30 January 2020
EMA/CHMP/86202/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nilemdo

International non-proprietary name: bempedoic acid

Procedure No. EMEA/H/C/004958/0000

Note

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

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Administrative information

Name of the medicinal product:	Nilemdo
Applicant:	FGK Representative Service GmbH Heimeranstrasse 35 80339 Munchen GERMANY
Active substance:	BEMPEDOIC ACID
International Non-proprietary Name/Common Name:	bempedoic acid
Pharmaco-therapeutic group (ATC Code):	Lipid modifying agents, other lipid modifying agents (C10AX15)
Therapeutic indication(s):	Nilemdo is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet: • in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin (see sections 4.2, 4.3, and 4.4) or, • alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	180 mg
Route(s) of administration:	Oral use
Packaging:	blister (PVC/alu)
Package size(s):	10 tablets, 28 tablets, 30 tablets, 90 tablets, 98 tablets and 100 tablets

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List of abbreviations

Abbreviation	Definition
ACC	American College of Cardiology
ACL	Adenosine triphosphate citrate lyase
ACSVL1	Very long-chain acyl-CoA synthetase 1
AHA	American Heart Association
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
apo B	Apolipoprotein B
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase increased
AUC	Area under the curve
BMI	Body mass index
BCS	Biopharmaceutics Classification System
BUN	Blood urea nitrogen
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
CETP	Cholesteryl ester transfer protein
CHD	Coronary heart disease
CK	Creatine kinase
CoA	Coenzyme A
C_{max}	maximum plasma concentration
CV	Cardiovascular
CVD	Cardiovascular disease
CVOT	Cardiovascular outcome(s) trial
CYP	Cytochrome P450
DMEP	Division of Metabolism and Endocrinology Products
eCTD	Electronic common technical document
EAS	European Atherosclerosis Society
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOP2	End of Phase 2
ESC	European Society of Cardiology
ESP15228	Active Phase 1 metabolite of ETC-1002
ESP15228-glucuronide	Inactive acyl glucuronide metabolite of ESP15228
ETC-1002	Analyte of bempedoic acid measured in plasma, urine, or feces
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FCMP	Fixed combination medicinal product

Abbreviation	Definition
FH	Familial hypercholesterolemia
HbA_{1c}	Hemoglobin A1c
HeFH	Heterozygous familial hypercholesterolemia
hERG	Human ether-à-go-go-related gene
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
hsCRP	High-sensitivity C-reactive protein
ICH	International Council for Harmonisation
IMP	Investigational medicinal product
IND	Investigational new drug
IR	Immediate release
IVRS	Interactive voice response system
LC-MS/MS	Liquid chromatography tandem mass spectrometry
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDL-R	Low-density lipoprotein receptor
LLN	Lower limit of normal
LMT	Lipid-modifying therapy
LS	Least square
MAA	Marketing Authorisation Application
MACE	Major adverse cardiovascular events
MDRD	Modification of Diet in Renal Disease
MEB	Medicines Evaluation Board
MHRA	Medicines and Healthcare products Regulatory Agency
NDA	New drug application
non-HDL-C	Non-high density lipoprotein cholesterol
NIH	National Institutes of Health
NOAEL	No-observed-adverse-effect level
NPC1L1	Niemann-Pick C1-Like 1
OAT	Organic anion transporter
OLE	Open-label extension
PCSK9	Proprotein convertase subtilisin/kexin type 9
PD	Pharmacodynamic(s)
PIP	Pediatric Investigational Plan
PK	Pharmacokinetic(s)
POPPK	Population pharmacokinetic
QD	Once daily
SAP	Statistical analysis plan
SAWP	Scientific Advice Working Party
SD	Standard deviation

Abbreviation	Definition
SMQ	Standard Medical Query
SOC	System Organ Class
t_{max}	Time to maximum observed plasma concentration
TC	Total cholesterol
UGT	Iridine 5' diphospho-glucuronosyltransferase
ULN	Upper limit of normal
US	United States
VLDL	Very-low density lipoprotein
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant FGK Representative Service GmbH submitted on 12 February 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Nilemdo, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 14 December 2017.

The applicant applied for the following indication:

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

- *in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,*
- *alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.*

The effect of Nilemdo on cardiovascular morbidity and mortality has not yet been determined.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is

composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0185/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0185/2018 was not yet completed as some measures were deferred.

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 applicant 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.

New active Substance status

The applicant requested the active substance bempedoic acid contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a

medicinal product previously authorised within the European Union.

Scientific advice

The applicant received Scientific advice from the CHMP on 26 May 2016 (EMEA/H/SA/3294/1/2016/SME/II) and 31 May 2018 (EMEA/H/SA/3294/1/FU/1/2018/SME/II) for the development programme supporting the indication granted by the CHMP. The Scientific Advices pertained to the following clinical aspects:

- Definition of statin intolerance and the approach to identify a statin intolerant (SI) population.
- Agreement on the design of the phase 3 studies 1002-044 and 1002-046.
- The size of the overall safety database, duration of exposure, and plan to evaluate potential signals for CV risk.
- The proposed cardiovascular outcomes trial (CVOT study 1002-043) in SI patients to support the indication for CV risk reduction, including the design, acceptability of the inclusion/exclusion criteria, primary endpoint, plan for adjudication of clinical endpoints, the proposed 4-week placebo run-in period, background therapy during the CVOT, safety monitoring/risk management plan, long-term exposure in the CVOT, strategy to enroll patients in a 1:1 randomisation of bempedoic acid compared to placebo, sample size/effect size/power calculations, analysis for time-to-event endpoints, definition and proposed statistical analysis of secondary endpoints, and interim analysis.
- The revision to the inclusion criteria for study 1002-043 to expand the eligibility criteria to include patients who are unwilling to attempt a second statin or low dose statin, and whether, with the expanded eligibility criteria, the CVOT will continue to provide the clinical data necessary to support the proposed indication.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Alar Irs

The application was received by the EMA on	12 February 2019
The procedure started on	28 February 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	21 May 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	23 May 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	3 June 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 June 2019

The applicant submitted the responses to the CHMP consolidated List of Questions on	13 September 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	23 October 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 October 2019
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	7 November 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 December 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	14 January 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Nilemdo on	30 January 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Primary hypercholesterolemia by definition is any hypercholesterolemia which is caused by a disorder (either familial- or nonfamilial) in lipid metabolism and is not caused by another condition, such as hypothyroidism, or a drug effect. The **heterozygous familial** form of this condition (HeFH) is more rare and is estimated to occur between 1:200 and 1:500 individuals globally. LDL-C levels in affected individuals are elevated, and in spite of aggressive statin use, there is still a 2-fold excess of CHD-related deaths relative to age-matched controls within this population.

Hyperlipidemia is the heterogeneous group of disorders characterized by an excess of lipids (ie, cholesterol, phospholipids, triglycerides) in the bloodstream. Hypercholesterolemia specifically refers to the presence of high levels of cholesterol in the blood. Primary hyperlipidemia is usually due to genetic causes (monogenetic or polygenetic) and environmental factors, such as diet and lifestyle. Primary nonfamilial hyperlipidemia is hyperlipidemia that is not due to a specific genetic disorder, although there are polygenetic influences. **Mixed dyslipidemia** is generally defined as elevated LDL-C and high triglycerides and/or low HDL-C.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Cardiovascular disease and high cholesterol

CVD remains the leading cause of death among Americans, Europeans, and other populations around the world (World Health Organization [WHO], 2015). Currently, over 93 million adults in the US have some form of CVD (Centers for Disease Control, 2018), which is responsible for one in every 4 deaths in the US (Centers for Disease Control, 2015). Across the European region, CVD causes more than half of all deaths (WHO, 2018). CVD is a tremendous economic burden to society in both the US and Europe. In Europe, CVD costs are €210 billion per year with approximately 53% due to health care costs, 26% associated with productivity losses, and 21% related to non-hospital related care (European Heart Network, 2017).

CVD risk factors are well established and include hypercholesterolemia, hypertension, smoking, diabetes, physical inactivity, obesity, and increasing age; the first 3 are the key risk factors. Lowering cholesterol has been proven to reduce the risk of CVD. In the most recent report by the WHO, the global prevalence of elevated TC in adults (≥ 5.0 mmol/l or 193 mg/dL) was 39%; the prevalence is higher in both Europe (54%) and the Americas (48%) (WHO, 2018). Hypercholesterolemia that is a result of the genetic disorder, familial hypercholesterolemia (FH), increases the risk of atherosclerotic cardiovascular disease (ASCVD) both in untreated and treated patients (Slack, 1969; Scientific Steering Committee, 1991; Kjaerggard et al, 2017).

Data from the Global Burden of Disease 2010 study indicated that 29% of global ischemic heart disease burden is attributable to high TC, the second leading risk factor after high blood pressure, which was responsible for 53% of global ischemic heart disease (Lim et al, 2012). During 2005–2012, an estimated 37% of US adults met 2013 AHA/American College of Cardiology (ACC) criteria for needing cholesterol lowering medication or were receiving cholesterol-lowering medication (Mercado et al, 2015). A meta-analysis of over 30 studies evaluating diet, drugs, or surgery to lower LDL-C has shown that for every 1 mg/dL reduction in LDL-C, total mortality is reduced by 1% (see Section 2.1.3.

CVD related mortality in both the US and Europe has been decreasing (Benjamin et al, 2017; Wilkins et al, 2017). Improvements in overall cardiovascular health are projected to reduce CHD deaths by 30% between 2010 and 2020; although by 2030, there will still be 43.9% of the US population projected to have some form of CVD. Several studies have attributed the declining heart disease mortality rates to improved risk factor control (44% to 58% of the decline) and medical and surgical therapies (23% to 47% of the decline) (Ford et al, 2007; Laatikainen et al, 2005; Unal et al, 2004). Cholesterol reduction was the leading contributor to the decline in CVD mortality in 2 of these studies (Laatikainen et al, 2005; Ford et al, 2007) and the second leading contributor in the third study (Unal et al, 2004). An analysis estimated that of the 316,100 fewer deaths attributable to all risk factor declines (cholesterol, smoking, blood pressure), 79% were attributed to risk factor declines in asymptomatic individuals (primary prevention) and 21% were in patients with CHD (secondary prevention). Cholesterol reduction accounted for the most significant proportion of CHD deaths prevented in primary prevention patients (Young et al, 2010). These data emphasize the importance of targeting cholesterol reduction for both primary and secondary prevention of reducing CV events. This is supported by current US and EU recommendations that recognize LDL C goals are not always achievable with statin therapy alone and thus there remains an unmet medical need to provide additional LDL-C lowering therapies for patients with elevated LDL-C who are receiving maximally tolerated statin therapy (which may mean no statin at all) (Grundy et al, 2018; Catapano et al, 2016). Collectively, these data suggest that if the prevalence of elevated LDL-C was more widely reduced, this would lead to even greater declines in ASCVD-associated morbidity and mortality.

2.1.3. Biologic features. Aetiology and pathogenesis.

LDL-C as a surrogate for CVD

Bempedoic acid is seeking marketing approval for an LDL-C lowering indication. Lowering LDL-C has been accepted as a surrogate endpoint for the reduction of CV events by clinicians and regulatory authorities for many years (Cannon et al, 2002; Jacobson et al, 2014; Ference et al, 2017a). To date, all cholesterol lipid-lowering drug approvals in the US and EU have been initially based on LDL C lowering without confirmed CV outcomes benefits. Initial approvals of PCSK9 inhibitors, based on an LDL-C lowering mechanism through the LDL receptor and validation by human genetics, are the most recent evidence of the continued acceptance of LDL C lowering as a validated surrogate (Repatha [evolocumab] US Prescribing Information, 2017; Repatha SmPC 2018; Silverman et al, 2016; Ference et al, 2016).

In 2017, the European Atherosclerosis Society (EAS) released a consensus statement to confirm the "LDL-C hypothesis" by stating that "there is a dose-dependent, log-linear association between absolute LDL cholesterol and cardiovascular risk, and this association is independent of other cardiovascular risk factors and is consistent across the multiple lines of evidence" (Ference et al, 2017a). Guidelines for LDL-C generally consider LDL-C < 100 mg/dL (2.6 mmol/L) as optimal for adults (Jellinger, et al, 2017; Grundy et al, 2018). In specific risk populations, the threshold of initiating or intensifying treatment is at LDL-C levels > 70 mg/dL (1.8 mmol/L) (Jellinger et al, 2017; Catapano et al, 2016; Stone et al, 2014; Grundy et al, 2018). Across the bempedoic acid Phase 3 clinical program, mean % change in LDL-C was the primary efficacy endpoint. All Phase 3 study eligibility criteria included patients having hyperlipidemia with at least LDL-C $\geq$ 70 mg/dL (1.8 mmol/L) on stable background lipid-modifying therapy (LMT).

Evidence for the direct correlation between LDL-C and CVD comes from 4 different categories of studies: preclinical, epidemiological, genetics, and interventional (Feig, 2014; Williams et al, 2008; Zadelaar et al, 2007) (Taylor et al, 2002; Taylor et al, 2004; Tardif et al, 2006; Stamler et al, 1986; Kannel et al, 1971) (Chen et al, 1991).

FH is a genetic condition that strongly supports the unique role of elevated LDL C in the risk of major CV events. Patients with single gene (typically in the LDL receptor) mutations (heterozygous familial hypercholesterolemia [HeFH]) have untreated LDL C levels usually in the range of 200 to 500 mg/dL. HeFH increases the risk of ASCVD both in untreated and treated patients (Slack, 1969; Scientific Steering Committee, 1991; Kjaerggard et al, 2017). Given the younger age of this at-risk population, patients with FH typically do not have an accumulation of the other traditional risk factors associated with CVD, such as hypertension, cigarette smoking, or diabetes typically seen in the general population, demonstrating the singular role that elevated LDL C can have in the progression of atherosclerosis and the development of premature major CV events.

2.1.4. Clinical presentation, diagnosis, prognosis

Over 30 CVOTs in several LDL-C lowering drug therapies (including statins, ezetimibe, PCSK9 inhibitors) have validated LDL-C as a surrogate endpoint of CV events (Baigent et al, 2010; Cannon et al, 2015; Sabatine et al, 2017; Silverman et al, 2016; Schwartz et al, 2018). A patient-level meta-analysis of statins including 26 large CVOTs and involving 170,000 participants showed a consistent relationship between LDL C reduction and CV outcomes. This meta-analysis demonstrated that a 38.7 mg/dL (1 mmol/L) lowering of LDL C was associated with a 22% reduction in the 5-year incidence of MACE, coronary revascularizations, and ischemic strokes (Baigent et al, 2010). This large meta-analysis has also demonstrated a consistency of the relationship between LDL-C lowering and reduction in CV event risk across a wide variety of patient populations including patients with primary and

secondary prevention, patients with diabetes, patients with hypertension, and across a wide range of baseline LDL-C levels. Similar CV risk reductions have been reported for PCSK9 inhibitors, evolocumab and alirocumab (Sabatine et al, 2017; Schwartz et al, 2018). There is no evidence for a threshold below which LDL C lowering is not beneficial. Most recent CVOTs have achieved LDL-C levels of 35 to 40 mg/dL, and recent trials have identified no apparent risk to achieving levels of LDL-C < 25 mg/dL (Boekholdt et al, 2014; Robinson et al, 2017).

Results from some earlier CVOTs that have tested drug candidates in the cholesteryl ester transfer protein (CETP)-inhibitor class have suggested a potential lack of relationship between changes in LDL C with this class of drug and lack of CV benefit. However, the most recent trial to complete in this class, REVEAL with anacetrapib, indicated a CV benefit that aligns with the absolute reduction in LDL C that was observed. In the REVEAL study, there was an 11 mg/dL difference in LDL-C that translated to a CV event hazard ratio of 0.91 ($p < 0.004$) (Bowman et al, 2017). These results further support the relationship between absolute reduction in LDL-C and reductions in major CV events as observed with statins. The 3 previous trials testing CETP inhibitors likely suffered from extraneous issues that impeded or inhibited the ability to demonstrate this LDL-C/CV event relationship ranging from off-target toxicity (torcetrapib; ILLUMINATE), lack of LDL C efficacy (dalcetrapib; dal-OUTCOMES), and a short patient follow-up period combined with a low baseline LDL C (evacetrapib; ACCELERATE). When looking at the CETP-inhibitor data as a whole and understanding the basis for the results in these trials, the science still provides an overall supportive relationship to LDL C and CV events.

A consistent role for lowering LDL-C to reduce the risk of major CV events has been established. Together, this evidence shows that lowering LDL-C with bempedoic acid meets the criteria as a valid surrogate endpoint for reducing CVD risk.

Data to support the relationship between LDL-C and CV events and specifically the relationship with inhibition of ACL has been shown in genetic studies of variations in the genes that influence LDL-C (Mendelian randomization studies) and from studies in patients with familial hypercholesterolemia (FH), a genetic form of hyperlipidemia. In Mendelian randomization studies evaluating multiple genetic targets that impact LDL-C levels, variants in genes that regulate LDL C levels (eg, HMG CoA reductase, LDL-R, PCSK9) have demonstrated lowering of LDL-C is associated with a lower risk for CV events (Kathiresan et al, 2008; Ference et al, 2016). Several publications and reports summarize the findings from a portfolio of Mendelian randomization studies aimed to approximate the effect of ACL inhibition by bempedoic acid alone and in combination with other LDL-C lowering therapies. Similar to findings mediated by polymorphisms in HMG CoA reductase, Niemann-Pick C1-Like 1 (NPC1L1), and PCSK9, reductions in LDL-C mediated by polymorphisms in ACL were causally associated with a similar relative risk reduction in major vascular events per unit change in LDL C. Furthermore, lower LDL-C and the associated CV risk mediated by polymorphisms in ACL were additive when combined with polymorphisms in HMG CoA reductase and NPC1L1. These findings suggest that treatment with any combination of an ACL inhibitor, statins, ezetimibe, or a PCSK9 inhibitor should have therapeutically equivalent effects on the risk of CV events per unit reduction in LDL-C in all adult patients with hyperlipidemia (Ference et al, 2017b).

2.1.5. Management

Available lipid lowering therapies include:

- Statins (oral tablets), as a cornerstone therapy, for which CV benefits have extensively been proven across a wide range of patients with different CV risk profiles.

The 2016 European Society of Cardiology (ESC)/EAS guidelines on the treatment of cholesterol focus on the benefits of statin therapy. Non-statin therapies, specifically ezetimibe, and PCSK9 inhibitors

(Catapano et al, 2016) could provide additional benefit or be used as alternative when patients are intolerant to statins or contra-indications to statins exist.

- Ezetimibe (oral tablets), can be used as additional therapy when treatment goals have not been achieved with statins or when statins are not tolerated or contraindicated. Cardiovascular benefits have been demonstrated in patients with ACS.

- PCSK9 inhibitors (injectable biologics), can be used as additional therapy when treatment goals have not been achieved with statins or when statins are not tolerated or contraindicated. Cardiovascular benefits have been demonstrated in patients with established cardiovascular disease.

Despite the positive safety and high potency of the PCSK9 inhibitor class, these products are biologic injectable products with proven access issues (pricing and reimbursement) despite having broad labelling, including CV risk reduction, and are still not widely used even with a first line monotherapy indication for both CV risk reduction and LDL-C lowering (Baum et al, 2017; Cohen et al, 2017; Navar et al, 2017; Whayne, 2018).

- Fibrates (oral tablets), omega-3 fatty acids (oral capsules), and bile acid sequestrants (oral tablets). Cardiovascular benefits have not been demonstrated.

Bile acid sequestrants and fibrates are generally less efficacious than statins at LDL C lowering, have recently demonstrated more neutral CV outcomes, and each have their own side effect profile that may limit their use, as is reflected in prescribing data (National Health Service, 2006). Fibrates have been relegated to a minimal role in recent medical guidelines (Grundy et al, 2018; Catapano et al, 2016). For omega-3 fatty acids (oral capsules), cardiovascular benefits have not (anymore) been accepted based on recent CHMP decision.

Results of a simulation model using data from a large US claims database showed that 31% of patients with ASCVD were unable to achieve an LDL-C of < 70 mg/dL with maximized statin therapy. This only dropped to 14% when ezetimibe was added to the maximized statin therapy in this model (Cannon et al, 2017). It is important to note that this model assumed maximal levels of patient compliance and adherence with the statin and ezetimibe and therefore represents the "best case scenario" for the treatment effect of these therapies. Any issues of partial or total intolerance of these therapies would create a treatment gap greater than 14%. The percentage of patients inadequately treated with statin therapy alone is even higher with real-world use. A study of the US National Health and Nutrition Examination Survey 2011-2012 estimated that 70.7% of overall statin-eligible patients were on a statin and not at LDL-C goals; this included 79.7% of patients with ASCVD, 98% of patients with an LDL $\geq$ 190 mg/dL, 42.3% of patients with diabetes and an LDL-C of 70 to 189 mg/dL, and 46.8% of patients with an estimated CV risk $\geq$ 7.5% and an LDL-C of 70 to 189 mg/dL (Wong et al, 2016).

As many as 10% of patients are unable to tolerate statins at any dose due to dose-limiting toxicities and adverse effects that result in intolerance and/or contraindications (Thompson et al, 2016; Jacobson et al, 2014), and as many as 15% to 20% of all patients on statins may experience statin-associated adverse events that may limit the dosage needed to reach LDL-C goals (Banach et al, 2015). All regions/countries recognize the importance of statin intolerance; however, regions/countries vary in their perspectives on defining "statin intolerance" and on prescription drug labelling using this terminology. For example, in the EU statin intolerance language is included in label indications for LDL-C lowering drugs (Repatha SmPC, 2018).

About the product

Mode of action

Bempedoic acid (ETC-1002, CION-08 or ESP55016) is an oral small molecule low-density lipoprotein cholesterol (LDL-C)-lowering drug being developed for the treatment of patients with hyperlipidemia.

Bempedoic acid is activated in the liver to ETC-1002-Coenzyme A (ETC-1002-CoA), which subsequently inhibits adenosine triphosphate citrate lyase (ACL), an enzyme upstream of 3-hydroxyl-3-methylglutaryl Coenzyme A (HMG-CoA) reductase in the cholesterol synthesis pathway. Inhibition of cholesterol synthesis triggers the upregulation of low-density lipoprotein (LDL) receptor (LDLR) expression in the liver resulting in increased clearance of LDL particles and lowering of LDL-C in the blood. Additionally, inhibition of ACL by ETC-1002-CoA results in concomitant suppression of hepatic fatty acid biosynthesis.

The applicant proposed the following indication:

"Nilemdo is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- *in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,*
- *alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.*

The effect of Nilemdo on cardiovascular morbidity and mortality has not yet been determined."

The CHMP agreed to the following indication:

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

- *in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin (see sections 4.2, 4.3, and 4.4) or,*
- *alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.*

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

Type of Application and aspects on development

Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0185/2018 on the agreement of a paediatric investigation plan (PIP).

The PDCO issued a compliance report for the PIP, number EMA/769856/2018 on 14 December 2018, concluding the summited studies are compliant.

The Applicant received European national scientific advice regarding bempedoic acid development in June 2015 with the following National Agencies:

- Medicines and Healthcare products Regulatory Agency (MHRA) (Reference 943/ETC-1002-bempedoic acid)
- Medicines Evaluation Board (MEB) (Reference JV/1570716)
- Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) (Reference 62-3320 1497 26/15)

A Scientific Advice meeting with the Scientific Advice Working Party (SAWP) was held in May 2016. This advice included, amongst other issues, an extensive discussion on the statin intolerance in which SAWP concluded that this should be defined as follows: patients not tolerating at least 2 different statins at the lowest approved daily dose, or to patients not tolerating at least 1 statin because of a severe safety effect that can be specifically attributed to statin use which precludes administration of a second statin. Patients tolerating statin doses below the approved dose range may be included. The proposed database size was supported. Other questions were related to the outcome trial.

In a clarification letter (24 June 2016), the SAWP accepted the definition of statin intolerance as: the inability to tolerate at least 2 statins, one statin at the lowest daily dose (defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg), AND another statin at any dose, due to skeletal muscle-related symptoms, other than those due to strain or trauma, such as pain, aches, weakness, or cramping, that began or increased during statin therapy and stopped when statin therapy was discontinued.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film coated tablets containing 180 mg of bempedoic acid as active substance. Other ingredients are:

Tablet core: Lactose monohydrate, Microcrystalline cellulose (E460), Sodium starch glycolate (Type A), Hydroxy propyl cellulose (E463), Magnesium stearate (E470b), Anhydrous colloidal silica (E551).

Film-coat: Partially hydrolysed poly(vinyl alcohol) (E1203), Talc (E553b), Titanium dioxide (E171), Macrogol 4000 (E1521).

The product is available in PVC/aluminium blisters as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of bempedoic acid is 8-hydroxy-2,2,14,14-tetramethylpentadecanedioic acid corresponding to the molecular formula $C_{19}H_{36}O_5$. It has a relative molecular mass of 344.49 g/mol and the following structure:

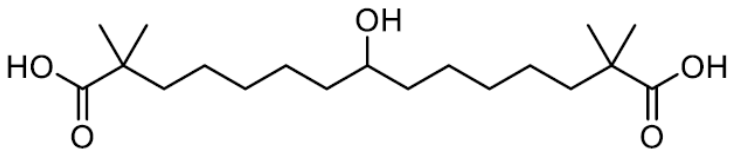


Figure 1: active substance structure

The chemical structure of bempedoic acid was elucidated by a combination of ^{1}H- and ^{13}C- NMR spectroscopy, mass spectrometry (MS-MS), Fourier Transform infrared spectroscopy (FT-IR), and UV spectroscopy. The solid-state properties of the active substance were measured by X-ray powder diffraction (XRPD), and single crystal X-ray diffraction (SCXRD).

Bempedoic acid is a white to off-white, crystalline powder. There are no chiral centres in the molecule. Only one crystalline form of bempedoic acid has been identified. This form has been the only form used in all toxicology and clinical studies. The solubility of bempedoic acid is pH-dependent, with solubility increasing with increasing pH over the normal physiological pH range. It is insoluble at low pH values, and solubility increases rapidly above pH 6. Based on its low solubility and high permeability, bempedoic acid is a BCS Class II compound.

Based on the review of the data provided by the applicant, it has been adequately substantiated that the active substance bempedoic acid contained in the medicinal product Nilemdo is considered to be qualified as a new active substance in itself.

Manufacture, characterisation and process controls

Bempedoic acid is synthesized using 3 well defined starting materials with acceptable specifications.

During the assessment some questions were devoted to the setting of the impurity specifications for the three starting materials. The overall control strategy for impurities from the starting materials is now adequate. The same is true for the control strategy for the GMP process, adequate understanding of the formation, fate and control of actual and theoretical impurities was demonstrated.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities is in accordance with the EU guideline on the chemistry of active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised. Of the organic impurities, some have been detected in drug substance batches and are controlled in the drug substance in accordance with ICH Q3A (R2) "Impurities in New Drug Substances" (2006). Potential degradation products arising from the synthesis have been identified. However, they have not been detected in the batches manufactured. In addition, no degradation of the bempedoic acid drug substance has been observed in stability testing performed to date.

In accordance with ICH M7, the compounds structure-based alert were evaluated for potential genotoxicity. These are controlled at 0.15% as per ICH Q3A(R2) as they were found not to be mutagenic following Ames testing. The active substance is tested for elemental impurities, lithium content and residue on ignition, at release to detect and quantify inorganic impurities. The results from all the batches manufactured to date are below the limits of quantitation / detection.

The synthesis strategy for the bempedoic acid manufacturing process has remained unchanged throughout development and for commercialisation. The process has been optimized for efficiency and

process controls have been amended. Changes introduced have been presented in sufficient detail and have been justified.

The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in polyethylene (PE) liners that are crimped closed and capped with a crimping system. The outer container (e.g., a PE or high-density polyethylene (HDPE) drum with a secure fitting lid or equivalent) is used as packaging to prevent damage to the primary container. The polyethylene liners comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

The manufacturing process has been developed using a combination of conventional univariate studies and elements of QbD such as risk assessment and design of experiment (DOE) studies.

The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed NORs and PARs.

Specification

The active substance specification includes tests for: appearance, identity (FT-IR, HPLC-UV), assay (HPLC-UV), impurities (HPLC-CAD), acid acetic (IC), residual solvents (GC), water content (KF), elemental impurities (ICP), residue on ignition (Ph. Eur.), particle size distribution (Ph. Eur. 2.9.31), microbial content (Ph. Eur.2.6.12) and E. Coli (Ph. Eur. 2.6.13).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Forced degradation studies are described in S.7.1. HPLC CAD and HPLC UV analytical methods were used to evaluate the degradation products of the active substance following exposure to stressed conditions. Both methods are considered stability indicating. Organic impurities have been studied, and most of them are purged from the process. Identified and unidentified impurities are limited by the DS specification in line with ICH Q3A.

No relevant degradation products from bempedoic acid have been detected. Potential genotoxic impurities have been adequately discussed. The specification requirements for elemental impurities, lithium, residue on ignition, and particle size have been sufficiently justified in S.4.5. (The PDE for lithium is 550 µg/day, so the proposed 500 ppm limit for lithium is suitable.) The arguments as provided for reduced testing (one batch per year) on microbial limit testing are acceptable.

Analysis data from 12 commercial scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 18 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Additionally, supporting stability data from 10 batches, manufactured at different previous facilities ranging from pilot to commercial scale, for up to 60 months were provided. These batches were representative of the commercial process. The following parameters were tested: appearance, assay, impurities, water content, and microbial examination. No significant changes were observed in the bempedoic acid primary stability samples stored after 18 months of long-term and 6

months of accelerated storage conditions. In addition, no significant changes were observed in the supporting active substance batches after 60 months.

Photostability testing following the ICH guideline Q1B was performed on one batch. Bempedoic acid samples were exposed to oxidative, basic, acidic, thermal, and light stress conditions. The active substance is stable under basic aqueous conditions and is photostable, but degrades under the other conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 30 months at controlled room temperature of 20°C to 25°C in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Bempedoic acid has been developed for commercialization as white to off-white, oval, film-coated 180 mg tablets, for oral administration. The tablets are debossed with '180' on one side and 'ESP' on the other side. The tablet dimensions are 13.97mm x 6.60mm x 4.80mm (+/- 0.2mm).

Pharmaceutical development of the finished product contains QbD elements. The initial risk assessment considered bempedoic acid drug substance physical and chemical properties that could impact the drug product critical quality attributes (CQA).

The free dicarboxylic acid form was selected as the drug substance early in development as it is anhydrous, crystalline, and non-hygroscopic. Bempedoic acid was determined to be very stable and not affected by hydrolysis Bempedoic acid's high solubility in the lower gastrointestinal tract and relatively high bioavailability ensure good drug absorption. Hence, based on its low solubility and high permeability, bempedoic acid is a BCS Class II compound.

Bempedoic acid is to be marketed as 180 mg white, oval, film-coated, IR tablets for oral administration. As such, bempedoic acid tablets do not contain any excipients that are intended to modify the drug release rate or influence the mechanism of absorption *in vivo*. The excipients selected for the tablet formulation ensure manufacturability and allow for QD (quaque die, i.e. once a day) administration. While the solubility of the bempedoic acid drug substance is low (<1 mg/mL in water), the long half-life in the body, and a high potency allowed for development of an immediate release tablet formulation without the use of solubilizers.

Bempedoic acid drug product is formulated using compendial excipients that have been demonstrated to be safe for oral administration. Film-coating is used to make the tablets easier to swallow and to ensure consistent colour. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. There are no overages used in the formulation of bempedoic acid tablets, 180 mg.

A discriminatory and quality control dissolution method was developed at a physiologically relevant, intermediate pH to ensure adequate solubility and sink conditions. The discriminatory power of the dissolution method has been demonstrated being able to show difference in composition and manufacturing processes.

Using compendial tablet excipients and a manufacturing process with well-defined process parameters resulted in successful scale-up to a commercial scale process.

The process parameters that may influence drug product's CQAs have been evaluated or have been fixed based on those used in clinical manufacture. Critical Process parameters (CPPs) were identified by risk assessment and subsequent experimentation and were either fixed or ranges were established that ensure the tablets meet acceptance criteria.

The bempedoic acid formulation and manufacturing process development work has been further evaluated and found acceptable during the manufacture of Phase 3 clinical supplies.

In accordance with International Council for Harmonisation (ICH) Q6A, "Specifications, Decision Tree 8 (Microbiological Attributes of Non-Sterile Drug Products)" in "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances" (1999), a non-routine microbiological testing plan is proposed to monitor the drug product. The reduced testing plan is based on microbiological controls in place for the ingoing materials, environmental controls, and extensive batch data.

The blister components that comprise the commercial container closure systems were selected for bempedoic acid tablets because these are commonly used primary packaging components for the storage and transportation of solid oral dosage forms.

The primary packaging is polyvinyl chloride (PVC)/aluminum blisters. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of 6 main steps. The process is considered to be a standard manufacturing process.

Validation of the finished product manufacturing process will be conducted prospectively on 3 production scale batches at the typical production scale. The critical process parameters for the manufacturing process, evaluated during validation, confirm they are adequate for consistently producing a product that meets the regulatory specification. The study was conducted according to approved validation protocols. Process validation and the final report will be completed before commercial drug product is released to the market.

Product specification

The finished product release specifications consist of appropriate tests for this kind of dosage form including appearance, dimensions, identity (HPLC-UV), potency (HPLC-UV), purity (HPLC-CAD), dissolution (, HPLC-UV), uniformity of dosage units (HPLC), water content (KF) and microbial limits (Ph. Eur. 2.6.12 and 2.6.13).

The potential presence of elemental impurities in the finished product has been assessed using a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Elemental contributions from excipients and drug substance were evaluated using Option 2b, and the results demonstrate that all Class 1 and 2A elemental impurities are controlled to below the 30% PDE threshold. The information on the control of elemental impurities is satisfactory.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay (potency) and impurities testing has been presented.

Batch analysis results are provided for 15 batches of the commercial formulation confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 primary commercial scale batches of finished product stored for up to 18 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, assay, related substances, dissolution, water content, and microbiological quality. The analytical procedures used are stability indicating. No significant changes to any to the above tested parameters were observed. No new degradation products were detected. The data show little to no change over time with little to no variability. In addition, no significant changes were observed in the supporting finished product batches after 24 months.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results of photostability studies indicate that the product is not light sensitive.

Based on available stability data, the proposed shelf-life of 30 months without any special temperature storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Magnesium stearate is derived from edible vegetable sources. The fatty acid used in production, is derived from palm and produced from the fruit of Elaeis guineensis.

Post approval change management protocol

A Post approval change management protocol has been proposed for the manufacture of the drug substance bempedoic acid to support the addition of alternate suppliers for the designated regulatory starting materials (RSMs) used in the manufacture of bempedoic acid drug substance. This protocol is acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress and to investigate the risk of presence of nitrosamine in their medicinal products, the CHMP recommends the following points for investigation:

- *It is recommended that an updated risk evaluation on the potential presence of nitrosamine impurities in (name active substance + finished product) is conducted within six months of the marketing authorisation. In the event that a risk of presence of nitrosamines is identified as a result of the risk evaluation, confirmatory testing should be carried out using appropriately validated and sensitive methods within a year after the marketing authorisation or at an earlier time if otherwise justified. If nitrosamine impurities are found to be present, appropriate risk mitigation steps should be implemented.*

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Primary pharmacodynamic studies

Bempedoic acid is a novel orally active small molecule with a molecular weight of 344.5 Da that upon activation by very long chain acyl-Coenzyme A synthetase 1 (ACSLV1) into bempedoyl-CoA (ETC-1002-CoA) functions as a competitive inhibitor of adenosine triphosphate-citrate lyase (ACL). ACL is an enzyme upstream of 3-hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) and of acyl-CoA carboxylase (ACC) in the cholesterol biosynthesis pathway. ACL converts citrate into acetyl-Coenzyme A (acetyl-CoA), which then is formed into HMG-CoA by ACC. Subsequently, this HMG-CoA is converted into mevalonic acid by HMG-CoA reductase. Selective inhibitors of HMG-CoA reductase, such as statins, decrease sterol (cholesterol) synthesis, while inhibitors of ACC reduce fatty acid synthesis and catabolism. An inhibition of ACL may, therefore, inhibit both cholesterol as fatty acid synthesis. Inhibition of cholesterol synthesis has been shown to result in an upregulation of hepatic LDL-R protein expression and increased the clearance of LDL-C by LDL-R from plasma.

Primary pharmacodynamics: In vitro

The Applicant demonstrated, using radiolabeled substrates, such as [^{14}C]acetate, [^{3}H]H_2O, [^{14}C]pyruvate, and [^{14}C]glucose, as metabolic precursors, that bempedoic acid inhibited de novo sterol and fatty acid synthesis in primary rat hepatocyte cultures and livers of treated rats. The [^{14}C]acetate incorporation into fatty acids and sterol fractions were reduced with an IC_{50} of 8.5 µM and 3 µM, respectively. Inhibition of lipid synthesis was also demonstrated in primary human liver cells, where bempedoic acid blocked both fatty acid and sterol synthesis using labelled precursors. In addition, in both primary human hepatocytes and rat hepatoma cells, bempedoic acid increased sterol response element binding protein 2 (SREBP2) gene transcription, LDL-R expression and LDL-R related uptake, which was also found with statin treatment.

To determine the enzyme in the lipid synthesis pathway targeted by bempedoic acid, a quantitative assessment of multiple metabolic intermediates of lipid synthesis was conducted and bempedoic acid was found to reduce several metabolites including the product of ACL, acetyl-CoA, while transient increases in its substrate, citrate, were observed suggesting that bempedoic acid inhibited the lipid synthesis pathway at the point of ACL.

Enzyme kinetic analyses in a cell free recombinant human ACL enzyme assay, however, demonstrated that not bempedoic acid but bempedoyl-CoA inhibited the ACL enzyme and that bempedoyl--CoA acted as a competitive inhibitor of ACL for CoA competition (Ki = 2 µM) and not on ATP competition. The formation of CoA ester of bempedoic acid was shown to occur primary in rat hepatocyte s incubated with bempedoic acid (up to 100 µM).

With respect to the other rate limiting enzymes within in the lipid biosynthetic pathway, neither bempedoic acid nor bempedoic acid-CoA inhibited HMG-CoA reductase, and that bempedoic acid did not inhibit ACC, while bempedoyl-CoA demonstrated a weak inhibition of ACC with an IC50 at 29 ± 5 µM. In line with the absence of inhibition of sterol synthesis downstream of HMG-CoA reductase, bempedoic acid did not inhibit [^{14}C]mevalonolactone incorporation in primary rat hepatocytes, which is consistent with an inhibition of sterol synthesis at the point of ACL and/or ACC.

Using selective inhibitors, ACSVL1 was found to be the specific acylCoA synthetase (ACS) isoform that catalyzes the CoA activation of bempedoic acid. In primary human liver microsomes (n=8) a mean activity of 784.8 ± 124 pmol/mg/min was found. In addition, gene silencing of ACSVL1, using siRNA, strongly reduced bempedoic acid-CoA formation and the effect of bempedoic acid on de novo lipid synthesis in McArdle (rat hepatoma) cells.

Primary pharmacodynamics: *in vivo*

The effects of bempedoic acid on lipid synthesis was studied in the diet-induced, and cholestyramine fed Sprague-Dawley (SD) rat models of enhanced lipogenesis. The ^{14}C-acetate incorporation in lipids (sterol and fatty acid) in serum and liver was dose-dependently reduced by bempedoic acid (3 - 100 mg/kg, po). Such an inhibition of lipid synthesis was not found in a (fasted) model with non-enhanced lipid synthesis. In high-fat high-cholesterol (HFHC)-fed male golden Syrian hamsters, bempedoic acid (30 mg/kg/day, po QD, 3 wks) induced a reduction in LDL-C and VLDL-C, triglycerides and cholesterol, while HDL-C levels remained unchanged.
Bempedoic acid was also administered daily to normal chow-fed male SD rats (2 weeks) and Golden Syrian Hamsters (3 weeks) to assess the effects on normal, non-enhanced, lipid metabolism. The initial changes (Week 1), such as a decrease in VLDL-C and triglyceride, were no longer observed after 2 weeks due to a metabolic compensatory "rebound" response. In hamsters, an increase in HDL-C levels without an effect on non-HDL-C levels was found.

The obese Zucker Fatty rat has a mutation in the leptin receptor that induces hypertriglyceridemia with increased VLDL-C and decreased HDL-C levels. Bempedoic acid dose-dependently increased HDL-C and

β-HBA and decreased non-HDL-C, triglycerides and non-esterified fatty acids, indicative of decreased de novo synthesis of fatty acids and increased metabolic utilization of triglycerides.

In the apolipoprotein E knockout (ApoE KO) mouse, a model of dyslipidemia and atherosclerosis in mice, bempedoic acid treatment (30 mg/kg, PO, daily for 14 days) decreased LDL by 61% and increased HDL (+300%) and VLDL (+23%), while total cholesterol did not change. The cholesteryl ester content in vascular tissues was not significantly changed. After long-term bempedoic acid treatment (30 mg/kg, PO, daily for 12 weeks) to ApoE mice, only LDL was reduced (38%), while no HDL or VLDL or total cholesterol change was seen. In addition to a reduction in plasma liver cholesterol (-28%) and liver triglycerides (-74%), a 2-fold upregulation of LDL-R in the liver was seen with bempedoic acid treatment. Whole aorta cholesterol content and vascular atherosclerotic lesion size, which were increased 2.5-fold and 7-fold, respectively, were attenuated 38% and 21%, respectively, by bempedoic acid treatment. In the ApoE & AMPKβ1 Double Knock-Out (DKO) mice similar lipid and LDL-R responses were seen with bempedoic acid treatment as found in the ApoE KO mouse although no liver AMPK activity was detected, suggesting independence of AMPK pathway.

In both $LDLR^{+/-}$ and $LDLR^{-/-}$ Yucatan miniature pigs fed an HFHC diet, plasma cholesterol and LDL-C increased over 160 days. Bempedoic acid treatment (120 or 240 mg/day, orally) reduced LDL-C leading to a ~50% and ~30% reduction in $LDLR^{+/-}$ and $LDLR^{-/-}$, respectively, as compared to placebo after 160 days of treatment. No consistent effects of bempedoic acid were observed on HDL-C, VLDL, liver lipids or triglycerides. Bempedoic acid treatment decreased aortic and abdominal lesion size in these minipigs with about 50% as compared to placebo.

Primary pharmacodynamics: Metabolites

ESP15228 (M1) is the 8-keto metabolite of bempedoic acid and is in humans a major metabolite. Therefore, also the pharmacological properties of this metabolite on lipid synthesis were analysed. ESP15228 inhibited the synthesis of both sterols and fatty acids in the primary rat hepatocyte model with an IC_{50} for both pathways of less than 3 µM, similar to bempedoic acid. In contrast to bempedoic acid or ESP15228, the glucuronides of bempedoic acid (M11) and of ESP15228 (M15) did not inhibit lipid synthesis *in vitro* at 100 µM in primary mouse hepatocytes, which corresponds to 7- and 50-times the circulating human Cmax.

In vivo in cholestyramine-primed rats, ESP15228 displayed reduced hepatic fatty acid and sterol synthesis in the liver and in the obese Zucker Fatty rat model, similar effects were found with ESP15228 as with bempedoic acid. ESP15228, however, did not inhibit ACC activity nor did ESP15228 activate the AMPK pathway.

Secondary pharmacodynamic studies

Bempedoic acid had no significant effect (IC_{50} <100 µM) in an *in vitro* binding screen using a broad panel of isolated human receptors, ion channels, transporters, and enzymes.

It was shown that ACSVL1 is not expressed in microsomes preparations from human skeletal muscle, or in primary human myotubes or L6 myotubes, while ACSVL1 expression was highest in liver microsomes and expression in human kidney microsomes was only 10% of that observed in liver. Consistent with the lack of ACSVL1 expression in skeletal muscle, bempedoic acid-CoA was not formed in these tissues, and bempedoic acid did not suppress sterol synthesis or promote cytotoxicity in rat and human myotube cultures. In addition, no signs of muscle-related toxicological effects were seen in rat, mouse or monkey upon long-term dosing. The muscle-related complaints found with statins, myalgia, may be related to its effect in cholesterol biosynthesis pathway (mevalonate depletion leading to subsequent myotoxicity). Bempedoic acid, however, does not seem to impact cholesterol synthesis in muscle.

Another difference with statins is its inhibitory effects on fatty acid biosynthesis. The coordination between fatty acid synthesis and fatty acid oxidation occurs at the level of acetyl-CoA carboxylase (ACC), the rate-limiting enzyme of fatty acid synthesis. ACC produces malonyl-CoA which is a potent allosteric inhibitor of the mitochondrial long chain fatty acid transporter protein carnitine palmitoyltransferase-I (CPT-I). In vitro studies with primary rat hepatocytes using a cofactor for CPT-I activity and a CPT-I inhibitor suggest that the suppression of fatty acid synthesis by bempedoic acid activates CPT-I-dependent import of long-chain fatty acids into mitochondria for subsequent β-oxidation and that bempedoic acid does not adversely affect intra-mitochondrial oxidation pathways.

In vitro and *in vivo* studies showed that treatment with bempedoic acid coincided with increases in AMPKα phosphorylation, a marker of AMPK activation, which was found to be due to a direct, allosteric, interaction of bempedoic acid-CoA but not bempedoic acid with AMPK complexes in a β1-dependent manner. The contribution of AMPK activation to the pharmacodynamic effect of bempedoic acid in humans, if any, is expected to be low as the liver predominately expresses not β1, but AMPK β2-containing complexes and ACSVL1 are mainly expressed in the liver.

In human monocyte-derived macrophages, bempedoic acid partially blocked the LPS-induced decreases in AMPK phosphorylation, which coincided with decreased production of some pro-inflammatory cytokines and chemokines. In vivo, bempedoic acid attenuates homing of leukocytes into inflammatory sites and inhibits adipose tissue inflammation in a mouse model of diet-induced obesity but whether these specific effects are observed in humans remains to be demonstrated.

Given the low binding affinity, peroxisome proliferator-activated receptor (PPAR) activation was not considered a viable molecular target responsible for the effects of bempedoic acid on the lipid biosynthesis pathway.

Secondary pharmacodynamics: In vivo

In mice, daily bempedoic acid treatment (30 mg/kg/day, po, QD) for seven days slightly increased faecal neutral cholesterol excretion and increased gallbladder biliary cholesterol compared to vehicle, without affecting gallbladder biliary phospholipid content. Bempedoic acid did not affect fractional cholesterol absorption, while ezetimibe (10 mg/kg/day, po, QD) completely blocked cholesterol absorption.

LDL-R deficient mice maintained on high cholesterol containing diets develop hyperlipidemia, hepatic steatosis, and atherosclerosis. Treatment with bempedoic acid (po, QD, 10 - 100 mg/kg) for 12 or 16 weeks induced strong reductions in diet-enhanced serum lipids, had profound reductions in aortic lipid content and dose-dependently reduced atherosclerotic lesions and an attenuation of the diet-induced inflammatory response in liver, plasma and aorta.

The effects of bempedoic acid on triglycerides, glycemic control (glucose, insulin) and body weight were investigated in the hypertriglyceridemic obese KKA^{y} mouse model of insulin resistance, diet-induced obese (DIO) mice, male golden Syrian hamsters, on a fructose diet to induce hyperglycemia. In these rodent models, bempedoic acid was found to reduce triglycerides, and partly improve glycemic control. However, given that these effects seem to be dependent on diet and bempedoic acid most of the times reduced body weight gain, the relevance of these effect for humans is unclear.

Following 12 weeks of daily oral dosing in KKA^{y} mice, which are hypertriglyceridemic, spontaneously obese and insulin resistant, bempedoic acid (10 & 60 mg/kg) reduces circulating and hepatic triglycerides and partly improved glucose tolerance. The combined effects observed in the KKAy mouse model suggests bempedoic acid acts as a metabolic regulator of lipid and carbohydrate imbalances.

DIO mice develop obesity, hyperinsulinemia, mild hyperglycemia, impaired insulin sensitivity, impaired glucose tolerance, and elevated hepatic triglycerides in response to the high (60%) fat diet. Treatment

of these mice with bempedoic acid for 9 weeks, dose-dependently attenuated body weight gain and resulted in reductions in hepatic (46%) and plasma (26%) triglyceride content, fasting glucose (16%), and fasting insulin (92%). Reductions in HOMA-IR suggest reduced insulin resistance, while increases in QUICKI scores and reductions in insulin tolerance test glucose indicate improved insulin sensitization. Glucose tolerance tests demonstrated that DIO mice had impaired glucose tolerance relative to the lean diet fed mice. Bempedoic acid, however, had no impact on glucose tolerance in this study.

In male golden Syrian hamsters, on a 60% fructose diet to induce hyperglycemia (acute insulin resistance marked by impaired glucose tolerance and insulin sensitivity), bempedoic acid treatment resulted in improved postprandial glucose, improved glucose tolerance, and improved insulin sensitivity unrelated to fasting glucose or insulin levels. Bempedoic acid treatment reduced body weight gain and produced reductions in hepatic and plasma triglycerides although no changes in plasma total cholesterol or ApoB were observed.

Finally, the effects of bempedoic acid on elevated blood pressure was investigated in female spontaneously hypertensive obese (SHROB) Koletsky rats but given that the SHROB rat model is a hyperphagic obesity driven model of hypertension, and that bempedoic acid was associated with reduced food consumption, it was not possible to determine whether the anti-hypertensive effects or improvements in other outcomes observed in this study were directly and/or indirectly related to bempedoic acid treatment.

Safety pharmacology programme

In safety pharmacology studies, bempedoic acid administration was not associated with adverse effects on CNS, pulmonary, or cardiovascular function.

Bempedoic acid had no significant effects on the inhibition of the hERG current at concentrations up to 300 µM, while a slight increase (5.4%) was found at 1000 µM (345 µg/mL), which is at 575 times the anticipated Cmax of unbound bempedoic acid (0.6 µg/mL) at the proposed human dose of 180 mg. Therefore, no hERG-related effects on QT interval would be expected in humans. Furthermore, up to 100 mg/kg given orally to male monkeys, bempedoic acid did not produce any significant change in cardiovascular parameters such as heart rate, blood pressure (systolic, diastolic, mean arterial), or ECG parameters (QRS duration, or PR, RR, or QT intervals). Thus, bempedoic acid did not affect cardiovascular function in monkeys.

Bempedoic acid did not have any physiologically significant acute or residual effects on arousal/activity, autonomic, neuromuscular, or physiological functions but significant decreases in thermal response were observed in the rat at 100 mg/kg 4 and 24 hours postdose.

There were no bempedoic acid related changes in any respiratory function parameters (respiratory rate, tidal volume, minute volume) in rats given single oral doses up to 100 mg/kg. Thus, bempedoic acid did not affect pulmonary function.

No stand-alone safety pharmacology studies have been performed concerning the potential effects of bempedoic acid to affect renal function/urinary parameters, but this is evaluated in the general toxicity studies (rat/monkey).

Pharmacodynamic drug interactions

No apparent and consistent pharmacodynamic interactions with respect to LDL-C lowering in LDL-R deficient mice was observed when 30, 100, or 300 mg/kg/day bempedoic acid was given for 2 weeks

alone or in combination with atorvastatin at 10 or 30 mg/kg/day as the LDL baseline levels and changes were highly variable, not consistent over the different doses, and troubled by rebound effects on lipogenesis.

In conclusion, bempedoic acid acts as a prodrug that requires activation by ACSLV1 to form bempedoic acid-CoA, which mediates competitive inhibition of ACL. Inhibition of ACL decreases cholesterol synthesis in the liver leading to increased SREBP2 and LDL-R expression and LDL clearance from the blood. Inhibition of ACL by bempedoic acid-CoA decreases LDL-C via the same pathway as HMG-CoA reductase inhibition by statins but at an upstream enzyme step. In addition, unlike statins, an inhibition of liver fatty acid biosynthesis and a reduction in triglycerides was seen.

2.3.3. Pharmacokinetics

The PK profile of bempedoic acid was investigated following oral administration of ^{14}C-bempedoic acid to rats, rabbits and monkeys. Toxicokinetic studies were performed in mice, rats, rabbits and monkeys.

Methods of analysis

Bempedoic acid and its active metabolite ESP15228 were analysed in the serum of mice, rats, rabbits and monkeys using validated LC-MS/MS methods. Regarding selectivity, carry-over, calibration, accuracy, precision, dilution integrity, matrix effect and stability, the methods were sufficiently validated. Validated LC-MS/MS methods were also used for the measurement of ezetimibe and ezetimibe glucuronide in the serum of rats and atorvastatin, and 2-hydroxyatorvastatin and 4-hydroxyatorvastatin in serum of monkeys in combination studies. In distribution studies in rats, radioactivity in tissues was analysed by whole-body autoradiography (single dose studies) or liquid scintillation counting (repeated dose study). Metabolite profiling in plasma, urine, bile (rats only), liver and feces of rats and monkeys and in plasma of rabbits was performed by HPLC. The metabolites were identified using LC-MS/MS on all peaks accounting for > 2% of sample radioactivity. Radioactivity in excreta was analysed using liquid scintillation counting.

Absorption

Bempedoic acid was highly permeable through Caco-2 cell monolayers. The efflux ratio of 0.7 indicates that bempedoic acid permeates Caco-2 cell monolayers primarily by a passive mechanism.

In repeated dose studies in mice, exposure increased approximately dose-proportionally. Exposure decreased with time.

In rats, Tmax was 8 h, and elimination half-life was 27 h after oral administration of a single dose of 100 mg/kg bempedoic acid. After administration of 10 mg/kg of ^{14}C-bempedoic acid, Tmax of radioactivity was 2 h, and elimination half-life was 18 h, suggesting delayed absorption at the higher dose. The volume of distribution of bempedoic acid was 123 mL/kg, indicating that it was not distributed beyond the extracellular fluid in rats. Comparison of intact and bile duct-cannulated rats showed the occurrence of enterohepatic recirculation (contributing approximately 39% to the total AUC). No study with IV administration was performed, and therefore, oral bioavailability could not be calculated. However, the mass balance study demonstrated that bioavailability was at least 90% in rats. In repeated dose studies in rats, concentrations of bempedoic acid and ESP15228 increased more than dose-proportionally up to 100 mg/kg/day, while it increased less than dose-proportionally at higher doses, suggesting saturation of the absorption mechanism at the higher doses. Exposure decreased with time, except in pregnant rats, where this effect was less. In juvenile rats, Cmax at 10 mg/kg/day was comparable to adult rats. AUC0-24h on day 1 in juvenile rats was slightly higher than in adult rats; afterwards, it was comparable.

After oral administration of 20 mg/kg of ^{14}C-bempedoic acid to rabbits, Tmax was 4 hours. The elimination half-life of radioactivity was 10-13 h. In pregnant rabbits, exposure increased in time from gestation day 6 to 18. Accumulation ratio was ≤ 2 for bempedoic acid and 2.6-4.0 for ESP15228 (based on AUC0-24h).

After oral administration of 10 mg/kg of ^{14}C-bempedoic acid to cynomolgus monkeys, Tmax was 1 hour. The elimination half-life of total radioactivity from plasma was 18 h. No evidence of enterohepatic recirculation was found. No study with IV administration was performed, and therefore, oral bioavailability could not be calculated. From the mass balance study, it can only be concluded that the bioavailability was at least 49%. In repeated dose studies in monkeys, AUC of bempedoic acid and ESP15228 increased more than dose-proportionally at doses from 10 to 60 mg/kg/day and approximately dose-proportionally from 50 to 500 mg/kg/day. Cmax increased approximately dose-proportionally in monkeys. Exposure increased in time. Accumulation ratio in monkeys was 2.0-2.4 for bempedoic acid and 2.0-2.9 for ESP15228.

No consistent gender effects were observed in mice and monkeys. In rats, no gender effect was observed in the exposure to bempedoic acid. Exposure to ESP15228 was slightly lower in females than in males in adult rats, but not in juvenile rats.

Food effect was not studied in the non-clinical studies.

Distribution

Protein binding of bempedoic acid was high and similar between species (mouse, rat, monkey and human) up to 100 µg/mL (94-97%). ESP15228 and bempedoic acid glucuronide were also highly protein bound in human plasma (99%). Radioactivity was quickly distributed in tissues of rats with maximal tissue concentrations at 2 h post-dose. For most tissues, except liver and kidney, the tissue-blood (T/B) ratio was found to be <1. The highest concentrations were found in liver, kidney and lung and contents of the GI tract. The liver is the main target organ of toxicity in rats (see section 4.2). There was no retention in melanin-containing tissue. At 168 h after administration, only low concentrations were found in liver, kidney and the GI tract. After 14 days dosing with 10 mg/kg/day, maximal concentration in the liver was approximately 2-fold higher compared to a single dose, while concentrations in kidney, skeletal muscle and whole blood were comparable to those after single dosing. Bempedoic acid-related radioactivity did not preferentially partition into red blood cells of rats, rabbits and monkeys. Placental transfer and excretion in milk have not been studied.

Metabolism

In hepatocytes of the mouse, rat, cynomolgus monkey and human, the largest metabolite found was bempedoic acid glucuronide conjugate and to a lesser extent ESP15228-glucuronide conjugate. In addition, 11 minor metabolites were found. A study in human hepatic microsomes showed that P450 enzymes are not involved in the metabolism of bempedoic acid and ESP15228. In human hepatic microsomes, UGT2B7 was identified as the enzyme responsible for the glucuronidation of bempedoic acid and ESP15228. Some induction of CYP2C8 activity by bempedoic acid was found at 300 µM in human hepatocytes of 3 donors. An increase in CYP2C8 mRNA content was found in 1 donor. At 300 µM, also some induction of CYP2C9, CYP2C19 and CYP3A4 was observed, but to a lower extent than CYP2C8 and with no increase in mRNA content. Since 300 µM corresponds to approximately 5x the human Cmax at a dose of 180 mg/day, and no significant induction was observed at 30 µM, these effects are not expected to be clinically significant. In human hepatic microsomes, no significant inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 by bempedoic acid was observed. UGT1A1 was inhibited by bempedoic acid and bempedoic acid glucuronide by ≥50%. UGT1A3 was inhibited by bempedoic acid by approximately 50%. Because the

study was performed using concentrations of 10x human Cmax, the potential for UGT inhibition at clinically relevant concentrations is expected to be low.

The parent compound bempedoic acid was the major component in plasma of rats, rabbits and monkeys. The most important metabolic pathway is conjugation, mainly with glucuronide but also (to a minor extent) with glutathione, taurine and glycerol. A minor pathway found in all investigated species was the formation of the keto-metabolite ESP15228. In rats, a relevant pathway was the formation of hydroxylated or acid metabolites of which the most important (rats) was M2, mono-hydroxymethyl bempedoic acid. In monkey, also a glucuronide of ESP15228 was formed (M15), while M2 could not be found in the plasma of monkeys. Metabolism in monkeys corresponded well to metabolism in humans, with the parent compound comprising the major part of radioactivity in plasma and the formation of ESP15228, bempedoic acid glucuronide (M11) and ESP15228 glucuronide (M15), though, in humans, larger parts are converted into M11 and M15 than in monkeys. Metabolism in rats corresponded less well to human metabolism since M11 and M15 were not found in the plasma of rats and ESP15228 in lower amounts than in humans and monkeys. There are no unique major human metabolites. However, M15 was found only in low amounts in the plasma of monkeys (1.8-2.7% of sample radioactivity between 4 and 24 h after dosing) and it was not found in rats. This is not expected to be a problem for safety though, because M15 is the glucuronide conjugate of ESP15228, which was formed in sufficient amounts in monkeys and can be considered sufficiently investigated, and the glucuronide of ESP15228 is not expected to be more toxic than ESP15228.

Excretion

Following oral administration of ^{14}C-bempedoic acid to rats, excretion of total radioactivity occurred primarily via the bile (86% of the dose) and to a lesser extent via urine (17% of the dose). The rat data show that bempedoic acid was well-absorbed in rats (oral bioavailability was at least 90%). Total recovery was high in rats (97% after 120 h in intact rats and 93% after 48 h in bile duct-cannulated rats) and slightly lower in monkeys (86% after 120 h). Following oral administration of ^{14}C-bempedoic acid to cynomolgus monkeys, excretion occurred for a larger part in urine (49% of the dose) than in feces (29% of the dose) at 120 h post-dose. Regarding oral bioavailability in monkeys, it can only be concluded that it was at least 49%. Excretion in humans occurred primarily via urine (~70% of the dose), and therefore, in this respect, the monkey is a more clinically relevant animal model than the rat.

Pharmacokinetic drug interactions

A combination of bempedoic acid (30 mg/kg/day) and ezetimibe (750 mg/kg/day in male rats, 250 mg/kg/day in non-pregnant female rats and 183-720 mg/kg/day in pregnant rats) had no effect on the exposure to bempedoic acid and ESP15228 in rats (males and non-pregnant females as well as pregnant rats), compared to administration of bempedoic acid alone. Effects of the combination on ezetimibe exposure were not consistent, most likely due to extensive enterohepatic cycling of ezetimibe/ezetimibe glucuronide. When ezetimibe was combined with 30 mg/kg/day bempedoic acid, exposure to ezetimibe + ezetimibe-glucuronide increased at least 2 times. In combination with 10 mg/kg/day bempedoic acid, only a slight increase in exposure to ezetimibe + ezetimibe glucuronide (approximately 10-30%) was observed. The exposures to bempedoic acid, ESP15228, atorvastatin and 2-hydroxyatorvastatin in cynomolgus monkeys were not significantly affected by the combination compared to when bempedoic acid (20 mg/kg/day) or atorvastatin (5 mg/kg/day) were administered alone.

2.3.4. Toxicology

Single dose toxicity

Bempedoic acid showed low oral acute toxic potential in rats and monkeys. The oral LD50 was > 1000 mg/kg in rats and >2000 mg/kg in monkeys.

In rats, body weight gain was decreased in males 14 days after dosing. In monkeys, body weight loss and emesis were observed in both sexes, but without a clear dose-relation. Food consumption was decreased at ≥500 mg/kg. Slight increases in liver and kidney related parameters and decreases in glucose were noted in both species.

Repeat dose toxicity

In mice, treatment with bempedoic acid by oral gavage was associated with decreased plasma glucose levels (starting at 300 mg/kg) and adverse effects on the liver (hepatocellular degeneration; hepatocellular cytoplasmic alteration; diffuse vacuolation; increased Kupffer cell pigment and centrilobular to panlobular hepatocellular hypertrophy at all doses, and increased ALP, AST and ALT levels and individual hepatocyte necrosis at doses ≥300 mg/kg/day). In addition, testes and seminal vesicle weight were decreased, associated with seminiferous tubule degeneration/atrophy. At the highest dose (1000 mg/kg), 3 females were found dead or were euthanatized in extremis due to poor condition and clinical signs. At this dose, erythrocyte count, hemoglobin, and hematocrit were also decreased.

Bempedoic acid-induced liver toxicity in rats, shown by increased liver enzymes (ALP, GGT, ALT, AST), accompanied by increased liver weight and microscopic findings (centrilobular to panlobular hepatocellular hypertrophy, individual hepatocyte necrosis, hepatocellular vacuolation, bile duct hyperplasia). The microscopic effects in the liver were not completely reversed after 4 weeks recovery. According to the applicant, hepatocellular hypertrophy without further microscopic hepatic changes such as necrosis is not considered adverse. However, there is a clear dose-relationship in all studies, with hepatocellular hypertrophy as the first sign of liver damage, which progresses at increasing doses. Therefore, according to the assessor, hypertrophy should be considered as the first sign of adverse liver damage.

Reduced erythrocytes, hemoglobin, and haematocrit were also observed in rats, as well as increased numbers of total leukocytes, neutrophils, and monocytes. In addition, decreases in prothrombin time (PT) and in activated partial thromboplastin time (APTT) were observed.

High dose levels induced clinical signs, as moribundity, impaired limb function, hunched posture, thin appearance, decreased activity, ataxia, tonic convulsions, prostration, skin cold to the touch, lateral recumbency, and abnormal breathing.

Furthermore, bempedoic acid treatment in rats resulted in decreased body weight and increased glucose, calcium, and cholesterol levels. Only at the highest dose in the 6-month study, a decrease in glucose levels was observed. Considering the pharmacologic effect of bempedoic acid, an increase in cholesterol is unexpected. However, this can be explained by a metabolic compensatory response at low doses (see 2.1.2)**.**

Kidney effects (increased creatinine and increased incidence and severity of the renal tubular dilatation) were observed in the 3-month study, but not in the 1- and 6-month studies. An enlarged spleen, accompanied by extramedullary hematopoiesis was only observed in the 1 month study.

In the monkey, decreased body weight, reduced circulating red cell mass, prolonged APTT and PT were observed. The effects on the liver were less prominent in the monkey compared to adverse liver effects in rodents and were restricted to increased liver weight, centrilobular hepatocellular hypertrophy and periportal hepatocellular vacuolation. This can be explained by the fact that bempedoic acid metabolism in rodents occurs predominantly via the liver, whereas in monkeys, it is shifted more towards the kidney. It is noted that, concerning metabolism, the monkey more closely resembles the human than the rodent, and therefore, liver effects observed in monkey are more relevant for humans.

Increased creatinine levels were observed in all pivotal monkey studies, however, no related microscopic changes were observed in the kidney.

In the 3-month study, morphological changes were observed in the bone marrow that were indicative of early myelofibrosis and cytotoxicity.

In all species, overall, adverse effects seemed to be slightly more pronounced in females.

Combination studies with bempedoic acid and ezetimibe in rats up to 3 months resulted in similar effects and with similar magnitude as bempedoic acid alone.

Combined administration of bempedoic acid and atorvastatin in monkeys resulted in mortality at dose levels where either of the products alone did not result in severe toxic effects. The combination resulted in an exaggeration of effects observed with atorvastatin alone and included gastrointestinal effects (red/watery feces, hemorrhage/inflammation in large intestine) and findings consistent with inflammation (increased neutrophils and/or monocytes and fibrinogen), correlating with bone marrow granulocytic hyperplasia at high doses. Depletion of splenic red pulp was also observed.

Hepatic toxicity, including an increase in liver enzymes, panlobular hepatocellular hypertrophy, centrilobular hepatocellular vacuolation and necrosis were also observed in the animals receiving combination treatment.

The results indicate that atorvastatin in combination with bempedoic acid can result in excessive toxicity. However, according to the applicant, no adverse effects were observed at a combination of 20 mg/kg bempedoic acid and 5 mg/kg atorvastatin, however, red and watery feces was observed in all treatment groups receiving atorvastatin (alone or in combination with bempedoic acid) which were not fully reversed in the recovery period.

Genotoxicity

Bempedoic acid was not mutagenic in the Ames test. Increases in chromosome aberration were observed in human peripheral blood lymphocytes *in vitro*, but only in the presence of S9 and at a concentration associated with a level of cytotoxicity that approached or exceeded the maximum permissible. No DNA damage in the liver (rat) and genotoxic effects in bone marrow in rats and mice were observed. It can, therefore, be concluded that these studies indicate that bempedoic acid is not genotoxic.

Carcinogenicity

The carcinogenic potential of bempedoic acid was evaluated in a 2-year study in mice and rats. In mice, bempedoic acid was administered daily orally at doses of 25, 75, or 150 mg/kg/day. In males, an increased incidence of hepatocellular adenomas and carcinomas was observed at the mid dose and higher in a dose-responsive manner.

In a 2-year study, rats were administered daily oral doses of 3, 10, and 30 mg/kg/day bempedoic acid. Treatment was associated with an increased incidence of hepatocellular adenomas and thyroid follicular cell adenomas in male rats. In both rats and mice, no carcinogenic potential was observed in females.

The applicant suggests that the bempedoic acid-related increases in tumor incidence are attributable to PPARα activity. Indeed, this theory is consistent with the results observed in the repeated dose studies in rats (but not monkeys) and *in vitro* studies showing low potency activation of PPARα in the liver, but the absence of PPAR-mediated adverse effects in other organs (heart, skeletal muscles and bone marrow). Furthermore, the carcinogenic response is similar to that observed in mice and rats treated with other PPARα agonists. Since it is known that PPARα activation-mediated mechanism of tumor development is rodent-specific, the observed carcinogenesis in the liver is not considered relevant for humans. In addition, the development of thyroid tumors in rats is considered to be secondary to increased liver metabolism of thyroid hormone (related with PPARα activators) and is therefore also not considered relevant for humans.

Reproduction Toxicity

In the repeated dose toxicity study in mice, testes and seminal vesicle weight were decreased, associated with seminiferous tubule degeneration/atrophy.

In the combined oral fertility Study in rats, treated males were mated with treated females from the same dose group. Although no effects were observed on fertility indices, a decreased number of corpora lutea, implantation sites, viable embryos, and litter size was observed at the mid dose and an increase in estrous cycle length and pre-implantation loss, as well as a decrease in sperm count (16%) were observed at the high dose.

Extrapolation from rat TK repeat dose studies indicates that exposure at the NOAEL was 5 times below those obtained in humans. These findings are likely relevant for humans.

In the rat embryo-fetal development study, maternal toxicity was evident from the mid-dose on, which, according to the applicant, resulted in foetal toxicity in the form of reduced fetal weight and an increased number of skeletal malformations and variations. These effects can be considered as skeletal retardations, associated with delays in ossification, and are transient and reversible after birth.

In the rabbit embryo-fetal development study, maternal toxicity was evident at the high dose, however, no effects on fetal development or induction of malformations or variations were observed in the rabbit. The NOAEL for development was 80 mg/kg (AUC0-24 of ETC-1002 plus ESP15228 3906 µg·hr/mL), associated with approximately 12 times human exposure at 180 mg/day.

In the pre- and postnatal development study in the rat, bempedoic acid produced excessive maternal toxicity and increased neonatal mortality at doses ≥ 30 mg/kg. The NOAEL for F1 pup growth, survival, and behavioural assessments (slower learning) was 5 mg/kg/day, and the NOAEL for the postweaning maturation and reproductive performance of the F1 generation was 20 mg/kg/day. Extrapolation from other studies indicates that exposures at the NOAEL for the postweaning maturation and reproductive performance were similar to those obtained in humans. These findings are likely relevant for humans.

In a dose range finding study in juvenile rats, toxicity leading to excessive body weight loss and moribundity was seen at a dose of 60/30 mg/kg/day. A dose of 10 mg/kg/day was therefore chosen as the high dose in the pivotal juvenile Study.

In the dose range finding study and the pivotal Study, a similar toxicological profile compared to that found in adult rats was observed, including decreased body weight gain, decreased red cell mass, increased cholesterol and reversible, adaptive liver changes. Exposures at the NOAEL in juvenile rats

(10 mg/kg/day) were approximately 0.2 times exposure in humans at 180 mg/day, comparable to exposures in adult rats at the NOAEL.

Toxicokinetic data

Maximal exposure multiples achieved in the toxicology studies were in general sufficient: Based on AUC0-24h, for bempedoic acid it was up to 26x, 18x, 11x and 16x human AUC (at MRHD) in mice, rats, rabbits and monkeys respectively. For ESP15228 it was up to 14x, 7.8x, 2.9x and 18x human AUC in mice, rats, rabbits and monkeys respectively. In juvenile rats, the exposure was low, maximally 1.2x the (adult) human exposure to bempedoic acid and below human exposure for ESP15228. It is noted that the applicant uses human systemic exposures (AUC0-24) of 289 and 51.2 µg·hr/mL for bempedoic acid and ESP15228, respectively (sum 340 µg·hr/mL). Since the origin of these values is not clear, the assessor has used the values derived from Study 1002-035 instead to calculate exposure margins.

The metabolite ESP15228 was a minor metabolite in mice, rats and rabbits (around 5% of bempedoic acid or less). ESP15228 was a larger metabolite in monkeys (around 10% of bempedoic acid or more).

In mice, rats and monkeys, mortality was observed starting at exposures between 7 and 14 times the systemic exposure in humans at 180 mg. The proposed mechanism for the mortality is severe hypoglycaemia occurring at exposures in excess of those required for the pharmacologic activity of bempedoic acid.

Effects on red blood cell mass in mice, rats and monkeys and were observed already at low dose levels, corresponding to 0.15 (rat) to 6.2 times the systemic exposure in humans at 180 mg. The effects were moderate (≤15%), and no meaningful effects were observed in the clinical studies and are therefore not considered relevant for humans. However, decreases in APTT and PT were also observed in rats at exposure levels ≥ 0.15 the systemic exposure in humans at MRHD. Although the findings lack microscopic correlates, we do not agree with the applicant that changes up to 38% are not clinically relevant. Especially in combination with anticoagulants risks due to interactions cannot be excluded.

Bempedoic acid also results in hepatic toxicity, starting with increased levels of hepatic enzymes and progressing via hepatocellular hypertrophy and vacuolation and in rats also to necrosis. The effects are more pronounced in rats and mice than in monkeys which can be explained by the known adaptive response of rodents as well as by the fact that bempedoic acid metabolism is shifted more towards the liver in rodents than in monkeys and humans. In the monkey, the most relevant species for humans, periportal or diffuse vacuolation in the liver was observed in the 12-month study at exposure levels twice the systemic exposure in humans at 180 mg.

Increased plasma creatinine and urea nitrogen levels were also observed in the 12 months starting at exposure levels twice the systemic exposure in humans at 180 mg. However, up to 13 times human exposure at 180 mg, no microscopic changes in the kidney were observed.

In the reproductive toxicity studies in rats, decreased corpora lutea and implantation sites, increased post-implantation loss and resorptions and reduced foetal body weight were observed at exposures 4 times the systemic exposure in humans at 180 mg. In addition, increased incidence of foetal skeletal findings in the scapula and long bones, as well as reductions in numbers of live pups and pup survival, pup growth and learning, were observed at exposures below the systemic exposure in humans at 180 mg. Considering the low or absent exposure margins, it is concluded that these effects might be relevant to humans.

A combination of bempedoic acid (30 mg/kg/day) and ezetimibe (750 mg/kg/day in male rats, 250 mg/kg/day in non-pregnant female rats and 183-720 mg/kg/day in pregnant rats) had no effect on the exposure to bempedoic acid and ESP15228 in rats (males and non-pregnant females as well as pregnant rats), compared to administration of bempedoic acid alone.

Effects of the combination on ezetimibe exposure were not consistent, most likely due to extensive enterohepatic cycling of ezetimibe/ezetimibe glucuronide. When ezetimibe was combined with 30 mg/kg/day bempedoic acid, exposure to ezetimibe + ezetimibe-glucuronide increased at least 2 times. In combination with 10 mg/kg/day bempedoic acid, only a slight increase in exposure (approximately 10-30%) was observed.

In the 3-month study in rats with combination treatment of bempedoic acid and ezetimibe, no adverse effects were observed up to 30/750 mg/kg/day (males) and 30/250 mg/kg/day (females). At these dose levels, systemic exposure (based on AUC0-24) to ezetimibe plus ezetimibe glucuronide is 23 times (males) or 191 times (females) exposure in humans at 10 mg/day. Systemic exposure to ETC-1002 plus ESP15228 at these doses is 1.5-2.5 times exposure in humans at 180 mg/day. This is considered sufficient.

The exposures to bempedoic acid, ESP15228, atorvastatin and 2-hydroxyatorvastatin in cynomolgus monkeys were not significantly affected by the combination compared to when bempedoic acid (20 mg/kg/day) or atorvastatin (5 mg/kg/day) were administered alone.

In the pivotal 3-month study in monkeys with combination treatment of bempedoic acid and atorvastatin, red and watery feces was observed in all treatment groups receiving 5 mg/kg atorvastatin. At this dose level, systemic exposure to atorvastatin plus 2-hydroxyatorvastatin is 0.8 times exposure in humans at 80 mg/day, which means that there is no safety margin. No bempedoic acid-related adverse effects were observed in the groups receiving up to 20 mg/kg bempedoic acid, a dose that resulted in systemic exposure levels to ETC-1002 plus ESP15228 of 3-4 times the exposure in humans at 180 mg/day, which is considered small, but sufficient.

Interspecies comparison

Bempedoic acid was absorbed moderately fast (Tmax 1-3.5 h in humans, 2 h in rats at 10 mg/kg, 4 h in pregnant rabbits, 1 h in monkeys). In rats at 100 mg/kg, Tmax was 8 h, but at that dose there was probably saturation of an absorption mechanism. Oral bioavailability was not directly investigated. It was at least 90% in rats and at least 49% in monkeys. Exposure to bempedoic acid increased dose-proportionally in mice. In rats and monkeys, exposure increased more than dose-proportionally at lower doses (rat up to 100 mg/kg/day, monkey up to 60 mg/kg/day) and less than dose-proportionally at higher doses. In humans, steady-state pharmacokinetics were generally linear over a range of > 60 mg to 220 mg.

No consistent gender effects were observed in mice and monkeys. In rats, no gender effect was observed in the exposure to bempedoic acid. Exposure to ESP15228 was slightly lower in females than in males in adult rats, but not in juvenile rats. In humans, females had a 41% greater increase in steady-state AUC compared with males.

In mice and rats, upon multiple dosing, an exposure generally decreased with time. In pregnant rabbits, monkeys and humans, exposure increased with time (accumulation ratio ≤ 2, 2.0-2.4 and 2.3 in pregnant rabbits, monkeys and humans respectively).

Protein binding of bempedoic acid was high and similar between species (mouse, rat, monkey, human) up to 100 µg/mL (94-97%). In rats, bempedoic acid distributed to a volume less than the extracellular fluid (Vd/F was 123 mL/kg). In humans, Vz/F was 18 L, corresponding approximately to the

extracellular fluid (Davies & Morris, 1993). In all species, bempedoic acid did not preferentially partition into red blood cells.

The major circulating metabolites in monkeys and humans were bempedoic acid, bempedoic acid glucuronide, ESP15228 and ESP15228 glucuronide. In rat plasma, the glucuronides of bempedoic acid and ESP15228 were not present. Instead, mono-hydroxymethyl bempedoic acid was present in the plasma of rats.

The elimination half-life was comparable in rats (18-27 h), monkeys (18 h) and humans (16-33 h). In pregnant rabbits, elimination half-life was shorter (10-13 h). In monkeys and humans, the largest part of a radioactive dose was excreted in urine (49% and 70% respectively), while in faeces, 29% and 30% of the dose was excreted respectively. In rats only 17% of the dose was excreted in urine while 86% was excreted in bile.

In combination studies with ezetimibe in rats and humans, ezetimibe did not affect the exposure to bempedoic acid. In rats, exposure to ezetimibe + ezetimibe-glucuronide increased at least 2 times in combination with 30 mg/kg/day bempedoic acid but not in combination with 10 mg/kg/day bempedoic acid. In humans, total ezetimibe increased 1.6-1.8 times in combination with bempedoic acid.

In combination studies with atorvastatin in monkeys and humans, atorvastatin did not affect the exposure to bempedoic acid. In monkey, bempedoic acid did not affect atorvastatin exposure while in humans only a small increase (1.4x) was observed.

Local Tolerance

Bempedoic acid is intended for oral route of administration, and therefore local tolerance studies are not needed.

Other toxicity studies

Impurities

Three alkyl compounds in the synthesis of bempedoic acid contain halides and may, therefore, be mutagenic. The starting material 1-bromo-5-chloropentane and a synthetic intermediate heptanoic acid, 2,2-dimethyl-7-iodo-ethyl ester (CION-02) were evaluated in bacterial mutagenicity assays. No evidence for mutagenicity was observed. The third compound (CION-01) is similar to CION-02 (contains chlorine instead of iodine) was considered to be not mutagenic given the results for CION-02.

In addition, the potential impurity CION-08-diol was evaluated for mutagenic potential using in silico methods. No structural alerts associated with mutagenicity were found.

PPAR activity

The applicant performed several *In Vitro* Peroxisome Proliferator Activated Receptor Assays. The results indicate that bempedoic acid binding has low potential to activate the PPARα or PPARγ pathways and no potential to activate the PPARδ pathway.

Exploratory mechanisms of toxicity

Studies towards the mechanism of toxicity of bempedoic acid were performed in rats and monkeys. In those studies, high doses of bempedoic acid (100-300 mg/kg) resulted in dose- and time-dependent decreases in plasma glucose in both species, with a reduction of up to 72%-80% in surviving animals, but even more in animals that needed to be euthanized. In addition, hypoglycemia-induced clinical signs were observed in rats and monkeys, including decreased activity, emesis and vomiting (repeated

and occurring in primates only), hunched posture, pallor and tremors. All these effects were reversed during recovery. Further studies indicated that glucose uptake and utilization pathways remain intact. In rat, mild increases in lactate and pyruvate were observed. Nevertheless, increased glucose oxidation as the mechanism for hypoglycemia is not likely to be a major contributor since analysis of lactate and pyruvate do not indicate a change in glucose oxidation in monkeys. Therefore, it is concluded that the mechanism leading to decreases in glucose after exposure to high doses of bempedoic acid likely is decreased gluconeogenesis.

2.3.5. Ecotoxicity/environmental risk assessment

Bempedoic acid is considered to be not PBT, nor vPvB. A risk to the STP, surface water, groundwater, sediment and terrestrial compartment is not anticipated based on the prescribed use of bempedoic acid.

2.3.6. Discussion on non-clinical aspects

In general, the non-clinical pharmacokinetics of bempedoic acid have been adequately investigated. However, in the validation of the LC-MS/MS methods which were used to analyse bempedoic acid and ESP15228 in serum, medium QC was chosen consequently lower than recommended in *the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev 1 Corr 2)* (at approximately 10% of the calibration curve range instead of at 30 – 50% as recommended in the guideline). The applicant has performed additional partial validations of the LC-MS/MS methods, including QCs at around 30 to 50% of the calibration curve range as recommended by the EMA guidance. Reported intra-run accuracy and precision values are adequate.

The results indicate that **atorvastatin in combination with bempedoic acid** can result in excessive toxicity. According to the applicant, no adverse effects were observed at a combination of 20 mg/kg bempedoic acid and 5 mg/kg atorvastatin. However, in the pivotal 3-month study in Cynomolgus monkeys (RR 1002-500-065), red and watery feces was observed in all treatment groups receiving atorvastatin (alone or in combination with bempedoic acid), which were not fully reversed in the recovery period. According to the applicant, changes in stool are common, stress related effects in monkeys. The fecal abnormalities were already observed in all groups before treatment started. Moreover, the discoloured feces in recovery animals were grey or green, but not red or bloody and the lack of clinical chemistry changes as well as the absence of gross or microscopic findings in the histological analysis at termination, indicates that no intestinal injuries were present. Since also in the clinical studies no meaningful gastrointestinal adverse events were observed, it can be concluded that the observed fecal abnormalities in monkeys do not raise concern for humans.

The bempedoic acid-dependent **hypoglycemia and clinical signs of moribundity** were evident with high dose exposure in non-clinical repeat-dose toxicity studies in rodent and monkeys. However, such effects occur only at exposure levels not relevant for humans. In addition, the biochemical changes leading to morbidity and death were reversible upon discontinuation of treatment, and upon administration of high carbohydrate nutritional supplements.

Decreases in APTT and PT were observed in rats at exposure levels $\geq$ 0.15 the systemic exposure in humans at 180 mg. The changes in coagulation parameters in the non-clinical studies were not consistent across species and no microscopic correlates were observed. More importantly, in clinical studies, APTT and PT were found not to be affected. The effects on coagulation as observed in animals, are therefore considered not relevant for humans.

In the rat **embryo-fetal** development study, maternal toxicity was evident from the mid-dose (30 mg/kg) on, which, according to the applicant, resulted in **foetal toxicity** in the form of reduced foetal weight and an increased number of skeletal malformations and variations. However, starting at the low dose (10 mg/kg), there was a statistically significant increase in bent scapula and bent ribs, without any evidence of maternal toxicity. These effects can be considered as skeletal retardations, associated with delays in ossification, and are transient and reversible after birth.

2.3.7. Conclusion on the non-clinical aspects

Overall, the primary pharmacodynamic studies provided adequate evidence that bempedoic acid mediates its effects on cholesterol metabolism via ACL-dependent inhibition of cholesterol synthesis.

From the pharmacokinetic point of view, the rats and monkeys were the most relevant species for non-clinical efficacy and safety studies.

Overall, the nonclinical safety profile of bempedoic acid has been adequately characterized.

2.4. Clinical aspects

2.4.1. Introduction

GCP

All clinical studies were undertaken in accordance with the principles of Good Clinical Practice as claimed by the applicant and applicable regulatory requirements and relevant precedence. There was no lack of concordance with current standard research approaches regarding the design or execution of the development program. All studies were conducted with the approval of Ethics Committees or Institutional Review Boards. Informed consent was obtained for all subjects, and the studies were performed by the version of the Declaration of Helsinki that applied at the time the studies were conducted.

The applicant 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.

- Tabular overview of clinical studies

Tabular overview of clinical studies

The pharmacokinetic (PK) and pharmacodynamic (PD) properties of bempedoic acid administered once daily (OD) were evaluated in a comprehensive clinical pharmacology programme, which included 17 studies (15 Phase 1 and 2 Phase 2), as well as 13 Phase 2 and Phase 3 studies that assessed trough plasma concentrations for population pharmacokinetic (PK) analyses. An overview of the clinical pharmacology programme is provided in Figure 1, Table 1 and Table 2.

Figure 2: Bempedoic Acid Clinical Pharmacology Program

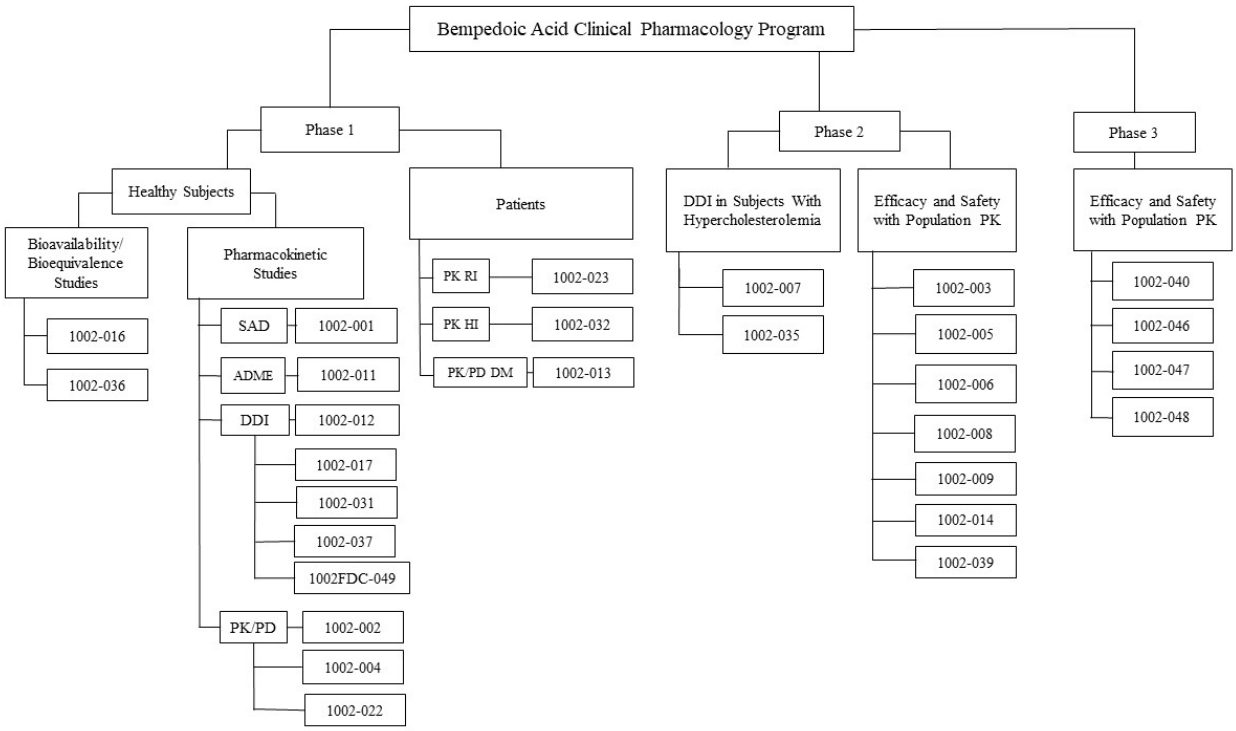


Table 1. Overview of *in vitro* studies using human biomaterial

Objective	**Analyte**		
	ETC-1002	**ESP15228**	**ETC-1002-glucuronide**
Plasma protein binding	RR1002-500-009 RR1002-500-059	RR1002-500-059	RR1002-500-059
Effects on hERG channels	RR1002-500-007	RR1002-500-007	-
Metabolism across species	RR1002-500-010	-	-
CYP isoenzymes			
Potential substrate	RR1002-500-045	RR1002-500-045	-
Induction potential	RR1002-500-012	-	-
Inhibition potential	RR1002-500-011	-	-
Cellular transporters			
Potential substrate	RR1002-500-033 RR1002-500-056 RR1002-500-071	RR1002-500-033 RR1002-500-045	RR1002-500-056 RR1002-500-073
Inhibition potential	RR1002-500-034	RR1002-500-034	RR1002-500-056

	RR1002-500-056 RR1002-500-057 RR1002-500-070		RR1002-500-057 RR1002-500-072
UGT isoenzymes			
Potential substrate	RR1002-500-046	RR1002-500-046	-
Inhibition potential	RR1002-500-058	-	RR1002-500-058

Table 2. Clinical pharmacology studies

Study	Objective	Population	Test product(s)	Dose	Number of subjects
1002-016	Bioequivalence tablet / capsule and food effect	HV	Formulation 1 tablets, 60 and 180 mg Capsules, 20 and 40 mg	180 mg	17 (13M,4F)
1002-036	Bioequivalence tablet formulations	HV	Formulation 1 tablet, 180 mg Formulation 2 tablet (commercial formulation), 180 mg	180 mg	60 (40M,20F)
1002-001	Single ascending dose	HV	Capsules 2.5 and 25 mg	2.5, 10, 45, 125 and 250 mg	18 (17M,1F)
1002-011	ADME	HV	Oral solution 240 mg	240 mg	6 (6M,0F)
1002-002	Multiple ascending dose	Mild dyslipidemia	Capsules 20 mg	20, 60, 100 or 120 mg QD	32 (18M,14F)
1002-004	Multiple ascending dose	HV	Capsules 2.5 and 25 mg	140, 180, or 220 mg QD	24 (22M,2F)
1002-023	Renal impairment	Renal impairment	Formulation 1 tablet 180 mg	180 mg	24 (15M,9F)
1002-032	Hepatic impairment	Hepatic impairment	Formulation 1 tablet 180 mg	180 mg	24 (16M,8F)
1002-012	DDI (low- and mid-dose statins)	HV	Capsules 40 mg, simvastatin 20 mg, pravastatin 40 mg, or rosuvastatin 10 mg	240 mg QD	35 (34M,1F)
1002-017	DDI (oral contraceptives)	HV	Formulation 1 tablet 180 mg, ON 1/35	180 mg QD,	19 (0M,19F)
1002-031	DDI (probenecid)	HV	Formulation 1 tablet 180 mg, probenecid	180 mg	20 (16M,4F)
1002-037	DDI (high dose statins)	HV	Formulation 1 tablet 180 mg, atorvastatin 80 mg, simvastatin 40 mg, pravastatin 80 mg, or rosuvastatin 40 mg	180 mg QD	49 (35M,14F)

Study	Objective	Population	Test product(s)	Dose	Number of subjects
1002FDC-049	DDI (ezetimibe)	HV	Formulation 1 tablet 180 mg, ezetimibe 10 mg	180 mg	40 (19M,21F)
1002-013	DDI (metformin)	T2D	Capsules 20 and 40 mg, metformin 500 mg IR QD	180 mg QD	32 (18M,14F)
1002-022	Thorough QT study	HV	Formulation 1 tablets, 60 and 120 mg	240 mg	162 (109M,53 F)
1002-007	DDI (atorvastatin)	Patients with hyperlipidemia	Capsules 20 and 40 mg, atorvastatin 10 mg	120, 180 and 240 mg QD	58 (32M,26F)
1002-035	DDI (atorvastatin)	Patients with hyperlipidemia	Formulation 1 tablet 180 mg, atorvastatin 80 mg	180 mg QD	64 (33M,31F)
Studies included in population pharmacokinetic analysis					
1002-003	Efficacy and dose-response	Patients with hyperlipidemia	Capsules 20 and 40 mg	40, 80, or 120 mg or placebo QD	177 (98M,79F)
1002-005	Efficacy	T2D	Capsules 40 mg	80 mg and 120 mg QD or placebo	60 (37M,23F)
1002-006	Efficacy	Patients with hyperlipidemia	Capsules 20 and 40 mg	60, 120, 180 and 240 mg QD or placebo	56 (28M,28F)
1002-008	Efficacy	Patients with hyperlipidemia	Capsules 20 and 40 mg, ezetimibe 10 mg	120 or 180 mg, 120+10 mg, 180+10mg	348 (166M, 182F)
1002-009	Efficacy	Patients with hyperlipidemia	Capsules 20 and 40 mg	120 or 180 mg QD or placebo	133 (54M, 79F)
1002-014	Efficacy	Patients with elevated LDL-C and hypertension	Capsules 20 and 40 mg	180 mg or placebo	143 (82M, 61F)
1002-039	Efficacy add on to evolocumab	Patients receiving PCSK9i	Formulation 1, 180 mg tablet, evolocumab 420 mg QM	180 mg or placebo	58 (22M, 36F)
1002-040	Safety add on existing lipid modifying therapy	Patients with hyperlipidemia and high CV risk	Formulation 1, 180 mg tablet	180 mg or placebo	2229 (1628M, 601F)

Study	Objective	Population	Test product(s)	Dose	Number of subjects
1002-046	Efficacy add on existing lipid modifying therapy	Patients with elevated LDL-C	Formulation 1, 180 mg tablet	180 mg or placebo	345 (151M, 194F)
1002-047	Efficacy add on existing lipid modifying therapy	Patients with hyperlipidemia and high CV risk	Formulation 1, 180 mg tablet	180 mg or placebo	779 (496M, 283F)
1002-048	Efficacy as add on to ezetimibe	Patients with elevated LDL-C	Formulation 1, 180 mg tablet	180 mg or placebo	269 (104M, 165F)

2.4.2. Pharmacokinetics

Bioanalytical method

Three bioanalytical methods were used for the quantitation of bempedoic acid (ETC-1002) and ESP15228 in plasma throughout the clinical development programme. Both ETC-1002 as ESP15228 were measured in plasma using LC-MS/MS. Protein precipitation with acetonitrile or solid phase extraction was used to extract both analytes from plasma. The concentrations of ECT-1002-glucuronide have not been quantified.

The applicant used a validated LC-MS/MS method for the analysis for Ezetimibe and Ezetimibe – glucuronide in plasma. Bioanalytical reports were also submitted for several drugs used in the DDI studies.

Statistical analysis

Standard pharmacokinetic parameters have been estimated using both non-compartmental methods and population pharmacokinetic analyses. In the statistical comparison of most studies, a mixed effects model was used with subject within sequence as random effect. The applicant also provided additional re-analysis for several bioequivalence and DDI studies using fixed-effects for sequence, subject within sequence, period, and formulation/treatment as a sensitivity analysis.

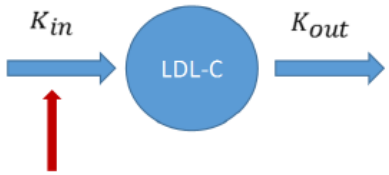
Two population pharmacokinetic analyses were submitted by the applicant. The first population pharmacokinetic analysis characterised the pharmacokinetics of both ETC-1002 and ESP15228 in 11 phase 1 and 2 studies. Mainly densely sampled studies were included in the analysis. The pharmacokinetics were best described using a 3-compartment model (central and peripheral compartment for the parent, and a central compartment for the metabolite). A model with parallel linear and non-linear formation of the metabolite was considered the base model with the lowest objective function value. Pre-defined covariates were fitted simultaneously with a pre-specified structure. Due to long runtimes, the model was reduced to a linear formation pathway of the metabolite. This is considered acceptable as the non-linear component appears to be primarily involved in the lower concentration range and not in the therapeutic exposure range

The second population pharmacokinetic analysis quantified the pharmacokinetics of the parent, ETC-1002, in 22 phase 1 to 3 studies. The final popPK dataset included 2232 subjects with 10347 quantifiable PK samples, 184 (8.2%) were healthy subjects, 1689 (75.6%) were hyperlipidemia patients and 359 (16%) had T2DM. Both dense and sparsely sampled studies were included in the

analysis. The pharmacokinetics of ETC-1002 was best described using a 2-compartment model (central and peripheral). A transit compartment was used to describe the absorption phase of bempedoic acid. Pre-defined covariates were fitted simultaneously with a pre-specified structure. Backward elimination was used to reduce the model. Main covariates were bodyweight and renal function. Also, covariate effects of atorvastatin on bioavailability (12.6% increase) and simvastatin on V2/F (15.2% decrease) were identified.

Also, a population pharmacokinetic/pharmacodynamic model was submitted based on data from 15 phase 1 to 3 studies. This model quantified the relationship between ETC-1002 and LDL-C lowering. A sequential based analysis for the PK/PD modelling was intended, where the PK/PD analysis was conditioned upon the fitting of the PK using the individual PK parameters. An indirect response model describing inhibition of cholesterol synthesis, incorporating serum LDL-C turnover with inhibitory drug effect on the production of serum LDL-C concentration (Kin), was used (Figure 2). Concomitant therapy with statins or ezetimibe influenced the Imax (lower) and baseline LDL-C parameters.

Figure 3. Indirect Response Base Model



$$K_{in} = K_{in,0} * \left[1 - \frac{Imax * C_{bempedoic\ acid}}{(IC_{50} + C_{bempedoic\ acid})}\right] \qquad K_{out}\ (hr^{-1}) = \frac{1}{TURN}$$

$$\text{At baseline}, K_{out} = \frac{K_{in,0}}{Baseline\ LDL\text{-}C}$$

Absorption

Bempedoic acid has pH dependent aqueous solubility, that is low below pH 6 but increases at higher pH levels. Bempedoic acid is classified as a BCS class 2 compound. Bempedoic acid and its active metabolite were not found to be substrates for intestinal efflux transporters P-gp and BCRP *in vitro*.

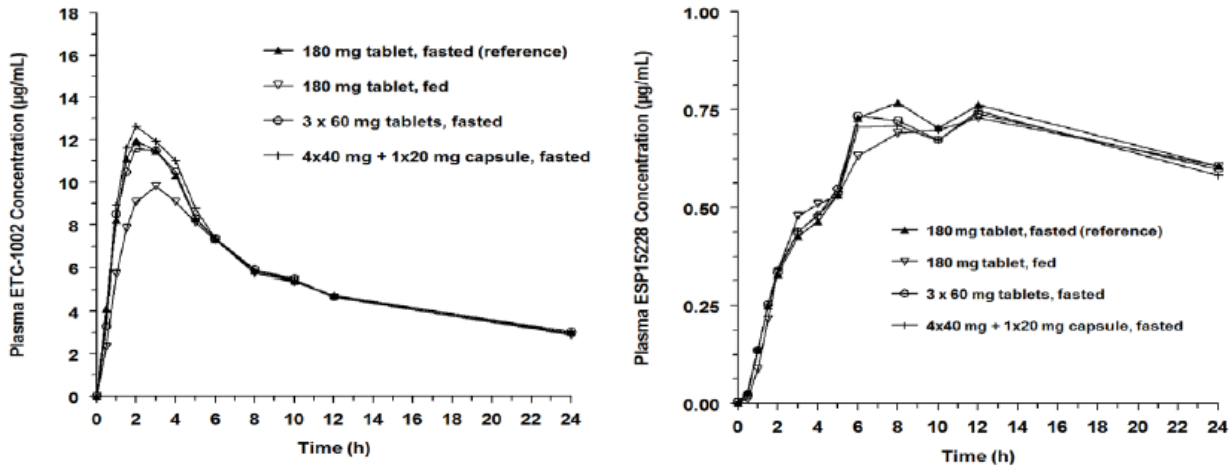
Bempedoic acid is absorbed with a median time to the maximum concentration of 3.5 hours when administered orally as 180 mg tablets. Bempedoic acid is partially converted to an active metabolite ESP15228, which has a median tmax of 7.0 hours. Concomitant food administration did not affect the oral bioavailability of bempedoic acid, a minor influence on Cmax (-12%) was observed and the absorption rate constant decreased by approximately 78%. No absolute bioavailability studies were conducted.

After absorption, bempedoic acid is activated in the liver by ACSVL1 to ETC-1002-CoA , which subsequently inhibits adenosine triphosphate citrate lyase (ACL), an enzyme upstream of 3-hydroxyl-3-methylglutaryl Coenzyme A (HMG-CoA) reductase in the cholesterol synthesis pathway.

Concomitant food administration did not affect the oral bioavailability of bempedoic acid and had a minor influence on C_{max}. In the food effect study a FDA-defined high-fat, high-calorie breakfast was given.

Bempedoic acid clinical program included four drug formulations, bioequivalence between developed formulations and to-be-marketed 180 mg immediate release tablet has been established.

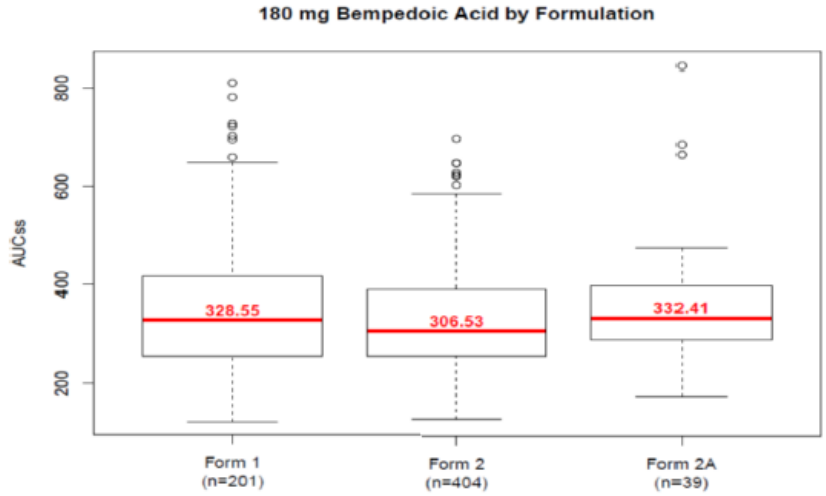
Figure 4. Arithmetic Mean Plasma Bempedoic Acid (left) and ESP-15228 (right) Concentrations Through the First 24 Hours Post-dose Following a Single 180-mg (Total) Oral Dose of ETC-1002 (n = 16), Study 1002-016



Steady state

Steady state is reached in approximately 7-14 days. Steady-state bempedoic acid AUC and average plasma concentrations in patients from the three placebo-controlled phase 3 studies were consistent across bempedoic acid formulations used in phase 3 studies, with an $AUC_{ss,\ 0\text{-}24hours}$ of about 310h.µg/mL for bempedoic acid, Figure 4.

Figure 5. Model predicted AUCss for studies 1002-046, 1002-047 and 1002-048



Distribution

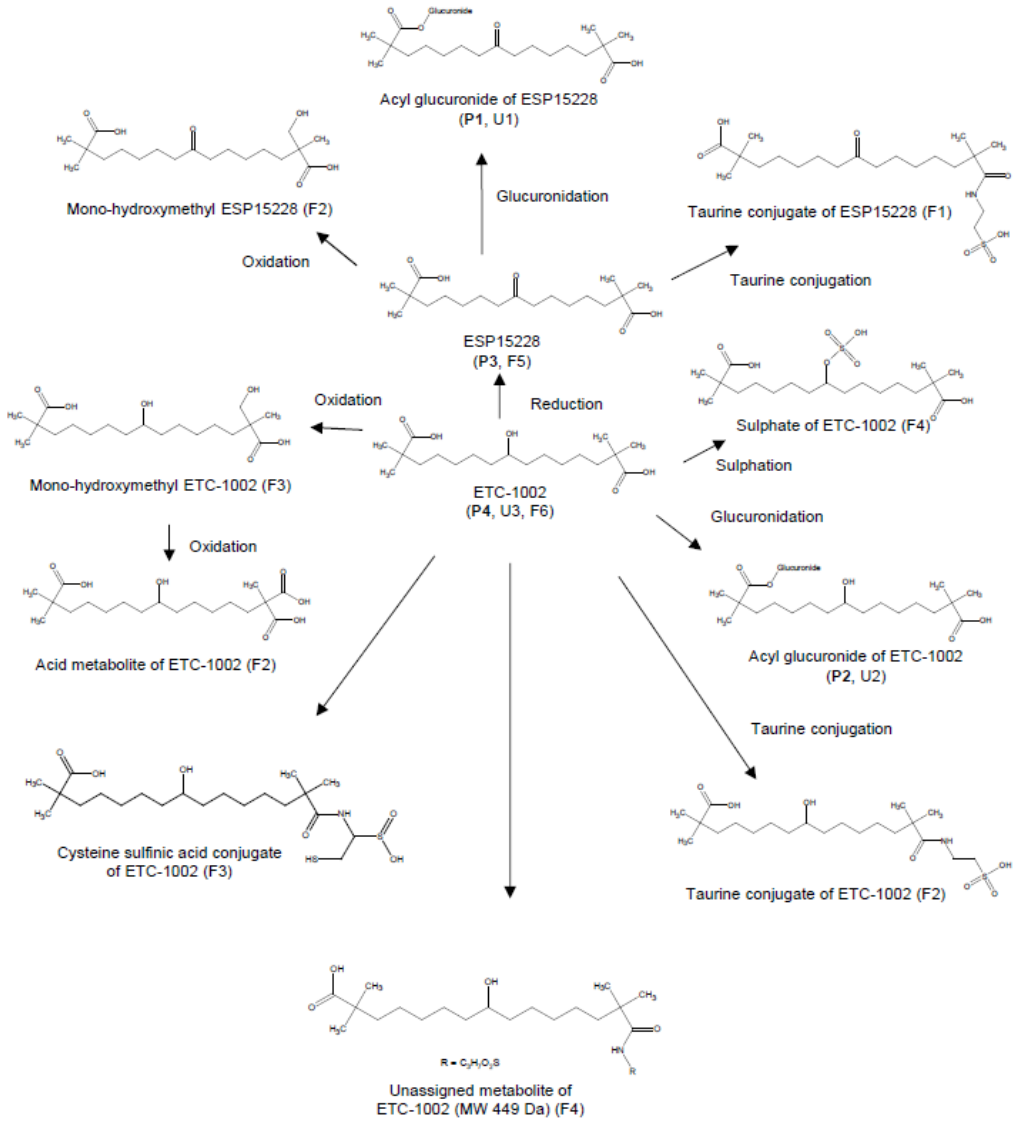
The apparent volume of distribution following oral administration of bempedoic acid was approximately 16-18L. The *in vitro* protein binding was high ranging from 95% for ETC-1002 (parent compound) to

99% for both ESP15228 (active metabolite) and ETC-1002-glucuronide (inactive metabolite). The extent of protein binding was independent of drug concentrations. The average blood: plasma ratio was found to be 0.5 indicating limited distribution to the blood cells. Plasma protein binding was slightly affected by the degree of renal impairment.

Elimination

The ADME study indicated that renal clearance is the main route of elimination of bempedoic acid (predominantly as glucuronide metabolites), approximately 62.1% and 25.4% of the radioactivity was recovered from urine and faeces respectively. Metabolism accounts for more than 95% of the elimination of bempedoic acid after oral administration. The primary route of elimination for bempedoic acid is metabolism to the acyl glucuronide (Figure 5). Bempedoic acid is also reversibly converted to an active metabolite (ESP15228). Mean plasma AUC metabolite/parent drug ratio for ESP15228 following repeat-dose administration was 18% and remained constant over time.

Figure 6. Biotransformation pathway for Bempedoic Acid



ECT1002 and ESP15228 are both converted to inactive glucuronide conjugates *in vitro* by UGT2B7. After administration of a single dose of bempedoic acid, ECT1002, ESP15228 and their respective conjugated

forms were detected in plasma with ECT1002 accounting for the majority (46%) of the AUC0-48h and its glucuronide being the next most prevalent (30%). ESP15228 and its glucuronide represented 10% and 11% of the plasma AUC0-48h, respectively. In the ADME study, the unchanged parent and its active metabolite could be detected in faeces but accounted for less than 2% of total administered radioactivity. In urine, the majority of the sample radioactivity was associated with an acyl glucuronide of bempedoic acid. Three additional metabolites: an acid metabolite of ETC-1002, mono hydroxymethyl-ESP15228, and a taurine conjugate of ETC-1002 where described in faeces.

The apparent steady-state clearance (CL/F) of bempedoic acid was 11.2 mL/min and the mean half-life was 19 hours at steady-state. The terminal half-life of ESP15228 was approximately 30 hours. In the population pharmacokinetic analysis, the pharmacokinetics of ESP15228 appeared to be formation rate limited and best described by Michaelis-Menten kinetics. The steady state concentrations of the major inactive metabolite, ETC-1002-glucuronide, have not been determined yet, but will be determined post marketing, see section VII.

Dose proportionality and time dependencies

Bempedoic acid $AUC_{0-24,ss}$ and C_{max} appear to increase more than proportional with increasing dose>120 mg to 250 mg.

No time dependency has been observed for bempedoic acid. Accumulation ratios were approximately 2.3 for ETC-1002 and approximately 3 for ESP15228.

Inter-individual variability

The inter-individual variability (CV%) of Cmax and AUCt values for bempedoic acid was moderate (30% and 33%, respectively) when 180 mg QD dosing regimen was used in healthy subjects. Similar inter-individual variability was reported for ESP15228 exposure parameters. Intra-individual variability is approximately 34%. Intra-individual variability is comparable between healthy subjects and patients, however inter-individual variability is higher in patients as indicated by the estimates of the population pharmacokinetic model

In a popPK analysis, the inter-individual variability estimates for apparent drug clearance (CL/F), apparent central distribution volume (V2/F) and absorption rate constant (Ka) were 29.7%, 100% and 73.9%, respectively.

Special populations

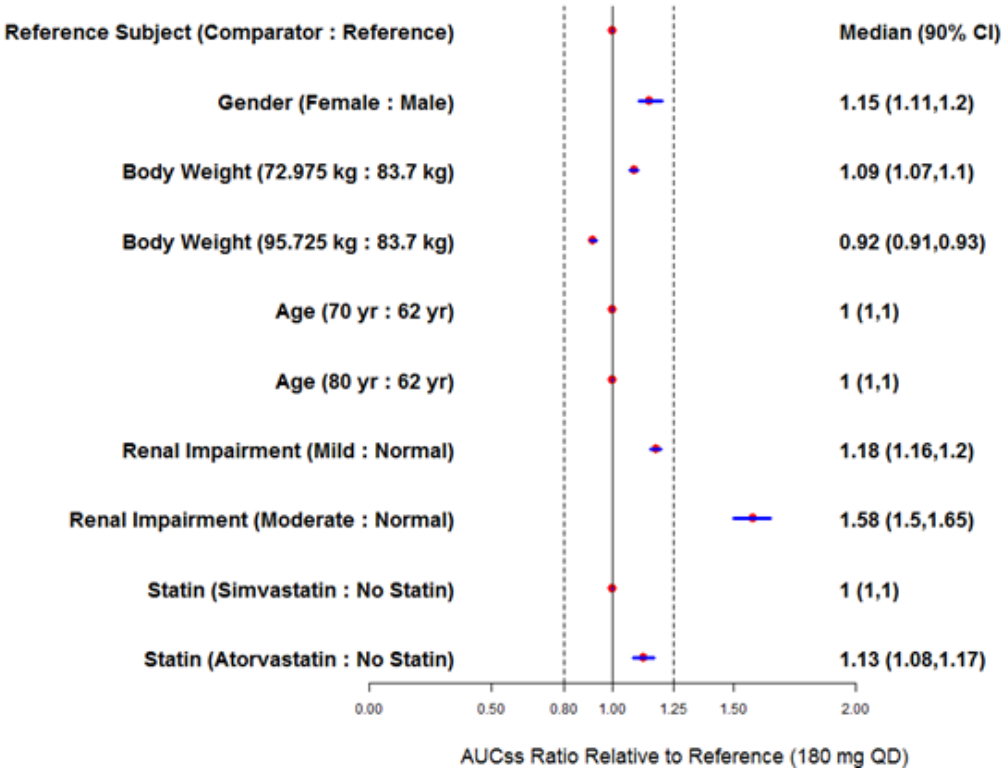
Bempedoic acid and ESP15228 exposure as measured by AUC increased with increasing degree of renal impairment; Cmax (after a single dose) was not substantially affected by renal impairment. The same trends have been observed for the unbound fractions of ETC-1002 and ESP15228. The clearance of ETC-1002 and ESP15228 is decreased in patients with renal impairment. An approximately 1.4-fold increase in AUC for patients with mild renal impairment and 1.9-fold increase in AUC for patients with moderate renal impairment have been observed in population PK analysis. No studies on patients with ESRD or on hemodialysis were performed.

Total bempedoic acid exposure (ETC-1002 and active metabolite ESP15228) was reduced by 27% and 21%in subjects with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment relative to subjects with normal hepatic function. This decrease is not expected to be clinically relevant, and no dose adjustments are required for subjects with hepatic impairment. Severe hepatic impairment was

not studied. The lack of data in patients with severe hepatic impairment is appropriately reflected in proposed SmPC.

From the population PK model, it can be determined that patients with a lower bodyweight will have an increased exposure. This is also confirmed by the additional analysis in which the applicant evaluated the relationship between observed trough concentrations with bodyweight. As the difference was relatively small, no dose adjustments are necessary. Females had a 40% higher exposure to bempedoic acid. However, this is most likely caused by weight differences between both genders. There appears to be a trend for increasing exposure with age in the population pharmacokinetic model and greater variability in black subject and a trend lower exposure in Hispanic subjects. However, the influence of age, race and ethnicity on the pharmacokinetics of bempedoic acid should be interpreted with caution as there are issues with the selection of covariates in the population pharmacokinetic model. The influence of age race and ethnicity should therefore be re-evaluated after model refinement.

Figure 7. Influence of Covariate Populations on Predicted Bempedoic Acid exposure at steady state



Pharmacokinetic interaction studies

In vitro

In *in vitro* studies bempedoic acid inhibits renal transporter OAT3 with IC50 values of about 40µg/mL. Bempedoic acid also inhibited the hepatic and renal transporter OAT2, but different IC50 values were observed for different substrates. The estimates IC50 was 1.24 µg/mL for uric acid, 88.9µg/mL for

creatinine and 142 µg/mL for cGMP. The substrate dependency is not understood and will be further evaluated post marketing, see section VII.

The IC50 bempedoic acid concentrations were 119 µg/mL for the hepatic transporters OATP1B1, and 152 µg/mL for OATP1B3 and the Inlet Cmax(u)*25 was 48 µg/mL so weak inhibition is expected. ETC-1002 glucuronide inhibits OATP1B1, and OATP1B3 at IC50 concentrations of 43 and 43 µg/mL, respectively.

No significant *in vitro* inhibition or induction of the of Cytochrome P450 enzymes by bempedoic acid or its active metabolite ESP15228 was observed.

Bempedoic acid is not an inducer of UGT1A1 and UGT1A4 enzymes at clinically relevant concentrations, however some induction of UGT1A1 and UGT1A4 has been observed at supra therapeutic concentrations. These results are in line with the results of clinical DDI studies.

Further, the applicant has conducted vitro study to investigate the potential interactions of the inactive ETC 1002-glucuronide. The interactions with Cytochrome P450 enzymes, the transporters OAT1, OAT3, and OCT2 and the transporters OATP1B1, OATP1B3, BCRP, and P-glycoprotein were investigated. ETC-1002-glucuronide was not a reversible or time dependent inhibitor *in vitro* of the CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A enzymes in the concentration range of 0 to 133 µM. No final conclusions on these studies can be drawn due to the lack of steady state concentration data on ETC 1002-glucuronide.

In vivo

The applicant conducted two drug-drug interaction studies with a statin in which the effect of steady-state bempedoic acid 180mg (Study 1002-037) or 240 mg (study1002-012) on the single-dose plasma pharmacokinetics of different statins was investigated. Study subjects were included in cohorts and treated with different statins (12 subjects per cohort). Elevations in systemic statin exposure as assessed by the steady-state AUC ratio were observed for the different statins in studies 1002-037 and 1002-012 (See table 3). In the study with the higher 240mg dose of bempedoic acid a 2-fold increase for pravastatin, 1.7-fold for rosuvastatin and 2-fold for simvastatin was observed. In the study with the 180 mg bempedoic acid an increased exposure of simvastatin of 2-fold, atorvastatin of 1.4-fold (with increases of relevant active metabolites of 1.5- and 2.2-fold), pravastatin 1.5-fold, and rosuvastatin 1.5-fold has been observed. Statin Cmax concentrations were also increased by a similar extent, suggesting that not only the excretion but also the first pass effect of statins is affected. According to the applicant, the interaction can probably be attributed to inhibition of OATP transport.

Steady state concentrations of bempedoic acid were not affected by a single dose administration of any of the statins. The effect of steady state statin on the exposure of bempedoic acid has not been estimated.

Table 3: Summary of the drug drug interaction studies 1002-037 and 1002-012 with statins

Statin	Analyte	Geometric Mean Ratio (%) of AUCinf (Test/Reference)	90% CI for Ratio of LS Means (%)
Study 1002-037 Statin with Steady-State Bempedoic Acid 180mg			
Atorvastatin 80mg	Atorvastatin	144	124–167
	Ortho-hydroxy Atorvastatin	146	131-162
	Para-hydroxy Atorvastatin	224	206-244
Simvastatin 40mg	Simvastatin	120	94-152

	Simvastatin acid	196	161-238
Pravastin 80mg	Pravastatin	146	122-174
Rosuvastatin 40mg	Rosuvastatin	145	121-175
Study 1002-012 Statin with steady state Bempedoic acid 240mg			
Simvastatin 20mg	Simvastatin	129	96-174
	Simvastatin acid	191	152-240
Pravastin 40mg	Pravastatin	199	160-246
Rosuvastatin 10mg	Rosuvastatin	169	153-187

The pharmacokinetics of bempedoic acid was not affected in the presence of ezetimibe at steady state. Increases in AUC and Cmax for unconjugated ezetimibe were observed, but these increases were less than 20% during steady-state exposure of bempedoic acid. Total ezetimibe (ezetimibe and its glucuronide form) and ezetimibe glucuronide AUC and Cmax increased approximately 1.6-fold and 1.8-fold, respectively. Due to inhibition of OATP1B1 by BA the hepatic uptake of ezetimibe-glucuronide is decreased and subsequently its elimination is decreased

The DDI study with the general UGT and OAT1/OAT3 inhibitor probenecid showed an increased exposure of 1.7 and 1.95-fold for ETC-1002 and ESP15228.

Although, *in vitro* studies indicated that there may be a clinically relevant interaction with the OAT3 or OAT2 transporters, no clinical interaction studies with substrates of OAT3 or OAT2 were conducted. In the clinical studies, elevations of uric acid and creatinine were observed. According to the applicant, these elevations can possibly be attributed to inhibition of OAT2.

The applicant proposes to further investigate the DDI liability of bempedoic acid as the precipitant of OAT2 interactions with clinically relevant drugs and the role of OAT2 in explaining the effects of bempedoic acid on creatinine and uric acid in five additional *in vitro* studies (see section VII) and one NC study.

Bempedoic acid did not influence the pharmacokinetics of hormonal contraceptives and metformin. Also, no effect was observed on the pharmacodynamics of metformin.

Based on popPK analysis, concomitant medications (statins, metformin, ezetimibe, and PCSK9 inhibitors) had no significant impact on bempedoic acid PK.

Exposure relevant for safety evaluation

The median maximal concentration of approximately 20 µg/mL observed after the administration of a 180 mg dose of bempedoic acid at steady can be used for the safety evaluation. However, it should be taken into account that some individuals demonstrated concentrations as high as 70 µg/mL after the administration of 180 mg bempedoic acid at steady state

2.4.3. Pharmacodynamics

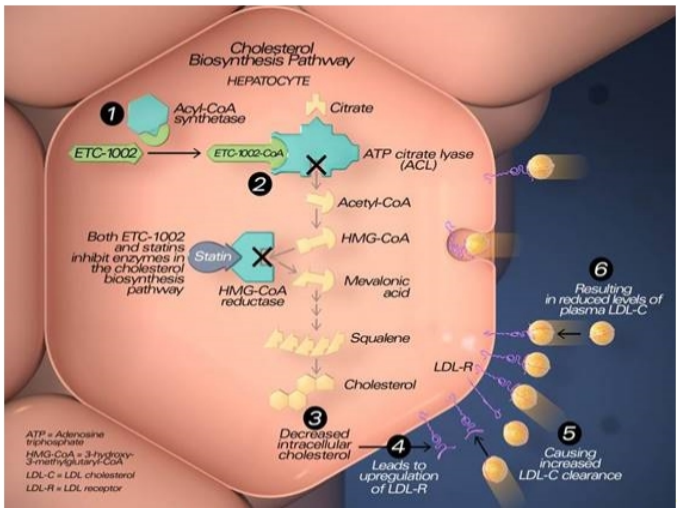
Mechanism of action

In the liver, bempedoic acid is activated to ETC-1002-Coenzyme A (ETC-1002-CoA), which subsequently inhibits adenosine triphosphate citrate lyase (ACL), an enzyme upstream of 3-hydroxyl-3-methylglutaryl Coenzyme A (HMG-CoA) reductase in the cholesterol synthesis pathway. Inhibition of cholesterol synthesis triggers the upregulation of low-density lipoprotein (LDL) receptor (LDLR) expression in the liver resulting in increased clearance of LDL particles and lowering of LDL-C in the blood.

Primary and Secondary pharmacology

Bempedoic acid requires coenzyme A (CoA) activation by very long-chain acyl-CoA synthetase 1 (ACSVL1) to ETC-1002-CoA (Pinkosky et al, 2016). Inhibition of ACL by ETC-1002-CoA results in decreased cholesterol synthesis in the liver and lowers LDL-C in blood via upregulation of LDL-Rs (Figure 7) ETC-1002-CoA (via ACL inhibition) and statins (via HMG-CoA reductase inhibition) both inhibit cholesterol synthesis in the liver; however, bempedoic acid is inactive in skeletal muscle. Additionally, inhibition of ACL by ETC-1002-CoA results in concomitant suppression of hepatic fatty acid biosynthesis and it is this aspect of the activity that is thought to lead to improvements in glycemic control in hyperglycemic animal models.

Figure 8. Mechanism of Action of Bempedoic Acid



Schematic overview of the mechanism of action of bempedoic acid (ETC-1002). **(1)** Bempedoic acid is converted to ETC-1002-Coenzyme A (ETC-1002-CoA) in the liver and **(2)** inhibits ATP citrate lyase (ACL), an enzyme upstream of 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase in the cholesterol synthesis pathway. Inhibition of cholesterol synthesis **(3)** reduces intracellular cholesterol levels, which **(4)** triggers the upregulation of low-density lipoprotein (LDL) receptor activity in the liver resulting in **(5)** increased clearance of LDL particles and reduced LDL-C in the blood.

Phase 1 PK/PD studies

Two randomized, double-blind, placebo-controlled ascending multiple-dose studies evaluated fasting lipid parameters in healthy subjects. Subjects (n=53) received bempedoic acid 20, 60, 100, or 120 mg or placebo QD in a 3:1 ratio (Study 1002-002, Cohorts 1-4); or (n=24) bempedoic acid 140, 180, 220 mg, or placebo (Study 1002-004) QD for 14 days. In both studies, blood samples for fasting lipids (calculated LDL-C, TC, HDL-C, and TGs) were collected predose and on Day 1, 4, 8, and 15.

Percent change from baseline to Day 15 in calculated LDL-C is illustrated in Figure 8 and Table 4 below. LDL-cholesterol lowering was evident starting at Day 4 and near maximum LDL-C lowering appear to have been achieved by Day 15.

Figure 9: Percent Change From Baseline to Day 15 in Calculated LDL-C by Dose (Study 1002-002, Cohorts 1-4; Study 1002-004)

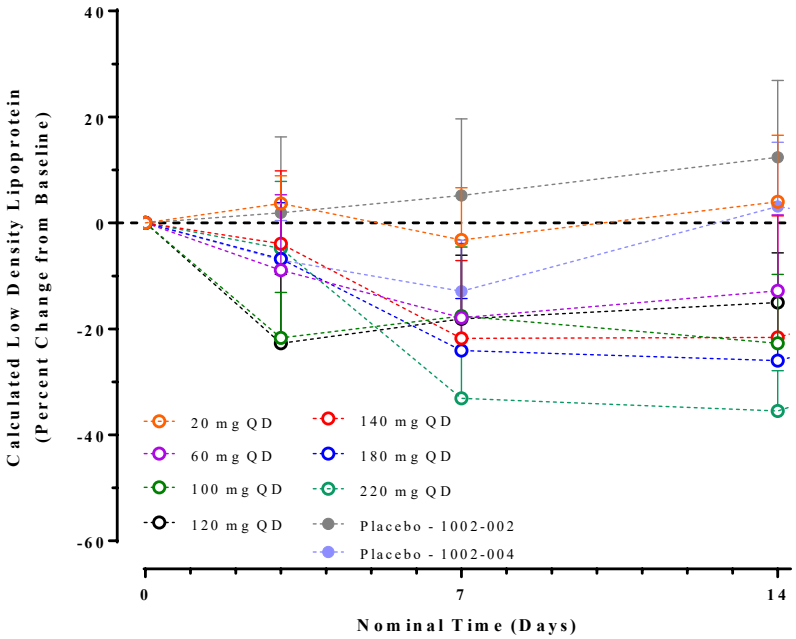


Table 4. Percent Change From Baseline to Day 15 in Lipid Levels (Study 1002-002, Cohorts 1-4; Study 1002-004)

Treatment	N	Mean (SD) Percent Change From Baseline at Day 15			
		LDL-C	TC	HDL-C	TGs
Study 1002-002					
Placebo QD	8	12.4 (14.53)	8.5 (12.72)	1.3 (21.68)	14.2 (45.95)
Bempedoic acid QD					
20 mg	6	4.0 (12.57)	6.6 (15.85)	0.3 (13.38)	26.2 (50.41)
60 mg	6	-12.8 (14.34)	-11.7 (11.03)	-10.2 (11.20)	-9.4 (11.73)
100 mg	6	-17.6 (13.08)	-9.6 (8.18)	-3.6 (11.68)	23.6 (26.79)
120 mg	6	-15.0 (9.38)	-7.5 (12.91)	0.4 (8.15)	7.4 (57.35)
Study 1002-004					
Placebo QD	6	3.1 (12.10)	1.4 (9.17)	-6.6 (6.19)	28.4 (26.72)
Bempedoic acid QD					
140 mg	6	-21.6 (22.93)	-16.0 (13.70)	-18.7 (16.63)	29.0 (58.45)
180 mg	6	-26.0 (10.83)	-15.4 (9.70)	-6.7 (10.04)	13.4 (47.92)
220 mg	6	-35.5 (7.63)	-25.6 (7.70)	-14.1 (8.98)	-5.2 (34.44)

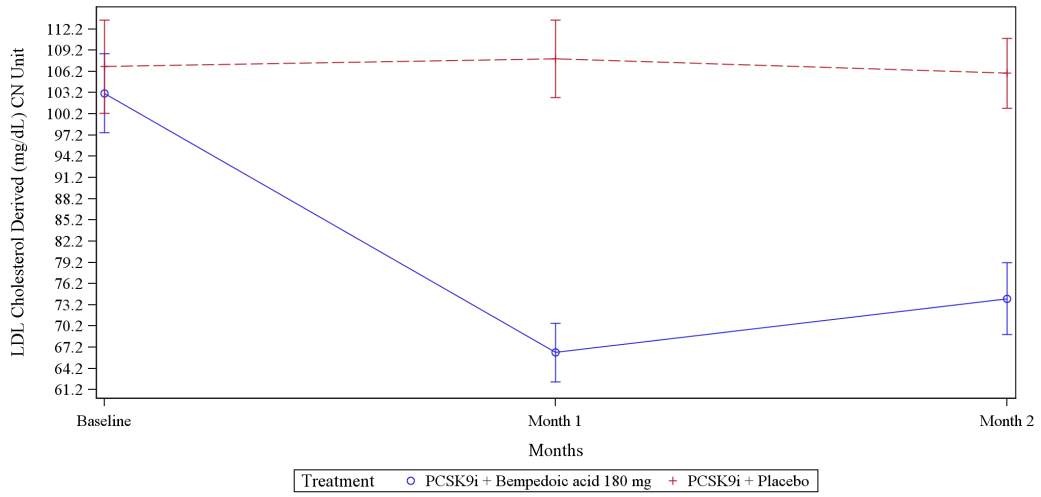
Interaction with PCSK9 inhibitors

Phase 2 Study 1002-039 was a randomized, double-blind, placebo-controlled, parallel-group study to assess 2-month efficacy of bempedoic acid 180 mg/day vs placebo in the reduction of LDL-C in

patients onto (PCSK9i) therapy (evolocumab). Following a washout period of all LMT, patients received run-in treatment with evolocumab for 3 months, after which they were randomized 1:1 to add on bempedoic acid 180 mg or placebo QD for 2 months. Basic fasting lipids, apo B, hsCRP, and trough plasma concentrations of ETC-1002 (parent compound) and ESP15228 (active metabolite) were assessed at baseline, Month 1, and Month 2.

An additive reduction in LDL-C was observed when bempedoic acid was added to evolocumab, with an LS mean change from baseline of -27.5% compared with 2.8% in the placebo + evolocumab group; the LS mean difference from placebo (-30.3%) was statistically significant (p <0.001), Figure 9.

Figure 10: Mean (± SEM) LDL-C Values by Visit (LOCF) (Study 1002-039)

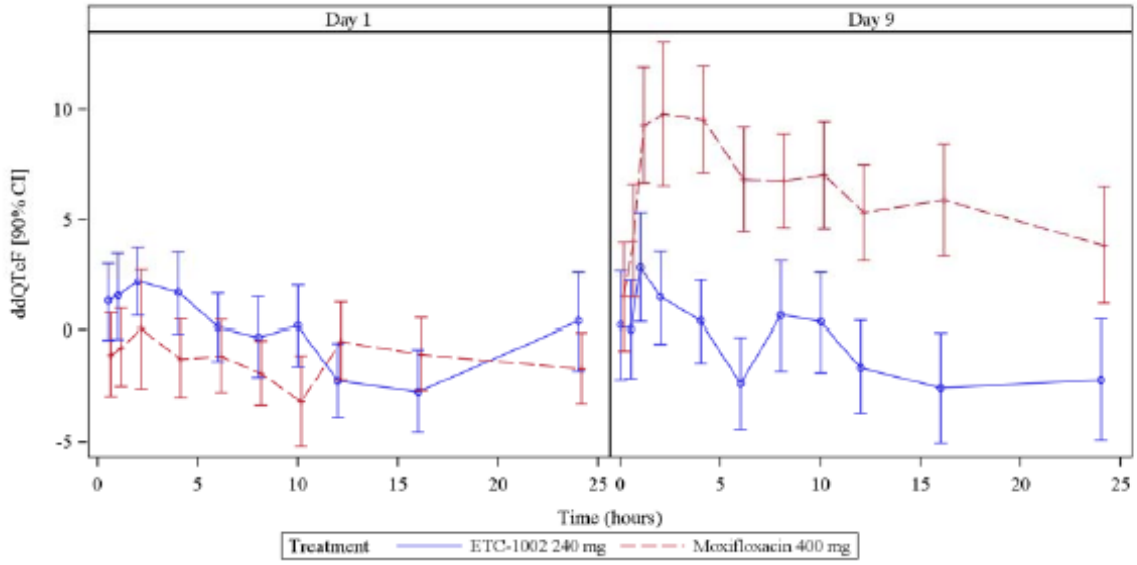


Secondary pharmacology: QT prolongation

A thorough QT study was performed to assess potential effects of bempedoic acid on the QT interval. Eligible subjects were randomized 1:1:1 to receive one of the following oral QD treatments on Days 1 through 9: (A) bempedoic acid 240 mg + matched-to-moxifloxacin placebo;
(B) matched-to-bempedoic acid placebo + 1 matched-to-moxifloxacin placebo; or (C) moxifloxacin 400 mg and matched-to-bempedoic acid placebo.

Based on the unadjusted and mixed-effects regression models using both time-matched and predose baselines, bempedoic acid did not affect QTcF. The expected extent and pattern of change in QTcF during moxifloxacin treatment was observed, with statistically significant elevations in time-matched, placebo- and baseline-adjusted QTcF (ddQTcF) from 1 to 16 hours postdose on Day 9, Figure 10.

Figure 11. Time-matched, Placebo- and Baseline-adjusted QTcF on Days 1 and 9 of Bempedoic Acid or Moxifloxacin Treatment (Study 1002-022).



ddQTcF = time-matched placebo- and baseline-adjusted QTcF interval; QTcF = QT interval corrected using Fridericia's formula.

Source: Study 1002-022 CSR, Appendix 16.6, Figure K.

The QTcF interval did not exceed 450 msec at any time point in the bempedoic acid group and change from baseline in QTcF did not exceed 30 msec in any bempedoic acid-treated subject. There were no clinically significant changes in heart rate, PR interval, or QRS duration in subjects who received bempedoic acid.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

In general, the pharmacokinetics were adequately characterised in the clinical pharmacology programme of bempedoic acid.

The submitted bioanalytical methods are validated and in general suitable for the analysis of ETC-1002 and the active metabolite ESP15228 in plasma, ultrafiltrate and urine. ETC-1002-glucuronide, the main metabolite (21-36% in plasma), was not analysed in the clinical development programme of bempedoic acid. The company committed to measure steady state concentrations of ETC-1002-glucuronide to enable correct interpretation of the *in vitro* interaction studies (PAM).

The analytical methods for the drugs used in the DDI studies were appropriately validated.

In the population pharmacokinetic and pharmacokinetic/pharmacodynamic models, some issues needed to be clarified during the procedure but the clarifications were accepted by the CHMP.

With respect to the **population PK/PD model**, individual ETAs for CL, V2 and KA were used for the prediction of exposure. It was unclear how the PK model, which is mainly fixed due to the sequential approach, influences the PD model. On top of that, the applicant stated that the structural PK model from the second population pharmacokinetic analysis was used in the PK/PD analysis. However, the PK/PD model included estimates (K25 and K52) for a third compartment from a model that was not submitted. The applicant was asked to submit the report of the PK model used in PK-PD analysis including model development, GOF plots, VPCs, parameter estimates and model code to allow correct

interpretation of the PK/PD model. The applicant submitted the requested information and conducted an additional sensitivity analysis, in which the PK/PD model was estimated using different PK model structures. The results indicated that the different structural model of the PK model only demonstrated a minimal influence on the parameter estimates. Therefore, this issue was sufficiently addressed. From the provided goodness-of-fit plots, there remain signs of structural model misspecification as most of the variability seems to be solved using interindividual random effects (IPRED vs DV and PRED vs DV plots, see population PK/PD report). The applicant performed additional outlier analysis (n = 37), however these outliers were not expected to influence the model structure.

This population PK/PD model has been used to justify that statin use was a significant covariate on bempedoic acid maximum inhibitory effect (Imax) and was associated with a reduction of LDL-C lowering when bempedoic acid was added to a stable statin regimen. The magnitude of the effect on Imax was dependent on statin-intensity, ie, higher statin intensities decreased the bempedoic acid Imax on LDL-C. Low-, moderate- and high-intensity statins were predicted to result in a typical maximum LDL-C lowering of -25%, -23% and -19%, respectively. The population PK/PD model cannot adequately describe the structural trends after inclusion of significant covariates. However, **the DDI studies with statins** demonstrated a similar trend as the population PK/PD, although the magnitude of the effects are slightly different. The DDI studies showed that a higher statin dose resulted in a lower LDL reduction by bempedoic acid. Therefore, the DDI studies are considered pivotal in this argumentation. Bempedoic acid peak plasma concentration are observed after 3.5 hours when administered as 180 mg tablets. Median tmax for the active metabolite ESP15228 was 7 hours. Bempedoic acid is extensively metabolised, to mainly to glucuronide conjugates. No pharmacokinetic profile of bempedoic acid-glucuronide, the most predominant metabolite, has been submitted.

The **aqueous solubility of bempedoic acid** is pH dependent - being low below pH 6 but increasing at higher pH levels. Although bempedoic acid exhibits pH-dependent solubility *in vitro*, the high oral absorption *in vivo* (of approximately 90%) and **a lack of food effect** support it can be assumed that impact of increasing pH induced by co-administrated medicinal products is not expected to have an effect on bempedoic acid absorption.

In patients with **moderate and severe renal impairment**, bempedoic acid exposure increases by 2-fold. At this stage as the exposure-response relationship of bempedoic acid has only been determined for LDL-C and no clear influence on other markers and safety parameters. The applicant discussed the mechanisms involved in the impaired elimination of bempedoic acid in patients with renal impairment. Possible explanations are a reduced activity of UGT2B7 or a possible higher contribution of enterohepatic cycling of the ETC-1002-glucuronide metabolite. These mechanisms still need to be confirmed. No studies on patients with ESRD/on hemodialysis were performed. Lack of data on these patient's groups is reflected in proposed SmPC. The slightly higher exposure for renally excreted drug in >75yrs patients compared to the patients < 65yrs is expected due to the well-described relationship between age and renal function.

Bempedoic acid mainly undergoes direct glucuronidation via UGTs and is not metabolised by CYP450 enzymes. Glucuronidation by UGT2B7 is the main route of elimination of bempedoic acid and ESP15228. As UGT2B7 is considered to be a highly polymorphic gene, no clear effects on clearance are however observed as indicated by the distribution of CL/F in the population pharmacokinetic model.

In vitro studies indicated that bempedoic acid and its active metabolite ESP15228 do not inhibit CYP450 enzymes and has minimal potential to induce CYP450 enzymes at clinically relevant concentrations.

Elevations of in systemic statin exposure as assessed by the steady-state AUC ratio were observed for the different statins in two drug-drug interaction studies in healthy volunteers in which the effect of steady state bempedoic acid 180mg (Study 1002-037) or 240 mg (study1002-012) on the

single-dose plasma pharmacokinetics of different statins was investigated. An increase of 1.5- to 2-fold for pravastatin, 1.5- to 1.7- fold for rosuvastatin, 1.4-fold for atorvastatin (with increases of relevant active metabolites of 1.5- and 2.2-fold increase) and 2-fold for simvastatin was observed. These studies are in line with the requirements of the *EMA Guideline on the investigation of drug interactions [CPMP/EWP/560/95/Rev. 1 Corr. 2**]* and would generally be acceptable as this approximately reflects the steady state interaction in clinical situations. The pharmacokinetic interaction between statins and bempedoic acid is probably caused by OATP1B1 inhibition. In *in vitro* studies, bempedoic acid and its glucuronide weakly inhibited OATP1B1 at clinically relevant concentrations. OATP1B1 is an uptake transporter expressed on the hepatocytes and involved in the hepatic uptake of statins. The hepatocyte is the site of action of statins and statins are metabolised in the hepatocyte. Due to a high first-pass effect (the absolute bioavailability is 5% for simvastatin, 12% for atorvastatin 17% for pravastatin and 20% for rosuvastatin) and efficient first uptake into the hepatocyte OATP inhibition may not only impact the systemic absolute bioavailability but also the pharmacodynamics of statins. OATP is not expressed in myocyte and therefore not involved in the uptake of statins into the myocyte. As the impact of the interaction with bempedoic acid appears to be dose dependent (a higher increase of rosuvastatin and pravastatin exposure was observed with the higher dose of bempedoic acid) the impact may potentially be higher in patients with a higher bempedoic acid exposure (e.g. patients with renal impairment).

In clinical studies, the total LDL-C reduction was a combined **effect of statin and bempedoic acid**. As both active substances act on the same pathway the contribution of the individual active substances to the lipid lowering effect cannot be measured accurately but has been estimated via modeling. These estimations should be interpreted with caution as dose-exposure-response relationships is not proportional, linear and similar for each statin. The observed interaction between bempedoic acid and statins may also contribute to tolerability issues observed.

The **combined administration of ezetimibe and bempedoic acid** resulted in an increase in exposure of 1.6-fold and 1.8-fold for total ezetimibe and ezetimibe-glucuronide, respectively. Some difference in efficacy is noticed in the subgroup analyses in the clinical studies, but the interaction was not significant (see clinical efficacy section). Further, it is known that the dose response relationship of ezetimibe is rather flat. The impact on clinical safety limited, no dose dependent safety issues are known for ezetimibe within the clinical dose range and no notable differences in adverse events profile could be identified between patients concomitantly treated with or without ezetimibe.

In *in vitro* studies bempedoic acid inhibits renal transporter OAT3 with IC50 values of about 40µg/mL In vitro data predict a weak inhibition of OAT3 and also by the limited impact of bempedoic acid on the pharmacokinetics of the OAT3-OATP1B1 substrate pravastatine. In DDI study 1002-037, a 1.46-fold increase of pravastatin exposure has been observed when coadministered with 180mg bempedoic acid and up to 2 fold increase with the supra therapeutic 240mg dose. Potential interaction mechanisms include interaction with hepatic uptake (via OATP1B1) and renal elimination (via OAT3) of pravastatin. Bempedoic acid has a combined effect on both mechanisms but the impact is limited.

Bempedoic acid also inhibited the hepatic and renal transporter OAT2, but different IC50 values were observed for different substrates. The estimates IC50 was 1.24 µg/mL for uric acid, 88.9µg/mL for creatinine and 142 µg/mL for cGMP. The substrate dependency is not understood. The applicant committed to further investigate the role of OAT2 inhibition by bempedoic acid in five *in vitro* studies and one animal model to elucidate the role of OAT2 in explaining the effects on creatinine and uric acid and potential interactions with other substrates of OAT2. The NC animal study is not to be considered of sufficient value with regard to the translation to humans, therefore the conduction of this study is not recommended. The company proposed to investigate different types of OAT2 expressing *in vitro* systems (MDCK-II and liver), different endogenous and drug substrates, and time and dose dependent inhibition. The proposed interaction program is expected to contribute to greater understanding of any

potential clinical role of OAT2 inhibition by bempedoic acid in the disposition of endogenous and administered substrates. As the observed increases of uric acid and creatinine were mild and reversible within 4 weeks, it was agreed that the role of OAT2 inhibition is elucidated post registration.

The applicant proposed to use PBPK to investigate inhibition of OAT2 and OATP1B1. Caution is recommended on the use of PBPK, given the acknowledged lack of data and hence uncertainties in the model, it should not be used in place of clinical data. However, it is accepted that a model may assist with the understanding of the interplay between transporters. Category 3 studies investigating OAT2 inhibition were added to the agreed version of the RMP.

Pharmacodynamics

Regarding the **mechanism of action** for bempedoic acid it appears that bempedoic acid inhibits adenosine triphosphate citrate lyase (ACL), an enzyme upstream of 3-hydroxyl-3-methylglutaryl Coenzyme A (HMG-CoA) reductase in the cholesterol synthesis pathway to inhibit cholesterol synthesis in the liver which triggers upregulation of low-density lipoprotein (LDL) receptor (LDLR) expression in the liver thereby increasing LDL-C uptake and reducing LDL-C in the blood. This specific mechanism could not be formally tested in any clinical setting, only the eventual PD result in terms of LDL-C could be demonstrated. However, some support comes from Mendelian randomised studies showing that absence of ACL gene expression results in the lowering of LDL-C. The PD marker of LDL-C lipid-lowering effect was demonstrated in several phase I studies in healthy volunteers, several phase 2 studies in a diseased population (see also efficacy section) and confirmed in several phase 3 studies (as discussed in the efficacy section). Two small short-term (15 days) phase I randomized, double-blind, placebo-controlled, multiple-dose study in healthy subjects tested the LDL-C lowering effect of bempedoic acid in a dose range of 20 mg to 220 mg in small cohorts of 6 subjects each. Dose-dependent reduction was observed from a 60 mg QD dose or higher and started at 4 days after start of treatment with maximum effect achieved after 15 days at the end of the study. No consistent patterns could be observed for other lipid parameters including TC, HDL-C and TG. The phase 2 studies (and phase 3 studies) provide further support for the primary PD effect as described in the efficacy section.

In vitro hERG data and nonclinical safety pharmacology studies indicate **an absence of effect potential QTc prolongation**. Further evaluation of a potential pro-arrhythmic effect was performed by a thorough QT study. A slightly higher dose than the intended to be registered dose (240 mg vs 180 mg) was investigated and compared to the positive moxifloxacin control. No indication for a QT prolonging effect of bempedoic acid was observed after multiple dosing with the 240 mg dose. These data do not raise any need for closer QT observation during the phase 3 studies.

The effect of PK/PD in renal impairment was studied by a PK/PD model. The PK/PD model suggests an absence of a significant effect of renal impairment on the bempedoic acid LDL-C lowering effect. This is in line with the observation in the clinical studies.

The effect of statins on the PD treatment effect of bempedoic acid has been explored using a PK/PD model. The model used the data from 3 phase 3 studies (studies 040, 047 (high risk, long term pool) and 046). It appeared that the model slightly overestimated the LDL-C lowering effect and thus may not exactly fit the observed effect. Bempedoic acid has an incremental effect on LDL-C reduction when added onto statin therapy. In the exposure-LDL-C response modelling, the additive LDL C lowering by bempedoic acid decreased with increasing statin dose. This is in line with the subgroup analyses in the clinical studies demonstrating the lowest effect with the highest statin intensity.

Further, one study specifically evaluated the PK and PD effect of bempedoic acid added to PCSK9 treatment (evolocumab). Both products have a different mode of action. Bempedoic acid showed an additional significant LDL-C lowering effect on top of PCSK9 treatment of -30.3% after 2 months of

treatment, which thus appears even slightly greater than the LDL-C lowering effect of bempedoic acid monotherapy.

As may be expected, no interaction was observed when metformin was co-administered with steady state bempedoic acid for lipid levels and postprandial and fasting glucose.

2.4.5. Conclusions on clinical pharmacology

In general, the pharmacokinetics of bempedoic acid have been adequately characterised.

A pharmacokinetic interaction between bempedoic acid and statins has been observed. The impact of this increased exposure of statins on the increased LDL-C lowering is not exactly clear as this has not been clinically tested, although subgroup analyses and additional modelling of the clinical data suggest that the relative contribution of bempedoic acid to the overall LDL lowering effect is highest with lower statin doses (see clinical efficacy and clinical safety section).

The mechanism behind the increase in ezetimibe, uric acid, and creatinine are currently not well established and will be further investigated post marketing as reflected in agreed RMP.

The potential interactions of the major inactive metabolite ECT-1002-glucuronide is not exactly clear as its steady state concentrations are unknown. The applicant committed to measure steady-state concentrations of ETC-1002-glucuronide to evaluate the interaction potential of ETC-1002-glucuronide post-authorisation.

The mode of action of bempedoic acid is reasonably well established. Lowering of the LDL-C has been demonstrated. Further, no interaction exists with PCSK9 inhibitors or metformin. There is no sign of a pro-arrhythmic effect. The LDL-C effect has been further explored with a PK/PD model.

2.5. Clinical efficacy

2.5.1. Dose response studies

In Table 5 the phase 2 studies are presented.

Table 5. Tabular Listing of Phase 2 Efficacy Studies

	Bempedoic Acid Monotherapy 180 mg/day	**Bempedoic Acid Monotherapy 40-240 mg/day**			**Bempedoic Acid 120 or 180 mg/day ± Ezetimibe**	**Bempedoic Acid + Ezetimibe+ Atorvastatin**	**Bempedoic Acid with Background Statin Therapy**			**Bempedoic Acid with PCSK9 inhibitor Background**
Study	**1002-014**	**1002-006**	**1002-003**	**1002-005**	**1002-008**	**1002-038**	**1002-007**	**1002-009**	**1002-035**	**1002-039**
Subject population	Elevated LDL-C and hypertension	Elevated LDL-C and statin intolerance	Elevated LDL-C and either normal or elevated TG (Fredrickson Type IIa or IIb dyslipidemia)	Type 2 diabetes mellitus	Elevated LDL-C ± statin intolerance	Elevated LDL-C	Elevated LDL-C	Elevated LDL-C despite ongoing statin therapy	Statin-treated patients	Elevated LDL-C
Fasting calculated LDL-C	Washed out of lipid-regulating drugs: ≥ 100 mg/dL and ≤ 220 mg/dL at Week -1 Not washed out of lipid-regulating drugs: ≥ 85 mg/dL at Week -6	Not on lipid-regulating drugs: ≥ 115 mg/dL and ≤ 270 mg/dL at Week -4 On lipid-regulating drugs: ≥ 100 mg/dL and ≤220 mg/dL at Week -4	Mean from Week -2 and Week -1 of ≥ 130 mg/dL and ≤ 220 mg/dL	≥ 100 mg/dL at Day -42 to -30	Washed out of lipid-regulating drugs: ≥ 130 mg/dL and ≤ 220 mg/dL at Week -1 Not washed out of lipid-regulating drugs: ≥ 100 mg/dL at Week -6	Washed out of lipid-regulating drugs and supplements: ≥ 130 mg/dL and ≤ 189 mg/dL at Week -1	Not on statin therapy: ≥ 115 mg/dL and ≤ 270 mg/dL at Week -5 On statin therapy: ≥ 100 mg/dL and ≤ 220 mg/dL at Week -5	Mean from Week-2 and Week -1: ≥ 115 mg/dL and ≤ 220 mg/dL	High-intensity statin[a] for 4 weeks: ≥ 100 mg/dL and ≤ 220 mg/dL at Day -35 Moderate or low intensity statin for 4 weeks: ≥ 115 mg/dL and 220 mg/dL at Day-35	≥ 160 mg/dL on no background therapy; ≥ 70 mg/dL on PCSK9 inhibitor background therapy

Table 5. Tabular Listing of Phase 2 Efficacy Studies

	Bempedoic Acid Monotherapy 180 mg/day	**Bempedoic Acid Monotherapy 40-240 mg/day**			**Bempedoic Acid 120 or 180 mg/day ± Ezetimibe**	**Bempedoic Acid + Ezetimibe+ Atorvastatin**	**Bempedoic Acid with Background Statin Therapy**			**Bempedoic Acid with PCSK9 inhibitor Background**
Study	**1002-014**	**1002-006**	**1002-003**	**1002-005**	**1002-008**	**1002-038**	**1002-007**	**1002-009**	**1002-035**	**1002-039**
Background therapy	None	None	None	None	None	None	Atorvastatin 10 mg	Statin therapy[b]	Atorvastatin 80 mg	evolocumab 420 mg
Lipid regulating therapy washout period prior to Screening	5 weeks	4 weeks	6 weeks	4 weeks	5 weeks	5 weeks	4 weeks	5 weeks with exception of statins	5 weeks	1.5-month screening and washout
Additional key inclusion/ exclusion criteria	Fasting TG ≤ 400 mg/dL at Week -1	On lipid-regulating drugs: fasting TG < 350 mg/dL at Week -4 Not on lipid-regulating drugs: fasting TG < 400 mg/dL	Mean fasting TG < 400 mg/dL Patients stratified into normal (< 150 mg/dL) or elevated (≥ 150 mg/dL) TG stratum	Minimum 6-month history of diabetes	Fasting TG ≤ 400 mg/dL at Week -1 and ≤ 500 mg/dL at Week -6	Fasting TG ≤ 400 mg/dL at Week -1	On statin therapy: fasting TG < 350 mg/dL at Week -5	Mean fasting TG ≤ 400 mg/dL from Week -2 and Week -1	Mean fasting TG ≤ 400 mg/dL at Week -4 and Week -1	Fasting TG ≥ 500 mg/dL
Age	≥ 18 to ≤ 80 years	≥ 18 to ≤ 80 years	≥ 18 to ≤ 80 years	≥ 18 to ≤ 70 years	≥ 18 to ≤ 80 years	≥ 18 years	≥ 18 to ≤ 80 years	≥ 18 to ≤ 80 years	≥ 18 to ≤ 70 years	≥ 18 years

Table 5. Tabular Listing of Phase 2 Efficacy Studies

	Bempedoic Acid Monotherapy 180 mg/day	**Bempedoic Acid Monotherapy 40-240 mg/day**			**Bempedoic Acid 120 or 180 mg/day ± Ezetimibe**	**Bempedoic Acid + Ezetimibe+ Atorvastatin**	**Bempedoic Acid with Background Statin Therapy**			**Bempedoic Acid with PCSK9 inhibitor Background**
Study	**1002-014**	**1002-006**	**1002-003**	**1002-005**	**1002-008**	**1002-038**	**1002-007**	**1002-009**	**1002-035**	**1002-039**
Treatment duration	6 weeks	8 weeks	12 weeks	4 weeks	12 weeks	6 weeks	8 weeks	12 weeks	4 weeks open label atorvastatin; and 4 weeks atorvastatin + double blind BA or placebo	8 weeks
Test product and dosage regimen	BA 180 mg; Placebo	BA 60 mg for 2 weeks, then 120 mg for 2 weeks then 180 mg for 2 weeks then 240 mg for 2 weeks; Placebo	BA of 40, 80, or 120 mg Placebo	BA 80 mg for 2 weeks then 120 mg 2 weeks Placebo	BA 120 mg; 180 mg; ezetimibe 10 mg; BA 120 mg + ezetimibe 10 mg; or Bempedoic aid 180 mg + ezetimibe 10 mg	BA 180 mg + ezetimibe 10 mg + atorvastatin 20 mg; Placebo	BA 60 mg (+ atorvastatin 10 mg) with up titration to 120 mg, 180 mg, then 240 mg at Weeks 2, 4, and 6 Placebo	BA 120 mg, 180 mg; Placebo	BA 180 mg + atorvastatin 80 mg; Placebo + atorvastatin 80 mg	BA 180 mg; placebo
Formulation	capsule	capsule	capsule	capsule	capsule	capsule	capsule	capsule	capsule	capsule

Table 5. Tabular Listing of Phase 2 Efficacy Studies

	Bempedoic Acid Monotherapy 180 mg/day	Bempedoic Acid Monotherapy 40-240 mg/day			Bempedoic Acid 120 or 180 mg/day ± Ezetimibe	Bempedoic Acid + Ezetimibe+ Atorvastatin	Bempedoic Acid with Background Statin Therapy			Bempedoic Acid with PCSK9 inhibitor Background
Study	**1002-014**	**1002-006**	**1002-003**	**1002-005**	**1002-008**	**1002-038**	**1002-007**	**1002-009**	**1002-035**	**1002-039**
Randomi-zation	1:1 BA 180 mg : placebo	2:1 BA 180 mg : placebo	1:1:1:1 BA 40 mg : BA 80 mg : BA 120 mg: placebo	1:1 BA 80/120 mg :placebo	4:4:4:1:1 BA 120 mg: BA 180 mg: ezetimibe 10 mg: BA 120 mg + ezetimibe 10 mg: BA 180 mg + ezetimibe 10 mg	2:1 triplet therapy : placebo	3:1 BA 60-180 mg : placebo	1:1:1 BA 120 mg: BA 180 mg: placebo	2:1 BA+ atorvastatin 80 mg: placebo+ atorvastatin 80 mg	1:1 BA 180 mg +PCSK9 inhibitor
Number of patients	143 (BA: 71; placebo: 72)	56 (BA: 37; placebo: 19)	177 (BA 40 mg: 45; BA 80 mg: 44; BA 120 mg: 44; placebo: 44)	60 (BA: 30; placebo: 30)	349 (BA 120 mg: 100; BA 180 mg: 100; ezetimibe 10 mg: 99; BA 120 mg + ezetimibe 10 mg 26; BA 180 mg + ezetimibe 24)	63 (180 mg + ezetimibe 10 mg + atorvastatin 20 mg: 43; placebo: 20)	58 (BA: 42; placebo: 16)	134 (120 mg: 44 , 180 mg: 45, placebo:45)	68 (BA: 45; placebo: 23)	59 (BA 180 mg + PCSK9 inhibitor: 28; placebo + PCSK9 inhibitor: 31)

Table 5. Tabular Listing of Phase 2 Efficacy Studies

	Bempedoic Acid Monotherapy 180 mg/day	Bempedoic Acid Monotherapy 40-240 mg/day			Bempedoic Acid 120 or 180 mg/day ± Ezetimibe	Bempedoic Acid + Ezetimibe+ Atorvastatin	Bempedoic Acid with Background Statin Therapy			Bempedoic Acid with PCSK9 inhibitor Background
Study	**1002-014**	**1002-006**	**1002-003**	**1002-005**	**1002-008**	**1002-038**	**1002-007**	**1002-009**	**1002-035**	**1002-039**

BA = bempedoic acid; LDL-C = low-density lipoprotein cholesterol, PCSK9 = proprotein convertase subtilisin/kexin type 9; PCSK9 = proprotein convertase subtilisin/kexin type 9; TG = triglycerides; triplet therapy = 180 mg bempedoic acid + 10 mg ezetimibe + 20 mg atorvastatin

[a] High-intensity statins included atorvastatin 40-80 mg, rosuvastatin 20-40 mg, and simvastatin 80 mg; moderate-intensity statins included atorvastatin 10-20 mg, rosuvastatin 5-10 mg, simvastatin 20-40 mg, pravastatin 40-80 mg, lovastatin 40 mg, Fluvastatin XL 80 mg, Fluvastatin 40 mg twice daily, and pitavastatin 2-4 mg; low-intensity statins included simvastatin 10 mg, pravastatin 10-20 mg, lovastatin 20 mg, Fluvastatin 20-40 mg, and pitavastatin 1 mg.

[b] atorvastatin (10 mg or 20 mg), simvastatin (5 mg, 10 mg, or 20 mg), rosuvastatin (5 mg or 10 mg), and pravastatin (10 mg, 20 mg, or 40 mg) daily for at least 3 months prior to Screening.

All Phase 2 studies were double-blind, randomized, parallel-group studies. Except for Study 1002-008, Phase 2 studies were placebo-controlled.

Source: Study 1002-003; Study 1002-005; Study 1002-006; Study 1002-007; Study 1002-008, Study 1002-009; Study 1002-014; Study 1002-035; Study 1002-038; Study 1002-039

A pooled analysis of 6 phase 2 studies in 832 patients (580 on bemepdoic) demonstrated a dose dependent effect up to 180 mg QD dose; see Table 6 below. Higher doses than the 180 mg QD dose did not provide an additional lipid lowering effect versus placebo. Also, on top of statins, the 180 mg dose provided the largest effect (-21.7%) with no additional effect with the 240 mg dose (-21.7%). Of note, the (additional) effect of bempedoic acid on top of statin was lower than compared to the bempedoic effect without statin background therapy. The effect of bempedoic acid plus ezetimibe versus placebo showed the largest treatment effect (-45.6% BA 120 mg + 10 mg eze, -50.1% BA 180 mg +10 mg.

Table 6. Change in LDL-C (mg/dL) From Baseline to End of Study, Pooled Phase 2 Studies (Studies 1002-003, 1002 005, 1002 006, 1002-007, 1002-008, and 1002-009)

Pairwise Comparisons	N		LS Mean (SE)		Placebo-adjusted LS Mean Change (95% CI)	P value
	Placebo	Bempedoic Acid	Placebo	Bempedoic Acid		
Bempedoic acid vs placebo						
40 mg	149	42	-2.9 (1.38)	-21.2 (2.96)	-18.3 (-24.5, -12.1)	<0.0001
80 mg	149	44	-2.9 (1.38)	-28.4 (2.91)	-25.5 (-31.6, -19.4)	<0.0001
120 mg	149	168	-2.9 (1.38)	-32.7 (2.03)	-29.8 (-34.8, -24.8)	<0.0001
180 mg	149	99	-2.9 (1.38)	-35.3 (2.83)	-32.4 (-39.0, -25.8)	<0.0001
240 mg	149	34	-2.9 (1.38)	-31.7 (4.17)	-28.8 (-37.5, -20.0)	<0.0001
Bempedoic acid + ezetimibe 10 mg vs placebo						
120 mg	149	24	-2.9 (1.38)	-48.5 (3.92)	-45.6 (-54.0, -37.1)	<0.0001
180 mg	149	22	-2.9 (1.38)	-53.0 (4.03)	-50.1 (-58.7, -41.4)	<0.0001
Ezetimibe 10 mg vs placebo	149	98	-2.9 (1.38)	-26.4 (2.84)	-23.5 (-30.1, -16.9)	<0.0001
Bempedoic acid + baseline statin vs placebo						
120 mg	149	41	-2.9 (1.38)	-16.5 (3.34)	-13.6 (-20.1, -7.1)	<0.0001
180 mg	149	43	-2.9 (1.38)	-24.6 (3.30)	-21.7 (-28.2, -15.3)	<0.0001
240 mg	149	42	-2.9 (1.38)	-24.6 (4.13)	-21.7 (-30.5, -12.9)	<0.0001

2.5.2. Main studies

The Phase 3 program included 4 randomized, double-blind, placebo-controlled, parallel-group studies. Studies 1002-040 and 1002-047 included patients treated on maximum tolerated statins and the substantial smaller studies 1002-046 and 1002-048 included statin-intolerant patients. The open-label extension study (1002 050) included patients from study 1002 040 and is still ongoing.

Phase 3 main studies

The phase 3 main studies included two studies on top of maximum tolerated statins and two studies in statin intolerant patients (none or low dose statin)

An integrated presentation of the four phase 3 studies is presented below as they present several common features. Individual study features will be presented where needed.

Methods

All phase 3 studies were double-blind, placebo-controlled, randomized (2:1), parallel-group, multicenter studies with bempedoic acid 180 mg per day or placebo in adult patients at risk for CV events with primary hyperlipidemia.

Studies on top of maximum tolerated statins

The largest study 040 used a 2-week screening period before randomization. Patients who met all enrollment criteria were instructed to continue their therapy(s) for lipid regulation and to maintain a consistent diet and exercise pattern throughout the study. Other lipid lowering medication was allowed after 24 weeks of treatment.

In study 047 patients were screened about 5 weeks before randomization. The 1-week screening could have been extended for an additional 4 weeks if needed, to adjust background medical therapy or for other reasons. A single-blind placebo run-in period was used. Patients who met all enrollment criteria continued their allowed stable background LMT and maintained consistent diet and exercise patterns throughout the study.

Studies in statin intolerant patients

In study 046 patients were screened about 5 weeks before randomization. The 1-week screening could have been extended for an additional 4 weeks if needed, to adjust background medical therapy or for other reasons. A single-blind placebo run-in period was used. Patients who met all enrollment criteria continued their allowed stable background LMT and maintained consistent diet and exercise patterns throughout the study.

In study 048 patients were screened about 5 weeks before randomization. The 1-week screening could have been extended for an additional 4 weeks if needed, to adjust background medical therapy or for other reasons. Eligible patients began the single-blind, placebo run-in period with study-supplied and labelled ezetimibe and placebo 4 weeks prior to randomisation. If a patient was already taking ezetimibe, they stopped taking their personal supply of ezetimibe and began taking study-supplied ezetimibe. The effect was evaluated prior to randomization.

Lipid sample collection

In the Phase 3 studies, samples were collected and analyzed for basic fasting lipids (calculated LDL-C, HDL-C, non-HDL-C, TC, and TGs), apo B and hsCRP at a central clinical laboratory in each study. Blood draws for lipids were required to be taken after a minimum 10-hour fast (water was allowed). LDL-C was calculated, or if TGs were > 400 mg/dL or LDL-C was < 50 mg/dL, LDL-C was measured directly.

Data monitoring and CV events adjudication

An unblinded independent data monitoring committee monitored accumulating patient safety and efficacy data until the last patient completed study treatment. A blinded independent expert Clinical Events Committee (CEC) adjudicated clinical endpoints including CV events.

Study Participants

The main inclusion criteria are provided in Table 7 below.

Table 7: Phase 3 Studies

Study Characteristic	High CV Risk/Long-Term Studies		No- or Low-Dose Statin Studies	
	Study 1002-047	**Study 1002-040**	**Study 1002-046**	**Study 1002-048**
Subject population	High CV risk (ASCVD and/or HeFH with hyperlipidemia)	High CV risk (ASCVD and/or HeFH) with hyperlipidemia	Primary prevention; secondary prevention (ASCVD and/or HeFH) and elevated LDL-C tolerating no more than very low dose statin	Elevated LDL-C tolerating no more than low dose statin
Fasting LDL-C	Week -5: ≥ 100 mg/dL Week -1: ≥ 70 mg/dL	Week -2: ≥ 70 mg/dL	Patients with no prior CV event (primary prevention): ≥ 130 mg/dL Patients with prior CV event or HeFH (secondary prevention): ≥ 100 mg/dL All patients at Week -1: ≥ 70 mg/dL	Patients taking ezetimibe prior to Week -5: ≥ 100 mg/dL Patients not taking ezetimibe prior to Week -5: ≥ 120 mg/dL All patients at Week -1: ≥ 70 mg/dL
Background therapy	Maximally tolerated statin and other LMT	Maximally tolerated statin and other LMT	No statin or < lowest approved starting dose statin ± other LMT	No statin or no more than the lowest approved starting dose statin and ezetimibe ^{stable} LMT
Lipid regulating therapy washout prior to Screening	LMTs were to remain stable ≥ 4 weeks prior to screening; fibrates were to remain stable 6 weeks prior to screening. PCSK9 inhibitors allowed during study but dose must have been stable for ≥ 3 injections prior to screening; if PCSK9 inhibitor was discontinued, must be ≥ 4 months since last injection	LMTs were to remain stable 4 weeks prior to screening visit; fibrates were to remain stable 6 weeks prior to the screening visit. PCSK9 inhibitors were not allowed at study entry	LMTs were to remain stable 4 weeks prior to the screening visit; fibrates were to remain stable 6 weeks prior to the screening visit. PCSK9 inhibitors allowed during study but dose must have been stable for ≥ 3 injections prior to screening; if PCSK9 inhibitor was discontinued, must be ≥ 4 months since last injection	LMTs were to remain stable 4 weeks prior to Week -5; fibrates were to remain stable 6 weeks prior to Week -5. PCSK9 inhibitors were not allowed with last use required to be ≥ 4 months prior to screening

Study Characteristic	High CV Risk/Long-Term Studies		No or Low-Dose Statin Studies	
	Study 1002-047	**Study 1002-040**	**Study 1002-046**	**Study 1002-048**
Additional key inclusion/exclusion criteria	Stable (≥ 4 weeks) maximally tolerated background statin TG < 500 mg/dL at Screening eGFR ≥ 30 mL/min 1.73 m^2 using MDRD formula at Week -5	Stable (≥ 4 weeks) background statins; TG ≤ 500 mg/dL at Screening eGFR ≥ 30 mL/min 1.73 m^2 using MDRD formula at Week -2	TG < 500 mg/dL at Week -5 eGFR ≥ 30 mL/min 1.73 m^2 using MDRD formula at Screening	Stable (≥ 4 weeks) background statin that did not exceed low-dose statin therapy; TG < 500 mg/dL at Week -5 eGFR ≥ 30 mL/min 1.73 m^2 using MDRD formula at Week -5
Age	≥ 18 years	≥ 18 years	≥ 18 years	≥ 18 years

CV risk definition

High risk was defined as a diagnosis of HeFH or ASCVD (with established CHD or CHD risk equivalents). Established CHD included 1 or more of either MI, silent MI, unstable angina, coronary revascularization procedure, or clinically significant CHD diagnosed by invasive or non-invasive testing. Risk of CHD included 1 or more of either peripheral arterial disease, previous ischemic stroke with a focal ischemic neurological deficit that persisted ≥ 24 hours. Diagnosis of HeFH must have been made by either genotyping or by clinical assessment using either the World Health Organization (WHO) criteria/Dutch Lipid Clinical Network Criteria with a score that was > 8 points or the Simon Broome Register Diagnostic Criteria with an assessment of Definite HeFH.

Maximum tolerated statin therapy

Maximally tolerated statin use needed to be at stable doses for at least 4 weeks prior to screening. Maximally tolerated statin included statin regimens other than daily dosing, including no to very low doses, with documented reasons for not using high-intensity statin dosing. Gemfibrozil was prohibited in patients taking a statin.

Statin intolerance

Statin intolerance defined in Study 1002-046 as the inability to tolerate 2 or more statins, one at a low dose, due to an adverse safety effect that started or increased during statin therapy and resolved or improved when statin therapy was discontinued and in Study 1002-048 as the inability to tolerate 1 or more statins.

Relevant other exclusion criteria

Liver disease or dysfunction, ALT/AST ≥2 × ULN, bilirubin ≥1.2 × ULN; creatine kinase (CK) >3 × ULN, and within 3 months CV disease or intervention.

Treatments

The main treatment features are provided below.

Table 8. Phase 3 Studies

Study Characteristic	High CV Risk/Long-Term Studies		No- or Low-Dose Statin Studies	
	Study 1002-047	**Study 1002-040**	**Study 1002-046**	**Study 1002-048**
Treatment duration	52 weeks	52 weeks	24 weeks	12 weeks
Test product(s) and dosage regimen	Bempedoic acid 180 mg Placebo	Bempedoic acid 180 mg Placebo	Bempedoic acid 180 mg Placebo	Bempedoic acid 180 mg Placebo
Formulation	tablet	tablet	tablet	tablet
Randomization	2:1 bempedoic acid:placebo	2:1 bempedoic acid:placebo	2:1 bempedoic acid:placebo	2:1 bempedoic acid:placebo
Number of patients	779 (522 bempedoic acid, 257 placebo)	2230 (1488 bempedoic acid; 742 placebo)	345 (234 bempedoic acid;111 placebo)	269 (181 bempedoic acid+ ezetimibe; 88 placebo+ ezetimibe)

Background therapy

Allowed background therapy is displayed in the Table 9 below.

Table 9. Allowed Background Lipid Modifying Therapies in the Phase 3 Studies

	1002-047	**1002-040**	**1002-046**	**1002-048**
Statins[1]				
atorvastatin (Lipitor, Sortis)	X	X	X	X
fluvastatin (Lescol)	X	X	X	X
lovastatin (Mevacor, Altoprev)	X	X	X	X
pravastatin (Pravachol)	X	X	X	X
pitavastatin (Livalo, Lipostat)	X	X	X	X
rosuvastatin (Crestor)	X	X	X	X
simvastatin (Zocor)	X	X[2]	X	X
Selective cholesterol and/or bile acid absorption inhibitors				
cholestyramine/colestyramine (Questran, Questran Light, Prevalite, Locholest, Locholest Light)	X	X	X	X
colestipol (Colestid)	X	X	X	X

	1002-047	1002-040	1002-046	1002-048
colesevelam hydrochloride (Welchol, Cholestagel)	X	X	X	X
ezetimibe (Zetia, Ezetrol)	X	X	X	X[3]
Fibrates				
fenofibrate (Antara, Lofibra, Tricor, Triglide, Lipantil, Supralip) [4]	X	X	X	X
bezafibrate (Bezalip)	X	X	X	X
ciprofibrate (Modalim)	X	X	X	X
PCSK9 inhibitors				
alirocumab (Praluent)	X	X[5]	X	–
evolocumab (Repatha)	X	X	X	–
Other				
ezetimibe/simvastatin combinations where simvastatin doses were < 40 mg/day (Vytorin 10 mg/10 mg and 10 mg/20 mg, Inegy 10 mg/20 mg)	X	X	–	–
atorvastatin/ezetimibe combinations (Atozet)	X	X	–	–
niacin (Niaspan, Niacor, Slo Niacin)	X	X	X	X
All prescription and nonprescription fish oil and n-3 fatty acid preparations	X	X	X	X

[1] Statins were allowed at specific doses in Study 1002-046 and Study 1002-048. In Studies 1002-046 and 1002-048, very low-dose statin therapy was allowed defined as an average daily dose of rosuvastatin < 5 mg, atorvastatin < 10 mg, simvastatin < 10 mg, lovastatin < 20 mg, pravastatin < 40 mg, fluvastatin < 40 mg, or pitavastatin < 2 mg. In Study 1002-048, low-dose statin therapy was also allowed defined as an average daily dose of rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg. At average daily doses < 40 mg
[2] At average daily doses ≤ 40 mg prior to Amendment 5 and < 40 mg after Amendment 5.
[3] Patients who were already receiving ezetimibe were switched to study supplied ezetimibe at the time of the run-in period. LDL C after the ezetimibe run-in period had to be ≥ 70 mg/dL.
[4] Gemfibrozil was excluded in patients on a statin per statin Rx. All others allowed but required to be stable for at least 6 weeks prior to screening.
[5] Prohibited within 4 weeks prior to screening, but allowed as adjunctive therapy starting at Week 24.

Statin therapy

Baseline statin intensity (high intensity statin, moderate intensity statin, low intensity was determined for each patient based on the patient's average daily dose at baseline.

High-dose statin was defined as rosuvastatin 40 mg, atorvastatin 80 mg, or simvastatin 40 or 80 mg per day. With the implementation of Amendment 5 in study 040, simvastatin at doses ≥ 40 mg/day, including simvastatin-containing therapies, was prohibited, due to a bempedoic induced increase of exposure of simvastatin considered to be of clinical relevance; at the time of the amendment, 98 patients were receiving daily doses of simvastatin of ≥ 40 mg and were discontinued for this reason. Gemfibrozil was prohibited during the study.

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

atorvastatin < 10 mg, simvastatin < 10 mg, lovastatin < 20 mg, pravastatin < 40 mg, fluvastatin < 40 mg, or pitavastatin < 2 mg, see Table 10.

Table 10. Baseline Statin Dose Categories

High Intensity Statins[a]	Moderate Intensity Statins	Low Intensity Statins[b]
Atorvastatin 40-80 mg	Atorvastatin 10-20 mg	Simvastatin 10 mg
Rosuvastatin 20-40 mg	Rosuvastatin 5-10 mg	Pravastatin 10-20 mg
	Simvastatin 20 mg	Lovastatin 20 mg
	Pravastatin 40-80 mg	Fluvastatin 20-40 mg
	Lovastatin 40 mg	Pitavastatin 1 mg
	Fluvastatin XL 80 mg	
	Fluvastatin 40 mg BID	
	Pitavastatin 2-4 mg	

BID = twice daily
[a] Simvastatin doses ≥ 40 mg/day were prohibited.
[b] Low intensity statins also included those patients taking low-dose statins using an alternate regimen (ie, every other day, or for a specified number of times per week) and in Study 1002-047, those unable to tolerate a statin at any dose.

Objectives

Study 1002-040: To evaluate the long-term safety and tolerability of bempedoic acid versus placebo in patients with hyperlipidemia (with underlying heterozygous familial hypercholesterolemia [HeFH] and/or atherosclerotic cardiovascular disease [ASCVD]) who were at high risk for a CV event and who had elevated LDL-C, despite receiving treatment with maximally-tolerated statin therapy with and without other LMT.

Study 1002-047: To assess the 12-week efficacy of bempedoic acid 180 mg versus placebo in decreasing LDL-C in high CV risk patients with hyperlipidemia (with atherosclerotic cardiovascular disease [ASCVD] and/or underlying heterozygous familial hypercholesterolemia [HeFH]) who are not adequately controlled with their maximally tolerated lipid-modifying therapy, defined as maximally-tolerated statin therapy with and without other LMT.

Study 1002-046: to assess the 12-week efficacy of bempedoic acid 180 mg/day vs placebo in decreasing LDL-C in patients with elevated LDL-C who are statin intolerant.

Study 1002-048: To assess the 12-week efficacy of bempedoic acid 180 mg/day vs placebo in decreasing LDL-C when added to ezetimibe therapy in patients with elevated LDL-C.

Outcomes/endpoints

The endpoints for the phase 3 studies are displayed in the Table 11

Table 11. Study Endpoints for Pivotal Phase 3 Studies

	Double-Blind Phase 3 Studies			
	High CV Risk		No or Low-Dose Statin	
Endpoints	**Study 1002-047**	**Study 1002-040**	**Study 1002-046**	**Study 1002-048**
Primary				
Percent change from baseline to Week 12 in LDL-C	X	X(1)	X	X
Secondary				
Percent change from baseline to Week 24 in LDL-C	X	X	X	–
Percent change from baseline to Week 12 in non-HDL-C, TC, apo B, and hsCRP	X	X	X	X
Percent change from baseline to Week 12 in TGs and HDL-C	–	–	–	X

[i] Primary endpoint was safety in Study 1002-040; however, percent change from baseline to Week 12 in LDL-C was the primary efficacy endpoint.

Sample size

A total of 1950 patients were planned to be enrolled in study 1002-040. The sample size was selected to determine the absolute risk with at least 95% power to detect adverse events that occur at rates similar to those seen in the placebo group for AESIs in the recently completed long-term safety study in the PCSK9i, alirocumab (Robinson et al, 2015).

In study 1002-046 (n=300), study 1002-047 (n=750) and study 1002-048 (n=225), the sample size was determined to provide more than 95% power to detect a difference of 15% in the percent change from baseline to Week 12 in calculated LDL-C between the bempedoic acid treatment group and the placebo group. This calculation was based on a 2-sided t-test at the 5% level of significance and a common standard deviation of 15%.

Randomisation and blinding

Patients were randomized 2:1 to bempedoic acid or matching placebo using an interactive web response system (IWRS). For studies on top of statins, randomization was stratified by CV risk (whether the patient had a diagnosis of HeFH) and baseline statin intensity.

In all studies, study medication was administered in a double-blind fashion. The Sponsor, all clinical site personnel (eg, investigator, pharmacist), other vendor personnel, and patients were blinded to the treatment group for each patient. Patients were also blinded to the treatment they received. Unblinded user(s) were designated for each clinical site and at the Sponsor (or designee) as needed to perform emergency unblinding of treatment for an individual patient e.g. in case the safety of the patient might have been at risk.

Post-randomization values for LDL-C, TGs, TC, HDL-C, non-HDL-C, apo B, and hsCRP, including any plasma concentration of the bempedoic acid analyte (ETC-1002) and its metabolite (ESP15228), were not available to personnel from the clinical site, the patient, the Sponsor, or CRO.

Statistical methods

The following populations were defined for analysis purposes (Table 12):

• The Full Analysis Set (FAS), also known as the intention-to-treat set, was used for all of the efficacy analyses and was defined as all randomized patients. Patients in the FAS were included in their randomized treatment group, regardless of their actual treatment.

• The Safety Analysis Set, used for all of the safety summaries, was defined as all randomized patients who received at least 1 dose of study medication. Patients in the Safety Analysis Set were included in the treatment group that they actually received, regardless of their randomized treatment.

• The PK analysis set included all patients in the Safety Analysis Set who had at least one PK assessment. These patients were included in plasma concentration summaries unless major protocol deviations identified during the protocol deviation review or if key dosing or sampling information was missing.

• In studies 046 and 048, a completer Analysis Set, used as a sensitivity analysis for the primary and secondary efficacy analyses, was defined as all patients in the FAS who completed both IMP and ezetimibe treatment per the end of treatment CRF page and had non-missing Week 12 LDL-C values.

Table 12. Statistical Methods for Phase 3 Studies

Endpoints	Statistical Methods[a]	Studies
Primary efficacy endpoint: Percent change in LDL-C from baseline to Week 12 in ITT population	ANCOVA model, with treatment group, CV risk (ASCVD only or HeFH with or without ASCVD), and baseline statin intensity (high, moderate, or low) as factors, and baseline LDL-C as a covariate.	1002-047 1002-040
	ANCOVA model, with treatment group and patient type (primary or secondary prevention) as factors, and baseline LDL-C as a covariate.	1002-046
	ANCOVA model, with treatment group as a factor and baseline LDL-C as a covariate.	1002-048
Secondary efficacy endpoints: Change and percent change from baseline in LDL-C, non-HDL-C, TC, apo B, and hsCRP in ITT population	A stepdown approach was used to test the primary and then key secondary endpoints. The sequence for the stepdown procedure was changed from baseline in LDL-C at Weeks 12 and 24 (only Week 12 for Study 1002-048) followed by non-HDL-C, TC, apo B, and hsCRP at Week 12. In this hierarchical testing structure, each hypothesis was tested at a significance level of 0.05, 2-sided, and statistical significance at each step was required to test the next lipid parameter.	1002-047 1002-040 1002-046 1002-048
	Percent change from baseline for LDL-C, non-HDL-C, TC and apo B was assessed using ANCOVA, with treatment group and	1002-047 1002-040

Endpoints	Statistical Methods[a]	Studies
	randomization strata (as applicable) as factors, and respective baseline value as a covariate.	1002-046 1002-048
	Due to skewed distribution attributed to extreme outliers and non-normal distribution, the hsCRP endpoint was assessed by non-parametric analysis based on Wilcoxon rank sum test and location shift estimate.	
	Similar ANCOVA model was also used to assess percent change in efficacy parameters at Week 52, excluding those started adjunctive LMT therapy.	1002-047 1002-040
	Actual value, change and percent change of efficacy parameters were summarized using summary statistics at protocol-specified time points	1002-047 1002-040 1002-046 1002-048

Results

Participant flow

Patient disposition is provided in Table 13 below.

Table 13. Patient Disposition in the Individual Pivotal Phase 3 Studies (All Patients)

	High CV Risk				No or Low-Dose Statin			
	Study 1002-047		Study 1002-040		Study 1002-046		Study 1002-048	
	Placebo (n = 257)	Bempedoic Acid (n = 522)	Placebo (N = 742)	Bempedoic Acid (n = 1488)	Placebo (N = 111)	Bempedoic Acid (n = 234)	Placebo (N = 88)	Bempedoic Acid (N = 181)
Randomized	257	522	742	1488	111	234	88	181
Completed study	250 (97.3)	490 (93.9)	706 (95.1)	1404 (94.4)	107 (96.4)	220 (94.0)	81 (92.0)	176 (97.2)
Withdrew from study	7 (2.7)	32 (6.1)	36 (4.9)	84 (5.6)	4 (3.6)	14 (6.0)	7 (8.0)	5 (2.8)
Adverse event	2 (0.8)	2 (0.4)	12 (1.6)	37 (2.5)	1 (0.9)	6 (2.6)	3 (3.4)	3 (1.7)
Withdrawal by patient	1 (0.4)	6 (1.1)	23 (3.1)	40 (2.7)	1 (0.9)	1 (0.4)	2 (2.3)	0
Protocol Deviation	0	3 (0.6)	0	2 (0.1)	0	0	0	0
Sponsor decision	0	0	0	1 (0.1)	2 (1.8)	5 (2.1)	1 (1.1)	0
Physician decision	0	1 (0.2)	0	1 (0.1)	0	0	0	0
Lost to Follow-up	1 (0.4)	9 (1.7)	1 (0.1)	2 (0.1)	0	0	0	2 (1.1)

	High CV Risk				No or Low-Dose Statin			
	Study 1002-047		Study 1002-040		Study 1002-046		Study 1002-048	
Death	3 (1.2)	8 (1.5)	NR	NR	0	0	0	0
Other	0	3 (0.6)	0	1 (0.1)	0	2 (0.9)	1 (1.1)	0
Completed IMP	214 (83.3)	415 (79.5)	600 (80.9)	1142 (76.7)	93 (83.8)	176 (75.2)	79 (89.8)	164 (90.6)
Discontinuation of IMP	43 (16.7)	107 (20.5)	142 (19.1)	345 (23.2)	18 (16.2)	58 (24.8)	8 (9.1)	17 (9.4)
Adverse event	21 (8.2)	54 (10.3)	55 (7.4)	160 (10.8)	13 (11.7)	43 (18.4)	5 (5.7)	13 (7.2)
Withdrawal by patient	0	5 (1.0)	51 (6.9)	96 (6.5)	0	0	2 (2.3)	0
Patient decision	11 (4.3)	22 (4.2)	0	0	3 (2.7)	3 (1.3)	0	1 (0.6)
Sponsor decision	1 (0.4)	3 (0.6)	32 (4.3)	71 (4.8)	2 (1.8)	5 (2.1)	0	0
Physician decision	6 (2.3)	5 (1.0)	0	12 (0.8)	0	0	0	1 (0.6)
Protocol deviation	1 (0.4)	5 (1.0)	2 (0.3)	3 (0.2)	0	0	0	0
Lost to follow-up	1 (0.4)	7 (1.3)	1 (0.1)	2 (0.1)	0	0	0	2 (1.1)
Death	1 (0.4)	3 (0.6)	NR	NR	0	0	0	0
Other	1 (0.4)	3 (0.6)	1 (0.1)	2 (0.1)	0	7 (3.0)	1 (1.1)	0

Baseline data

Demographic and other baseline characteristics for the studies in the Phase 3 program are presented in Table 14 below.

Table 14: Patient Demographic Characteristics in Pivotal Phase 3 Studies (Full Analysis Set)

	High CV Risk				No- or Low-Dose Statin			
	Study 1002-047		Study 1002-040		Study 1002-046		Study 1002-048	
	Placebo (N = 257)	Bempedoic Acid (n = 522)	Placebo (N = 742)	Bempedoic Acid (N = 1488)	Placebo (N = 111)	Bempedoic Acid (n = 234)	Placebo (N = 88)	Bempedoic Acid (n = 181)
Age (years)								
Mean (SD)	64.7 (8.73)	64.1 (8.82)	66.8 (8.64)	65.8 (9.11)	65.1 (9.21)	65.2 (9.66)	63.7 (11.32)	63.8 (10.77)
Median	65.0	64.0	67.0	67.0	66.0	66.0	66.0	66.0
Sex, n (%)								
Men	168 (65.4)	328 (62.8)	529 (71.3)	1099 (73.9)	50 (45.0)	101 (43.2)	32 (36.4)	72 (39.8)
Women	89 (34.6)	194 (37.2)	213 (28.7)	389 (26.1)	61 (55.0)	133 (56.8)	56 (63.6)	109 (60.2)

Table 14: Patient Demographic Characteristics in Pivotal Phase 3 Studies (Full Analysis Set)

	High CV Risk				No- or Low-Dose Statin			
	Study 1002-047		Study 1002-040		Study 1002-046		Study 1002-048	
	Placebo (N = 257)	Bempedoic Acid (n = 522)	Placebo (N = 742)	Bempedoic Acid (N = 1488)	Placebo (N = 111)	Bempedoic Acid (n = 234)	Placebo (N = 88)	Bempedoic Acid (n = 181)
Race, n (%)								
American Indian or Alaska Native	1 (0.4)	0	1 (0.1)	2 (0.1)	0	1 (0.4)	–	–
Asian	0	4 (0.8)	8 (1.1)	14 (0.9)	2 (1.8)	6 (2.6)	1 (1.1)	3 (1.7)
Black or African American	12 (4.7)	24 (4.6)	15 (2.0)	42 (2.8)	10 (9.0)	16 (6.8)	10 (11.4)	11 (6.1)
Native Hawaiian or Other Pacific Islander	0	1 (0.2)	0	2 (0.1)	2 (1.8)	0	0	2 (1.1)
White	244 (94.9)	491 (94.1)	716 (96.5)	1423 (95.6)	96 (86.5)	211 (90.2)	75 (85.2)	165 (91.2)
Other	0	0	2 (0.3)	4 (0.3)	0	0	0	0
Multiple	0	2 (0.4)	0	1 (0.1)	1 (0.9)	0	2 (2.3)	0
Ethnicity, n (%)								
Hispanic or Latino	19 (7.4)	43 (8.2)	11 (1.5)	24 (1.6)	4 (3.6)	13 (5.6)	23 (26.1)	43 (23.8)
Not Hispanic or Latino	238 (92.6)	479 (91.8)	731 (98.5)	1464 (98.4)	107 (96.4)	221 (94.4)	65 (73.9)	138 (76.2)
Region, n (%)								
United States	68 (26.5)	145 (27.8)	259 (34.9)	507 (34.1)	78 (70.3)	173 (73.9)	67 (76.1)	136 (75.1)
Canada	4 (1.6)	10 (1.9)	0	0	33 (29.7)	61 (26.1)	6 (6.8)	11 (6.1)
Europe	185 (72.0)	367 (70.3)	483 (65.1)	981 (65.9)	0	0	15 (17.0)	34 (18.8)

	High CV Risk				No or Low-Dose Statin			
	Study 1002-047		Study 1002-040		Study 1002-046		Study 1002-048	
	Placebo (N = 257)	Bempedoic Acid (N = 522)	Placebo (N = 742)	Bempedoic Acid (N = 1488)	Placebo (N = 111)	Bempedoic Acid (N = 234)	Placebo (N = 88)	Bempedoic Acid (N = 181)
BMI (kg/m^2), mean (SD)	30.64 (5.048)	30.01 (5.192)	29.40 (4.935)	29.74 (4.919)	30.59 (5.155)	30.14 (5.760)	30.45 (5.787)	29.52 (4.740)

Table 14: Patient Demographic Characteristics in Pivotal Phase 3 Studies (Full Analysis Set)

	High CV Risk				No- or Low-Dose Statin			
	Study 1002-047		Study 1002-040		Study 1002-046		Study 1002-048	
	Placebo (N = 257)	Bempedoic Acid (n = 522)	Placebo (N = 742)	Bempedoic Acid (N = 1488)	Placebo (N = 111)	Bempedoic Acid (n = 234)	Placebo (N = 88)	Bempedoic Acid (n = 181)
Stratification for CVD Risk Category								
HeFH (with or without ASCVD)	16 (6.2)	27 (5.2)	35 (4.7)	73 (4.9)	3 (2.7)	4 (1.7)	NA	NA
ASCVD Only (without HeFH)	241 (93.8)	495 (94.8)	707 (95.3)	1415 (95.1)	44 (39.6)(1)	90 (38.5) 1)	NA(2)	NA2)
History of hypertension								
Yes	224 (87.2)	438 (83.9)	594 (80.1)	1174 (78.9)	75 (67.6)	153 (65.4)	48 (54.5)	109 (60.2)
eGFR category at baseline (mL/min/1.73m^2)								
≥ 90	56 (21.8)	107 (20.5)	167 (22.5)	320 (21.5)	16 (14.4)	58 (24.8)	17 (19.3)	45 (24.9)
60- < 90	164 (63.8)	338 (64.8)	468 (63.1)	945 (63.6)	69 (62.2)	139 (59.4)	57 (64.8)	110 (60.8)
30- < 60	36 (14.0)	76 (14.6)	107 (14.4)	222 (14.9)	26 (23.4)	36 (15.4)	14 (15.9)	25 (13.8)
15- < 30	1 (0.4)	1 (0.2)	0	0	0	1 (0.4)	0	1 (0.6)
History of diabetes								
Yes	81 (31.5)	155 (29.7)	212 (28.6)	425 (28.6)	26 (23.4)	63 (26.9)	17 (19.3)	35 (19.3)
Tobacco Use								
Current	57 (22.2)	110 (21.1)	103 (13.9)	251 (16.9)	11 (9.9)	30 (12.8)	12 (13.6)	21 (11.6)
Former	109 (42.4)	214 (41.0)	405 (54.6)	742 (49.9)	35 (31.5)	73 (31.2)	22 (25.0)	48 (26.5)
LDL-C (mg/dL)Mean (SD)	122.43 (38.295)	119.44 (37.749)	102.30 (30.048)	103.60 (29.127)	155.6 (38.81)	158.5 (40.39)	123.0 (27.20)	129.8 (30.87)
Non-HDL-C (mg/dL), mean (SD)	153.66 (44.361)	150.69 (42.745)	129.37 (33.855)	130.92 (33.677)	190.7 (43.78)	193.5 (45.10)	151.6 (32.73)	162.4

	High CV Risk				No or Low-Dose Statin			
	Study 1002-047		Study 1002-040		Study 1002-046		Study 1002-048	
	Placebo (N = 257)	Bempedoic Acid (N = 522)	Placebo (N = 742)	Bempedoic Acid (N = 1488)	Placebo (N = 111)	Bempedoic Acid (N = 234)	Placebo (N = 88)	Bempedoic Acid (N = 181)
TC (mg/dL), mean (SD)	204.79 (46.057)	202.06 (42.706)	178.64 (35.65)	179.66 (35.143)	241.1 (44.29)	245.7 (47.25)	208.6 (35.71)	218.2 (35.88)
apo B (mg/dL), mean (SD)	118.6 (30.53)	116.2 (29.58)	86.8 (21.82)	88.5 (21.57)	141.9 (30.44)	141.0 (31.64)	115.8 (23.47)	123.3 (26.48)
hsCRP (mg/L), mean (SD)	3.686 (5.6241)	3.004 (4.3313)	3.28 (7.188)	3.48 (8.194)	4.15 (5.123)	5.60 (15.911)	3.43 (3.307)	3.70 (4.878)
Background LMT, n (%)								
Statins	231 (89.9)	474 (90.8)	742 (100)	1486 (99.9)	11 (9.9)	18 (7.7)	25 (28.4)	59 (32.6)
Baseline statin intensity, n (%)								
Low	40 (15.6)	78 (14.9)	48 (6.5)	100 (6.7)	11 (9.9)	18 (7.7)	25 (28.4)	59 0(32.6)
Medium	82 (31.9)	166 (31.8)	324 (43.7)	646 (43.4)	–	–	–	–
High	135 (52.5)	278 (53.3)	370 (49.9)	742 (49.9)	–	–	–	–
Background ezetimibe during study, n (%)	24 (9.3)	38 (7.3)	56 (7.5)	115 (7.7)	15 (13.5)	35 (15.0)	88 (100)	181 (100)

The background therapy used in each of the studies is provided in Table 15, Table 16, Table 17 and Table 18 below.

Table 15. Concomitant LLT medication in study 040

ATC Class Level 4 Preferred Term	Placebo (N = 742) n (%)	Bempedoic Acid (N = 1487) n (%)
Patients with concomitant statin medications	742 (100.0)	1485 (99.9)
HMG-CoA reductase inhibitors	742 (100.0)	1485 (99.9)
Atorvastatin	409 (55.1)	854 (57.4)
Rosuvastatin	145 (19.5)	262 (17.6)
Simvastatin	117 (15.8)	234 (15.7)
Pravastatin	55 (7.4)	92 (6.2)
Pitavastatin	6 (0.8)	23 (1.5)
Fluvastatin	7 (0.9)	13 (0.9)
Lovastatin	3 (0.4)	7 (0.5)
HMG-CoA reductase inhibitors in combination with other lipid-modifying agents	1 (0.1)	0
Inegy (simvastatin/ezetimibe)	1 (0.1)	0

Table 16. Concomitant LLT medication in study 047

ATC Class Level 4 Preferred Term	Placebo (N = 257) n (%)	Bempedoic Acid (N = 522) n (%)	Overall (N = 779) n (%)
Patients with ≥1 background LMT	244 (94.9)	494 (94.6)	738 (94.7)
HMG CoA reductase inhibitors	244 (94.9)	493 (94.4)	737 (94.6)
Atorvastatin	170 (66.1)	352 (67.4)	522 (67.0)
Rosuvastatin	86 (33.5)	184 (35.2)	270 (34.7)
Simvastatin	67 (26.1)	136 (26.1)	203 (26.1)
Pravastatin	23 (8.9)	43 (8.2)	66 (8.5)
Fluvastatin	4 (1.6)	10 (1.9)	14 (1.8)
Pitavastatin	5 (1.9)	6 (1.1)	11 (1.4)
Lovastatin	3 (1.2)	6 (1.1)	9 (1.2)
Cerivastatin	1 (0.4)	0	1 (0.1)
Other lipid-modifying agents	37 (14.4)	63 (12.1)	100 (12.8)
Ezetimibe	24 (9.3)	38 (7.3)	62 (8.0)
Alirocumab	2 (0.8)	1 (0.2)	3 (0.4)
Evolocumab	1 (0.4)	1 (0.2)	2 (0.3)

Table 17. Concomitant LLT medication in study 046

ATC Level 4 Preferred Term	Placebo (N = 111) n (%)	Bempedoic Acid (N = 234) n (%)
Number of patients with ≥ 1 concomitant LMT	44 (39.6)	106 (45.3)
Other lipid modifying agents	28 (25.2)	80 (34.2)
Fish oil	12 (10.8)	41 (17.5)
Ezetimibe	15 (13.5)	35 (15.0)
Omega-3 fatty acids	3 (2.7)	4 (1.7)
Alirocumab	1 (0.9)	4 (1.7)
Omega-3-acid ethyl ester	1 (0.9)	1 (0.4)
Eicosapentaenoic acid	1 (0.9)	0
Eicosapentaenoic acid ethyl ester	0	1 (0.4)
Kolestop	1 (0.9)	0
Sitosterol	0	1 (0.4)
HMG-CoA reductase inhibitors	11 (9.9)	21 (9.0)
Rosuvastatin	4 (3.6)	7 (3.0)
Pravastatin	3 (2.7)	5 (2.1)
Atorvastatin	1 (0.9)	5 (2.1)
Simvastatin	0	3 (1.3)
Lovastatin	2 (1.8)	0
Pitavastatin	1 (0.9)	1 (0.4)

Table 18. Concomitant statin medication in study 048

ATC Level 4 Preferred Term	Placebo (N = 87)	Bempedoic Acid (N = 181)
Number of patients with ≥ 1 concomitant LMT	34 (39.1)	86 (47.5)
HMG-CoA reductase inhibitors	24 (27.6)	59 (32.6)
Atorvastatin	10 (11.5)	21 (11.6)
Simvastatin	6 (6.9)	18 (9.9)
Rosuvastatin	3 (3.4)	13 (7.2)
Pravastatin	6 (6.9)	5 (2.8)
Lovastatin	0	3 (1.7)

Table 19. Individual Statin Doses in Pool 1 (study 040 and 047)

Analysis Group	Doses Included	Placebo N=999 n (%)	Bempedoic Acid N=2009 n (%)
Atorvastatin			
80 mg dose group	≥80 mg QD	82 (8.2)	167 (8.3)
40 mg dose group	≥40 to <80 mg QD	281 (28.1)	596 (29.7)
20 mg dose group	≥20 to <40 mg QD	144 (14.4)	278 (13.8)
10 mg and other lower doses group	≥10 to <20 mg QD	30 (3.0)	78 (3.9)
	Other (<10 mg)	3 (0.3)	6 (0.3)
Rosuvastatin			
40 mg dose group	≥40 mg QD	52 (5.2)	81 (4.0)
20 mg dose group	≥20 to <40 mg QD	94 (9.4)	175 (8.7)
10 mg and other lower doses group	≥10 to <20 mg QD	42 (4.2)	87 (4.3)
	≥5 to <10 mg QD	18 (1.8)	34 (1.7)
	Other (<5 mg)	7 (0.7)	10 (0.5)
Simvastatin			
40 mg dose group	≥40 to <80 mg QD	34 (3.4)	82 (4.1)
20 mg dose group	≥20 to <40 mg QD	86 (8.6)	155 (7.7)
10 mg and other lower doses group	≥10 to <20 mg QD	14 (1.4)	29 (1.4)
	≥5 to <10 mg QD	1 (0.1)	3 (0.1)
	Other (<5 mg)	0	2 (<0.1)
Pravastatin			
single statin dose group	≥80 mg QD	5 (0.5)	12 (0.6)
	≥40 to <80 mg QD	34 (3.4)	59 (2.9)
	≥20 to <40 mg QD	18 (1.8)	30 (1.5)
	≥10 to <20 mg QD	8 (0.8)	10 (0.5)
	Other (<10 mg)	0	3 (0.1)
Other statin[a]			
single statin dose group	Other	18 (1.8)	57 (2.8)

Numbers analysed

Study 040: 2230 patients for efficacy (1488 bempedoic acid, 742 placebo) and 2229 patients for safety (1487 bempedoic acid, 742 placebo).

Study 047: 779 patients for efficacy and safety (522 bempedoic acid, 257 placebo); 493 bempedoic acid patients for pharmacokinetic (PK) analysis.

Study 046: Of the 602 patients who entered screening, 345 were randomized at 64 sites in North America. 345 patients for efficacy and safety; 230 bempedoic acid patients for pharmacokinetic (PK) analysis.

Study 048: 269 patients enrolled and randomized, 268 patients treated.

Outcomes and estimation

Primary endpoint

In patients on maximally tolerated statin therapy reduction from baseline in LDL-C at week 12 for bempedoic acid compared with placebo was -15.1% vs 2.4%, respectively, in Study 1002-047 and -16.5% vs -1.6%, respectively, in Study 1002-040.

In the statin intolerant studies, the reduction from baseline in LDL-C for bempedoic acid versus placebo was -22.6% vs -1.2%, respectively in Study 1002-046 and –23.5% vs 5.0%, respectively in Study 1002-048.

Secondary endpoints

For LDL-C at Week 24, the difference between bempedoic acid and placebo was -14.8% for Study 1002-047, -16.1% for Study 1002-040, and -18.9% for Study 1002-046.

For non-HDL-C at week 12, this was -13.0% for Study 1002-047, -13.3% for Study 1002-040, -17.9% for Study 1002-046, and -23.6% in Study 1002-048.

For TC at week 12, this was -11.2% for Study 1002-047, -11.1% for Study 1002-040, and -14.8% for Study 1002-046, and -15.1% in Study 1002-048.

For Apo B at week 12, this was -13.0% for Study 1002-047, -11.9% for Study 1002-040, and -15.0% for Study 1002-046, and -19.3% in Study 1002-048.

For hsCRP at week 12, median percent change from baseline was -18.7% and -9.4% for Study 1002-047, -22.4% and 2.6% for Study 1002-040, -25.4% and 2.7% for Study 1002-046, and -32.5 and 2.1% in Study 1002-048.

Ancillary analyses

Long term LDL-C lowering efficacy

Phase 3 studies on top of statins (study 1002-040 and 1002-047)

The LDL-C lowering effect of bempedoic acid for the studies on top of a maximum tolerated statin therapy is provided below in Figure 11 and Figure 12.

Figure 12. LDL-C Observed Values (Mean ± SE) by Visit (Observed Data) in Study 1002-040 (Full Analysis Set)

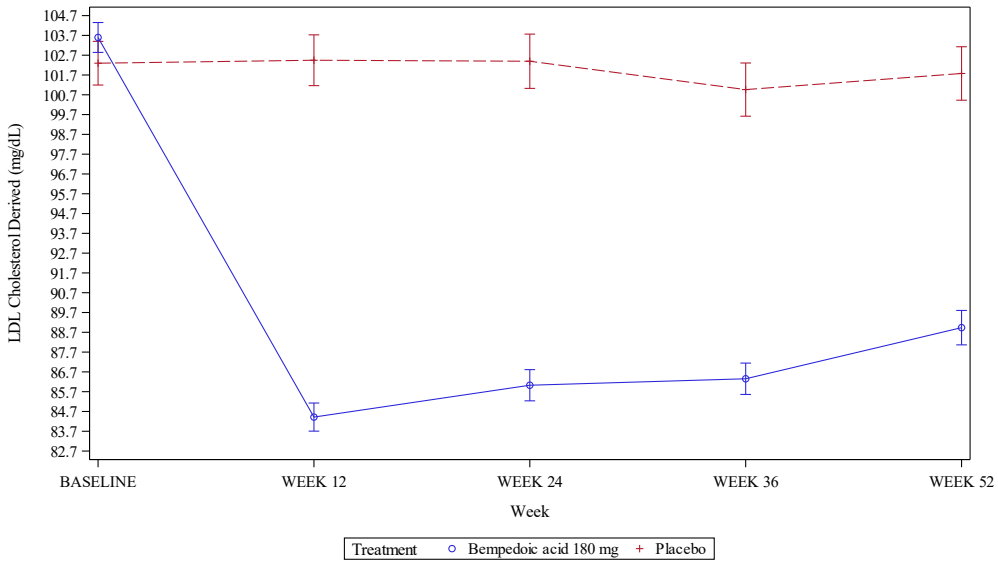
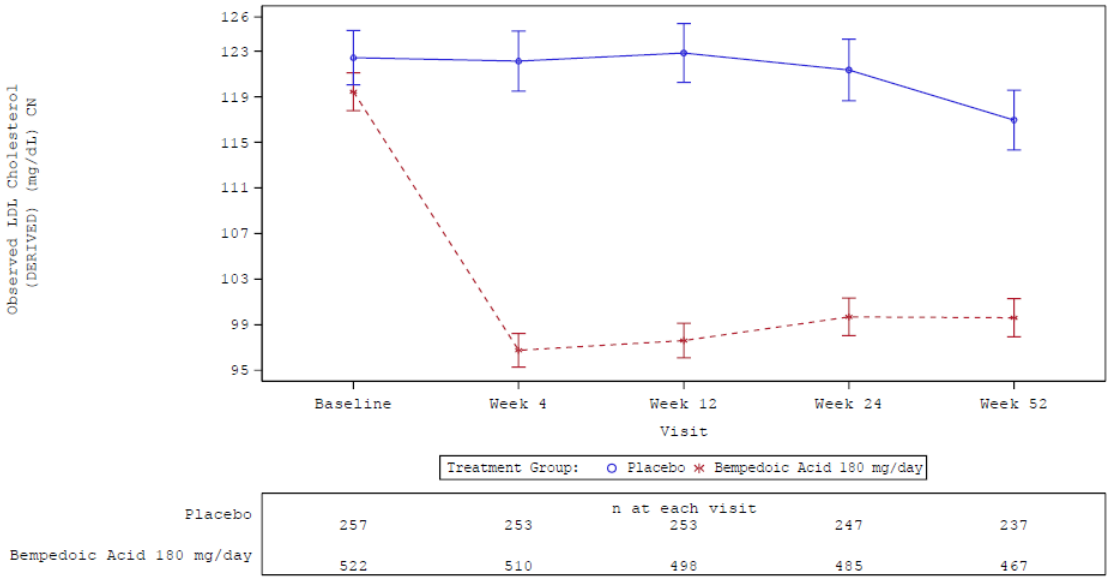


Figure 13. LDL-C Observed Values (Mean ± SE) by Visit (Observed Data) in Study 1002-047 (Full Analysis Set)



Changes were made to the background therapy after week 24 as indicated below. Background LLT therapy was slightly less intensified the bempedoic acid treatment arm than in the placebo arm (8.8% vs 10.1%; n= 278). This was mainly adjunctive therapy of statins (7.0% vs 8.0%), while evolocumab and alirocumab use was very limited (5 (0.2%) vs 4 (0.4%) and 3 (0.4%) vs 1 (0.1%)).

Table 20. : Summary of Patients with Changes in Concomitant Lipid-modifying Therapy after First Dose of IMP in Pool 1, High Risk/Long-term Pool by Anatomical Therapeutic Chemical Class and Preferred Term (Safety Population)

Anatomical therapeutic chemical class Preferred term	Placebo N=999 n (%)	Bempedoic Acid 180 mg N=2009 n (%)	Total N=3008 n (%)
Subjects requiring additional adjunctive LMT	101 (10.1)	177 (8.8)	278 (9.2)
BILE ACID SEQUESTRANTS	1 (0.1)	6 (0.3)	7 (0.2)
COLESTYRAMINE	0	3 (0.1)	3 (<0.1)
COLESEVELAM HYDROCHLORIDE	0	2 (<0.1)	2 (<0.1)
COLESEVELAM	0	1 (<0.1)	1 (<0.1)
COLESTIPOL	1 (0.1)	0	1 (<0.1)
FIBRATES	5 (0.5)	8 (0.4)	13 (0.4)
FENOFIBRATE	4 (0.4)	8 (0.4)	12 (0.4)
BEZAFIBRATE	1 (0.1)	0	1 (<0.1)
HMG COA REDUCTASE INHIBITORS	80 (8.0)	140 (7.0)	220 (7.3)
ATORVASTATIN	35 (3.5)	52 (2.6)	87 (2.9)
ROSUVASTATIN	19 (1.9)	30 (1.5)	49 (1.6)
ROSUVASTATIN CALCIUM	9 (0.9)	17 (0.8)	26 (0.9)
ATORVASTATIN CALCIUM	8 (0.8)	17 (0.8)	25 (0.8)
SIMVASTATIN	9 (0.9)	15 (0.7)	24 (0.8)
PRAVASTATIN	6 (0.6)	10 (0.5)	16 (0.5)
LOVASTATIN	0	3 (0.1)	3 (<0.1)
FLUVASTATIN	1 (0.1)	1 (<0.1)	2 (<0.1)
PITAVASTATIN CALCIUM	0	2 (<0.1)	2 (<0.1)
PRAVASTATIN SODIUM	0	1 (<0.1)	1 (<0.1)
HMG COA REDUCTASE INHIBITORS IN COMBINATION WITH OTHER LIPID MODIFYING AGENTS	1 (0.1)	0	1 (<0.1)
INEGY	1 (0.1)	0	1 (<0.1)

Anatomical therapeutic chemical class Preferred term	Placebo N=999 n (%)	Bempedoic Acid 180 mg N=2009 n (%)	Total N=3008 n (%)
NICOTINIC ACID AND DERIVATIVES	1 (0.1)	0	1 (<0.1)
NICOTINIC ACID	1 (0.1)	0	1 (<0.1)
OTHER LIPID MODIFYING AGENTS	23 (2.3)	38 (1.9)	61 (2.0)
EZETIMIBE	12 (1.2)	20 (1.0)	32 (1.1)
EVOLOCUMAB	4 (0.4)	5 (0.2)	9 (0.3)
FISH OIL	1 (0.1)	7 (0.3)	8 (0.3)
ALIROCUMAB	4 (0.4)	3 (0.1)	7 (0.2)
EICOSAPENTAENOIC ACID ETHYL ESTER	0	3 (0.1)	3 (<0.1)
OMEGA-3-ACID ETHYL ESTER	0	2 (<0.1)	2 (<0.1)
KOLESTOP	1 (0.1)	0	1 (<0.1)
OMEGA-3 FATTY ACIDS	1 (0.1)	0	1 (<0.1)

Phase 3 open label ongoing extension study (study 1002-050)

In the ongoing phase 3 open label study 050 the results are displayed in Table 21 below (as of 28 September 2018). Efficacy was assessed as a secondary objective. Patients who received either bempedoic acid 180 mg or placebo daily for the duration of Study 1002-040 receive bempedoic acid 180 mg daily in the OLE Study 1002-050 for 78 weeks followed by a 4-week follow-up period off study drug. For patients randomized to bempedoic acid 180 mg in the parent study 1002-040, total patient exposures from the combined treatment in Study 1002-040 and Study 1002-050 are up to 2.5 years.

To maintain the integrity of the parent study, which was ongoing at the time enrollment into Study 1002-050 began, investigators, site staff, patients, and the study team were masked to study lipid levels until the Week 12 study visit, after which time lipid values were made available to sites. Visit occur at every 3 months.

Table 21. Low-Density Lipoprotein Cholesterol (mg/dL) Change and Percent Change in Study 1002-050 from Study 1002 040 Baseline, Safety Population.

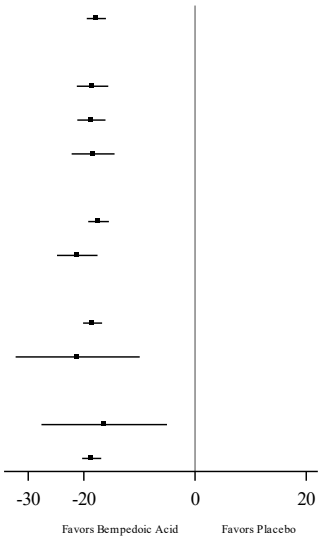
Time Point Statistic	Former Placebo Patients	Former Bempedoic Acid Patients
Study 1002-040 baseline		
n	492	970
Mean (SD), mg/dL	98.96 (24.170)	102.94 (29.899)
Study 1002-050 baseline		
n	492	970
Mean change from baseline (SD), mg/dL	0.53 (22.623)	-16.35 (26.709)
Mean percent change from baseline (SD)	1.71 (21.788)	-14.40 (23.097)
Study 1002-050, Week 12		
n	476	948
Mean change from baseline (SD), mg/dL	-15.44 (22.920)	-17.02 (27.082)
Mean percent change from baseline (SD)	-14.47 (21.189)	-15.18 (23.550)
Study 1002-050, Week 52		
n	131	288
Mean change from baseline (SD), mg/dL	-18.29 (27.892)	-18.85 (29.870)
Mean percent change from baseline (SD)	-16.81 (23.422)	-15.82 (24.618)

LDL-C effect according to subgroups

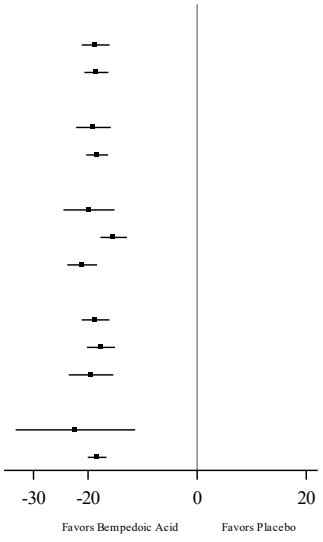
The treatment effect at week 12 according to several subgroups is provided in Figure 13 for the combined studies on top of statins (1002-040, 1002-047) and in Figure 14 for the statin intolerant patients (1002-046, 1002-048).

Figure 14. Forest Plot of Treatment Effect on Percent Change from Baseline to Week 12 in LDL C by Subgroup in Pool 1 (High-Risk/Long-Term Pool) (Efficacy Population).

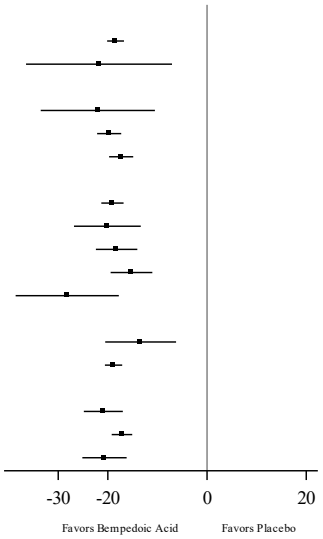
	Pbo LS mean of % change from baseline (N)	BA 180 mg LS mean of % change from baseline (N)	LS Mean Diff [95% CI]
Overall	1.765 (978)	-15.985 (1922)	-17.750 (-19.473, -16.027)
Age			
18 - <65 years	1.250 (374)	-17.183 (827)	-18.433 (-21.260, -15.606)
65 - <75 years	2.010 (442)	-16.630 (800)	-18.640 (-21.173, -16.108)
>=75 years	2.647 (162)	-15.687 (295)	-18.334 (-22.192, -14.476)
Gender			
Male	1.547 (685)	-15.806 (1372)	-17.352 (-19.210, -15.495)
Female	2.274 (293)	-18.907 (550)	-21.181 (-24.824, -17.538)
Race			
White	1.670 (940)	-16.755 (1833)	-18.425 (-20.135, -16.716)
non-White	5.219 (38)	-15.890 (89)	-21.109 (-32.266, -9.951)
Ethnicity			
Hispanic	7.048 (30)	-9.285 (61)	-16.334 (-27.621, -5.046)
non-Hispanic	1.633 (948)	-16.954 (1861)	-18.587 (-20.302, -16.873)



	Pbo LS mean of % change from baseline (N)	BA 180 mg LS mean of % change from baseline (N)	LS Mean Diff [95% CI]
Region			
North America	0.920 (324)	-17.685 (625)	-18.605 (-21.159, -16.051)
Europe	2.236 (654)	-16.242 (1297)	-18.478 (-20.682, -16.275)
History of Diabetes			
Yes	0.302 (286)	-18.709 (553)	-19.011 (-22.187, -15.834)
No	2.425 (692)	-15.907 (1369)	-18.331 (-20.339, -16.323)
Baseline BMI			
<25 kg/m^2	4.082 (141)	-15.753 (292)	-19.835 (-24.513, -15.157)
25 - <30 kg/m^2	0.423 (421)	-14.882 (799)	-15.305 (-17.733, -12.876)
>=30 kg/m^2	2.336 (415)	-18.744 (829)	-21.080 (-23.809, -18.352)
Baseline LDL-C Category			
<100 mg/dL	6.137 (497)	-12.486 (959)	-18.623 (-21.169, -16.076)
100 - <130 mg/dL	-0.803 (297)	-18.435 (612)	-17.632 (-20.217, -15.048)
>=130 mg/dL	-5.766 (184)	-25.219 (351)	-19.453 (-23.529, -15.377)
Baseline HeFH Status			
Yes	1.834 (36)	-20.489 (71)	-22.323 (-33.279, -11.367)
No	1.787 (942)	-16.560 (1851)	-18.346 (-20.059, -16.634)



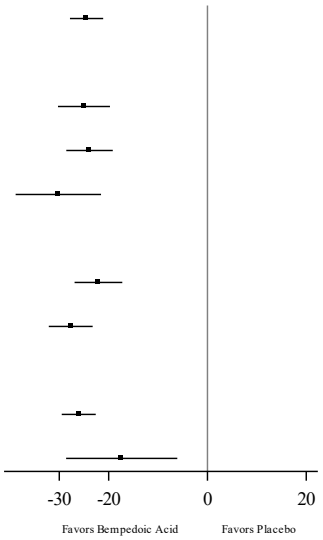
	Pbo LS mean of % change from baseline (N)	BA 180 mg LS mean of % change from baseline (N)	LS Mean Diff [95% CI]
Prior ASCVD			
Yes	1.800 (953)	-16.643 (1869)	-18.442 (-20.139, -16.746)
No	2.387 (25)	-19.387 (53)	-21.775 (-36.487, -7.063)
Baseline Statin Intensity			
No	-1.509 (29)	-23.528 (51)	-22.019 (-33.528, -10.511)
Low/Moderate	2.222 (451)	-17.509 (882)	-19.731 (-22.158, -17.303)
High	1.646 (498)	-15.665 (989)	-17.311 (-19.741, -14.882)
Baseline Statin Medication			
Atorvastatin	1.642 (528)	-17.428 (1080)	-19.070 (-21.311, -16.829)
Pravastatin	0.896 (63)	-19.198 (106)	-20.094 (-26.824, -13.363)
Simvastatin	0.718 (132)	-17.513 (255)	-18.231 (-22.405, -14.056)
Rosuvastatin	3.438 (209)	-11.796 (376)	-15.234 (-19.437, -11.030)
Other	6.044 (17)	-22.142 (54)	-28.186 (-38.586, -17.786)
Baseline Ezetimibe Use			
Yes	-2.852 (73)	-16.236 (144)	-13.385 (-20.527, -6.243)
No	2.123 (905)	-16.723 (1778)	-18.846 (-20.587, -17.105)
Baseline eGFR Category			
>=90 mL/min/1.73m^2	2.569 (217)	-18.339 (411)	-20.908 (-24.836, -16.980)
60 - 89 mL/min/1.73m^2	1.233 (621)	-15.918 (1223)	-17.152 (-19.220, -15.083)
<=59 mL/min/1.73m^2	2.985 (140)	-17.688 (288)	-20.673 (-25.136, -16.210)

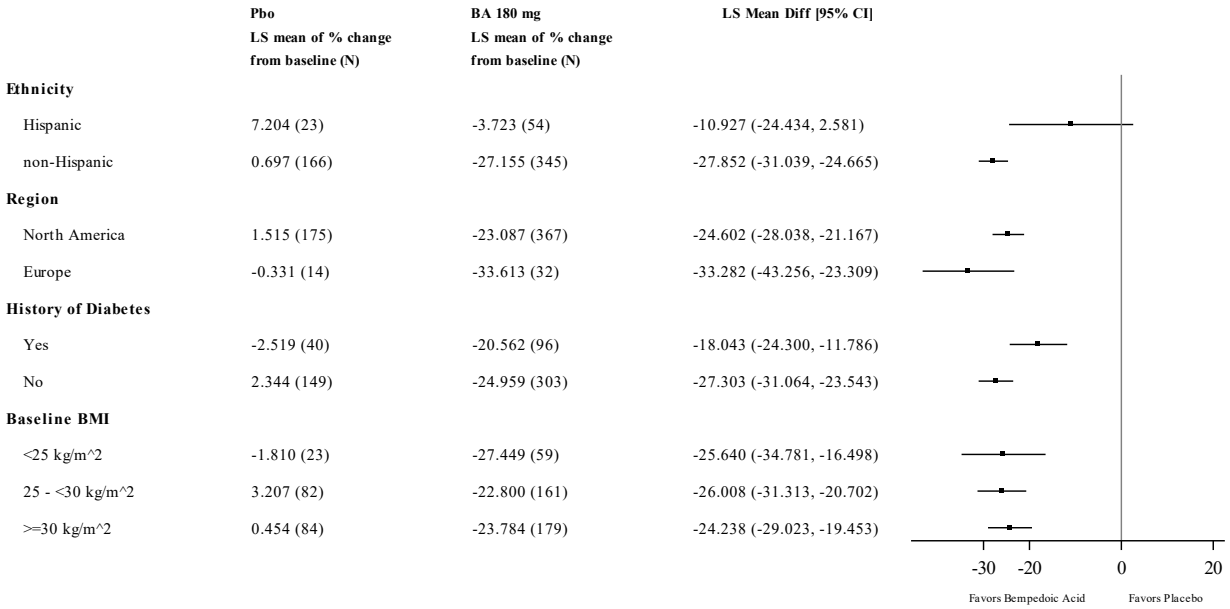


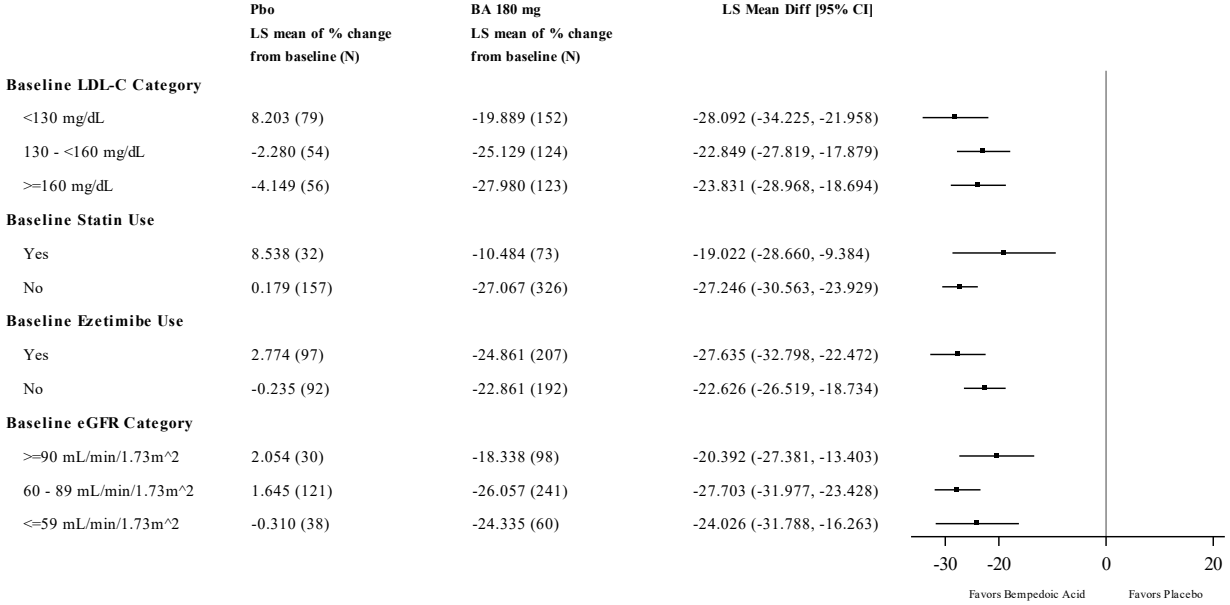
For the high risk pool, **p values for interaction** were significant for gender (0.044), baseline BMI category (0.007), and borderline significant for baseline statin intensity (0.060).

Figure 15. Forest Plot of Treatment Effect on Percent Change from Baseline to Week 12 in LDL C by Subgroup in Pool 2 (No or Low-Dose Statin Pool) (Efficacy Population).

	Pbo LS mean of % change from baseline (N)	BA 180 mg LS mean of % change from baseline (N)	LS Mean Diff [95% CI]
Overall	1.474 (189)	-23.000 (399)	-24.474 (-27.836, -21.113)
Age			
18 - <65 years	2.200 (84)	-22.801 (172)	-25.000 (-30.262, -19.739)
65 - <75 years	-0.863 (75)	-24.738 (167)	-23.875 (-28.578, -19.171)
>=75 years	5.071 (30)	-25.121 (60)	-30.192 (-38.836, -21.549)
Gender			
Male	1.525 (81)	-20.547 (165)	-22.073 (-26.902, -17.243)
Female	1.335 (108)	-26.348 (234)	-27.683 (-32.123, -23.243)
Race			
White	0.872 (163)	-25.188 (361)	-26.061 (-29.502, -22.619)
non-White	5.039 (26)	-12.322 (38)	-17.361 (-28.614, -6.108)







For the low statin dose pool (Figure 14), **p for interaction** were significant for ethnicity (<0.001), history of diabetes (0.032), and baseline statin use (0.032).

Summary of main studies

Table 22, Table 23, Table 24 and Table 25 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 22. Summary of efficacy for study 1002-040

Title: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Long-Term Safety and Tolerability Study of Bempedoic Acid (ETC-1002) in Patients With Hyperlipidemia at High Cardiovascular Risk Who are not Adequately Controlled by Their Lipid-Modifying Therapy	
Study identifier	1002-040

Design	Randomized, multicenter, double-blind, placebo-controlled, long-term study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks 2 weeks (screening period) 82-week OLE study (1002-50)
Hypothesis	Superiority of bempedoic acid over the lipid-modifying therapy alone in reducing respective lipid values		
Treatments groups	Bempedoic Acid		Bempedoic acid 180 mg. 52 weeks, n= 1488
	Placebo		Placebo. 52 weeks, n= 742
Endpoints and definitions	Primary efficacy endpoint	% change from baseline in LDL-C at week 12	Percent change from baseline to Week 12 in LDL-C
	Secondary endpoint	% change from baseline in LDL-C at week 24	Percent change from baseline to Week 24 in LDL C
	Secondary endpoint	% change from baseline in non-HDL-C at week 12	Percent change from baseline to Week 12 in non HDL-C
	Secondary endpoint	% change from baseline in TC at week 12	Percent change from baseline to Week 12 in TC
	Secondary endpoint	% change from baseline in apoB at week 12	Percent change from baseline to Week 12 in apo B
	Secondary endpoint	% change from baseline in hsCRP at week 12	Percent change from baseline to Week 12 in hsCRP
Database lock	Not provided.		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (Full analysis set) in patients at high CV risk 12 weeks		
Descriptive statistics and estimate variability	Treatment group	Bempedoic Acid	Placebo
	Number of subjects	1488	742
	% change from baseline in LDL-C at week 12 (LS mean (SE))	-16.5 (0.52)	1.6 (0.86)
Effect estimate per comparison	Primary efficacy endpoint	Comparison groups	Bempedoic Acid vs Placebo
		Difference (Bempedoic Acid-placebo) (LS mean)	-18.1

		95%CI	-20.0, -16.1
		P-value	<0.001
Notes	<free text>		
Analysis description	**Secondary analysis**		
Analysis population	Intent to treat (Full analysis set) in patients at high CV risk		
Descriptive statistics and estimate variability	Treatment group	Bempedoic Acid	Placebo
	% change from baseline in LDL-C at week 24 (LS mean (SE))	-14.9 (0.60)	1.2 (0.88)
		Difference (Bempedoic Acid-placebo) (LS mean)	-16.1
		95%CI	-18.2, -14.0
		P-value	< 0.001
	% change from baseline in non-HDL-C at week 12 (LS mean (SE))	-11.9 (0.48)	1.5 (0.76)
		Difference (Bempedoic Acid-placebo) (LS mean)	-13.3
		95%CI	-15.1, -11.6
		P-value	<0.001
	% change from baseline in TC at week 12 (LS mean (SE))	-10.3 (0.37)	0.8 (0.57)
		Difference (Bempedoic Acid-placebo) (LS mean)	-11.1
		95%CI	-12.5, -9.8
		P-value	<0.001
	% change from baseline in apoB at week 12 (LS mean (SE))	-8.6 (0.47)	3.3 (0.70)
		Difference (Bempedoic Acid-placebo) (LS mean)	-11.9
		95%CI	-13.6, -10.2
		P-value	<0.001
	% change from baseline in hsCRP at week 12 (median (IQR))	-22.4 (72.5)	2.6 (91.9)
		Location shift	-21.5
		95%CI	-26.96, -16.00
		P-value	<0.001

Table 23. Summary of efficacy for study 1002-047

Title: Long-Term, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy of Bempedoic Acid (ETC-1002) in Patients With Hyperlipidemia at High Cardiovascular Risk not Adequately Controlled by Their Lipid-Modifying Therapy	
Study identifier	1002-047
Design	Randomized, multicenter, double-blind, placebo-controlled, long-term study

	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks 1 week screening period (extended for additional 4 week if needed) and 4 week placebo run-in period n.a.
Hypothesis	Superiority of bempedoic acid over the lipid-modifying therapy alone in reducing respective lipid values		
Treatments groups	Bempedoic Acid		Bempedoic acid 180 mg. 52 weeks, n= 522
	Placebo		Placebo. 52 weeks, n= 257
Endpoints and definitions	Primary endpoint	% change from baseline in LDL-C at week 12	Percent change from baseline to Week 12 in LDL-C
	Secondary endpoint	% change from baseline in LDL-C at week 24	Percent change from baseline to Week 24 in LDL C
	Secondary endpoint	% change from baseline in non-HDL-C at week 12	Percent change from baseline to Week 12 in non HDL-C
	Secondary endpoint	% change from baseline in TC at week 12	Percent change from baseline to Week 12 in TC
	Secondary endpoint	% change from baseline in apoB at week 12	Percent change from baseline to Week 12 in apo B
	Secondary endpoint	% change from baseline in hsCRP at week 12	Percent change from baseline to Week 12 in hsCRP
Database lock	Not provided		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (Full analysis set) in patients at high CV risk 12 weeks		
Descriptive statistics and estimate variability	Treatment group	Bempedoic Acid	Placebo
	Number of subjects	522	257
	% change from baseline in LDL-C at week 12 (LS mean (SE))	-15.1 (1.07)	2.4 (1.45)
Effect estimate per comparison	Primary efficacy endpoint	Comparison groups	Bempedoic Acid vs Placebo
		Difference (Bempedoic Acid-placebo) (LS mean)	-17.4
		95%CI	-21.0, -13.9

		P-value	<0.001
Notes	<free text>		
Analysis description	**Secondary analysis**		
Analysis population	Intent to treat (Full analysis set) in patients at high CV risk		
Descriptive statistics and estimate variability	Treatment group	Bempedoic Acid	Placebo
	% change from baseline in LDL-C at week 24 (LS mean (SE))	-12.1 (1.48)	2.7 (1.91)
		Difference (Bempedoic Acid-placebo) (LS mean)	-14.8
		95%CI	-19.5, -10.0
		P-value	<0.001
	% change from baseline in non-HDL-C at week 12 (LS mean (SE))	-10.8 (0.95)	2.3 (1.35)
		Difference (Bempedoic Acid-placebo) (LS mean)	-13.0
		95%CI	-16.3, -9.8
		P-value	<0.001
	% change from baseline in TC at week 12 (LS mean (SE))	-9.9 (0.69)	1.3 (1.01)
		Difference (Bempedoic Acid-placebo) (LS mean)	-11.2
		95%CI	-13.6, -8.8
		P-value	<0.001
	% change from baseline in apoB at week 12 (LS mean (SE))	-9.3 (0.85)	3.7 (1.34)
		Difference (Bempedoic Acid-placebo) (LS mean)	-13.0
		95%CI	-16.1, -9.9
		P-value	<0.001
	% change from baseline in hsCRP at week 12 (median (IQR))	-18.7 (69.9)	-9.4 (71.56)
		Location shift	-8.7
		95%CI	-17.2, -0.4
		P-value	0.039

Table 24. Summary of efficacy for study 1002-046

Title: A Randomized, Double-Blind, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg Compared to Placebo Added to Background Lipid-Modifying Therapy in Patients with Elevated LDL-C who are Statin Intolerant		
Study identifier	1002-046	
Design	Randomized, multicenter, double-blind, placebo-controlled study	
	Duration of main phase:	24 weeks
	Duration of Run-in phase:	1 week screening period (extended for additional 4 week if needed) and 4 week placebo run-in period
	Duration of Extension phase:	Not applicable
Hypothesis	Superiority of bempedoic acid over placebo in reducing respective lipid values	

Treatments groups	Bempedoic Acid		Bempedoic acid 180 mg. 24 weeks, n= 234
	Placebo		Placebo. 24 weeks, n= 111
Endpoints and definitions	Primary endpoint	% change from baseline in LDL-C at week 12	Percent change from baseline to Week 12 in LDL-C
	Secondary endpoint	% change from baseline in LDL-C at week 24	Percent change from baseline to Week 24 in LDL C
	Secondary endpoint	% change from baseline in non-HDL-C at week 12	Percent change from baseline to Week 12 in non HDL-C
	Secondary endpoint	% change from baseline in TC at week 12	Percent change from baseline to Week 12 in TC
	Secondary endpoint	% change from baseline in apoB at week 12	Percent change from baseline to Week 12 in apo B
	Secondary endpoint	% change from baseline in hsCRP at week 12	Percent change from baseline to Week 12 in hsCRP
Database lock	Not provided		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (Full analysis set) in statin intolerant patients 12 weeks		
Descriptive statistics and estimate variability	Treatment group	Bempedoic Acid	Placebo
	Number of subjects	234	111
	% change from baseline in LDL-C at week 12 (LS mean (SE))	-22.6 (1.29)	-1.2 (1.42)
Effect estimate per comparison	Primary efficacy endpoint	Comparison groups	Bempedoic Acid vs Placebo
		Difference (Bempedoic Acid-placebo) (LS mean)	-21.4
		95%CI	-25.1, -17.7
		P-value	<0.001
Notes	<free text>		
Analysis description	**Secondary analysis**		
Analysis population	Intent to treat (Full analysis set) in statin intolerant patients		
Descriptive statistics	Treatment group	Bempedoic Acid	Placebo

and estimate variability	% change from baseline in LDL-C at week 24 (LS mean (SE))	-21.2 (1.41)	-2.3 (1.55)
		Difference (Bempedoic Acid-placebo) (LS mean)	-18.9
		95%CI	-22.95, -14.87
		P-value	<0.001
	% change from baseline in non-HDL-C at week 12 (LS mean (SE))	-18.1 (1.11)	-0.14 (1.17)
		Difference (Bempedoic Acid-placebo) (LS mean)	-17.9
		95%CI	-21.1, -14.8
		P-value	<0.001
	% change from baseline in TC at week 12 (LS mean (SE))	-15.4 (0.88)	-0.6 (0.96)
		Difference (Bempedoic Acid-placebo) (LS mean)	-14.8
		95%CI	-17.3, -12.2
		P-value	<0.001
	% change from baseline in apoB at week 12 (LS mean (SE))	-14.7 (1.08)	0.3 (1.18)
		Difference (Bempedoic Acid-placebo) (LS mean)	-15.0
		95%CI	-18.06, -11.87
		P-value	<0.001
	% change from baseline in hsCRP at week 12 (median (IQR))	-25.4 (63.53)	2.7 (69.11)
		Location shift	-24.3
		95%CI	-35.89, -12.71
		P-value	<0.001

Table 25. Summary of efficacy for study 1002-048

Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicenter Study to Evaluate the Efficacy and Safety of Bempedoic Acid (ETC-1002) 180 mg/day as Add-on to Ezetimibe Therapy in Patients with Elevated LDL-C on Low Dose or Less Than Low Dose Statins			
Study identifier	1002-048		
Design	Randomized, multicenter, double-blind, placebo-controlled study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks 1 week screening period (extended for additional 4 week if needed) and 4 week placebo run-in period not applicable
Hypothesis	Superiority of bempedoic acid over placebo in reducing respective lipid values		
Treatments groups	Bempedoic Acid		Bempedoic acid 180 mg. 12 weeks, n= 181
	Placebo		Placebo. 12 weeks, n= 88
Endpoints and definitions	Primary endpoint	% change from baseline in LDL-C at week 12	Percent change from baseline to Week 12 in LDL-C

	Secondary endpoint	% change from baseline in LDL-C at week 24	Percent change from baseline to Week 24 in LDL C
	Secondary endpoint	% change from baseline in non-HDL-C at week 12	Percent change from baseline to Week 12 in non HDL-C
	Secondary endpoint	% change from baseline in TC at week 12	Percent change from baseline to Week 12 in TC
	Secondary endpoint	% change from baseline in apoB at week 12	Percent change from baseline to Week 12 in apo B
	Secondary endpoint	% change from baseline in hsCRP at week 12	Percent change from baseline to Week 12 in hsCRP
Database lock	Not provided		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (Full analysis set) in patients on low dose or less than low dose statins		
Descriptive statistics and estimate variability	Treatment group	Bempedoic Acid	Placebo
	Number of subjects	181	88
	% change from baseline in LDL-C at week 12 (LS mean (SE))	-23.5 (1.95)	5.0 (2.30)
Effect estimate per comparison	Primary efficacy endpoint	Comparison groups	Bempedoic Acid vs Placebo
		Difference (Bempedoic Acid-placebo) (LS mean)	-28.5
		95%CI	-34.38, -22.53
		P-value	<0.001
Notes	<free text>		

Analysis description	**Secondary analysis**		
Analysis population	Intent to treat (Full analysis set) in patients on a low dose or less than low dose statins		
Descriptive statistics and estimate variability	Treatment group	Bempedoic Acid	Placebo
	% change from baseline in non-HDL-C at week 12 (LS mean (SE))	-18.4 (1.67)	5.2 (2.20)
		Difference (Bempedoic Acid-placebo) (LS mean)	-23.6
		95%CI	-29.0, -18.12
		P-value	<0.001
	% change from baseline in TC at week 12 (LS mean	-15.1 (1.28)	-2.9 (1.55)
		Difference (Bempedoic Acid-placebo) (LS mean)	-18.0

	(SE))	95%CI	-21.94, -14.03
		P-value	<0.001
	% change from baseline in apoB at week 12 (LS mean (SE))	-14.6 (1.50)	4.7 (1.79)
		Difference (Bempedoic Acid-placebo) (LS mean)	-19.3
		95%CI	-23.90, -14.73
		P-value	<0.001
	% change from baseline in hsCRP at week 12 (median (IQR))	-32.5 (66.27)	2.09 (81.37)
		Location shift	-31.0
		95%CI	-44.76, -17.40
		P-value	<0.001

Analysis performed across trials (pooled analyses and meta-analysis)

In addition to the results presented above, the following data are also available.

<u>High risk/Long term pool (on top of statins)</u>

Treatment with bempedoic acid resulted in greater reductions in LDL-C from baseline to Week 12 compared with placebo of -16.7% (SD 20.9) versus 1.8% (23.5), respectively. The difference was -17.8, with 95% CI -19.5, -16.0, ($p < 0.001$).

Treatment goals

Higher percentages of patients in the bempedoic acid group achieved LDL-C < 70 mg/dL (26.2% to 28.9%) compared with patients in the placebo group (8.0% to 9.3%) at Weeks 12, 24, and 52 in the studies on top of statins (see Table 26).

Table 26. Proportion of Patients With LDL-C < 70 mg/dL in the Phase 3 High-Risk/Long-Term Pool (Full Analysis Set).

Visit **Number (%) of Patients with LDL-C < 70 mg/dL**	**Placebo (N = 742)**	**Bempedoic Acid (N = 1488)**	**P Value**
Week 12, n			
Number (%) of patients	78/978 (8.0)	556/1922 (28.9)	< 0.001
Week 24, n			
Number (%) of patients	89/954 (9.3)	541/1882 (28.7)	< 0.001
Week 52, n			
Number (%) of patients	84/922 (9.1)	479/1831 (26.2)	< 0.001

LDL-C = low-density lipoprotein cholesterol
P value of comparisons between treatment groups was calculated using Chi-square test.
Source: ISE Table 5.8.1

No or Low-Dose Statin Pool (statin intolerant)

Treatment with bempedoic acid resulted in greater reductions in LDL-C from baseline to Week 12 compared with placebo of -24.1% (SD 22.3) versus 1.7% (17.6), respectively. The difference was -24.5% with 95% CI -27.8, -21.1,($p < 0.001$). In a post hoc analysis of Study 1002-046, 8.1% of all patients treated with bempedoic acid reached their ESC/EAS indicated LDL-C target at Week 24 of <70 mg/dL.

Clinical studies in special populations

Table 27 presents the results according to age for the phase 3 studies.

Table 27. Treatment effect on LDL-C according to age in the combined phase 3 studies.

	High-Risk/Long-Term Pool				No or Low-Dose Statin Pool			
	LS Mean Percent Reduction		Difference From Placebo	p-value	Mean Percent Reduction		Difference From Placebo	p-value
Subgroup	BA	PBO			BA	PBO		
Age (years)								
< 65	-17.2	1.2%	-18.4%	< 0.001	-22.8	2.2	-25.0	< 0.001
65 to < 75	-16.6	2.6	-18.6	< 0.001	-24.7	-0.86	-23.9	< 0.001
≥ 75	-15.7	2.6	-18.3	< 0.001	-25.1	5.1	-30.2	< 0.001

Data on the age group of ≥ 85 years are not displayed as patient numbers were very limited (n=22 in the high risk pool; n=7 in the statin intolerant pool).

Supportive study

For the results of long-term efficacy in the ongoing open label study 1002-050, see above.

Further data were presented on the effect of bempedoic acid in patients with no lipid modifying background therapy (Table 28).

Table 28. Summary of Week 12 LDL-C Efficacy for Bempedoic Acid Among Patients Enrolled in Phase 3 Studies on No Background Lipid Modifying Therapy.

	Bempedoic Acid		Placebo			
Dataset	LS Mean % Change From Baseline in LDL-C	N	LS Mean % Change From Baseline in LDL-C	N	LS Mean Diff % (95% CI) of % Change From Baseline in LDL-C	p-value
Pool 1[a]	-23.4	31	3.3	14	-26.7 (-40.0, -13.4)	<0.001
Pool 2[b]	-22.2	127	-0.1	64	-22.1 (-26.8, -17.4)	<0.001

Dataset	Bempedoic Acid		Placebo		LS Mean Diff % (95% CI) of % Change From Baseline in LDL-C	p-value
	LS Mean % Change From Baseline in LDL-C	N	LS Mean % Change From Baseline in LDL-C	N		
Study 1002FDC-053	-20.7	22	0.3	13	-21.0 (-33.4, -8.5)	0.002
Meta-analysis[c]	-22.2	180	0.4	91	-22.7 (-26.9, -18.5)	<0.001
Phase 2: Study 1002-008	-30.1	99	N/A	N/A	N/A	N/A

[a] Studies 1002-040 and 1002-047
[b] Studies 1002-046 and 1002-048
[c] Studies 1002-040,1002-046, 1002-047,1002-048 and 1002FDC-053

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Statin intolerance

Two **placebo-controlled studies** (046 and 048) were performed to investigate and confirm the LDL-C lipid lowering treatment effect of bempedoic acid in statin-intolerant patients. Patients with high CV risk eligible for further lipid lowering therapy based on their LDL-C level were included.

The general design of double-blind, placebo-controlled, randomized (2:1), parallel-group studies should allow for the primary objective of an adequate evaluation of the bempedoic acid treatment effect on LDL-C reduction. The studies were limited in duration with respectively 24 and 12 weeks of treatment and included a relatively limited number of patients. In study 048 no PCSK9 inhibitors were allowed, limiting interpretation in terms of reflecting clinical practice options in lipid lowering treatment. A 2:1 randomisation is acceptable to optimise exposure to the investigational product. The primary endpoint of LDL-C lowering was assessed at 12 weeks, which is sufficiently long to establish the maximum stable LDL-C treatment effect. The secondary endpoints of the Week 24 percentage LDL-C reduction (as evaluated in study 046) can be supportive for the primary endpoint and is acceptable. Other parameters of the lipid profile (nonHDL-C, TC, apoB) were evaluated as secondary endpoints, which is considered relevant and supported. The relevance of evaluation of hsCRP as the secondary endpoint is considered of less importance as the clinical implication is less clear. A 4-week run-in period is relatively short but acceptable to stabilise for background diet/exercise and LLT therapy. Specific stabilisation periods have been included for fibrates (6 weeks) and PCSK9 inhibitors (at least 3 injections), which is appropriate. To establish baseline LDL-C levels in phase 3 studies based on week -1 and 0 is appropriate.

Identification of **patients eligible for lipid lowering therapy** was based on the combination of CV risk classification and LDL-C level. In study 046, LDL-C had to be ≥70 mg/dL (1.8 mmol/L) at baseline. Although that for study 048 inclusion was only based on LDL-C level LDL-C ≥70 mg/dL (1.8 mmol/L) at baseline without any CV risk level requirement, post-hoc analyses demonstrate that these patients satisfy to lipid-modifying therapy (LMT) treatment criteria.

Whether the population could be defined as a population with **hypercholesterolemia** as proposed in the requested indication, screening criteria before entering the run-in phase of the studies needs to be

considered. For studies 046 and 048 the screening inclusion criteria were meeting the definition of hypercholesterolemia. At screening, this was an LDL-C level of ≥ 130 mg/dL in primary prevention patients and ≥ 100 mg/dL in secondary prevention while in study 046, and ≥ 100 mg/dL in patients taking ezetimibe and ≥ 120 mg/dL in patients not taking ezetimibe in study 048.

Definition of statin intolerance for study 046 was defined as an inability to tolerate 2 or more statins, one at a low dose, due to an adverse safety effect that started or increased during statin therapy and resolved or improved when statin therapy was discontinued. In this respect, to consider patient statin intolerant who are treated with lower than the defined very-low dose can be acceptable. Whether patients in study 048 would be statin intolerant based on the inclusion criteria is less clear. Patients had to have attempted one statin treatment and were being unable to tolerate it due to an adverse safety effect that started or increased during statin therapy and resolved or improved when statin therapy was discontinued or the dose lowered. The exclusion criteria are generally acceptable to optimize study adherence and reduce potential dropouts, comply with inclusion criteria, reduce potential tolerability issues with background medication, and exclude any possible relevant confounding.

Lipid sample collection by a centralised laboratory is appropriate and according to current study standards. Sample sizes were calculated to provide 95% power to observe a difference of 15% on the percent change from baseline in LDL-C, which is considered clinically relevant. The statistical analysis plans for the studies were considered acceptable.

On top of statins

Two placebo-controlled studies (047 and 040) were performed to investigate and confirm the LDL-C lipid lowering treatment effect of bempedoic acid. In these studies the effect was evaluated on top of maximum tolerated statin therapy with other lipid lowering therapy. Patients with high CV risk eligible for further lipid lowering therapy based on their LDL-C level were included. The larger study 040 was limited in the sense that no PCSK9 inhibitors treatment was allowed as background therapy in contrast to the considerable smaller study 047, including comparable study patients and with comparable study evaluation period (52 weeks). Overall, these studies potentially allow for a short- and intermediate term evaluation of the lipid lowering effect of bempedoic acid in patients eligible for lipid lowering therapy according to current guideline standards. An open-label long-term study which is currently ongoing should provide additional data on the maintenance of effect beyond one year of therapy. Although, data will be limited as the study is currently ongoing.

The general design of double-blind, placebo-controlled, randomized (2:1), parallel-group studies should allow for the primary objective of an adequate evaluation of the bempedoic acid treatment effect on LDL-C reduction either on top of lipid lowering therapy including maximum tolerated statin therapy or in patients who are statin intolerant. A 2:1 randomisation is acceptable to optimise exposure to the investigational product. The primary endpoint of LDL-C lowering was assessed at 12 weeks, which is sufficiently long to establish the maximum stable LDL-C treatment effect. The 52 weeks treatment period should support for longer maintenance of effect. However, it was not fully understood why the largest 040 study is primarily designed as a safety study, although the efficacy was evaluated in a comparable method as the other studies. The secondary endpoints of the Week 24 percentage LDL-C reduction can be supportive for the primary endpoint and is acceptable. Other parameters of the lipid profile (nonHDL-C, TC, apoB) were evaluated as secondary endpoints, which is considered relevant and supported. The specific 2-week run-in for the largest 040 study is very short to exclude any possible confounding of background therapy on the efficacy treatment evaluation, however, patients needed already be on stable therapy prior to this run-in phase. To establish baseline LDL-C levels in phase 3 studies based on week -1 and 0 is appropriate. Adjunctive LMT could be

initiated after 24 weeks in both 52 weeks studies per investigator discretion if protocol-defined LDL-C threshold criteria were met, which is acceptable and would not favour any study treatment outcomes.

Identification of patients eligible for lipid lowering therapy was appropriately based on the combination of CV risk classification and LDL-C level, and in accord with treatment guidelines of learned societies (ESC, AHA). Patients were included based on LDL-C ≥70 mg/dL at Week -2 (study 040) or baseline (study 047) and high CV risk (diagnosis of HeFH or ASCVD [established CHD or CHD risk equivalent]).

Whether the population could be defined as a population with hypercholesterolemia as proposed in the requested indication, screening criteria before entering the run-in phase of the studies needs to be considered. For study 047, the screening inclusion criteria were meeting the definition of hypercholesterolemia. At screening, this was a LDL-C level of ≥ 100 mg/dL. However, for study 040 in patients on stable maximum tolerated statin dose, LDL-C had to be ≥ 70 mg/dL at Screening (Week -2), which is not necessarily hypercholesterolemia, but these patients would likely had hypercholesterolemia at start of statin therapy in the past (start of therapy unknown). The exclusion criteria are generally acceptable to optimize study adherence and reduce potential dropouts, comply with inclusion criteria, reduce potential tolerability issues with background medication, and exclude any possible relevant confounding.

Lipid sample collection by a centralised laboratory and data monitoring and CV events adjudication by independent committees is appropriate and according to current study standards.

Sample sizes were calculated to provide 95% power to observe a difference of 15% on the percent change from baseline in LDL-C, which is considered clinically relevant. The statistical analysis plans for the studies are considered acceptable.

Phase 2 studies

Several phase 2 studies were performed to evaluate the lipid lowering effect of bemepdoic acid either as monotherapy (1) including dose finding studies (3), concomitantly with other lipid lowering therapy of atorvastatin (1) and atorvastatin+ezetimibe (1), and on top of statin therapy with one being a dose finding study (3) or PCSK9 therapy (1). Study treatment including other LLT of atorvastatin and/or ezetimibe was controlled by a washout period of LLT prior to evaluation in the studies. Almost all studies used LDL-C lowering as the primary endpoint with evaluation after 4 weeks to 12 weeks. Only study 007 (study on top of statins) was a safety study but LDL-C lowering efficacy was evaluated after 8 weeks of treatment. These studies allow for a first evaluation of the treatment effect of bempedoic acid either alone or in combination with other lipid lowering therapies and to identify the optimal dose for the phase 3 confirmatory phase.

Efficacy data and additional analyses

Phase 2 studies

Four dose finding phase 2 studies were performed in hyperlipidemic patients with either normal or elevated TGs designed as randomized, double-blind, placebo-controlled, phase 2 studies. These studies included 177 with hyperlipidemia, 56 (statin-intolerant), 349 (with or without statin intolerance) and 134 patients (stable statin dose), respectively.

An LDL-C lowering effect was observed in the range of 40 to 120 mg bempedoic acid dose after 12 weeks (-15.7%, -22.9%, and -24.5%; p<0.001), 60 mg uptitrated to 120 mg and 180 mg uptitrated to 240 mg (each dose 2 weeks) ((60 mg, -18.0%; 120 mg, -30.0%; 180 mg, -28.8%, 240 mg -28.5%). In another study, the LS mean difference from ezetimibe monotherapy for percent change in LDL-C from baseline to Week 12 was -6.5% for bempedoic acid 120 mg (p = 0.0008), -8.91% for

bempedoic acid 180 mg (p <0.0001), -21.86% for bempedoic acid 120 mg + ezetimibe (p <0.0001), and -26.5% for bempedoic acid 180 mg + ezetimibe (p <0.0001). In a study of 120 and 180 mg bempedoic acid on top of statins after 12 weeks, the LS mean relative to placebo was -13.1% (p = 0.0055), and -20.1% (p <0.0001), respectively.

A pooled analysis of 6 phase 2 studies in 832 patients (580 on BA) also demonstrated a dose dependent effect up to 180 mg QD dose; placebo adjusted LDL-C: -18.3%, -25.5%, -29.8%, -32.4%, and -28.8% with bempedoic acid 60, 80, 120, 180, and 240 mg QD, respectively. Higher doses than the 180 mg QD dose did not provide an additional lipid lowering effect versus placebo. Also, on top of statins, the 180 provided the largest effect (-21.7%) with no additional effect with the 240 mg dose (-21.7%). The (additional) effect of bempedoic acid on top of statin was lower than compared to the bempedoic effect versus placebo. The effect of bempedoic acid plus ezetimibe obviously showed the largest treatment effect (-45.6% BA 120 mg + 10 mg eze, -50.1% BA 180 mg +10 mg eze). Overall, these data reasonably support the choice for the 180 mg QD dose as evaluated in the phase 3 studies.

Statin intolerance

A limited number of patients (345 in study 046 and 269 patients in study 048) were included. In these studies a large proportion of patients completed the study and this was comparable for bempedoic acid (94-97%) versus placebo (92-96%). Main reasons for discontinuations of treatment were adverse event. The lowest discontinuation of study treatment was found in the 048 statin intolerant patients (9.4% vs 9.1%), which could likely partly explained by the shorter follow up. For the longer follow-up 046 study in statin intolerant patients, discontinuation of study medication was substantially higher (24.8% vs 16.2%). Adverse events were the main cause of study drug discontinuation (18.4% vs 11.7% in study 046 and 7.2% vs 5.7% in study 048). Other reasons that contributed most but in variable proportion across the different studies were patients withdrawals, patient decision and sponsor decision.

All studies represent a study population of primarily Caucasians at high or very high CV risk and at relative increased age (mean 64 to 65 years of age; Caucasian 85% to 91%). CV risk estimation was distributed across patients with ASCVD (39-40%) and patients at increased CV risk based on CV risk factors including e.g. hypertension (58-68%), diabetes (19-27%) and (history of) smoking (approximately 40%). The 046 study in statin intolerant patients was only performed in US and Canada, and thus may be less representative for the EU situation, although these patients would also be eligible for LMT according to the EU criteria. In these studies, 8-10% in study 046 used statins, and in study 048 28-33% used statins with most patients below low dose and some at a low dose. Further, these studies largely present a hypercholesterolemic patient population as baseline mean LDL-C level ranged from 123.0 (27.20) to 158.5 (40.39) mg/dL (3.18 – 4.1 mmol/L). Screening levels also represent those of a hypercholesterolemic population.

Randomisation was successful, with only slight differences between treatment groups for almost all patient characteristics. Efficacy analysis based on the FAS is an acceptable approach.

A significant reduction (p<0.001) on the primary endpoint of percent LDL-C reduction after 12 weeks of treatment was observed with -21.4% (95%CI -25.1, -17.7%) and -28.5% (95%CI -34.4, -22.5%) for study 046 and 048, respectively. The effect on LDL-C reduction was slightly diminished during 24 weeks in study 046 (-18.9%; p<0.001). The primary LDL-C lowering effect was supported by secondary analysis demonstrating significant reductions for other lipid parameters including non-HDL-C, TC, and apoB (p<0.001) after 12 weeks of treatment. Some significant percent reduction was also observed in the hsCRP level, being assessed as a secondary endpoint. Results on the proportion of patients achieving hsCRP levels of < 2 mg/L showed that more patients met this criterion in the statin intolerant pool (43.3% vs 16.7% at week 12, p<0.001). However, the clinical meaning of these results is unclear.

Comparable results across many of the subgroups were noticed for the treatment effect of bempedoic acid after 12 weeks. However, differences in effect on LDL-C were noticed for some subgroups including non-Hispanic vs Hispanic (ethnicity; <0.001), diabetes (0.032) and statin use (0.032). Also, the effect was larger when ezetimibe was present compared to no ezetimibe use. This effect is mainly driven by the difference in effect on LDL-C between study 046 and 048. Because in study 048 all patients used ezetimibe while in study 046 approximately 14% used ezetimibe and the overall LDL-C effect in study 048 was larger. Furthermore, for the age subgroups of age categories of < 65, 65 to 75 and ≥ 75 and <85 and ≥ 85 years no substantial differences or trends for the difference in effect was noticed, although the number of patients in the ≥ 85 years of age group was very limited.

On top of statins

For the phase 3 studies on top of maximum tolerated statin therapy, a large number of patients were included with 2230 patient in the largest 040 study, and 779 patients in the 047 study. A large proportion of patients completed the study, this was comparable for bempedoic acid (93-94%) versus placebo (95-97%). Main reasons for discontinuations of treatment were adverse events and withdrawal by the patient. Discontinuation of study treatment was higher for bempedoic acid than for placebo (20.5%-23.2% vs 16.7-19.1%). Adverse events were a main cause of study drug discontinuation (10.3-10.8% vs 7.4-8.2%). Other reasons that contributed most but in variable proportion across the different studies were patients withdrawals, patient decision and sponsor decision.

Several amendments were made in these studies. Most of these amendments likely have a low impact on the overall results, while sensitivity analyses were proposed to check on the consequences of these amendments. Increase of sample size to increase the overall numbers to further support the safety assessment is acceptable. Amendment 5 in study 040 and amendment 3 in study 047 were relevant (considering the non-allowance of doses of simvastatin of 40 mg or higher). Those patients treated with a 40 mg dose (n=98) have discontinued in study 040. This amendment was introduced as a significant increase in simvastatin exposure was observed that was induced by bempedoic acid. Currently in the labelling it is proposed to limit the simvastatin dose to 20 mg in general and 40 mg for high risk patients prior to introducing bempedoic acid therapy (see further safety discussion).

All studies represent a study population of primarily Caucasians at high or very high CV risk and at relatively increased age (mean age range 64 to 67 years; Caucasian 94% to 97%). In these studies, 50-53% were on high intensity statin, and 31-43% on medium intensity statin. Very high CV risk was mainly identified based on the presence of ASVCD (93-95%) while few patients with HeFH were included (5-6%). Also, these studies were largely performed within Europe (66-72%) and thus are representative for the EU situation. In these studies, high intensity statins of atorvastatin (55-67%,) and rosuvastatin (17-33%) were used most, especially the 40 mg dose of atorvastatin (29%). Although PCSK9 inhibitors were allowed in study 047, there use was minimal (0.2-0.4%), which could be due to the timing of the studies, when CV outcome was not yet available. The studies largely include a hypercholesterolemic patient population as baseline mean LDL-C level ranged from 102.3 (30.05) mg/dL (2.63 mmol/L) to 122.4 (38.30) mg/dL (3.15 mmol/L) as a result of the specific inclusion criteria for these trials. LDL-C at screening also indicate that patients were well above the 2.6 mmol/L threshold to consider them to be hypercholesterolemic.

Randomisation was successful, with only slight differences between treatment groups for almost all patient characteristics. Efficacy analysis based on the FAS is an acceptable approach.

A significant reduction (p<0.001) on the primary endpoint of percent LDL-C reduction after 12 weeks of treatment was observed. This reduction was clinically relevant with -18.1% (95%CI -20.0, -16.1%) and -17.4% (95%CI -20.9, -13.8%) for the 040 and 047 studies, respectively, although this was lower than for the statin intolerant study pool. The relative lower effect in patients on background maximum tolerated statin therapy may partly be explained by the lower LDL-C baseline levels (more optimally

treated) than the statin intolerant studies. However, the net effect is also the sum of the likely diminished PD effect due to inhibition in the similar pathway of bempedoic acid and statins, and the likely increased PD effect of bempedoic acid induced increased exposure of statins. The effect on LDL-C reduction was maintained during 24 weeks in the studies 040 and 047 on top of statins (-19.5%, -18.2%, respectively; p<0.001). The LDL-C lowering treatment effect resulted in significantly more patients meeting the LDL-C < 70 mg/dL goal (28.9% vs 8.0% at week 12 and 26.2% vs 9.1% at week 52). The primary LDL-C lowering effect was supported by secondary analysis demonstrating significant reductions for other lipid parameters including non-HDL-C, TC, and apoB (p<0.001) after 12 weeks of treatment.

These primary and secondary evaluations were supported by additional analyses on the maintenance of effect and effects according to subgroups. In the studies with maximum tolerated statin background therapy (study 040, 047) the LDL-C lowering treatment effect of bempedoic acid was maintained, although slightly diminished up to 52 weeks (-13.6% and -12.3%, respectively). The slightly diminished effect could have been partly caused by the allowance of change of the background therapy (9.2% of the patients) after 24 weeks. More specifically, background LLT therapy was slightly less intensified in the bempedoic acid treatment arm than in the placebo arm (8.8% vs 10.1%; n= 278). This was mainly adjunctive therapy of statins (7.0% vs 8.0%), while evolocumab and alirocumab use was very limited (5 (0.2%) vs 4 (0.4%) and 3 (0.4%) vs 1 (0.1%)) and the latter may likely not have significantly contributed to the diminished effect. Of notice, the addition of statin therapy could be of interest to substantiate the additional effect of statin in combination with bempedoic acid to provide some support for the current dose recommendation for statins in the labelling; these data have currently however not been presented. Further support for the maintenance of effect is provided in the ongoing open-label extension study where the LDL-C lowering effect after one year (2 years in total) was -16.8% (23.4%) in the former placebo patients (n = 131) and -15.8% (24.6%) in the former bempedoic acid patients from study 040 (n = 288)).

Further, comparable results across many of the subgroups were noticed for the treatment effect of bempedoic acid after 12 weeks. However, differences were noticed for some subgroups: the effect was increased for female vs male (gender; p interaction 0.044), different for BMI categories (0.007), and lower with increased statin intensity (0.060). A difference was also noted with background ezetimibe therapy (lower with ezetimibe), however, p for interaction was apparently not significant. Differences in exposure between male and female may have contributed to the different treatment effect. For background, statin intensity findings may comply with what can be expected. In line with the phase 2 studies, the treatment effect appears less in case of (increased intensity) statin use compared to less or no statin use at baseline. Moreover, this complies with PK/PD modelling data demonstrating statin intensity to be a significant factor for LDL-C reduction. In the studies with background statin therapy, no obvious differences in effect were observed between the individual different statins. Furthermore, for the age subgroups of age categories of < 65, 65 to 75 and ≥ 75 and <85 and ≥ 85 years no substantial differences or trends for the difference in effect was noticed, although the number of patients in the ≥ 85 years of age group was very limited.

2.5.4. Conclusions on the clinical efficacy

Bempedoic acid has demonstrated the capacity to lower the LDL-C, although this effect was only moderate and declined with the highest doses of background statin therapy. In the absence of background statin therapy the effect of bempedoic acid on LDL-C reduction was larger than with statin background therapy. Further, a larger LDL-C lowering effect was observed in females as compared to male subjects. The long-term reduction of the LDL-C appeared to slightly diminish, although

background therapy may have played a role. Bempedoic acid induced increase in statin exposure that was of relevance and this significant interaction was appropriately reflected in the SmPC.

2.6. Clinical safety

Patient exposure

In the bempedoic acid clinical program, 3627 subjects/patients received bempedoic acid, including 383 healthy subjects, 34 otherwise healthy subjects with hepatic or renal impairment, and 3210 patients with hyperlipidemia. In addition, 1628 subjects/patients participated in clinical studies and did not receive bempedoic acid but received placebo and/or other investigational medicinal product.

In the studies on top of statins (high risk pool) mean days of exposure to IMP was similar between the bempedoic acid and placebo groups (308.9 days and 322.4 days, respectively). Median days of IMP exposure was the same for both placebo and bempedoic acid groups (364.0 days).

In the statin intolerant studies, mean days of exposure to IMP was similar between the bempedoic acid and placebo groups (117.8 days and 122.4 days, respectively). Median days of IMP exposure was lower for the bempedoic acid group (91.0 days) compared with the placebo group (112.0 days).

In the ongoing extension Study 1002-050 includes 1462 patients, mean exposure to IMP as of 28 September 2018 was 318.3 days.

A summary of the exposure is given below in Table 29.

Table 29. Categorical Summary of Duration of Exposure to Investigational Medicinal Product, Phase 3 Studies

	Number of Patients	
Pool	**Bempedoic Acid 180 mg QD**	**Placebo QD**
High-Risk/Long-Term Pool		
N	2009	999
Duration of treatment, n (%)		
≥ 12 weeks	1826 (90.9)	938 (93.9)
≥ 24 weeks	1681 (83.7)	884 (88.5)
≥ 36 weeks	1608 (80.0)	847 (84.8)
≥ 48 weeks	1558 (77.6)	817 (81.8)
No- or Low-Dose Statin Pool		
N	415	198
Duration of treatment, n (%)		
≥ 6 weeks	387 (93.3)	190 (96.0)
≥ 12 weeks	332 (80.0)	160 (80.8)

	Number of Patients	
Pool	**Bempedoic Acid 180 mg QD**	**Placebo QD**
Overall Phase 3 Pool		
N	2424	1997

	Number of Patients	
Pool	**Bempedoic Acid 180 mg QD**	**Placebo QD**
Duration of treatment, n (%)		
≥ 12 weeks	2158 (89.0)	1098 (91.7)
≥ 24 weeks	1811 (74.7)	949 (79.3)
≥ 36 weeks	1608 (66.3)	847 (70.8)
≥ 48 weeks	1558 (64.3)	817 (68.3)
Study1002-050[a]		
N	1462	NA
Duration of treatment, n (%)		
≥ 12 weeks	1424 (97.4)	NA
≥ 24 weeks	1399 (95.7)	NA
≥ 36 weeks	1193 (81.6)	NA
≥ 52 weeks	416 (28.5)	NA
≥ 64 weeks	107 (7.3)	NA
≥ 78 weeks	19 (1.3)	NA

Adverse events

Overall safety profile

Information on the overall safety profile is provided in Table 30.

Table 30. Overview of Treatment-emergent Adverse Events, Placebo-Controlled Phase 3 Studies (Safety Analysis Set).

	High Risk/Long-Term Poo1 (Pool 1)		No- or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
	BA N = 2009 n (%)	PBO N = 999 n (%)	BA N = 415 n (%)	PBO N = 198 n (%)	BA N = 2424 n (%)	PBO N = 1197 n (%)
TEAE[a]	1533 (76.3)	766 (76.7)	238 (57.3)	102 (51.5)	1771 (73.1)	868 (72.5)
Serious TEAE	322 (16.0)	152 (15.2)	19 (4.6)	7 (3.5)	341 (14.1)	159 (13.3)
TEAE related to IMP[b]	493 (24.5)	215 (21.5)	90 (21.7)	28 (14.1)	583 (24.1)	243 (20.3)
TEAE leading to IMP discontinuation	219 (10.9)	75 (7.5)	54 (13.0)	18 (9.1)	273 (11.3)	93 (7.8)
TEAE by maximum severity						
Mild	452 (22.5)	247 (24.7)	118 (28.4)	48 (24.2)	570 (23.5)	295 (24.6)
Moderate	815 (40.6)	412 (41.2)	101 (24.3)	47 (23.7)	916 (37.8)	459 (38.3)
Severe	266 (13.2)	107 (10.7)	19 (4.6)	7 (3.5)	285 (11.8)	114 (9.5)
TEAE with fatal outcome	19 (0.9)	4 (0.4)	0	0	19 (0.8)	4 (0.3)

The most common adverse events observed in the studies are provided in Table 31.

Table 31. Treatment-emergent Adverse Events in Placebo-Controlled Phase 3 Studies With Incidence ≥ 2% by Preferred Term in Bempedoic Acid Group for Any Pool (Safety Analysis Set).

	High Risk/Long-Term Poo1 (Pool 1)		No- or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
Preferred Term	BA N = 2009 n (%)	PBO N = 999 n (%)	BA N = 415 n (%)	PBO N = 198 n (%)	BA N = 2424 n (%)	PBO N = 1197 n (%)
Nasopharyngitis	173 (8.6)	100 (10.0)	7 (1.7)	6 (3.0)	180 (7.4)	106 (8.9)
Myalgia	104 (5.2)	53 (5.3)	14 (3.4)	10 (5.1)	118 (4.9)	63 (5.3)
Urinary tract infection	97 (4.8)	52 (5.2)	13 (3.1)	14 (7.1)	110 (4.5)	66 (5.5)
Arthralgia	83 (4.1)	52 (5.2)	17 (4.1)	5 (2.5)	100 (4.1)	57 (4.8)
Upper respiratory tract infection	91 (4.5)	40 (4.0)	3 (0.7)	4 (2.0)	94 (3.9)	44 (3.7)
Muscle spasms	73 (3.6)	23 (2.3)	16 (3.9)	8 (4.0)	89 (3.7)	31 (2.6)
Dizziness	73 (3.6)	40 (4.0)	10 (2.4)	1 (0.5)	83 (3.4)	41 (3.4)
Diarrhoea	77 (3.8)	37 (3.7)	5 (1.2)	2 (1.0)	82 (3.4)	39 (3.3)
Back pain	67 (3.3)	22 (2.2)	8 (1.9)	5 (2.5)	75 (3.1)	27 (2.3)
Pain in extremity	61 (3.0)	17 (1.7)	14 (3.4)	4 (2.0)	75 (3.1)	21 (1.8)
Headache	56 (2.8)	31 (3.1)	12 (2.9)	6 (3.0)	68 (2.8)	37 (3.1)
Bronchitis	60 (3.0)	25 (2.5)	7 (1.7)	7 (3.5)	67 (2.8)	32 (2.7)

Preferred Term	High Risk/Long-Term Poo1 (Pool 1)		No- or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
	BA N = 2009 n (%)	PBO N = 999 n (%)	BA N = 415 n (%)	PBO N = 198 n (%)	BA N = 2424 n (%)	PBO N = 1197 n (%)
Hypertension	50 (2.5)	32 (3.2)	11 (2.7)	3 (1.5)	61 (2.5)	35 (2.9)
Anaemia	57 (2.8)	19 (1.9)	3 (0.7)	0	60 (2.5)	19 (1.6)
Cough	55 (2.7)	27 (2.7)	4 (1.0)	4 (2.0)	59 (2.4)	31 (2.6)
Fatigue	44 (2.2)	34 (3.4)	10 (2.4)	8 (4.0)	54 (2.2)	42 (3.5)
Nausea	44 (2.2)	23 (2.3)	9 (2.2)	3 (1.5)	53 (2.2)	26 (2.2)
Blood uric acid increased	33 (1.6)	4 (0.4)	18 (4.3)	2 (1.0)	51 (2.1)	6 (0.5)
Angina pectoris	47 (2.3)	30 (3.0)	2 (0.5)	0	49 (2.0)	30 (2.5)
Lower respiratory tract infection	49 (2.4)	27 (2.7)	1 (0.2)	0	49 (2.0)	27 (2.3)
Musculoskeletal pain	43 (2.1)	20 (2.0)	5 (1.2)	0	48 (2.0)	20 (1.7)
Osteoarthritis	46 (2.3)	31 (3.1)	2 (0.5)	4 (2.0)	48 (2.0)	35 (2.9)
Sinusitis	33 (1.6)	21 (2.1)	9 (2.2)	1 (0.5)	42 (1.7)	22 (1.8)

In the **ongoing open label study**, a total of 934 patients overall (63.9%) had an adverse event, 13.5% of patients had serious adverse events, 9.3% had adverse events considered related to IMP, and 4.1% had adverse events leading to IMP discontinuation. Most adverse events were mild or moderate. Six patients (0.4%) had fatal treatment-emergent adverse events during the study.

The most common adverse events **by system organ class (SOC)** are mentioned in Table 32. Infection and infestations, musculoskeletal and connective tissue disorders, and gastrointestinal disorders were the SOCs with highest frequencies.

Table 32. Treatment-emergent Adverse With Incidence ≥ 2% by System Organ Class in the Bempedoic Acid Group for Any Pool, Placebo-Controlled Phase 3 Studies (Safety Analysis Set).

System Organ Class	High Risk/Long-Term Poo1 (Pool 1)		No- or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
	BA N = 2009 n (%)	PBO N = 999 n (%)	BA N = 415 n (%)	PBO N = 198 n (%)	BA N = 2424 n (%)	PBO N = 1197 n (%)
Infections and infestations	659 (32.8)	324 (32.4)	63 (15.2)	38 (19.2)	722 (29.8)	362 (30.2)
Musculoskeletal and connective tissue disorders	513 (25.5)	234 (23.4)	71 (17.1)	37 (18.7)	584 (24.1)	271 (22.6)
Gastrointestinal disorders	367 (18.3)	165 (16.5)	44 (10.6)	17 (8.6)	411 (17.0)	182 (15.2)
Nervous system disorders	292 (14.5)	152 (15.2)	34 (8.2)	16 (8.1)	326 (13.4)	168 (14.0)
Investigations	250 (12.4)	110 (11.0)	47 (11.3)	8 (4.0)	297 (12.3)	118 (9.9)
Metabolism and nutritional disorders	219 (10.9)	113 (11.3)	29 (7.0)	11 (5.6)	248 (10.2)	124 (10.4)
Cardiac disorders	224 (11.1)	123 (12.3)	12 (2.9)	3 (1.5)	236 (9.7)	126 (10.5)

System Organ Class	High Risk/Long-Term Poo1 (Pool 1)		No- or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
	BA N = 2009 n (%)	PBO N = 999 n (%)	BA N = 415 n (%)	PBO N = 198 n (%)	BA N = 2424 n (%)	PBO N = 1197 n (%)
General disorders and administration site conditions	187 (9.3)	118 (11.8)	30 (7.2)	13 (6.6)	217 (9.0)	131 (10.9)
Respiratory, thoracic, and mediastinal disorders	179 (8.9)	93 (9.3)	16 (3.9)	11 (5.6)	195 (8.0)	104 (8.7)
Injury, poisoning and procedural complications	160 (8.0)	73 (7.3)	14 (3.4)	9 (4.5)	174 (7.2)	82 (6.9)
Renal and urinary disorders	155 (7.7)	64 (6.4)	11 (2.7)	8 (4.0)	166 (6.8)	72 (6.0)
Skin and subcutaneous tissue disorders	146 (7.3)	80 (8.0)	16 (3.9)	3 (1.5)	162 (6.7)	83 (6.9)
Vascular disorders	117 (5.8)	79 (7.9)	17 (4.1)	8 (4.0)	134 (5.5)	87 (7.3)
Eye disorders	72 (3.6)	44 (4.4)	8 (1.9)	2 (1.0)	80 (3.3)	46 (3.8)
Blood and lymphatic disorders	73 (3.6)	32 (3.2)	4 (1.0)	1 (0.5)	77 (3.2)	33 (2.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	68 (3.4)	27 (2.7)	5 (1.2)	2 (1.0)	73 (3.0)	29 (2.4)
Psychiatric disorders	57 (2.8)	38 (3.8)	11 (2.7)	3 (1.5)	68 (2.8)	41 (3.4)
Reproductive system and breast disorders	53 (2.6)	7 (0.7)	2 (0.5)	3 (1.5)	55 (2.3)	10 (0.8)
Hepatobiliary disorders	41 (2.0)	20 (2.0)	2 (0.5)	1 (0.5)	43 (1.8)	21 (1.8)

Treatment related adverse events were 24.5% for bempedoic acid and 21.5% for placebo in the studies on top of statins (Table 33). The most common treatment related adverse events were myalgia (3.1% , 3.7%), muscle spasm (2.2%, 1.3%), diarrhea (1.3%, 1.1%) and headache (1.3%, 1.7%). For the statin intolerant studies this was 21.7% vs 14.1% and the most common treatment related adverse events were myalgia (3.0% , 3.8%), muscle spasm (2.3%, 1.7%), headache (1.3%, 1.5%), blood uric acid increased (1.2%, 0.2%), diarrhea (1.2%, 0.9%), and dizziness (1.1%, 1.1%).

The most common treatment related adverse events by system organ class (SOC) and for adverse events of specific interest are mentioned in the table below. Musculoskeletal and connective tissue disorders and gastrointestinal disorders were the SOCs with highest frequencies and higher for bempedoic acid than the comparator group.

Table 33. Treatment-related adverse events of most relevance or specific interest in the Bempedoic Acid Group for Any Pool, Placebo-Controlled Phase 3 Studies (Safety Analysis Set) (modified by assessor).

System Organ Class	High Risk/Long-Term Poo1 (Pool 1)		No- or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
	BA N = 2009 n (%)	PBO N = 999 n (%)	BA N = 415 n (%)	PBO N = 198 n (%)	BA N = 2424 n (%)	PBO N = 1197 n (%)
Important SOCs						
Musculoskeletal and connective tissue disorders	157 (7.8)	69 (6.9)	32 (7.7)	18 (9.1)	189 (7.8)	87 (7.2)
Gastrointestinal disorders	105 (5.2)	43 (4.3)	10 (2.4)	3 (1.5)	115 (4.7)	46 (3.8)
Renal and urinary disorders	30 (1.5)	9 (0.9)	2 (0.5)	0	32 (1.3)	9 (0.8)
Hepatobiliary disorders	3 (0.1)	1 (0.1)	2 (0.5)	0	5 (0.2)	1 (<0.1)
Important adverse events						
Hypoglycemia	18 (0.9)	10 (1.0)	1 (0.2)	0	19 (0.8)	10 (0.8)
Blood glucose increased	2 (<0.1)	1 (0.1)	0	0	2 (<0.1)	1 (<0.1)
Type 2 diabetes mellitus	4 (0.2)	1 (0.1)	0	0	4 (0.2)	1 (<0.1)
Diabetes mellitus	3 (0.1)	2 (0.2)	1 (0.2)	0	4 (0.2)	2 (0.2)
Hyperglycemia	0	2 (0.2)	0	2 (1.0)	0	4 (0.3)
ALT increased	12 (0.6)	1 (0.1)	4 (1.0)	0	16 (0.7)	1 (<0.1)
AST increased	14 (0.7)	1 (0.1)	4 (1.0)	0	18 (0.7)	1 (<0.1)
Hepatic enzyme increased	6 (0.3)	1 (0.1)	1 (0.2)	0	7 (0.3)	1 (<0.1)
GFR decreased	4 (0.2)	0	3 (0.7)	0	7 (0.3)	0
Renal failure	7 (0.3)	1 (0.1)	1 (0.2)	0	8 (0.3)	1 (<0.1)
Renal impairment	6 (0.3)	3 (0.3)	1 (0.2)	0	7 (0.3)	3 (0.3)
Blood creatinine increased	3 (0.1)	0	2 (0.5)	0	8 (0.3)	1 (<0.1)
Blood CK levels increased	15 (0.7)	9 (0.9)	4 (1.0)	0	19 (0.8)	9 (0.8)
Myalgia	63 (3.1)	37 (3.7)	10 (2.4)	8 (4.0)	73 (3.0)	45 (3.8)
Muscle spasm	45 (2.2)	13 (1.3)	10 (2.4)	7 (3.5)	55 (2.3)	20 (1.7)
Pain in extremity	15 (0.7)	4 (0.4)	5 (1.2)	2 (1.0)	20 (0.8)	6 (0.5)
Arthralgia	13 (0.6)	11 (1.1)	7 (1.7)	0	20 (0.8)	11 (0.9)
Hyperuricemia	6 (0.3%)	0	2 (0.5)	0	8 (0.3)	0
Blood uric acid increased	18 (0.9%)	1 (0.1%)	12 (2.9)	1 (0.5)	30 (1.2)	2 (0.2)
Gout	3 (0.1)	0	1 (0.2)	0	4 (0.2)	0
Hemoglobin decreased	3 (0.1)	2 (0.2)	0	0	3 (0.1)	2 (0.2)

Adverse events of special interest

- New onset diabetes/hyperglycemia

Based on experience with statins drugs, new onset diabetes/hypoglycemia was analyzed as an adverse event of special interest, see tables Table 34 and Table 35 below. This was reported to be 7.1% for bempedoic acid vs 8.9% for placebo in patients with diabetes at baseline, and 3.1% vs 4.7% in patients without diabetes in the studies on top of statins. This was reported to be 5.1% for bempedoic acid vs 9.3% for placebo in patients with diabetes at baseline, and 1.9% vs 2.6% in patients without diabetes in the statin intolerant pool.

Table 34. New Onset Diabetes/ Hyperglycemia Adverse Events and Laboratory Values of Interest in Patients with a History of Diabetes at Baseline, Placebo-Controlled Phase 3 Studies (Safety Population).

	High Risk/Long-Term Poo1 (Pool 1)		No or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
	BA N = 580	**PBO N = 293**	**BA N = 98**	**PBO N = 43**	**BA N =678**	**PBO N = 336**
Treatment-Emergent Adverse Events, n (%)						
New onset diabetes/ hyperglycemia	**41 (7.1)**	**26 (8.9)**	**5 (5.1)**	**4 (9.3)**	**46 (6.8)**	**30 (8.9)**
Diabetes mellitus	15 (2.6)	11 (3.8)	3 (3.1)	2 (4.7)	18 (2.7)	13 (3.9)
Hyperglycaemia	9 (1.6)	4 (1.4)	1 (1.0)	1 (2.3)	10 (1.5)	5 (1.5)
Type 2 diabetes mellitus	7 (1.2)	0	1 (1.0)	0	8 (1.2)	0
Blood glucose increased	5 (0.9)	1 (0.3)	0	0	5 (0.7)	1 (0.3)
Diabetes mellitus inadequate control	4 (0.7)	4 (1.4)	0	1 (2.3)	4 (0.6)	5 (1.5)
Glycosuria	1 (0.2)	2 (0.7)	0	0	1 (0.1)	2 (0.6)
Glucose urine present	0	1 (0.3)	0	0	0	1 (0.3)
Glycosylated haemoglobin increased	0	4 (1.4)	0	0	0	4 (1.2)
Laboratory Values of Interest						
HbA1c (%)						
Mean baseline value	6.86 (0.978)	6.85 (1.047)	6.82 (1.166)	6.98 (0.815)	6.85 (1.007)	6.87 (1.020)
Mean change from baseline to Week 12	-0.13 (0.490)	0.07 (0.643)	-0.03 (0.781)	0.20 (0.738)	-0.11 (0.544)	0.09 (0.656)
Mean change from baseline to Week 52	0.04 (0.681)	0.18 (0.814)	--	--	0.04 (0.681)	0.18 (0.814)
Fasting Glucose						
Mean baseline value, mmol/L	7.354 (2.151)	7.219 (2.131)	7.314 (2.303)	7.623 (2.255)	7.349 (2.172)	7.271 (2.148)

	High Risk/Long-Term Poo1 (Pool 1)		No or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
	BA N = 580	PBO N = 293	BA N = 98	PBO N = 43	BA N =678	PBO N = 336
Mean change from baseline at Week 12	0.025 (1.798)	0.246 (2.169)	0.123 (2.343)	0.437 (3.196)	0.268 (2.307)	0.039 (1.887)
Mean change from baseline to Week 52	0.126 (2.341)	0.423 (2.147)	--	--	0.126 (2.341)	0.423 (2.147)

Table 35. New Onset Diabetes/ Hyperglycemia Adverse Events and Laboratory Values of Interest in Patients with no History of Diabetes at Baseline, Placebo Controlled Phase 3 Studies (Safety Population).

	High Risk/Long-Term Poo1 (Pool 1)		No or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
	BA N = 1429	PBO N = 706	BA N = 317	PBO N = 155	BA N =1746	PBO N = 861
Treatment-Emergent Adverse Events, n (%)						
New onset diabetes/ hyperglycaemia	44 (3.1)	33 (4.7)	6 (1.9)	4 (2.6)	50 (2.9)	37 (4.3)
Type 2 diabetes mellitus	18 (1.3)	14 (2.0)	0	1 (0.6)	18 (1.0)	15 (1.7)
Blood glucose increased	13 (0.9)	11 (1.6)	0	0	13 (0.7)	11 (1.3)
Glucose tolerance impaired	7 (0.5)	1 (0.1)	0	0	7 (0.4)	1 (0.1)
Impaired fasting glucose	4 (0.3)	2 (0.3)	2 (0.6)	0	6 (0.3)	2 (0.2)
Hyperglycaemia	3 (0.2)	4 (0.6)	2 (0.6)	1 (0.6)	5 (0.3)	5 (0.6)
Blood glucose abnormal	1 (<0.1)	1 (0.1)	0	0	1 (<0.1)	1 (0.1)
Diabetes mellitus	1 (<0.1)	2 (0.3)	1 (0.3)	1 (0.6)	2 (0.1)	3 (0.3)
Glycosylated haemoglobin increased	0	1 (0.1)	1 (0.3)	1 (0.6)	1 (<0.1)	2 (0.2)
Laboratory Values of Interest						
HbA1c (%)						
Mean baseline value	5.72 (0.374)	5.71 (0.369)	5.70 (0.384)	5.73 (0.438)	5.72 (0.376)	5.71 (0.382)
Mean change from baseline to Week 12	-0.05 (0.236)	-0.01 (0.220)	0.00 (0.282)	0.00 (0.225)	-0.04 (0.246)	-0.01 (0.220)

	High Risk/Long-Term Poo1 (Pool 1)		No or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
	BA N = 1429	**PBO N = 706**	**BA N = 317**	**PBO N = 155**	**BA N =1746**	**PBO N = 861**
Mean change from baseline to Week 52	0.03 (0.286)	0.04 (0.387)	--	--	0.03 (0.286)	0.04 (0.387)
Laboratory Values of Interest						
Fasting glucose						
Mean baseline value, mmol/L	5.467 (0.654)	5.476 (0.700)	5.493 (0.741)	5.460 (0.690)	5.472 (0.670)	5.473 (0.698)
Mean change from baseline at Week 12	0.044 (0.525)	0.076 (0.628)	-0.059 (0.598)	0.036 (0.557)	0.026 (0.540)	0.069 (0.616)
Mean change from baseline to Week 52	0.002 (0.644)	0.013 (0.624)	--	--	0.002 (0.644)	0.013 (0.624)

- Hepatic enzyme elevations

Liver abnormalities were higher for bempedoic acid than for placebo with 2.8% vs 1.3% overall, 2.5% vs 1.5% on top of statins, and 3.9% vs 0 in statin-intolerance, mainly due to AST/ALT increases with more increased of > 3 x ULN, but no cases of potential Hy's law.

Table 36: Laboratory Values of Interest, Placebo-Controlled Phase 3 Studies (Safety Analysis Set).

	High Risk/Long-Term Poo1 (Pool 1)		No- or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
	BA N = 2009 n (%)	**PBO N = 999 n (%)**	**BA N = 415 n (%)**	**PBO N = 198 n (%)**	**BA N = 2424 n (%)**	**PBO N = 1197 n (%)**
Preferred Term						
Any	51 (2.5)	15 (1.5)	16 (3.9)	0	67 (2.8)	15 (1.3)
AST increased	26 (1.3)	3 (0.3)	4 (1.0)	0	30 (1.2)	3 (0.3)
ALT increased	19 (0.9)	2 (0.2)	4 (1.0)	0	23 (0.9)	2 (0.2)
Hepatic enzyme increased	8 (0.4)	2 (0.5)	2 (0.5)	0	10 (0.4)	2 (0.2)
Liver function test increased	5 (0.2)	2 (0.2)	8 (1.9)	0	13 (0.5)	2 (0.2)
Transaminases increased	4 (0.2)	2 (0.2)	0	0	4 (0.2)	2 (0.2)
Blood bilirubin increased	2 (< 0.1)	3 (0.3)	0	0	2 (< 0.1)	3 (0.3)
Liver function test abnormal	2 (< 0.1)	2 (0.2)	2 (0.5)	0	4 (0.2)	2 (0.2)
Hepatic enzyme abnormal	1 (< 0.1)	0	0	0	1 (< 0.1)	0
Laboratory Values						

Table 36: Laboratory Values of Interest, Placebo-Controlled Phase 3 Studies (Safety Analysis Set).

	High Risk/Long-Term Poo1 (Pool 1)		No- or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
ALT and/or AST > 3× ULN[a]	13 (0.6)	3 (0.3)	5 (1.2)	0	18 (0.7)	3 (0.3)
ALT and/or AST > 5× ULN	4 (0.2)	2 (0.2)	2 (0.5)	0	6 (0.2)	2 (0.2)
ALP > 1.5× ULN	10 (0.5)	9 (0.9)	3 (0.7)	1 (0.5)	13 (0.5)	10 (0.8)
TB > 2 × ULN	0	2 (0.2)	0	0	0	2 (0.2)
Potential Hy's Law[b]	0	0	0	0	0	0

No difference in hepatobiliary disorders (SOC) was observed in each pool between both treatment arms (2.0% each and 0.5% each in both pools, respectively).

- Muscular Disorders

Because statins are associated with muscle-related adverse effects, muscular disorders were evaluated as an AESI in Phase 3 clinical studies based on a prespecified list of preferred terms and associated changes in CK. Muscular disorders were higher for bempedoic acid vs placebo on top of statins (13.2% vs 10.2%). The highest frequency and largest difference in the SOC term musculoskeletal and connective tissue disorders (Table 38) was observed in low intensity statins (37.6% vs 23.7%). No difference was found for muscular disorders in statin intolerance (11.3% vs 11.6%), see Table 37.

Table 37: Adverse Events of Special Interest: Muscular Disorder Adverse Events and Laboratory Values of Interest, Placebo-Controlled Phase 3 Studies (Safety Analysis Set).

	High Risk/Long-Term Poo1 (Pool 1)		No- or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
	BA N = 2009 n (%)	PBO N = 999 n (%)	BA N = 415 n (%)	PBO N = 198 n (%)	BA N = 2424 n (%)	PBO N = 1197 n (%)
Muscular disorders	265 (13.2)	102 (10.2)	47 (11.3)	23 (11.6)	312 (12.9)	125 (10.4)
Muscle spasms	73 (3.6)	23 (2.3)	16 (3.9)	8 (4.0)	89 (3.7)	31 (2.6)
Myalgia	104 (5.2)	53 (5.3)	14 (3.4)	10 (5.1)	118 (4.9)	63 (5.3)
Pain in extremity	61 (3.0)	17 (1.7)	14 (3.4)	4 (2.0)	75 (3.1)	21(1.8)
Blood creatine phosphokinase increased	39 (1.9)	16 (1.6)	8 (1.9)	0	47 (1.9)	16 (1.3)
Muscular weakness	11 (0.5)	5 (0.5)	2 (0.5)	2 (1.0)	13 (0.5)	7 (0.6)
Myositis	3 (0.1)	0	0	0	3 (0.1)	0
Blood creatine phosphokinase abnormal	0	0	0	0	0	0

Myositis was reported in 3 patients (0.1%) in Study 1002-040. One serious adverse event in a patient receiving bempedoic acid on a background of 40 mg simvastatin (CK levels were > 10 × ULN) resolved after discontinuation of IMP. One in a patient receiving 20 mg atorvastatin and one in a patient receiving 80 mg atorvastatin were moderate with peak elevations in CK levels were < 3 × ULN in these 2 patients. These patients completed the study.

Table 38. Adverse Events in the Musculoskeletal and Connective Tissue Disorders SOC by Baseline Statin Intensity Reported in ≥ 2% of Bempedoic-Acid Treatment Patients in Any Statin Intensity Category, High Risk/Long-Term Pool (Pool 1) (Safety Analysis Set).

SOC Preferred Term	No Statin		Statin Intensity					
			Low		Moderate		High	
	BA N = 55 n (%)	PBO N = 29 n (%)	BA N =125 n (%)	PBO N = 59 n (%)	BA N = 810 n (%)	PBO N = 404 n (%)	BA N = 1019 n (%)	PBO N = 507 n (%)
Musculoskeletal and connective tissue disorders	18 (32.7)	9 (31.0)	47 (37.6)	14 (23.7)	200 (24.7)	97 (24.0)	248 (24.3)	114 (22.5)
Arthralgia	6 (10.9)	3 (10.3)	7 (5.6)	1 (1.7)	30 (3.7)	24 (5.9)	40 (3.9)	24 (4.7)
Muscle spasms	1 (1.8)	1 (3.4)	8 (6.4)	0	24 (3.0)	12 (3.0)	40 (3.9)	10 (2.0)
Myalgia	5 (9.1)	4 (13.8)	12 (9.6)	7 (11.9)	47 (5.8)	24 (5.9)	40 (3.9)	18 (3.6)
Pain in extremity	0	0	8 (6.4)	1 (1.7)	25 (3.1)	8 (2.0)	28 (2.7)	8 (1.6)
Musculoskeletal pain	0	0	4 (3.2)	1 (1.7)	12 (1.5)	11 (2.7)	27 (2.6)	8 (1.6)
Back pain	4 (7.3)	1 (3.4)	6 (4.8)	0	31 (3.8)	9 (2.2)	26 (2.6)	12 (2.4)
Osteoarthritis	1 (3.4)	1 (1.8)	4 (3.2)	3 (3.4)	21 (2.6)	9 (2.2)	20 (2.0)	19 (3.7)

A consistent slight increase in skeletal muscle adverse events is observed for atorvastatin (25.5% (287) vs 23.6% (127) Musculoskeletal and Connective Tissues; 13.3% vs 9.8% Any Muscular Disorders), rosuvastatin (22.5% (87) vs 21.1% (45); 12.4% vs 8.0%), simvastatin (25.8% (70) vs 23.7% (32); 12.2% vs 7.4%), and pravastatin (30.7% (35) vs 21.5% (14); 17.5% vs 15.4%), while a lower rate in the BA group was observed for the other statins (n=75). For the largest subgroups the increase was seen in atorvastatin 40 mg dose (24.8% (148) vs 19.9% (56); 12.9 (77) vs 7.1% (20)) and somewhat in the rosuvastatin 20 mg dose (22.4% (39) vs 23.4% (22); 12.0% (21) vs 7.4 (7)), while no increase was seen in the simvastatin 20 mg dose (24.5% (38) vs 31.4% (27); 10.3% (16) vs 10.5% (9)). For the highest doses only an increase in simvastatin 40 mg dose was observed (22.0% (18) vs 5.9% (2); 11.0% (9) vs 2.9% (1)), while no such increase was seen for atorvastatin 80 mg (28.1% (47) vs 34.1% (28); 14.4% (24) vs 14.6% (12)) or rosuvastatin 40 mg (16.0% (13) vs 15.4% (8); 6.2% (5) vs 5.8% (3)), although these data are limited (Table 40).

Table 39: Treatment-emergent Skeletal Muscle Adverse Events in the High Risk/Long-term Pool (Pool 1) by Baseline Statin Type (Safety Population).

Baseline Statin Type **TEAE Category**	**Placebo** **% (n)**	**Bempedoic Acid** **% (n)**
Atorvastatin, N	**539**	**1125**
Any TEAE: Musculoskeletal and Connective Tissues SOC	23.6% (127)	25.5% (287)
Any Muscular Disorders AESI	9.8% (53)	13.3% (150)
Rosuvastatin, N	**213**	**387**
Any TEAE: Musculoskeletal and Connective Tissues SOC	21.1% (45)	22.5% (87)
Any Muscular Disorders AESI	8.0% (17)	12.4% (48)
Simvastatin, N	**135**	**271**
Any TEAE: Musculoskeletal and Connective Tissues SOC	23.7% (32)	25.8% (70)
Any Muscular Disorders AESI	7.4% (10)	12.2% (33)
Pravastatin, N	**65**	**114**
Any TEAE: Musculoskeletal and Connective Tissues SOC	21.5% (14)	30.7% (35)
Any Muscular Disorders AESI	15.4% (10)	17.5% (20)
Other statins (lovastatin, pitavastatin, fluvastatin), N	**18**	**57**
Any TEAE: Musculoskeletal and Connective Tissues SOC	38.9% (7)	28.1% (16)
Any Muscular Disorders AESI	33.3% (6)	14.0% (8)

Table 40. Treatment-emergent Skeletal Muscle Adverse Events in the High Risk/Long-term Pool (Pool 1) by Baseline Statin Dose (Safety Population).

Baseline Atorvastatin Dose **TEAE Category**	**Placebo** **% (n)**	**Bempedoic Acid** **% (n)**
Atorvastatin 80 mg, N	**82**	**167**
Any TEAE: Musculoskeletal and Connective Tissues SOC	34.1% (28)	28.1% (47)
Any Muscular Disorders AESI	14.6% (12)	14.4% (24)
Atorvastatin 40 mg, N	**281**	**596**
Any TEAE: Musculoskeletal and Connective Tissues SOC	19.9% (56)	24.8% (148)
Any Muscular Disorders AESI	7.1% (20)	12.9% (77)
Atorvastatin 20 mg, N	**144**	**278**
Any TEAE: Musculoskeletal and Connective Tissues SOC	23.6% (34)	23.7% (66)
Any Muscular Disorders AESI	11.1% (16)	12.6% (35)
Atorvastatin Other Doses, N	**33**	**84**

Table 40. Treatment-emergent Skeletal Muscle Adverse Events in the High Risk/Long-term Pool (Pool 1) by Baseline Statin Dose (Safety Population).

Baseline Atorvastatin Dose **TEAE Category**	**Placebo** **% (n)**	**Bempedoic Acid** **% (n)**
Any TEAE: Musculoskeletal and Connective Tissues SOC	27.3% (9)	31.0% (26)
Any Muscular Disorders AESI	15.2% (5)	16.7% (14)
Rosuvastatin 40 mg, N	**52**	**81**
Any TEAE: Musculoskeletal and Connective Tissues SOC	15.4% (8)	16.0% (13)
Any Muscular Disorders AESI	5.8% (3)	6.2% (5)
Rosuvastatin 20 mg, N	**94**	**175**
Any TEAE: Musculoskeletal and Connective Tissues SOC	23.4% (22)	22.3% (39)
Any Muscular Disorders AESI	7.4% (7)	12.0% (21)
Rosuvastatin 10 mg + Other Doses, N	**67**	**131**
Any TEAE: Musculoskeletal and Connective Tissues SOC	22.4% (15)	26.7% (35)
Any Muscular Disorders AESI	10.4% (7)	16.8% (22)
Simvastatin 40 mg, N	**34**	**82**
Any TEAE: Musculoskeletal and Connective Tissues SOC	5.9% (2)	22.0% (18)
Any Muscular Disorders AESI	2.9% (1)	11.0% (9)
Simvastatin 20 mg, N	**86**	**155**
Any TEAE: Musculoskeletal and Connective Tissues SOC	31.4% (27)	24.5% (38)
Any Muscular Disorders AESI	10.5% (9)	10.3% (16)
Simvastatin 10 mg + Other Lower Doses, N	**15**	**34**
Any TEAE: Musculoskeletal and Connective Tissues SOC	20.0% (3)	41.2% (14)
Any Muscular Disorders AESI	0% (0)	23.5% (8)

In study 048, adverse events related to muscular safety events occurred in 6.1% of patients in the bempedoic acid group, compared with 5.7% in the placebo group. In study 1002-048, Musculoskeletal and connective tissue disorders were 4 (6.8%) and 1 (4.2%) for bempedoic acid and for placebo in patients treated with statins background therapy, and 15 (12.3%) vs 8 (12.7%) for patients on other lipid lowering background therapy.

- Neurocognitive disorders

Based on a possible association between statins and cognitive impairment, neurocognitive disorders were evaluated as an AESI in Phase 3 clinical studies using a prespecified list of preferred terms. There have been anecdotal reports of cognitive impairment linked to statin use. However, a meta-analysis of statin clinical studies did not demonstrate an increased incidence of cognitive impairment. In the phase 3 studies comparable low frequencies were observed between treatment arms (0.7% vs 0.8%), Table 41.

Table 41. Adverse Events of Special Interest: Neurocognitive Disorders Adverse Events, Placebo-Controlled Phase 3 Studies (Safety Analysis Set)

	High Risk/Long-Term Poo1 (Pool 1)		No- or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
	BA N = 2009 n (%)	PBO N = 999 n (%)	BA N = 414 n (%)	PBO N = 198 n (%)	BA N = 2424 n (%)	PBO N = 1197 n (%)
Neurocognitive disorders	14 (0.7)	8 (0.8)	2 (0.5)	1 (0.5)	16 (0.7)	9 (0.8)
Memory impairment	7 (0.3)	4 (0.4)	0	0	7 (0.3)	4 (0.3)
Amnesia	3 (0.1)	4 (0.4)	0	1 (0.5)	3 (0.1)	5 (0.4)
Cognitive disorder	2 (< 0.1)	0	0	0	2 (0.1)	0
Confusional state	2 (< 0.1)	0	1 (0.2)	0	3 (0.1)	0
Disorientation	2 (< 0.1)	0	1 (0.2)	0	3 (0.1)	0

- Hypoglycemia and metabolic acidosis

Hypoglycemia with associated metabolic acidosis was initially identified as a potential risk based on findings in nonclinical toxicology studies of bempedoic acid. Hypoglycemia was reported with a comparable frequency (1.7% vs 2.1%), Table 42.

Table 42. Adverse Events of Special Interest: Adverse Events of Hypoglycemia and Related Laboratory Values of Interest, Placebo-Controlled Phase 3 Studies (Safety Analysis Set).

	High Risk/Long-Term Poo1 (Pool 1)		No- or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
	BA N = 2009 n (%)	PBO N = 999 n (%)	BA N = 415 n (%)	PBO N = 198 n (%)	BA N = 2424 n (%)	PBO N = 1197 n (%)
Preferred Term						
Any	40 (2.0)	25 (2.5)	1 (0.2)	0	41 (1.7)	25 (2.1)
Hypoglycemia	39 (1.9)	24 (2.4)	1 (0.2)	0	40 (1.7)	24 (2.0)
Blood glucose decreased	1 (< 0.1)	0	0	0	1 (< 0.1)	0
Blood glucose abnormal	1 (< 0.1)	1 (0.1)	0	0	1 (< 0.1)	1 (< 0.1)
Laboratory Parameters						
Glucose ≤ 50 mg/dL Baseline status						
Normal fasting glucose	0	0	0	0	0	0
Impaired fasting glucose	1 (0.1)	1 (0.2)	0	0	1 (< 0.1)	1 (0.2)

- Renal disorders

Based on nonclinical findings and minimal mean increases in creatinine reported in Phase 1 and Phase 2 studies, renal disorders were assessed as an AESI in Phase 3 studies, based on a prespecified list of adverse event preferred terms and associated laboratory parameters.

Renal disorders were higher for bempedoic acid versus placebo (2.8% vs 1.3%), with difference in renal failure (0.8% vs 0.2%), renal impairment (0.5% vs 0.3%), and blood creatinine increased (0.8% vs 0.3%), Table 43.

Table 43. Adverse Events of Special Interest: Renal Disorder Adverse Events and Related Laboratory Values in Phase 3 Studies (Safety Analysis Set).

AESI Category SOC Preferred Term	High Risk/Long-Term Poo1 (Pool 1)		No- or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
	BA N = 2009 n (%)	PBO N = 999 n (%)	BA N = 415 n (%)	PBO N = 198 n (%)	BA N = 2424 n (%)	PBO N = 1197 n (%)
Renal disorders	59 (2.9)	13 (1.3)	10 (2.4)	2 (1.0)	69 (2.8)	15 (1.3)
Renal and urinary disorders	32 (1.6)	8 (0.8)	6 (1.4)	2 (1.0)	38 (1.6)	10 (0.8)
Renal failure	16 (0.8)	1 (0.1)	4 (1.0)	1 (0.5)	20 (0.8)	2 (0.2)
Renal impairment	11 (0.5)	4 (0.4)	2 (0.5)	0	13 (0.5)	4 (0.3)
Acute kidney injury	6 (0.3)	3 (0.3)	0	1 (0.5)	6 (0.2)	4 (0.3)
Investigations	28 (l.4)	5 (0.5)	4 (1.0)	0	32 (1.3)	5 (0.4)
Blood creatinine increased	16 (0.8)	4 (0.4)	3 (0.7)	0	19 (0.8)	4 (0.3)
Glomerular filtration rate decreased	12 (0.6)	1 (0.1)	4 (1.0)	0	16 (0.7)	1 (< 0.1)
Blood urea increased	3 (0.1)	1 (0.1)	0	0	3 (0.1)	1 (< 0.1)
eGFR < 15 mL/min/1.73m^2	2 (< 0.1)	0	0	0	2 (< 0.1)	0
eGFR 15-< 30 mL/min/1.73m^2	23 (1.1)	6 (0.6)	2 (0.5)	0	25 (1.0)	6 (0.5)
Creatinine						
Mean (%) change from baseline to Week 4	0.053 (5.61)	-0.002 (0.27)	0.045 (5.46)	0.005 (0.68)	0.051 (5.59)	-0.001 (0.34)
Mean (%) change from baseline to Week 12	0.048 (5.06)	-0.002 (0.39)	0.039 (5.05)	0.003 (0.46)	0.046 (5.06)	-0.002 (0.40)
Change from baseline > 1 mg/dL at any postbaseline assessment	7 (0.3)	1 (0.1)	0	0	7 (0.3)	1 (< 0.1)
Increase from baseline > 30% within 4 weeks after first dose of IMP	29 (1.4)	1 (0.1)	16 (3.9)	1 (0.5)	45 (1.9)	5 (0.4)

- Uric acid increases/gout

Based on increases in mean serum uric acid levels observed in patients who received bempedoic acid in Phase 1 and Phase 2 studies, uric acid increases were evaluated as an AESI in Phase 3 clinical studies based on a prespecified list of preferred terms and associated changes in serum uric acid levels. More blood uric acid increased, hyperuricemia and gout were found for bempedoic acid (see Table 44).

Table 44: Adverse Events of Special Interest: Uric Acid Increases/Gout, Placebo-Controlled Phase 3 Studies (Safety Analysis Set).

	High Risk/Long-Term Poo1 (Pool 1)		No- or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
	BA N = 2009 n (%)	PBO N = 999 n (%)	BA N = 415 n (%)	PBO N = 198 n (%)	BA N = 2424 n (%)	PBO N = 1197 n (%)
Uric acid elevations/gout	97 (4.8)	15 (1.5)	24 (5.8)	3 (1.5)	121 (5.0)	18 (1.5)
Blood uric acid increased	33 (1.6)	4 (0.4)	18 (4.3)	2 (1.0)	51 (2.1)	6 (0.5)
Hyperuricemia	37 (1.8)	7 (0.7)	3 (0.7)	0	40 (1.7)	7 (0.6)
Gout	29 (1.4)	4 (0.4)	4 (1.0)	1 (0.5)	33 (1.4)	5 (0.4)

- Decreased hemoglobin

Because of mean decreases in hemoglobin observed in Phase 1 and Phase 2 studies, hemoglobin decreases were evaluated based on a prespecified list of adverse event preferred terms and changes in laboratory measures of hemoglobin. More events of decreased hemoglobin and anemia were found for bempedoic acid, see Table 45.

Table 45. Adverse Events of Special Interest: Adverse Events of Decrease in Hemoglobin and Laboratory Values of Interest, Placebo-Controlled Phase 3 Studies (Safety Analysis Set).

	High Risk/Long-Term Poo1 (Pool 1)		No- or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
	BA N = 2009 n (%)	PBO N = 999 n (%)	BA N = 415 n (%)	PBO N = 198 n (%)	BA N = 2424 n (%)	PBO N = 1197 n (%)
Adverse Events						
Any	65 (3.2)	22 (2.2)	4 (1.0)	0	69 (2.8)	22 (1.8)
Decreased hemoglobin	8 (0.4)	3 (0.3)	1 (0.2%)	0	9 (0.4)	3 (0.3)
Decreased hematocrit	1 (< 0.1)	0	1 (0.2%)	0	2 (< 0.1)	0
Anemia	57 (2.8)	19 (1.9)	3 (0.7)	0	60 (2.5)	19 (1.6)
Laboratory Values						
Hgb decrease from baseline						
≥ 2g/dL and < LLN	103 (5.1)	23 (2.3)	9 (2.2)	0	112 (4.6)	23 (1.9)
≥ 3g/dL and < LLN	29 (1.4)	13 (1.3)	5 (1.2)	0	34 (1.4)	13 (1.1)
≥ 5g/dL and < LLN	3 (0.1)	2 (0.2)	2 (0.5)	0	5 (0.2)	2 (0.2)
Hgb						
< LLN and normal at baseline	30 (1.5)	4 (0.4)	3 (0.7)	1 (0.5)	33 (1.4)	5 (0.4)
< 8g/dL	1 (< 0.1)	0	0	0	1 (< 0.1)	0

Serious adverse event/deaths/other significant events

Serious adverse events

A summary of serious adverse events is provided below in Table 46. The number of serious adverse events were slightly higher (14.1% vs 13.3%) for bempedoic acid.

Table 46: Treatment-emergent Serious Adverse Events, Placebo-Controlled Phase 3 Studies (Safety Analysis Set).

System Organ Class Preferred Term	High Risk/Long-Term Poo1 (Pool 1)		No- or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
	BA N = 2009 n (%)	PBO N = 999 n (%)	BA N = 414 n (%)	PBO N = 198 n (%)	BA N = 2424 n (%)	PBO N = 1197 n (%)
Any SAE	322 (16.0)	152 (15.2)	19 (4.6)	7 (3.5)	341 (14.1)	159 (13.3)
Angina unstable	27 (1.3)	18 (1.8)	3 (0.7)	0	30 (1.2)	18 (1.5)
Angina pectoris	23 (1.1)	7 (0.7)	1 (0.2)	0	24 (1.0)	7 (0.6)
Coronary artery disease	16 (0.8)	12 (1.2)	3 (0.7)	0	19 (0.8)	12 (1.0)
Acute myocardial infarction	13 (0.6)	8 (0.8)	0	0	13 (0.5)	8 (0.7)
Atrial fibrillation	11 (0.5)	2 (0.2)	0	0	11 (0.5)	2 (0.2)
Myocardial infarction	10 (0.5)	7 (0.7)	1 (0.2)	0	11 (0.5)	7 (0.6)
Non-cardiac chest pain	8 (0.4)	6 (0.6)	1 (0.2)	0	9 (0.4)	6 (0.5)
Pneumonia	8 (0.4)	2 (0.2)	0	0	8 (0.3)	2 (0.2)
Syncope	7 (0.3)	3 (0.3)	1 (0.2)	0	8 (0.3)	3 (0.3)
Cardiac failure congestive	6 (0.3)	1 (0.1)	0	0	6 (0.2)	1 (< 0.1)
Ischaemic stroke	5 (0.2)	2 (0.2)	1 (0.2)	0	6 (0.2)	2 (0.2)
Myocardial ischaemia	6 (0.3)	5 (0.5)	0	0	6 (0.2)	5 (0.4)
Osteoarthritis	5 (0.2)	5 (0.5)	1 (0.2)	0	6 (0.2)	5 (0.4)
Urinary tract infection	5 (0.2)	1 (0.1)	1 (0.2)	0	6 (0.2)	1 (< 0.1)
Cardiac failure	5 (0.2)	5 (0.5)	0	0	5 (0.2)	5 (0.4)
Cholelithiasis	5 (0.2)	5 (0.5)	0	0	5 (0.2)	2 (0.2)
Diverticulitis	5 (0.2)	1 (0.1)	0	0	5 (0.2)	1 (< 0.1)
Benign prostatic hyperplasia	4 (0.2)	1 (0.1)	0	0	4 (0.2)	1 (< 0.1)
Cardiac failure chronic	4 (0.2)	1 (0.1)	0	0	4 (0.2)	1 (< 0.1)
Cerebrovascular accident	3 (0.1)	2 (0.2)	1 (0.2)	0	4 (0.2)	2 (0.2)
Chronic obstructive pulmonary disease	4 (0.2)	3 (0.3)	0	0	4 (0.2)	3 (0.3)
Peripheral arterial occlusive disease	4 (0.2)	4 (0.4)	0	0	4 (0.2)	4 (0.3)
Tendon rupture	4 (0.2)	0	0	0	4 (0.2)	0

In the open-label extension Study 1002-050, 13.5% of patients reported a serious adverse event. The most frequent serious adverse events were coronary artery disease (11 patients [0.8%]), angina pectoris (9 patients [0.6%]), and unstable angina, atrial fibrillation, and myocardial ischemia (7 patients [0.5%] each). Serious adverse events were considered related to treatment in 7 patients

(0.5%); these were hepatic enzymes increased, pancreatitis, cholelithiasis, contact dermatitis, brain death/hemorrhage intracranial, pain in extremity, and atrial fibrillation.

Deaths

The number of deaths in phase 3 studies is provided in Table 47; 19 (0.8%) vs. 4 (0.3%). In the overall phase 2 pool, 1 patient died.

Table 47. Treatment-emergent Adverse Events with Fatal Outcome, Placebo-Controlled Phase 3 Studies (Safety Analysis Set).

System Organ Class Preferred Term	High Risk/Long-Term Poo1 (Pool 1)		No- or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
	BA N = 2009 n (%)	PBO N = 999 n (%)	BA N = 414 n (%)	PBO N = 198 n (%)	BA N = 2424 n (%)	PBO N = 1197 n (%)
Any TEAE[a] with fatal outcome	19 (0.9)	4 (0.4)	0	0	19 (0.8)	4 (0.3)
Cardiac disorders	8 (0.4)	2 (0.2)	0	0	8 (0.3)	2 (0.2)
Cardiac arrest	1 (< 0.1)	0	0	0	1 (< 0.1)	0
Cardiac failure	2 (< 0.1)	0	0	0	2 (< 0.1)	0
Atherosclerosis coronary	1 (< 0.1)	0	0	0	1 (< 0.1)	0
Acute coronary syndrome	0	1 (0.1)	0	0	0	1 (< 0.1)
Coronary artery disease	0	1 (0.1)	0	0	0	1 (< 0.1)
Myocardial infarction	3 (0.1)	0	0	0	3 (0.1)	0
Hypertensive heart disease	1 (< 0.1)	0	0	0	1 (< 0.1)	0
Myocardial ischemia	1 (< 0.1)	0	0	0	1 (< 0.1)	0
Gastrointestinal disorders	1 (< 0.1)	0	0	0	1 (< 0.1)	0
Pancreatic pseudocyst	1 (< 0.1)	0	0	0	1 (< 0.1)	0
General disorders and administration site conditions	2 (< 0.1)	1 (0.1)	0	0	2 (< 0.1)	1 (< 0.1)
Multiple organ dysfunction syndrome	1 (< 0.1)	0	0	0	1 (< 0.1)	0
Death	1 (0.1)	1 (< 0.1)	0	0	1 (< 0.1)	1 (< 0.1)
Infections and infestations	2(< 0.1)	1 (0.1)	0	0	2 (< 0.1)	1 (< 0.1)
Sepsis	1 (< 0.1)	0	0	0	1 (< 0.1)	0
Peritonitis	0	1 (0.1)	0	0	1 (< 0.1)	0
Septic shock	1 (< 0.1)	1 (0.1)	0	0	1 (< 0.1)	1 (< 0.1)
Injury, poisoning, and procedural complications	1 (< 0.1)	0	0	0	1 (< 0.1)	0

System Organ Class Preferred Term	High Risk/Long-Term Poo1 (Pool 1)		No- or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
	BA N = 2009 n (%)	PBO N = 999 n (%)	BA N = 414 n (%)	PBO N = 198 n (%)	BA N = 2424 n (%)	PBO N = 1197 n (%)
Gas poisoning	1 (< 0.1)	0	0	0	1 (< 0.1)	0
Fall	0	0	0	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (0.2)	0	0	0	5 (0.2)	0
Lung neoplasm malignant	2 (< 0.1)	0	0	0	2 (< 0.1)	0
Lung adenocarcinoma	1 (< 0.1)	0	0	0	1 (< 0.1)	0
Lung squamous cell carcinoma metastatic	1 (< 0.1)	0	0	0	1 (< 0.1)	0
Metastases to liver	1 (< 0.1)	0	0	0	1 (< 0.1)	0
Metastatic gastric cancer	0	0	0	0	0	0
Nervous system disorders	1 (< 0.1)	0	0	0	1 (< 0.1)	0
Haemorrhage intracranial	0	0	0	0	0	0
Ischaemic cerebral infarction	1 (< 0.1)	0	0	0	1 (< 0.1)	0
Respiratory, thoracic and mediastinal disorders	1 (< 0.1)	0	0	0	1 (< 0.1)	0
Chronic obstructive pulmonary disease	1 (< 0.1)	0	0	0	1 (< 0.1)	0
General disorders and administration site conditions	0	0	0	0	0	0
Brain death	0	0	0	0	0	0

The imbalance in fatal events (safety set) was 19 (0.9%) vs 4 (0.4%) and all occurred within the high-risk pool (on top of statins). Fourteen bempedoic acid and 4 placebo patients had treatment-emergent deaths within 30 days of the last dose of IMP and were adjudicated by a CEC; these deaths were adjudicated as CV deaths (10 bempedoic acid, 3 placebo) or non-CV deaths (4 bempedoic acid, 1 placebo), see MACE events table below; 5 remaining death events (all bempedoic acid) were part of the safety population (non-CEC adjudicated) as they were outside the 30 days treatment –emergent time frame (but started within this time frame).

Adjudicated CV deaths (10 vs 3) could be explained by the cardiac disorder SOC in study 040 (5 (0.3%) vs 0) and study 047 (3 (0.6%) vs 2 (0.8%)), ischaemic cerebral infarction (1 vs 0) and death (with unknown origin) (1 vs 1).

Imbalance in neoplasm SOC were only observed in study 040 (5 (0.3%) vs 0). Of these, 4 cases were adjudicated as non-CV death (see MACE events table). Three out of five events occurred within 90 days of study period.

Fatality rate was substantially higher in the placebo controlled pool in comparison to the open-label extension phase; For the placebo controlled pool this was 0.9 per 100 person-years based on a mean exposure of 306 days in 1487 patients for bempedoic acid and was 0.3 per 100 person-years in 742 placebo patients based on a mean exposure of 319 days. This was 0.5 patients per 100 person-years with a mean exposure to bempedoic acid of 456.2 days during the open-label study 050 (second interim analysis of Study 1002-050 (15 March 2019)).

In study 050, fatal events were 1 each for myocardial infarction, accidental death, brain death, death, b-cell lymphoma, metastatic gastric cancer, fall, haemorrhagic intracranial), with 8 of 9 events not considered related to study drug and patients suffered from multiple risk factors that could have contributed to the fatal event.

MACE events

The number of adjudicated major adverse cardiovascular events and analyses on hazard ratios are provided below in Table 48 and Table 49, and were lower for bempedoic acid (5.0% vs 5.7%).

Table 48. Adjudicated Major Adverse Cardiovascular Events (MACE) and non-MACE Events by Event Type in the Overall Phase 3 Pool (Safety Analysis Set).

	High-Risk/Long-Term Poo1		No- or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool	
	BA N = 2009	PBO N = 999	BA N = 414	PBO N = 198	BA N = 2424	PBO N = 1197
Any positively adjudicated event (MACE or non-MACE)	111 (5.5)	68 (6.8)	9 (2.2)	0	120 (5.0)	68 (5.7)
Any adjudicated MACE	111 (5.5)	68 (6.8)	9 (2.2)	0	120 (5.0)	68 (5.7)
CV death	10 (0.5)	3 (0.3)	0	0	10 (0.4)	3 (0.3)
Nonfatal myocardial infarction	25 (1.2)	22 (2.2)	1 (0.2)	0	26 (1.1)	22 (1.8)
Nonfatal stroke	9 (0.4)	4 (0.4)	2 (0.5)	0	11 (0.5)	4 (0.3)
Hospitalization for unstable angina	25 (1.2)	15 (1.5)	5 (1.2)	0	30 (1.2)	15 (1.3)
Coronary revascularization	59 (2.9)	40 (4.0)	7 (1.7)	0	66 (2.7)	40 (3.3)
Other adjudicated non-MACE events						
Non-CV death	4 (0.2)	1 (0.1)	0	0	4 (0.2)	1 (0.1)
Non-coronary arterial revascularization	11 (0.5)	12 (1.2)	0	0	11 (0.5)	12 (1.0)
Hospitalization for heart failure	14 (0.7)	3 (0.3)	0	0	14 (0.6)	3 (0.3)

All 9 patients in the statin intolerant pool with MACE were from Study 1002-046 and had a history of ASCVD. Seven of the 9 patients had coronary revascularization, 5 of whom had unstable angina and 1 had a nonfatal myocardial infarction; the remaining 2 patients had a non-fatal stroke.

Table 49. MACE Composite with Hazard Ratio for Cox Regression Model for Time to First Adjudicated MACE Composite (Safety Analysis Set).

	High-Risk/Long-Term Poo1 (Pool 1)			Overall Phase 3 Pool (Pool 3)		
	BA N = 2009 n (%)	**PBO N = 999** n (%)	**Hazard Ratio (95% CI)**	**BA N = 2424** n (%)	**PBO N = 1197** n (%)	**Hazard Ratio (95% CI)**
5-component MACE	89 (4.4)	55 (5.5)	0.83 (0.594, 1,164)	98 (4.0)	55 (4.6)	0.91 (0.656, 1.271)
4-component MACE	84 (4.2)	50 (5.0)	0.86 (0.608, 1.225)	93 (3.8)	50 (4.2)	0.95 (0.676, 1.344)
3-component MACE	42 (2.1)	27 (2.7)	0.80 (0.491, 1.292)	45 (1.9)	27 (2.3)	0.85 (0.529, 1.373)
5-component MACE + hospitalization for heart failure	100 (5.0)	57 (5.7)	0.90 (0.653, 1.252)	109 (4.5)	57 (4.8)	0.98 (0.713, 1.354)
4-component MACE + hospitalization for heart failure	95 (4.7)	52 (5.2)	0.94 (0.671, 1.320)	104 (4.3)	52 (4.3)	1.03 (0.736, 1.433)
3-component MACE + hospitalization for heart failure	54 (2.7)	29 (2.9)	0.96 (0.610, 1.503)	57 (2.4)	29 (2.4)	1.01 (0.645, 1.577)

In the ongoing open label study, 52 (3.6%) patients had a positively-adjudicated CV clinical endpoint; coronary revascularization (n=27, 1.8%) was the only clinical endpoint that occurred in ≥1% of patients, Table 50.

Table 50. Treatment-emergent and Positively Adjudicated Adverse Cardiovascular Events by Event Type, Safety Population in open label study.

Event Type	Overall (N=1462) n (%)
Patients with any adjudicated adverse cardiovascular events	52 (3.6)
Patients with any adjudicated major adverse cardiovascular event (MACE)	41 (2.8)
CV death	4 (0.3)
Non-fatal myocardial infarction	12 (0.8)
Non-fatal stroke	6 (0.4)
Coronary revascularization	27 (1.8)
Hospitalization for unstable angina	9 (0.6)
Patients with any non-MACE-related events	16 (1.1)
Non-CV death	1 (0.1)
Non-coronary revascularization	9 (0.6)
Hospitalization for heart failure	6 (0.4)

Laboratory findings

Glucose and HbA_{1c}

Changes in glucose and HbA_{1c} and significant alterations in these parameters are displayed below, Table 51 and Table 52.

Table 51. Shifts and Mean Change in Glucose and HbA1c Values in Patients With Diabetes, Placebo-Controlled Phase 3 Studies (Safety Analysis Set).

	High-Risk/Long-Term Pool (Pool 1)		No- or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
	BA N = 629	PBO N = 318	BA N = 56	PBO N = 111	BA N = 740	PBO N = 374

HbA_{1c}						
Mean baseline value	6.84	6.82	6.78	6.88	6.83	6.83
Mean change from baseline to Week 12	-0.13	0.06	-0.03	0.15	-0.12	0.08
Baseline/maximum postbaseline shift, n (%)						
≤ 5.5%/5.5%-6.4%	14 (2.3)	8 (2.5)	7 (6.3)	1 (1.9)	21 (2.9)	9 (2.4)
≤ 5.5%/≥ 6.5%	0	0	0	0	0	0
5.5%-6.4%/≥ 6.5%	44 (7.2)	39 (12.4)	6 (5.4)	6 (11.3)	50 (7.0)	45 (12.2)
Fasting Glucose						
Mean baseline value, mg/dL	131.6	129.6	130.5	132.4	131.4	130.0
Mean change from baseline at Week 12	0.2	3.5	1.7	7.9	0.4	4.1
Baseline/maximum postbaseline shift, n (%)						
50-100 mg/dL/100-126 mg/dL	58 (9.4)	25 (7.9)	6 (5.5)	4 (7.3)	64 (8.8)	29 (7.8)
50-100 mg/dL/≥ 126 mg/dL	18 (2.9)	20 (6.3)	1 (1.8)	5 (4.5)	23 (3.2)	21 (5.7)
100-126 mg/dL/≥ 126 mg/dL	139 (22.5)	74 (23.5)	8 (7.3)	9 (16.4)	147 (20.2)	83 (22.4)

Table 52. Significant alterations in glucose and HbA1c for patients with normal fasting glucose at baseline and impaired fasting glucose at baseline.

AESI Category Preferred Term	High Risk/Long-Term Poo1 (Pool 1)		No- or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
	BA n (%)	PBO n (%)	BA n (%)	PBO n (%)	BA n (%)	PBO n (%)
Post-Baseline Laboratory Values for Patients with Normal Fasting Glucose at Baseline						
N	**467**	**241**	**108**	**61**	**575**	**302**
Fasting glucose ≥ 126 mg/dL	9 (1.9)	9 (3.7)	0	1 (1.6)	9 (1.6)	10 (3.3)
≤ 50 mg/dL	0	0	0	0	0	0
HbA_{1c} ≥ 6.5	1 (0.2)	2 (0.8)	0	0	1 (0.2)	2 (0.7)
Post-Baseline Laboratory Values for Patients with Impaired Fasting Glucose at Baseline						
N	**913**	**440**	**196**	**81**	**1109**	**521**
Fasting glucose ≥ 126 mg/dL	78 (8.1)	44 (10.0)	17 (8.7)	4 (4.9)	91 (8.2)	48 (9.2)
≤ 50 mg/dL	1 (0.1)	1 (0.2)	0	0	1 (< 0.1)	1 (0.2)
HbA_{1c} ≥ 6.5	31 (3.4)	21 (4.8)	5 (2.6)	3 (3.7)	36 (3.2)	24 (4.6)

CK levels

Adverse events of blood creatine phosphokinase are displayed in the table below. At baseline, mean CK values were 134.1 and 132.3 U/L in the bempedoic acid and placebo groups, respectively. Shifts from normal CK to high CK levels were 19.8% vs 16.4% for bempedoic acid and placebo.

Table 53. Adverse Events of Special Interest: Muscular Disorder Adverse Events and Laboratory Values of Interest, Placebo-Controlled Phase 3 Studies (Safety Analysis Set) (Continued).

	High Risk/Long-Term Poo1 (Pool 1)		No- or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
	BA N = 2009 n (%)	PBO N = 999 n (%)	BA N = 415 n (%)	PBO N = 198 n (%)	BA N = 2424 n (%)	PBO N = 1197 n (%)
Creatine kinase						
> 5 × ULN	7 (0.3)	2 (0.2)	1 (0.2)	0	8 (0.3)	2 (0.2)
> 10 × ULN	4 (0.2)	1 (0.1)	0	0	4 (0.2)	1 (< 0.1)

Vital signs

Vital signs examined were systolic blood pressure, diastolic blood pressure, and sitting heart rate. There were no clinically meaningful changes in vital signs with bempedoic acid treatment in clinical studies. For Phase 3 studies, pool analyses of vital signs were performed for the High-Risk/Long-Term Pool only. No clinically meaningful changes were noted.

Safety in special populations

Adverse events by age

Adverse events are summarized by age categories 18 to < 65, 65 to < 75, and ≥ 75 years for phase 3 studies, Table 54 .

Table 54. Overall Incidence of Adverse Events by Age, Placebo-Controlled Phase 3 Studies (Safety Analysis Set).

Pool	18 < 65 years		65 < 75 years		≥ 75 years	
	Bempedoic Acid	Placebo	Bempedoic Acid	Placebo	Bempedoic Acid	Placebo
High-Risk/Long-Term Poo1 (Pool 1)	N = 871 619 (71.1%)	N = 385 279 (72.5%)	N = 826 661 (80.0%)	N = 449 352 (78.4%)	N = 312 253 (81.1%)	N = 165 135 (81.8%)
No- or Low-Dose Statin Pool (Pool 2)	N = 178 104 (58.4%)	N = 89 46 (51.7%)	N = 175 100 (57.1%)	N = 77 39 (50.6%)	N = 62 34 (54.8%)	N = 32 17 (53.1%)
Overall Phase 3 Pool (Pool 3)	N = 1049 723 (68.9%)	N = 474 325 (68.6%)	N = 1001 761 (76.0%)	N = 526 391 (74.3%)	N = 374 287 (76.7%)	N = 197 152 (77.2%)

Adverse events by gender

The overall incidences of adverse events by sex for the Phase 3 pools are summarized in the table below.

Table 55: Overall Incidence of Adverse Events by Sex, Placebo-Controlled Phase 3 Studies (Safety Analysis Set).

Pool	Male		Female	
	BA	PBO	BA	PBO
High-Risk/Long-Term Poo1 (Pool 1)	N = 1427 1083 (75.9%)	N = 697 521 (74.7%)	N = 582 450 (77.3%)	N = 302 245 (81.1%)
No- or Low-Dose Statin Pool (Pool 2)	N = 173 92 (53.2%)	N = 82 42 (51.2%)	N = 242 146 (60.3%)	N = 116 60 (51.7%)
Overall Phase 3 Pool (Pool 3)	N = 1600 1175 (73.4%)	N = 779 563 (72.3%)	N = 824 596 (72.3%)	N = 418 305 (73.0%)

Renal impairment

In the phase 3 studies, 1894 patients with renal impairment at baseline (1532 mild, 359 moderate, 3 severe) received bempedoic acid.

Immunological events

No immunological events are reported.

Safety related to drug-drug interactions and other interactions

See discussion on concomitant use with statins.

Discontinuation due to adverse events

In the Overall Phase 3 Pool, the most frequent adverse events that led to discontinuation of study drug are provided below in Table 56. Also, most frequent adverse events that led to discontinuation according to SOC are provided, differentiated for the studies on top of statins and studies in statin intolerant patients. More patients on bempedoic acid discontinued due to an AE (11.3% vs 7.8%), mostly due to GI disorders (1.5% vs 0.7%) or musculoskeletal and connective tissue disorders (2.8% vs 1.9%) on top of statins, Table 57.

Table 56. Treatment-emergent Adverse Events Leading to Investigational Medicinal Product Discontinuation by System Organ Class, Placebo-Controlled Phase 3 Studies (Safety Analysis Set).

TEAE leading to discontinuation of IMP (SOC)	High Risk/Long-Term Poo1 (Pool 1)		No- or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
	BA N = 2009 n (%)	PBO N = 999 n (%)	BA N = 415 n (%)	PBO N = 198 n (%)	BA N = 2424 n (%)	PBO N = 1197 n (%)
Any	219 (10.9)	75 (7.5)	54 (13.0)	18 (9.1)	273 (11.3)	93 (7.8)
Blood and lymphatic system disorders	4 (0.2)	0	0	0	4 (0.2)	0

Table 56. Treatment-emergent Adverse Events Leading to Investigational Medicinal Product Discontinuation by System Organ Class, Placebo-Controlled Phase 3 Studies (Safety Analysis Set).

TEAE leading to discontinuation of IMP (SOC)	High Risk/Long-Term Poo1 (Pool 1)		No- or Low-Dose Statin Pool (Pool 2)		Overall Phase 3 Pool (Pool 3)	
	BA N = 2009 n (%)	PBO N = 999 n (%)	BA N = 415 n (%)	PBO N = 198 n (%)	BA N = 2424 n (%)	PBO N = 1197 n (%)
Cardiac disorders	25 (1.2)	8 (0.8)	4 (1.0)	0	29 (1.2)	8 (0.7)
Ear and labyrinth disorders	1 (< 0.1)	1 (0.1)	0	1 (0.5)	1 (< 0.1)	2 (0.2)
Eye disorders	2 (< 0.1)	0	0	0	2 (< 0.1)	0
Gastrointestinal disorders	31 (1.5)	7 (0.7)	7 (1.7)	1 (0.5)	38 (1.6)	8 (0.7)
General disorders	9 (0.4)	9 (0.9)	7 (1.7)	3 (1.5)	16 (0.7)	12 (1.0)
Hepatobiliary disorders	2 (< 0.1)	0	1 (0.2)	0	3 (0.1)	0
Infections and infestations	11 (0.5)	3 (0.3)	1 (0.2)	2 (1.0)	12 (0.5)	5 (0.4)
Injury, poisoning, procedural complications	4 (0.2)	1 (0.1)	0	1 (0.5)	4 (0.2)	2 (0.2)
Investigations	27 (1.3)	4 (0.4)	5 (1.2)	0	32 (1.3)	4 (0.3)
Metabolism and nutritional disorders	8 (0.4)	3 (0.3)	0	0	8 (0.3)	3 (0.3)
Musculoskeletal and connective tissue disorder	57 (2.8)	19 (1.9)	25 (6.0)	11 (5.6)	82 (3.4)	30 (2.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	11 (0.5)	4 (0.4)	1 (0.2)	0	12 (0.5)	4 (0.3)
Nervous system disorders	21 (1.0)	16 (1.6)	5 (1.2)	2 (1.0)	26 (1.1)	18 (1.5)
Psychiatric disorders	6 (0.3)	3 (0.3)	3 (0.7)	0	9 (0.4)	3 (0.3)
Renal disorders	4 (0.2)	2 (0.2)	2 (0.5)	1 (0.5)	6 (0.2)	3 (0.3)
Reproductive system and breast disorders	0	0	1 (0.2)	0	1 (< 0.1)	0
Respiratory, thoracic, mediastinal disorders	9 (0.4)	1 (0.1)	2 (0.5)	0	11 (0.5)	1 (< 0.1)
Skin and subcutaneous tissue	8 (0.4)	4 (0.4)	4 (1.0)	0	12 (0.5)	4 (0.3)
Vascular disorders	2 (< 0.1)	1 (0.1)	1 (0.2)	1 (0.5)	3 (0.1)	2 (0.2)

Table 57. Treatment-Emergent AE Leading to IMP Discontinuation Reported at a ≥ 0.2%Higher Rate With Bempedoic Acid vs. Placebo by SOC and a ≥ 0.3% Higher Rate With

Bempedoic Acid vs. Placebo by Preferred Term, High-Risk/Long-Term Pool (Pool 1 Safety Analysis).

SOC Preferred Term	BA N = 2009 n (%)	PBO N = 999 n (%)
Gastrointestinal disorders	31 (1.5)	7 (0.7)
Diarrhoea	9 (0.4)	1 (0.1)
Musculoskeletal and connective tissue disorders	57 (2.8)	19 (1.9)
Pain in extremity	6 (0.3)	0

Table 58. Treatment-Emergent AE Leading to IMP Discontinuation Reported at a ≥ 0.2% Higher Rate With Bempedoic Acid vs. Placebo by SOC and a ≥ 0.3% Higher Rate With Bempedoic Acid vs. Placebo by Preferred Term, No- or Low-Dose Statin Pool (Pool 2 Safety Analysis).

SOC Preferred Term	BA N = 415 n (%)	PBO N = 198 n (%)
Gastrointestinal disorders	7 (1.7)	1 (0.5)
Diarrhoea	2 (0.5)	0
Investigations	5 (1.2)	0
Alanine aminotransferase increased	2 (0.5)	0
Aspartate aminotransferase increased	2 (0.5)	0
Liver function test abnormal	2 (0.5)	0
Musculoskeletal disorders	25 (6.0)	11 (5.6)
Muscle spasms	7 (1.7)	0
Arthralgia	4 (1.0)	1 (0.5)
Pain in extremity	4 (1.0)	0
Back pain	2 (0.5)	0
Nervous system disorders	5 (1.2)	2 (1.0)
Dizziness	3 (0.7)	0
Headache	2 (0.5)	0

In the open-label extension Study 1002-050, adverse events that led to discontinuation of study drug occurred in 4.1% of patients. The most frequent adverse events that led to discontinuation were myalgia, dizziness, and headache, each of which led to discontinuation in 3 patients (0.3%).

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

Statin intolerance

In the statin-intolerant pool a limited number of 613 were included. In the statin intolerant pool of studies 046 (lipid lowering therapy and no or lower than lowest approved dose of statins) and 048 (no or low dose statins and study medication of ezetimibe) the median exposure was limited to 91 and 112 days for study treatment and placebo, due to the shorter follow-up period (24 weeks and 12 weeks, respectively).

TEAEs were slightly higher for bempedoic acid compared to placebo (57.3% vs 51.5%) as well as for serious AEs (4.6% vs 3.5%, respectively) and treatment related Aes (21.7% vs 14.1%).

Adverse events were mostly reported in the infection and infestations (15.2% vs 19.2%), and musculoskeletal and connective tissue disorders (17.1% vs 18.7%) categories. The most frequent adverse events were urinary tract infections (3.1% vs 7.1%), myalgia (3.4% s 5.1%), and arthralgia (4.1% vs 2.5%).

The frequency of **serious Aes** was slightly higher (4.6% vs 3.5%). However, these were without substantial differences (<0.5% and without meaningful absolute differences in numbers) or any notable pattern. Therefore, these data do not allow for any meaningful conclusions. Cardiovascular events and deaths are of major interest (see also below in on top of statin discussion). MACE events were very rarely observed but higher for bempedoic acid (9 vs 0). This was mainly attributed to coronary revascularisation. All patients had a history of ASCVD and thus such events may not be unexpected and likely to be imbalanced due to chance finding. Any fatal events were not observed in the statin intolerant study pool, which is reassuring.

Specific attention has been given to reporting on **known adverse events from treatment with statins** including new-onset diabetes/hypoglycaemia, hepatic enzyme elevations, muscular disorders, and neurocognitive disorders as discussed below. Further, specific attention was also given to some other Aes due to non-clinical findings and findings observed in phase 1 and 2 studies including hypoglycaemia (and associated metabolic acidosis), renal disorders, uric acid increases/gout, and decreased haemoglobin.

Although based on limited numbers, there is no sign that treatment with bempedoic acid would increase **diabetes** risk. Worsening of hyperglycemia was reported to be 5.1% for bempedoic acid vs 9.3% for placebo in patients with diabetes at baseline, and new-onset diabetes was reported to be 1.9% vs 2.6% in patients without diabetes at baseline. Further support for an absence of an effect on diabetes with bempedoic acid comes from data on the changes in HbA_{1c} and fasting glucose, which showed no risk of increase or shifts in these parameters for bempedoic acid. Mean change was in HbA_{1c} was -0.03% vs 0.20%. No shifts from ≤ 5.5% to ≥ 6.5% were observed and shifts from 5.5%-6.4% to ≥ 6.5% were lower in bempedoic acid (5.4% vs 11.3%), although shifts from ≤ 5.5% to 5.5%-6.4% were higher (6.3% vs 1.9%) based on limited numbers.

As with statins, **laboratory hepatic enzyme** elevations were observed with a higher frequency with bempedoic acid than placebo (16 (3.9%) vs 0), with AST increased (4 (1.0%) vs 0) and ALT increased (4 (1.0% vs 0) being higher. ALT and/or AST > 3 x ULN elevation occurred in 5 (1.2%) vs 0, while no cases of potential Hy's Law were observed.

Muscular disorders were observed at a comparable frequency between bempedoic acid and placebo (11.3% vs 11.6%) and for treatment related Aes (7.7% vs 9.1%) and there was an absence of any increase according to specific definition of muscular disorders (myalgia, muscle spasm, pain in extremity). Although, the highest frequency of discontinuations due to Aes (although generally relative low) was in the SOC of musculoskeletal and connective tissue disorders also in the statin intolerant

studies (25 (6.0%) vs 11 (5.6%)). Levels of > 5x ULN or > 10 x ULN were rarely observed, only for one patient treated with bempedoic acid a >5 x ULN was observed.

Neurocognitive disorders were very rarely observed (2 (0.5%) vs 1 (0.5%)), although this was not specifically evaluated. Similarly, adverse events of hypoglycaemia were only observed in one patient treated with bempedoic acid.

Similar to phase 1 and 2 study findings, the suggested reversible **increase in creatinine** effect observed in the phase 1 and 2 program can also be observed in the phase 3 studies with difference in (mean) change in baseline to week 12 in creatinine of 0.039 vs 0.003, and blood creatinine increased (3 (0.7%) vs 0) and GFR decreased (4 (1.0%) vs 0). Further, comparable limited patients (6 patients (0.6%)) vs 1 patients (0.5%)) dropped below the eGFR of < 30 ml/min/1.73m^2 level. Further, an increase in **renal disorders** was observed for bempedoic acid treatment (10 (2.4%) vs 2 (1.0%)). This was consistently observed across some different Aes reported including renal failure (4 (1.0%) vs 1 (0.5%)), and renal impairment (2 (0.5%) vs 0), but not for acute kidney injury (0 vs 1 (0.5%), although data were rare. Treatment related renal disorders and urinary disorders were rarely reported (2 (0.5% vs 0).

As in the phase 1 and 2 studies an **increased frequency of uric acid** (18 (4.3%) vs 2 (1.0%), hyperuricemia (3 (0.7%) vs 0) and gout (4 (1.0%) vs 1 (0.5%)) were observed in the phase 3 studies. Treatment related hyperuricemia (2 (0.5%) vs 0), blood uric acid increased (12 (2.9%) vs 1 (0.5%)) and gout (1 (0.2%) vs 0) were also systematically higher for bempedoic acid treatment though based on limited numbers.

In the phase 1 and 2 studies, a **decrease in haemoglobin** was observed. During the phase 3 studies, an increased frequency of anaemia (3 (0.7%) vs 0), decreased haemoglobin (1 (0.2%) vs 0) and decreased haematocrit (1 (0.2%) vs 0) was observed with bempedoic acid treatment, although cases were rare. The level of decrease of haemoglobin was however limited, as this was particularly observed for ≥ 2g/dL and < LLN decrease (2.2% vs 0), while higher decreases were more rare (1.2% vs 0 for ≥ 3g/dL and < LLN, and 0.5% for ≥ 5g/dL and < LLN).

Bempedoic acid was relatively **well tolerated** with 13.0% vs 9.1% who discontinued due to an AE. The slightly higher discontinuation rate in comparison to the studies on top of statins may be (partly) explained by the history of generally less tolerant patients (confounded by indication). The highest frequency of discontinuations due to Aes was in the SOC of musculoskeletal and connective tissue disorders (25 (6.0%) vs 11 (5.6%)). Also, gastrointestinal problems were reported with one of the highest frequencies (1.7% vs 0.5%).

Treatment related Aes were more reported for bempedoic acid than for placebo (21.7% vs 14.1%). Apart from the uric acid increased (12 (2.9% vs 1 (0.5%)), no other adverse events definitions clearly and substantially contributed to the higher treatment related Aes.

Incidence of **adverse events** according to age (18-65, 65 to 75 and over 75 years of age categories) did not indicate any increase in Aes with increased age. Number of patients over 85 years of age are very limited. A slightly higher incidence of Aes was observed for females (60.3%) than for males (53.2%).

On top of statins

The studies with statin background therapy were substantially larger (n=3008) than the statin intolerant pool (n=613). The studies (040, 047) with background statin therapy had a one year of controlled follow-up with a median exposure to study treatment of 364 days. In these studies, 1558 patients have been treated for more than 48 weeks, which may still be considered limited for an intended life-long therapy. Further data will be obtained from the ongoing 1002-050 open-label

extension study in which 1462 patients have been included from the largest 040 study, with 416 patients currently treated with bempedoic acid for more than 52 weeks (2 years in total for those on bempedoic acid in the 040 study). Also, a cardiovascular outcome study is currently recruiting statin intolerant patients who are at increased risk of CV events to obtain an estimated 12600 patients with study results to be presented in 2024.

TEAEs were frequently reported, although the number of Aes were approximately similar between bempedoic acid and placebo (76.3% vs 76.7%). A consistent slightly higher frequency was also observed for serious Aes (16.0% vs 15.2%), related Aes (24.5% vs 21.5%), and severe Aes (13.2% vs 10.7%), while moderate and mild Aes were approximately similar.

Adverse events were mostly reported in the infection and infestations (32.8% vs 32.4%), and musculoskeletal and connective tissue disorders (25.5% vs 23.4%) categories. The most frequent adverse events were nasopharyngitis (8.6% bempedoic acid, 10.0% placebo), myalgia (5.2% and 5.3%), urinary tract infection (4.8% and 5.2%, respectively), and arthralgia (4.1% and 5.2%). Approximately similar types of Aes in the ongoing open-label study were reported as most frequently observed Aes including nasopharyngitis (4.7%), urinary tract infection (3.6%), arthralgia (2.8%), dizziness (2.7%), and upper respiratory tract infection (2.3%).

The frequency of **serious Aes** was slightly higher for bempedoic acid (16.0% vs 15.2%). The higher incidence was likely mainly due to cardiac disorders and most likely as a result of the high cardiovascular risk characteristics of these patients. The numbers for each specific individual cardiac serious Aes was limited (30 or less) and without substantial differences (<0.5% and without meaningful absolute differences in numbers) or any notable pattern. Therefore, these data do not allow for any meaningful conclusions.

Cardiovascular events and deaths are of major interest, as a harmful effect should at least be excluded prior to marketing authorisation for a new pharmacological product according to the *EMA Guideline on clinical investigation of medicinal products in the treatment of lipid disorders (EMA/CHMP/748108/2013)* and the *EMA Reflection paper (RP) on assessment of cardiovascular risk of medicinal products for the treatment of cardiovascular and metabolic diseases (EMA/CHMP/50549/2015)*. A lower frequency of independent committee adjudicated MACE events were reported for bempedoic versus placebo (120 (5.0%) vs 68 (5.7%)), primarily attributed to a lower incidence of nonfatal MI (26 (1.1%) vs 22 (1.8%)) (and coronary revascularization (66 (2.7%) vs 40 (3.3%)). Although not formally powered, this resulted in a numerical beneficial effect on the 3 component MACE (CV death, MI, stroke) in the studies on maximum statin background therapy (HR 0.80 (95%CI 0.491, 1.292) and overall phase 3 studies (HR 0.85 (95%CI 0.529, 1.373; additional 9 events from the statin intolerant pool included) as well as other MACE definitions (except for those including hospitalisation for heart failure (HR 1.03 and 1.01 for 4 MACE + HF and 5 MACE + HF). An adequate number of patients was studied to obtain a lower than the 1.8 upper limit of the confidence interval mentioned in the above-mentioned RP to reasonably exclude any possible off target risk of cardiovascular safety.

Although the frequency for treatment-emergent **fatal adverse events** was higher for bempedoic acid (n=19; 0.8%) than for placebo (n= 4; 0.3%), the number was very limited with 23 among 3621 patients, making any conclusions on this imbalance uncertain. Further, this is likely an outlier result as this fatality rate was substantially higher than observed in the ongoing single arm open-label study (0.9 per 100 person-years based on a mean exposure of 306 days in 1487 bempedoic acid patients and 0.3 per 100 person-years in 742 placebo patients based on a mean exposure of 319 days, versus 0.5 patients per 100 person-years with a mean exposure to bempedoic acid of 456.2 days during the open-label study). Furthermore, the imbalance was largely explained by the imbalance in CV events (10 (0.5%) vs 3 (0.3%) adjudicated) and likely due to the high CV risk profile of these patients. Of

note, a lower frequency was observed for bempedoic acid vs placebo in study 047 (3 (0.6%) vs 2 (0.8%)), although numbers were limited. Further, although an imbalance in the fatal Aes of the SOC of Neoplasm benign, malignant and unspecified (including cysts and polyps) of 5 (0.2%) vs 0 was observed, events were very rare and thus any conclusion on this issue remains uncertain. Moreover, these are unlikely to be associated with bempedoic acid as 3 out of 5 events occurred within 90 days after start of the study. Also, in the ongoing open-label study, any consistent pattern for the 9 fatal events with association to study drug could not be observed, which is reassuring. As already mentioned, specific attention has been given to reporting on known adverse events from treatment with statins AEs due to non-clinical findings and findings observed in phase 1 and 2 studies.

There is no sign that treatment with bempedoic acid would increase **diabetes** risk. Worsening of hyperglycemia was reported to be 7.1% for bempedoic acid vs 8.9% for placebo with diabetes at baseline, and new-onset diabetes was reported to be 3.1% vs 4.7% in patients without diabetes at baseline. Further support for a likely absence of an effect on diabetes with bempedoic acid comes from data on the changes in HbA_{1c} and fasting glucose, which showed no risk of increase or shifts in these parameters for bempedoic acid in both study pools. Mean change was of HbA_{1c} was -013% vs 0.07%. No shifts from ≤ 5.5% to ≥ 6.5% were observed and shifts from 5.5%-6.4% to ≥ 6.5% were lower in bempedoic acid (7.2% vs 12.4%) and ≤ 5.5% to 5.5%-6.4% (2.0% vs 2.5%).

As with statins, laboratory **hepatic enzyme elevations** were observed with a higher frequency with bempedoic acid than placebo (2.5% vs 1.5%), with AST increased (1.3% vs 0.3%) and ALT increased (0.9% vs 0.2%). ALT and/or AST > 3 x ULN elevation occurring in 13 (0.6%) vs 3 (0.3%), while no cases of potential Hy's Law were observed. For treatment related hepatic disorders numbers were limited but higher for bempedoic acid (3 (0.1%) vs 1 (0.1%)) and with higher frequency for laboratory values (ALT increased (0.6% vs 0.1%) and AST increased (0.7% vs 0.1%)).

Muscular disorders are known to be dose dependently associated with statins. A higher frequency of muscular disorders is found for bempedoic acid vs placebo in the patients treated on top of statin therapy (13.2% vs 10.2%), while no increase was present in the statin intolerant study pool (see above). A bempedoic acid induced increase in exposure of statins by 1.2 to 2 in AUC for the different statins as observed in two small dedicated PK studies where a single dose statin dose was added to steady state bempedoic acid, could be the main driver of this observation. Due to this increased exposure, an amendment in both studies was implemented **limiting the dose of (only) simvastatin to less than 40 mg**. Those patients who were already on 40 mg (n=98) were discontinued treatment. Currently, a dose recommendation and warning statement in the SmPC has been proposed to limit the simvastatin dose to 20 mg in general, and 40 mg in more high CV risk patients. The low intensity statin category showed the highest frequency and highest difference versus placebo in muscular disorders (37.6% vs 23.7%; 24.7% vs 24.0%; 24.3 vs 22.5% - low, moderate, high). This may be likely explained by possibly relative statin intolerability in these patients with patients likely to be more sensitive to muscle disorders upon increased statin exposure induced by concomitant bempedoic acid use (confounding by indication). Further, a consistent slight increase in any muscle adverse events is observed for atorvastatin (13.3% vs 9.8%, rosuvastatin 12.4% vs 8.0%), simvastatin (12.2% vs 7.4%), and pravastatin (17.5% vs 15.4%), while a lower rate in the bempedoic acid group was observed for the other statins (n=75). An increase in muscle related events was observed in the limited subgroup patients on 40 mg simvastatin (muscle disorders 11.0% (n=9) vs 2.8% (n=1); musculoskeletal disorders (22.0% (n=18) vs 5.9% (n=2)). Three cases of **myositis** (0.1%) were reported all with statin background therapy, one resolved after discontinuation of study medication, while the other 2 non-serious cases in 2 patients continued treatment. Consistent increased levels and shifts in CK levels for bempedoic acid were also found. AEs of increased CK levels were higher (1.9% vs 1.3%). Although levels of > 5x ULN or > 10 x ULN were rarely observed, a higher frequency for bempedoic acid was found compared to placebo (4 (0.2%) and 1 (0.1%)), supporting the increased

incidence of muscular disorders. Further, a higher incidence was observed in treatment related AEs in Musculoskeletal and connective tissue disorders (7.8% vs 6.9%), although with a less clear pattern for the individual related AEs of muscle spasm (2.2% vs 1.3%), pain in extremity (0.7% vs 0.4%), myalgia (3.1% vs 3.7%), arthralgia (0.6% vs 1.1%) and blood CK increased (0.7% vs 0.9%). Based on these data it is proposed to limit the dose of simvastatin (including a contra-indication for >40 mg simvastatin) and include a warning statement for other statins when muscle related events occur. There was no increased frequency of neurocognitive disorders with the treatment of bempedoic acid versus placebo (14 (0.7%) vs 8 (0.8%)), although this has not been specifically investigated.

In contrast to non-clinical findings, no increased frequency of **hypoglycaemia** with treatment of bempedoic acid was observed in the clinical studies (2.0% vs 2.5%). Also, only one patient in each randomised group had impaired fasting glucose.

Similar to phase 1 and 2 study findings, a reversible **increase in blood creatinine** observed in the phase 1 and 2 program can also be observed in the phase 3 studies with difference in (mean) change in baseline to week 12 in creatinine of 0.048 vs -0.002, and blood creatinine increased (16 (0.8%) vs 4 (0.4%)), GFR decreased (12 (0.6%) vs 1 (0.1%)), and blood urea increased (3 (0.1%) vs 1 (0.1%)). Also, the proposed mechanism of interference with the renal OAT2 pathway appears not well justified (see PK). Further, more patients treated with bempedoic acid (23 patients (1.1%)) vs 6 patients (0.6%) dropped below the eGFR of < 30 ml/min/1.73m^2 level. Further, an increase in **renal disorders** was observed for bempedoic acid treatment (2.9% vs 1.3%). This was consistently observed across all different AEs reported including renal failure (16 (0.8%) vs 1 (0.1%)), renal impairment (11 (0.5%) vs 4 (0.4%), and acute kidney injury (6 (0.3%) vs 3 (0.3%)). Treatment related renal disorders and urinary disorders were also systematically reported at a higher frequency for bempedoic acid than placebo (1.5% vs 0.9%) also on an individual AE level (GFR decrease 0.2% vs 0, renal failure 0.3% vs 0.1%, but not renal impairment (0.3% vs 0.3%)), although numbers were limited. These findings were explained by the creatinine increase effect. For the other events other comorbidities may have been involved.

As in the phase 1 and 2 studies an increased frequency of uric acid (1.6% vs 0.4%), hyperuricemia (1.8% vs 0.7%) and gout (1.4% vs 0.4%) were observed. Treatment related hyperuricemia (0.3% vs 0), blood uric acid increased (0.9% vs 0.1%) and gout (0.2% vs 0) were also systematically higher for bempedoic acid treatment though based on limited numbers.

In the phase 1 and 2 studies a **decrease in haemoglobin** was observed. During the phase 3 studies, especially an increased frequency of anaemia was observed with bempedoic acid treatment (2.8% vs 1.9%), while decreased haemoglobin (8 (0.4%) vs 3 (0.3%)) or decreased haematocrit (1 vs 0) was rarely observed. The level of decrease of haemoglobin was however limited, as this was particularly observed for ≥ 2g/dL and < LLN decrease (5.1% vs 2.3%), while higher decreased were more rare (1.4% vs 1.3 % for ≥ 3g/dL and < LLN, and 3 (0.1%) vs 2 (0.2%) for ≥ 5g/dL and < LLN).

Bempedoic acid was relatively well tolerated with 10.9% vs 7.5% who discontinued treatment due to an AE. The highest frequency of discontinuations due to AEs was in the SOC of musculoskeletal and connective tissue disorders (75 (2.8%) vs 19 (1.9%))). Also, gastrointestinal problems (1.5% vs 0.7%) and cardiac disorders (1.2% vs 0.8%) were reported with one of the highest frequencies. Discontinuation due to specific AEs of muscle spasms, diarrhoea, nausea, and pain in extremity were more frequent for bempedoic acid. For the open-label phase discontinuations due to AEs were 4.1% and occurred less than in the controlled studies. This may indicate better tolerability during longer term.

Treatment related AEs were more reported for bempedoic acid than for placebo (24.5% vs 21.5%). For several of the AEs of specific interest frequencies were low and comparable between treatment groups including hypoglycaemia, blood glucose increase and diabetes mellitus, hyperglycemia, haemoglobin

decreased. While for others including muscular disorders, hepatic disorders and enzyme elevations, renal disorders, and uric acid elevations treatment related AEs were systematically increased in line with the increased reporting of TEAEs for bempedoic acid. Musculoskeletal disorders and gastrointestinal disorders were treatment related adverse event reported at a relatively high frequency and were higher for bempedoic acid (7.8% vs 6.9% (on top of statins) and 4.7% vs 3.8% (overall study pool)).

Incidence of adverse events according to age has been provided for the 18-65, 65 to 75 and over 75 years of age categories. Adverse events were slightly higher with increasing age category. Data on patients over 85 years of age were very limited. The frequency of AEs was slightly higher in women in the studies with statin background therapy, which could be related to the higher exposure.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Additional expert consultations

N/A

Assessment of paediatric data on clinical safety

N/A

2.6.2. Conclusions on the clinical safety

As it has been evaluated in a relatively limited **database of statin intolerant patients**, bempedoic acid was well tolerated although some specific side effects occurred including an increase in uric acid with a risk of gout, increase in serum creatinine and decrease in haemoglobin with a risk of anaemia. Also, some side effects known from statin use were seen also with bempedoic acid including an increase in liver enzymes and renal disorders.

The safety profile was also characterised in the much larger **database of patients treated on top of maximum tolerated statin** therapy. An increased incidence of muscle disorders was seen when used on top of statins. This was likely driven by the increase in exposure of statin that was induced by bempedoic acid as identified in two dedicated PK studies. With the available numbers, CV harm can currently be excluded in accordance with the requirements detailed in the *Reflection paper on assessment of cardiovascular safety profile of medicinal products [EMA/CHMP/50549/2015]*. The imbalance found in the very limited number of MACE events in the statin intolerant pool is likely a chance finding in association with the high baseline risk of the patients. The slight imbalance in fatal events is likely to be an outlier result not supported by any clear pattern in reasons for fatality.

Overall, the clinical database is sufficient to characterise the safety profile of bempedoic acid although long term data is still limited and will be provided post-authorisation.

The ongoing long term CVOT study (Study 1002-043) in 12600 statin intolerant patients treated for 3.5 years should provide further data regarding impact of bempedoic acid on cardiovascular morbidity and mortality.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns

Important identified risks	Not applicable
Important potential risks	Myopathy with concomitant use of statins Gout Drug interactions with substances of OAT2
Missing information	Use in patients with severe renal impairment and in patients with ESRD receiving dialysis

Pharmacovigilance plan

Summary 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				
Long-term extension study (Study 1002-050) Ongoing	To characterize the safety, tolerability, and efficacy of long-term administration of bempedoic acid 180 mg	Myopathy with concomitant use of statins, gout	Final CSR	Q3 2020
Study of FDC in T2DM (Study1002FDC-058) Ongoing	To evaluate the efficacy and safety of FDC versus ezetimibe (lipid lowering, hsCRP lowering) and placebo in patients	Gout	Final CSR	Q1 2020

	with T2DM after 12 weeks of treatment			
In vitro inhibition of rat and monkey OAT2 by bempedoic acid in MDCK-II cells Planned	Assess rat and monkey Oat2 for inhibition by bempedoic acid *in vitro* using a polarized MDCK-II cell model with clinical drugs that are human OAT2 substrates to assess the potential utility of these substrates in animal models to characterize OAT2- mediated drug-drug interactions.	Drug interactions with substrates of OAT2	Protocol final: Study completion: Final report:	Q1 2020 Q2 2020 Q3 2020
In vitro inhibition of select human OAT2 substrates by bempedoic acid in MDCK-II cells Planned	Screen a limited number of clinically relevant substrates at bempedoic acid concentrations equivalent to human Cmax *in vitro* using an OAT2 polarized MDCK-II cell model. Further characterize bempedoic acid OAT2-mediated inhibition for drugs showing *in vitro* inhibition consistent with clinically relevant bempedoic acid concentrations.	Drug interactions with substrates of OAT2	Protocol final: Study completion: Final report:	Q2 2020 Q3 2020 Q4 2020
In vitro inhibition of human OAT2 substrates in cryopreserved	Evaluate effect of bempedoic acid on the intrinsic clearance of two	Drug interactions with substrates of OAT2	Protocol final: Study completion:	Q2 2020 Q3 2020 Q4 2020

human hepatocytes Planned	OAT2 substrates whose primary clearance mechanism is hepatic in sandwich hepatocyte culture. The identified substrates are warfarin (R- and S-enantiomers) and naproxen.		Final report:	
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.	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:	Q3 2020 Q3 2021 Q1 2022

Risk minimisation measures

Summary of Risk minimisation measures

Safety Concern	**Risk Minimisation Measure**
Identified Risks	
Not applicable	
Potential Risks	
Myopathy with concomitant use of statins	Routine risk minimization measures: SmPC Section 4.2 (simvastatin only), Section 4.3 (simvastatin only), Section 4.4, Section 4.5 PIL Section 2 Additional risk minimization measures: None
Gout	Routine risk minimization measures: SmPC Sections 4.4 and 4.8

	PIL Section 2 and 4 Additional risk minimization measures: None
Drug interactions with substrates of OAT2	Routine risk minimization measures: SmPC Section 4.5 Additional risk minimization measures: None
Missing information	
Use in patients with severe renal impairment and patients with ESRD receiving dialysis	Routine risk minimization measures: SmPC Sections 4.4 and 5.2 PIL Section 2 Additional risk minimization measures: None

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.5 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The CHMP, based on the available data, considers bempedoic acid to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Nustendi (bempedoic acid/ezetimibe). The bridging report submitted by the applicant has been found acceptable.

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Nilemdo (bempedoic acid) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Primary hypercholesterolemia is any hypercholesterolemia which is caused by a disorder (either familial- or nonfamilial) in lipid metabolism and is not caused by another condition, such as hypothyroidism, or a drug effect. The heterozygous familial form of this condition (HeFH) is more rare and is estimated to occur between 1:200 and 1:500 individuals globally. LDL-C levels in affected individuals are elevated, and in spite of aggressive statin use, there is still a 2-fold excess of CHD-related deaths relative to age-matched controls within this population.

Hyperlipidemia is the heterogeneous group of disorders characterized by an excess of lipids (ie, cholesterol, phospholipids, triglycerides) in the bloodstream. Hypercholesterolemia specifically refers to the presence of high levels of cholesterol in the blood. **Primary hyperlipidemia** is usually due to genetic causes (monogenetic or polygenetic) and environmental factors, such as diet and lifestyle. Primary nonfamilial hyperlipidemia is hyperlipidemia that is not due to a specific genetic disorder, although there are polygenetic influences. Mixed dyslipidemia is generally defined as elevated LDL-C and high triglycerides and/or low HDL-C.

A large body of epidemiological evidence exists demonstrating a strong positive correlation and causal relationship between LDL-C levels and risk of coronary heart disease (CHD). Other clinical manifestations of atherosclerosis also appear linked to LDL-C levels such as cerebrovascular disease (i.e. stroke) or peripheral vascular disease. In addition, clinical trials have shown that LDL-C lowering therapy especially with statins reduces the risk for CHD. The relationship between LDL-C levels and CHD risk holds over a broad range of LDL levels. Epidemiologic data indicate a continuous increasing relative risk from very low to "normal" and high levels of LDL-C, but with higher absolute risk in patients at the higher end of LDL-C levels.

Bempedoic acid is an oral small molecule that is activated in the liver to ETC-1002-Coenzyme A (ETC-1002-CoA), which subsequently inhibits adenosine triphosphate citrate lyase (ACL), an enzyme upstream of 3-hydroxyl-3-methylglutaryl Coenzyme A (HMG-CoA) reductase in the cholesterol synthesis pathway. Inhibition of cholesterol synthesis triggers the upregulation of low-density lipoprotein (LDL) receptor (LDLR) expression in the liver resulting in increased clearance of LDL particles and lowering of LDL-C in the blood. Additionally, inhibition of ACL by ETC-1002-CoA results in concomitant suppression of hepatic fatty acid biosynthesis.

The following indication was agreed which includes the use on top of maximum tolerated statins, and the use in patients who are statin intolerant:

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

- *in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL C goals with the maximum tolerated dose of a statin (see sections 4.2, 4.3, and 4.4) or,*
- *alone or in combination with other lipid-lowering therapies in patients who are statin intolerant, or for whom a statin is contraindicated.*

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3.1.2. Available therapies and unmet medical need

Statins are the cornerstone therapy for patients with primary hypercholesterolaemia (heterozygous familial and nonfamilial) or mixed dyslipidaemia, as an adjunct to diet to reduce low-density lipoprotein cholesterol (LDL-C). Statins have robustly demonstrated CV benefits in patients at increased CV risk. Clinical guidelines strongly recommend the use of statins in patients with elevated LDL-C levels. If baseline levels are between 1.8 mmol/L and 3.5 mmol/L (70 mg/dL and 135 mg/dL) than treatment aims are to reduce LDL-C levels below 1.8 mmol/L (70 mg/dL) or at least reduce LDL-C by 50%. In patients at very high risk of CV events, 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 or have limitations in statin tolerability and are not reaching LDL-C goals. It is well known that patients may experience statin-associated adverse effects (e.g. muscular adverse effects) 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 and **PCSK9 inhibitors** could provide additional LDL-C lowering and are indicated in adults with primary hypercholesterolaemia (heterozygous familial and nonfamilial) or mixed dyslipidaemia, as an adjunct to diet to reduce low-density lipoprotein cholesterol (LDL-C), in combination with a statin or statin with other lipid lowering therapies when additional LDL-C lowering is needed (according to learned society guidelines as mentioned). 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 maximally tolerated statin dose or in patients intolerant to statins or with contraindications to statins. These recommendations are based on the demonstrated CV benefit of ezetimibe in the IMPROVE-IT trial, even if the absolute CV benefit from adding ezetimibe was limited in line with its modest effect. Further, PCSK9 inhibitors lower LDL-C levels very effectively and have also demonstrated CV in clinical trials in patients with established cardiovascular disease. PCSK9 inhibitors are, however, not widely used (<5% of lipid lowering treatment) which may be (partly) due to these products being relatively new and primarily pricing and reimbursement issues. Further, PCSK9 inhibitors 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 patient's preferences.

Although **fibrates, omega-3 fatty acids,** and **bile acid sequestrants** may provide a 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 as an add-on 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 treat hyperlipidemia for patients requiring additional LDL C lowering.

3.1.3. Main clinical studies

Statin intolerance

The Phase 3 program included 2 randomized, double-blind, placebo-controlled, parallel-group studies in patients with hyperlipidemia who are at risk of CV disease and were SI (used no or low dose of statins):

- Study 1002 046 (n=345): a 24 weeks randomized, double-blind, parallel group, multicenter study to evaluate the efficacy and safety of bempedoic acid (etc-1002) 180 mg compared to placebo added to background lipid-modifying therapy in patients with elevated LDL C who are SI;

- Study 1002 048 (n= 269): a 12 weeks randomized, double-blind, placebo-controlled, parallel group, multicenter study to evaluate the efficacy and safety of bempedoic acid (etc-1002) as an add-on to ezetimibe therapy in patients with elevated LDL C on low-dose or less than low-dose statins.

On top of statins

The Phase 3 program included 2 randomized, double-blind, placebo-controlled, parallel-group studies in patients with hyperlipidemia who are at risk of CV disease on top of maximum tolerated statin therapy:

- Study 1002 047 (n= 779): a 52 weeks, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy of bempedoic acid (etc-1002) in patients with hyperlipidemia at high cardiovascular risk not adequately controlled by their lipid-modifying therapy.

- Study 1002 040 (n= 2230): a 52 weeks randomized, double-blind, placebo-controlled, multicentered long-term safety and tolerability study of etc-1002 in patients with hyperlipidemia at high cardiovascular risk who are not adequately controlled by their lipid-modifying therapy.

- One Phase 3 OLE study (Study 1002 050) assessing 1-year safety and efficacy is ongoing. This document includes interim data for 1462 enrolled patients from study 1002-040 based on a last patient visit of 28 September 2018.

3.2. Favourable effects

Statin intolerance

Bempedoic acid at a dose of 180 mg/day demonstrated a significant placebo-corrected reduction at 12 weeks in LDL-C from baseline of approximately **-21% to -28% in patients using no statin or very low to low doses of statins,** and/or using other lipid lowering therapy. The patients in these trials had baseline LDL-C levels between 3.2 – 4.1 mmol/L. Efficacy was supported by significant and beneficial changes in other relevant parameters of the cholesterol profile, i.e. non-HDL (-17% to -24%), TC (-15%) and ApoB (-15% to -19%).

The LDL-C effect of bempedoic acid was consistent across several subgroups, i.e. age, race, gender, ethnicity, region, history of diabetes, baseline BMI, baseline LDL-C, ezetimibe use, and baseline GFR category.

On top of statins

Bempedoic acid at a dose of 180 mg/day demonstrated a modest placebo-corrected reduction at 12 weeks in LDL-C from baseline of **-17% to -18% on top of a maximum tolerated statin background therapy** (2010 patients on bempedoic acid and 999 patients on placebo, respectively). The patients in these trials had baseline LDL-C levels between 2.6-3.2 mmol/L. Patients were at high to very high CV risk based on their established cardiovascular disease or equivalent CV risk estimation, or presence of HeFH and eligible for (additional) lipid lowering therapy according to learned societies guidelines criteria (ESC, AHA). Efficacy was supported by significant and beneficial changes in other relevant parameters of the cholesterol profile, i.e. non-HDL (-13%), TC (-11%) and ApoB (-12% to -13%).

The LDL-C effect of bempedoic acid was **consistent across several subgroups**, i.e. age, race, ethnicity, region, history of diabetes, baseline LDL-C, HeFH status, prior ASCVD, ezetimibe use, baseline GFR category.

A sustained effect of LDL-C reduction has been demonstrated up to 52 weeks in the 2 placebo controlled studies on top of statin therapy, although **the effect slightly diminished over time** in the ongoing open label long term study including patients from the largest controlled study 040 on top of statin therapy. The LDL-C lowering treatment effect resulted in significantly more patients reaching the LDL-C < 1.8 mmol/L goal (28.9% vs 8.0% at week 12 and 26.2% vs 9.1% at week 52 on top of statins).

3.3. Uncertainties and limitations about favourable effects

Statin intolerance

Bempedoic acid has demonstrated to reduce LDL-C level, an established surrogate marker for CV disease, but **its impact on clinical outcomes has not been formally tested yet**. MACE events were very rarely observed. Although this was higher for bempedoic acid (9 vs 0; mainly attributed to coronary revascularisation), all patients had a history of ASCVD and thus such events may not be unexpected and likely to be imbalanced due to chance finding. This does not likely meet the requirement of the upper limit of the CI to be below 1.8 which could exclude any sign of CV harm (*Reflection paper on assessment of cardiovascular safety profile of medicinal products [EMA/CHMP/50549/2015]*). However, this requirement was met for the overall phase 3 program.

Maintenance of LDL-C lowering effect has not been fully demonstrated. The phase 3 studies were only 12 weeks and 24 weeks. Moreover, only patients from the studies on top of statins have been enrolled in the ongoing long-term open label study.

Differences in efficacy were noted in some subgroup analyses including ethnicity, and (low dose) statin. The use of background low statin dose showed smaller reductions in LDL-C than patients not using any statin (p for interaction 0.032). Furthermore, subgroup analyses were presented across the following age categories of < 65 years, 65 to 75 and ≥ 75 with no substantial differences in effects observed. Data in patients over 85 years of age were very limited.

Relevant subgroups of patients with HeFH (0-1.7%), and patients with severe renal impairment (0-0.6%) were underrepresented.

On top of statins

Bempedoic acid has demonstrated to reduce LDL-C level, an established surrogate marker for CV disease, but its impact on clinical outcomes has not been formally tested yet. Reassuringly, a numerical beneficial effect on the 3 component MACE (CV death, MI and stroke) in the statin background studies (HR 0.80 (95%CI 0.491, 1.292) and overall phase 3 studies (HR 0.85 (95%CI 0.529, 1.373) was observed. The upper limit of the CI was well below 1.8 and this excludes any sign of CV harm (*Reflection paper on assessment of cardiovascular safety profile of medicinal products [EMA/CHMP/50549/2015])*.

A bempedoic acid-induced **increase in exposure of AUC (and Cmax) of statins** was demonstrated. Administration of a single dose of simvastatin 40 mg with steady-state bempedoic acid 180 mg resulted in a 2-fold increase in simvastatin acid exposure. Elevations of 1.4-fold for rosuvastatin, 1.5-fold for atorvastatin, and 1.5-fold for pravastatin (administered as single doses) and/or their major metabolites were observed when coadministered with bempedoic acid 180 mg. (study 1002-073) Higher elevations have been observed when these statins were coadministered with a supratherapeutic 240mg dose of bempedoic acid (study 1002-012). Bempedoic acid exposure was increased in patients with renal impairment. The impact of the pharmacokinetic interaction with statins may be higher in

these patients. Patients who were on maximum tolerated statin therapy were not down-titrated prior to randomisation in the phase 3 studies. The impact of this increased exposure of statins (caused by coadministration of BA) and the impact on the increased LDL-C lowering was not exactly clear as this has not been clinically tested, although subgroup analyses and additional modelling of the clinical data suggest that the relative contribution of bempedoic acid to the overall LDL lowering effect is highest with lower statin doses. Data on the addition of statin therapy after 24 weeks of therapy, as allowed by protocol (7.0% bempedoic acid vs 8.0% placebo), may have likely provided some support to substantiate the additional effect of statin in combination with bempedoic acid, however, data on this have not been provided and are likely very limited.

Differences in efficacy were noted in some subgroup analyses. **Females had larger reductions in LDL-C** than males in the studies **on top of statins**. Differences in exposure between males and females may have contributed to these different treatment effects. For BMI a slightly different effect was observed, but these differences are clinically manageable. Furthermore, subgroup analyses were presented across the following age categories of < 65 years, 65 to 75 and ≥ 75 with no substantial differences in effects observed. Data in patients over 85 years of age are very limited.

The treatment effect is smaller, as observed also in the phase 2 studies, in patients treated with higher intensity statin therapy compared to low/moderate or no statin use at baseline (p for interaction 0.060). Equally, for patients using any statin in the SI studies, even low dose showed smaller reductions in LDL-C than patients not using any statin (p for interaction 0.032). No obvious differences in effect were observed between the individual different statins in those studies where patients received bempedoic acid on top of statin therapy, but the specific doses used have not been mentioned.

Relevant subgroups of patients with HeFH (4.7-6.2%), Asians (0-1.1%), and patients with severe renal impairment (0-0.4%) were underrepresented.

3.4. Unfavourable effects

Statin intolerance

The exposure to assess clinical safety is **limited in patients who are SI**. A total of 415 SI patients were treated with bempedoic acid with 332 treated for 12 weeks or more.

While the total percentage of patients with adverse events was approximately similar between bempedoic acid and placebo groups (57.3% vs 51.5%, respectively) a consistent and slightly higher frequency of serious adverse events was observed for bempedoic acid (4.6% vs 3.5%), treatment related adverse events (21.7% vs 14.1%), and severe adverse events (4.6% vs 3.5%), while moderate and mild AEs were approximately similar.

Bempedoic acid was reasonably **well tolerated** as relatively few patients discontinued treatment due to adverse events, although more patients on bempedoic acid discontinued than in the control group (13.0% vs 9.1%), with only a clear difference in gastrointestinal problems (1.7% vs 0.5%) and cardiac disorders (1.0% vs 0) based on limited numbers.

As with statins, **laboratory hepatic enzyme elevations** were observed with a higher frequency with bempedoic acid than placebo (3.9% vs 0%), with AST increased (1.0% vs 0%) and ALT increased 1.0% vs 0%. ALT and/or AST > 3 x ULN elevation occurring in 5 (1.2%) vs 0, while no cases of potential Hy's Law were observed.

In the phase 3 studies in SI patients, no deaths were reported.

On top of statins

An adequate number of patients has been evaluated for safety according to ICH guideline on the extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life-threatening conditions (ICH E1). A total of 3008 patients were treated with bempedoic acid or placebo on a background of maximum tolerated statin therapy. Among those who received bempedoic acid, 1681 patients were treated for at least 24 weeks, and 416 patients were treated for more than 2 years.

While the total percentage of patients with adverse events was approximately similar between bempedoic acid and placebo groups (76.3% vs 76.7%, respectively) a consistent and slightly higher frequency of serious adverse events was observed (16.0% vs 15.2%, respectively) in patients using statins. Treatment related adverse events (24.5% vs 21.5%), and severe adverse events (13.2% vs 10.7%) were also all slightly higher in bempedoic acid- than in placebo-treated patients, respectively, while moderate and mild AEs were approximately similar.

Bempedoic acid was reasonably well-tolerated as relatively few patients discontinued treatment due to adverse events, although more patients on bempedoic acid discontinued than in the control group (10.9% vs 7.5%). This was mainly due to muscular disorders (2.8 vs 1.9%), gastrointestinal problems (1.6% vs 0.7%), and cardiac disorders (1.2% vs 0.8%). An incidence of discontinuations due to AEs of 4.1% during the first and 2 years of treatment were reported.

The number of **muscular disorders**, a known dose dependent adverse effect of statin treatment, was increased when bempedoic acid was used on top of statins (13.2% vs 10.2% all AEs; 7.8% vs 6.9% treatment related). Increases in confirmed CK levels > 5 x ULN were 7 (0.3%) vs 2 (0.2%) and > 10 x ULN were 4 (0.2%) vs 1 (0.1%), supporting the muscular disorders adverse event profile. The low intensity statin category (n= 184) showed the highest frequency and highest difference versus placebo in musculoskeletal disorders compared to moderate (n=1214) and high intensity (n=1526) statins (37.6% vs 23.7%; 24.7% vs 24.0%; 24.3 vs 22.5%). Consistent slightly increased muscle related adverse events were observed for coadministration of atorvastatin (13.3% vs 9.8%, rosuvastatin 12.4% vs 8.0%), simvastatin (12.2% vs 7.4%), and pravastatin (17.5% vs 15.4%), while a lower rate in the bempedoic acid group was observed for the other statins (n=75). Also, in the limited subgroup of simvastatin 40 mg an increased incidence of muscle related adverse events was observed (muscle disorders 11.0% (n=9) vs 2.9% (n=1); musculoskeletal disorders (22.0% (n=18) vs 5.9% (n=2)).

As with statins, laboratory **hepatic enzyme elevations** were observed with a higher frequency with bempedoic acid than placebo (2.5% vs 1.5%), with AST increased (1.3% vs 0.3%) and ALT increased 0.9% vs 0.2%. ALT and/or AST > 3 x ULN elevation occurring in 13 (0.6%) vs 3 (0.3%), while no cases of potential Hy's Law were observed.

3.5. Uncertainties and limitations about unfavourable effects

Statin intolerance

The **long-term exposure** is very limited as both phase 3 studies were no longer than 12 and 24 weeks.

The number of adjudicated **cardiovascular events** within the phase 3 SI patient studies are very limited but higher for bempedoic acid than for placebo with 9 vs 0. This was mainly attributed to coronary revascularisation. All patients had a history of ASCVD and thus such events may not be unexpected and likely to be imbalanced due to chance finding. No specific MACE analysis has been

provided for the SI pool, although the 3 component MACE in the overall phase 3 program was 0.85 (95% CI 0.53, 1.37).

No relevant effect on the **incidence of new onset of diabetes or HbA1C**, suggested to be associated with statin therapy, was found for bempedoic acid. Worsening of hyperglycemia was reported to be 5.1% for bempedoic acid vs 9.3% for placebo in patients with diabetes at baseline, and new-onset diabetes was reported to be 1.9% vs 2.6% in patients without diabetes at baseline. Mean change for HbA1c was -0.03% vs 0.20%. This was based on limited data.

A reversible **increase in creatinine** is observed mainly during the first 4 weeks of treatment with bempedoic acid (mean change in baseline to week 12 in creatinine of 0.039 vs 0.003, and blood creatinine increased (3 (0.7%) vs 0), GFR decreased (4 (1.0%) vs 0). Based on *in vitro* tests it is suggested that bempedoic acid interferes with the renal pathway (OAT2 excretion pathway) and that the effect is reversible; however, clinical interaction data to support this are lacking. Further, an increase in **renal disorders** was observed for bempedoic acid treatment (2.4% vs 1.0%), although data were limited. Renal failure was 4 (1.0%) vs 1 (0.5%)) and renal impairment 2 (0.5%) vs 0.

There was a reversible **increase frequency of uric acid** (4.3% vs 1.0%), hyperuricemia (0.7% vs 0%) and gout (1.0% vs 0.5%) although data are limited. It is suggested that bempedoic acid interferes with the renal pathway (OAT2 excretion pathway), however, data on reversibility and support for this proposed mechanism have not been clearly presented.

Adverse events of **anaemia** were observed with bempedoic acid treatment (3 vs 0), decreased haemoglobin (1 vs 0) and decreased haematocrit (1 vs 0) although rarely observed.

No effect on **neurocognitive adverse events** was found (2 (0.5%) vs 1 (0.5%)), although this was not specifically investigated, and numbers of spontaneous reported neurocognitive AEs are few.

The adverse events profile according to **subgroups** of all relevant age categories and according to renal status have not been presented.

<u>On top of statins</u>

A bempedoic induced **increase in exposure of AUC (and Cmax) of statins** of 1.4-1.7 for rosuvastatin, 1.5 for atorvastatin, 1.5-2.0 for pravastatin and 1.9-2.0 for simvastatin acid is observed after single dose administration of the statin on top of steady state bempedoic acid as evaluated in two specific PK studies (study 1002-012 low-mid dose statin, 240 mg bempedoic acid; study 1002-037 high dose statin, 180 mg bempedoic acid). This could likely be the main driver of the observed increased incidence of muscular disorders as observed for the most often used statins (atorvastatin, rosuvastatin and simvastatin) during the studies.

The **long-term exposure** is still limited to 416 patients treated for 2 years, while 1558 patients have been treated for more than 48 weeks with bempedoic acid.

The number of adjudicated **cardiovascular events** within the phase 3 program are still limited with 188 in 3621 patients, although the event frequency was slightly lower in the bempedoic acid versus control groups, with 111 (5.5%) vs 68 (6.8%) in the studies on top of statins and 120 (5.0%) vs 68 (5.7%) in the overall phase 3 studies. This analysis is primarily driven by coronary revascularisations (66 (2.7%) vs 40 (3.3%) in the overall Phase 3). Although the studies were not powered for analysis of adjudicated MACE events, a relative risk analysis excludes evidence of cardiovascular harm for bempedoic acid with an observed hazard ratio (95% CIs) on the 3 component MACE in the statin background studies of 0.80 (0.49, 1.29) and overall phase 3 program of 0.85 (0.53, 1.37). Analyses in SI patients separately have not been provided. Any signs of harm were also not noticed for any analyses on other MACE definitions.

In the phase 3 studies, a limited number of **23 deaths** have been reported. Although the frequency was higher for bempedoic acid (n=19; 0.8%) than for placebo (n= 4; 0.3%), the number of events was very limited. This is likely an outlier result as this fatality rate in the controlled phase was substantially higher than in the ongoing single arm open-label study (0.9 per 100 person-years based on a mean exposure of 306 days in 1487 bempedoic acid patients and 0.3 per 100 person-years in 742 placebo patients based on a mean exposure of 319 days, versus 0.5 patients per 100 person-years with a mean exposure to bempedoic acid of 456.2 days during the open-label study). Furthermore, the imbalance is largely explained by the imbalance in CV events (10 (0.5%) vs 3 (0.3%) adjudicated) and likely due to the underlying high CV risk of the patients. This observation is not consistent across studies as a lower frequency was observed for bempedoic acid vs placebo in study 047 (3 (0.6%) vs 2 (0.8%)), which is reassuring.

Further, although an imbalance in **benign and malignant neoplasm** was observed (5 (0.2%) vs 0), the numbers are very limited making any conclusions on this issue uncertain. Further, any association with therapy is unlikely as 3 out of 5 events occurred within 90 days after start of the study. Also, in the ongoing open-label study, any consistent pattern for the 9 fatal events with association to study drug could not be observed, which is reassuring.

No relevant effect on the incidence of new onset of **diabetes** or **HbA1C**, suggested to be associated with statin therapy, was found for bempedoic acid. Worsening of hyperglycemia was reported to be 7.1% for bempedoic acid vs 8.9% for placebo with diabetes at baseline, and new-onset diabetes was reported to be 3.1% vs 4.7% in patients without diabetes at baseline. Mean change for HbA1c was -0.13% vs 0.07%.

A reversible **increase in creatinine** was observed mainly during the first 4 weeks of treatment with bempedoic acid. Mean change from baseline to week 12 in creatinine was 0.048 vs -0.002, and blood creatinine increased (16 (0.8%) vs 4 (0.4%)), GFR decreased (12 (0.6%) vs 1 (0.1%)). Some *in vitro* data suggested that bempedoic acid interferes with the renal pathway (OAT2 excretion pathway), however, these *in vitro* data are inconsistent and clinical data to support this proposed mechanism have not been clearly presented. The applicant has committed to further investigate the role of OAT2 in the renal excretion of creatinine and uric acid (PAM)Further, an increase in renal disorders was observed for bempedoic acid treatment (2.9% vs 1.3%). Renal failure was 16 (0.8%) vs 1 (0.1%)), renal impairment (11 (0.5%) vs 4 (0.4%), but acute kidney injury was 6 (0.3%) vs 3 (0.3%).

There was a reversible increased frequency of **uric acid** (1.6% vs 0.4%), hyperuricemia (1.8% vs 0.7%) and gout (1.4% vs 0.4%) and treatment related hyperuricemia (0.3% vs 0), and blood uric acid increased (0.9% vs 0.1%).

Adverse events of **anaemia** were observed with bempedoic acid treatment (2.8% vs 1.9%), while AEs of decreased haemoglobin (8 (0.4%) vs 3 (0.3%)) or decreased haematocrit (1 vs 0) were rarely observed.

No effect on **neurocognitive adverse events** was found (14 (0.7%) vs 8 (0.8%)), although this was not specifically investigated and numbers of spontaneous reported neurocognitive AEs are few.

The adverse events profile according to **subgroups** of all relevant age categories and according to renal status have not been presented.

The potential **interactions** of the major inactive metabolite ETC-1002-glucuronide is not exactly clear as its steady state concentrations are unknown and will be investigated post-authorisation.

Decreases in bleeding time (APTT and PT) were observed in rats at exposure levels equivalent to the human dose. Data in two short term phase 2 studies did not show such an effect. The effect is likely to be an artefact of alterations in blood cell to plasma ratios due to the anemia.

3.6. Effects Table

Table 59. : Effects table statin intolerant pool (studies 1002-046 (n=345) and 1002-048 (n=269), no or low dose statins).

Effect	Short Description	Unit	BA 180 mg	PLB	Uncertainties/ Strength of evidence	References
Favourable Effects						
LDL-C lowering	Change from baseline to week 12 (LS mean (SE)) [primary endpoint]	% (SE)	-22.6 (1.29)	-1.2 (1.42)	SoE -21.4% (95%CI -25.1%, -17.7%) p<.001 supported by secondary analysis for other lipid parameters including non-HDL-C, TC, and apoB p<0.001) Efficacy consistent across both studies	1002-046
			-23.5 (1.95)	5.0 (2.30)	SoE -28.5% (95%CI -34.4%, -22.5%) p<.001 supported by secondary analysis for other lipid parameters including non-HDL-C, TC, and apoB p<0.001) Efficacy consistent across both studies	1002-048
CV risk lowering	MACE (CV death, non-fatal MI, and nonfatal stroke)	(n)	9	0	CV events: 9 BA vs 0 PLB	1002-046 (046 (no CV events in 1002-048)
		% (n)	1.9 (n=45)	2.3 (n=27)	Hazard ratio: 0.85 95%CI: 0.529, 1.373 Not a prespecified efficacy endpoint	Overall phase 3 pool[2]
Unfavourable Effects						
Hepatic enzyme elevations		% (n)	3.9 (16)	0	No cases of potential Hy's law. ALT and/or AST > 3 x ULN BA 1.2 % vs PLB 0%	Statin intolerant pool[2]
Muscular disorders		% (n)	11.3 (47)	11.6 (23)		
Renal disorders		% (n)	2.4 (10)	1.0 (2)	Creatinine increased/GFR decreased evident by 4 weeks and stable during treatment, suggested to be reversible. Renal failure BA 1.0% vs PLB 0.5%	
Uric acid elevations/gout		%	5.8 (24)	1.5 (3)	Uric acid increase starting in first 4 weeks and stable during treatment, suggested to be reversible.	

Effect	Short Description	Unit	BA 180 mg	PLB	Uncertainties/ Strength of evidence	References
Anaemia		%	0.7 (3)	0	Change is evident in first 4 weeks and stable during treatment; It is suggested that the effect is reversible. Mechanism not understood.	

Abbreviations:
Notes: [2] Overall phase 3 pool includes Study 1002-047, Study 1002-040, Study 1002-046, and Study 1002-048. [3] No-or low-dose statin pool includes Study 1002-046 and Study 1002-048.

Table 60. Effects table bempedoic acid on top of statins (Studies 1002-047 (n=779) and 1002-040 (n=2230), high risk/long term pool).

Effect	Short Description	Unit	BA 180 mg	PLB	Uncertainties/ Strength of evidence	References
Favourable Effects						
LDL-C lowering	Change from baseline to week 12 (LS mean (SE)) [primary endpoint]	% (SE)	-15.1 (1.07)	2.4 (1.45)	SoE -17.4% (95%CI -21.0, -13.9%) p<.001 Supported by secondary analysis for other lipid parameters including non-HDL-C, TC, and apoB p<0.001)	1002-047
			-16.5 (0.52)	1.6 (0.86)	SoE -18.1% (95%CI -20.0, -16.1%) p<.001 Supported by secondary analysis for other lipid parameters including non-HDL-C, TC, and apoB p<0.001) Efficacy consistent across both studies	1002-040
CV risk lowering	MACE (CV death, non-fatal MI, and nonfatal stroke)	% (n)	2.1 (42)	2.7 (27)	Hazard ratio: 0.80 95%CI: 0.491, 1.292 Not a prespecified efficacy endpoint	High risk/long-term pool [1]
Unfavourable Effects						
Hepatic enzyme elevations		% (n)	2.5 (51)	1.5 (15)	No cases of potential Hy's law. ALT and/or AST > 3 x ULN BA 0.6% vs Pl 0.3%	High risk/long-term pool [1]
Muscular disorders		%(n)	13.2 (265)	10.2 (102)		
Musculoskeletal and connective tissue disorders						
Low intensity statin		% (n)	37.6 (47)	23.7 (14)		

Effect	Short Description	Unit	BA 180 mg	PLB	Uncertainties/ Strength of evidence	References
Moderate intensity statin		% (n)	24.7 (200)	24.0 (97)	Low intensity statin category showed the highest frequency of AEs.	
High intensity statin		% (n)	24.3 (248)	22.5 (114)		
Renal disorders		% (n)	2.9 (59)	1.3 (13)	Creatinine increase evident by 4 weeks and stable during treatment and is reversible. Renal failure BA 0.8% vs Pl 0.1%	
Uric acid elevations/gout		% (n)	4.8 (97)	1.5 (15)	Uric acid increase starting in first 4 weeks and stable during treatment and is reversible.	
Anaemia		% (n)	2.8 (57)	1.9 (19)	Change is evident in first 4 weeks and stable during treatment; effect is reversible. Mechanism not understood.	

3.6.1. Benefit-risk assessment and discussion

3.6.2. Importance of favourable and unfavourable effects

Statin intolerance

Bempedoic acid used in patients with hypercholesterolaemia, mixed dyslipidaemia and in patients with heterozygous familial hypercholesterolemia who were SI has demonstrated significant consistent reduction in LDL-C and other relevant lipid parameters like non-HDL, TC and ApoB. Furthermore, the effect was robust across several subgroups including age, race, gender, ethnicity, region, history of diabetes, baseline BMI, baseline LDL-C, ezetimibe use, and baseline GFR category. **Bempedoic acid displays an acceptable safety profile, with a relatively low number of patients discontinuing treatment and/or suffering a serious adverse event**. However, bempedoic acid has some specific adverse effects including reversible increases in uric acid and gout, and a sustained increase in serum creatinine. Further, a decrease in haemoglobin with increased anaemia is observed for which the long-term impact remains uncertain. Also, bempedoic acid demonstrates some of the side effects known to be associated with lipid lowering therapy including liver- and renal disorders. In contrast, no association is suggested between the use of bempedoic acid and the risk of diabetes or muscular side effects, side effects associated with the use of statins.

For SI patients, long term effects beyond 24 weeks are lacking. Despite a very limited increase in CV events, information about long term potential cardiovascular harm, deduced by extrapolating the results from the bempedoic acid MACE data on top of statins, likely excludes any trend towards the risk of cardiovascular harm. Further data will be provided with the ongoing CV outcome study in SI patients.

On top of statins

Bempedoic acid used in patients on top of maximum statin therapy including ezetimibe and very limited use of PCSK9 inhibitors has demonstrated a modest reduction in LDL-C. The effect was consistent for other relevant lipid parameters like non-HDL, TC and ApoB and robust across several subgroups including age, race, ethnicity, region, history of diabetes, baseline LDL-C, HeFH status, prior ASCVD, ezetimibe use, and baseline GFR category.

Although the effect was modest, it can be considered to be **clinically relevant** as the reduction in LDL-cholesterol is an established surrogate marker for cardiovascular outcome. The 18% reduction in LDL-C from a baseline LDL-C level of 2.6-3.2 mmol/L could potentially translate in a clinically relevant risk reduction of approximately 15% of major CV events based on this relationship established for statin therapy (over 5 years).

Analyses of MACE events on top of statins did exclude any trend towards cardiovascular harm, as required before approval (*Reflection paper on assessment of cardiovascular safety profile of medicinal products [EMA/CHMP/50549/2015]*). The slight increase in deaths with bemepdoic acid in the randomised studies is based on very limited numbers making any conclusions uncertain; this is likely an outlier result as the death rate on bempedoic acid treatment was substantially higher than in the ongoing open-label study and deaths could largely be explained by the high CV risk profile of the patients. Further, the higher frequency of very rare cases of neoplasms occurred mostly short after study start, which makes any association with bemepdoic acid treatment unlikely. The actual impact of the long-term lipid reduction with bempedoic acid in terms of improved cardiovascular outcome is still missing and will be addressed in the post-authorisation phase. A long-term outcome study in 12600 SI patients treated for 3.5 years is ongoing and should provide more insight on these uncertainties.

Although in general a comparable safety profile of bempedoic acid is demonstrated when compared with the group characterized by statin intolerance, an increased frequency of muscular disorders was observed. This is most likely driven by the bempedoic acid induced increased exposure of statins. Administration of a single dose of simvastatin 40 mg with steady-state bempedoic acid 180 mg resulted in a 2-fold increase in simvastatin acid exposure. Elevations of 1.4-fold for rosuvastatin, 1.5-fold for atorvastatin, and 1.5-fold for pravastatin and/or their major metabolites were observed when coadministered with bempedoic acid 180 mg. The current proposed dose recommendation, to limit the simvastatin dose prior to use of bempedoic acid, is considered acceptable.

Long term data of bempedoic acid on top of statins; beyond one year of treatment, can be considered limited since the intended treatment may be lifelong. However, the data available indicate that efficacy is maintained over time and safety so far does not suggest any long-term major concerns.

3.6.3. Balance of benefits and risks

The applicant has proposed an indication for bempedoic acid in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet either in combination with maximum tolerated statins (with or without other lipid lowering therapies) or in patients with statin-intolerance or for whom statins are contra-indicated.

Statin intolerance

Patients included in the studies were generally in need of further treatment to reduce LDL-C levels due to their increased cardiovascular risk. A substantial clinically relevant lipid reduction is observed, with an acceptable safety profile including some statin like, but less outspoken, adverse events and some more specifically related to the use of bempedoic acid of which some of these appear to be reversible. The safety findings are based on limited data, but the findings are largely consistent with the safety profile observed in bempedoic acid on top of statins.

On top of statins

The strategy of patient inclusion was generally in line with clinical practice guidelines as the included patients had elevated LDL-C levels despite treatment with statins and other lipid lowering therapy. All patients were in need for further treatment to reduce LDL-C levels due to their high cardiovascular risk. Ezetimibe and PCSK9 inhibitors were only used in up to 15% and 2%, respectively, of the patients despite proven cardiovascular benefit and are indicated for a similar patient population as agreed for bempedoic acid. This may potentially limit the external validity of the currently obtained data. In both studies, only a modest incremental lipid reduction was seen with adding bempedoic acid to statins, especially on top of high intensity statins and/or on top of ezetimibe.

The combined use of **bempedoic acid and statins appears to be complex as both target a similar pathway for cholesterol inhibition.** Bempedoic acid also increases statin exposure. Elevations of 2-fold for simvastatin and 1.4-fold to 1.5-fold in AUC of atorvastatin, pravastatin, and rosuvastatin and/or their major metabolites were observed when coadministered with bempedoic acid 180 mg. This increased statin exposure is likely to be the **main driver of the increased incidence of muscle disorders** as observed in the pool of bempedoic acid on top of statins and seen for atorvastatin, rosuvastatin and simvastatin as the most used statins during the studies; a side effects being absent in the SI pool. However, this does not exclude any other potential factors for this observed safety issue. To address this potential problem, the simvastatin dose should be limited to 20 mg generally and 40 mg for high risk patients prior to initiation of bempedoic acid treatment (section 4.2 of the SmPC), to contra-indicate higher doses than 40 mg simvastatin, and to reduce any statin dose when muscle related events occur (section 4.4 of the SmPC). It is acknowledged that this approach has not been formally tested in the clinical studies. Data on the addition of statin therapy 24 weeks after randomisation as allowed by protocol (7.0% bempedoic acid vs 8.0% placebo) in the phase 3 studies has not been provided due to the limited numbers. Nevertheless, a 2- fold dose reduction of simvastatin, as would be needed for patients already on a 80 mg simvastatin dose, is expected to result in an approximately 2-fold reduction in exposure based on the data as presented in the single dose PK study and may thus match a comparable exposure as prior to bempedoic acid use. Differentiation in recommendations for simvastatin as compared to recommendations regarding other statins was considered acceptable. This risk is likely to be higher for simvastatin (e.g. based on the SEARCH study), higher doses of simvastatin were largely excluded by the introduction of a specific amendment during the study (simvastatin use < 40 mg), and the interaction with bempedoic acid-induced increase exposure is the strongest for simvastatin (2-fold vs 1.5-fold for other statins). But given that an increased risk is already observed with simvastatin 40 mg, although based on limited data (higher frequency of muscle related events with the 40 mg dose in the study with one case of myositis), and exclusion of higher doses than 40 mg with the proposed dose recommendation, a contra-indication for simvastatin > 40 mg in section 4.3 of the SmPC was included. Currently, a warning statement for the potential risk of myopathy with concomitant use of other statins than simvastatin is also included in section 4.4 of the SmPC.

The effect of bempedoic acid on cardiovascular morbidity and mortality has not yet been determined in a dedicated CV outcome trial. Although a reduction in LDL-C is considered to be a valid surrogate for cardiovascular risk reduction, this finding is mainly based on outcome data obtained with statins. It is acknowledged that more recent studies in ezetimibe and PCSK9 inhibitors strengthen the value of LDL-C as a surrogate marker. However, bempedoic acid has a **new mechanism of action** for which a similar relationship has eventually to be established. The cardiovascular outcome trial (Study 1002-043) in SI patients) is already ongoing and should provide further data regarding cardiovascular morbidity and mortality in patients treated with bempedoic acid.

3.6.4. Additional considerations on the benefit-risk balance

Proposed indication for statin intolerant patients

For SI patients the proposed indication refers to adults with primary hypercholesterolaemia (heterozygous familial and non-familial), or mixed dyslipidaemia as an adjunct to diet ***alone*** or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated. This suggests that bempedoic acid could be the preferred therapy in SI patients (after statins have been tried (and found to be not tolerated) over other available therapies. Data on the specific lipid lowering effect of bempedoic acid in patients without lipid lowering therapy demonstrates a significant 22% reduction of LDL-C (95%Ci -26.9, -18.5, p<0.001) for the combined data of bempedoic acid in patients with no lipid lowering background therapy based on 180 vs 91 patients (bempedoic acid vs placebo). This is largely in line with the effects observed in the studies 046 and 048 in patients with no or low dose of statins. It is scientifically plausible that the reduction in LDL-C by bempedoic acid will confer comparable benefits as existing drugs including statins, ezetimibe, and PCSK9 inhibitors, but adequately powered confirmatory data are not available.

3.7. Conclusions

The overall B/R of Nilemdo is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Nilemdo is favourable in the following indication:

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

- *in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin (see sections 4.2, 4.3, and 4.4) or,*
- *alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.*

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that bempedoic acid is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Paediatric Data

No significant studies in the agreed paediatric investigation plan P/0185/2018 have been completed, in accordance with Article 45(3) of Regulation (EC) No 1901/2006, after the entry into force of that Regulation.