, a lower rate of fatal and nonfatal nonhemorrhagic stroke was noted in the bempedoic acid group compared with the placebo group (HR: 0.78; 95% CI: [0.61, 0.99]; nominal p = 0.0437). Hazard ratios >1.0 for hemorrhagic stroke events have been observed for statins in the CTT meta-analysis (Cholesterol Treatment Trialists' Collaboration, 2010) as well as in the statin CVOT that enrolled patients with a history of stroke or transient ischemic attack, SPARCL (Amarenco et al, 2006). Some observational analyses have linked higher levels of LDL-C to lower rates of hemorrhagic stroke (Banach et al, 2023). Unlike ischemic strokes, risk of hemorrhagic strokes does not appear to be modifiable with LDL-C lowering. Overall, it remains questionable as to whether reductions in LDL-C impart a risk for hemorrhagic stroke.

- *Time to hospitalization for unstable angina*

Hospitalization for unstable angina (HR: 0.66; 95% CI: [0.50, 0.86]; nominal p = 0.0018).

- *Time to first occurrence of new-onset type 2 diabetes mellitus*

Among patients who had no diabetes at baseline (including prediabetes and normoglycaemia), there was no significant difference between the treatment groups in the risk of NODM. The difference in the incidence of NODM between the bempedoic acid and placebo groups was ≤1.0% for patients with baseline glycaemic status of no diabetes (11.1% and 11.5%, respectively), including prediabetes (13.8% and 14.3%, respectively), and normoglycaemia (3.0% and 2.3%, respectively).

A total of 429 (11.1%) of 3848 patients with baseline glycaemic status of no diabetes developed NODM as verified by the DC in the bempedoic acid group, which was similar to the placebo group (433 [11.5%] of 3749 patients; HR: 0.95; 95% CI: [0.83, 1.09]; p = 0.4842; Table 21).

Table 21: Time to First Occurrence of New-onset Diabetes Mellitus (Full Analysis Set).

Glycemic status **Statistic**	**Bempedoic Acid**	**Placebo**
No Diabetes, N	3848	3749
NODM, n (%)	429 (11.1)	433 (11.5)
Hazard ratio (95% CI)	0.95 (0.83, 1.09)	
p-value	0.4842	
Prediabetes, N	2911	2885
NODM, n (%)	401 (13.8)	413 (14.3)
Hazard ratio (95% CI)	0.95 (0.83, 1.09)	
p-value	0.4544	
Normoglycemia, N	937	864
NODM, n (%)	28 (3.0)	20 (2.3)
Hazard ratio (95% CI)	1.29 (0.72, 2.28)	
p-value	0.3879	

CI = confidence interval; NODM = new-onset diabetes mellitus. Note: NODM was reviewed and verified by the Diabetes Committee. Note: Hazard ratio and corresponding 95% CI were based on a Cox proportional hazard model fitting treatment as explanatory variable. The nominal p-value was based on log rank test.

Secondary Efficacy Lipid and Biomarker Endpoints

- *Percent change from baseline to Month 6 in LDL-C*

Percent change from baseline in LDL-C at Month 6 is summarized in Table 22.

At the first analysis timepoint (Month 3), bempedoic acid treatment was associated with a clinically meaningful decrease in LDL-C from baseline compared with placebo (LS mean difference: -22.7%; 95% CI: [-23.59%, -22.0%]; Figure 7).

Analyses of LDL-C included specification of missing data using a pattern mixed model (PMM), as well as using observed case data only (supportive). Using the PMM, a 21.1% LS mean reduction from baseline in LDL-C was noted for the bempedoic acid group compared with a 0.8% reduction in the placebo group after 6 months of treatment, which represents a placebo-corrected reduction from baseline of -20.3% (95% CI: [-21.1%, -19.5%]; p <0.0001).

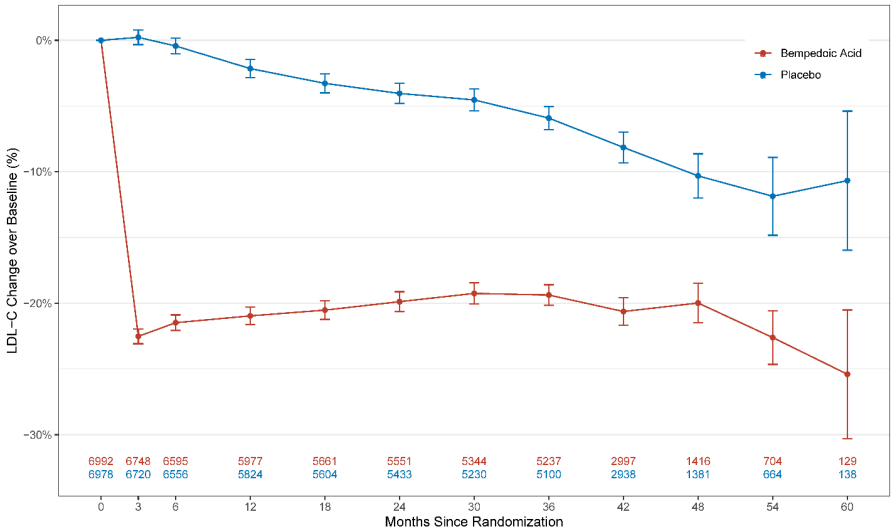
More patients in the bempedoic acid group than the placebo group achieved LDL-C <100 mg/dL (<2.6 mmol/L [44.1% vs 16.4%], respectively) and LDL-C <70 mg/dL (<1.8 mmol/L [12.6% vs 3.6%], respectively) after 6 months of treatment. A 25% decrease from baseline in LDL-C was also achieved by a higher percentage of patients in the bempedoic acid group compared with the placebo group (47.7% vs 10.9%, respectively).

Table 22: Percent Change from Baseline in LDL-C (Full Analysis Set).

Visit	Statistic	Bempedoic Acid (N = 6992)		Placebo (N = 6978)	
		Conventional unit (mg/L)	Standardized unit (mmol/L)	Conventional unit (mg/L)	Standardized unit (mmol/L)
Baseline[a]	n	6992		6978	
	Mean (SD)	139.04 (34.864)	3.6012 (0.90302)	139.02 (35.221)	3.6005 (0.91221)
	Median	134.50	3.4850	134.50	3.4850
	Min, Max	37.0, 459.0	0.955, 11.890	28.5, 417.5	0.740, 10.815
Month 6	n	6595		6556	
	Mean (SD)	106.96 (36.657)	2.7701 (0.94945)	135.97 (41.183)	3.5215 (1.06664)
	Median	102.00	2.6400	133.00	3.4400
	Min, Max	6.0, 366.0	0.160, 9.480	13.0, 428.0	0.340, 11.090
Percent change from Baseline to Month 6	LS Mean (SE) percent change from baseline[b]	-21.06 (0.293)	-21.08 (0.293)	-0.78 (0.298)	-0.81 (0.298)
	Difference (BA-Placebo) of LS Means (SE)	-20.28 (0.414)			
	Difference of LS Means 95% CI	(-21.09, -19.46)			

BA = bempedoic acid; CI = confidence interval; LDL-C = low-density lipoprotein cholesterol; LS = least square; max = maximum; min = minimum; SD = standard deviation; SE = standard error. a Baseline was defined as the mean of the last 2 non-missing values on or prior to randomization. If only 1 value was available, then that single value was used as baseline. If the patient had no fasting LDL-C values available at baseline, non-fasting values were used. b A pattern mixture model was used to take into account the missing LDL-C data at Month 6 using multiple imputation method, with a linear model with percent change from baseline as the dependent variable, treatment and baseline as covariates. Percent change from baseline statistics (LS means and nominal p-value) were based on the final combined estimators from Rubin's method.

Figure 7: Percent Change from Baseline in LDL-C with 95% Confidence Intervals Over Time Through End of Study (Full Analysis Set).



CLEAR Outcomes allowed for blinded alerts to be sent to investigators in the event that an increase in LDL-C of 25% or more above baseline was observed at any time after Month 6. A total of 1630 patients (11.7%; 582 [8.3%] in the bempedoic acid group and 1048 [15.0%] in the placebo groups) met the criteria for these alerts. Of these patients, 269 (1.9%) subsequently started a cross-in LMT regimen, including 63 (0.9%) patients in the bempedoic acid group and 206 (3.0%) patients in the placebo group.

Overall, any cross-in to a new or higher intensity LMT occurred in 12.5% of all patients during the course of the study, including a greater percentage of patients in the placebo group (1089 [15.6%] patients) compared with the bempedoic acid group (660 [9.4%] patients). The most common adjunctive cross-in LMTs reported were statins (4.0% and 6.5% in the bempedoic acid and placebo groups, respectively), ezetimibe (2.7% and 5.5% in the bempedoic acid and placebo groups, respectively), and PCSK9 inhibitors (2.8% and 4.5% in the bempedoic acid and placebo groups, respectively). Given the potential for unintended LDL-C unblinding occurring during a long trial of patients with elevated CV risk, the overall higher LDL-C levels in the placebo group compared with the bempedoic acid group, and the higher IMP discontinuation rate in the placebo group, it is not surprising that the LMT cross-in rate was higher in the placebo group. Nonetheless, treatment with bempedoic acid resulted in clinically meaningful reductions in LDL-C over the course of the trial that translated into significant reductions in major CV events.

While there are outstanding questions about the prevalence of "true" statin intolerance, it is worth noting that at any time during the trial, only 337 patients (4.8%) and 505 patients (7.2%) in the bempedoic acid and placebo groups, respectively, received a moderate- or high-intensity statin. At the end of the study, the proportion of patients who continued to use moderate- or high-intensity statins decreased in both groups and was proportionately lower in the bempedoic acid group (198 [2.8%] patients and 345 [4.9%] patients in the bempedoic acid and placebo groups, respectively), indicating that >30% of the patients who initiated a moderate-high intensity statin during the study were unable to maintain this dose.

Patients with Baseline Ezetimibe Use

A reduction from baseline in LDL-C was noted for the bempedoic acid group compared with the placebo group after 6 months of treatment. Patients who were using ezetimibe at baseline had absolute and percent changes of -36.97 mg/dL (-27.0%) and +0.40 mg/dL (+1.1%) for the bempedoic acid and placebo groups, respectively.

- *Percent change from baseline to Month 6 in hsCRP*

A core element of the atherosclerotic process is chronic inflammation. Numerous epidemiological and observational studies have indicated an association between elevated CRP and the risk of ASCVD events. Additionally, the CANTOS (Ridker et al, 2017) and COLCOT (Bouabdallaoui et al, 2020) studies have demonstrated that specifically targeting inflammation can significantly reduce the risk of major CV events. Treatment with bempedoic acid resulted in a significant reduction in hsCRP, while hsCRP was generally stable relative to baseline in the placebo group. After 6 months of treatment, median changes of hsCRP from baseline were -22.2% and +2.4%, respectively, with a location shift of -21.6% (95% CI: [-23.7%, -19.6%]; p <0.0001). Among patients with baseline hsCRP level ≥2 mg/L, a greater proportion of patients treated with bempedoic acid achieved hsCRP levels <2 mg/L postbaseline (31.8%) compared with placebo (19.4%). Reductions in hsCRP may be an additional mechanism beyond LDL-C lowering for bempedoic acid to reduce CV risk.

Table 23: Percent Change from Baseline in hsCRP (Full Analysis Set).

Visit	Statistic	Bempedoic Acid (N = 6992)	Placebo (N = 6978)
Baseline[a]	n	6917	6911
	Mean (SD)	4.166 (8.0464)	4.201 (7.8732)
	Median	2.300	2.310
	Q1, Q3	1.150, 4.460	1.150, 4.480
	Min, Max	0.11, 193.80	0.11, 182.62
Month 6	n	6630	6580
	Mean (SD)	3.544 (9.0470)	4.441 (9.7415)
	Median	1.730	2.360
	Q1, Q3	0.890, 3.520	1.140, 4.590
	Min, Max	0.11, 308.37	0.11, 301.92
Percent change from baseline to Month 6	n	6558	6520
	Median	-22.24	2.41
	Wilcoxon Two Sample Test *p*-value	<0.0001	
	Location Shift	-21.64	
	Asymptomatic Confidence Limits	(-23.68, -19.62)	

hsCRP = high-sensitivity C-reactive protein; max = maximum; min = minimum; Q = quartile; SD = standard deviation. a Baseline was defined as the mean of the last 2 non-missing values on or prior to randomization. If only 1 value was available, then that single value was used as baseline.

In patients who were using ezetimibe at baseline, bempedoic acid resulted in significant reduction in hsCRP from baseline compared with placebo after 6 months of treatment. Median changes in hsCRP in patients who were using ezetimibe at baseline were –26.9% and +7.6% in the bempedoic acid and placebo groups, respectively, at Month 6.

- *Change from baseline to Month 12 in HbA1C in patients with inadequately controlled type 2 diabetes mellitus*

While there was a trend for HbA1C levels to be numerically lower in the bempedoic acid group compared with the placebo group, regardless of baseline glycaemic status, these differences did not reach the level of statistical significance. Overall, between-group differences in mean HbA1C were generally <0.1% lower in the bempedoic acid group in comparison with the placebo group.

Table 24: Change from Baseline in HbA1C by Baseline Glycaemic Status (Full Analysis Set).

Baseline Glycemic Status Visit	Statistic	Bempedoic Acid	Placebo
Inadequately Controlled Diabetes	N	1356	1369
Baseline	n	1356	1369
	Mean (SD)	8.05 (0.886)	8.06 (0.900)
	Median	7.80	7.80
	Min, Max	7.0, 11.8	7.0, 11.9
Month 12	n	1148	1134
	Mean (SD)	7.98 (1.480)	8.02 (1.422)
	Median	7.70	7.75
	Min, Max	4.9, 16.3	4.9, 15.4
Change from baseline to Month 12	n	1148	1134
	LS Mean (SE)	-0.04 (0.038)	-0.01 (0.038)
	Difference (BA-Placebo) of LS Means (SE)	-0.03 (0.055)	
	Difference of LS Means 95% CI	(-0.14, 0.08)	
	p-value	0.5901	
Diabetes	N	3144	3229
Baseline	n	3139	3227
	Mean (SD)	6.99 (1.150)	6.99 (1.157)
	Median	6.70	6.80
	Min, Max	4.7, 11.8	3.8, 11.9
Month 12	n	2693	2678
	Mean (SD)	7.02 (1.414)	7.08 (1.381)
	Median	6.70	6.70
	Min, Max	4.0, 16.3	4.0, 15.5
Change from baseline to Month 12	n	2688	2678
	LS Mean (SE)	0.05 (0.020)	0.10 (0.019)
	Difference (BA-Placebo) of LS Means (SE)	-0.05 (0.027)	
	Difference of LS Means 95% CI	(-0.10, 0.00)	
	p-value	0.0716	

BA = bempedoic acid; CI = confidence interval; HbA1C = haemoglobin A1C; LS = least square; max = maximum; min = minimum; SD = standard deviation; SE = standard error. Data presented as %, except for the number of patient (N, n) and p-value.

Tertiary Efficacy Lipid and Other Biomarker Endpoints

- *Absolute change and percent change from baseline to Months 3, 6, 12, 24, then every 6 months through the end-of-study in LDL-C*

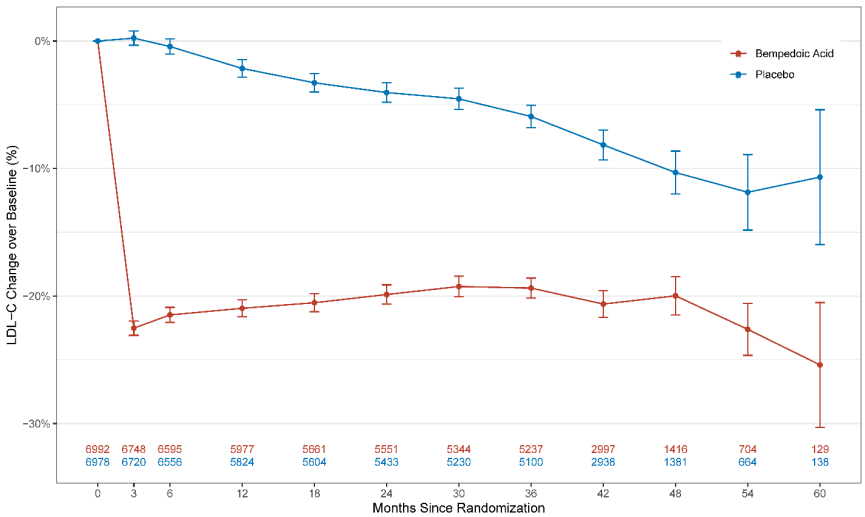
Mean, median, and absolute reductions from baseline in LDL-C over time based on an analysis of covariance (ANCOVA) using observed data are presented graphically in Figure 8. At the first analysis timepoint (Month 3), bempedoic acid treatment was associated with a clinically meaningful decrease in LDL-C from baseline compared with placebo (LS mean difference: -22.7%; 95% CI: [-23.49%, -22.00%]).

Over time, LDL-C levels remained consistently lower in the bempedoic acid group; however, the treatment differential between bempedoic acid and placebo lessened over time likely due to the effect of LMT cross-ins, which occurred with greater frequency in the placebo group than in the bempedoic acid group (15.6% and 9.4%, respectively) and IMP discontinuations which were numerically greater in the placebo group but only impact the bempedoic acid group (31.7% and 29.1%, respectively). An evaluation

of the effect of treatment in the absence of cross-in LMTs revealed that LDL-C levels were higher in both treatment groups; however, the difference was most pronounced in the placebo group.

Trends in LDL-C over time in patients with baseline ezetimibe use based on an ANCOVA were generally consistent with the overall population. At Month 3, bempedoic acid treatment was associated with a clinically meaningful decrease in LDL-C from baseline compared with placebo (LS mean difference: 29.68%; 95% CI: [-31.63, -27.73]). Over time, LDL-C levels were consistently lower in the bempedoic acid group; however, the treatment differential lessened over time.

Figure 8: Percent Change from Baseline (95% CI) in LDL-C Over Time Through End of Study (Full Analysis Set).



CI = confidence interval; LDL-C = low-density lipoprotein cholesterol. Note: Error bars represent 95% confidence intervals.

- *Absolute change and percent change from baseline to Months 3, 6, 12, 24, then every 6 months through the end of study in non-HDL-C, TC, HDL-C, and TG.*

Mean percent changes from baseline in non-HDL-C, TC, HDL-C, and TGs through Month 6 are presented for the FAS in Table 25 using conventional units.

Treatment with bempedoic acid resulted in decreases in non-HDL-C and TC that were consistent with changes observed for LDL-C. Changes in TGs were similar between the treatment groups. Although slight decreases from baseline in HDL-C were noted in the bempedoic acid group compared with the placebo group (mean [SD] -5.80% [17.986%] and 0.66% [15.111%], respectively), these were not deemed clinically meaningful.

Table 25: Percent Change from Baseline to Month 6 in HDL-C, non-HDL-C, TC, and Triglycerides (Full Analysis Set).

Visit	Statistic	HDL-C (mg/dL)		Non-HDL-C (mg/dL)		TC (mg/dL)		Triglycerides (mg/dL)	
		Bempedoic Acid (N = 6992)	Placebo (N = 6978)	Bempedoic Acid (N = 6992)	Placebo (N = 6978)	Bempedoic Acid (N = 6992)	Placebo (N = 6978)	Bempedoic Acid (N = 6992)	Placebo (N = 6978)
Baseline[a]	n	6992	6978	6992	6978	6992	6978	6992	6978
	Mean (SD)	49.65 (13.276)	49.43 (13.291)	173.83 (39.451)	173.90 (40.216)	223.48 (40.607)	223.34 (41.091)	178.23 (87.398)	178.43 (88.560)
	Median	47.50	47.50	169.50	169.50	219.50	219.00	159.50	158.50
	Min, Max	12.0, 136.0	13.0, 149.5	49.0, 531.0	49.0, 453.5	93.5, 562.5	89.5, 533.5	40.0, 1501.0	32.5, 1044.5
Month 6	n	6598	6556	6595	6555	6596	6556	6595	6556
	Mean (SD)	46.48 (14.306)	49.42 (14.036)	142.01 (42.263)	170.86 (46.735)	188.49 (43.015)	220.29 (47.813)	181.04 (116.304)	177.78 (102.669)
	Median	45.00	47.00	136.00	167.00	184.00	217.00	153.00	153.00
	Min, Max	5.0, 146.0	13.0, 147.0	21.0, 491.0	22.0, 532.0	51.0, 546.0	66.0, 570.0	26.0, 2172.0	36.0, 1674.0
Percent change from baseline to Month 6	n	6598	6556	6595	6555	6596	6556	6595	6556
	Mean (SD)	-5.80 (17.986)	0.66 (15.111)	-17.20 (21.196)	-0.44 (21.410)	-14.83 (16.716)	-0.57 (16.316)	4.78 (46.664)	3.57 (38.027)
	Median	-6.06	0.00	-19.86	-0.80	-16.86	-0.59	-3.40	-1.74
	Min, Max	-84.6, 138.7	-69.2, 157.1	-87.2, 189.0	-87.2, 295.9	-73.6, 107.9	-67.4, 163.5	-85.9, 789.2	-85.4, 460.0

HDL-C = high-density lipoprotein cholesterol; max = maximum; min = minimum; SD = standard deviation; TC = total cholesterol. a Baseline for non-HDL-C, TC, HDL-C and triglycerides was defined as the mean of the last 2 non-missing fasting values on or prior to randomization. If only 1 value was available, then that single value was used as baseline. If the patient had no fasting values available at baseline, non-fasting values were used.

- *Percent change from baseline to Month 12 and at the end of study in hsCRP*

After 6 months of treatment, bempedoic acid resulted in a reduction in hsCRP from baseline compared with placebo. Throughout the study, bempedoic acid continued to be associated with a reduction in hsCRP from baseline whereas hsCRP levels in the placebo group remained near baseline. After 12 months of treatment, median changes of -20.6% and 0.0% were observed in the bempedoic acid and placebo groups, respectively. The trend continued through EOS with median changes of -19.1% and -1.9% observed in the bempedoic acid and placebo groups, respectively.

- *Change from baseline to Month 3, 6, 12, then every 6 months through the end of study in HbA1C*

There was no meaningful difference in HbA1C level between the bempedoic acid and placebo groups over time in patients with baseline glycaemic status of diabetes and inadequately controlled diabetes. Although, the bempedoic acid group had a slightly lower HbA1C level compared with the placebo group after 3 months of treatment (LS mean difference [SE] of -0.12% [0.019%] for baseline glycaemic status of diabetes and -0.16% [0.038%] for baseline glycaemic status of inadequately controlled diabetes), no notable differences were observed during the remainder of the study.

Similarly, there was no difference in the change from baseline in HbA1C level between the bempedoic acid and placebo groups for those patients with prediabetes or normoglycaemia. These trends were consistent across the study in the FAS and PPS.

- *Change from baseline to Month 3, 6, 12, then every 6 months through the end of study in fasting glucose.*

Observed values and change from baseline in fasting glucose were similar between treatment group regardless of the baseline glycaemic status. Results were consistent in the PPS.

Ancillary analyses

See sensitivity analyses and subgroup analyses above.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 26: Summary of Efficacy for the CLEAR Outcomes trial (study 1002-043)

Title: CLEAR Outcomes trial (study 1002-043) A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Effects of Bempedoic Acid (ETC-1002) on the Occurrence of Major Cardiovascular Events (MACE) in Patients with, or at high risk for, Cardiovascular Disease who are Statin Intolerant			
Study identifier	study 1002-043		
Design	Phase 3, long-term, randomized, double-blind, placebo-controlled study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	minimum 24 months 4 weeks not applicable	
Hypothesis	Superiority		
Treatments groups	Bempedoic acid group	Bempedoic acid 180 mg once daily, n= 6992	
	Placebo group	Placebo once daily, n= 6978	
Endpoints and definitions	Primary endpoint	MACE-4	The time to first occurrence of a MACE, where MACE is defined as the composite endpoint of CV death, nonfatal MI, nonfatal stroke, or coronary revascularization (MACE-4).
	Key secondary endpoint 1	MACE-3	Time to first occurrence of the composite endpoint of CV death, nonfatal MI, or nonfatal stroke (MACE-3)
	Key secondary endpoint 2	Fatal + nonfatal MI	Time to first occurrence of (fatal + nonfatal) MI
	Key secondary endpoint 3	Coronary revascularization	Time to first occurrence of coronary revascularization
	Key secondary endpoint 4	Fatal + nonfatal stroke	Time to first occurrence of (fatal + nonfatal) stroke
	Key secondary endpoint 5	CV death	Time to CV death
	Key secondary endpoint 6	All-cause mortality	Time to all-cause mortality
Database lock	15 October 2022		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Bempedoic acid group (N (n%))	Placebo group (N (n%))	
	Number of subject (n)	6992	6978	
	MACE-4 HR (95% CI, p-value)	819 (11.7%)	927 (13.3%)	0.87 (0.79-0.96; p=0.0037)
	MACE-3 HR (95% CI, p-value)	575 (8.2%)	663 (9.5)	0.85 (0.76 - 0.96; p=0.0058)
	Fatal + nonfatal MI HR (95% CI, p-value)	261 (3.7)	334 (4.8)	0.77 (0.66 - 0.91; p=0.0016)

	Coronary revascularization HR (95% CI, p-value)	435 (6.2)	529 (7.6)	0.81 (0.72 - 0.92; p=0.0013)
	Fatal + nonfatal stroke HR (95% CI, p-value)	135 (1.9)	158 (2.3)	0.85 (0.67 - 1.07; p=0.1593)
	CV death HR (95% CI, p-value)	269 (3.8)	257 (3.7)	1.04 (0.88 - 1.24; p=0.6227)
	All-cause mortality HR (95% CI, p-value)	434 (6.2)	420 (6.0)	1.03 (0.90 - 1.18; p=0.6608)
Notes	The secondary endpoints were performed according to a hierarchical testing'.			

2.4.2. Discussion on clinical efficacy

This concerned a variation procedure for Nustendi (bempedoic acid / ezetimibe 180/10 mg) with an extension of a therapeutic indication for adults with established or at high risk for atherosclerotic cardiovascular disease (CVD) to reduce the cardiovascular risk.

Design and conduct of clinical studies

The applicant submitted the efficacy and safety results from **Study 1002-043**, known as the **CLEAR Outcomes trial**, to evaluate whether long-term treatment with bempedoic acid reduces the risk of major adverse cardiovascular events (MACE) in patients with CVD, or at high risk for CVD, with a fasting screening LDL-C ≥100 mg/dL (2.6 mmol/L) while taking stable and optimized background LDL-C-modifying therapies and with a history of statin intolerance. The CLEAR Outcomes trial was a multi-centre randomised, double-blind, two-arm placebo-controlled, event-driven trial, comparing the treatment of bempedoic acid, a one film-coated tablet of 180 mg taken once daily, versus background therapy (placebo arm), which comparator is considered acceptable. The dose regimen for bempedoic acid is similar to the dose regimen as recommended in the SmPC. However, it should be noted, that the fixed combination medicinal product (FCMP) of bempedoic acid 180 mg plus ezetimibe 10 mg itself has not been evaluated, as the FCMP was not used as study drug and as the FCMP was not part of a study arm (it was only a two-arm trial and not a four-arm trial as in the original dossier). However, from the CLEAR Outcomes data a consistent CV risk reduction and LDL-C was observed in patients with and without ezetimibe. Further, an additive effect on LDL-C reduction with the FCMP compared to the individual components alone was demonstrated in the previous 1002FDC-053 study, which was considered as primary evidence for a positive benefit/risk for the FCMP for the hypercholesterolaemia/mixed dyslipidaemia indication. Based on this, the CVD risk reduction indication with the use of the combination of bempedoic acid and ezetimibe can be acceptable, although the wording of the proposed CVD indication needs to be amended (see further discussion in section 'Other considerations').

Overall, the study design is largely in accordance with the CHMP's scientific advices (SAs; EMEA/H/SA/3294/1/2016/SME/II and EMEA/H/SA/3294/1/FU/1/2018/SME/II) and therefore broadly agreed. The applicant included independent panels, especially for adjudication of efficacy events, which is supported.
The trial consisted of an approximate 1-week screening period, a 4-week placebo run-in period, and a double-blind, randomized, placebo-controlled treatment period. The placebo run-in of 4 weeks was used to optimize baseline therapy according to the respective treatment guidelines, in case they are not on

optimal baseline therapy prior to inclusion, which can be considered appropriate and acceptable.
The duration of the study was designed to be flexible and continued until 3 conditions were met: 1) at least 1620 patients experienced a positively adjudicated primary MACE-4 endpoint consisting of nonfatal MI, nonfatal stroke, coronary revascularization, or CV death, 2) a minimum of 810 patients to experience 3-component MACE before the study was completed to ensure that results for the 4-component MACE were consistent with results for the 3-component secondary endpoint (CV death, nonfatal MI, and nonfatal stroke), which enabled a meaningful confirmatory analysis of this important secondary endpoint, and 3) a minimum of 24 months have elapsed, since the last patient was randomised. This duration is generally agreed, as this will provide sufficient long-term exposure to support the proposed indication. Further, in general, this approach by meeting the 3 conditions to determine the study duration, is acceptable and in line with the discussion during the SA.

Overall **inclusion and exclusion** criteria are considered acceptable, and have been agreed in the SAs EMEA/H/SA/3294/1/2016/SME/II and EMEA/H/SA/3294/1/FU/1/2018/SME/II. The study population selected is considered largely reflective of the target population indicated for the reduction of CVD, although some concerns have been identified.
Key eligibility for the study included patients with a history of statin intolerance. This has been liberally defined, but was agreed in the Scientific Advices for this study plan (see further below). Further, patients needed to have, a fasting LDL-C ≥100 mg/dL (2.6 mmol/L), while taking stable and optimized background LDL-C-lowering therapies which could include very low dose statin treatment. This can be supported as these patients are eligible for further treatment according to ESC guideline recommendations for both the inclusion criteria of primary prevention in patients at high risk and in secondary prevention for patients at very high risk (see ESC Guideline on Dyslipidemia 2019). The definitions to establish a history of, or at high risk for, CVD are generally used and thus acceptable. Most definitions, as used to define a primary prevention population at high CV risk, have been discussed and agreed at the SAs. Further, the definitions as used in the inclusion criteria to specify a primary prevention population at high risk for CVD, i.e. 'coronary artery calcium score >400 Agatston units at any time in the past', and 'patients with type 1 or type 2 diabetes, aged >65 years (women) or >60 years (men)' can be considered acceptable.
Statin-intolerant patients were liberally defined. This was also clearly discussed and agreed earlier during the SAs. The inclusion criterion consisting of patient-reported statin intolerance due to an adverse safety effect that started or increased during statin therapy and resolved or improved when statin therapy was discontinued resulting in an inability to tolerate 2 or more statins at any dose, or 1 statin at any dose and unwilling to attempt a second statin or advised by a physician to not attempt a second statin, or very low dose statin therapy, is therefore agreed and accepted.
It is mentioned in the newly proposed wording of the therapeutic indication of CVD that Nustendi is indicated:

- in patients on a maximum tolerated dose of a statin and not adequately controlled with additional ezetimibe treatment or,
- in patients who are either statin-intolerant, or for whom a statin is contraindicated, and not adequately controlled with ezetimibe treatment or,
- in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets.

The first bullet point concerns an add-on therapeutic indication of bempedoic acid plus ezetimibe on top of statins (with or without other lipid-lowering therapies). However, only statin-intolerant patients were included in the study. Nevertheless the applicant has justified that data could be extrapolated to a population optimally treated with a statin based on the totally of data available demonstrating consistency in lipid lowering effect and (underpowered) CV outcome data. This is considered sufficient considering the

established surrogacy of LDL-C lowering across multiple lipid lowering classes.
Further, it seems that the patients were not pre-stratified according to ezetimibe use, at baseline, while specific evaluation with ezetimibe is important to support the use of the FCMP of bempedoic acid and ezetimibe use versus the mono-components. However, ezetimibe patients were well balanced over the study groups.

The **objectives** are considered acceptable. According to the *Reflection paper on assessment of cardiovascular safety profile of medicinal products* (EMA/CHMP/50549/2015), the preferred endpoint for dedicated cardiovascular outcome studies is a composite of all major cardiovascular events (MACE): i.e. cardiovascular death, nonfatal myocardial infarction and nonfatal stroke.
For the current study 1002-043, the **primary endpoint** is considered a 4-composite MACE endpoint, defined as CV-death, nonfatal MI, nonfatal stroke, or coronary revascularization. The applicant chose a broader, 4-composite, primary endpoint, compared to the 3-composite endpoint mentioned in the reflection paper.
Investigating CV-death is acceptable and has been accepted as composite of the primary endpoint in previous CV intervention studies, though there is current preference to investigate overall mortality. Sufficient confidence regarding overall mortality and non-CV mortality is necessary in this case. All-cause mortality will be investigated as important secondary endpoint, which is acceptable. Further evaluation of other single components of cardiovascular events is acceptable as they could further support the key analyses and provide further knowledge of the treatment effect on cardiovascular prevention. According to the EMA guideline (EMA/CHMP/748108/2013), decision based components (coronary revascularization) are not encouraged to be part of the primary endpoint, as it is expected that these softer components may drive the overall result, weakening the clinical relevance of any observed differences in contrast to a MACE-3 endpoint.
Taken together, a MACE-3 primary composite endpoint (CV death, nonfatal MI, nonfatal stroke) was clearly preferred. In addition, it should be kept in mind that partial unblinding during the study (e.g. patients´ at-home cholesterol measurements, laboratory test by general practitioner) cannot be entirely avoided. MACE-3 components are less likely to be influenced by an informed guess about treatment than coronary revascularization and possibly acute coronary syndrome (ACS). However, this concern has been discussed and agreed earlier in the SAs (EMEA/H/SA/3294/1/2016/SME/II and EMEA/H/SA/3294/1/FU/1/2018/SME/II). Therefore, providing that the significant reduction in MACE-3 is consistent with the findings on MACE-4, this 4-composite endpoint could be acceptable and can be supported for the proposed indication.
All other **secondary and tertiary endpoints** can be considered supportive of the primary endpoint and are acceptable. The adjudication strategy by an independent committee is considered standard procedure in large CV intervention trials and acceptable.

The **sample size** was estimated to be approximately 14,000 patients (approximately 7000 in the bempedoic acid group and 7000 in the placebo group) to achieve 1620 patients experiencing a primary MACE-4 event, with 810 patients experiencing a MACE-3. This was based on a treatment effect (relative CV event risk reduction in HR) of 15% and a statistical power of greater than 90% at an overall study significance level (alpha) of 0.05. The sample-size calculation is solid and the additional request to observe a minimum number of the traditional (strict) 3-composite MACE-endpoint is appreciated, although, in a situation where definitive superior efficacy is supposed to be demonstrated, preference was to be given to MACE-3 as the primary endpoint. However, as mentioned earlier, the MACE-4 approach can ultimately be acceptable, providing the trend when analysing MACE-3 is consistent.
Of note, the sample size was not powered for evaluation of bempedoic acid and ezetimibe, but only for bempedoic acid alone.
Also, patients were **randomized** 1:1 to bempedoic acid or matching placebo using an interactive web response system (IWRS). Randomization and blinding is considered adequate.

Regarding the **statistical analysis**, three analysis sets were defined: the Full Analysis Set (FAS), the Safety Analysis Set (SAS) and the Per-Protocol Analysis Set (PPS). FAS was used for the primary analysis which is considered acceptable.
The primary and key secondary efficacy endpoints were tested sequentially in a pre-specified order in a gate-keeping testing procedure to control the study-wise type I error rate at 5%. Each endpoint was tested at a 2-sided significance level of 0.05 and tested only if the previous endpoint achieved statistical significance. Overall, the secondary endpoints and the statistical analysis are acceptable.
A hierarchical testing procedure is an acceptable strategy to control for multiplicity and to have additional confirmatory conclusions beyond the assessment of the primary endpoint.

Efficacy data and additional analyses

In total, 22,084 subjects were screened and of which 13,970 were **randomized** in the study. Main reason for screening failure was not meeting the in- and exclusion criteria. From the 13,970 randomized patients, only a small group of 1612 (12%) patients were on baseline ezetimibe use, including 809 patients on placebo and 803 patients on bempedoic acid.
In general, **study disposition** was balanced in each treatment group (bempedoic acid vs placebo). The percentage of subjects who completed with study medication in the general study population was 68.3% in the placebo group, and 71.8% in the bempedoic acid group.

In the general study population, discontinuation was primarily due to patient decision (13.7% and 16.4%, respectively) or adverse events (AEs; 11.3% and 10.7%, respectively). The patients with AEs further discussed under the safety section.
The applicant has also monitored the protocol deviations. The percentage of important protocol deviations in the study was moderately high, and was similar in the placebo group (58.8%%) as compared with the bempedoic acid group (55.7%). Approximately 30% of patients in both treatment groups had protocol deviations related to the COVID-19 pandemic, which is expected. In general, the most common deviations across the groups were laboratory assessment criteria, informed consent, concomitant medication criteria and visit schedule criteria. An explanation and additional sensitivity analysis on how these protocol deviations have impacted the study outcomes was requested. The MAH provided a modified sensitivity analysis based on the requested PPS by excluding participants with protocol deviations important enough to have an impact on study integrity and patient safety. It demonstrated that the exclusion of these participants from analysis does not pose a practical risk on the study results as they remained similar enough in the modified analysis when compared to the original sensitivity analysis.

Randomisation was successful as can be expected from a study this size. Generally, the recruited patients reflect a statin-intolerant population with a high risk on CVD regarding demographics and medical history.
The **demographic data** of the general study population are well distributed across the two treatment groups and no large differences between groups have been identified. The majority of the patients in the study were older (i.e. 59% >65 years of age), white (91%), from Central/Eastern Europe (48%) and nearly half of patients were female (48%).
The majority of patients (78.5%) met the statin intolerance criterion by failing 2 or more statins, and 21.5% of patients failed 1 statin. A very small number of <0.1% of the patients received high dose of statins at randomisation. A very low intensity statin was used by 22.3% of patients at baseline; 18.5% of patients were using other LMT without a statin and 11.5% of patients were using ezetimibe at baseline. Overall, 58.8% of patients were not taking any background LMT.
Further, 45.6% of patients overall had diabetes, including 19.5% who had inadequately controlled diabetes. Further, 85% of patients had a history of hypertension. The majority of patients had a baseline estimated glomerular filtration rate (eGFR) of 60 to <90 mL/min/1.73 m2 (61.6%), indicating mild renal

impairment; 6.7% of patients had a history of chronic kidney disease. A total of 69.9% of patients had a documented history of CVD (secondary prevention), including CAD (50.9%), symptomatic peripheral arterial disease (11.6%), and cerebrovascular atherosclerotic disease (14.8%); 30.1% met criteria for high-risk primary prevention. Baseline laboratory parameters, including lipoproteins and hsCRP, were generally consistent between treatment groups. Mean (standard deviation [SD]) baseline LDL-C was 3.60 [0.91] mmol/L.
Of note, although data were not provided, the applicant stated that demographic and baseline characteristics in the subgroup of **patients with baseline ezetimibe use** were generally consistent with the overall population. However, there have been observed some slight differences in these findings presented for patients with baseline ezetimibe use and the general study population, such as the percentage of patients with diabetes, hypertension, CVD risk category (whether secondary or primary prevention), alcohol consumption, and baseline LMT etc. However, the potential impact on these findings is expected to be minor.

In the **primary analysis** (general study population), treatment with bempedoic acid resulted in less patients experiencing at least 1 **MACE-4** during the study (819; 11.7%) compared to treatment with placebo (927; 13.3%), representing an absolute risk reduction of 1.6%. The difference of a reduction in risk of a first occurrence of a MACE-4 was statistically significant with a HR of 0.87 (95% CI: 0.79, 0.96; p = 0.0037) on which outcome it can be concluded that the primary composite endpoint was met. With the use of bempedoic acid the risk remained lower over the years, seen by diverging KM lines over time, as compared to no use, although there appears a lag-time of approximately 6 months before the KM curve starts to separate throughout the period of the study showing the benefit of bempedoic acid treatment.
This effect is mostly accountable to the benefit on the two MACE-4 components nonfatal MI and coronary revascularization, since a statistically significant risk reduction was noted for nonfatal MI (HR: 0.73; 95% CI: 0.62, 0.87; nominal p = 0.0003) and coronary revascularization (HR: 0.81; 95% CI: 0.72, 0.92; p = 0.0013).
Further, the effect on nonfatal stroke pointed into the same direction, although this effect was not statistically significant (HR: 0.82; 95% CI: 0.64, 1.05; nominal p = 0.1091). The effect on CV death, however, showed a HR of 1.04 (95% CI: 0.88, 1.24; nominal p = 0.6227). Both of these observations create uncertainty on the effect of bempedoic acid treatment on CV risk reduction, but it cannot be excluded that study duration may have been too short to observe any beneficial (or detrimental) effect of bempedoic acid treatment.
Consistent with the primary analysis, the outcome of the 4 **sensitivity analysis** supported the outcome of the primary efficacy analysis, as these also demonstrated an statistically significant beneficial treatment effect (reduction in CVD risk) with the use of bempedoic acid.
Subgroup analyses performed for the primary analysis with respect to demographic subgroups, and status of with or without background statin use and with or without background ezetimibe use, among others showed generally consistency. However, there was seen some variability in the subgroup of regions (European vs American), this was probably due to the difference in baseline LDL-C between regions. Further, the cardiovascular disease risk category (primary prevention vs secondary prevention) had a nominally significant interaction with treatment (p = 0.0302)
In line with the outcomes in the general study population, the effect on the risk of MACE-4 in the **subgroup of patients with baseline ezetimibe use** compared to placebo seem to point towards the same direction with a HR, which was estimated to be 0.94 (95% CI: [0.74, 1.20]).

In the general study population, treatment with bempedoic acid, as compared to placebo, was also associated with a statistically significant reduction in the risk of **MACE-3** (HR: 0.85; 95% CI: 0.76, 0.96; p = 0.0058). MACE-3 was experienced by 8.2% and 9.5% of patients in the bempedoic acid and placebo groups, respectively, showing an absolute reduction 1.3%. Also here, the Kaplan-Meier curve (KM) starts to separate by approximately 5 months after first use of bempedoic acid. This beneficial effect on MACE-3

is consistent with the findings seen in the risk of MACE-4, which is reassuring.
Regarding the **sensitivity analyses**, consistent findings were observed and therefore these results can be considered robust.
Regarding the subgroup analyses, baseline CVD risk category and BMI category showed inconsistency of data (p = 0.0080 and p = 0.0202, resp.). For baseline CVD risk category, the greatest benefit was observed for bempedoic acid treatment in patients with a baseline CVD risk category of primary prevention (HR: 0.61; 95% CI: 0.46, 0.80), compared with secondary prevention patients (HR: 0.92; 95% CI: 0.81, 1.04), which is in line with the findings on the subgroup analyses on the primary endpoint with regard to baseline CVD risk category.
Further, in the **patients with baseline ezetimibe use**, the group on bempedoic acid pointed to a reduced risk of MACE-3 compared with placebo, with a HR of 0.85 (95% CI: 0.62, 1.16). Therefore, the findings do point towards the outcomes of the MACE-3 key secondary analysis, although this is not statistically significant, as the study is not powered for analysis in this subgroup.
A hierarchical approach was followed to test the primary efficacy endpoint and then key secondary efficacy endpoints sequentially in order to preserve the study-wise type 1 error at 5%.

Regarding the **key secondary** endpoints in the whole study population, treatment with bempedoic acid was associated with a statistically significant reduction in risk of fatal and nonfatal MI overall compared with placebo (HR: 0.77; 95% CI: 0.66, 0.91; p = 0.0016). This effect was also seen with the risk for coronary revascularization overall compared with placebo (HR: 0.81; 95% CI: [0.72, 0.92]; p = 0.0013). However, the reduction was not statistically significant for fatal and nonfatal stroke at the 0.05 level (HR: 0.85; 95% CI: 0.67, 1.07; p = 0.1593). The hierarchical testing was, therefore, violated at this endpoint. Also, no difference in frequency was noted for all-cause mortality, which was similar in the bempedoic acid (434 patients, 6.2%) and placebo (420 patients, 6.0%) group. This resulted in no difference for the risk of all-cause mortality (HR: 1.03; 95% CI: 0.90, 1.18; p = 0.6608). Occurrence of CV-death was similar in the bempedoic acid (269 patients, 3.8%) and placebo (257 patients, 3.7%) groups.

Regarding **the other secondary and tertiary endpoints** in the general study population, all-cause mortality + MI + stroke + coronary revascularization, MACE-5, non-fatal MI, non-fatal stroke, fatal+non-fatal non-haemorrhagic stroke and hospitalization for unstable angina showed a (mostly statistically) significant consistent reduction. However, pointing to a detrimental effect was observed on fatal MI (HR:1.38; 95% CI: 0.79, 2.42; p = 0.2604), fatal stroke (HR: 1.12; 95% CI: 0.57, 2.20; p = 0.7383) and a statistical significant detrimental effect of fatal+non-fatal haemorrhagic stroke (HR: 2.21; 95% CI: 1.01, 4.85; p = 0.0425). However, the number of these events was low overall (in n=29, n=18 and n=20 patients on bempedoic acid, respectively). All fatal strokes occurred at a similar frequency between treatment groups (0.3% and 0.2% in the bempedoic acid and placebo groups, respectively), although, a lower rate of fatal and nonfatal non-haemorrhagic stroke was noted in the bempedoic acid group compared with the placebo group (HR: 0.78; 95% CI: [0.61, 0.99]; nominal p = 0.0437).
Importantly, the **lipid lowering reduction** was also evaluated and showed a substantial placebo-corrected decrease of -20.3% (95% CI: -21.1%, -19.5%; p <0.0001) at month 6 on LDL-C from a mean baseline level of mg/dL 139 mg/dL (3.60 mmol/L). A beneficial effect was also observed in the patients with baseline ezetimibe use, although the placebo-corrected decrease at month 6 on LDL-C has not been provided. The effect on LDL-C seemed to diminish over time from -23% at month 3 to -20% at month 6 and a level of ≈-10% at month 48 and ≈-14% at month 60 , as the placebo effect increased over time, but it can be considered that the on-treatment effect of LDL-C lowering was maintained throughout the study. The applicant stated that his effect was also seen in the subgroup analyses with baseline ezetimibe use. Treatment resulted in similar patterns on HDL-C, non-HDL-C and TC that were consistent with changes observed for LDL-C. Changes in TGs were similar between the treatment groups.
Also after 6 months of treatment, median changes of hsCRP from baseline were -22.2% and +2.4%, respectively, with a location shift of -21.6% (95% CI: -23.7%, -19.6%; p <0.0001). Similar findings were observed for patients with baseline ezetimibe use. For HbA1C levels a numerically lower change in

the bempedoic acid group compared with the placebo group, regardless of baseline glycaemic status, but these differences did not reach the level of statistical significance. Overall, between-group differences in mean HbA1C were generally <0.1% lower in the bempedoic acid group in comparison with the placebo group. Also over time no meaningful difference in HbA1C level between the bempedoic acid and placebo groups over time in patients with baseline glycaemic status of diabetes and inadequately controlled diabetes.
Although data have been shown for lipid lowering reduction and hsCRP, no data for the other secondary and tertiary endpoints have been presented on the **patients with baseline ezetimibe use**, as the numbers are too small for further evaluation.

2.4.3. Conclusions on the clinical efficacy

The applicant submitted the results for the CLEAR Outcomes study, a multi-centre randomised, double-blind, two-arm placebo-controlled, event-driven trial, including patients with CVD, or at high risk for CVD, with a fasting screening LDL-C ≥100 mg/dL (2.6 mmol/L) while taking background LDL-C-modifying therapies and with a history of statin intolerance, demonstrating a statistically significant effect on the primary efficacy composite endpoint of MACE-4, consisting of nonfatal MI, nonfatal stroke, coronary revascularization, or CV death (HR: 0.87; 95% CI: 0.79, 0.96; p = 0.0037). The patients were treated with bempedoic acid, a one film-coated tablet of 180 mg taken once daily, versus background therapy (placebo arm). Robustness was shown with 4 sensitivity analyses. Also a consistent effect was generally observed across subgroups, including the baseline ezetimibe group. This beneficial effect was, further, generally supported with a consistent effect in the (regulatory preferred) composite endpoint of MACE-3 (nonfatal MI, nonfatal stroke, CV death; HR: 0.85; 95% CI: 0.76, 0.96; p = 0.0058), and across several secondary endpoints, although the hierarchical testing was lost for fatal and nonfatal stroke (HR: 0.85; 95% CI: 0.67, 1.07; p = 0.1593) and all-cause mortality (HR: 1.03; 95% CI: 0.90, 1.18; p = 0.6608).

2.5. Clinical safety

Introduction

The Safety Analysis Set (SAS) included all randomized patients who received at least 1 dose of double-blind IMP (n = 13,965). Patients in the SAS were summarized according to the actual treatment received, irrespective of their randomized treatment (ie, included in the bempedoic acid group if they received at least 1 dose of double-blind bempedoic acid IMP).

Patient exposure

The SAS of CLEAR Outcomes included 13,965 patients who received at least 1 dose of bempedoic acid or placebo (7001 and 6964 patients, respectively). The extent of exposure to IMP in the SAS was generally similar between treatment groups (Table 27). The mean (SD) exposure to IMP was 2.9 (1.210) years (range, 0.0-5.6 years) and 2.8 (1.227) years (range, 0.0-5.2 years) for the bempedoic acid and placebo groups, respectively; however, a higher proportion of patients in the placebo group (22.8%) ended treatment within 2 years compared with the bempedoic acid group (20.9%). Most patients received IMP for 2 to 5 years (78.9% of patients for bempedoic acid, 76.9% for placebo), including 44.2% of patients overall with duration of treatment of 3 to 4 years.

Extent of exposure was similar for patients with baseline ezetimibe use, as for the 1612 patients, median exposure to IMP was 3.1 years (range: 0.0-5.3 years, see table 4a below).

Table 27: Summary of Exposure (Safety Analysis Set).

Parameter	Bempedoic Acid (N = 7001)	Placebo (N = 6964)	Total (N = 13,965)
Exposure to study treatment (years)			
Mean (SD)	2.86 (1.210)	2.80 (1.227)	2.83 (1.219)
Median	3.11	3.07	3.09
Minimum, maximum	0.0, 5.6	0.0, 5.2	0.0, 5.6
Duration of treatment exposure, n (%)			
<1 year	874 (12.5)	964 (13.8)	1838 (13.2)
1 to 2 years	585 (8.4)	627 (9.0)	1212 (8.7)
2 to 3 years	1422 (20.3)	1423 (20.4)	2845 (20.4)
3 to 4 years	3154 (45.1)	3024 (43.4)	6178 (44.2)
4 to 5 years	945 (13.5)	911 (13.1)	1856 (13.3)
5 to 6 years	21 (0.3)	15 (0.2)	36 (0.3)
>6 years	0	0	0

IMP = investigational medicinal product; SD = standard deviation. Note: Exposure was calculated in years as (date of last dose of IMP – date of first dose of IMP + 1)/365.25. If the date of last dose of IMP was missing, it was imputed as the earliest date of a) the last day of the month (if the month and year were present), b) the Date of Study Completion (which was the date of death for patients who died during the study), and c) the date of the last IMP dispensed plus the number of tablets taken.

Table 28: Summary of Exposure patients with baseline ezetimibe use *(Safety Analysis Set).*

	Statistic	Bempedoic Acid (N=806)	Placebo (N=806)	Total (N=1612)
Exposure to Study Treatment (year)	n	806	806	1612
	Mean (SD)	2.85 (1.291)	2.76 (1.280)	2.81 (1.286)
	Median	3.12	3.10	3.11
	Q1, Q3	2.07, 3.64	1.99, 3.53	2.02, 3.59
	Min, Max	0.0, 5.3	0.0, 5.0	0.0, 5.3
Study treatment exposure				
<1 year	n (%)	115 (14.3)	123 (15.3)	238 (14.8)
1 to 2 years	n (%)	79 (9.8)	81 (10.0)	160 (9.9)
2 to 3 years	n (%)	136 (16.9)	144 (17.9)	280 (17.4)
3 to 4 years	n (%)	349 (43.3)	348 (43.2)	697 (43.2)
4 to 5 years	n (%)	123 (15.3)	109 (13.5)	232 (14.4)
5 to 6 years	n (%)	4 (0.5)	1 (0.1)	5 (0.3)
>6 years	n (%)	0	0	0

Adverse events

Common Adverse Events

TEAEs reported most frequently (≥5% in either treatment group) in CLEAR Outcomes occurred at similar rates in the 2 treatment groups (Table 29) with the exception of preferred terms reflecting hyperuricemia. The most frequently occurring TEAEs (≥10% incidence) in the bempedoic acid group compared with the placebo group by preferred term were COVID-19 (11.2% vs 12.5%), hypertension (11.0% vs 11.8%), and hyperuricemia (10.9% vs 5.6%).

Among the TEAEs occurring in ≥5% of patients, the single preferred term of diabetes mellitus occurred in 6.7% and 6.4% of patients, respectively, in the bempedoic acid and placebo groups. This single term is not representative of the risk of NODM or worsening of hyperglycaemia. Both were AESIs with predefined assessments based on a collection of preferred terms and/or laboratory values that were assessed in predefined patient populations based on baseline glycaemic status. Thus, it is more appropriate to assess risk of NODM or worsening of hyperglycaemia from a combination of terms and laboratory assessments vs a single term.

The incidence of TEAEs when adjusted for exposure was generally similar between treatment groups. The TEAEs with the greatest difference in exposure-adjusted incidence rate (EAIR) between the bempedoic acid and placebo groups were COVID-19 (3.9 and 4.5 per 100 patient years, respectively), hyperuricemia (3.8 and 2.0 per 100 patient-years, respectively), and blood uric acid increased (2.0 and 1.0 per 100 patient-years, respectively).

Table 29: Treatment-emergent Adverse Events Reported in ≥5% of Patients in Either Treatment Group (Safety Analysis Set).

System Organ Class Preferred Term	Bempedoic Acid (N = 7001) n (%)	Placebo (N = 6964) n (%)
Patients with at least 1 TEAE	6040 (86.3)	5919 (85.0)
COVID-19	784 (11.2)	872 (12.5)
Hypertension	771 (11.0)	820 (11.8)
Hyperuricaemia	763 (10.9)	393 (5.6)
Arthralgia	558 (8.0)	562 (8.1)
Urinary tract infection	553 (7.9)	535 (7.7)
Headache	482 (6.9)	493 (7.1)
Diabetes mellitus	467 (6.7)	447 (6.4)
Back pain	419 (6.0)	457 (6.6)
Myalgia	393 (5.6)	471 (6.8)
Blood uric acid increased	394 (5.6)	186 (2.7)
Nasopharyngitis	351 (5.0)	389 (5.6)
Osteoarthritis	330 (4.7)	349 (5.0)

COVID-19 = coronavirus disease 2019; SOC = system organ class; TEAE = treatment-emergent adverse event. Note: Patients with multiple occurrences of an adverse event of the same SOC or preferred term are counted only once for that SOC or preferred term.

Adverse Events by Severity

The majority of TEAEs were mild or moderate in severity; mild TEAEs were reported in 27.6% of patients in the bempedoic acid group and 26.2% of patients in the placebo group and moderate TEAES were reported in 41.3% of patients in the bempedoic acid group and 41.1% of patients in the placebo group. The most common events of severe intensity were related to COVID-19, including TEAEs of COVID-19 (0.5% in the bempedoic acid group, 0.8% in the placebo group) and COVID-19 pneumonia (0.7% in the bempedoic acid group, 0.9% in the placebo group). Severe TEAEs of pneumonia (0.6% in the bempedoic acid group, 0.7% in the placebo group), angina pectoris (0.4% in the bempedoic acid group, 0.6% in the placebo group), and osteoarthritis (0.4% in the bempedoic acid group, 0.6% in the placebo group) were reported in >0.5% of patients; all other events were reported in ≤0.5% of patients. The majority of severe TEAEs were considered not related to IMP.

Adverse Events by Relationship to Investigational Medicinal Product

Adverse events were assessed by the Investigator as related to IMP in 20.5% of the bempedoic acid group and 17.0% of the placebo group. The most common IMP-related TEAEs in the bempedoic acid and placebo groups were myalgia (3.3% and 3.6%, respectively), hyperuricemia (2.7% and 1.1%, respectively), blood uric acid increased (1.8% and 0.6%, respectively), muscle spasm (1.7% and 1.3%, respectively), and arthralgia (1.1% and 1.2%, respectively). All other treatment-related events were reported in <1% of patients. Few events had a treatment differential of ≥1% between treatment groups. Of note, AEs with the largest treatment differential were primarily related to laboratory abnormalities known to be related to bempedoic acid, including the aforementioned hyperuricemia (2.7% and 1.1%, respectively) and blood uric acid increased (1.8% and 0.6%, respectively), AST increased (0.7% and 0.3%, respectively), and ALT increased (0.7% and 0.4%, respectively).

Adverse Events by Baseline Ezetimibe Use

The incidence of TEAEs in patients with baseline ezetimibe use was the same in the bempedoic acid and placebo groups (89.8% in both; see table below). Treatment emergent AEs reported in >10% of patients in the bempedoic acid or placebo group included hypertension (13.3% and 14.4%, respectively), arthralgia (12.3% and 10.5%, respectively), COVID-19 (11.8% and 14.1%, respectively), and myalgia (9.6% and 11.3%, respectively). The only TEAEs with treatment differential >2% were hyperuricemia (8.7% of bempedoic acid group and 2.7% of placebo group), COVID-19 (11.8% of bempedoic acid group and 14.1% of placebo group), blood uric acid increased (6.0% of bempedoic acid group and 1.1% of placebo group), renal impairment (4.5% of bempedoic acid group and 1.1% of placebo group), and angina pectoris (5.3% of bempedoic acid group and 7.4% of placebo group).

Results were generally similar based on exposure-adjusted patient incidence rates. The TEAEs with the greatest difference in exposure-adjusted patient incidence rates between the bempedoic acid and placebo groups were hyperuricemia (3.0 and 1.0 per 100 patient-years, respectively), blood uric acid increased (2.1 and 0.4 per 100 patient-years, respectively), and renal impairment (1.6 and 0.4 per 100 patient-years, respectively).

Table 30: Overview of Treatment-Emergent Adverse Events (TEAEs) for Patients with Baseline Ezetimibe Use Safety Analysis Set.

	Bempedoic Acid (N=806)	Placebo (N=806)
	n (%)	n (%)
Number of Patients with		
At least one TEAE	724 (89.8)	724 (89.8)
At least one TEAE related to the IMP	225 (27.9)	168 (20.8)
At least one serious TEAE	288 (35.7)	264 (32.8)
At least one serious TEAE related to the IMP	7 (0.9)	10 (1.2)
A TEAE leading to IMP discontinuation	120 (14.9)	109 (13.5)

Adverse events of special interest

Adverse events of special interest for this study were predefined and monitored as described in The study protocol. Adverse events of special interest are discussed by category in the sections that follow and, when appropriate, include additional adverse event and laboratory data.

Hepatic Events

Hepatic AESIs were identified by elevations in hepatic enzymes based on laboratory test results or prespecified AEs as detailed in the SAP. The overall incidence of hepatic AESIs was slightly higher in the bempedoic acid group (7.9%) compared with placebo group (5.9%).

Laboratory Abnormalities in Hepatic Enzymes

The number of patients with single elevations in ALT or AST >3 × ULN or >5 × ULN, TB >2 × ULN, or ALP >1.5 × ULN were summarized. In addition, the number of patients with confirmed ALT and/or AST >3 × and >5 × ULN based on repeat evaluation were summarized.

Laboratory values indicating ALT or AST>3 × ULN were to be repeated and confirmed as soon as possible, preferably within 3 to 7 days of the laboratory result being available.

The overall incidence of hepatic enzyme laboratory abnormalities was slightly higher in the bempedoic acid group (5.8%) compared with placebo group (4.7%; Table 31). The incidence of ALT and/or AST >3 × ULN repeated and confirmed was 1.6% and 1.0% in the bempedoic acid and placebo groups, respectively. Single occurrences of ALT >3 × ULN occurred in 2.4% of patients in the bempedoic acid group and 1.9% of patients in the placebo group. The proportion of patients with single occurrences of

AST >3 × ULN was slightly higher in the bempedoic acid group (2.8%) compared with the placebo group (1.4%). The incidence of repeat and confirmed values >3 × ULN was similar between treatment groups for both ALT (1.2% and 0.8% in the bempedoic acid and placebo groups, respectively) and AST (1.1% and 0.6% in the bempedoic acid and placebo groups, respectively).

The incidence of ALT and/or AST >5 × ULN repeated and confirmed was 0.4% in both treatment groups. Single occurrences of ALT >5 × ULN occurred in 0.6% and 0.7% of patients in the bempedoic acid and placebo groups, respectively. Single occurrences of AST >5 × ULN was similar in the bempedoic acid group (0.7%) and placebo group (0.5%). The incidence of ALT abnormalities of >5 × ULN that were repeated and confirmed was 0.3% in both treatment groups. The incidence of AST abnormalities of >5 × ULN that were repeated and confirmed was 0.3% in the bempedoic acid group and 0.1% in the placebo group.

There was no notable difference in the occurrence of total bilirubin >2 × ULN or ALP >1.5 × ULN between the treatment groups.

At Months 12, 24, and 36, there were mean (percent) increases in AST values of 3.4 U/L (21.4%), 3.1 U/L (20.5%), and 2.2 U/L (17.2%), respectively, from a baseline value of 21.5 U/L among those who received bempedoic acid compared with mean (percent) increases in AST values of 0.5 U/L (6.6%), 0.9 U/L (9.0%), and 1.1 U/L (10.6%), respectively, from a baseline value of 21.0 U/L among those who received placebo. There were few notable differences between bempedoic acid and placebo in ALT and ALP changes from baseline over time. These trends were generally consistent based on on-treatment analysis.

Shifts from low/normal ALT at baseline to maximum levels that were >ULN (ie, high) were reported for 1654 (26.2%) of 6309 patients in the bempedoic acid group and for 1413 (22.2%) of 6357 patients in the placebo group and for AST, in 1981 (30.0%) of 6594 patients in the bempedoic acid group and 1205 (18.3%) of 6577 patients in the placebo group.

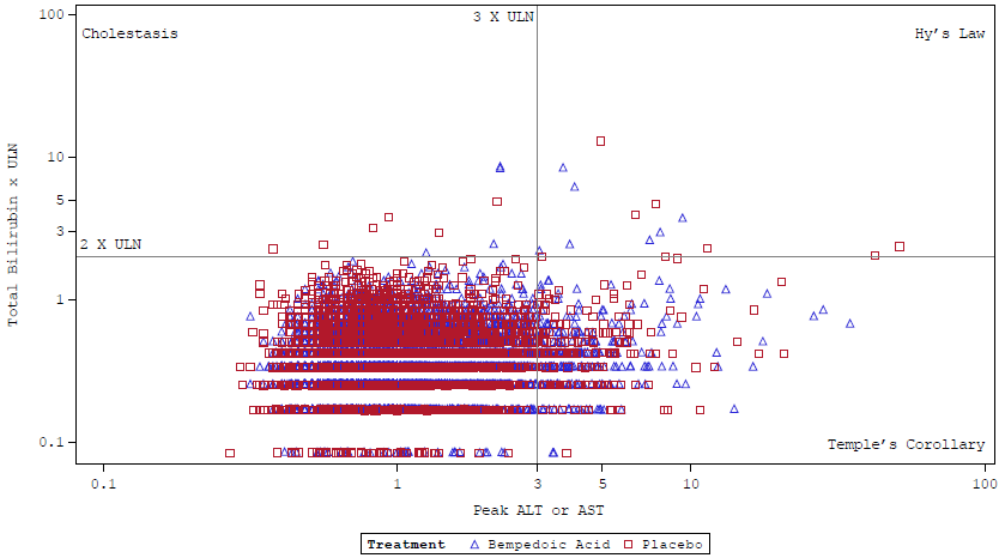
Table 31: Laboratory Abnormalities in Hepatic Enzyme Parameters (Safety Analysis Set).

Parameter	Criteria	Bempedoic Acid (N = 7001) n (%)	Placebo (N = 6964) n (%)
Any laboratory abnormality		407 (5.8)	325 (4.7)
ALT	>3 × ULN (single occurrence)	166 (2.4)	130 (1.9)
	>3 × ULN (repeat and confirmed)	83 (1.2)	53 (0.8)
	>5 × ULN (single occurrence)	43 (0.6)	49 (0.7)
	>5 × ULN (repeat and confirmed)	19 (0.3)	21 (0.3)
AST	>3 × ULN (single occurrence)	194 (2.8)	99 (1.4)
	>3 × ULN (repeat and confirmed)	80 (1.1)	43 (0.6)
	>5 × ULN (single occurrence)	48 (0.7)	34 (0.5)
	>5 × ULN (repeat and confirmed)	20 (0.3)	9 (0.1)
AST and/or ALT	>3 × ULN (repeat and confirmed)	113 (1.6)	68 (1.0)
	>5 × ULN (repeat and confirmed)	28 (0.4)	27 (0.4)
Total bilirubin	>2 × ULN (single occurrence)	19 (0.3)	28 (0.4)
	>2 × ULN (repeat and confirmed)	9 (0.1)	15 (0.2)
Potential Hy's Law cases	ALT and/or AST >3 × ULN with concurrent TB >2 × ULN	8 (0.1)	7 (0.1)
ALP	>1.5 × ULN (single occurrence)	179 (2.6)	186 (2.7)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TB = total bilirubin; ULN = upper limit of normal. Note: An elevation was considered "repeated and confirmed" if 2 consecutive incidences met the criteria regardless of time in between, or last on-treatment value meeting the criteria, or last on-study value (last measurement in the study data) meeting the criteria.

A plot of maximum on-treatment ALT/AST values and total bilirubin relative to baseline is provided in Figure 9. Peak AST or ALT vs peak total bilirubin are plotted as multiples of ULN, with horizontal and vertical lines dividing the figure into quadrants; the upper right quadrant identifies patients who met the laboratory thresholds for Hy's law. The proportion of patients who met the laboratory criteria of Hy's law was similar between the treatment groups (8 patients in the bempedoic acid group and 7 patients in the placebo group [0.1% in both groups]; Table 31).

Figure 9: Plot of Maximum On-treatment ALT/AST and Total Bilirubin Relative to Baseline (Safety Analysis Set).



The number of cases in bempedoic acid and placebo was balanced. Review of the pertinent clinical and diagnostic information for these patients shows the following that suggests none of these are cases of drug induced liver injury:

- There are other compelling potential aetiologies (including viral hepatitis, cardiac failure, cholelithiasis, and hepatic cancer; concomitant medications associated with development of Hy's Law; or alcohol abuse) in all of the cases in patients treated with bempedoic acid.
- Concomitant alkaline phosphatase >2 × ULN occurred in 3 patients in the bempedoic acid group and 5 patients in the placebo group.
- There was no temporal relationship between initiation of IMP and development of potential Hy's Law. In the bempedoic acid group, the onset of meeting the Hy's Law laboratory criteria occurred on Study Days 253-1598; in the placebo group, the onset occurred on Study Days 52-1025.
- In the bempedoic acid group, 7 of the 8 cases had repeat values on treatment where laboratory criteria were not confirmed. Dosing with bempedoic acid was not changed for the elevations in these 7 patients. The additional case met laboratory criteria at the last visit and treatment was stopped per protocol. The patient refused to return to the clinic for a repeat laboratory tests.
- Among the 7 placebo patients, 3 patients had repeat laboratory values. Among these 3 patients, one patient demonstrated a confirmation of the elevations seen initially and the other two saw a return to baseline in their laboratory values. Four of the placebo patients have no follow-up laboratory values.

Given the presence of compelling alternative aetiologies, the balance in number of potential cases between bempedoic acid and placebo, the lack of temporal relationship as well as the lack of other

significant hepatic safety signals (most importantly balance in ALT and/or AST elevations >5 × ULN), the totality of data do not indicate a signal for hepatic injury.

Adverse Events Related to Hepatic Biochemical Parameters

Hepatic AESIs were also identified based on AE reporting using the following PTs: ALT abnormal, ALT increased, AST abnormal, AST increased, blood bilirubin abnormal, blood bilirubin increased, hepatic enzyme abnormal, hepatic enzyme increased, hypertransaminasaemia, liver function test abnormal, liver function test increased, transaminases abnormal, and transaminases increased.

The overall incidence of TEAEs in this AESI category was 4.5% in the bempedoic acid group compared with 3.0% in the placebo group (Table 32). The only preferred terms reported in >1% of patients in the bempedoic acid and placebo groups were ALT increased (2.4% and 1.6%, respectively) and AST increased (2.2% and 1.1%, respectively). The majority of events were mild or moderate in severity and not related to IMP.

Hepatic AESIs led to IMP discontinuation in 0.5% of patients in the bempedoic acid group and 0.2% of patients in the placebo group, including events of ALT increased (0.2% and 0.1%, respectively), AST increased (0.2% and 0.1%, respectively), hepatic enzyme increased (0.1% each), transaminases increased (<0.1%), and liver function test abnormal (0% and <0.1%, respectively).

Table 32: Adverse Events of Special Interest by Preferred Term: Elevations in Hepatic Enzymes (Safety Analysis Set).

Category Preferred Term	Bempedoic Acid (N = 7001) n (%)	Placebo (N = 6964) n (%)
Any AE	317 (4.5)	209 (3.0)
Alanine aminotransferase increased	169 (2.4)	111 (1.6)
Aspartate aminotransferase increased	154 (2.2)	77 (1.1)
Hepatic enzyme increased	53 (0.8)	36 (0.5)
Transaminases increased	28 (0.4)	13 (0.2)
Liver function test increased	22 (0.3)	23 (0.3)
Blood bilirubin increased	6 (0.1)	10 (0.1)
Liver function test abnormal	4 (0.1)	4 (0.1)
Hypertransaminasaemia	3 (<0.1)	5 (0.1)

Cholelithiasis

Although not a predetermined AESI, 2.2% of patients in the bempedoic acid group compared with 1.2% of patients in the placebo group reported cholelithiasis. The majority of events were mild or moderate in severity in both treatment groups; events were assessed as severe in 21 (0.3%) patients in the bempedoic acid group and 9 (0.1%) patients in the placebo group. When accounting for patient exposure, the incidence of cholelithiasis was 0.8 and 0.4 per 100 patient-years for bempedoic acid and placebo, respectively.

Serious AEs of cholelithiasis occurred in 38 (0.5%) patients in the bempedoic acid group and 15 (0.2%) patients in the placebo groups. Most of the SAEs were considered not related to IMP and mild or moderate in intensity. Cholelithiasis was considered related to IMP in a similar percentage of patients in the bempedoic acid (11 patients, 0.2%) and placebo (2 patients, <0.1%) groups.

The incidence of AEs related to complications of cholelithiasis was generally similar between the treatment groups (Table 33). In the SOC of hepatobiliary disorders, 3 patients who had AEs related cholelithiasis died during the study, including 1 patient in the bempedoic acid group who experienced cholecystitis acute and 2 patients in the placebo group, 1 each who experienced bile duct stenosis and

cholangitis. Of note, the incidence of pancreatitis was consistent between the bempedoic acid and placebo groups (0.2% in both).

As observed for TEAEs of COVID-19 and myalgia, in which the incidence was ≥1% higher in the placebo group compared with the bempedoic acid group, treatment differential ≥1% can occur due to chance alone. This may be the case for cholelithiasis, which is not expected to be induced by treatment with bempedoic acid. Bempedoic acid was generally not associated with increases in complications or procedures related to cholelithiasis compared to placebo.

Table 33: Treatment-Emergent Adverse Events by Preferred Term Related to Cholelithiasis (Safety Analysis Set).

Preferred Term	Bempedoic Acid (N = 7001) n (%)	Placebo (N = 6964) n (%)
Patients with ≥1 TEAE related to cholelithiasis	216 (3.1)	152 (2.2)
Cholelithiasis	152 (2.2)	81 (1.2)
Cholecystitis	25 (0.4)	22 (0.3)
Cholecystitis acute	22 (0.3)	21 (0.3)
Cholecystitis chronic	13 (0.2)	18 (0.3)
Bile duct stone	11 (0.2)	2 (<0.1)
Biliary colic	8 (0.1)	10 (0.1)
Cholestasis	3 (<0.1)	2 (<0.1)
Jaundice	3 (<0.1)	4 (<0.1)
Biliary obstruction	2 (<0.1)	1 (<0.1)
Cholangitis	2 (<0.1)	4 (<0.1)
Biliary dyspepsia	1 (<0.1)	0
Cholangitis acute	1 (<0.1)	0
Cholelithiasis migration	1 (<0.1)	0
Hepatitis cholestatic	1 (<0.1)	0
Jaundice cholestatic	1 (<0.1)	1 (<0.1)
Cholelithiasis obstructive	0	2 (<0.1)
Gallbladder rupture	0	1 (<0.1)

Muscular Safety Events

Muscular AESIs were identified by elevations in creatine kinase or prespecified AEs as defined in the SAP. The overall incidence of muscular AESIs balanced in the bempedoic acid group (15.2%) compared with placebo group (15.6%).

Laboratory Abnormalities in Creatine Kinase >5 × and >10 × ULN

Laboratory abnormalities in CK that reached thresholds >5 × and >10 × ULN were uncommon and occurred in a similar percentage of patients in both treatment groups (≤1%; Table 34). Per protocol, CK elevations >5 × ULN required a repeat confirmatory assessment as soon as possible, preferably within 3 to 7 days. Repeated and confirmed elevations >5 × and >10 × ULN occurred in ≤0.1% of patients in both treatment groups.

Table 34: Laboratory Abnormalities in Creatine Kinase (Safety Analysis Set).

Creatine Kinase Criteria	Bempedoic Acid (N = 7001) n (%)	Placebo (N = 6964) n (%)
Any laboratory abnormality	45 (0.6)	40 (0.6)
>5 × ULN (single incidence)	45 (0.6)	40 (0.6)
>5 × ULN (repeated and confirmed)	8 (0.1)	8 (0.1)
>10 × ULN (single incidence)	18 (0.3)	15 (0.2)
>10 × ULN (repeated and confirmed)	2 (<0.1)	4 (0.1)

Adverse Events Related to Muscular Safety Events

Adverse events potentially related to muscular safety were based on a predefined set of MedDRA PTs deemed related to statin-induced muscle adverse events and included the following: muscular weakness, muscle necrosis, muscle spasms, myalgia, myositis, myoglobin blood increased, myoglobin blood present, myoglobin urine present, myoglobinemia, myoglobinuria, myopathy, myopathy toxic, necrotising myositis, pain in extremity rhabdomyolysis, blood creatine phosphokinase increased, musculoskeletal discomfort, red blood cells urine positive, muscle fatigue, and muscle tightness.

The incidence of AEs related to muscular safety was comparable between treatment groups (15.0% bempedoic acid and 15.4% placebo; Table 35). The most commonly reported events in the bempedoic acid and placebo groups were myalgia (5.6% and 6.8%, respectively), pain in extremity (4.2% and 4.3%, respectively), muscle spasms (3.9% and 3.4%, respectively), and blood creatine phosphokinase increased (2.3% and 2.0%, respectively). The majority of events were mild or moderate in severity and not related to IMP.

Seven (0.1%) patients in the bempedoic acid group experienced investigator-reported events of rhabdomyolysis compared with 1 (<0.1%) patient in the placebo group (Table 35). Among all 8 cases, there were external factors that could be potentially etiological (including exercise/physical effort, fall, sepsis, extended periods on floor, hyperkalaemia, and background medications associated with rhabdomyolysis including statin). Among the 8 cases, five (4 patients treated with bempedoic acid and 1 treated with placebo) were serious adverse events.

Using the ACC/AHA/NHBLI criteria for rhabdomyolysis, 2 of the 8 patients (1 treated with bempedoic acid and 1 treated with placebo) met the clinical definition for rhabdomyolysis ("Rhabdomyolysis—muscle symptoms with marked CK elevation [typically substantially greater than 10 × ULN] and with creatinine elevation [usually with brown urine and urinary myoglobin];" Pasternak 2002). The same 2 events met the clinical definition for rhabdomyolysis as defined by the European Atherosclerosis Society Consensus Panel (CK elevation >40 × ULN with myoglobinaemia or myoglobinuria; Stroes 2015). Both events were judged as not related by the investigator and Sponsor.

- Patient (bempedoic acid): Diagnosed with sepsis concurrently with rhabdomyolysis; patient was unconscious on floor for an extended period; no action taken with study drug; recovered/resolved; assessed as due to sepsis and not related to IMP by investigator;
- Patient (placebo): Ongoing pemphigoid, initiated Bactrim 17 days prior to rhabdomyolysis; spent 9 hours on floor overnight; study drug had been discontinued 15 days prior to the event; recovered/resolved; assessed as due to Bactrim and not related to IMP by investigator.

Events often associated with rhabdomyolysis (myositis and myalgia) were numerically lower in bempedoic acid vs placebo in the overall population (Table 35) and CK elevations >5 and 10 × ULN were balanced.

A similar number of other SAEs related to muscular safety were experienced in each treatment group, including events of myalgia (1 event) in the bempedoic acid group and a single event of muscular

weakness in the placebo group. The event of myalgia in the bempedoic acid group was considered possibly related to IMP; the event of muscular weakness in the placebo group was considered not related to IMP.

Muscular disorder AESIs led to IMP discontinuation in 2.9% and 3.2% of patients in the bempedoic acid and placebo groups, respectively. The only event that led to discontinuation in >1% of patients was myalgia (1.8% and 1.9% of patients in the bempedoic acid and placebo groups, respectively).

Exposure adjusted patient incidence rate of events in this AESI category results were generally consistent when accounting for exposure.

In summary, the 8 cases reported by investigators as rhabdomyolysis have alternative aetiologies and only 2 cases (one in each treatment arm) meet US and European expert panel criteria for actual rhabdomyolysis. These 2 cases have compelling alternate aetiologies and assessed as not related to IMP by the investigator. Considering the lack of activity of bempedoic acid in muscle tissue, the general balance in the reports of other muscle-related adverse events and clinically meaningful elevations in CK levels trials, there is no supportive data to suggest an association of rhabdomyolysis or muscle safety concerns with bempedoic acid treatment.

Table 35: Adverse Events of Special Interest by Preferred Term: Muscular Safety Events (Safety Analysis Set)

Category Preferred Term	Bempedoic Acid (N = 7001) n (%)	Placebo (N = 6964) n (%)
Any AE	1052 (15.0)	1070 (15.4)
Myalgia	393 (5.6)	471 (6.8)
Pain in extremity	296 (4.2)	296 (4.3)
Muscle spasms	275 (3.9)	240 (3.4)
Blood creatine phosphokinase increased	161 (2.3)	140 (2.0)
Muscular weakness	60 (0.9)	63 (0.9)
Musculoskeletal discomfort	8 (0.1)	6 (0.1)
Rhabdomyolysis	7 (0.1)	1 (<0.1)
Myopathy	5 (0.1)	6 (0.1)
Muscle fatigue	3 (<0.1)	8 (0.1)
Muscle tightness	3 (<0.1)	4 (0.1)
Myositis	3 (<0.1)	7 (0.1)
Red blood cells urine positive	2 (<0.1)	3 (<0.1)

New Onset or Worsening Diabetes Mellitus

Adverse Events Related to New-onset Diabetes

A broader definition of new-onset diabetes mellitus was applied for safety analyses compared with the efficacy analyses among the patients with baseline glycaemic status of no diabetes. In addition to verified cases of NODM as determined by the DC as part of the efficacy analysis, AESIs also included patients who met the laboratory criteria for NODM, patients who initiated a diabetes medication after first dose of IMP, or selected AE preferred terms.

Overall, among patients with baseline glycaemic status of no diabetes, 16.1% (621/3856 patients) of the bempedoic acid group and 17.1% (640/3740 patients) of the placebo group met any AESI criteria for new onset diabetes (Table 36). Patients with baseline glycaemic status of prediabetes had more AESIs of NODM (569/2918 [19.5%] patients and 586/2877 [20.4%] patients in the bempedoic acid and placebo

groups, respectively) than patients with normoglycaemia (52/938 [5.5%] patients and 54/863 [6.3%] patients in the bempedoic acid and placebo groups, respectively).

The proportion of patients who initiated a diabetes medication after the first dose of IMP was similar between bempedoic acid (137/3856 [3.6%] patients) and placebo (131/3740 [3.5%] patients) groups for patients with baseline glycaemic status of no diabetes Discontinuations from IMP due to AESIs of new-onset diabetes mellitus were rare. One patient in the bempedoic acid group and 1 in the placebo group discontinued IMP due to AESIs of Type 2 diabetes mellitus and blood glucose increased, respectively.

Exposure adjusted patient incidence rate for treatment-emergent AESIs of NODM by baseline glycaemic status results were generally consistent when accounting for exposure.

Table 36: Adverse Events of Special Interest by Preferred Term Reported in >1 Patient: New Onset Diabetes Mellitus by Baseline Glycaemic Status (Safety Analysis Set).

Category Preferred Term	Prediabetes		Normoglycemia		No Diabetes	
	Bempedoic Acid (N = 2918) n (%)	Placebo (N = 2877) n (%)	Bempedoic Acid (N = 938) n (%)	Placebo (N = 863) n (%)	Bempedoic Acid (N = 3856) n (%)	Placebo (N = 3740) n (%)
Any AESI of NODM	569 (19.5)	586 (20.4)	52 (5.5)	54 (6.3)	621 (16.1)	640 (17.1)
Verified NODM[a]	401 (13.7)	413 (14.4)	28 (3.0)	20 (2.3)	429 (11.1)	433 (11.6)
Use of antidiabetic medication	127 (4.4)	113 (3.9)	10 (1.1)	18 (2.1)	137 (3.6)	131 (3.5)
Any AE	282 (9.7)	284 (9.9)	28 (3.0)	31 (3.6)	310 (8.0)	315 (8.4)
Type 2 diabetes mellitus	145 (5.0)	125 (4.3)	9 (1.0)	7 (0.8)	154 (4.0)	132 (3.5)
Hyperglycaemia	61 (2.1)	60 (2.1)	8 (0.9)	14 (1.6)	69 (1.8)	74 (2.0)
Blood glucose increased	56 (1.9)	75 (2.6)	8 (0.9)	9 (1.0)	64 (1.7)	84 (2.2)
Glycosylated haemoglobin increased	41 (1.4)	46 (1.6)	6 (0.6)	3 (0.3)	47 (1.2)	49 (1.3)
Diabetes mellitus	7 (0.2)	10 (0.3)	1 (0.1)	0	8 (0.2)	10 (0.3)
Metabolic syndrome	3 (0.1)	1 (<0.1)	0	0	3 (0.1)	1 (<0.1)
Blood glucose abnormal	0	2 (0.1)	1 (0.1)	0	1 (<0.1)	2 (0.1)
Blood glucose fluctuation	1 (<0.1)	1 (<0.1)	0	0	1 (<0.1)	1 (<0.1)
Diabetes mellitus inadequate control	1 (<0.1)	4 (0.1)	0	0	1 (<0.1)	4 (0.1)
Type 1 diabetes mellitus	1 (<0.1)	2 (0.1)	0	0	1 (<0.1)	2 (0.1)

AE = adverse event; AESI = adverse event of special interest; NODM = new onset diabetes mellitus. Note: Patients with multiple occurrences of an AE of the same AESI category or preferred term are counted only once for that AESI category or preferred term. Note: For baseline glycaemic status, the No Diabetes population includes (mutually exclusive) Normoglycaemic and Prediabetes Populations. a Verified cases of NODM as determined by the Diabetes Committee.

Laboratory Abnormalities

Laboratory abnormalities associated with new onset diabetes occurred in a similar percentage of patients in each treatment group (Table 37). In the bempedoic acid and placebo groups, the percentage of patients with HbA1C ≥6.5% was consistent across subgroups with baseline glycaemic status of no diabetes (8.6% and 8.8% respectively), including prediabetes (10.5% and 10.7%, respectively) and normoglycaemia (2.6% and 2.4%, respectively).

In patients with a baseline glycaemic status of no diabetes, shifts from baseline in HbA1C were as follows:

- Shifts in HbA1C ≥5.7% to <6.5% at baseline to a worst postbaseline level ≥6.5% were reported for 253 (14%) of 1811 patients in the bempedoic acid group and for 263 (15%) of 1752 patients in the placebo group.

- Shifts in HbA1C <5.7% at baseline to a worst postbaseline level ≥6.5% were reported for 75 (3.7%) of 2031 patients in the bempedoic acid group and 67 (3.4%) of 1975 patients in the placebo group.

In the bempedoic acid and placebo groups, the percentage of patients with fasting glucose ≥126 mg/dL anytime postbaseline was similar between treatment groups for patients with baseline glycaemic status of no diabetes (17.2% and 19.3% respectively), including prediabetes (20.3% and 22.8%, respectively) and normoglycaemia (7.5% and 7.6%, respectively; Table 37).

In patients with a baseline glycaemic status of no diabetes, shifts from fasting glucose levels of ≥51 to <100 mg/dL at baseline to a worst postbaseline level ≥126 mg/dL were reported for 162 (8.3%) of 1951 patients in the bempedoic acid group and for 171 (9.3%) of 1843 patients in the placebo group. For patients with fasting glucose ≥100 to <126 mg/dL at baseline, shift to a worst postbaseline level ≥126 mg/dL were reported for 453 (24.9%) of 1821 patients in the bempedoic acid group and 498 (27.3%) of 1826 patients in the placebo group. No patients with baseline glycaemic status of normoglycaemia at baseline had fasting glucose ≥126 mg/dL during the study.

Table 37: Laboratory Abnormalities Potentially Related to New Onset Diabetes by Baseline Glycaemic Status (Safety Analysis Set).

Parameter Criteria	Prediabetes		Normoglycemia		No Diabetes	
	Bempedoic Acid (N = 2918) n (%)	Placebo (N = 2877) n (%)	Bempedoic Acid (N = 938) n (%)	Placebo (N = 863) n (%)	Bempedoic Acid (N = 3856) n (%)	Placebo (N = 3740) n (%)
HbA_{1C}						
≥6.5%	307 (10.5)	309 (10.7)	24 (2.6)	21 (2.4)	331 (8.6)	330 (8.8)
Fasting Glucose						
≥126 mg/dL	592 (20.3)	656 (22.8)	70 (7.5)	66 (7.6)	662 (17.2)	722 (19.3)

Worsening of Hyperglycaemia in Patients with Diabetes

Worsening of hyperglycaemia was assessed in patients with baseline glycaemic status of diabetes and inadequately controlled diabetes using the PTs in SAP.

Bempedoic acid did not result in worsening of hyperglycaemia for patients that had diabetes at baseline (Table 38). The percentage of patients experiencing any AESI of worsening of hyperglycaemia was similar between treatment groups among patients with baseline glycaemic status of diabetes (22.7% vs 23.1% in the bempedoic acid and placebo groups, respectively) and among patients with inadequately-controlled diabetes (32.6% in both treatment groups).

The majority of events in each treatment group were mild or moderate in intensity and considered not related to IMP. Serious events in this AESI category occurred in a similar number of patients in the bempedoic acid (22 events) and placebo (29 events) groups; none of the events were considered related to IMP.

Worsening of hyperglycaemia AESIs leading to IMP discontinuation were rare.

A single patient in the bempedoic acid group discontinued IMP due to an AESI of diabetes mellitus. In the placebo group, single AESIs of blood glucose increased and hyperglycaemia led to discontinuation of IMP.

Exposure adjusted patient incidence rate for treatment-emergent AESIs of worsening of hyperglycaemia by baseline glycaemic status results were generally consistent when accounting for exposure.

Table 38: Adverse Events of Special Interest by Preferred Term Reported in >1% of Patients: Worsening of Hyperglycaemia by Baseline Glycaemic Status (Safety Analysis Set).

Category Preferred Term	Diabetes		Inadequately Controlled Diabetes	
	Bempedoic Acid (N = 3145) n (%)	Placebo (N = 3224) n (%)	Bempedoic Acid (N = 1357) n (%)	Placebo (N = 1367) n (%)
Any AESI of worsening diabetes	713 (22.7)	746 (23.1)	443 (32.6)	446 (32.6)
Any AE	713 (22.7)	746 (23.1)	443 (32.6)	446 (32.6)
Diabetes mellitus	459 (14.6)	437 (13.6)	304 (22.4)	283 (20.7)
Hyperglycaemia	85 (2.7)	87 (2.7)	56 (4.1)	62 (4.5)
Diabetes mellitus inadequate control	78 (2.5)	84 (2.6)	58 (4.3)	55 (4.0)
Blood glucose increased	47 (1.5)	37 (1.1)	28 (2.1)	18 (1.3)
Glycosylated haemoglobin increased	39 (1.2)	40 (1.2)	22 (1.6)	21 (1.5)
Type 2 diabetes mellitus	36 (1.1)	55 (1.7)	5 (0.4)	9 (0.7)
Neuropathy peripheral	24 (0.8)	35 (1.1)	13 (1.0)	16 (1.2)
Diabetic retinopathy	8 (0.3)	22 (0.7)	7 (0.5)	17 (1.2)

AE = adverse event; AESI = adverse events of special interest. Note: Patients with multiple occurrences of an AE of the same AESI category or preferred term are counted only once for that AESI category or preferred term.

Hypoglycaemia Associated with Metabolic Acidosis

Hypoglycaemia associated with metabolic acidosis was evaluated based on a predefined set of PTs identified in the SAP as well as laboratory abnormalities in serum glucose (<70 mg/dL and ≥54 mg/dL and <54 mg/dL).

Hypoglycaemia associated with metabolic acidosis was assessed using PTs for severe manifestations hypoglycaemia (hypoglycaemic coma, hypoglycaemic encephalopathy, hypoglycaemic seizure, shock hypoglycaemic , hypoglycaemic unconsciousness) and PTs for acidosis (lactic acidosis, metabolic acidosis, and diabetic ketoacidosis). These results are summarized by PT in Table 39.

No patients experienced any prespecified terms of hypoglycaemia as described above. Overall, rates of acidosis AEs were similar at 0.2% each for bempedoic acid and placebo. Few patients experienced any individual AEs related to acidosis (metabolic acidosis, diabetic ketoacidosis, or lactic acidosis), with a similar incidence between treatment groups (13 and 11 patients in the bempedoic acid and placebo groups, respectively; 0.2% of both). The majority of events in each treatment group were mild or moderate in intensity and considered not related to IMP. Serious events in this AESI category occurred in a similar number of patients in the bempedoic acid (4 events) and (3 events) placebo groups; none of the events were considered related to IMP.

No events in this AESI category led to IMP discontinuation.

Exposure adjusted patient incidence rate of events in this AESI category results were generally consistent when accounting for exposure.

A similar percentage of patients in the bempedoic acid (4.3%) and placebo (3.8%) groups experienced hypoglycaemia, the majority of which had serum glucose <70 mg/dL and ≥54 mg/dL (3.3% and 2.6%, respectively; Table 39) as well as serum glucose of <54 mg/dL (1.1% and 1.2%, respectively).

Table 39: Adverse Events of Special Interest by Preferred Term: Hypoglycaemia Associated with Metabolic Acidosis (Safety Analysis Set).

Category Preferred Term	Bempedoic Acid (N = 7001) n (%)	Placebo (N = 6964) n (%)
Acidosis	13 (0.2)	11 (0.2)
Metabolic acidosis	5 (0.1)	8 (0.1)
Diabetic ketoacidosis	4 (0.1)	1 (<0.1)
Lactic acidosis	4 (0.1)	3 (<0.1)
Hypoglycemia	304 (4.3)	267 (3.8)
Level 1: Serum Glucose <70 mg/dL and ≥54 mg/dL	228 (3.3)	184 (2.6)
Level 2: Serum Glucose <54 mg/dL	76 (1.1)	83 (1.2)
Level 3: Any Hypoglycemia AEs	0	0

Renal Impairment

Laboratory Data Related to Renal Impairment

More patients in the bempedoic acid group (3765 patients, 53.8%) experienced an abnormality related to AESI defined renal laboratory parameters compared with patients in the placebo group (2978 patients; 42.8%; Table 40).

Creatinine

Mean creatinine values increased early postbaseline in the bempedoic acid group but did not worsen over time with mean (percent) changes of 0.049 mg/dL (5.8%) and 0.066 mg/dL (7.7%) at Month 3 and 36, respectively, compared with mean changes of 0.007 mg/dL (1.8%) and 0.032 mg/dL (4.5%) in the placebo group, respectively. These trends were generally consistent based on on-treatment analysis.

The treatment differential in creatinine levels between the bempedoic acid and placebo groups was consistent over time and across eGFR categories. The mean (percent) change from baseline in creatine level for each eGFR category are as follows:

- ≥90 mL/min/1.73 m^2
    - Month 3: 0.076 mg/dL (11.0%) and 0.058 mg/dL (8.4%) in bempedoic acid and placebo groups, respectively; difference: 2.6%
    - Month 36: 0.093 mg/dL (13.5%) and 0.073 mg/dL (10.7%) in bempedoic acid and placebo groups, respectively; difference: 2.8%
- 60 to <90 mL/min/1.73 m^2
    - Month 3: 0.045 mg/dL (5.3%) and 0.010 mg/dL (1.2%) in the bempedoic acid and placebo groups, respectively; difference: 4.1%
    - Month 36: 0.060 mg/dL (7.0%) and 0.034 mg/dL (4.1%), in the bempedoic acid and placebo groups, respectively; difference: 2.9%
- 30 to <60 mL/min/1.73 m^2
    - Month 3: 0.042 mg/dL (3.4%)- and 0.030 mg/dL- (2.1%) in the bempedoic acid and placebo groups, respectively; difference: 5.5%
    - Month 36: 0.069 mg/dL (5.3%) and 0.001 mg/dL (0.3%) in bempedoic acid and placebo groups, respectively; difference: 5.0%

A summary of specific changes from baseline in creatinine is presented in Table 40

Abnormalities in creatinine were generally balanced between treatment groups. Change from baseline of >1 mg/dL occurred in 83 (1.2%) patients in the bempedoic acid group and 76 (1.1%) patients in the placebo group; ≤0.1% of patients in either treatment group experienced a change from baseline >30% within 30 days after 1st dose. A change from baseline of >0.5 mg/dL occurred in 498 (7.1%) patients in the bempedoic acid group and 385 (5.5%) patients in the placebo group.

Estimated Glomerular Filtration Rate

Generally mirroring the observations in creatinine, there was an early decrease in mean eGFR at Month 3 among patients in the bempedoic acid group (mean [percent] changes of -3.6 mL/min/1.73 m2 [-4.1%]) that did not worsen overtime (mean [percent] changes of -4.7 mL/min/1.73 m2 [-5.3%] at Month 36). Mean (percent) changes in eGFR for the placebo group were -0.6 mL/min/1.73 m2 (0.4%) and -2.6 mL/min/1.73 m2 (-2.1%) at Month 3 and Month 36, respectively. These trends were generally consistent based on on-treatment analysis.

Shifts from mild renal impairment to moderate impairment occurred in a higher proportion of patients in the bempedoic acid group than in the placebo group (43.8% and 35.9%, respectively). A similar percentage of patients in the bempedoic acid and placebo groups experienced a worst postbaseline shift to severe impairment from baseline categories of normal (0.3% and 0.4%, respectively), and mild impairment (0.7% and 0.8%, respectively); a slight imbalance in the shift to severe impairment among patients with moderate impairment at baseline was noted (10.5% and 8.0%, respectively).

During the study, a similar percentage of patients in the bempedoic acid and placebo groups had calculated eGFR levels ≥15 and <30 mL/min/1.73m2 (2.7% and 2.2%, respectively) and <15 mL/min/1.73m2 (0.2% in both groups; Table 40).

Blood Urea Nitrogen

Changes from baseline in BUN were similar in pattern to those observed for creatinine in the bempedoic acid and placebo groups in that mean values increased early postbaseline and did not worsen over time. In the bempedoic acid group, mean (percent) changes of 1.9 mg/dL (14.5%) and 2.3 mg/dL (16.8%) occurred at Month 3 and Month 36, respectively, compared with 0.0 mg/dL (3.4%) and 0.7 mg/dL (7.8%), respectively, in the placebo group. These trends were generally consistent based on on-treatment analysis. The treatment differential in BUN levels between the bempedoic acid and placebo groups was consistent over time and across eGFR categories. The mean (percent) change from baseline in BUN level for each eGFR category are as follows:

- ≥90 mL/min/1.73 m^2
    - Month 3: 1.776 mg/dL (16.2%) and 0.673 mg/dL (8.6%) in bempedoic acid and placebo groups, respectively; difference: 7.6%
    - Month 36: 2.014 mg/dL (18.3%) and 0.888 mg/dL (10.7%) in bempedoic acid and placebo groups, respectively; difference: 7.6%
- 60 to <90 mL/min/1.73 m^2
    - Month 3: 1.900 mg/dL [14.5%] and 0.063 mg/dL (3.1%) in the bempedoic acid and placebo groups, respectively; difference: 11.4%
    - Month 36: 2.310 mg/dL [17.2%] and 0.750 mg/dL (7.9%), in the bempedoic acid and placebo groups, respectively; difference: 9.3%
- 30 to <60 mL/min/1.73 m^2

- Month 3: 2.204 mg/dL (13.4%) and -0.578 mg/dL (0.1%) in the bempedoic acid and placebo groups, respectively; difference: 13.3%
- Month 36: 2.474 mg/dL (14.8%) and 0.497 mg/dL (5.0%) in bempedoic acid and placebo groups, respectively; difference: 9.8%

A higher percentage of patients in the bempedoic acid group experienced BUN >2 × baseline (667 patients, 9.5%) during the study compared with the placebo group (431 patients, 6.2%; Table 40). This trend was consistent for patients with a change from baseline in BUN/creatinine ratio >30%, which occurred in 3480 (49.7%) patients in the bempedoic acid group and 2743 (39.4%) patients in the placebo group.

Table 40: Summary of Laboratory Abnormalities Related to Renal Impairment (Safety Analysis Set).

Laboratory Criteria	Bempedoic Acid (N = 7001) n (%)	Placebo (N = 6964) n (%)
Any laboratory abnormality	3765 (53.8)	2978 (42.8)
Creatinine		
Change from baseline >1 mg/dL	83 (1.2)	76 (1.1)
Change from baseline >0.5 mg/dL	498 (7.1)	385 (5.5)
Change from baseline >30% within 30 days after 1st dose	7 (0.1)	1 (<0.1)
eGFR		
<15 mL/min/1.73m^2	12 (0.2)	14 (0.2)
≥15 and <30 mL/min/1.73m^2	190 (2.7)	156 (2.2)
BUN		
>2 × baseline	667 (9.5)	431 (6.2)
BUN/Creatinine change from baseline >30%	3480 (49.7)	2743 (39.4)

Adverse Events Potentially Related to Renal Impairment

Adverse events potentially related to renal impairment were assessed using the following PTs from the renal and urinary disorders SOC or Investigations SOC: acute kidney injury; acute prerenal failure; blood creatinine abnormal; blood creatinine increased; blood urea abnormal; blood urea increased; blood urea nitrogen/creatinine ratio increased; creatinine renal clearance abnormal; creatinine renal clearance decreased; glomerular filtration rate abnormal; glomerular filtration rate decreased; oliguria; prerenal failure; renal failure; renal function test abnormal; renal impairment, blood urine present, proteinuria, nephropathy, protein urine present, red blood cells urine positive, haematuria.

Adverse events in the AESI category of renal impairment occurred in 11.5% of patients in the bempedoic acid group and 8.6% of patients in the placebo group (Table 41). The most common renal AEs were glomerular filtration rate decreased (3.6% and 2.9% of patients in the bempedoic acid and placebo groups, respectively) and renal impairment (3.1% and 1.9% of patients in the bempedoic acid and placebo groups, respectively). The higher incidence of these AEs in patients in the bempedoic acid group compared with the placebo group likely reflects the small increases seen in creatinine in the bempedoic acid group. The incidence of acute kidney injury, renal failure, haematuria, and blood creatinine increased was balanced across treatment groups.

Renal impairment AESIs leading to IMP discontinuation were rare (0.4% and 0.2% of patients in the bempedoic acid and placebo groups, respectively. No single AE PT led to IMP discontinuation in >0.1% of patients. In the bempedoic acid group, 3 AEs of acute kidney injury and 1 AE of renal failure resulted in death; none of the events were considered related to treatment.

Table 41: Adverse Events of Special Interest Reported in ≥1% of Patients by Preferred Term: Renal Impairment (Safety Analysis Set).

Category Preferred Term	Bempedoic Acid (N =7001) n (%)	Placebo (N = 6964) n (%)
Any AE	802 (11.5)	599 (8.6)
Glomerular filtration rate decreased	252 (3.6)	201 (2.9)
Renal impairment	217 (3.1)	134 (1.9)
Blood creatinine increased	124 (1.8)	106 (1.5)
Haematuria	84 (1.2)	74 (1.1)
Renal failure	80 (1.1)	60 (0.9)
Acute kidney injury	79 (1.1)	69 (1.0)

Adverse Events by Baseline eGFR

The overall incidence of TEAEs was generally similar between treatment groups across eGFR categories, with a treatment differential of ≤2% between the bempedoic acid and placebo groups. In the bempedoic acid group, the percentage of patients experiencing events of blood uric acid increased and renal impairment was similar across baseline eGFR categories. These TEAEs occurred in a similar proportion of patients in each eGFR category.

In the overall population, AEs of blood uric acid increased occurred 5.6% and 2.7% of the bempedoic acid and placebo groups, respectively. The incidence of blood uric acid increased was generally similar between the bempedoic acid and placebo groups for patients with baseline eGFR of ≥90 mL/min/1.73m2 (50 [4.1%] patients and 27 [2.2%] patients, respectively) and 60-<90 mL/min/1.73m2 (222 [5.1%] patients and 99 [2.3%] patients, respectively). In patient with baseline eGFR 30-<60 mL/min/1.73m2, the treatment differential was greater with a higher incidence of blood uric acid increased in the bempedoic acid group (120 patients, 8.3%) compared with the placebo group (60 patients, 4.2%).

In the overall population, AEs of renal impairment occurred 3.1% and 1.9% of the bempedoic acid and placebo groups, respectively. There was no notable treatment difference in incidence of the PT of renal impairment in patients with baseline eGFR ≥90 mL/min/1.73m2 (9 [0.7%] and 8 [0.6%] patients in the bempedoic acid and placebo groups, respectively) and 60-<90 mL/min/1.73m2 (112 [2.6%] and 71 [1.7%] patients in the bempedoic acid and placebo groups, respectively). In patient with baseline eGFR 30-<60 mL/min/1.73m2, the treatment differential was slightly greater with a higher incidence of renal impairment in the bempedoic acid group (95 patients, 6.6%) compared with the placebo group (55 patients, 3.8%).

Slight increases in the incidence of gout were noted as eGFR decreased; however, the incidence was comparable in the bempedoic acid and placebo groups across eGFR categories.

Interpretation of TEAEs reported in patients with eGFR <30 mL/min/1.73m2 is limited due to the low number of patients (17 patients in bempedoic acid group, 18 patients in placebo group

<u>Neurocognitive/Neurologic Events</u>

Neurocognitive/neurologic events were assessed using the following PTs: cognitive disorder, confusional state, disorientation, memory impairment, and mental status changes. Neurocognitive/neurologic AEs occurred at a similar incidence in the bempedoic acid (0.8%) and placebo (1.0%) groups. The most common AE was memory impairment, occurring in 0.4% of patients in both treatment groups. The majority of events were mild or moderate in severity and not related to IMP.

Adverse events of special interest in this category led to IMP discontinuation in ≤1% of patients in both treatment groups.

Exposure adjusted patient incidence rate of events in this AESI category were generally consistent when accounting for exposure.

Atrial fibrillation

Atrial fibrillation was assessed using the PT atrial fibrillation. Of note, ECGs were reviewed against AEs to ensure Investigator assessed, clinically significant treatment emergent events of new atrial fibrillation that were noted on the ECG CRF were captured in the AE dataset. Adverse events of atrial fibrillation occurred in 3.3% and 3.5% of patients in the bempedoic acid and placebo groups, respectively. The majority of events were mild or moderate in severity and not related to IMP.

Atrial fibrillation led to IMP discontinuation in 0.1% of patients in both treatment groups

Exposure adjusted patient incidence rate of events in this AESI category were generally consistent when accounting for exposure.

Tendinopathies and Tendon Rupture

Tendinopathies

Adverse events potentially related to tendinopathy were assessed using the following PTs: muscle rupture, rotator cuff syndrome, tendon discomfort, tendon disorder, tendon injury, tendon necrosis, tendon pain, and tendonitis.

Adverse events in this AESI category are summarized in Table 42; AESIs of tendinopathy occurred in a similar percentage of patients in the bempedoic acid (1.7%) and placebo (1.8%) groups. The only events reported in >0.1% of patients in either the bempedoic acid or placebo group were rotator cuff syndrome (0.9% in both), tendonitis (0.5% in both), and tendon disorder (0.1% and 0.2%, respectively). The majority of events were mild or moderate in severity and not related to IMP.

Preferred terms within this AESI led to IMP discontinuation in 0.1% of patients in the bempedoic acid group, including single events of muscle rupture, tendon disorder, and tendon pain, and 2 events of tendonitis; tendonitis led to IMP discontinuation in 2 (<0.1%) patients in the placebo group.

Exposure adjusted patient incidence rate of events in this AESI category results were generally consistent when accounting for exposure.

Table 42: Adverse Events of Special Interest by Preferred Term: Tendinopathies (Safety Analysis Set).

Category **Preferred Term**	**Bempedoic Acid** **(N = 7001)** **n (%)**	**Placebo** **(N = 6964)** **n (%)**
Any tendinopathies AESI	118 (1.7)	128 (1.8)
Rotator cuff syndrome	66 (0.9)	66 (0.9)
Tendonitis	34 (0.5)	38 (0.5)
Muscle rupture	9 (0.1)	10 (0.1)
Tendon disorder	6 (0.1)	13 (0.2)
Tendon injury	6 (0.1)	1 (<0.1)
Tendon pain	3 (<0.1)	5 (0.1)
Tendon discomfort	0	1 (<0.1)

Tendon Rupture

Tendon rupture was reported as a preferred term in the safety database in 24 (0.3%) patients in the bempedoic acid group and 19 (0.3%) patients in the placebo group. The number of patients with tendon rupture events that were considered serious by the investigator was consistent between the bempedoic acid and placebo groups (4 patients, 0.1% in both). No SAEs of tendon rupture were considered related to IMP.

Adverse events potentially related to tendon rupture were adjudicated based on the TRAC Charter. Possible cases of tendon rupture for inclusion in the tendon rupture adjudication process were identified through predefined procedures and AE PTs within relevant high-level terms and SMQ for tendinopathies and ligament disorders. The TRAC rendered an assessment as to whether the case represented a confirmed event (positively adjudicated event where the event met the definition with all necessary documentation) or a non-tendon rupture event (negatively adjudicated event where the event did not meet the definition and likely represented an alternative or nonevent diagnosis).

A summary of tendon rupture adjudication results, including severity, location, and cause is presented in Table 43. Treatment-emergent tendon rupture AESIs were positively adjudicated in 86 (1.2%) patients (95 events) in the bempedoic acid group and 66 (0.9%) patients (73 events) in the placebo group. Rotator cuff was the most common tendon rupture location (72.6% and 75.3% of all tendon rupture events in the bempedoic acid and placebo groups, respectively). Among the 95 tendon rupture events in the bempedoic acid group, 64 (67.4%) events were complete tears; among the 73 tendon rupture events in the placebo group, 46 (63.0%) events were complete tears. The proportion of events that were partial tears was similar between the treatment groups (32.6% and 34.2%, respectively).

Tendon rupture AESIs led to IMP discontinuation in 3 patients in the bempedoic acid group, including AESIs of muscle rupture, tendon disorder, and tendonitis; no events of tendon rupture led to IMP discontinuation in the placebo group.

Of those patients who had a positively adjudicated tendon rupture, a history of previous tendon rupture was reported by 15.1% and 13.6% of patients in the bempedoic acid and placebo groups, respectively (Table 43). Prior use of fluoroquinolones was reported by 12.8% and 10.6% of patients in the bempedoic acid and placebo groups, respectively, and prior use of corticosteroids was reported by 10.5% and 9.1% of patients in the bempedoic acid and placebo groups, respectively.

Of the patients who were using statins at baseline, positively adjudicated TEAEs of tendon rupture occurred in 1.0% of patients in both treatment groups; positively adjudicated TEAEs occurred in 1.3% and 0.9% of patients without baseline statin use in the bempedoic acid and placebo groups, respectively. However, considering only patients who had a positively adjudicated tendon rupture, 18.6% of patients in the bempedoic acid group and 24.2% of patients in the placebo group were using statins at baseline.

The EAIR for positively adjudicated tendon rupture was similar between the bempedoic acid and placebo groups (0.36 and 0.28 per 100 patient-years, respectively).

Overall, the incidence of tendon rupture, as well as severity, location and primary cause of tendon rupture is similar between treatment groups. No patterns were observed within these categories.

Table 43: Adverse Events of Special Interest: Tendon Rupture (Safety Analysis Set).

Category Classification	Bempedoic Acid (N = 7001) n (%)	Placebo (N = 6964) n (%)
Patients with any positively adjudicated tendon rupture	86 (1.2)	66 (0.9)
Number of positively adjudicated events	95	73
Severity[a]		
Complete tear	64 (67.4)	46 (63.0)
Partial tear	31 (32.6)	25 (34.2)
Unable to determine	0	2 (2.7)
Location[a]		
Rotator cuff	69 (72.6)	55 (75.3)
Other	11 (11.6)	8 (11.0)
Biceps tendon proximal	5 (5.3)	6 (8.2)
Quadraceps tendon	3 (3.2)	1 (1.4)
Achilles tendon	3 (3.2)	0
Biceps tendon distal	2 (2.1)	1 (1.4)
Gastrocnemius tendon	1 (1.1)	1 (1.4)
Wrist tendon	1 (1.1)	1 (1.4)
Patellar tendon	0	0
Primary Cause[a]		
Spontaneous	49 (51.6)	38 (52.1)
Nonspontaneous	40 (42.1)	35 (47.9)
Unknown	6 (6.3)	0
Patients with any positively adjudicated tendon rupture[a]	86 (1.2)	66 (0.9)
With statin use at baseline[b]	16 (18.6)	16 (24.2)
With history of previous tendon rupture[b]	13 (15.1)	9 (13.6)
With prior use of fluoroquinolones[b]	11 (12.8)	7 (10.6)
With prior use of corticosteroids[b]	9 (10.5)	6 (9.1)

a Denominator for percentage is the number of patients in the respective treatment group. b Denominator for percentage is the number of patients with positively adjudicated tendon rupture events.

Malignancy

Adverse events potentially related to malignancy were assessed using the following SMQs: malignancy-related conditions, hematological malignant tumors, haematological tumors of unspecified malignancy, non-haematological malignant tumors, and non-haematological tumors of unspecified malignancy.

The incidence of malignancy AESIs was similar between the bempedoic acid (4.6%) and placebo (4.9%) groups. Events were most commonly reported under the non-haematological malignant tumors SMQ (4.1% and 4.3% in bempedoic acid and placebo groups, respectively). The most common malignancies in this SMQ were basal cell carcinoma (0.9% in both groups), prostate cancer (0.4% and 0.5% in bempedoic acid and placebo groups, respectively), squamous cell carcinoma of skin (0.2% and 0.5% in bempedoic acid and placebo groups, respectively), and breast cancer (0.2% and 0.4% in bempedoic acid and placebo groups, respectively); all other PTs were reported in ≤0.2% of patients.

In agreement with the commonly reported SMQ, the primary location of tumors was predominantly skin/melanoma (88/353 [1.3%] patients in bempedoic acid group and 109/364 [1.6%] patients in placebo group) and genitourinary (71/353 [1.0%] patients in bempedoic acid group and 70/364 [1.0%] patients in placebo group); the location was considered other/unspecified for malignancies in 93/353 [1.3%] patients in bempedoic acid group and 103/364 [1.5%] patients in placebo group.

The majority of events were mild or moderate in severity and not related to IMP.

Malignancy AESIs led to IMP discontinuation in a similar percentage of patients in the bempedoic acid (0.7%) and placebo (0.6%) groups. All AESIs of malignancy leading to IMP discontinuation were reported in <0.1% of patients, with a similar incidence in each group. Serious AES in the SOC of neoplasms benign, malignant, and unspecified (including cysts and polyps) were experienced by 206 (2.9%) patients in the bempedoic acid group and 209 (3.0%) patients in the placebo group.

Other adverse events

Uric Acid levels and Relationship to Adverse Events of Gout

Based on increases in mean serum uric acid levels observed in patients who received bempedoic acid in previous studies, uric acid increases and events of gout and gouty arthritis were examined.

Mean uric acid levels increased early postbaseline in the bempedoic acid group but did not worsen over time with mean (percent) changes of 0.81 mg/dL (16.0%) and 0.52 mg/dL (12.0%) at Month 3 and 36, respectively, compared with mean changes of 0.01 mg/dL (1.6%) and -0.09 mg/dL (0.9%) in the placebo group, respectively. These trends were generally consistent based on on-treatment analysis.

Shifts from low/normal uric acid at baseline to maximum levels that were >ULN were reported for 3143 (64.9%) of 7001 patients in the bempedoic acid group and for 1819 (37.9%) of 6964 patients in the placebo group. Treatment-emergent AEs of hyperuricemia occurred in a higher percentage of patients in the bempedoic acid group (16.4%) than in the placebo group (8.2%), which included events of hyperuricemia (10.9% and 5.6%, respectively) and blood uric acid increased (5.6% and 2.7%, respectively).

The overall incidence of gout was 215 (3.1%) and 143 (2.1%) patients in the bempedoic acid and placebo groups, respectively. Gouty arthritis was reported for 15 (0.2%) patients in the bempedoic acid group and 9 (0.1%) patients in the placebo group. The majority of events were considered not related to treatment.

A review of the on-study incidence of gout and gouty arthritis in relation to baseline uric acid levels revealed a slightly higher percentage of patients in the bempedoic acid group with high baseline uric acid levels experienced TEAEs of gout and gouty arthritis on study (7.7%) compared with patients in the placebo group who had high baseline uric acid levels (5.2%). Incidence of TEAEs of gout or gouty arthritis was similar between treatment groups for patients with low or normal uric acid levels at baseline (1.2% in bempedoic acid group, 0.8% in placebo group).

For patients with a history of gout or gouty arthritis, a lower percentage of patients in the bempedoic acid group experienced TEAEs of gout or gouty arthritis on study (14.7%) compared with patients in the placebo group (19.4%); the incidence in patients with no history of gout or gouty arthritis was 2.6% and 1.3% in the bempedoic acid and placebo groups, respectively.

Decreased Haemoglobin

Mean haemoglobin levels decreased early postbaseline in the bempedoic acid group but did not worsen over time with mean (percent) changes of -0.44 g/dL (-2.97%) and -0.60 g/dL (-4.07%) at Month 3 and 36, respectively, compared with mean changes of -0.05 g/dL (-0.20%) and -0.30 g/dL (-1.93%) in the placebo group, respectively. These trends were consistent based on on-treatment analysis of haemoglobin levels.

Patients in both treatment groups experienced decreases from baseline in haemoglobin values (Table 44). The incidence of decreases from baseline of ≥2 g/dL and <LLN and ≥3 g/dL and <LLN were more common among subjects in the bempedoic acid group (755 patients, 10.8% and 350 patients, 5.0%, respectively) compared with the placebo group (517 patients, 7.4% and 248 patients, 3.6%, respectively). The

incidence of decreases from baseline of ≥5 g/dL and <LLN (1.1% and 0.7% in the bempedoic acid and placebo groups, respectively) and levels <8 g/dL (0.3% in both treatment groups) were similar between treatment groups.

Table 44: Laboratory Abnormalities in Haemoglobin (Safety Analysis Set).

Parameter	Criteria	Bempedoic Acid (N = 7001) n (%)	Placebo (N = 6964) n (%)
Hemoglobin	Decrease from baseline ≥2 g/dL and <LLN	755 (10.8)	517 (7.4)
	Decrease from baseline ≥3 g/dL and <LLN	350 (5.0)	248 (3.6)
	Decrease from baseline ≥5 g/dL and <LLN	79 (1.1)	51 (0.7)
	<8 g/dL	21 (0.3)	19 (0.3)

LLN = lower limit of normal. Note: Patients who had at least one laboratory value at any post-baseline time point that met the abnormal laboratory criteria were counted as meeting the criteria; these categories are not mutually exclusive.

In general, changes in haematocrit and erythrocytes mirrored haemoglobin results. There was an early decrease in mean haematocrit in the bempedoic acid group at Month 3 (mean [percent] change from baseline: -1.0% [-2.27%]) that did not worsen over time (mean [percent] change from baseline: -1.31% [-2.88%] at Month 36). Haematocrit levels in the placebo group followed a similar trend with mean (percent) change from baseline of 0.21% (0.65%) and -0.41% (-0.75%) at Month 3 and Month 36, respectively. An early decrease in erythrocytes was also noted in the bempedoic acid that did not worsen over time with mean (percent) changes of -0.16 × 106/µL (-3.26%) and -0.14 × 106/µL (-2.88%) at Month 3 and 36, respectively, compared with mean changes of -0.01 × 106/µL (-0.11%) and -0.05 × 106/µL (-0.97%) in the placebo group at Month 3 and 36, respectively. Of note, there were no meaningful differences between treatment groups in mean corpuscular haemoglobin concentration or mean corpuscular haemoglobin volume. These trends were generally consistent based on on-treatment analysis.

Anaemia was reported in 332 (4.7%) patients in the bempedoic acid group and 272 (3.9%) patients in the placebo group. The majority of events were considered not related to treatment. Decreases in haemoglobin were generally asymptomatic and did not require medical intervention.

COVID-19 and Related Adverse Events

Patient enrollment into this study occurred in 2016 through 2019, and study close out initiated in May 2022. Therefore, a substantial portion of the study was conducted during the COVID-19 pandemic. In Protocol Amendment 5 (24 September 2020), COVID-19-specific CRFs were added to record positive COVID-19 test result.

Adverse events of COVID-19 were identified by HLT "Coronavirus Infection." Events with a start date ±14 days of the positive PCR test results, or in the same month if either the event start date or test date was partially missing, were considered.

A total of 545 (7.8%) and 604 (8.7%) patients treated with bempedoic acid and placebo, respectively, had a positive COVID-19 PCR test during the study, of which 479 (6.8%) and 539 (7.7%), respectively, reported COVID-19 AEs within -14 days/+30 days of a COVID-19 positive PCR test. The most common AEs reported in the bempedoic acid and placebo groups were COVID-19 (5.7% and 6.5%, respectively), COVID-19 pneumonia (1.2% and 1.1%, respectively), and SARS-CoV-2 test positive (0.5% in both groups).

COVID-19 events led to death in 25 (0.4%) and 26 (0.4%) patients treated with bempedoic acid and placebo, respectively, including events of COVID-19, COVID-19 pneumonia, and suspected COVID-19.

An additional 466 (6.7%) and 467 (6.7%) patients treated with bempedoic acid and placebo, respectively, were suspected of having COVID-19 (ie, the type of positive COVID-19 test was rapid antigen, antibody, or unknown) during the study, of which 440 (6.3%) and 452 (6.5%), respectively, reported COVID-19 AEs. The most common AEs reported in the bempedoic acid and placebo groups were COVID-19 (5.4% and 5.8%, respectively) and COVID-19 pneumonia (0.7% and 0.6%, respectively). In patients who were suspected of having COVID-19, COVID-19 events led to death in 35 (0.5%) and 32 (0.5%) patients treated with bempedoic acid and placebo, respectively, including events of COVID-19, COVID-19 pneumonia, and suspected COVID-19.

Serious adverse event/deaths/other significant events

Serious adverse events

The overall incidence of SAEs was similar in the bempedoic acid (25.2%) and placebo (24.9%) groups. EAIRs of SAEs were the same between treatment groups (8.9 per 100 patient-years in each).

The most common SAEs in >1% of patients in the bempedoic acid and/or placebo groups were COVID-19 pneumonia (1.2% and 1.3%, respectively), pneumonia (1.2% in each), atrial fibrillation (1.2% and 1.4%, respectively), osteoarthritis (1.0% in each), COVID-19 (0.8% and 1.1%, respectively), and angina pectoris (0.8% and 1.2%, respectively).

Serious AEs were considered related to IMP in 0.6% and 0.5% of patients in the bempedoic acid and placebo groups, respectively; all related SAEs by preferred term were reported in <0.1% of patients.

Patients with baseline ezetimibe use

The incidence of SAEs in patients with baseline ezetimibe was 35.7% for the bempedoic acid group and 32.8% for the placebo group. There were no treatment emergent SAE preferred terms >1% between treatments. Commonly reported SAEs in this group occurring in >1% of patients were generally consistent with the overall population but also included angina unstable (1.6% and 0.6%, respectively), non-cardiac chest pain (1.1% and 1.6%, respectively), and cholelithiasis (1.4% and 0.5%, respectively). Most of the common events were largely related to cardiac disorders and infections.

Deaths

All on-study deaths were adjudicated as CV or non-CV deaths by the CEC and were included as efficacy endpoints; deaths were not reported as SAEs.

The incidence of non-CV (non-MACE) deaths was balanced between the bempedoic acid and placebo groups (2.4% and 2.3%, respectively). Most non-CV deaths in the bempedoic acid and placebo groups were related to infections (1.1% and 1.0%, respectively) and malignancy (0.8% and 0.7%, respectively).

Additional information regarding adjudicated non-CV deaths, as well as the risk of non-CV deaths in relation to pandemic periods. A noted increase occurred in undetermined deaths (classified under CV death category per the CEC Charter) and non-CV deaths, including deaths related to infection and pulmonary causes, in both treatment groups during the portion of the study conducted during the COVID-19 pandemic (after 11 March 2020), as compared with the period before the pandemic. The observations of increased undetermined deaths as well as infection and pulmonary deaths under the non-CV category after the start of the pandemic compared to prepandemic rates generally mirror the observations that were made globally by the WHO regarding the increase in deaths during 2020 and 2021. During these 2 years, the WHO observed a total of over 14 million excess deaths globally that consisted of approximately 5 million directly related to COVID-19, but also an approximate 9 million additional excess deaths. These 9 million deaths were not directly attributed to COVID-19 but were likely related to the pandemic.

Table 45 summarizes non-CV (non-MACE) deaths. Of the non-CV deaths (165 deaths in the bempedoic acid group [2.4%], 163 deaths in the placebo group [2.3%]), the majority were adjudicated as infections (75 [1.1%] deaths in the bempedoic acid group, 71 [1.0%] deaths in the placebo group) or malignancy (58 [0.8%] deaths in the bempedoic acid group, 51 [0.7%] deaths in the placebo group).

Table 45: Summary of Adjudicated non-Cardiovascular Deaths (Full Analysis Set).

Category	Bempedoic Acid (N = 6992) n (%)	Placebo (N = 6978) n (%)
All non-CV Death (non-MACE)	165 (2.4)	163 (2.3)
Infection	75 (1.1)	71 (1.0)
Malignancy	58 (0.8)	51 (0.7)
Pulmonary	6 (0.1)	10 (0.1)
Trauma	6 (0.1)	9 (0.1)
Neurological	6 (0.1)	3 (<0.1)
Gastrointestinal	5 (0.1)	8 (0.1)
Renal	5 (0.1)	1 (<0.1)
Hepatobiliary	1 (<0.1)	4 (0.1)
Pancreatic	1 (<0.1)	2 (<0.1)
Suicide	1 (<0.1)	1 (<0.1)
Other noncardiovascular	1 (<0.1)	1 (<0.1)
Hemorrhage	0	2 (<0.1)

Given that a portion of the follow-up time period of the trial occurred during the global COVID-19 pandemic, an ad hoc analysis was conducted to examine the potential impact of the COVID-19 pandemic on the rate of non-CV deaths before and after 11 March 2020, the date when the WHO declared COVID-19 was a global pandemic. The time period after this date was divided into 2 periods of similar lengths based on the remaining follow-up time in the trial (Table 46). Across the study, rates of non-CV deaths per 100 patient-years were balanced between the bempedoic acid and placebo groups (0.69 and 0.68 per 100 patient-years, respectively). Prior to the pandemic the non-CV deaths occurred at a rate of 0.37 per 100 patient-years in the bempedoic acid group and 0.38 per 100 patient-years in the placebo group. After the start of the pandemic, the rate increased, but remain balanced and ranged from 0.78-0.95 per 100 patient-years in the bempedoic acid group and 0.77-0.99 per 100 patient-years in the placebo group. Similarly, the rate of deaths in the combined categories of infection and pulmonary deaths were low and balanced prior to the pandemic (0.10 per 100 patient-years in both groups) and increased after the start of the pandemic with rates ranging from 0.33-0.58 in the bempedoic acid group and 0.45-0.50 in the placebo group.

Table 46: Risk of Non-cardiovascular Deaths in Relation to Pandemic Periods (Full Analysis Set).

Time Period Type of Death	Bempedoic Acid (N=6992) n (per 100 patient-year)		Placebo (N=6978) n (per 100 patient-year)	
Overall study period	TPY	23,944.66	TPY	23,883.05
Non-CV deaths	165 (0.69)		163 (0.68)	
Infection and pulmonary deaths	81 (0.34)		81 (0.34)	
Period 1: Before 11 March 2020	TPY	8919.27	TPY	8886.08
Non-CV deaths	33 (0.37)		34 (0.38)	
Infection and pulmonary deaths	9 (0.10)		9 (0.10)	
Period 2: 11 March 2020 to 30 June 2021	TPY	8744.72	TPY	8730.17
Non-CV deaths	83 (0.95)		67 (0.77)	
Infection and pulmonary deaths	51 (0.58)		44 (0.50)	
Period 3: On or after 01 July 2021	TPY	6280.67	TPY	6266.80
Non-CV deaths	49 (0.78)		62 (0.99)	
Infection and pulmonary deaths	21 (0.33)		28 (0.45)	

COVID-19 = coronavirus disease 2019; CV = cardiovascular; TPY = total patient-years Note: The overall study follow-up was divided into three periods: Period 1, prior to the onset of the COVID-19 pandemic (11 March, 2020); Period 2, between the onset of the pandemic through the approximate mid-point (30 June, 2021); Period 3,) the rest through the end of study. The total patient years at risk in each period was the sum of the time the patients were alive and in the study in the time period. Note: Ukraine patients are censored at the onset of conflict, 24 February 2022

The impact of the global pandemic on deaths also is reflected by investigator reported preferred terms. As reported by the Investigator, death of any cause occurred in 6.2% and 6.0% of patients in the bempedoic acid and placebo groups, respectively (Table 47). The most common preferred terms reported by the Investigator for events leading to death in the bempedoic acid and placebo groups were death (primarily deaths of unknown cause based on verbatim terms; 1.5% and 1.0%, respectively), COVID-19 pneumonia (0.5% and 0.3%, respectively), and COVID-19 (0.4% and 0.5%, respectively). The high number of deaths (not otherwise specified) may be directly linked to the COVID-19 pandemic, consistent with the high number of undetermined CV deaths that occurred during the pandemic in adjudicated data. These data in combination with the data presented in Table 46 for the adjudicated causes of death reveal that the COVID-19 pandemic had was associated with an increase in the number and type of deaths, but these were balanced between treatments.

Table 47: Summary of Investigator-Reported Events Leading to Death in ≥0.2% of Patients in Either Treatment Group (Safety Analysis Set).

Preferred Term	Bempedoic Acid (N = 7001) n (%)	Placebo (N = 6964) n (%)
Number of Patients Who Died	437 (6.2)	420 (6.0)
Reported Cause of Death		
Death (not otherwise specified)	103 (1.5)	68 (1.0)
COVID-19 pneumonia	34 (0.5)	24 (0.3)
COVID-19	28 (0.4)	33 (0.5)
Sudden cardiac death	18 (0.3)	17 (0.2)
Acute myocardial infarction	13 (0.2)	17 (0.2)
Cardiac arrest	13 (0.2)	16 (0.2)
Cardiac failure	11 (0.2)	16 (0.2)
Cerebrovascular accident	12 (0.2)	12 (0.2)
Myocardial infarction	13 (0.2)	18 (0.3)
Sudden death	6 (0.1)	11 (0.2)

Other Serious Adverse Events

Treatment-emergent SAEs occurring in >0.5% of patients in either treatment group are summarized by PT in Table 48. The overall incidence of SAEs was similar in the bempedoic acid (25.2%) and placebo (24.9%) groups. Additionally, exposure-adjusted patient incidence rate of SAEs was the same between treatment groups (8.9 per 100 patient-years).

The most common SAEs in the bempedoic acid and placebo groups were COVID-19 pneumonia (1.2% and 1.3%, respectively), pneumonia (1.2% in both), atrial fibrillation (1.2% and 1.4%, respectively), osteoarthritis (1.0% in both), COVID-19 (0.8% and 1.1%, respectively), and angina pectoris (0.8% and 1.2%, respectively).

Serious AEs were considered related to IMP in 0.6% and 0.5% of patients in the bempedoic acid and placebo groups, respectively; all related SAEs by PT were reported in <0.1% of patients.

Table 48: Treatment-emergent Serious Adverse Events Occurring in >0.5% of Patients in Either Treatment Group by Preferred Term (Safety Analysis Set).

Preferred Term	Bempedoic Acid (N = 7001) n (%)	Placebo (N = 6964) n (%)
Patients with at least 1 serious TEAE	1767 (25.2)	1733 (24.9)
COVID-19 pneumonia	84 (1.2)	90 (1.3)
Pneumonia	84 (1.2)	81 (1.2)
Atrial fibrillation	81 (1.2)	95 (1.4)
Osteoarthritis	71 (1.0)	69 (1.0)
COVID-19	56 (0.8)	75 (1.1)
Angina pectoris	56 (0.8)	82 (1.2)
Angina unstable	56 (0.8)	53 (0.8)
Non-cardiac chest pain	50 (0.7)	57 (0.8)
Transient ischaemic attack	41 (0.6)	36 (0.5)
Cardiac failure congestive	39 (0.6)	37 (0.5)

Laboratory findings

Haematology

Laboratory Parameters Over Time

For most haematology parameters, there were generally few notable differences between bempedoic acid and placebo in changes from baseline across visits, with the exception of haemoglobin, platelet count, leukocytes, and neutrophils:

- Haemoglobin: Refer to Section 12.2.3.3.2 for discussion of changes in haemoglobin, haematocrit, and erythrocyte values.
- Platelet count: In both the bempedoic acid and placebo groups there was an initial increase in platelet count (mean [percent] change of 19.2 × 103/µL [9.0%] and 2.1 × 103/µL [2.0%], respectively) at Month 3 from a baseline value of 245 × 103/µL in both groups. Platelet count remained stable at or near the Month 3 level through Month 36 (mean [percent] change of 25.2 × 103/µL [11.8%] and 7.0 × 103/µL [4.2%] in the bempedoic acid and placebo groups, respectively at Month 36). These trends were consistent based on on-treatment analysis.
    - Almost 19% of patients in the bempedoic acid group (1304, 18.6%) had an increase from baseline in platelet count of >100 × 103/µL compared with approximately 10% of patients in the placebo group (712 patients, 10.2%.
    - The incidence of AEs related to platelet count was similar across treatment groups, including thrombocytopenia (0.3% and 0.4% in the bempedoic acid and placebo groups, respectively), platelet count decreased (0.1% in both treatment groups), and platelet count increased (≤0.1% in both treatment groups;
- Leukocytes: At Month 3, there was an initial decrease in leukocyte count in the bempedoic acid group, with an increase observed in the placebo group (mean [percent] change from baseline of -0.23 × 103/µL [-1.43%] and 0.01 × 103/µL [2.40%], respectively) from a baseline value of 6.8 × 103/µL in both groups. Over time, mean percent changes in leukocyte values in the bempedoic acid group were generally negligible (mean [percent] change from baseline of -0.23 × 103/µL [-1.11%], -0.10 × 103/µL [0.88%], and -0.20 × 103/µL [-0.48%] at Months 12, 24, and 36, respectively), while patients in the placebo group experienced mean percent increases of 2% to 4% (2.98% at Month 36); a net treatment differential of 3.46% was noted at Month 36. These trends were consistent based on on-treatment analysis.
    - The incidence of related AEs was similar across treatment groups, including in the overall SOC of infection and infestations (43.5% and 44.3% in the bempedoic acid and placebo groups, respectively; Table 14.3.1.2.1A). There were no notable differences in PTs within this SOC between treatment groups. The incidence was also similar across treatment groups in leukopenia (0.2% and 0.3% in the bempedoic acid and placebo groups, respectively), leukocytosis (0.2% and 0.3% in the bempedoic acid and placebo groups, respectively).
    - Among patients with normal baseline leukocyte values, a larger proportion of those in the bempedoic acid group compared with the placebo group (650 patients, 9.3% and 473 patients, 6.8%, respectively) had decreases to <4 × 103/µL.
- Neutrophils: Changes from baseline in neutrophil values were similar in pattern to those observed for leukocytes. At Month 3, there were mean percent changes of -0.42% and 5.0% for the bempedoic acid and placebo groups, respectively, from baseline levels of 4.097 × 103/µL and

4.096 × 103/µL, respectively. The treatment differential was stable through Month 36 (2.48% and 7.33%, respectively). These trends were consistent based on on-treatment analysis.

- The incidence of related AEs was similar across treatment groups, including neutropenia (0.5% and 0.3% in the bempedoic acid and placebo groups, respectively), neutrophil count decreased (0.4% and 0.3% in the bempedoic acid and placebo groups, respectively), and neutrophil count increased (<0.1% in both treatment groups).

Chemistry

Laboratory Parameters Over Time

For most chemistry parameters, including electrolytes, there were generally no notable differences between bempedoic acid and placebo in changes from baseline to Months 12, 24, and 36. Notable differences were observed, however, between the 2 treatment groups in the change from baseline for the parameters of creatinine, BUN, uric acid, eGFR, alkaline phosphatase, ALT, and AST and are discussed earlier.

Vital signs

There were no clinically significant abnormal shifts in ECG measurements from baseline to EOS.

Treatment-emergent AEs related to vital signs occurred in a similar proportion of patients in the bempedoic acid and placebo groups, including hypertension (11.0 % and 11.8%, respectively), dyspnoea (3.2% and 3.3%, respectively), and hypotension (1.5% and 1.6%, respectively). Incidence of SAEs related to vital signs was also similar between treatment groups and generally occurred in ≤1% of patients.

Notable decreases in weight were observed among patients with a baseline BMI ≥30 kg/m2 in the bempedoic acid group. Mean (SD) baseline weight in the bempedoic acid and placebo groups was 96.16 (15.325) and 96.49 (15.415) kg, respectively. Over time, weight among patients in the bempedoic acid group decreased incrementally, while smaller changes were observed in the placebo group. At Month 36, the change from baseline in mean (SD) weight was -2.28 (6.271) and -1.37 (6.131) kg, respectively.

Treatment-emergent findings were reported as adverse events as appropriate.

Safety in special populations

The incidence of AEs by subgroup was similar to that observed in the overall patient population and in each treatment group.

Demographic Characteristics

There were no meaningful differences in the incidence of TEAEs across subgroup categories by age, sex, or race. Results were generally consistent when patient exposure was considered. It was notable that in the 15.1% of patients ≥75 years of age, there were no overall differences in safety between treatment groups, similar to patients <65 and 65 to 75 years of age.

Baseline eGFR Category

The overall incidence of TEAEs was generally similar between treatment groups across eGFR categories, with a treatment differential of ≤2% between the bempedoic acid and placebo groups. Incidence rates of AESIs within the renal impairment category were numerically higher in the bempedoic acid group compared with the placebo group; however, the differential was consistent across eGFR categories as well as the overall population.

Baseline Glycaemic Status

The incidence of TEAEs was similar across the baseline glycaemic status categories of normoglycaemic , prediabetes, and diabetes. In each subgroup category and between treatment groups >80% of patients experienced at least 1 TEAE. The incidence of TEAEs was generally similar between treatment groups in the patients with diabetes and those without diabetes at baseline. There were no noteworthy differences across baseline diabetes status in the various analyses of AEs.

Baseline Ezetimibe Use

There were 1612 patients (806 patients in each treatment group) or 11.5% of the overall patient population who received baseline ezetimibe. The incidence of TEAEs in patients with baseline ezetimibe use was similar to the overall patient population and between treatment groups (89.8% in each). In addition, SAEs and AEs leading to discontinuation, as well as investigator-reported deaths among patients with baseline ezetimibe use occurred in a similar percentage of patients in the bempedoic acid and placebo groups. Similar to what was observed in the overall patient population, regarding TEAEs occurring in >10% of patients in either treatment group, hyperuricemia, and blood uric acid increased were the only events with a treatment differential >1% (bempedoic acid > placebo). The incidence of AESIs in patients with background ezetimibe use was generally similar to the overall patient population with the exception of the following categories:

- A higher proportion of patients with baseline ezetimibe use experienced muscular safety AESIs (22.5% bempedoic acid, 23.2% placebo) than the overall patient population (15.2% bempedoic acid, 15.6% placebo).
- The incidence of atrial fibrillation in patients with baseline ezetimibe use (5.3% bempedoic acid group, 4.0% placebo) was higher than in the overall patient population (3.3% bempedoic acid, 3.5% placebo).
- A higher proportion of patients with baseline ezetimibe use experienced tendinopathies (3.7% bempedoic acid, 2.5% placebo) than the overall patient population (1.7% bempedoic acid, 1.8% placebo).
- The incidence of malignancies was higher in patients with baseline ezetimibe use (6.2% bempedoic acid, 8.7% placebo) than in the overall patient population (4.6% bempedoic acid, 4.9% placebo).

In general, the incidence of AESIs in these categories among patients with baseline ezetimibe use were similar between the bempedoic acid and placebo groups.

The safety profile of bempedoic acid in patients receiving ezetimibe at baseline was similar to that observed in the overall patient population (SAS), which is also consistent with data from the Phase 3 primary hyperlipidaemia studies. When making comparisons of AE rates with the overall study population, however, caution should be taken because of the smaller number of patients who were receiving ezetimibe at baseline.

Other Observations Related to Safety

Beyond the previously described changes in creatinine, BUN, uric acid, and haemoglobin, changes were also observed in platelets (increases) and leukocytes (decreases). These changes are known to occur during treatment with bempedoic acid and are consistent with those observed in the Phase 3 primary hyperlipidaemia studies. None of these changes in laboratory parameters were associated with meaningful clinical consequences. Other safety assessments revealed no notable treatment-related findings in vital signs, ECGs, or physical examinations, with the exception of a modest reduction in body

weight in patients in the bempedoic acid group compared with those in the placebo group (-2.28 vs -1.37 kg at Month 36) among patients in the bempedoic acid group with a baseline BMI of ≥30 kg/m2.

Overall, there were no safety signals associated with the laboratory parameters noted above or with vital signs, ECGs, or physical examinations.

Pregnancy and Lactation

At present, there are no data available regarding the presence of bempedoic acid in human milk, the effects on the breastfed infant, or the effects on milk production. The Sponsor is currently evaluating the effect of bempedoic acid during pregnancy in an ongoing worldwide descriptive study. A lactation study is planned, but no patients are enrolled to date. Bempedoic acid should be discontinued as soon as pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the foetus. There are no significant data available on use of bempedoic acid in pregnant women. Because bempedoic acid decreases cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, and cholesterol and cholesterol derivatives are needed for normal foetal development, bempedoic acid may cause foetal harm when administered to pregnant women.

Discontinuation due to adverse events

Table 49 summarizes TEAEs that led to discontinuation of IMP that occurred in >0.2% of patients. The only event that led to discontinuation of IMP in >0.5% of patients was myalgia, which led to discontinuation in a similar proportion of patients in the bempedoic acid (1.8%) and placebo (1.9%) groups. Discrepancies were noted between the disposition data and AEs leading to discontinuation of IMP, with respect to the number of patients who discontinued treatment due to AEs.

- Three patients (1 in bempedoic acid group, 2 in placebo group) who reported discontinuing treatment due to AEs based on the disposition data did not have events with an action of drug withdrawn reported in the AE data. Upon further review of the disposition data, the reason for treatment discontinuation for all 3 patients was AE due to pandemic. The patients had corresponding AEs of COVID-19; however, the action with IMP was drug interrupted.
- Four patients (3 in the bempedoic acid group and 1 in the placebo group) had 1 or more TEAE with action of drug withdrawn in the AE data. These patients also reported discontinuing due to AE in the disposition data; however, the End of Treatment CRFs were linked to other non-treatment emergent AEs and thus would not appear in the summary table of TEAEs leading to discontinuation.
- Based on the 51 events leading to death inadvertently residing in the AE dataset:
    - For 13 patients, TEAEs that led to discontinuation were determined to be the events leading to death that had been inadvertently reported as AEs.

Table 49: Treatment-emergent Adverse Events that Led to Discontinuation of IMP Reported in >0.2% of Patients in Either Treatment Group by Preferred Term (Safety Analysis Set).

Preferred Term	Bempedoic Acid (N = 7001) n (%)	Placebo (N = 6964) n (%)
Patients with any TEAE leading to IMP discontinuation	759 (10.8)	722 (10.4)
Myalgia	124 (1.8)	129 (1.9)
Pain in extremity	35 (0.5)	31 (0.4)
Arthralgia	31 (0.4)	39 (0.6)
Muscle spasms	31 (0.4)	49 (0.7)
Headache	22 (0.3)	9 (0.1)
Diarrhoea	18 (0.3)	16 (0.2)
Dyspepsia	18 (0.3)	15 (0.2)

Patients on Baseline Ezetimibe Use.

In the subgroup of patients in the bempedoic acid and placebo groups with baseline ezetimibe use, 14.8% and 13.5% of patients experienced a TEAE that led to IMP discontinuation. There were no events with >1% differential between treatments. Myalgia was the most frequent event that led to discontinuation of IMP, occurring in 3.2% of patients in the with bempedoic acid group compared to 2.2% of the placebo group. Investigator-reported events of death for patients with baseline ezetimibe use were generally similar to the overall population.

Post marketing experience

Bempedoic acid (Nexletol) and bempedoic acid/ezetimibe (FCMP; Nexlizet) were authorized for marketing in the US in 2020 as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or established ASCVD who require additional lowering of LDLC. In the EU and UK, bempedoic acid (Nilemdo) and bempedoic acid/ezetimibe (FCMP; Nustendi, 2020) were authorized for marketing in 2020. Both bempedoic acid and the FCMP drug product have also been approved in Switzerland (2020), Turkey (2023), and Hong Kong (2023).

Pharmacovigilance and Risk Management

Since the first launch of Nexletol/Nilemdo and Nexlizet/Nustendi, the cumulative exposure from marketing experience from 21 February 2020 to 20 February 2023 was approximately 160,698 and 198,739 patients, respectively (PSUR/PBRER 11 April 2023). The safety of bempedoic acid has been further characterized from postmarketing data; the recent PSUR/PBRER 11 April 2023 did not identify any new significant safety concerns and the safety data were found to be consistent with the known safety profile of the drug. Cumulatively, the most frequently reported serious ADRs have been gout, arthralgia, myalgia, and pain in extremity. Bempedoic acid exhibits an acceptable safety profile with adequate mitigation measures for the potential risks of myopathy with concomitant use with statins, gout, and for the missing information on use in severe end-stage renal disease. The overall benefit-risk profile for bempedoic acid continues to remain positive.

In December 2022 and January 2023, respectively, the FDA notified the Sponsor that rhabdomyolysis and hypersensitivity had been identified as potential newly identified safety signals (NISS). The FDA classified rhabdomyolysis and hypersensitivity as potential risks. On 12 May 2023, the FDA notified the Sponsor that the adverse reaction of hypersensitivity has been identified during postapproval use of Nexletol and Nexlizet. Consequently, the FDA proposed changes to the postmarketing experience section of the

approved labels with the change being effective immediately on submission. The Sponsor is evaluating the notification and will update the labels accordingly within the timeframe provided. Further, at the time of preparation of this Module 2.5 addendum, no other action had been taken by the FDA or the Sponsor in response to the available data. However, potential risks will be monitored and evaluated, and labelling changes will be implemented as appropriate.

The current risk mitigation measures and pharmacovigilance activities outlined in the Bempedoic Acid Risk Management Plan are sufficient to manage potential safety concerns of bempedoic acid. There are no changes to the known adverse reactions for bempedoic acid; minor data updates to Section 4.8 of the Summary of Product Characteristics based on data from CLEAR Outcomes are summarized in Section 7.2.

2.5.1. Discussion on clinical safety

The Safety Analysis Set (SAS) included all randomized patients who received at least 1 dose of double-blind IMP (n = 13,965). Patients (n=7001) were treated for a mean (SD) of 2.9 years with bempedoic acid with 6106 (88%) patients exposed for ≥12 months, 5521 (79%) patients for ≥2 years, 4009 (59%) for ≥3 years, and 966 (14%) for ≥4 years, and 21 (0.3%) patients for ≥5 years. The **exposure** of patients with baseline ezetimibe use was largely similar with 3.1 years (range: 0.0-5.3 years). The extend of exposure within the study is substantially longer than previously done in the original MAA. There was no meaningful difference in exposure between the treatment and placebo groups, which is encouraging. Almost 90% of the patients with baseline ezetimibe reported to continue combined treatment until the end of the study.

Treatment-emergent adverse events (TEAEs) were commonly reported, but were approximately similar between bempedoic acid and placebo treatment (86% vs 85%). Also no relevant differences in severity of TEAEs were reported. The **most common TEAEs** in the bempedoic acid and placebo groups were COVID-19 (11.2% and 12.5%, respectively), hypertension (11.0% and 11.8%, respectively), hyperuricaemia (10.9% and 5.6%, respectively). The imbalance of hyperuricaemia is known as an ADR for bempedoic acid. Apart from the COVID-19 events, outcomes were similar as seen in the original dossier.
Further, similarly to the general population, the incidence of TEAEs in patients with baseline ezetimibe use was the same in the bempedoic acid and placebo groups (89.8% in both). Most commonly reported AEs included hypertension (13.3% and 14.4%, respectively), arthralgia (12.3% and 10.5%, respectively), COVID-19 (11.8% and 14.1%, respectively), and myalgia (9.6% and 11.3%, respectively).

Special attention has been given to certain **AEs of interest** including hepatic events, muscular safety events, new-onset diabetes/hypoglycaemia, neurocognitive disorders, hypoglycaemia (and associated metabolic acidosis), renal disorders, uric acid increases/gout, and decreased haemoglobin, as was also done within the earlier MAA.
Regarding the **hepatic events**, the overall incidence of hepatic enzyme laboratory abnormalities was slightly higher in the bempedoic acid group (5.8%) compared with placebo group (4.7%), which is expected, with ALT increased (2.4%) vs 1.9%) and AST increased (2.8% vs 1.4%) being higher. ALT and/or AST > 3 x ULN elevation occurred in 1.6% vs 1.0%, while no large difference in cases of potential Hy's Law were observed ((n=8 (0.1%) vs n=7 (0.1%)). The overall incidence of TEAEs related to hepatic biochemical parameters was 4.5% in the bempedoic acid group compared with 3.0% in the placebo group. The majority of events were mild or moderate in severity and not related to IMP. According to these data no new relevant information on hepatic safety could be identified. Hepatic enzyme elevations are known and currently appropriately covered within sections 4.4 and 4.8 of the SmPC.
Regarding **cholelithiasis**, 2.2% of patients in the bempedoic acid group compared with 1.2% of patients in the placebo group reported cholelithiasis. This imbalance was also seen in the serious AEs (SAEs). Further, a numerical difference exists in CLEAR Outcomes for the incidence of cholelithiasis with 0.8 and

0.4 per 100 patient years for bempedoic acid and placebo, respectively. However, the incidence of AEs related to complications of cholelithiasis was generally similar between the treatment groups, which is reassuring. Also, among patients who were receiving ezetimibe at baseline, cholelithiasis was the TEAE with a treatment differential >1% in the bempedoic acid and placebo groups (3.1% and 2.0%, respectively). Cholelithiasis is currently covered as an ADR in the SmPC. No further safety concerns could be revealed from these data.

Muscular disorders were observed at a comparable frequency between bempedoic acid and placebo (15.2% vs 15.6%). The incidence of AEs related to muscular safety was comparable between treatment groups (15.0% bempedoic acid and 15.4% placebo). The most commonly reported events in the bempedoic acid and placebo groups were myalgia (5.6% and 6.8%, respectively), pain in extremity (4.2% and 4.3%, respectively), muscle spasms (3.9% and 3.4%, respectively), and blood creatine phosphokinase increased (2.3% and 2.0%, respectively), which showed no increase or treatment discontinuation according to specific definition of muscular disorders. Also, levels of > 5x ULN or > 10 x ULN were rarely observed with no clear imbalance (i.e. 0.6% in each group). However, among patients in the bempedoic acid and placebo groups who received ezetimibe at baseline, 14.8% and 13.5%, respectively, experienced a TEAE leading to discontinuation of IMP. Myalgia was the only event that led to discontinuation of IMP in >1% of patients treated with bempedoic acid (3.2%) or placebo (2.2%). Myalgia/rhabdomyolysis is currently covered as an ADR in the SmPC. No further safety concerns could be revealed from these data.

Regarding **new-onset diabetes**, overall, among patients with baseline glycaemic status of no diabetes, 16.1% (621/3856 patients) of the bempedoic acid group and 17.1% (640/3740 patients) of the placebo group met any AESI criteria for new onset diabetes. Also, no differences in frequency has been identified across subgroups of baseline glycaemic status. Further, no imbalances were seen in adverse events potentially related to diabetes in the difference groups and subgroups. Further support for a likely absence of an effect on diabetes with bempedoic acid comes from data on the abnormalities in HbA1c and fasting glucose, which showed no imbalance in these parameters for bempedoic acid. Also no worsening of hyperglycaemia was demonstrated, as the percentage of patients experiencing any AESI of worsening of hyperglycaemia was similar between treatment groups among patients with baseline glycaemic status of diabetes (22.7% vs 23.1% in the bempedoic acid and placebo groups, respectively) and among patients with inadequately-controlled diabetes (32.6% in both treatment groups).

Also the occurrence of **hypoglycaemia associated with metabolic acidosis** was assessed and did not show any new relevant safety concerns, as a similar frequency of patients experienced any hypoglycaemia related events (4.3% in bempedoic acid patients vs 3.8% in placebo patients) and with a similar incidence of AEs related to acidosis between treatment groups (13 and 11 patients in the bempedoic acid and placebo groups, respectively; 0.2% of both).

Regarding **renal impairment**, more patients in the bempedoic acid group (3765 patients, 53.8%) experienced an abnormality related to AESI defined renal laboratory parameters compared with patients in the placebo group (2978 patients; 42.8%). Data in the original dossier were limited. No further safety concerns could have been revealed from these data.

Neurocognitive disorders were rarely observed with no large differences between groups (0.8% in bempedoic acid vs 1.0% in placebo). No new relevant safety concern have been derived from these data. Further, AEs of atrial fibrillation were similarly seen in both treatment groups (3.3% vs 3.5%). No trend could be identified from these data.

No imbalances in frequencies have been reported for the occurrence of **tendinopathy** related AEs with 1.7% patients in the bempedoic acid group and 1.8% in the placebo group. Similar findings were seen for tendon rupture in 24 (0.3%) patients in the bempedoic acid group and in 19 (0.3%) patients in the placebo group. No trend or pattern could be associated with the use of bempedoic acid.

Also, no effect on **malignancies** were seen between the bempedoic acid (4.6%) and placebo (4.9%) groups, also when this was substantiated by most common malignancies. No new relevant safety concern could have been revealed from these data.

Also no differences in **COVID-19 infections** were identified between groups, also when assessing the severity, SAEs and related AEs.
However, based on increases in mean serum uric acid levels observed in patients who received bempedoic acid in previous studies, **uric acid increases** and events of **gout** and gouty arthritis were examined. There was seen an imbalance in shifts from low/normal uric acid at baseline to maximum levels that were >ULN with 3143 (64.9%) of 7001 patients in the bempedoic acid group and for 1819 (37.9%) of 6964 patients in the placebo group. Also, treatment-emergent AEs of hyperuricemia occurred in a higher percentage of patients in the bempedoic acid group (16.4%) than in the placebo group (8.2%), which included events of hyperuricemia (10.9% and 5.6%, respectively) and blood uric acid increased (5.6% and 2.7%, respectively). Further the incidence of gout was slightly higher in the bempedoic acid group with 3.1% vs 2.1% in the placebo group. But the worsening of increases in uric acid did not worsen over time. A warning on uric acid increases and gout symptoms is currently appropriately mentioned in the SmPC of Nustendi. Further, gout is an ADR. No new relevant safety concerns could have been revealed from the information provided.
Similar to the findings in the phase 3 studies, an increased frequency of **anaemia** was seen 332 (4.7%) patients in the bempedoic acid group and 272 (3.9%) patients in the placebo group. The level of **decreases in haemoglobin** from baseline was mostly limited to ≥2 g/dL and <LLN and ≥3 g/dL and <LLN with 755 patients, 10.8% and 350 patients, 5.0%, respectively, in the bempedoic acid group, compared with the placebo group (517 patients, 7.4% and 248 patients, 3.6%, respectively). No new significant findings on haemoglobin decreases have been seen with these data, as this has already been assessed as an ADR in the original dossier.

Serious adverse events (SAEs) were reported at comparable frequency (25.2% vs 24.9%) confirming previous findings in the initial MAA. The most frequently reported SAEs were COVID-19 pneumonia (1.2% and 1.3%, respectively), pneumonia (1.2% in each), atrial fibrillation (1.2% and 1.4%, respectively), osteoarthritis (1.0% in each), COVID-19 (0.8% and 1.1%, respectively), and angina pectoris (0.8% and 1.2%, respectively), all at comparable frequencies. Apart from the COVID-19 related events, no new significant changes in SAEs were seen with the data from this long-term outcome study, and data also generally in line with the findings from the original dossier, which is re-assuring. The incidence of SAEs in patients with baseline ezetimibe was higher and largely in line with the data from the general population.
Regarding **death**, a similar frequency of non-CV deaths was reported with bempedoic acid (2.3% vs 2.4). Most non-CV deaths in the bempedoic acid and placebo groups were related to infections (1.1% and 1.0%, respectively) and malignancy (0.8% and 0.7%, respectively). An ad hoc analysis on the impact of COVID-19 demonstrated an increased rate from 0.37 to 0.78-0.95 per 100 patient-years in the bempedoic acid group and from 0.38 to 0.77-0.99 per 100 patient-years in the placebo group, although no imbalance between groups was observed.

No notable differences between the two treatment groups have been observed in **haematology and biochemistry**, other than discussed earlier within this AR.

No meaningful differences were observed in **vital signs** including blood pressure. However, a notable decrease in weight was observed in patients on bempedoic acid, as compared to the placebo group in patients with a high BMI. At Month 36, the change from baseline in mean (SD) weight was -2.28 (6.271) and -1.37 (6.131) kg, respectively, in patients with a BMI >30. Since weight loss has been observed associated with higher BMI in patients over time and since this AE could be explained by the mechanism of action of the active substance of bempedoic acid, the applicant was requested to include weight loss as an ADR in section 4.8 of the SmPC.

In general, there were no meaningful differences in the incidence of TEAEs across **subgroup** categories by age, sex, or race, eGFR category, baseline glycaemic status and patients on baseline ezetimibe use.

Bempedoic acid was relatively well tolerated with 10.8% vs 10.4% on placebo who discontinued due to a TEAE. The highest frequency of **discontinuations** was due to myalgia in the bempedoic acid (1.8%) and placebo (1.9%) groups. No discrepancies between groups, and also not in the subgroup of patients on baseline ezetimibe use, have been observed in the discontinuations.

Regarding **post-marketing safety data**, data in the latest PSUR presented that the cumulative exposure of Nustendi from marketing experience from 21 February 2020 to 20 February 2023 was approximately 198,739 patients. No new significant safety concerns have been identified from these data.

2.5.2. Conclusions on clinical safety

With the presentation of safety data of the current CLEAR Outcomes study 1002-043, the placebo-controlled safety data for bempedoic acid have been extensively increased with a mean exposure of 2.9 years. Bempedoic acid, also together with ezetimibe, was generally well tolerated with 10.8% vs 10.4% on placebo, who discontinued due to a TEAE. The most common TEAEs were COVID-19, hypertension, hyperuricaemia, and arthralgia. Safety data, also the AEs of special interest, were generally in line with those observed in the original dossier. No new relevant safety concerns have been observed with the use of bempedoic acid. Although the data on patient with baseline ezetimibe use were limited, no new relevant safety concerns could be revealed.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 5.0 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 5.0 with the following content:

Safety concerns

Table 50: Summary of the Safety Concerns

Important identified risks	Not applicable
Important potential risks	Not applicable
Missing information	Use in patients with severe renal impairment and in patients with ESRD receiving dialysis

Pharmacovigilance plan

Table 51: Summary Table of Additional Pharmacovigilance Activities

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1: Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorization				
Not applicable				
Category 2: Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3: Required additional pharmacovigilance activities				
Effects of ESRD and ESRD requiring dialysis on the PK of bempedoic acid (Study 1002-071) Planned	To characterize the PK of ETC-1002, ESP15228, and ETC-1002-glucuronide in subjects with normal renal function, ESRD, and ESRD requiring dialysis following single-dose bempedoic acid administration.	Safety concern addressed: use in patients with severe renal impairment and in patients with ESRD receiving dialysis (note: only part of the safety concern, patients with severe ESRD and ESRD requiring dialysis, is addressed by this study)	Protocol final: Study completion: Final CSR:	Completed Q4 2023 Q2 2024

Risk minimisation measures

Table 52: Summary of Risk Minimization Measures

Safety Concern	Risk Minimization Measures
Important Identified Risks	
Not applicable	
Important Potential Risks	
Not applicable	

Safety Concern	Risk Minimization Measures
Missing Information (continued)	
Use in patients with severe renal impairment and patients with ESRD receiving dialysis (bempedoic acid)	Routine risk minimization measures: SmPC Section 4.2 and 5.2 PIL Section 2 Additional risk minimization measures: None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are being updated to incorporate the data of the CLEAR Outcomes trial. The Package Leaflet has been updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- In accordance with articles 59(3) and 61(1) of Directive 2001/83/EC, the marketing authorisation holder (MAH) completed a full user test of the PL during the review of the initial Marketing Authorisation Application (MAA) for Nustendi in 2020 (EMEA/H/C/004959/0000) which received positive feedback.
- The target patient population remains unchanged with the proposed indication, and the updates to the package leaflet are consistent with other lipid modifying therapies (LMTs).
- The posology and method of administration remains unchanged for the proposed PL.

- The updates to the PL, including the safety sections, are not significant and utilise well recognised lay terms.
- Furthermore, the PL will be kept identical in format size, colours, layout/design as illustrated in the agreed mock-ups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The extension of the therapeutic indication of Nustendi (bempedoic acid and ezetimibe 180/10 mg) proposed by the MAH at initial submission was:

"Cardiovascular disease

Nustendi is indicated in adults with established or at high risk for atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

- *in combination with a statin with or without other lipid-lowering therapies in patients previously treated with a statin and ezetimibe or,*
- *alone or in combination with other lipid-lowering therapies in patients who are either statin-intolerant, or for whom a statin is contraindicated, and previously treated with ezetimibe alone,*
- *in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without statin.*

For study results with respect to effects on LDL-C, cardiovascular events and populations studied see section 5.1."

Atherosclerotic **cardiovascular disease** (ASCVD), which includes coronary heart disease, cerebrovascular disease, and peripheral artery disease (PAD), is the most common form of CVD. Ischemic heart disease and ischemic stroke jointly account for more than half of all CVD deaths.

Elevated **low-density lipoprotein cholesterol** (LDL-C) is a major modifiable risk factor that plays a central role in the initiation and progression of ASCVD. The accumulation of low-density lipoprotein (LDL) particles in the artery wall is a central event in the initiation and continued progression of ASCVD. Randomized controlled trials have unequivocally demonstrated that lowering LDL-C with statins and other therapies that reduce LDL-C through the LDL receptor reduces CV events in both primary and secondary prevention patients.

Bempedoic acid is an oral, first-in class, small molecule that inhibits adenosine triphosphate-citrate lyase (ACL) in the cholesterol biosynthesis pathway, resulting in decreased hepatic cholesterol synthesis, an increase in low-density lipoprotein (LDL)-receptors, and reduction in circulating LDL-C.

Ezetimibe's molecular target is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and phytosterols. This causes a reduction of hepatic cholesterol stores and an increase in LDL receptors, resulting in clearance of cholesterol from the blood.

The initial approval of bempedoic acid with ezetimibe was based on significant reduction of LDL-C, a validated surrogate marker for CV risk reduction, compared with placebo, and did not include studies designed to evaluate the effect of bempedoic acid on CV outcomes.

With submission of current cardiovascular outcomes trial (CVOT), the applicant claims to demonstrate CV risk reduction with the use of bempedoic acid and ezetimibe. This may be used alone (without requirement of a background statin) or in combination with other LMTs in order to achieve LDL-C-lowering goals in patients who are either statin-intolerant or for whom a statin is contraindicated, and are unable to reach LDL-C goals with ezetimibe alone (*add-on indication*), or in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets (*substitution indication*) with or without a statin.

3.1.2. Available therapies and unmet medical need

There are 3 categories of lipid-lowering drugs that are registered for the prevention of CV risk including statins (HMG CoA reductase inhibitors), ezetimibe (inhibitor of the intestinal absorption of cholesterol and related plant sterols), and PCSK9 inhibitors.

Statins are the cornerstone therapy in CVD prevention. Although they are considered as the gold-standard for CV risk prevention in clinical guidelines, a need exists for additional therapies for LDL-C lowering and CVD prevention, because some patients who are already receiving a maximum tolerated dose of a statin still have a residual CVD risk due to high baseline LDL-C or limitations in statin tolerability. It is well known that some patients suffer from statin side effects (eg, myalgia) that limit their ability to take a statin or a high enough dose of statin to reach their LDL-C goal. Statin-intolerant patients are at higher risk of not achieving target LDL-C levels appropriate to their level of CV risk given that non-statin therapies, other than PCSK9 inhibitors, typically provide only about a 15-20% reduction in LDL-C.

Ezetimibe is also registered in several countries to reduce the risk of CV events in adult patients with CHD and a history of ACS when added to ongoing statin therapy or initiated concomitantly with a statin. In clinical guidelines ezetimibe is recommended to be used as second-line therapy in association with statins when the therapeutic goal is not achieved at the maximal tolerated statin dose or in patients intolerant to statins or with contraindications to these drugs, although the absolute benefit from adding ezetimibe may be limited in line with its modest effect.

Other available therapies could include **PCSK9 inhibitors** which have also demonstrated CV benefit in established CVD. PCSK9 inhibitors are, however, not widely used (<5% of lipid lowering treatment) which may be (partly) due to its formulation, as it should be administered by injection (every 2 or 4 weeks) instead of orally, which may either be perceived as an advantage or a limitation depending on the patients preferences.

Although **fibrates**, omega-3 fatty acids, and bile acid sequestrants may provide reduction of some lipid parameters including moderate reductions in LDL-C , cardiovascular benefits of these products have not been demonstrated.

The use of **bempedoic acid with ezetimibe** as treatment to other lipid modifying therapies, including maximally tolerated statins, and/or in patients who are SI could potentially provide an additional tool in the armamentarium to reduce CVD.

3.1.3. Main clinical studies

Within this variation procedure the efficacy and safety results from **Study 1002-043**, known as the **CLEAR Outcomes trial**, have been submitted.

The CLEAR Outcomes trial was a multi-centre randomised, two-arm double-blind, placebo-controlled, event-driven trial, which includes a comparison of bempedoic acid with placebo in patients with CVD. The study had a minimum duration of 24 months. In total 13,970 patients (n=6992 on bempedoic acid and

n=6978 on placebo) were randomized of which 1612 (12%) patients were on baseline ezetimibe use (n=803 on bempedoic acid and n=809 on placebo). Key inclusion criteria were CVD patients with a history of statin intolerance who were identified to have, or be at high risk for, CVD with a fasting LDL-C ≥ 100 mg/dL (2.6 mmol/L) while taking stable and optimized background LDL-C-lowering therapies which could include very low dose statin treatment. The **primary endpoint** analysis consisted of demonstration of superiority of bempedoic acid over placebo in reduction in time to first occurrence of a 4-composite MACE endpoint, defined as CV death, nonfatal MI, nonfatal stroke, or coronary revascularization. The **key secondary endpoints** evaluated reduction in time to first occurrence of a 3-composite MACE endpoint (consisting of CV death, nonfatal MI, nonfatal stroke), fatal + nonfatal MI, coronary revascularization, fatal + nonfatal stroke, CV death and all-cause mortality, according to hierarchical testing. Also **lipid lowering reduction** was evaluated.

The requested variation proposed amendments in section 4.1, 4.8 and 5.1 to the SmPC. The PL is proposed to be updated accordingly.

3.2. Favourable effects

In the CLEAR Outcomes Trial, **the primary composite endpoint was met**, as the difference of a reduction in time of a first occurrence of a **MACE-4** (i.e. CV death, nonfatal MI, nonfatal stroke, or coronary revascularization) was statistically significant with a HR of 0.87 (95% CI: 0.79, 0.96; p = 0.0037), when bempedoic acid (n=819; 11.7%) was compared with placebo (n=927; 13.3%). This translated in an absolute risk reduction of approximately 1.6% for the mean study period of 2.9 years for the primary endpoint.
The 4 **sensitivity analyses** also demonstrated a statistically significant beneficial treatment effect on MACE-4 with the use of bempedoic acid. The primary endpoint demonstrated a consistent beneficial effect across a wide range of **subgroups**, such as demographics, and status of with or without background statin use and with or without background ezetimibe use. Further, both CV risk categories showed a beneficial effect for bempedoic acid, although the effect was more pronounced in the primary prevention category at high risk for atherosclerotic cardiovascular disease.

The primary endpoint was further supported by the hierarchical testing of **key secondary composite endpoints** of a statistically significant risk reduction of fatal and nonfatal MI (HR: 0.77; 95% CI: 0.66, 0.91; p = 0.0016) and coronary revascularization (HR: 0.81; 95% CI: 0.72, 0.92; p = 0.0013). Further, a trend in reduction was observed for fatal and nonfatal stroke (HR: 0.85; 95% CI: 0.67, 1.07; p = 0.1593).
Also, the effect on the risk of MACE-4 in the subgroup of patients with baseline ezetimibe use compared to placebo seems to point towards the same direction with a HR of 0.94 (95% CI: 0.74, 1.20).

Treatment with bempedoic acid, as compared to placebo, was also associated with a statistically significant reduction in the risk of the (regulatory preferred) **MACE-3** (i.e. CV death, nonfatal MI, nonfatal stroke; HR: 0.85; 95% CI: 0.76, 0.96; p = 0.0058), with consistent findings in the sensitivity and most of the subgroup analyses.

Also, the **other secondary and tertiary endpoints** of all-cause mortality + MI + stroke + coronary revascularization, MACE-5, non-fatal MI, non-fatal stroke, fatal+non-fatal non-haemorrhagic stroke and hospitalization for unstable angina showed a reduction in risk, supporting the primary composite endpoint.

The **lipid lowering reduction** was also evaluated and showed a placebo-corrected decrease of -20.3% (95% CI: -21.1%, -19.5%; p <0.0001) at month 6 on LDL-C from a mean baseline level of 139 mg/dL (3.60 mmol/L). A similar effect was seen for patients with baseline ezetimibe use. The on-treatment

effect of LDL-C lowering was maintained throughout the study. Treatment resulted in similar patterns on **HDL-C, non-HDL-C and TC** that were consistent with changes observed for LDL-C.

3.3. Uncertainties and limitations about favourable effects

The fixed combination medicinal product (**FCMP**) of **bempedoic acid 180 mg with ezetimibe 10 mg** has not been specifically evaluated for CV risk reduction as compared to either of the components or placebo. The FCMP was not used as study treatment, the study was not powered for the evaluation of efficacy and safety of the FCMP and an analysis plan was lacking for patients on bempedoic acid and ezetimibe. Only, ezetimibe was used in a limited number of patients at baseline (12%), but almost 90% of patients on ezetimibe use at baseline reported use of ezetimibe at the end of the study.

Despite an elevated LDL-C and suboptimal or absence of statin therapy, included patients appear not to be on optimal lipid-lowering therapy (LLT), as relative low numbers were treated with other LLT known to reduce CV risk (only approximately 10% received ezetimibe and very low numbers were on PCSK-9 inhibitors), but this is consistent with findings in other studies.

The observed effect of the primary endpoint in the relatively limited subgroup of **patients with baseline ezetimibe use** for bempedoic acid compared to placebo appeared to be consistent with the overall findings for the MACE-4 (HR 0.94 (95% CI: [0.74, 1.20]) and the MACE-3 endpoints (HR of 0.85 (95% CI: 0.62, 1.16).
Further, no data for the other secondary and tertiary endpoints have been presented on the patients with baseline ezetimibe use.

A numerically (when hierarchical testing was already violated) slight increase in risk for **CV death** (HR 1.04; 95% CI: 0.88, 1.24; nominal p = 0.6227) and **all-cause mortality** was observed (HR: 1.03; 95% CI: 0.90, 1.18; p = 0.6608; (n=434 on bempedoic acid, 6.2%) and n=420 on placebo, 6.0%)).

Regarding the **key secondary endpoints,** the reduction was not statistically significant for **fatal and nonfatal stroke** at the 0.05 level (HR: 0.85; 95% CI: 0.67, 1.07; p = 0.1593). The hierarchical testing was, therefore, violated at this endpoint.

3.4. Unfavourable effects

The placebo-controlled safety data from the CLEAR OUTCOME trial have shown an **exposure** of 6992 subjects treated with bempedoic acid (of which n=803 on baseline ezetimibe use) for a mean exposure of 2.9 years (of which 3.1 years for ezetimibe) and can be considered sufficient.

Comparable to the initial dossier, treatment-emergent **adverse events** (TEAEs) were commonly reported, with 86% on bempedoic acid vs 85% on placebo treatment, with COVID-19 (11.2% and 12.5%, respectively), hypertension (11.0% and 11.8%, respectively), hyperuricaemia (10.9% and 5.6%, respectively), as most commonly reported AEs. No relevant differences were observed in the subgroup of patient with baseline ezetimibe use.

Regarding the **AEs of interest**, no new relevant safety concerns have been observed for **neurocognitive disorders, atrial fibrillation, new-onset diabetes, hypoglycaemia, muscular disorders, tendinopathy, malignancies**, also when these were substantiated by most common malignancies, or **COVID-19 infections**.

- Similar to the data of the original dossier, TEAEs of **hyperuricemia** occurred in a higher percentage of patients in the bempedoic acid group (16.4%) than in the placebo group (8.2%). Increased in uric acid was seen, but they did not worsen over time. Further the incidence of **gout** was slightly higher in the bempedoic acid group with 3.1% vs 2.1% in the placebo group.

A warning on uric acid increases and gout symptoms is currently appropriately mentioned in the SmPC of Nustendi, and gout is an ADR in the SmPC. No new relevant safety concerns could have been revealed from the long-term safety data.

- Similar to the findings in the phase 3 studies, an increased frequency of **anaemia** was seen 332 (4.7%) patients in the bempedoic acid group and 272 (3.9%) patients in the placebo group. The level of decreases in haemoglobin from baseline was mostly limited to ≥2 g/dL and <LLN and ≥3 g/dL and <LLN with 755 patients, 10.8% and 350 patients, 5.0%, respectively, in the bempedoic acid group, compared with the placebo group (517 patients, 7.4% and 248 patients, 3.6%, respectively). No new significant findings on haemoglobin decreases have been seen with these data, as this has already been assessed as an ADR.
- Regarding the hepatic events, the overall incidence of **hepatic enzyme laboratory abnormalities** (AST and ALT) was slightly higher in the bempedoic acid group (5.8%) compared with placebo group (4.7%), which is in line with the initial MAA data. Hepatic enzyme elevations are known and currently appropriately covered within sections 4.4 and 4.8 of the SmPC.
- Regarding cholelithiasis, 2.2% of patients in the bempedoic acid group compared with 1.2% of patients in the placebo group reported cholelithiasis. This imbalance was also seen in the serious AEs (SAEs). However, the incidence of AEs related to complications of cholelithiasis was generally similar between the treatment groups. No new information should have been revealed from the clinical study. Cholelithiasis is mentioned as an ADR in the SmPC.

Serious adverse events (SAEs) were reported at comparable frequencies in the bempedoic acid and placebo groups, i.e. 25.2% vs 24.9%, respectively. The most frequently reported SAEs were COVID-19 pneumonia (1.2% and 1.3%, respectively), pneumonia (1.2% in each), atrial fibrillation (1.2% and 1.4%, respectively), osteoarthritis (1.0% in each), COVID-19 (0.8% and 1.1%, respectively), and angina pectoris (0.8% and 1.2%, respectively), all at comparable frequencies. Apart from the COVID-19 related events, no new significant changes in SAEs were seen with the data from this long-term outcome study, and data were also generally in line with the findings from the original dossier. No relevant differences were observed in the subgroup of patient with baseline ezetimibe use.

A similar frequency of **non-CV deaths** was reported with bempedoic acid (2.3%) vs placebo (2.4%). Most non-CV deaths in the bempedoic acid and placebo groups were related to infections, such as COVID-19 (1.1% and 1.0%, respectively) and malignancy (0.8% and 0.7%, respectively). Of note, CV death was part of the primary evaluation, see efficacy section.

Bempedoic acid was relatively well tolerated with 10.8% vs 10.4% on placebo, who **discontinued** due to a TEAE. The highest frequency of discontinuations was due to myalgia in the bempedoic acid (1.8%) and placebo (1.9%) groups. No discrepancies between groups, and also not in the subgroup of patients on baseline ezetimibe use, have been observed in the discontinuations.

3.5. Uncertainties and limitations about unfavourable effects

Not applicable.

3.6. Effects Table

Table 53: Effects Table for bempedoic acid and cardiovascular disease, based on CLEAR Outcomes Trial (study 1002-043).

Effect	Short description	Unit	Bemp acid n=6992	Placebo n=6978	Uncertainties / Strength of evidence
Favourable Effects					
MACE-3	Time to first occurrence of a MACE, the 3-composite endpoint of CV death, nonfatal MI, or nonfatal stroke (regulatory preferred) secondary endpoint	N (%)	575 (8.2%)	663 (9.5)	**SoE:** • Statistically significant reduction with HR: 0.85 (CI 95% 0.76 - 0.96; p=0.0058). • 4 sensitivity analyses were consistent. • Most subgroups were consistent. • Benefit in both CV risk categories. • MACE-4 findings were similar: Statistically significant reduction with HR: 0.87 (CI 95% 0.79- 0.96; p=0.0037). • Effect in patients with baseline ezetimibe use pointed towards same direction HR: 0.85 (CI 95% 0.62, 1.16). • Lipid lowering reduction (placebo corrected -30.3% (CI 95% -21.1%, -19.5%; p<0.0001). **Uncertainties:** • Effect in patients on baseline ezetimibe use not statistically significant, and analysis not powered. • Subgroups baseline CVD risk category and BMI category showed inconsistency (p = 0.0080 and p = 0.0202, resp.).
All-cause mortality	Time to all-cause mortality	N (%)	434 (6.2)	420 (6.0)	**SoE:** • Also balanced frequencies of CV deaths (bempedoic acid 3.8% vs placebo 3.7% with HR: 1.04 (CI 95% 0.88 - 1.24; p=0.6227) • Also balanced frequencies of non-CV deaths (bempedoic acid 2.3% vs placebo 2.4%). **Uncertainties:** • HR: 1.03 (CI 95% 0.90 -1.18; p=0.6608) • Effect not statistically significant. • Hierarchical testing violated.
Unfavourable Effects					
AE	Hepatic enzyme elevations (AST and ALT increases)	N (%)	(5.8%)	(4.7%)	**SoE:** • In line with safety data of original dossier • No cases of potential Hy's law. **Uncertainties:** • No information provided on whether these AEs have led to clinical symptoms/ complications.
AE	Renal disorders, laboratory abnormalities	N (%)	3765 (53.8%)	2978 (42.8%)	**SoE:** In line with safety data of original dossier
AE	Uric acid elevations/gout	N (%)	16.4% 3.1%	8.2% 2.1%	**SoE:** • In line with safety data of original dossier • Mentioned in SmPC as ADR • No worsening over time

Bemp acid = Bempedoic acid;

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Bempedoic acid is an oral, first-in class, small molecule acting in the cholesterol biosynthesis pathway leading to decreased hepatic cholesterol synthesis, an increase in low-density lipoprotein (LDL)-receptors, and reduction in circulating LDL-C. Ezetimibe's molecular target is the sterol transporter, causing a reduction of hepatic cholesterol stores and an increase in LDL receptors, resulting in clearance of cholesterol from the blood. Current results have been submitted to be able to confirm that the known treatment effect of bempedoic acid (in combination with ezetimibe) of reduction of LDL-C, a validated surrogate marker, is expected to result in CVD risk reduction (which is the proposed indication).

The current variation is primarily based on the results of one trial, the CLEAR Outcomes trial (study 1002-43), in patients with CVD with a history of statin intolerance who were identified to have, or be at high risk for, CVD with a fasting LDL-C ≥100 mg/dL (2.6 mmol/L) while taking stable and optimized background LDL-C-lowering therapies which could include very low dose statin treatment. This patient population is considered to be representative for the target population with established or at high risk for atherosclerotic CVD. Only patients who are statin-intolerant have been included in the currently submitted study which needed some extrapolation to be able to accept the proposed indication (see 'Additional considerations'). It was considered justified that such data could be extrapolated to a population optimally treated with a statin based on the totality of data including the presented consistency in treatment effect with or without statins, on the robust LDL-C surrogate, and consistency in the relationship between LDL-C reduction and CV risk reduction across the overall study program (internal consistency) and in comparison to the known effect from external data sources (external consistency). Further, despite an elevated LDL-C and suboptimal or absence of statin therapy, the use of other lipid-lowering therapy (LLT) appears relatively limited (only approximately 10% received ezetimibe and very low numbers were on PCSK-9 inhibitors), although this is consistent with other studies (see 'Additional considerations').

The study was, in general, well conducted. The investigated endpoints related to reduction in time to first occurrence of a MACE are robust and the endpoints on the individual CVD-related concerns and lipid lowering reduction are relevant to subjects with established or high risk on CVD. Although, the long-term follow-up is somewhat limited, the duration of the study of 2.9 years has met the requirement of study-follow-up of a minimum of 2 years and is considered acceptable. The choice to select placebo as a comparator is also considered acceptable.

Results of CLEAR Outcomes trial show a significant and clinically relevant treatment effect on the reduction in time to first occurrence of (i.e. the secondary, but regulatory preferred endpoint with the lowest possible subjective endpoint components of MI, stroke, and CV death) MACE-3, with a HR of 0.85 (95% CI: 0.76, 0.96; p = 0.0058). The slight numerical increase in CV death and overall mortality slightly outbalances the positive findings, although no specific pattern on reasons of death could be observed based on current data available. A comparable reduction in time to first occurrence was observed with (primary endpoint) MACE-4 (HR of 0.87 (CI 95%: 0.79-0.96; p=0.0037). Sensitivity analyses showed consistency across the investigated subgroups and several key secondary endpoints reinforce these findings. Bempedoic acid showed beneficial results in both CV risk categories, although most pronounced in the primary prevention category. Also, reduction of lipid parameters were congruent with these results.

The FCMP of bempedoic acid and ezetimibe has not been specifically evaluated as study treatment. Nevertheless, ezetimibe was used as background therapy and almost 90% of patients on ezetimibe use at

baseline reported use of ezetimibe at the end of the study. . As mentioned these data demonstrate additional efficacy on top of ezetimibe considering comparable efficacy to those in absence of ezetimibe background therapy. The justification for a CV risk reduction indication for the FCMP should be evaluated based on current provided study data, but also on available evidence of the surrogate LDL-C findings and the robustness of such surrogate data as supportive evidence. Based on that, the proposed indications are considered largely justified, which would also be consistent with acceptance of the indication as proposed for the single bempedoic acid (Nilemdo) indication (see 'Additional considerations').

The clinical safety database of 6992 patients treated with bempedoic acid for a mean of 2.9 years, substantially increases understanding of the safety profile of bempedoic acid. However, of these patients only 803 patients were on baseline ezetimibe use with an exposure of 3.1 years on bempedoic acid and ezetimibe. The patients were dosed according to the registration dose of bempedoic in the SmPC. The presented clinical data do not raise major particular safety concerns, with COVID-19, hypertension and hyperuricaemia being the most common adverse events (AEs). Bempedoic acid is well-tolerated, since the majority of the adverse events are mild to moderate in severity, without relevant differences between the ezetimibe subgroups. Further, the discontinuations due to drug-related adverse events are low (3.1%), which is re-assuring. Although minor uncertainties regarding hepatic enzyme elevations, renal impairment and weight need to be solved.

3.7.2. Balance of benefits and risks

In terms of benefit, bempedoic acid provides a significant and clinically meaningful benefit over placebo in reduction of CVD in patients, as measured by reductions in MACE (MI, stroke, CV death), fatal and nonfatal MI and coronary revascularization during a mean treatment period of 2.9 years. These beneficial effects were accompanied by an expected alteration in the lipid profiles. The use of bempedoic acid appeared to be generally well tolerated with an acceptable safety profile, and without major safety signals. The benefit/risk balance for FCMP of bempedoic acid with ezetimibe can be considered positive based on the totality of data available and treatment expectation by extrapolation from a robust established surrogate of LDL-C. (see also 'Additional considerations').

3.7.3. Additional considerations on the benefit-risk balance

To facilitate the discussion in this section, it is worthwhile to mention the proposed extension of indication of the FCMP of Nustendi (bempedoic acid plus ezetimibe 180/10 mg) and the approved CV indication of the ezetimibe component.

The following extension of indication has been proposed for the FCMP of Nustendi (bempedoic acid plus ezetimibe 180/10 mg):

"Cardiovascular disease

Nustendi is indicated in adults with established or at high risk for atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

- *in combination with a statin with or without other lipid-lowering therapies in patients previously treated with a statin and ezetimibe or,*
- *alone or in combination with other lipid-lowering therapies in patients who are either statin-intolerant, or for whom a statin is contraindicated, and previously treated with ezetimibe alone,*
- *in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without statin.*

For study results with respect to effects on LDL-C, cardiovascular events and populations studied see section 5.1."

For ezetimibe the following indication has been approved through a decentralised procedure:

"Ezetrol is indicated to reduce the risk of cardiovascular events (see section 5.1) in patients with coronary heart disease (CHD) and a history of acute coronary syndrome (ACS) when added to ongoing statin therapy or initiated concomitantly with a statin."

In the overall clinical development program, a considerable number of patients were included based on their CV risk without being hypercholesterolaemic at the time of inclusion. In those patients, a consistent lowering in LDL-C was seen, similar to patients who were hypercholesterolemic at baseline. The submitted CV outcome study was enriched with patients at somewhat higher level of LDL-C, but extrapolation to patients not (yet) covered by the original indication (but already evaluated) is considered justified based on current totality of consistent LDL-C lowering data across the entire spectrum of patients evaluated and given the strength of the LDL-C surrogacy. Therefore, in principle, inclusion of a CV statement as a separate indication is acceptable in order to ensure that the indication also includes those patients that have previously not been covered by the current indication primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia.

For the proposed FCMP of Nustendi (bempedoic acid plus ezetimibe 180/10 mg), in line with the EMA Guideline on the clinical development of fixed combination medical products, (EMA/CHMP/158268/2017), the basic requirements for any fixed combination medicinal product are:

- Justification of the pharmacological and medicinal rationale for the combination. As both products (bempedoic acid and ezetimibe) have distinct but complementary mechanisms of action, the pharmacological rationale appears reasonable, as already discussed in the initial MAA.
- Establishment of the evidence base for the relevant contribution of all active substances to the desired therapeutic effect.
- Establishment of the evidence base for the positive benefit risk for the combination in the targeted population.

Several elements of the proposed extension of indication in relation to these requirements are discussed below:

- **…indicated in adults with established or at high risk for atherosclerotic cardiovascular disease….**

Bempedoic acid showed beneficial results in both CV risk categories, although most pronounced in the primary prevention category at high risk of cardiovascular disease. Also, reduction of lipid parameters were congruent with these results. Therefore, efficacy has been demonstrated across the continuum of risk profile of high risk to very high risk.

For those patient treated with both bempedoic acid and ezetimibe, extrapolation is considered justified based on the totality of data including the presented consistency in treatment effect for those patients on ezetimibe in comparison to absence of ezetimibe on CV risk reduction and on the robust LDL-C surrogate, and consistency in the relationship between LDL-C reduction and CV risk reduction across the entire study program (internal consistency).

Further, despite that specific data in the high risk population of bempedoic acid with ezetimibe has not been provided and such patients were limited included, it is not expected that the effect in high risk patients would be different from those with established CV disease, especially considering than even a

greater effect has been observed in these high risk patients vs very high risk patients (established CV risk) on CV risk reduction in current study (for the totality of data), and a greater LDL-C lowering effect has been observed compared to the overall study effect in this subgroup of patients with high CV risk treated with both bempedoic acid and ezetimibe (LDL-C reduction of -26.7% (95% CI; -30.9%, -22.4%)). Moreover, this would be consistent with the proposed indication for Nilemdo. Nevertheless, such a limitations have been requested to be specifically mentioned in the product information (PI).

Further, the following sub-indications have been proposed:

- **In combination with a statin with or without other lipid-lowering therapies in patients previously treated with a statin and ezetimibe ("add-on indication')**

"in combination with a statin": Extrapolation to a population optimally treated with a statin is considered justified based on the totality of data including the presented consistency in treatment effect with or without statins on the robust LDL-C surrogate, and consistency in the relationship between LDL-C reduction and CV risk reduction across the entire study program (internal consistency) and in comparison to the known effect from external data sources (external consistency). Further, a comparable reduction on the robust surrogate of LDL-C reduction and a related consistent (underpowered) CV risk reduction has been demonstrated for patients on a background of statins vs absence of statins and treated with both bempedoic acid and ezetimibe.

However, the indication should state *'on a maximum tolerated dose of a statin"* instead of *''in combination with a statin"*, to emphasize the required optimal treatment with a statin before treatment with bempedoic acid (with or without ezetimibe). This would also be in line with the hypercholesterolemia indication statement.

Further, the following issue have been noticed:

"other lipid lowering therapies": The proposed new indication includes patients who also are on other lipid-lowering therapies, apart from statins or ezetimibe. This is not acceptable. First, such a statement is not already covered by the original LDL-lowering indication for Nustendi. The use of other LLT other than ezetimibe is very limited, and thus there is insufficient support for cardiovascular prevention efficacy in the ezetimibe patient group with concomitant treatment with other lipid-lowering therapies (with or without statins).

- **Alone or in combination with other lipid-lowering therapies in patients who are either statin intolerant, or for whom a statin is contraindicated, and previously treated with ezetimibe alone ('add-on indication')**

The following issues have been noticed:

"other lipid lowering therapies": see above, not acceptable.

Further, some improvements to the wording of the CVD indication in section 4.1 of the SmPC are proposed.

"Cardiovascular disease

Nustendi is indicated in adults with established or at high risk for atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:

- *in* ***patients on*** ~~***combination with the***~~ *a* ***maximum tolerated dose of*** *a statin*~~***, with or without other lipid-lowering therapies in patients with ongoing therapy of previously treated with a statin***~~ *and* ***not adequately controlled*** *with* ***additional*** *ezetimibe* ***treatment*** *or,*

• ~~***alone or in combination with other lipid-lowering therapies***~~ *in patients who are either statin-intolerant, or for whom a statin is contraindicated, and* ~~***in patients with ongoing therapy of 'previously treated***~~ ***not adequately controlled*** *with ezetimibe treatment* ~~***alone***~~ ***or****,*

• *in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets* ~~***with or without a statin***~~*.*

For study results with respect to effects on LDL-C, cardiovascular events and populations studied see section 5.1."

3.8. Conclusions

The overall B/R of the proposed new indication for Nustendi is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends , by a majority of 29 out of 31 votes, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adults with established or at high risk for atherosclerotic cardiovascular disease to reduce cardiovascular risk for NUSTENDI, based on results from Study 1002-043, known as the CLEAR [Cholesterol Lowering via Bempedoic Acid, an ATP citrate lyase (ACL) Inhibiting Regimen] Outcomes Trial; this is a Phase 3, randomized, double-blind, placebo-controlled study to assess the effects of bempedoic acid (ETC-1002) on the occurrence of major cardiovascular events in patients with, or at high risk for, cardiovascular disease who are statin intolerant; As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.0 of the RMP has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Divergent position(s) to the majority recommendation is appended to this report.

Appendices

1. Divergent position dated 21 March 2024

APPENDIX

DIVERGENT POSITION DATED 21 March 2024

The undersigned member(s) of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the following indication for Nustendi (bempedoic acid plus ezetimibe):

> Nustendi is indicated in adults with established or at high risk for atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:
>
> - *patients on a maximum tolerated dose of a statin*

The reasons for the divergent opinion are the following:

No dedicated cardiovascular outcome trial (CVOT) is available in the "on a maximum tolerated dose of a statin" population. The extrapolation exercise from the statin-intolerant patients to the patients on a maximum tolerated dose of a statin that has been provided is not considered appropriate due to several reasons mentioned hereafter.

Firstly, this extrapolation exercise is not straightforward as the populations are not comparable. Secondly, there is an interaction between being on statins and having a lower effect of bempedoic acid on reducing LDL-C. Thirdly, although it is accepted that a reduction in LDL-c will likely be translated into some CV risk reduction, the extent of such benefit cannot be quantified with confidence by means of an extrapolation. Finally, in the absence of a CVOT with bempedoic acid in the mentioned population, there is a risk that the benefit is marginal and the treatment with bempedoic acid could deprive patients of a benefit from other lipid-lowering therapies that have demonstrated a significant reduction in CV events in patients on a maximum tolerated dose of a statin in appropriate CVOT.

In conclusion, based on the available data, a positive benefit/risk balance cannot be considered demonstrated in the reduction of CV risk in adults with established or at high risk for atherosclerotic CV disease in patients on a maximum tolerated dose of a statin.

CHMP Member(s) expressing a divergent opinion:

María Concepción Prieto Yerro

Sol Ruiz Antúnez