30 January 2020
EMA/CHMP/86205/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Nustendi

International non-proprietary name: bempedoic acid / ezetimibe

Procedure No. EMEA/H/C/004959/0000

Note

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

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

Administrative information

Name of the medicinal product:	Nustendi
Applicant:	FGK Representative Service GmbH Heimeranstrasse 35 80339 Munchen GERMANY
Active substance:	BEMPEDOIC ACID / EZETIMIBE
International Non-proprietary Name/Common Name:	bempedoic acid / ezetimibe
Pharmaco-therapeutic group (ATC Code):	not yet assigned
Therapeutic indication(s):	Nustendi 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 in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin in addition to ezetimibe (see sections 4.2, 4.3, and 4.4), • alone in patients who are either statin-intolerant or for whom a statin is contraindicated, and are unable to reach LDL-C goals with ezetimibe alone, • in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without statin.
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	180 mg / 10 mg
Route(s) of administration:	Oral use

Packaging:	blister (PVC/Aclar/alu)
Package size(s):	10 tablets, 28 tablets, 30 tablets, 90 tablets, 98 tablets and 100 tablets

Table of contents

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 bempedoic acid (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
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

Abbreviation	Definition
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
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 Nustendi, 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:

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

Ezetimibe 10 mg has been shown to reduce the frequency of cardiovascular events. The effect of bempedoic acid on cardiovascular morbidity and mortality has not 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) EMEA-002200-PIP01-17 on the granting of a (product-specific) waiver for the paediatric population from birth to less than 18 years of age.

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).

The approval of the FCMP for use as an add-on treatment to other LMTs, including maximally tolerated statins, and/or in patients who are statin intolerant would be consistent with global treatment guidelines for patients with hyperlipidemia who require additional LDL-C lowering.

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% (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.

Add-On Therapy

A recent review of guidelines and clinical trials evaluating non-statin agents (Russell et al, 2018) confirms the growing base of evidence and expert opinion supporting the use of combination lipid-lowering therapies and the need for additional therapies. While the recommended first-line treatment is a statin monotherapy, combination therapies represent an opportunity for an individualized, patient-centered approach to LDL-C lowering and ASCVD risk reduction in patients intolerant of statins and/or unable to reach individualized serum LDL-C levels.

The 2016 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines on the treatment of cholesterol focus on the benefits of statin therapy, but in certain circumstances, recommend non-statin therapies, specifically bile acid sequestrants, ezetimibe, and PCSK9 inhibitors (Catapano et al, 2016). For patients at very high CV risk, the ESC/EAS recommends an LDL-C treatment target of < 70 mg/dL (1.8 mmol/L) or a reduction in LDL-C of 50% from baseline. Also, several US healthcare organizations including the American Heart Association (AHA) and American College of Cardiology (ACC) recently announced 2018 guidelines on the management of blood cholesterol (hereafter referred to as AHA/ACC guidelines). These guidelines focus on the benefits of statin therapy but recommend considering adding non-statin therapies (ezetimibe, bile acid sequestrants, and PCSK9 inhibitors) to maximally tolerated statin therapy in patients with multiple ASCVD events or at least 1 ASCVD event plus additional risk factors if LDL-C is ≥ 70 mg/dL (1.8 mmol/L). In patients with primary hypercholesterolemia (LDL-C ≥ 190 mg/dL) who have LDL-C ≥ 100 mg/dL with statin therapy, non-statin therapies may be needed (Grundy et al, 2018).

Additionally, the ACC expert consensus documents provide decision pathways for selection of add-on non-statin therapies if the patients in the 4 statin benefit groups experience unacceptable adverse effects or insufficient LDL-C lowering when taking the recommended intensity of statin (Lloyd-Jones et al, 2016; Lloyd-Jones et al, 2017). In each of these 4 patient management groups, ezetimibe was recommended as second-line treatment options for patients who required additional LDL-C lowering beyond their statin.

Current therapeutic guidelines identify the following 4 patient management groups for whom the evidence for ASCVD risk reduction with LDL-C lowering clearly outweighs the risk of adverse events from statin therapy:

- Adults with clinical ASCVD
- Adults with severe hypercholesterolemia (LDL-Cholesterol ≥ 190 mg/dL [≥ 4.9 mmol/L])
- Adults with diabetes mellitus and LDL-C 70 mg/dL to 189 mg/dL (1.8-4.9 mmol/L)
- Primary prevention for adults with elevated risk for ASCVD

Patients requiring additional LDL-C lowering and patients eligible for non-statin LDL-C lowering therapies would benefit from FCMP therapy.

Statin Intolerance

In the UK, the National Institute of Care and Clinical Excellence (NICE) released a new guideline in February 2016 entitled Ezetimibe for Treating Primary Heterozygous-Familial and Non-Familial Hypercholesterolaemia (NICE, 2016). This guideline sought to provide formalized guidance on the use of ezetimibe in light of the evidence from the IMPROVE-IT trial. Ezetimibe monotherapy was recommended as an option for treating primary hypercholesterolemia (heterozygous familial hypercholesterolemia [HeFH] and nonfamilial) in patients in whom statin therapy was contraindicated, or in patients who were unable to tolerate statin therapy. The ESC produced, in conjunction with other societies on CVD prevention, updated guidelines on CVD prevention in June 2016. These guidelines suggest the use of ezetimibe monotherapy when patients are intolerant of statins (Piepoli et al, 2016). Therefore, current major clinical applications center on the use of ezetimibe monotherapy in patients intolerant of statins or in whom they are contraindicated (Serban 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 15-20% 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). In the EU statin intolerance language is included in label indications for LDL-C lowering drugs (Repatha SmPC, 2018; Praluent SmPC, 2015).

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 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 ≥ 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 and stage/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 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 ≥ 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 ≥ 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

Bempedoic acid and ezetimibe lower LDL-C by distinct, but complementary mechanisms of action described below and in Figure 1.

Bempedoic Acid Mechanism of Action

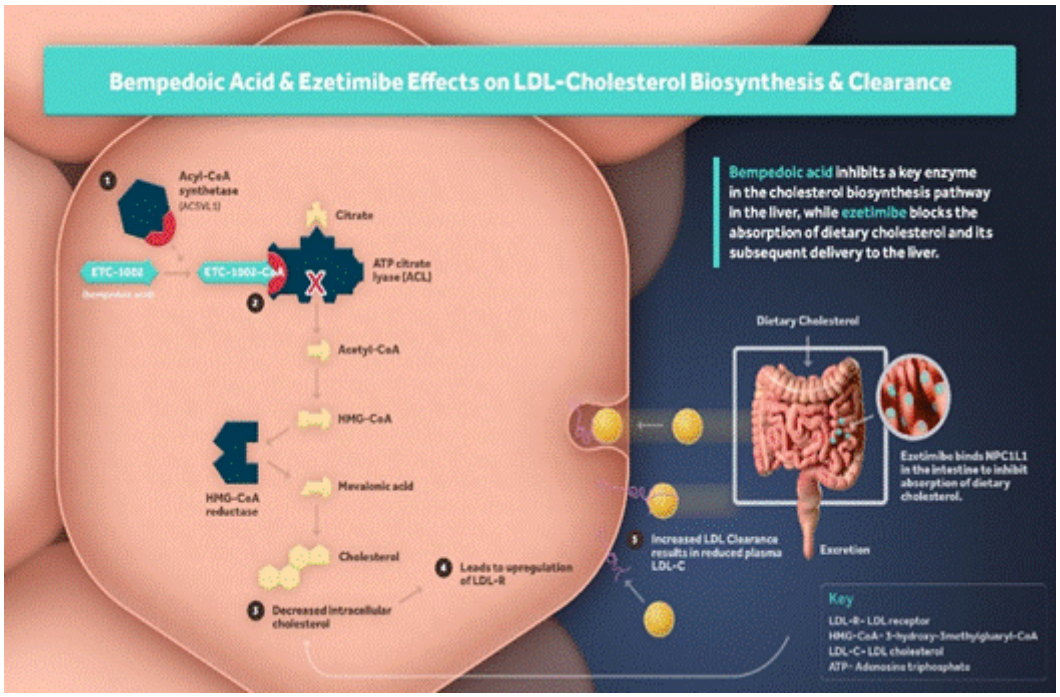
Bempedoic acid is an ACL inhibitor that lowers LDL-C by inhibition of cholesterol synthesis in the liver. ACL is an enzyme upstream of HMG-CoA reductase in the cholesterol biosynthesis pathway. Bempedoic acid requires coenzyme A (CoA) activation by very long-chain acyl-CoA synthetase 1

(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 low-density lipoprotein (LDL) receptors. 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.

Ezetimibe Mechanism of Action

The molecular target of ezetimibe has been shown to be the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is involved in the intestinal uptake of cholesterol and phytosterols. Ezetimibe localizes at the brush border of the small intestine and inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in LDL receptors, resulting in clearance of cholesterol from the blood. This distinct mechanism is complementary to that of bempedoic acid. Ezetimibe undergoes enterohepatic recirculation with minimal systemic exposure, where it again can inhibit the NPC1L1 protein (Ezetrol SmPC, 2018; Zetia USPI, 2013; Nutescu et al, 2003; Toth et al, 2005; and Toth, 2010).

Figure 1: Mechanism of Action of Bempedoic Acid + Ezetimibe



Schematic overview of the mechanism of action of bempedoic acid (ETC-1002) and ezetimibe. **(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.

Type of Application and aspects on development

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. In a follow-up European Medicines Agency (EMA) Scientific Advice in March 2018 expanded eligibility criteria for statin intolerance were agreed with the Committee for Medicinal Products for Human Use (CHMP).

A Scientific Advice meeting with the Scientific Advice Working Party (SAWP) was held in May 2016. This included 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 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 tablet containing a fixed dose combination (FDC) of 180 mg of bempedoic acid and 10 mg of ezetimibe.

Other ingredients are:

Tablet core: Lactose monohydrate, Microcrystalline cellulose (E460), Sodium starch glycolate (Type A), Hydroxypropyl cellulose (E463), Magnesium stearate (E470b), Silica colloidal anhydrous (E551), Sodium lauryl sulfate (E487), Povidone K30 (E1201).

Film-coat: Partially hydrolysed polyvinyl alcohol (E1203), Talc (E553b), Titanium dioxide (E11), Indigo Carmine Aluminum Lake (E132), Glyceryl monocaprylocaprate, Sodium lauryl sulfate (E48), Brilliant Blue FCF Aluminum Lake (E133).

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

2.2.2. Active substances

Bempedoic acid

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:

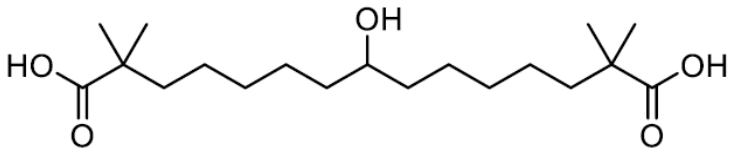


Figure 2: active substance structure

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.

Ezetimbe

General information

The chemical name of ezetimbe is *(3R,4S)*-1-(4-fluorophenyl)-3-[*(3S)*-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one corresponding to the molecular formula $C_{24}H_{21}F_2NO_3$. It has a relative molecular mass of 409.43 g/mol and the following structure:

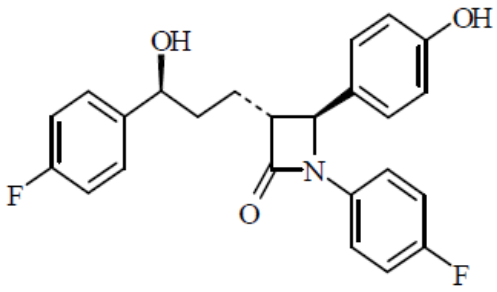


Figure 3: active substance structure

The chemical structure of ezetimbe was elucidated by a combination of ^{1}H and ^{13}C-NMR spectroscopy, UV spectroscopy, IR spectroscopy, mass spectrometry and elemental analysis. The solid-state properties of the active substance were measured by x-ray diffraction (XRD) and differential scanning calorimetry (DSC).

Ezetimibe is a white to off-white crystalline powder. It is practically insoluble in water, and freely soluble in organic solvents like ethanol, methanol, isopropyl alcohol and acetone. It contains a chiral centre and exhibits optical isomerism. The other potential isomer (*R*-isomer) is in the release specifications. Ezetimibe exhibits polymorphism as per the available literature. However, based on the XRD spectra, it is found that crystalline Form–X is routinely produced by the ezetimibe proposed commercial manufacturer.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Ezetimibe is synthesized using two commercially available well-defined starting materials with acceptable specifications.

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 are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in polyethylene a bag which complies with the EC directive 2002/72/EC and EC 10/2011 as amended. The primary pack is then placed into a black polyethylene bag with silica gel bag and tied.

Specification

The active substance specification includes tests for description, solubility, identity (IR, XRD, HPLC), water content (KF), specific optical rotation (polarimeter), residue on ignition (Ph. Eur.), assay (HPLC), impurities (HPLC), chiral purity (chiral HPLC), residual solvents (GC), particle size (dynamic light scattering), bulk density, tapped bulk density and specific microorganisms.

Microbial tests on specified micro-organisms are included, but not the usual TAMC and TYMC. The applicant was asked either to demonstrate that a specification on microbial purity is not needed (Note for Guidance Specifications – Q6A (CHMP/ICH/ 367/96), Decision Tree #6), or to apply a usual routine specification (TAMC, TYMC, E. coli). Finally, the applicant introduced Ph. Eur. requirements (methods 2.6.12 and 2.6.13) for routine release.

The absence of genotoxic impurities is sufficiently discussed. A risk assessment on elemental impurities was performed as per ICH Q3D guidelines. No class 1 or 2A elemental impurities were detected in tested batches and it can be concluded that no tests are needed in the active substance specification. All analytical methods have been adequately described. Quantitative methods are considered adequately validated. Compliance with the pre-defined acceptance criteria of ICH Q2 R1 has been shown.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data from 3 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 number 60 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. Supporting data from 9 more commercial scale batches under long term and accelerated conditions was also provided. The following parameters were tested: description, identity, water content, impurities, assay, chiral purity and particle size.

All tested parameters were within the specifications. The accelerated data did not reveal any significant change during the study period of 6 months. The long-term study of 60 months did not show any significant change in the impurity profile and other characteristics studied. No clear up- or downward

trends are observed, under accelerated or long term conditions, for all batches up to the maximum period tested.

Photostability testing following the ICH guideline Q1B was performed on one batch. Ezetimibe is not photosensitive.

Results from forced degradation studies under stress conditions (heat, acid and basic hydrolysis, aqueous and oxidation) were also provided on one batch. Degradation is observed under aqueous conditions (heated, acid, base) but no significant degradation was observed under oxidative conditions or when the sample was exposed to heat in the solid state.

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 60 months stored in the proposed container under nitrogen in order to protect from moisture.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is presented as blue oval film-coated tablets containing 180 mg of bempedoic acid and 10 mg of ezetimibe. The tablets are debossed with '818' on one side and 'ESP' on the other side. The tablet dimensions are 15.00 mm x 7.00 mm x 5.00 (±0.30) mm.

The pharmaceutical development has been well described in the dossier. Pharmaceutical development of the finished product contains QbD elements. The development of the FDC tablets is based on QTTP of the tablets, and iterative risk assessments for the two drug substances and their potential impact on the critical quality attributes (CQAs)., as well as iterative risk assessments of formulation variables on CQAs of the drug product. CQAs were defined as appearance, assay, content uniformity, degradation, stability, disintegration, dissolution of both APIs, hardness, friability, water content and microbiology. Iterative risk assessments were conducted to identify the potential impact of formulation variables on the CQAs and used to guide development activities.

The FDC formulation development was adequately described including FDC development focused on optimizing the ezetimibe granulation, choice between mono- or bilayer tablet formulations, and biostudies on the monolayer and bilayer tablets in a clinical study as a formulation-screening tool. The two active substances have different physicochemical properties which requires them to be granulated separately. The two granulation processes were optimised separately and then combined into a single tablet separately in a bilayer, or pre-mixed in a monolayer. Both tablets had acceptable properties *in vitro* so a clinical study was conducted to assess relative bioavailability which led to the selection of the monolayer tablet for further development and subsequent commercialisation. The FDC tablet was bridged to the individually administered single API tablets (Zetia and bempedoic acid) in a randomised controlled pivotal study in accordance with the EMA's FDC Guideline.

The applicant described the manufacturing process development for bempedoic acid and ezetimibe granulations in detail, based on QTTP, risk assessments of drug substance and formulation attributes, and earlier drug product experiences.

In the final risk assessment all identified initial high and medium risks were downgraded by mitigating the risks based on the formulation optimisation studies and setting of proven acceptable ranges.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. 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.

The dissolution method development has been adequately described in full detail. The discriminatory power of the dissolution method has been demonstrated.

The primary packaging is PVC/PCTFE/aluminum blisters. The material complies 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 3 main steps. The process is considered to be a standard manufacturing process.

The manufacturing steps are adequately described. Critical process parameters (CPPs) and in-process controls (IPCs) have been clearly indicated in the process descriptions.

Product specification

The finished product release specifications include test for appearance, dimensions, identity (HPLC), assay (HPLC), impurities (HPLC) dissolution (HPLC), uniformity of dosage units (Ph. Eur.), water content (KF), microbial limits (Ph. Eur.).

The finished product specifications are considered to be adequate.

The applicant has provided a satisfactory risk assessment report on elemental impurities in accordance with guideline ICH Q3D. Based on the presented risk assessment and available results, it can be concluded that there is no need to specify any elemental impurities in the final product.

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 and impurities testing has been presented.

Batch analysis results were provided for 3 batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Additional data from supporting batches were also provided.

Stability of the product

Stability data from 3 commercial scale batches of finished product stored for up to 15 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. Additional data from 2 supportive stability batches were also 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 assay (both actives), bempedoic acid and ezetimibe related impurities, dissolution (both actives), uniformity of dosage units (both actives), water content, and microbial purity. The analytical procedures used are stability indicating. All test results remain within the acceptance limits and no changes were observed. No significant changes in appearance, assay, degradation products, dissolution, water content, or microbial limits were observed in the FDC tablet primary stability samples at long-term and at accelerated storage conditions.

One batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Nustendi is not photosensitive.

Additionally, one finished product batch was exposed to oxidative, basic, acidic, and thermal stress. Significant degradation occurs under basic and acidic aqueous conditions but not under oxidative conditions or heat stress.

Based on available stability data, the proposed shelf-life of 27 months stored in the original package in order to protect from moisture 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 used does not contain, nor is manufactured with any raw material containing bovine or other animal related products. These Stearates are derived from edible vegetable sources. The fatty acid used in production are derived from palm and produced from the fruit of Elaeis guineensis.

Post approval change management protocol

A post-approval change management protocol (PACMP) has been proposed to facilitate 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 and therefore, new manufacturers can be introduced by Type 1AIN variation provided that the steps and conditions in the protocol are met.

2.2.4. Discussion on chemical, and pharmaceutical 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 processes. 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. Recommendations 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

GLP

Pivotal repeat-dose toxicology, genetic toxicology, carcinogenicity, and developmental and reproductive toxicology studies and safety pharmacology studies were conducted in compliance with US FDA Good Laboratory Practice (GLP) regulations and ICH guidelines. Based on memos of understanding or mutual recognition agreements, studies conducted under US FDA GLP regulations are considered compliant in Organisation for Economic Co-operation and Development (OECD)-member and European Union (EU), member countries.

The GLP status for test facilities was in general in compliance but the status GLP status of the ChanTest Corporation (Cleveland, OH USA; 2008-2009) performing the hERG assay could not be confirmed.

2.3.2. Pharmacology

Bempedoic acid

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 ACL converts citrate into acetyl-Coenzyme A (acetyl-CoA), which then is formed into HMG-CoA by ACC. S, 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. An inhibition of cholesterol synthesis has been shown to result in an upregulation of hepatic LDL-R protein expression and increased clearance of LDL-C by LDL-R from plasma.

Ezetimibe

Ezetimibe, 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone has the empirical formula $C_{24}H_{21}F_2NO_3$ and a molar mass of 409.4 g/mol. The substance is highly soluble in ethanol, methanol, and acetone but practically insoluble in water.

Primary pharmacodynamics

Primary pharmacodynamics: *In vitro*

Bempedoic acid

The Applicant demonstrated, using radiolabeled substrates, such as [^{14}C]acetate, [^{3}H]H_2O, [^{14}C]pyruvate, and [^{14}C]glucose, as a metabolic precursors, that bempedoic acid inhibited de novo

sterol and fatty acid synthesis in primary rat hepatocyte cultures and in livers of treated rats. The [^{14}C]acetate incorporation into fatty acids and sterol fractions was 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 bempedoic acid-CoA acted as a competitive inhibitor of ACL with respect to CoA competition (Ki = 2 µM) and not on ATP competition. The formation of CoA ester of bempedoic acid was shown to occur in rat liver microsomes incubated with bempedoic acid (10 µM) and up to 100 µM CoA.

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 bempedoic acid did not inhibit ACC, while bempedoic acid-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.

Ezetimibe

Ezetimibe is a selective inhibitor of the sterol transporter Niemann-Pick C1-Like 1 (NPC1L1) protein, which is involved in the intestinal absorption of cholesterol and related phytosterols. NPC1L1 is localized at the brush-border of the small intestine; and inhibition of NPC1L1 results in decreased absorption of biliary and dietary cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver.

Primary pharmacodynamics: *in vivo*

Bempedoic acid

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 a HFHC diet, plasma cholesterol and LDL-C increased over the course of 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.

Ezetimibe

Cell culture and knock-out experiments in mice confirmed that ezetimibe reduces the small intestinal enterocyte uptake and absorption of cholesterol by binding to Niemann-Pick C1 Like 1 (NPC1L1), which keeps cholesterol in the intestinal lumen for excretion. Furthermore, the uptake of structurally related phytosterols seems to be mediated by the same mechanism.

In rodent studies, ezetimibe was a selective cholesterol absorption inhibitor, potently inhibiting the absorption of biliary and dietary cholesterol from the small intestine without affecting the absorption of fat-soluble vitamins, triglycerides, fatty acids, progesterone, ethinyl estradiol, or bile acids irrespective of pancreatic function. Data in rats suggest that ezetimibe does discriminate by blocking the movement of exogenous cholesterol in the enterocyte before it reaches the intracellular cholesterol pool to be incorporated into intestinal lipoproteins, without affecting the incorporation of newly synthesized cholesterol into intestinal lipoproteins.

Ezetimibe has been shown to be most potent preclinically in cholesterol-fed rhesus monkeys, where a dose-dependent effect occurred at a dose of 10 µg/kg, having a significant decrease in total cholesterol from 275 mg/dL to normal levels (approximately 150 mg/dL). A significant decrease in plasma concentrations of LDL-C from 140 to about 50 mg/dL was also noted. Furthermore, crossover studies (in which animals were first fed a high-cholesterol diet without ezetimibe and then switched to a high-cholesterol diet with the compound, and vice versa) found that plasma cholesterol and LDL-C declined toward normal levels with the addition of the drug and rose when it was not administered.

When intestinal cholesterol absorption is decreased the chylomicrons formed by the intestine contained less cholesterol and thus the delivery of cholesterol from the intestine to the liver was reduced in experiments using miniature pigs. This resulted in a decrease in the cholesterol content of the liver,

leading to the activation of sterol regulatory element binding proteins (SREBPs), which enhance the expression of LDL receptors resulting in an increase in LDL receptors on the plasma membrane of hepatocytes. Thus, a key element of the mechanism of action of ezetimibe is to decrease the levels of cholesterol in the liver resulting in an increase in the number of LDL receptors leading to the increased clearance of circulating LDL-C. In addition, the decreased cholesterol delivery to the liver may also decrease the formation and secretion of the precursor very-low density lipoprotein.

Experiments in mice showed that, in addition to NPC1L1 expression in the intestine, this protein is also expressed in the liver where it mediates the transport of cholesterol from the bile back into the liver. The inhibition of NPC1L1 in the liver resulted in the increased secretion of cholesterol in bile and thereby could also contribute to a decrease in the cholesterol content of the liver and an increase in LDL receptor expression and a decrease in VLDL-C production.

Primary pharmacodynamics: Metabolites

Bempedoic acid

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.

Ezetimibe

After oral administration, ezetimibe is rapidly and extensively metabolised to a pharmacologically active phenolic glucuronide in humans and animal species. Ezetimibe undergoes glucuronidation to a single metabolite and localizes at the intestinal wall, where it binds with higher affinity for NPC1L1 to prevent cholesterol absorption. Enterohepatic recirculation of ezetimibe and/or its glucuronide ensures repeated delivery to the intestinal site of action and limited peripheral exposure.

Secondary pharmacodynamic studies

Secondary pharmacodynamics: *in vitro*

Bempedoic acid

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 cytoxicity 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 the 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 is 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*

Bempedoic acid

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 had no effect on 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. But 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 are unclear.

Following 12 weeks of oral daily 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 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.

Ezetimibe

Ezetimibe inhibited the development of carotid artery (decrease of 97%) and aortic (decrease of 71–87%) atherosclerosis in animal models.

Safety pharmacology programme

Bempedoic acid

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 parameter 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 was 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 had no effect on 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).

Ezetimibe

From Halleck et al (2009) it is clear that safety pharmacology studies have been performed to evaluate neurological, cardiovascular, and respiratory safety in animals. Considering that the large clinical experience to date with ezetimibe products, it is not expected that new safety concerns may be identified.

Pharmacodynamic drug interactions

Bempedoic acid & Ezetimibe

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 (ETC-1002-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.

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

2.3.3. Pharmacokinetics

Bempedoic acid

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 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 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. 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. 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. 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 in 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 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 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 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 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 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 dose) and to a lesser extent via urine (17% of 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 dose) than in feces (29% of 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.

Ezetimibe

Ezetimibe is rapidly absorbed from the intestinal lumen and undergoes extensive first-pass metabolism (>95% glucuronidation) in the intestinal wall to form the active metabolite. After oral administration of 5 mg/kg ezetimibe for 14 days, wild type rats showed a mean (± standard deviation [SD]) area under the plasma concentration time curve from time 0 to 24 h (AUC_{0-24h}) of 74.6 ± 26.3 ng·h/mL for ezetimibe and 556 ± 591 ng·h/mL for the glucuronide. In bile duct-cannulated rats, ezetimibe was glucuronidated, moved through the intestinal wall, into portal plasma, through the liver, and into bile. Via bile, the drug was then delivered back to its intestinal site of action. The glucuronidated ezetimibe localises more avidly to the intestine than ezetimibe itself. Ezetimibe is primarily metabolised in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary and renal excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated. The major part of ezetimibe is conjugated to the benzylic glucuronide by uridine diphosphate (UDP) -glucuronosyltransferases 1A1, 1A3, and 2B15. A minor amount of ezetimibe is conjugated to the phenolic glucuronide by UDP -glucuronosyltransferase 2B7. Ezetimibe is predominantly excreted via faeces.

2.3.4. Toxicology

Single dose toxicity

Bempedoic acid

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 was 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.

Ezetimibe

Although it is indicated by the applicant that in the original marketing application for ezetimibe acute oral gavage and intraperitoneal studies in rats and mice were performed, as well as an oral capsule study in dogs, no results are included in the dossier.

Repeat dose toxicity

Bempedoic acid

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 cholesterel 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, with respect to 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. Combination resulted in 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.

Ezetimibe

Exposure to high doses (20x and 8-10x the human exposure in rats and dogs) of ezetimibe induce toxicity in heart and lymph nodes in rats and dogs and in kidney and bone marrow in rats. The combination with statins also induces liver effects in rats and dogs, but such effects are not observed in humans receiving combination therapy with ezetimibe and statins.

Genotoxicity and Carcinogenicity

Bempedoic acid

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 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.

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 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 liver, but 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 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.

Ezetimibe

A standard battery of *in vitro* and *in vivo* genotoxicity assays did not indicate any genotoxic potential for Ezetimibe. Overall, it is not likely that ezetimibe alone or in combination with statins, is carcinogenic.

Reproduction Toxicity

Bempedoic acid

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

In the combined oral fertility Study with bempedoic acid 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 indicate that exposures 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 indicate 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 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.

Ezetimibe

In rats, increased incidences of common fetal skeletal findings (extra pair of thoracic ribs, unossified cervical vertebral centra, shortened ribs) were observed at 1000 mg/kg/day (approximately 10 times the human exposure). Extra thoracic ribs were also observed in high dosed rabbits (150 times the human dose). Studies in rats and rabbits showed that ezetimibe can cross the placenta and is transferred to the milk.

Bempedoic acid & ezetimibe

Similar effects were observed in the rat embryo-fetal development study with bempedoic acid plus ezetimibe as in the study with only bempedoic acid.

Toxicokinetic data

Bempedoic acid

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 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 month 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 for humans.

Bempedoic acid & ezetimibe

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 the 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.

Bempedoic acid & statins

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 exposure in humans at 180 mg/day, which is considered small, but sufficient.

Local Tolerance

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

Other toxicity studies

Interspecies comparison

Bempedoic acid

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, 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 plasma of rats.

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.

Bempedoic acid & ezetimibe

In combination studies with ezetimibe in rats and humans, ezetimibe had no effect on 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.

Bempedoic acid & atorvastatin

In combination studies with atorvastatin in monkeys and humans, atorvastatin had no effect on the exposure to bempedoic acid. In monkey, bempedoic acid had no effect on atorvastatin exposure while in humans only a small increase (1.4x) was observed.

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.

Other

Bempedoic acid

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 euthanised. 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

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.

Ezetimibe

An ERA has not yet been provided for ezetimibe, but will be provided to EMA by 31 July 2020, assuming that required laboratory testing is limited. In the event terrestrial testing is triggered, the ERA report will be completed in January 2021.

2.3.6. Discussion on non-clinical aspects

Bempedoic acid

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.

Ezetimibe

The nonclinical pharmacology, pharmacokinetics and toxicology of ezetimibe have been adequately described. However, **no ERA has been submitted for ezetimibe**. The present application is made under Art. 8(3) – full application where the full data set has to be provided, including ERA for both active substances.

The argumentation for a non-increase in environmental exposure due to fixed combination was considered not appropriate. The product literature does not state explicitly its use as substitution for

the active substances previously given concomitantly in single products. Furthermore, an increase in consumption of ezetimibe is indicated for EU5 with a significant increase of 16.5% according to the data provided by the applicant. Thus an increase in environmental exposure can be expected indeed and an ERA would be necessary. It was recommended to submit the ERA for ezetimibe for assessment when it is completed in January 2021.

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.

The nonclinical pharmacology, pharmacokinetics and toxicology of ezetimibe have been adequately described.

Overall, the nonclinical safety profile of FDC bempedoic acid/ezetimibe has been adequately characterized. It was recommended to submit the ERA for ezetimibe for assessment when it is completed in January 2021.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

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.

Study 1002FDC-053

The FCMP Phase 3 program included 1 randomized, double-blind, placebo-controlled, parallel-group study. Study 1002FDC-053 enrolled patients with documented ASCVD and/or HeFH and/or multiple CV risk factors and who required additional LDL-C lowering therapy despite already receiving maximally tolerated statin background therapy.

Following database lock, a careful review of the data including PK data at the per patient level (plasma bempedoic concentrations and plasma ezetimibe concentrations), it became apparent that an unusual number of patients who reported routinely ingesting IMP had no detectable IMP in their PK blood samples. Subsequent investigation of this data revealed that of the 78 sites included in this study, most of these patients referenced above were from 3 sites. Based on this finding, a detailed investigation root cause analysis (RCA) was conducted by the study Sponsor to determine the cause, and, data from these sites were excluded in a post hoc sensitivity analysis. In the clinical overview, data from both the original and post hoc sensitivity analysis are presented. The post hoc sensitivity analyses with all data from these sites removed also produced efficacy results that were statistically and clinically significant and generally recapitulated the safety findings of the original analysis. It is the

position of the Applicant that the post hoc sensitivity analysis most accurately reflects the efficacy and safety profile of the FCMP within the context of a clinical study.

- 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 2, Table 1 and Table 2. Three additional clinical pharmacology studies were conducted for the fixed-dose combination Table 3.

Figure 4. Bempedoic Acid Clinical Pharmacology Program

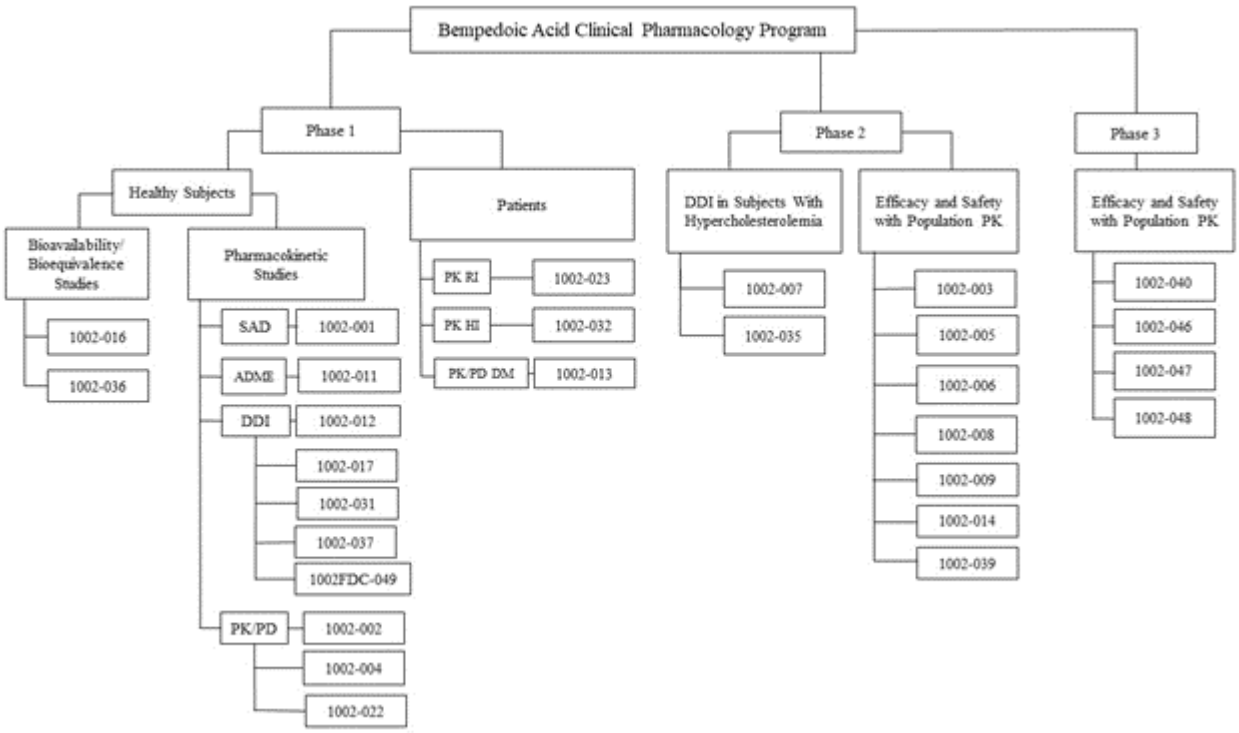


Table 1. Overview of *in vitro* studies using human biomaterial

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 RR1002-500-056 RR1002-500-057 RR1002-500-070	RR1002-500-034	RR1002-500-056 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,	180 mg	20 (16M,4F)

Study	Objective	Population	Test product(s)	Dose	Number of subjects
			probenecid		
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)
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,53F)
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)

Study	Objective	Population	Test product(s)	Dose	Number of subjects
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)
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)

Table 3. Clinical PK development programme of the FCMP of bempedoic acid and ezetimibe

Study	Objective	Population	Test product(s)	Dose	Number of subjects
1002FDC-034	Relative oral bioavailability of FCMP tablet relative to coadministration of bempedoic acid and ezetimibe tablets	HV	FCMP monolayer tablet FCMP bilayer tablet Bempedoic acid (Formulation 1) Ezetimibe (Zetia®)	180/10 mg	24 (17M,7F)
1002FDC-049	Effect of steady-state bempedoic acid on the single-dose PK of ezetimibe and the effect of steady-state ezetimibe on the single-dose PK of bempedoic acid	HV	Bempedoic acid (Formulation 1) Ezetimibe	180/10 mg	40 (19M,21F)
1002FDC-053	Efficacy and trough plasma concentrations of bempedoic acid and ezetimibe administered as an FCMP	Patients with hyperlipidemia at high risk for CVD	FCMP tablet Bempedoic acid		382b (180M, 202F)

			(Formulation 1) Ezetimibe		
1002FDC-055	Food effect study	HV	FCMP monolayer tablet	180/10 mg	17 (6M,11F)

2.4.2. Pharmacokinetics

The pharmacokinetics of bempedoic acid and ezetimibe are described in section 2.4.2.2 and in section 2.4.2.3, respectively. The pharmacokinetic aspects of the FCMP are described in section 2.4.2.4.

2.4.2.1. Methodology

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.

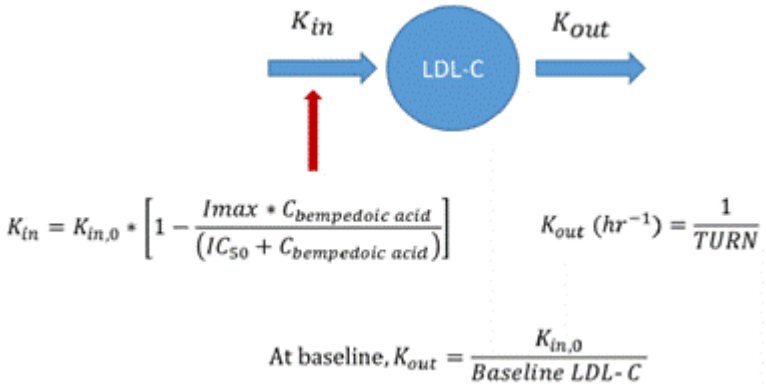
Two population pharmacokinetic analyses were submitted by the applicant. The first population pharmacokinetic analysis characterised the pharmacokinetics of both ETC-1002 and ESP15228 in 11 phase 1 and 2 studies. Mainly densely sampled studies were included in the analysis. The pharmacokinetics were 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 sparse sampled studies were included in the analysis. The pharmacokinetics of ETC-1002 were 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 body weight and renal function. Also, covariate effects of atorvastatin on bioavailability (12.6% increase) and simvastatin on V_2/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 3**). Concomitant therapy with statins or ezetimibe influenced the Imax (lower) and baseline LDL-C parameters.

Figure 5. Indirect Response Base Model



2.4.2.2. Pharmacokinetics of bempedoic acid

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*.

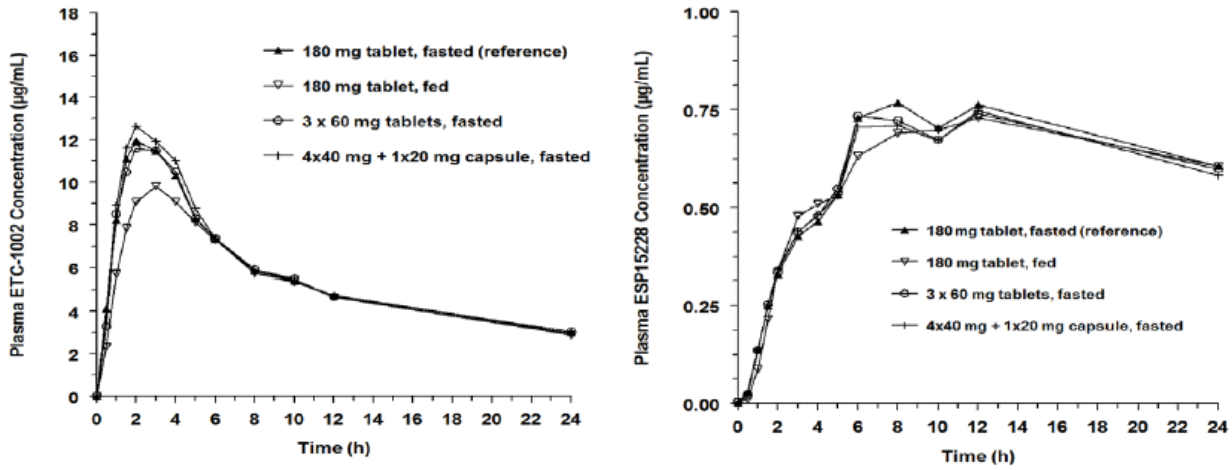
Bempedoic acid is absorbed with a median time to a maximum concentration of 3.5 hours when administered orally as 180 mg tablets. Bempedoic acid is partially converted to an active metabolite ESP15228, which has a median tmax of 7.0 hours. Concomitant food administration had no effect on the oral bioavailability of bempedoic acid, a minor influence on Cmax (-12%) and decreased the absorption rate constant 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}. The food effect study, an 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.

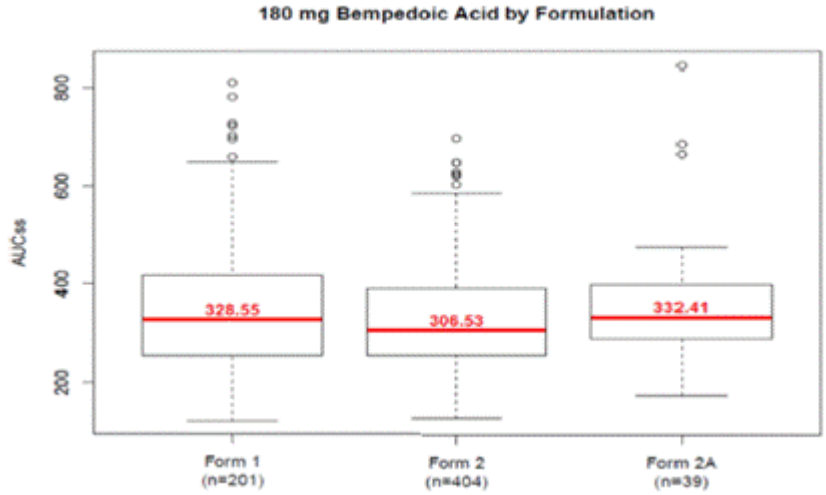
Figure 6. Arithmetic Mean Plasma Bempedoic Acid (left) and ESP-15228 (right) Concentrations Through the First 24 Hours Post-dose Following a Single 180-mg (Total) Oral Dose of ETC-1002 (n = 16), Study 1002-016



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 5.

Figure 7. Model predicted AUCss for studies 1002-046, 1002-047 and 1002-048



Distribution

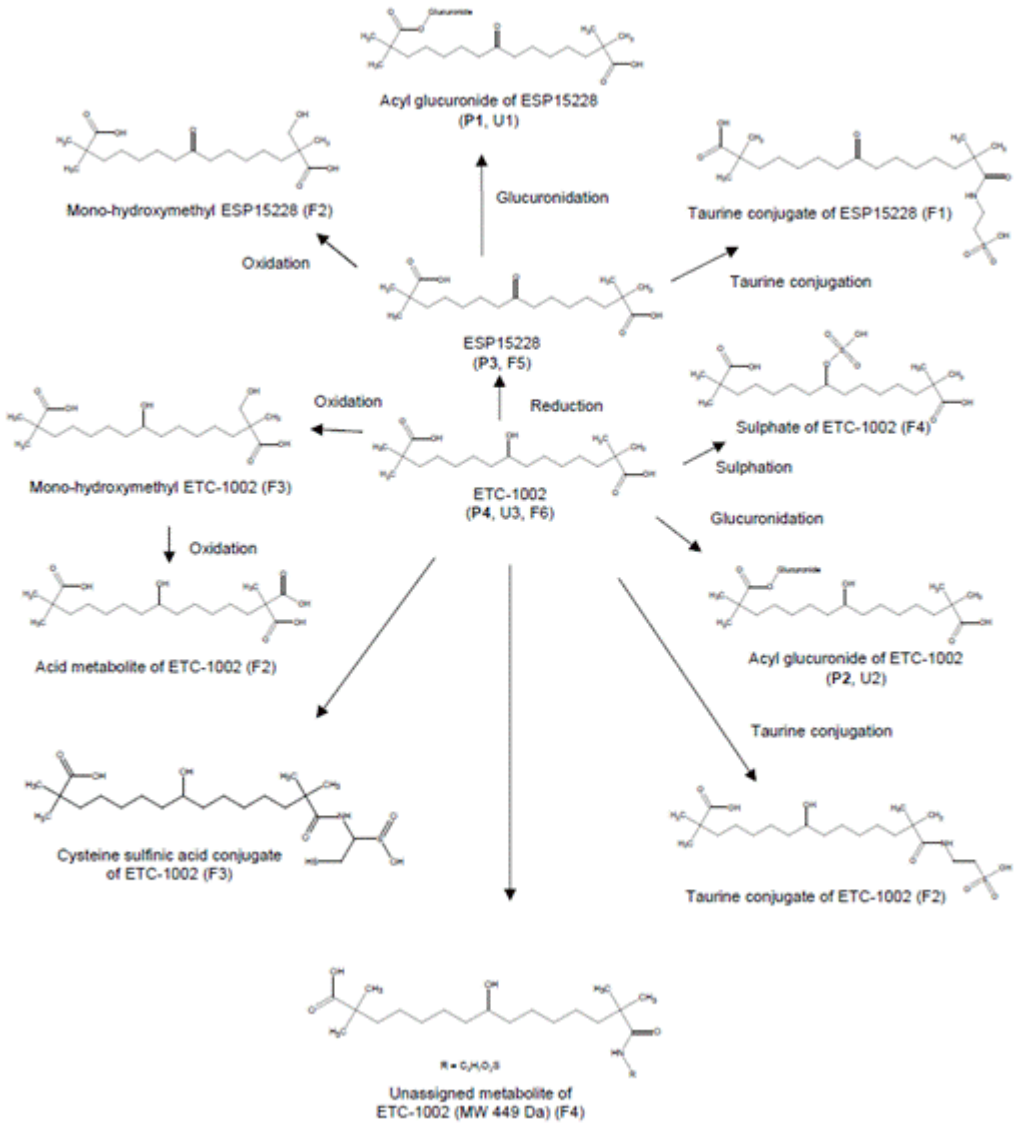
The apparent volume of distribution following oral administration of bempedoic acid was approximately 16-18L. The *in vitro* protein binding was high ranging from 95% for ETC-1002 (parent compound) to 99% for both ESP15228 (active metabolite) and ETC-1002-glucuronide (inactive metabolite). The extent 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 through metabolism to the acyl glucuronide (Figure 6). 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 8. 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 and, 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 were 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 recommendations section VII.

Dose proportionality and time dependency

Bempedoic acid $AUC_{0\text{-}24,\ ss}$ 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 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%, 100.0% and 73.9%, respectively.

2.4.2.2.1. Pharmacokinetics in the target population

Overall, steady state PK properties of bempedoic acid 180 mg appeared to be consistent across trials in the patient population. Bempedoic acid trough concentrations in patients with hyperlipidemia are approximately 10 ug/mL after the administration of 180 mg bempedoic acid.

2.4.2.2.2. Special Populations

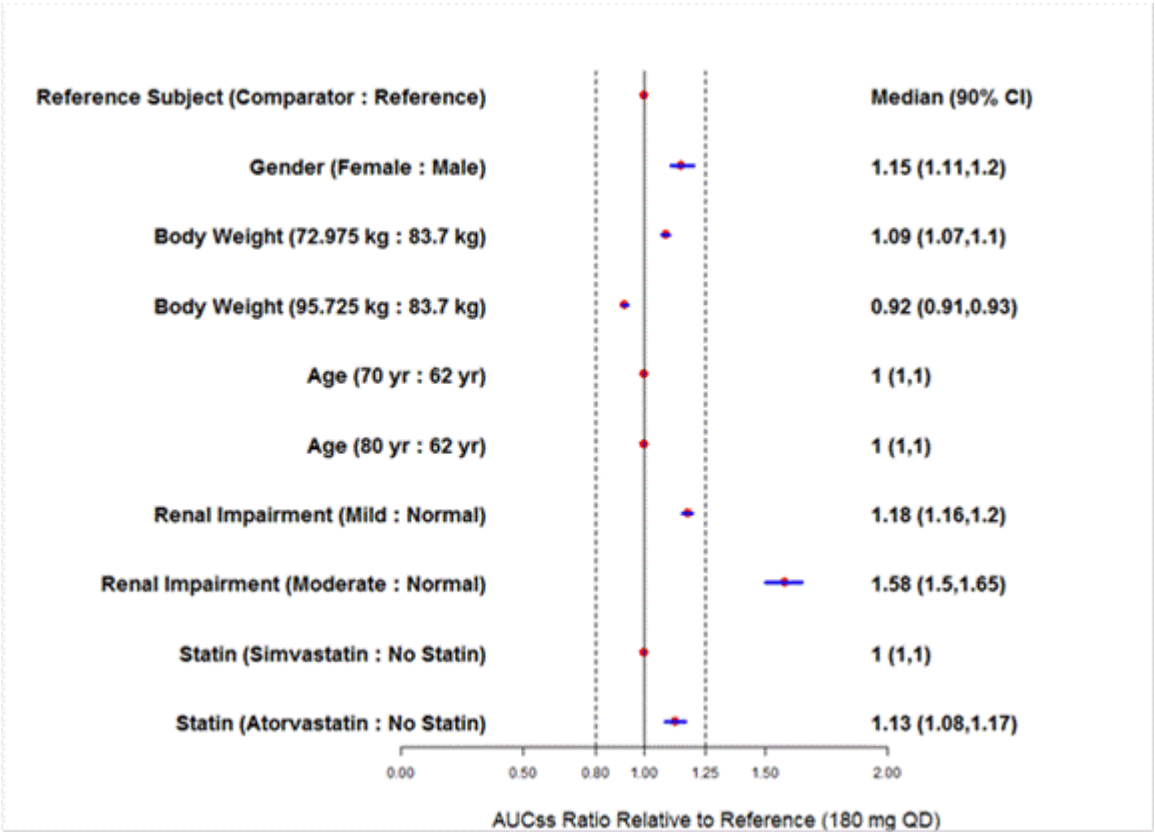
Bempedoic acid and ESP15228 exposure as measured by AUC increased with increasing degree of renal impairment; Cmax (after a single dose) was not substantially affected by renal impairment. The same trends have been observed for the unbound fractions of ETC-1002 and ESP15228. The clearance of ETC-1002 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 (ECT1002 and ESP15228) exposure 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, 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 body weight 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 the 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 9. Influence of Covariate Populations on Predicted Bempedoic Acid exposure at steady state



2.4.2.2.3. Interactions

In vitro

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 C_{max} 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 4. Summary of the drug drug interaction studies 1002-037 and 1002-012with 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 C_{max} 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 C_{max} 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.

2.4.2.2.4. 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.

2.4.2.3. Pharmacokinetics of ezetimibe

The pharmacokinetics of ezetimibe were mainly described using literature review and have briefly been described below.

After oral administration, ezetimibe was absorbed and extensively conjugated to a phenolic glucuronide form (ezetimibe-glucuronide) that is at least as pharmacologically active as the parent drug. Ezetimibe undergoes enterohepatic recirculation. Multiple peaks of unconjugated ezetimibe are observed. Ezetimibe-glucuronide constitutes 80-90% of plasma drug levels with unconjugated ezetimibe the remaining 10-20%. After a single dose of ezetimibe 10 mg in fasting adults, mean ezetimibe Cmax was 3.4 to 5.5 ng/mL, with tmax of 4 to 12 hours, and ezetimibe-glucuronide mean Cmax was 45 to 71 ng/mL and tmax was 1 to 2 hours.

The *in vitro* human plasma protein binding ranged from 99.5% to 99.8% and 87.8% to 92.0% for ezetimibe and ezetimibe-glucuronide, respectively.

Ezetimibe is metabolized primarily in the small intestine and liver via glucuronide conjugation with subsequent biliary and renal excretion. *In vitro* studies identified intestinal and hepatic contribution by UGT1A1, UGT1A3, and UGT2B15 to the formation of the phenolic glucuronide. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

Following oral administration of 14C-ezetimibe (20 mg) to human subjects, total ezetimibe (ezetimibe and ezetimibe-glucuronide) accounted for approximately 93% of the total radioactivity in plasma. Approximately 78% and 11% of the administered radioactivity were recovered in the feces and urine, respectively.

The mean AUC for total ezetimibe after a single dose of 10 mg increased approximately 1.7-fold in patients with mild hepatic impairment (Child-Pugh score 5 to 6), compared with healthy subjects; and in a multiple-dose study in patients with moderate hepatic impairment, the mean AUC values for total ezetimibe and ezetimibe were increased approximately 4-fold compared with healthy subjects. Ezetimibe is not recommended for patients with moderate or severe hepatic impairment due to the unknown effects of these increases in exposure.

No adjustment to ezetimibe dose is needed when administered as a monotherapy in patients with renal impairment.

The inter-individual variability of ezetimibe and ezetimibe-glucuronide was characterized as moderate. with published %CV values of 49% and 53% for C_{max} and AUC, respectively, in a meta-analysis across a wide range of studies. For variability of the FDC was moderate as well with values of C_{max} (%CV 48% to 65%) and AUC (%CV 45% to 65%).

Ezetimibe is reported to exhibit dose-proportional exposure for both C_{max} and AUC across a dose range from 5 to 20 mg following a single dose and across a dose range of 10 to 50 mg following multiple doses.

For the exposure relevant for safety The C_{max} and AUC for ezetimibe-glucuronide and total ezetimibe observed in the FDC studies using a 10 mg QD ezetimibe regimen in combination with bempedoic acid were similar to steady-state levels in historical studies with 20 mg QD regimen of ezetimibe because of the known interaction between bempedoic acid and ezetimibe-glucuronide. Published values for the 20 mg dose for total ezetimibe Cmax and AUC are 103 ng/mL and 1314 ng·h/mL, respectively

2.4.2.4. Pharmacokinetics of fixed dose combination

In study **1002FDC-034**, the relative bioequivalence of bempedoic acid and ezetimibe was compared between the FCMP and the single components. According to the Guideline on the clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017), demonstration of similar pharmacokinetics of the fixed combination medicinal product versus its individual active substances can be used to bridge clinical data establishing the contribution of each active substance and the positive risk balance. Therefore, study **1002FDC-034** is considered a pivotal study for the MAA of the FCMP.

The bioequivalence results of study **1002FDC-034** are displayed below in Table 5 for bempedoic acid (ETC-1002) and the active metabolite (ESP15228) and in Table 6 for ezetimibe unconjugated and ezetimibe-glucuronide. The ANOVA analysis has been conducted on subjects with evaluable data for both Test and Reference product, in line with the bioequivalence guideline.

Table 5: Relative Bioavailability Evaluation Comparing the Bempedoic Acid-Ezetimibe FDC (Test) with Bempedoic Acid and Ezetimibe Tablets Coadministered (Reference): by 2 Methods, Mixed-Effect Model and Fixed-Effects ANOVA: Bempedoic Acid Parent Compound (ETC-1002) and Active Metabolite (ESP15228) (Study 1002FDC-034).

		Mixed Effects		ANOVA – Fixed Effects	
PK Parameter	**Treatment**	**Geometric LS Means**	**Ratio of Geometric LS Means (90% CI of the Ratio)**	**Geometric LS Means**	**Ratio of Geometric LS Means (90% CI of the Ratio)**
ETC-1002					
C_{max} (µg/mL)	Reference	13.1	--	13.2	--
	Test	12.2	0.934 (0.861, 1.013)	12.2	0.923 (0.829, 1.028)
AUC_{inf} (µg·h/mL)	Reference	196.8	--	200.7	--
	Test	194.8	0.990 (0.950, 1.032)	198.3	0.988 (0.892, 1.095)
AUC_{last} (µg·h/mL)	Reference	195.0	--	198.9	--
	Test	193.2	0.991 (0.948, 1.035)	196.7	0.989 (0.891, 1.098)
ESP15228					
C_{max} (µg/mL)	Reference	0.7	--	0.7	--
	Test	0.7	1.017 (0.956, 1.081)	0.7	1.017 (0.924, 1.120)
AUC_{inf} (µg·h/mL)	Reference	36.3	--	37.9	--
	Test	37.8	1.043 (0.985, 1.104)	39.3	1.038 (0.887, 1.215)
AUC_{last} (µg·h/mL)	Reference	35.1	--	36.7	--
	Test	36.5	1.041 (0.980, 1.105)	38.0	1.036 (0.886, 1.212)

Table 6: Relative Bioavailability Evaluation Comparing the Bempedoic Acid-Ezetimibe FDC (Test) with Bempedoic Acid and Ezetimibe Tablets Coadministered (Reference): by 2 Methods, Mixed-Effect Model and Fixed-Effects ANOVA: Ezetimibe (Unconjugated), Ezetimibe-glucuronide, and Total Ezetimibe (Study 1002FDC-034).

Analyte		Mixed Effects		ANOVA – Fixed Effects	
Ezetimibe (unconjugated)					
PK Parameter	**Treatment**	**Geometric LS Means**	**Ratio of Geometric LS Means (90% CI of the Ratio)**	**Geometric LS Means**	**Ratio of Geometric LS Means (90% CI of the Ratio)**
C_{max} (ng/mL)	Reference	3.7	--	3.6	--
	Test	3.2	0.874 (0.739, 1.034)	2.9	0.825 (0.688, 0.989)
AUC_{inf} (ng·h/mL)	Reference	64.7	--	62.5	--
	Test	68.0	1.051 (0.775, 1.426)	55.8	0.893 (0.493, 1.619)
AUC_{last} (ng·h/mL)	Reference	50.0	--	49.4	--
	Test	50.1	1.001 (0.864, 1.159)	47.7	0.965 (0.763, 1.221)
Ezetimibe-glucuronide					
C_{max} (ng/mL)	Reference	130.9	--	127.7	--
	Test	101.8	0.778 (0.671, 0.902)	99.6	0.780 (0.640, 0.951)
AUC_{inf} (ng·h/mL)	Reference	1155.2	--	1350.3	--
	Test	1096.0	0.949 (0.838, 1.075)	1222.2	0.905 (0.708, 1.156)
AUC_{last} (ng·h/mL)	Reference	1050.4	--	1052.2	--
	Test	981.4	0.934 (0.843, 1.035)	974.4	0.926 (0.708, 1.211)
Total Ezetimibe					
PK Parameter	**Treatment**	**Geometric LS Means**	**Ratio of Geometric LS Means (90% CI of the Ratio)**	**Geometric LS Means**	**Ratio of Geometric LS Means (90% CI of the Ratio)**
C_{max} (nmol/L)	Reference	234.4	--	228.2	--
	Test	183.0	0.781 (0.677, 0.901)	178.1	0.781 (0.646, 0.944)
AUC_{inf} (nmol·h/L)	Reference	2440.8	--	2405.9	--
	Test	2364.9	0.969 (0.717, 1.310)	1803.6	0.750 (0.498, 1.129)
AUC_{last} (nmol·h/L)	Reference	1934.4	--	1933.7	--
	Test	1817.0	0.939 (0.848, 1.040)	1798.4	0.930 (0.718, 1.204)

Bempedoic acid and the active metabolite are within the acceptance criteria of 80.00 – 125.00%. However, the $AUC_{0\text{-}inf}$ and C_{max} of ezetimibe (unconjugated), ezetimibe-glucuronide and total ezetimibe are outside the acceptance criteria of 80.00-125.00%. We consider the clinical Study 1002FDC-053 as primary evidence. This study demonstrated a positive benefit/risk for the FDC. Therefore, we do not expect a clinical difference from switching from the monocomponents to the FDC.

Study **1002FDC-055** demonstrated that for bempedoic acid mean Cmax was reduced 30% after fed relative to fasted administration and median tmax was delayed 2 hours. Similarly, ezetimibe mean AUCs were not affected by a high-fat meal; mean ezetimibe Cmax was reduced 12% and median tmax was prolonged 2.5 hours under fed relative to fasted conditions. For ezetimibe-glucuronide, AUCinf and Cmax were decreased by 12% and 42%, respectively, under fed relative to fasted conditions.

In study **1002FDC-053**, trough plasma concentrations were collected for bempedoic acid and ezetimibe. These concentrations were compared with the other study. After exclusion of three clinical sites, the trough concentrations appeared to be similar for bempedoic acid between studies. Mean trough concentrations for ezetimibe-glucuronide were higher with administration of the FCMP (85.2 to 109 ng/mL) than when ezetimibe was administered as monotherapy (49.2 to 52.8 ng/mL).

2.4.3. Pharmacodynamics

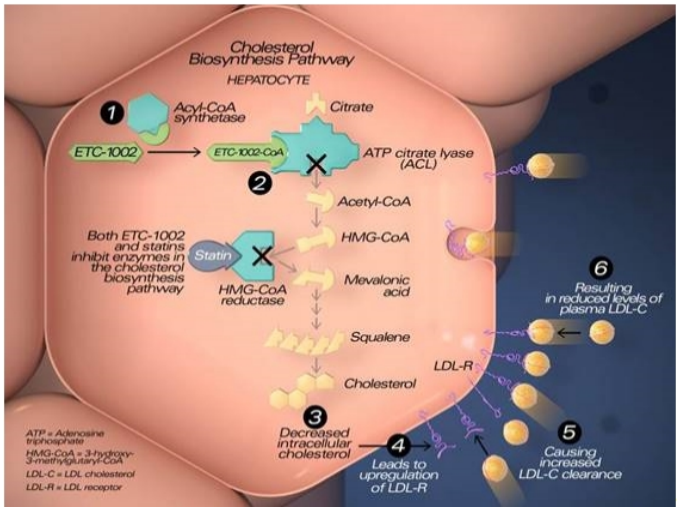
Mechanism of action

Bempedoic Acid 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.

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 LDL-Rs (Figure 8). 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 activity that is thought to lead to improvements in glycemic control in hyperglycemic animal models.

Figure 10. Mechanism of Action 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.

Ezetimibe Mechanism of Action

The molecular target of ezetimibe inhibits the absorption of cholesterol by inhibition of the Niemann-Pick C1-Like 1 (NPC1L1) receptor leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in LDL receptors, resulting in clearance of cholesterol from the blood. This distinct mechanism is complementary to that of bempedoic acid.

Primary and Secondary pharmacology

Bempedoic Acid PD effect

The mechanism of action could not be formally tested in any clinical setting, only the eventual PD result in terms of LDL-C could be demonstrated.

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, 200 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 9 and Table 7 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 11. Percent Change From Baseline to Day 15 in Calculated LDL-C by Dose (Study 1002-002, Cohorts 1-4; Study 1002-004)

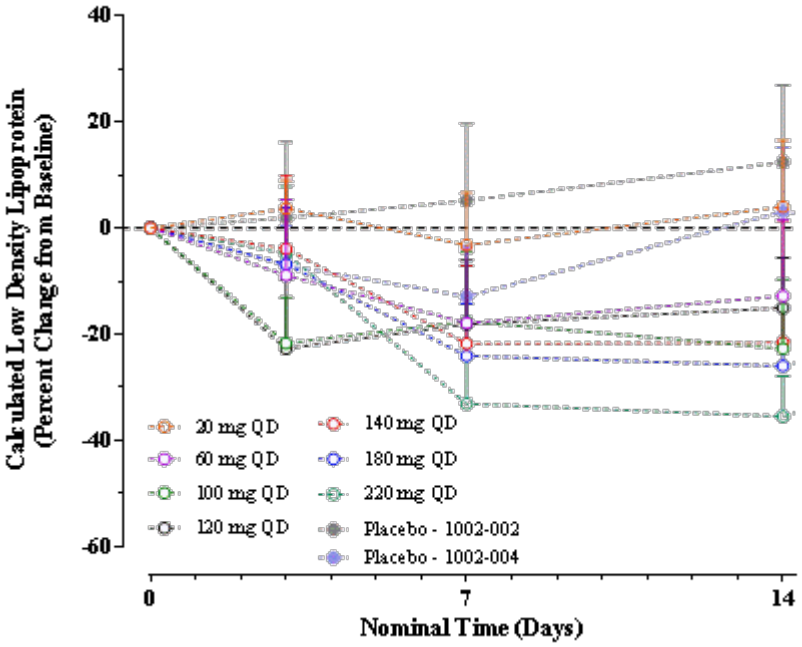


Table 7. Percent Change From Baseline to Day 15 in Lipid Levels (Study 1002-002, Cohorts 1-4; Study 1002-004)

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)

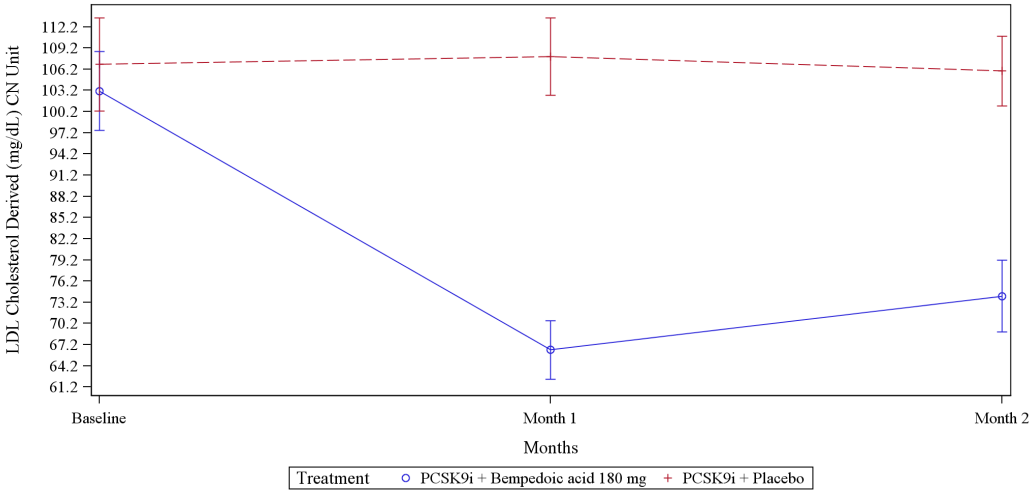
Interaction with PCSK9 inhibitors

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 a 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 10.

Figure 12. Mean (± SEM) LDL-C Values by Visit (LOCF) (Study 1002-039)



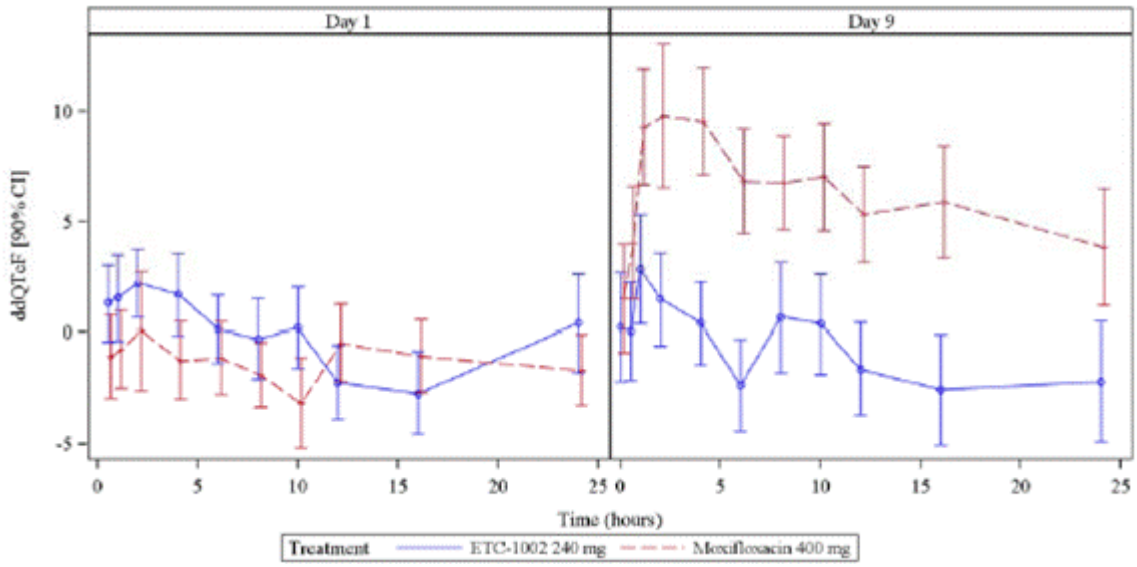
Secondary pharmacology: QT prolongation

A thorough QT study was performed to assess the 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 11.

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.

Figure 13. 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.

Ezetimibe PD effect

Evidence of effectiveness of ezetimibe as a single-agent product comes from previous findings of efficacy for ezetimibe, including published information on ezetimibe available in the scientific literature (Ezetrol SmPC, 2018; Zetia USPI, 2013).

Bempedoic Acid with Ezetimibe PD effects

The PD effects of the FCMP are discussed in the efficacy section.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

In general, the pharmacokinetics were adequately characterised in the clinical pharmacology programme of bempedoic acid. The pharmacokinetics of ezetimibe were characterised in the FDC studies and summarised based on literature review.

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.

The bioanalytical methods for ezetimibe are validated and generally acceptable for the analysis of ezetimibe in plasma. 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.

For all models developed by the applicant, covariates were fit simultaneously with a pre-defined structure but without a formal covariate step (e.g. backwards elimination). Additional analyses were conducted by the applicant using a more formal covariate step (e.g. backwards elimination, forward-selection procedure). There appears to be misspecification present in the VPC, mainly in the early time course of the trials. Therefore, the model predicted influence of the covariates should be interpreted with care. The model is not fit for extrapolation.

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.

Ezetimibe

The pharmacokinetics of ezetimibe is well known and were adequately summarised by the applicant.

FCMP

The demonstration of bioequivalence is necessary to bridge the benefit-risk balance of the individual components of both bempedoic acid and ezetimibe to the FCMP. In the pivotal study **1002FDC-034**, bioequivalence between the FCMP and the mono components bempedoic acid and ezetimibe could not be demonstrated for ezetimibe. However, the clinical study 1002FDC-053 was considered as primary evidence. This study demonstrated a positive benefit/risk for the FDC. Therefore, it was agreed a clinical difference is not expected when switching from the monocomponents to the FDC.

Exposure of ezetimibe increased after the coadministration with the OATP1B1 inhibitor bempedoic acid. It is known that the dose response relationship of ezetimibe is rather flat and the impact on clinical safety is limited as 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. Therefore the FDC can be administered safely.

In the food effect study, the AUCinf and Cmax of ezetimibe-glucuronide decreased 12% and 42%, respectively, under fed relative to fasted conditions. These changes were not considered to significantly impact the safety and efficacy of the FCMP. Therefore, the FCMP can be administered irrespective of food intake.

Pharmacodynamics

Bempedoic acid

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.

The PD marker of LDL-C lipid-lowering effect was sufficiently demonstrated in several short term 15 days phase I studies in healthy volunteers, several phase 2 studies (6 to 12 weeks) in a diseased population, and confirmed in several phase 3 studies.

Specific evaluation of the QT effect has been explored in a thorough QT study (in addition to non-clinical evaluation) and did not suggest any pro-arrhythmic effect of bempedoic acid. For ezetimibe this has not been specifically investigated, although there is sufficient experience with ezetimibe in clinical practice to conclude that no specific effect is identified, and QT prolongation has not been identified as an adverse drug reaction.

Ezitimibe

Ezetimibe inhibits the absorption of cholesterol in the small intestine by inhibition of the Niemann-Pick C1-Like 1 (NPC1L1) sterol transporter, as described.

FCMP

There is sufficient rationale to combine bempedoic acid with ezetimibe as both products have a distinct but complementary mechanism of action. Bempedoic acid is an ACL inhibitor that lowers LDL-C by inhibition of cholesterol synthesis in the liver, while ezetimibe inhibits the absorption of cholesterol in the small intestine by inhibition of the Niemann-Pick C1-Like 1 (NPC1L1) sterol transporter.

2.4.5. Conclusions on clinical pharmacology

Bempedoic acid

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.

Ezetimibe

The PK and PD effects of ezetimibe have adequately been summarised.

FCMP

Bioequivalence between the FCMP and the monocomponents has only been demonstrated for bempedoic acid. Although the pharmacokinetic parameters of ezetimibe are currently outside the 80.00-125.00% bioequivalence acceptance criteria, the FDC can be accepted as the pivotal clinical study 1002FDC-053 is considered as primary evidence. This study demonstrated a positive benefit/risk for the FDC.

Exposure of ezetimibe increased approximately 2- fold after the coadministration with the OATP1B1 inhibitor bempedoic acid, however, as it has been shown that the FCMP can be administered safely this increase is considered acceptable.

From a pharmacodynamic point of view, the mode of action of bempedoic acid has reasonably well established. LDL-C lowering has been demonstrated. There is no sign of any proarrhythmic effect for both products.

2.5. Clinical efficacy

2.5.1. Dose response studies and Main studies

In Table 8 the phase 2 studies are presented.

Table 8. 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 8. 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 8. 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 8. 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 8. 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 9 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 9. 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 clinical studies of bempedoic acid

There are 4 phase 3 main studies that provided evidence of the effectiveness of bempedoic acid as monocomponent. These included two studies on top of maximum tolerated statins (studies 1002-040 and 1002-047) and two studies in statin intolerant patients (none or low dose statin)(studies 1002-046

and 1002-048). The open-label extension study (1002 050) included patients from study 1002 040 and is still ongoing.

- Study 1002-047: Safety and Efficacy in Patients with HeFH and/or ASCVD
  A 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 1002-040: Safety Study in Patients with HeFH and/or ASCVD
  A 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.

- Study 1002-046: Bempedoic Acid Added to Background Lipid Modifying Therapy.
  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 1002-048: Bempedoic Acid Added to Ezetimibe Background Therapy
  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 1002-050: Open-label extension study
  A Multicenter Open-Label Extension (OLE) Study to Assess the Long-Term Safety and Efficacy of Bempedoic Acid (ETC-1002) 180 mg

These studies are discussed below.

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 randomsiation. Patients who met all enrollment criteria were instructed to continue their therapy(s) for lipid regulation and to maintain consistent diet and exercise patterns 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 labeled 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 10 below.

Table 10. 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[a] (ASCVD and/or HeFH with hyperlipidemia)	High CV risk[a] (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[plus other 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[b] 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[c] 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 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 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 11. 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 12 below.

Table 12. 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 13.

Table 13. 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 14.

Table 14. 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[i]	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%.

and a common standard deviation of 15%.

Randomisation and blinding (masking)

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 15):

• 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 15. 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	A stepdown approach was used to test the primary and then key secondary endpoints. The sequence for the stepdown procedure was change 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	1002-047 1002-040 1002-046 1002-048

Endpoints	Statistical Methods[a]	Studies
from baseline in LDL-C, non-HDL-C, TC, apo B, and hsCRP in ITT population	statistical significance at each step was required to test the next lipid parameter.	
	Percent change from baseline for LDL-C, non-HDL-C, TC and apo B were assessed using ANCOVA, with treatment group and randomization strata (as applicable) as factors, and respective baseline value as a covariate.	1002-047 1002-040 1002-046 1002-048
	Due to skewed distribution attributed to extreme outliers and non-normal distribution, 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

Disposition

Patient disposition is provided in **Table 16** below.

Table 16. 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

	High CV Risk				No or Low-Dose Statin			
	Study 1002-047		Study 1002-040		Study 1002-046		Study 1002-048	
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)
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 17 below.

Table 17. 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

Table 17. 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)
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)
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)

Table 17. 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)
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)
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)	NA2.	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 the Table 18, Table 19, Table 20 and Table 21 below.

Table 18. 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 19. 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 20. 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 21. 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 22. 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, 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, 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.

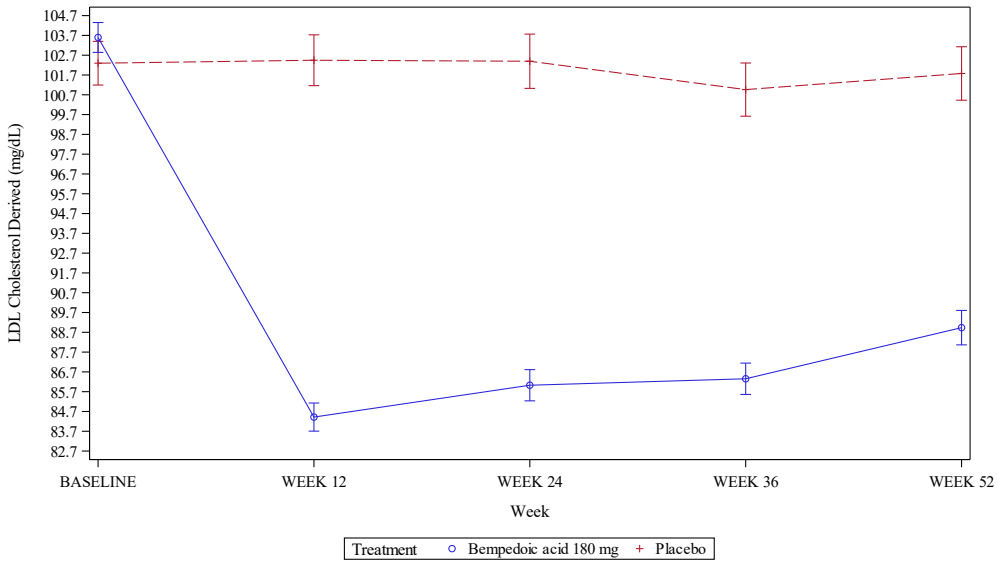
Anncillary analyses

Long term LDL-C lowering efficacy

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

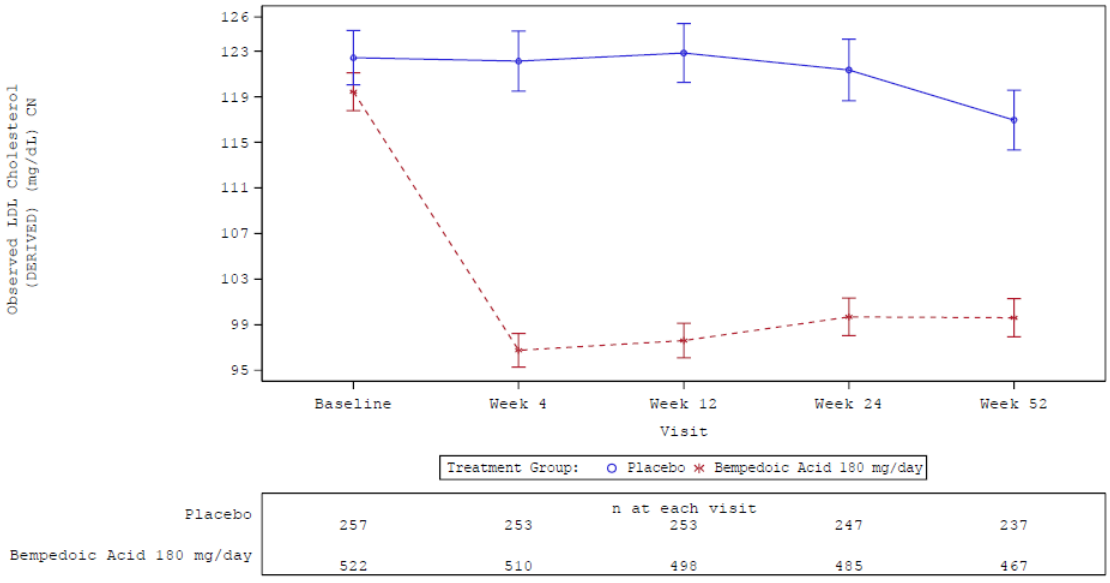
The LDL-C lowering effect of bempedoic acid for the studies on top of maximum tolerated statin therapy is provided below in Figure 12and Figure 13.

Figure 14. LDL-C Observed Values (Mean ± SE) by Visit (Observed Data) in Study 1002-040 (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%)).

Figure 15. LDL-C Observed Values (Mean ± SE) by Visit (Observed Data) in Study 1002-047 (Full Analysis Set)



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

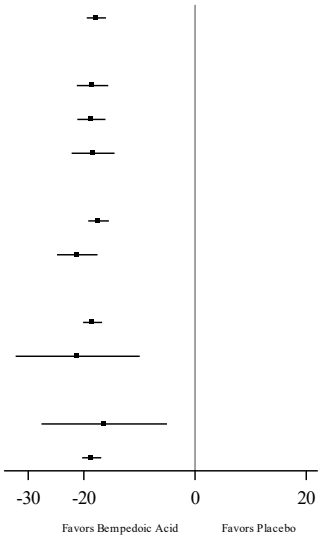
Time Point Statistic	Former Placebo Patients	Former Bempedoic Acid Patients
Study 1002-040 baseline		
n	492	970
Mean (SD), mg/dL	98.96 (24.170)	102.94 (29.899)
Study 1002-050 baseline		
n	492	970
Mean change from baseline (SD), mg/dL	0.53 (22.623)	-16.35 (26.709)
Mean percent change from baseline (SD)	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

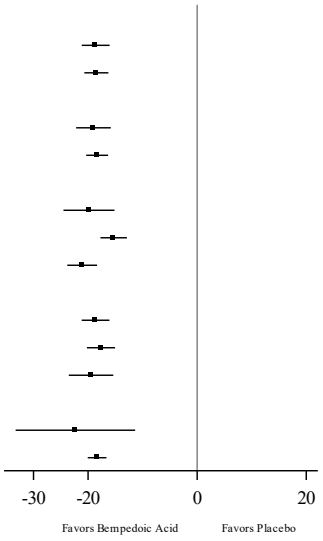
The treatment effect at week 12 according to several subgroups is provided in Figure 14 for the combined studies on top of statins (1002-040, 1002-047) and in Figure 15 for the statin intolerant patients (1002-046, 1002-048).

Figure 16. 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)

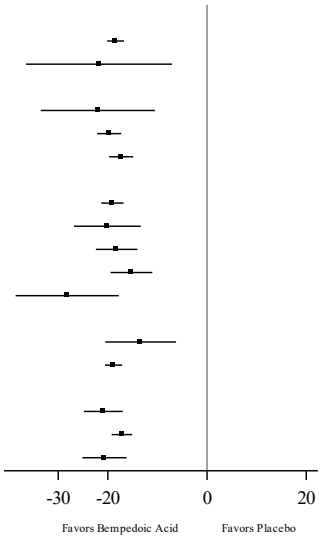
	Pbo LS mean of % change from baseline (N)	BA 180 mg LS mean of % change from baseline (N)	LS Mean Diff [95% CI]
Overall	1.765 (978)	-15.985 (1922)	-17.750 (-19.473, -16.027)
Age			
18 - <65 years	1.250 (374)	-17.183 (827)	-18.433 (-21.260, -15.606)
65 - <75 years	2.010 (442)	-16.630 (800)	-18.640 (-21.173, -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)



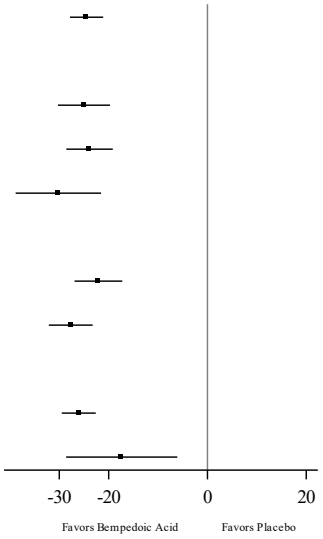
	Pbo LS mean of % change from baseline (N)	BA 180 mg LS mean of % change from baseline (N)	LS Mean Diff [95% CI]
Prior ASCVD			
Yes	1.800 (953)	-16.643 (1869)	-18.442 (-20.139, -16.746)
No	2.387 (25)	-19.387 (53)	-21.775 (-36.487, -7.063)
Baseline Statin Intensity			
No	-1.509 (29)	-23.528 (51)	-22.019 (-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)



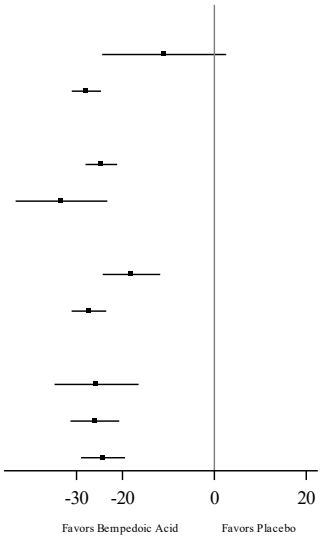
For the high risk pool, **p for interaction** were significant for gender (0.044), baseline BMI category (0.007), and borderline significant for baseline statin intensity (0.060).

Figure 17. 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)

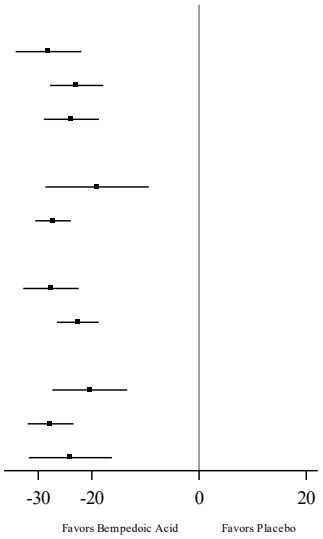
	Pbo LS mean of % change from baseline (N)	BA 180 mg LS mean of % change from baseline (N)	LS Mean Diff [95% CI]
Overall	1.474 (189)	-23.000 (399)	-24.474 (-27.836, -21.113)
Age			
18 - <65 years	2.200 (84)	-22.801 (172)	-25.000 (-30.262, -19.739)
65 - <75 years	-0.863 (75)	-24.738 (167)	-23.875 (-28.578, -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)



	Pbo LS mean of % change from baseline (N)	BA 180 mg LS mean of % change from baseline (N)	LS Mean Diff [95% CI]
Ethnicity			
Hispanic	7.204 (23)	-3.723 (54)	-10.927 (-24.434, 2.581)
non-Hispanic	0.697 (166)	-27.155 (345)	-27.852 (-31.039, -24.665)
Region			
North America	1.515 (175)	-23.087 (367)	-24.602 (-28.038, -21.167)
Europe	-0.331 (14)	-33.613 (32)	-33.282 (-43.256, -23.309)
History of Diabetes			
Yes	-2.519 (40)	-20.562 (96)	-18.043 (-24.300, -11.786)
No	2.344 (149)	-24.959 (303)	-27.303 (-31.064, -23.543)
Baseline BMI			
<25 kg/m^2	-1.810 (23)	-27.449 (59)	-25.640 (-34.781, -16.498)
25 - <30 kg/m^2	3.207 (82)	-22.800 (161)	-26.008 (-31.313, -20.702)
>=30 kg/m^2	0.454 (84)	-23.784 (179)	-24.238 (-29.023, -19.453)



	Pbo LS mean of % change from baseline (N)	BA 180 mg LS mean of % change from baseline (N)	LS Mean Diff [95% CI]
Baseline LDL-C Category			
<130 mg/dL	8.203 (79)	-19.889 (152)	-28.092 (-34.225, -21.958)
130 - <160 mg/dL	-2.280 (54)	-25.129 (124)	-22.849 (-27.819, -17.879)
>=160 mg/dL	-4.149 (56)	-27.980 (123)	-23.831 (-28.968, -18.694)
Baseline Statin Use			
Yes	8.538 (32)	-10.484 (73)	-19.022 (-28.660, -9.384)
No	0.179 (157)	-27.067 (326)	-27.246 (-30.563, -23.929)
Baseline Ezetimibe Use			
Yes	2.774 (97)	-24.861 (207)	-27.635 (-32.798, -22.472)
No	-0.235 (92)	-22.861 (192)	-22.626 (-26.519, -18.734)
Baseline eGFR Category			
>=90 mL/min/1.73m^2	2.054 (30)	-18.338 (98)	-20.392 (-27.381, -13.403)
60 - 89 mL/min/1.73m^2	1.645 (121)	-26.057 (241)	-27.703 (-31.977, -23.428)
<=59 mL/min/1.73m^2	-0.310 (38)	-24.335 (60)	-24.026 (-31.788, -16.263)



For the low statin dose pool (Figure 15) **p for interaction** were significant for ethnicity (<0.001), history of diabetes (0.032), and baseline statin use (0.032).

Summary of main efficacy results Bempedoic Acid

Table 24, Table 25, Table 26 and Table 27 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 24. 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 subject	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 25. 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 subject	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	Primary	Comparison groups	Bempedoic Acid vs Placebo

comparison	efficacy endpoint	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 26. 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: Duration of Run-in phase: Duration of Extension phase:		24 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. 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 subject	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 and estimate variability	Treatment group	Bempedoic Acid	Placebo
	% 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 27. 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:	12 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. 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 subject	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 low dose or less than low dose statins		
Descriptive statistics	Treatment group	Bempedoic Acid	Placebo

and estimate	% 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 (SE))	-15.1 (1.28)	-2.9 (1.55)
		Difference (Bempedoic Acid-placebo) (LS mean)	-18.0
		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 28).

Table 28. 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[a]
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
[a] P value of comparisons between treatment groups was calculated using Chi-square test.

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 29 presents the results according to age for the phase 3 studies.

Table 29. 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

Main clinical studies of Ezetimibe

For ezetimibe monotherapy, a meta-analysis covering eight randomized, double-blind, placebo-controlled clinical trials (all 12 weeks) in individuals (over 18 years of age) with heterozygous familial and nonfamilial hypercholesterolaemia (Pandor et al, 2009) was used to present efficacy and safety data (see Table 1 for details on the trials). In total, 2,722 individuals were enrolled into these trials.

For ezetimibe combination therapy with statins, the lipid lowering efficacy is presented based on a meta-analysis of 27 published clinical trials (n = 21,794) conducted between 1999 and 2008. All studies were randomized, double-blind, active- or placebo-controlled trials that randomised hypercholesterolaemic adults to either statin (simvastatin, lovastatin, atorvastatin, rosuvastatin; n = 10,517) or statin plus ezetimibe (n = 11,714) for 6 to 24 weeks (Morrone et al, 2012). Thirteen trials evaluated first-line therapy, while 14 trials evaluated second-line treatment. The results on efficacy in the prevention of cardiovascular events was mainly based on the IMPROVE-IT study (Cannon et al, 2015). This was a study spanning 10 years, that assessed the impact of ezetimibe therapy in conjunction with simvastatin compared with simvastatin monotherapy on the rate of major cardiovascular events in high-risk patients (n = 18,144 patients). Additional meta-analyses including up to 109,244 patients in 11 randomized clinical trials were used to substantiate efficacy in the prevention of cardiovascular events (Ip et al, 2015).

Ezetimibe monotherapy

Relevant studies investigating ezetimibe monotherapy are presented in the table below.

Table 30. Summary of Characteristics of Studies Included in Meta-analysis of Ezetimibe Monotherapy Studies

Study	Design	Participant characteristics	Relevant Study treatments[a]
Ballantyne et al, 2003; USA	Multi-arm,[a] randomized double-blind, placebo-controlled, 2 x 5 factorial design 12-week study	Adult men and women (aged ≥18 years) with primary hypercholesterolaemia (LDL-C between 3.77 and 6.50 mmol/L and triglyceride level of ≤3.85 mmol/L after 6–12 weeks lipid lowering drug washout) **CV risk:** patients with the following diseases were excluded: congestive heart failure (NYHA class III or IV), uncontrolled cardiac arrhythmias, myocardial infarction, coronary bypass surgery, or angioplasty within 6 months of study entry, history of unstable or severe peripheral artery disease within 3 months, unstable angina pectoris; For 9 % of patients in the ezetimibe group a history of CHD was confirmed	Ezetimibe, 10 mg per day (n = 65) vs. placebo (n = 60)
Bays et al. 2004; USA	Multi-arm,[a] multi-centre, randomized, double-blind, placebo-controlled, 2 x 2 factorial design 12-week study	Adult men and women (aged 18 to 80 years) with primary hypercholesterolaemia (LDL-C between 3.77 and 6.50 mmol/L; triglyceride level of ≤3.85 mmol/L after 6–8 weeks of lipid lowering drug washout) **CV risk:** For about 13 % of patients overall, a history of CHD was confirmed	Ezetimibe, 10 mg per day (n = 149) vs. placebo (n = 148)
Davidson et al, 2002; USA	Multi-arm,[a] multi-centre, randomized, double-blind, placebo-controlled, 2 x 5 factorial	Adult men and women (aged ≥18 years) with primary hypercholesterolaemia (LDL-C between 3.77 and 6.50 mmol/L and triglyceride level of ≤3.85 mmol/L after adequate lipid lowering drug washout) **CV risk:** patients with the following diseases were excluded: congestive heart failure (NYHA class III or IV);	Ezetimibe, 10 mg per day (n = 61) vs. placebo (n = 70)

	design 12-week study	uncontrolled cardiac arrhythmias; history of unstable or severe peripheral artery disease within three months of study entry; unstable angina pectoris; myocardial infarction, coronary bypass surgery, or angioplasty within six months of study entry; uncontrolled or newly diagnosed (within one month of study entry) diabetes mellitus	
Dujovne et al, 2002; USA	Multi-centre, randomized double-blind, placebo-controlled, trial factorial design 12-week study	Adult men and women (aged ≥18 years) with a diagnosis of primary hypercholesterolaemia (LDL-C between 3.38 and 6.50 mmol/L and triglyceride level of ≤3.85 mmol/L after 6–12 weeks lipid lowering drug washout) **CV risk:** patients with the following diseases were excluded: congestive heart failure (NYHA class III or IV), uncontrolled cardiac arrhythmia, myocardial infarction, coronary bypass surgery or angioplasty within 6 months of study entry, history of unstable or severe peripheral artery disease within 3 months of study entry; unstable angina pectoris; disorders of	Ezetimibe, 10 mg per day (n = 666) vs. placebo (n = 226) (randomisation, 3:1 ratio)
Goldberg et al, 2004; USA	Multi-arm,[a] multi-centre randomized, double-blind, placebo-controlled, 2 x 2 factorial design 12-week study	Adult men and women (aged ≥18 years) with primary hypercholesterolaemia (LDL-C between 3.77 and 6.50 mmol/L and triglyceride level of ≤3.85 mmol/L after 6–8 weeks lipid lowering drug washout) **CV risk:** patients with the following diseases were excluded: congestive heart failure (NYHA class III or IV), uncontrolled cardiac arrhythmias, history of unstable or severe peripheral artery disease, myocardial infarction, coronary bypass surgery or angioplasty (within 3 months). For about 7 % of patients overall, a history of CHD was confirmed	Ezetimibe, 10 mg per day (n = 92) vs. placebo (n = 93)
Kerzner et al, 2003; USA	Multi-arm,[a] multi-centre, double-blind, randomized, placebo-controlled, 2 x 4 factorial design 12-week study	Adult men and women (aged ≥18 years) with primary hypercholesterolaemia (LDL-C between 3.75 and 6.47 mmol/L and triglyceride level of ≤3.99 mmol/L after adequate lipid lowering drug washout) **CV risk:** patients with the following diseases were excluded: congestive heart failure (NYHA class III or IV), uncontrolled cardiac arrhythmias, history of unstable or severe peripheral artery disease within 3 months, unstable angina pectoris, myocardial infarction, coronary bypass surgery, or angioplasty within 6 months For 3 % of patients in the ezetimibe group a history of CHD was confirmed	Ezetimibe, 10 mg per day (n = 72) vs. placebo (n = 64)
Knopp et al, 2003; USA	Multi-centre, randomized double-blind, placebo-controlled, balanced-parallel group 12-week trial	Adult men and women (aged ≥18 years) with a diagnosis of primary hypercholesterolaemia (LDL-C between 3.36 and 6.47 mmol/L and triglyceride level of ≤3.95 mmol/L after 6–12 weeks lipid lowering drug washout) **CV risk:** patients with the following diseases were excluded: congestive heart failure (NYHA class III or IV), uncontrolled cardiac arrhythmia, myocardial infarction, coronary bypass surgery, or angioplasty within 6 months, history of unstable or severe peripheral artery disease within 3 months, unstable angina pectoris. For 8 % of patients in the ezetimibe group a history of CHD was confirmed	Ezetimibe, 10 mg per day (n = 622) vs. placebo (n = 205) (randomisation, 3:1 ratio)
Melani et al, 2003; USA	Multi-arm,[a] multi-centre, double-blind, randomized, placebo-	Adult men and women (aged ≥18 years) with primary hypercholesterolaemia (LDL-C between 3.8 and 6.5 mmol/L and triglyceride level of ≤4.0 mmol/L after adequate lipid lowering drug washout)	Ezetimibe, 10 mg per day (n = 64) vs. placebo (n = 65)

	controlled, balanced-parallel-group, 2 x 4 factorial design 12-week study	**CV risk:** patients with the following diseases were excluded: congestive heart failure (NYHA class III or IV), uncontrolled cardiac arrhythmia, history of unstable or severe peripheral artery disease within 3 months, unstable angina pectoris, myocardial infarction, coronary bypass surgery, or angioplasty (within 6 months) For 7 % of patients overall, a history of CHD was confirmed, and 57% of patients had risk factors or a history of CVD.	

The % change from baseline compared with placebo in LDL-C in the individual studies varied from -16.70% (Bays et al, 2004) to -24.30% (Ballantyne et al, 2003).

In the pooled set of patients with primary hypercholesterolaemia, ezetimibe monotherapy significantly ($p < 0.00001$) reduced LDL-C concentrations by -18.58% (95% confidence interval [CI]: -19.67 to -17.48) compared with placebo. Ezetimibe monotherapy also significantly ($p < 0.00001$) improved total cholesterol (-13.46%, 95% CI: -14.22 to -12.70), high-density lipoprotein (HDL) cholesterol (3.00%, 95% CI: 2.06–3.94) and triglyceride concentrations (-8.06%, 95% CI: -10.92 to -5.20) compared with placebo.

Ezetimibe combination therapy

(Morrone et al, investigated 2012) the lipid-altering efficacy of ezetimibe/statin combination therapy versus statin monotherapy based on 27 published clinical trials (n = 21,794) conducted between 1999 and 2008. All studies were randomized, double-blind, active- or placebo-controlled trials that randomised hypercholesterolaemic adults to either statin (simvastatin, lovastatin, atorvastatin, rosuvastatin; n = 10,517) or statin plus ezetimibe (n = 11,714) for 6 to 24 weeks.

Thirteen trials evaluated first-line therapy, enrolling patients who were either drug naïve or underwent washout of previous lipid-modifying therapy. An additional 14 trials evaluated second-line treatment in patients previously on statins or receiving statins during the run-in period. Baseline characteristics were generally well balanced across the treatment overall population as well as within first- and second-line therapy subgroups. The mean age of study participants was 60 years with 36% ≥65 and 9% ≥75 years of age. The majority of participants were Caucasian (84%), there were slightly more men than women (52% vs. 48%), approximately 1/3 were diagnosed with CHD (34%) or diabetes mellitus (30%). Subjects enrolled in first-line studies had higher mean baseline levels for LDL-C, non-HDL-C, total C, and triglycerides than participants in second-line studies with prior statin therapy. HDL-C baseline levels were generally similar across all study populations.

In the large pool of patients with primary hypercholesterolaemia, ezetimibe+statin treatment showed significant additional improvements in lipid levels compared with statin monotherapy. The treatment difference for percent change from baseline, ie, the effect of ezetimibe on top of the statin treatment effect, was -15.1% ($p < 0.0001$) for LDL-C concentrations, -13.5% ($p < 0.0001$) for non-HDL cholesterol levels, -10.1% ($p < 0.0001$) for total cholesterol, -4.7% ($p < 0.0001$) for triglycerides, -8.6% ($p < 0.0001$) for hs-CRP, and 1.6% ($p < 0.0001$) for HDL cholesterol.

In addition, the percentage of patients achieving lipid concentration goals were higher in the group receiving ezetimibe+statin treatment compared with statin monotherapy. An LDL-C concentration goal of <100 mg/dL was achieved by 75.3% vs 51.9% in the ezetimibe+statin and the statin monotherapy groups, respectively. An LDL-C concentration goal of <70 mg/dL was achieved by 33.3% vs 15.1% in the ezetimibe+statin and the statin monotherapy groups, respectively. A non-HDL cholesterol concentration goal of <130 mg/dL was achieved by 75.3% vs 52.9% in the ezetimibe+statin and the statin monotherapy groups, respectively. A non-HDL cholesterol concentration goal of <100 mg/dL

was achieved by 40.6% vs 20.7% in the ezetimibe+statin and the statin monotherapy groups, respectively.

Efficacy in the prevention of atherosclerosis and cardiovascular events

IMPROVE-IT (Cannon et al, 2015) was the landmark trial, spanning a 10-year period, which assessed the impact of ezetimibe therapy in conjunction with simvastatin 40 mg (ezetimibe/simvastatin; n = 9067 patients) compared with simvastatin 40 mg monotherapy (n = 9077 patients) on the rate of major cardiovascular events in high-risk adult patients (n = 18,144 patients). Eligible patients were those who had been hospitalized within the preceding 10 days for a myocardial infarction or an ACS, who had an LDL-C <125 mg/dL (3.2 mmol/ L) for patients not receiving lipid lowering therapy or <100 mg/dL (2.6 mmol/L) for patients who were receiving lipid lowering therapy. The patients were followed for a median of 6 years during which time they were assessed for major cardiovascular events, assessed as cardiovascular death, nonfatal myocardial infarction, unstable angina requiring hospital admission, coronary revascularization ($\geqslant$ 30 days after randomization), or nonfatal stroke. The study found that the addition of ezetimibe to simvastatin 40 mg resulted in a significant reduction in LDL-C (median time-weighted average LDL-C during the study of 53.7 mg/dL [1.4 mmol/L] in the simvastatin/ezetimibe group versus 69.5 mg/dL [1.8 mmol/L] in the simvastatin-monotherapy group; p <0.001) and that the cardiovascular event rate at 7 years was 32.7% in the simvastatin/ezetimibe group compared with 34.7% in the simvastatin monotherapy group (absolute risk reduction 2.0%; HR 0.936; 95% CI 0.89-0.99; p = 0.016). This reduction in serious adverse outcomes was against a control group already demonstrating a very well treated lipid profile with a mean LDL-C of 69.5 mg/dL (1.8 mmol/L), which is well below current target guidelines. Adverse effects were similar in the two groups, demonstrating the safety profile of ezetimibe. This study provided evidence that ezetimibe conferred a protective benefit against major cardiovascular events when used in addition to a statin in high-risk patients through further reducing serum LDL-C levels (Banach et al, 2016).

The PRECISE-IVUS trial assessed patients with coronary artery disease, adopting a different approach to assess the effect of ezetimibe on atherosclerotic plaque burden. This randomized, controlled, prospective study compared ezetimibe in combination with atorvastatin with atorvastatin monotherapy, utilizing serial volumetric intravascular ultrasound studies to assess and compare coronary plaque burden and subsequent plaque regression between the two treatment arms at baseline, 9- and 12-month intervals after commencing treatment. There was a superior absolute change in percent atheroma volume (PAV) in the atorvastatin/ezetimibe arm compared with the atorvastatin monotherapy arm (−1.4% [95% CI: −3.4 to −0.1] vs. −0.3% [95% CI: −1.9% to 0.9%] with atorvastatin monotherapy; p = 0.001]. For PAV, a significantly greater percentage of patients in the atorvastatin/ezetimibe arm showed coronary plaque regression (78% versus 58%; p = 0.004) (Tsujita et al, 2015). This study therefore demonstrated that ezetimibe in combination with atorvastatin induced greater coronary plaque regression than atorvastatin monotherapy in patients with coronary artery disease.

The first major trial assessing the impact of ezetimibe on cardiovascular outcomes was the Study of Heart and Renal Protection (SHARP) trial (Baigent et al, 2011). This double blind, randomized trial assessed a group of patients with chronic kidney disease, investigating whether treatment with simvastatin 20 mg daily plus ezetimibe 10 mg daily had an impact on the incidence of major cardiovascular events compared with placebo. The study confirmed simvastatin/ezetimibe therapy significantly reduced both the LDL-C levels and the rate of cardiovascular events. However, it was unclear how much of this beneficial effect was attributed to ezetimibe versus simvastatin.

2.5.3. Main clinical studies of FCMP

There are 2 main studies that provided evidence of the effectiveness of the FCMP.

On top of statins (factorial design study)

- Study 1002FDC-053: This is a factorial pivotal 4-arm Phase 3, randomized, 12-week, controlled study comparing the FCMP with bempedoic acid alone, ezetimibe alone, and placebo added on to stable, maximally-tolerated statin therapy.

Statin intolerance (non-responders study)

- Study 1002-048: This is a phase 3 randomized, controlled bempedoic acid study that compared bempedoic acid with placebo as add-on therapy to ezetimibe (and no or no more than low doses of statins) for 12 weeks.

Both studies are discussed below. Study 1002-048 has already been discussed above in the context of no or-low-dose statin pool (see section "main studies of bempedoic acid as monocomponent"), however, this study is also discussed separately in the context of the effectiveness of the FCMP below.

Factorial design study 1002FDC-053 (on top of statins)

A Randomized, Double-Blind, Parallel Group Study to Evaluate the Efficacy and Safety of Bempedoic Acid 180 mg + Ezetimibe 10 mg Fixed Dose Combination Compared to Bempedoic Acid, Ezetimibe, and Placebo Alone in Patients Treated with Maximally Tolerated Statin Therapy (1002FDC-053) (ClinicalTrials.gov No. NCT03337308)

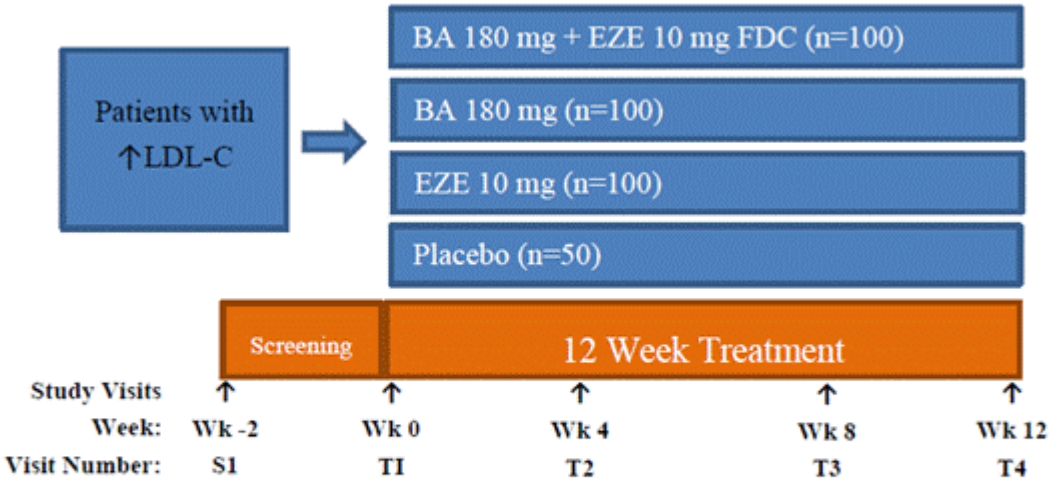
Methods

The primary support for efficacy of the *FCMP is provided by Study 1002FDC-053, a 4-arm, randomized, double-blind, parallel-group, multicenter study of the FCMP compared with bempedoic acid, ezetimibe, and placebo as individual components QD added on to a background of maximally tolerated statins in patients with high CV risk and hyperlipidemia.*

Screening occurred approximately within 2 weeks prior to randomization. It was planned to randomize approximately 350 eligible patients from approximately 125 sites in North America in a 2:2:2:1 ratio on Day 1/Week 0 to receive either bempedoic acid 180 mg + ezetimibe 10 mg FCMP (n = 100), bempedoic acid 180 mg (n = 100), ezetimibe 10 mg (n = 100), or placebo (n = 50) for 12 weeks. Randomized patients returned for clinic visits at Week 4, Week 8, and Week 12, see Figure 16. Patients who withdrew from study drug treatment were asked to continue to be followed for safety and efficacy.

Patients were required to be on maximally tolerated statin therapy with doses stable for at least 4 weeks prior to screening. Patients may have continued to use stable doses of TG-lowering medications (except fibrates and niacin including its derivatives) during the study. Post-randomization, pre-defined TG thresholds were set to notify investigators to provide an opportunity to adjust the patient's standard of care regimen. To control for effects of diet and exercise on efficacy endpoints, patients were counseled to follow a lipid-lowering diet as per local or regional guidelines and encouraged to participate in a regular exercise program throughout the study. Baseline LDL-C was defined as the mean of the values from Week -2 and pre-dose at Day 1/Week 0. Post-randomization, LDL-C and other efficacy endpoint results were masked to investigators and all study staff to maintain the blind.

Figure 18. Study Flow Chart



BA = bempedoic acid; EZE = ezetimibe; FDC = fixed dose combination; LDL-C = low-density lipoprotein cholesterol; S = Screening (Period); T = Treatment (Period); Wk = week.
Source: SAP Figure 1.

Study Participants

Patients were included if they had a high/very high CV risk (ASCVD, HeFH and/or multiple CV risk factors) with hyperlipidemia defined as LDL-C at Week -2: ≥100 mg/dL if ASCVD and/or HeFH ≥130 mg/dL if multiple CV risk factors were present.

CV risk definition

High risk was defined as 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.

Multiple cardiovascular risk factors defined as diabetes + 1 other risk factor or 3 risk factors that may have included, increased age (>45 men, >55 women), family history, smoking, hypertension, low HDL-C, coronary calcium score >95% for age/sex.

Relevant other exclusion criteria

TGs ≥500 mg/dL (5.6 mmol/L), eGFR (MDRD) <30 mL/min/1.73 m2, 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

Patients were randomized to receive either bempedoic acid 180 mg + ezetimibe 10 mg FCMP, bempedoic acid 180 mg, ezetimibe 10 mg, or placebo QD by mouth with or without food in a 2:2:2:1 randomisation for 12 weeks.

Objectives

The co-primary objectives were to assess LDL-C lowering efficacy in patients receiving maximally tolerated statin therapy and treated for 12 weeks with bempedoic acid 180 mg + ezetimibe 10 mg FCMP vs placebo, bemepdoic acid 180 mg, and ezetimibe 10 mg.

Outcomes/endpoints

Co-primary efficacy endpoints consisted of 3 comparisons of the percent change from baseline to week 12 in LDL-C for the FCMP versus placebo, FCMP versus ezetimibe, and FCMP versus bempedoic acid.

Secondary efficacy endpoints included the percent change from baseline to Week 12 in hsCRP, non-HDL-C, apo B, and TC.

Sample size

The assumed treatment difference in percent change in LDL-C at Week 12 between FDC and ezetimibe or bempedoic acid would be 13% with a standard deviation (SD) of 25%, and versus placebo 33% with SD of 25%. A sample size of 100 patients per active treatment group and 50 patients in the placebo arm (2:2:2:1) was selected to provide 95% power to detect a difference between FDC and ezetimibe or bempedoic acid at an alpha level of 0.05 using a 2-sided t-test, and >99% power to detect a difference between FDC and placebo.

Randomisation and blinding (masking)

Patients were randomized by an interactive web response system (IWRS) in a 2:2:2:1 ratio. The randomization was stratified by baseline statin intensity (high intensity (atorvastatin 40 to 80 mg/day and rosuvastatin 20 to 40 mg/day) vs other) and disease characteristics (ASCVD and/or HeFH vs multiple cardiovascular risk factors).

Statistical methods

An analysis of covariance (ANCOVA) with treatment group and randomization stratification as factors and baseline LDL-C as a covariate were performed to compare treatment groups (LDL-C: FDC vs placebo, FDC vs ezetimibe, and FDC vs bempedoic acid) for the primary endpoint using the FAS. In cases where the number of patients within a stratum was too small for a meaningful analysis, the strata were combined to obtain a larger cell size. The LS mean and SE, 95% confidence interval (CI) and associated p values for each treatment group, as well as for each treatment group comparison are provided. To account for the possibility of unequal variances between the groups, the ANCOVA model was implemented within a mixed model framework, where the <repeated/group=> option was used to allow separate estimation of residual variances for different groups.

Each of the comparisons within the co-primary endpoint family was conducted at a significance level of 0.05. If all 3 tests within the co-primary endpoint family achieved statistical significance, the hypothesis testing continued to the secondary endpoints; otherwise, all statistical comparisons for secondary endpoints were to be considered descriptive only.

Missing data was primarily handled using a pattern mixture model. Patients with missing lipid data that also discontinued study medication had their data imputed using placebo based imputation. Patients with missing data who were still taking study medication had data imputed using active arm imputation. Sensitivity analyses were performed using observed cases only, using on-treatment, completer and observed data analysis.

Results

Participant flow

The patient disposition is provided below in Table 31.

Table 31. Patient Disposition, All Screened Patients (Study 1002FDC-053)

Disposition	FCMP[a] (N = 108) n (%)	Bempedoic Acid 180 mg (N = 110) n (%)	Ezetimibe 10 mg (N = 109) n (%)	Placebo (N = 55) n (%)	Overall (N = 382) n (%)
Screened	-	-	-	-	821
Screen failure[b]	-	-	-	-	439 (53.5)
Randomized	108 (100.0)	110 (100.0)	109 (100.0)	55 (100.0)	382 (100.0)
Completed IMP	97 (89.8)	96 (87.3)	96 (88.1)	49 (89.1)	338 (88.5)
Withdrew from IMP	10 (9.3)	14 (12.7)	13 (11.9)	6 (10.9)	43 (11.3)
Withdrawal by patient	3 (2.8)	2 (1.8)	3 (2.8)	2 (3.6)	10 (2.6)
Protocol deviation	0	1 (0.9)	0	1 (1.8)	2 (0.5)
Lost to follow-up	0	2 (1.8)	0	0	2 (0.5)
Adverse event	7 (6.5)	9 (8.2)	10 (9.2)	2 (3.6)	28 (7.3)
Other	0	0	0	1 (1.8)	1 (0.3)
Completed study	103 (95.4)	103 (93.6)	104 (95.4)	53 (96.4)	363 (95.0)
Withdrew from study	5 (4.6)	7 (6.4)	5 (4.6)	2 (3.6)	19 (5.0)
Withdrawal by patient	2 (1.9)	1 (0.9)	2 (1.8)	1 (1.8)	6 (1.6)
Protocol deviation	0	1 (0.9)	0	0	1 (0.3)
Lost to follow-up	1 (0.9)	2 (1.8)	0	0	3 (0.8)
Adverse event	2 (1.9)	3 (2.7)	3 (2.8)	1 (1.8)	9 (2.4)

In the post hoc analysis that excluded three sites, a total of 301 patients were enrolled into the study and randomized, as follows: 86 patients in the FCMP group, 88 patients in the bempedoic acid group, 86 patients in the ezetimibe group, and 41 patients in the placebo group Table 32. Most patients (94.4%) completed the study (ie, completed all protocol-defined visits). IMP was discontinued in 13.6% of patients (11.6% FCMP, 14.8% bempedoic acid, 15.1% ezetimibe, 12.2% placebo). The most common reason for IMP discontinuation across all groups was adverse event (8.1% FCMP, 10.2% bempedoic acid, 11.6% ezetimibe, 4.9% placebo).

Table 32. Patient Disposition, Post Hoc Sensitivity Analysis

Disposition	FDC[a] (N = 108) n (%)	Bempedoic Acid 180 mg (N = 110) n (%)	Ezetimibe 10 mg (N = 109) n (%)	Placebo (N = 55) n (%)	Overall (N = 382) n (%)
Screened	-	-	-	-	686

Disposition	FDC[a] (N = 108) n (%)	Bempedoic Acid 180 mg (N = 110) n (%)	Ezetimibe 10 mg (N = 109) n (%)	Placebo (N = 55) n (%)	Overall (N = 382) n (%)
Screen failure[b]	-	-	-	-	385 (56.1)
Randomized	86 (100.0)	88 (100.0)	86 (100.0)	41 (100.0)	301 (100.0)
Completed IMP	75 (87.2)	75 (85.2)	73 (84.9)	36 (87.8)	259 (86.0)
Withdrew from IMP	10 (11.6)	13 (14.8)	13 (15.1)	5 (12.2)	41 (13.6)
Withdrawal by patient	3 (3.5)	2 (2.3)	3 (3.5)	1 (2.4)	9 (3.0)
Protocol deviation	0	1 (1.1)	0	1 (2.4)	2 (0.7)
Lost to follow-up	0	1 (1.1)	0	0	1 (0.3)
Adverse event	7 (8.1)	9 (10.2)	10 (11.6)	2 (4.9)	28 (9.3)
Other	0	0	0	1 (2.4)	1 (0.3)
Completed study	81 (94.2)	82 (93.2)	81 (94.2)	40 (97.6)	284 (94.4)
Withdrew from study	5 (5.8)	6 (6.8)	5 (5.8)	1 (2.4)	17 (5.6)
Withdrawal by patient	2 (2.3)	1 (1.1)	2 (2.3)	0	5 (1.7)
Protocol deviation	0	1 (1.1)	0	0	1 (0.3)
Lost to follow-up	1 (1.2)	1 (1.1)	0	0	2 (0.7)
Adverse event	2 (2.3)	3 (3.4)	3 (3.5)	1 (2.4)	9 (3.0)

Baseline data

Baseline data are provided below in Table 33, Table 34 and Table 35.

Table 33. Demographics and Disease Characteristics in Phase 3 Study 1002FDC-053 (Safety Population)

Characteristic	FCMP[a] (N = 107)	Bempedoic acid 180 mg (N = 110)	Ezetimibe 10 mg (N = 109)	Placebo (N = 55)	Overall (N = 381)
Age (years)					
n	107	110	109	55	381
Mean (SD)	63.1 (9.97)	65.2 (9.54)	64.4 (8.91)	65.6 (10.74)	64.4 (9.68)
Median	64.0	65.0	66.0	65.0	65.0
Q1, Q3	57.0, 70.0	59.0, 71.0	59.0, 70.0	58.0, 75.0	58.0, 71.0
Minimum, maximum	30, 85	38, 89	42, 87	39, 86	30, 89
Age group (years), n (%)					
18-40	1 (0.9)	1 (0.9)	0	1 (1.8)	3 (0.8)
41-64	56 (52.3)	50 (45.5)	48 (44.0)	26 (47.3)	181 (47.2)
65-74	37 (34.6)	40 (36.4)	46 (42.2)	13 (23.6)	136 (35.7)
≥75	13 (12.1)	19 (17.3)	15 (13.8)	15 (27.3)	62 (16.3)
Gender, n (%)					
Male	50 (46.7)	45 (40.9)	52 (47.7)	33 (60.0)	180 (47.2)
Female	57 (53.3)	65 (59.1)	57 (52.3)	22 (40.0)	201 (52.8)

Characteristic	FCMP[a] (N = 107)	Bempedoic acid 180 mg (N = 110)	Ezetimibe 10 mg (N = 109)	Placebo (N = 55)	Overall (N = 381)
Race, n (%)					
American Indian or Alaska Native	1 (0.9)	0	0	0	1 (0.3)
Asian	2 (1.9)	1 (0.9)	1 (0.9)	0	4 (1.0)
Black or African American	20 (18.7)	19 (17.3)	16 (14.7)	7 (12.7)	62 (16.2)
Native Hawaiian or Other Pacific Islander	0	0	1 (0.9)	0	1 (0.3)
White	84 (78.5)	90 (81.8)	91 (83.5)	48 (87.3)	313 (82.2)
Ethnicity, n (%)					
Hispanic or Latino	31 (29.0)	33 (30.0)	32 (29.4)	20 (36.4)	116 (30.4)
Not Hispanic or Latino	76 (71.0)	77 (70.0)	77 (70.6)	35 (63.6)	265 (69.6)
BMI (kg/m^2)					
Mean (SD)	31.23 (5.893)	30.55 (5.489)	30.37 (4.371)	30.49 (4.691)	30.68 (5.197)
Median	31.20	30.10	30.40	29.90	30.60
Q1, Q3	27.10, 34.50	26.20, 34.70	26.70, 33.70	27.20, 34.70	26.80, 34.30
Minimum, Maximum	17.6, 61.6	18.2, 41.6	19.8, 39.6	19.6, 41.6	17.6, 61.6
Disease diagnosis					
ASCVD and/or HeFH	59 (55.1)	63 (57.3)	62 (56.9)	31 (56.4)	215 (56.4)
Multiple cardiovascular risk factors	48 (44.9)	47 (42.7)	47 (43.1)	24 (43.6)	166 (43.6)
History of diabetes, n (%)					
Yes	48 (44.9)	62 (56.4)	61 (56.0)	24 (43.6)	195 (51.2)
No	59 (55.1)	48 (43.6)	48 (44.0)	31 (56.4)	186 (48.8)
eGFR category at baseline, n (%)					
Normal: ≥90 mL/min/1.73m²	38 (35.5)	35 (31.8)	41 (37.6)	25 (45.5)	139 (36.5)
Mild renal impairment: 60-89 mL/min/1.73m²	51 (47.7)	49 (44.5)	52 (47.7)	20 (36.4)	172 (45.1)
Moderate renal impairment: 30-59 mL/min/1.73m²	18 (16.8)	26 (23.6)	16 (14.7)	10 (18.2)	70 (18.4)

Table 34. Baseline Efficacy Parameters (Full Analysis Set)

Characteristic	FCMP[a] (N = 108) n (%)	Bempedoic Acid 180 mg (N = 110) n (%)	Ezetimibe 10 mg (N = 109) n (%)	Placebo (N = 55) n (%)	Overall (N = 382) n (%)
LDL-C (mg/dL)					

Mean (SD)	152.02 (38.869)	146.36 (36.345)	147.45 (38.723)	152.63 (42.357)	149.17 (38.583)
Median	142.50	139.50	139.50	152.00	142.50
Non-HDL-C					
Mean (SD)	185.85 (44.654)	178.48 (38.538)	179.10 (44.268)	182.24 (45.344)	181.28 (42.912)
Median	174.00	173.00	168.00	184.00	173.25
TC (mg/dL)					
Mean (SD)	235.01 (46.591)	228.24 (40.745)	230.37 (47.006)	232.28 (45.938)	231.34 (44.911)
Median	225.00	225.75	222.50	233.00	225.25
apo B (mg/dL)					
Mean (SD)	119.4 (29.83)	114.6 (26.36)	115.3 (29.36)	116.3 (29.54)	116.4 (28.64)
Median	117.5	114.0	107.0	117.0	113.0
Missing	4	3	2	3	12
hsCRP (mg/L)					
Mean (SD)	5.78 (10.346)	4.94 (6.351)	5.51 (5.938)	3.95 (3.774)	5.20 (7.341)
Median	3.12	2.95	3.03	3.01	3.02
Missing	2	1	1	1	5
TGs					
Mean (SD)	173.99 (87.863)	164.72 (73.078)	166.19 (77.834)	152.27 (58.676)	165.97 (77.116)
Median	157.50	149.75	146.00	141.50	148.00
HDL-C					
Mean (SD)	49.20 (13.465)	49.78 (12.139)	50.72 (14.782)	50.05 (12.726)	49.92 (13.353)
Median	47.50	50.25	48.00	46.00	48.00
Disease Diagnosis					
ASCVD and/or HeFH	60 (55.6)	63 (57.3)	62 (56.9)	31 (56.4)	216 (56.5)
Multiple cardiovascular risk factors	48 (44.4)	47 (42.7)	47 (43.1)	24 (43.6)	166 (43.5)
Statin Medications at Baseline					
No statin	33 (30.6)	27 (24.5)	32 (29.4)	14 (25.5)	106 (27.7)
High statin intensity	42 (38.9)	40 (36.4)	39 (35.8)	21 (38.2)	142 (37.2)
Other statin intensity	33 (30.6)	43 (39.1)	38 (34.9)	20 (36.4)	134 (35.1)
Concomitant statin therapy	75 (70.1)	83 (75.5)	77 (70.6)	42 (76.4)	277 (72.7)

In the post hoc sensitivity analysis, patient characteristics generally are similar to those of overall population except that the percentage of randomized patients of Hispanic and Latino ethnicity

decreased from 30.4% to 11.7% of the randomized population because a large proportion of the patients enrolled at the three sites were of Hispanic or Latino ethnicity.

Table 35. Demographics and Disease Characteristics in Phase 3 Study 1002FDC-053 (Safety Population Excluding Three Sites)

Characteristic	FCMP[a] (N = 85) n (%)	Bempedoic Acid 180 mg (N = 88) n (%)	Ezetimibe 10 mg (N = 86) n (%)	Placebo (N = 41) n (%)	Overall (N = 300) n (%)
Age (years)					
n	85	88	86	41	300
Mean (SD)	62.3 (9.47)	65.0 (9.77)	65.1 (8.43)	65.4 (10.75)	64.3 (9.50)
Median	62.0	65.0	66.0	64.0	64.0
Q1, Q3	56.0, 69.0	58.0, 71.5	59.0, 71.0	57.0, 73.0	58.0, 70.5
Minimum, maximum	30, 80	38, 86	42, 87	39, 86	30, 87
Age group (years), n (%)					
18-40	1 (1.2)	1 (1.1)	0	1 (2.4)	3 (1.0)
41-64	49 (57.6)	41 (46.6)	38 (44.2)	20 (48.8)	148 (49.3)
65-74	25 (29.4)	30 (34.1)	35 (40.7)	10 (24.4)	100 (33.3)
≥75	10 (11.8)	16 (18.2)	13 (15.1)	10 (24.4)	49 (16.3)
Gender, n (%)					
Male	42 (49.4)	40 (45.5)	43 (50.0)	24 (58.5)	149 (49.7)
Female	43 (50.6)	48 (54.5)	43 (50.0)	17 (41.5)	151 (50.3)
Race, n (%)					
American Indian or Alaska Native	1 (1.2)	0	0	0	1 (0.3)
Asian	2 (2.4)	1 (1.1)	1 (1.2)	0	4 (1.3)
Black or African American	16 (18.8)	17 (19.3)	12 (14.0)	7 (17.1)	52 (17.3)
Native Hawaiian or Other Pacific Islander	0	0	1 (1.2)	0	1 (0.3)
White	66 (77.6)	70 (79.5)	72 (83.7)	34 (82.9)	242 (80.7)

Characteristic	FCMP[a] (N = 85) n (%)	Bempedoic Acid 180 mg (N = 88) n (%)	Ezetimibe 10 mg (N = 86) n (%)	Placebo (N = 41) n (%)	Overall (N = 300) n (%)
Ethnicity, n (%)					
Hispanic or Latino	9 (10.6)	11 (12.5)	9 (10.5)	6 (14.6)	35 (11.7)
Not Hispanic or Latino	76 (89.4)	77 (87.5)	77 (89.5)	35 (85.4)	265 (88.3)
BMI (kg/m^2)					
Mean (SD)	85	88	86	41	300
Median	31.12 (6.348)	30.59 (5.459)	29.92 (4.436)	30.65 (4.187)	30.56 (5.305)
Q1, Q3	31.20	30.40	29.95	30.30	30.45
Minimum, Maximum	26.50, 34.50	25.90, 34.50	26.30, 33.00	27.60, 33.50	26.55, 34.00
Disease diagnosis					
ASCVD and/or HeFH	52 (61.2)	55 (62.5)	54 (62.8)	26 (63.4)	187 (62.3)
Multiple cardiovascular risk factors	33 (38.8)	33 (37.5)	32 (37.2)	15 (36.6)	113 (37.7)
History of diabetes, n (%)					
Yes	34 (40.0)	45 (51.1)	43 (50.0)	17 (41.5)	139 (46.3)
No	51 (60.0)	43 (48.9)	43 (50.0)	24 (58.5)	161 (53.7)
eGFR category at baseline, n (%)					
Normal: ≥90 mL/min/1.73m²	29 (34.1)	27 (30.7)	29 (33.7)	19 (46.3)	104 (34.7)
Mild renal impairment: 60-89 mL/min/1.73m²	40 (47.1)	41 (46.6)	43 (50.0)	14 (34.1)	138 (46.0)
Moderate renal impairment: 30-59 mL/min/1.73m²	16 (18.8)	20 (22.7)	14 (16.3)	8 (19.5)	58 (19.3)

Numbers analysed

Study 1002FDC-053: 382 patients enrolled and randomized, 381 patients treated.

Outcomes and estimation

Treatment with the FCMP resulted in significantly greater reductions from baseline for LS mean LDL-C (-31.5%) compared with placebo (-2.5%), compared with ezetimibe (-21.0%), and compared with bempedoic acid (-17.7%). The differences from placebo, ezetimibe and bempedoic acid for LS means were -29.0 % ($p<0.001$), -10.5% ($p=0.001$), and -13.8% ($p<0.001$), respectively. Mean absolute changes from baseline to Week 12 in LDL-C were -1.32, -0.70, -0.85, and -0.13 mmol/L for the FCMP, bempedoic acid, ezetimibe, and placebo groups, respectively (observed data).

For the post-hoc (sensitivity) analysis treatment with the FCMP resulted in significantly greater reductions from baseline for LS mean LDL-C (-36.2%) compared with placebo (+1.8%) ($p <0.001$),

compared with ezetimibe (-23.2%) (p < 0.001), and compared with bempedoic acid (-17.2%)(p <0.001).

Ancillary analyses

Subgroup analysis for the FCMP versus placebo, bempedoic acid, and ezetimibe, respectively, are presented in the figures below.

Figure 19. Study 1002FDC-053: Forest Plots of the Statistical Analysis on Percent Change from Baseline in Low Density Lipoprotein Cholesterol (LDL C) at Week 12 by Subgroup (Observed Data), Fixed Dose Combination Compared With Placebo (Full Analysis Set)

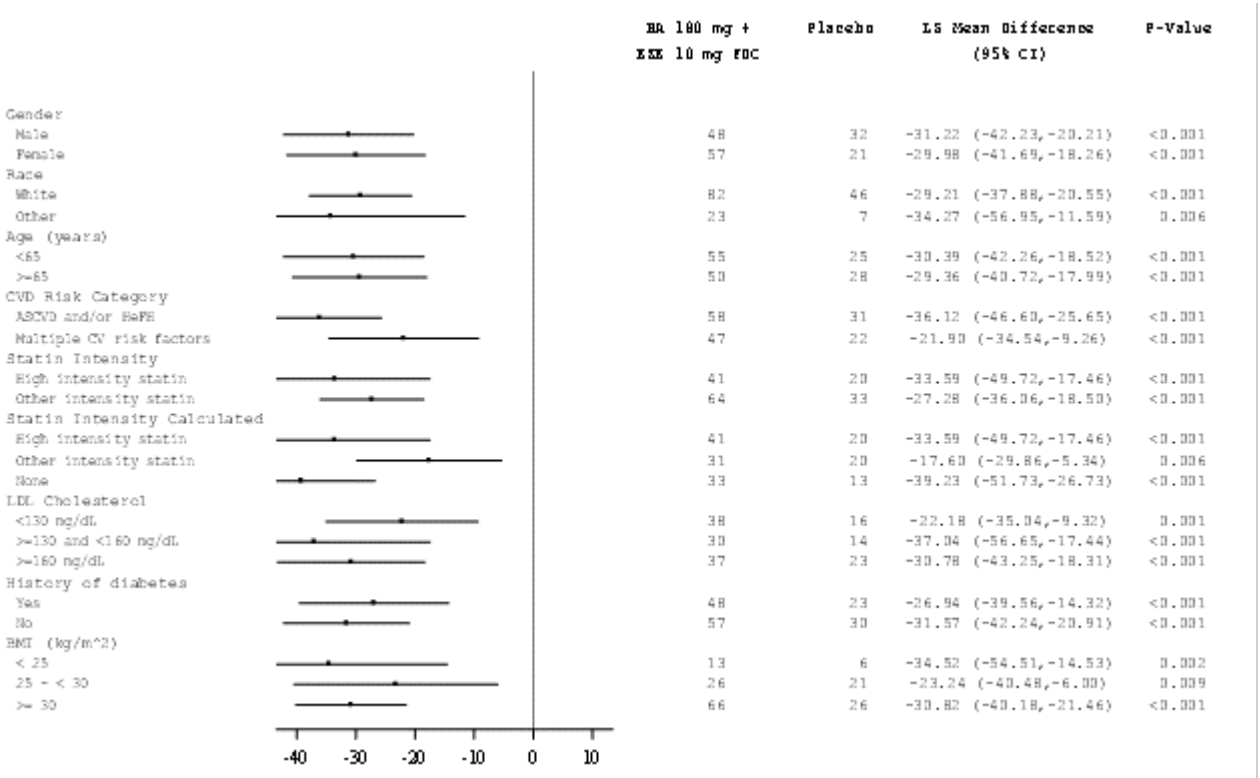


Figure 20. Study 1002FDC-053: Forest Plots of the Statistical Analysis on Percent Change from Baseline in Low Density Lipoprotein Cholesterol (LDL C) at Week 12 by Subgroup (Observed Data), Fixed Dose Combination Compared With Bempedoic Acid 180 mg (Full Analysis

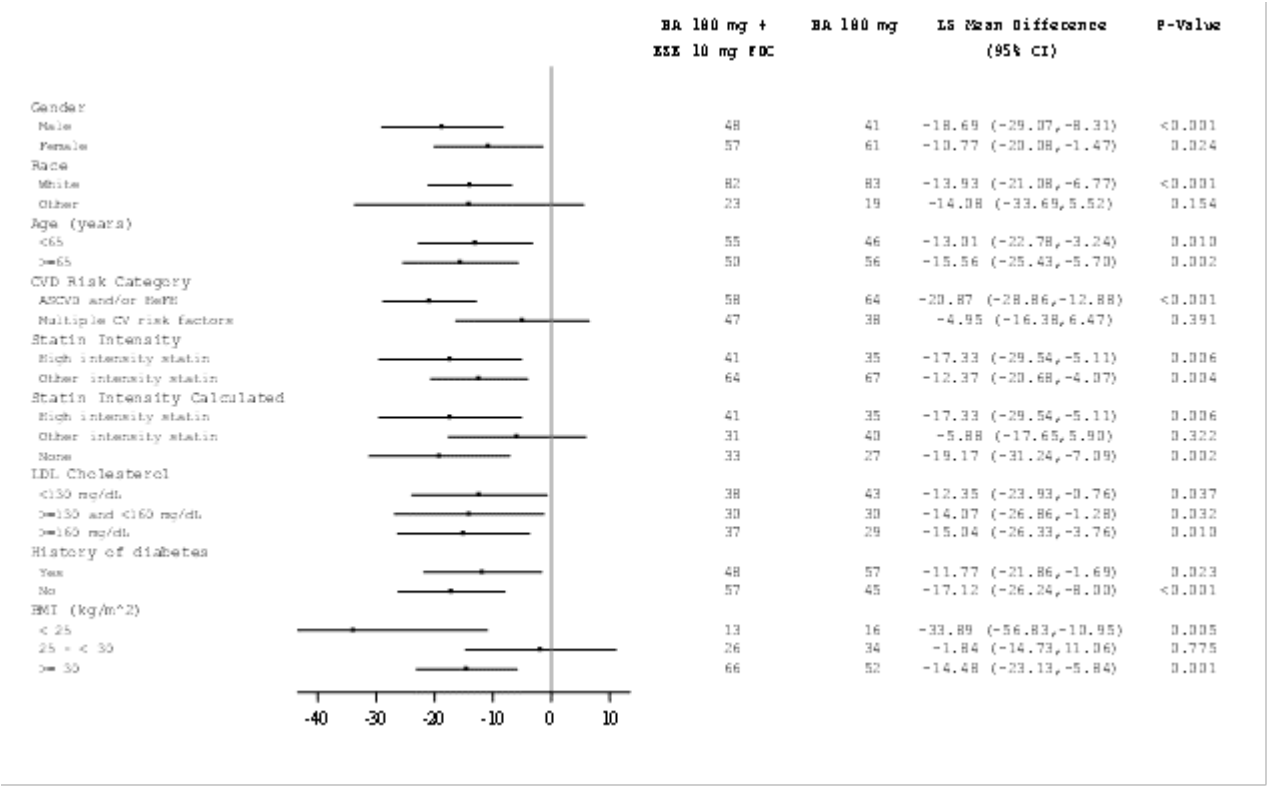
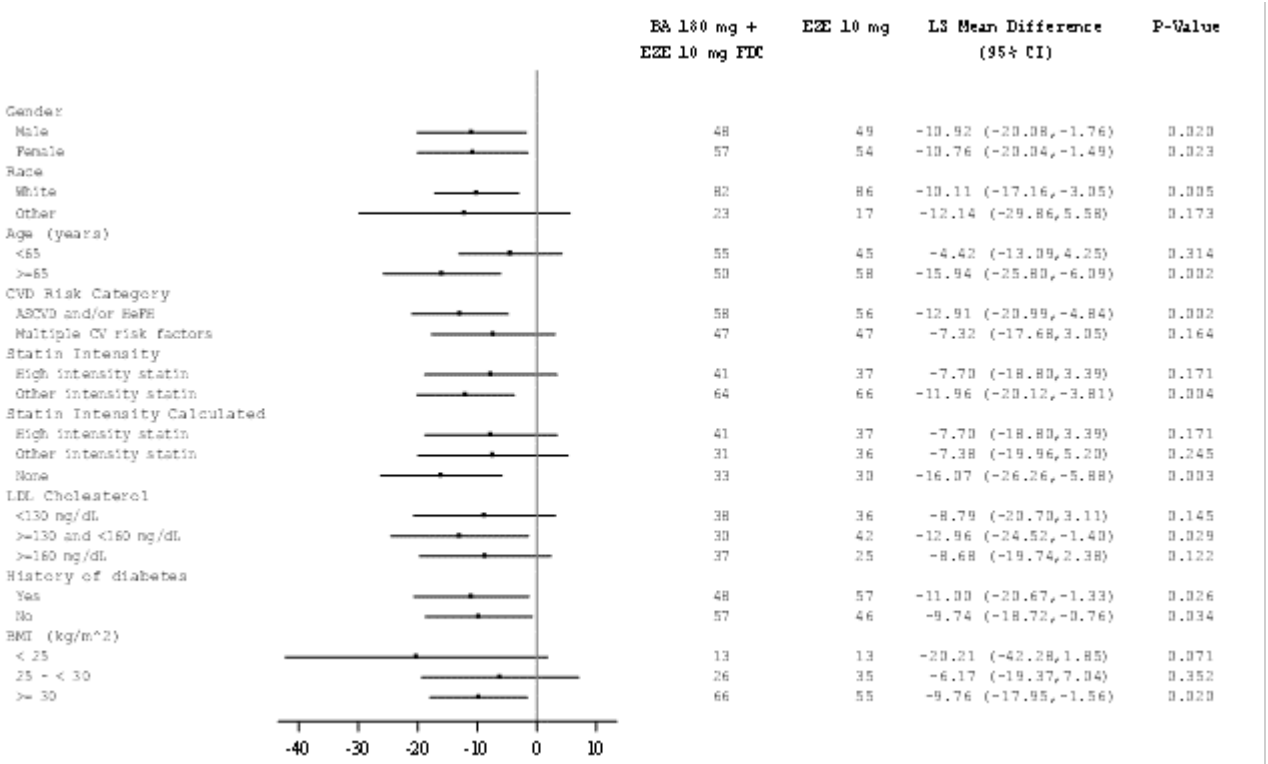


Figure 21. Study 1002FDC-053: Forest Plots of the Statistical Analysis on Percent Change from Baseline in Low Density Lipoprotein Cholesterol (LDL C) at Week 12 by Subgroup (Observed Data) Fixed Dose Combination Compared With Ezetimibe 10 mg (Full Analysis Set)

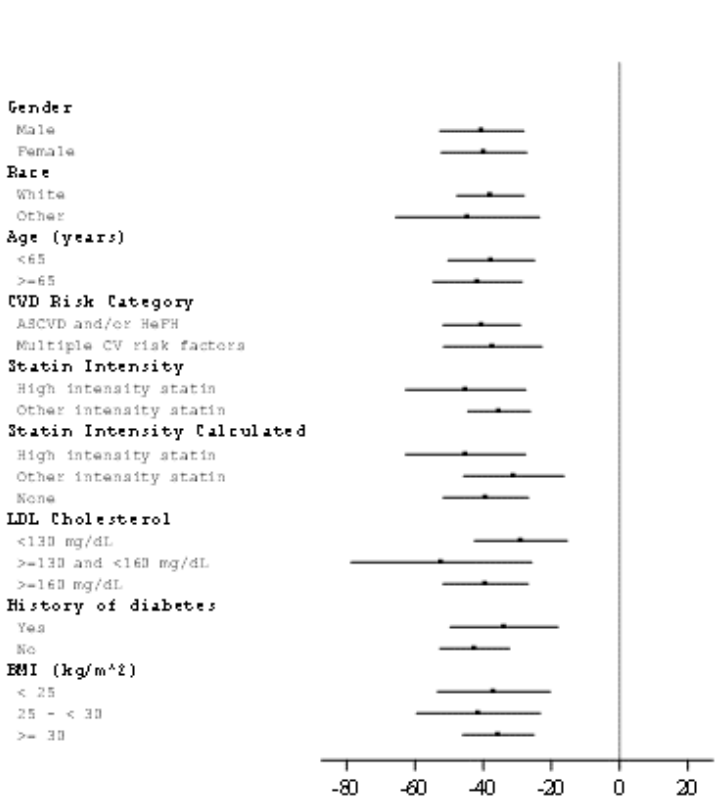


Results of sensitivity analyses for key secondary endpoints were as follows.

The LS mean difference with the FDC was statistically significantly different from ezetimibe, bempedoic acid, and placebo for non-HDL-C (-33.7% vs plb, -12.1% vs eze, -17.8% vs bempedoic acid) , TC (-27.1%, -10.4%, -14.2%), and apo B (-30.1%, -9.3%, -12.8%) for all 3 comparisons.

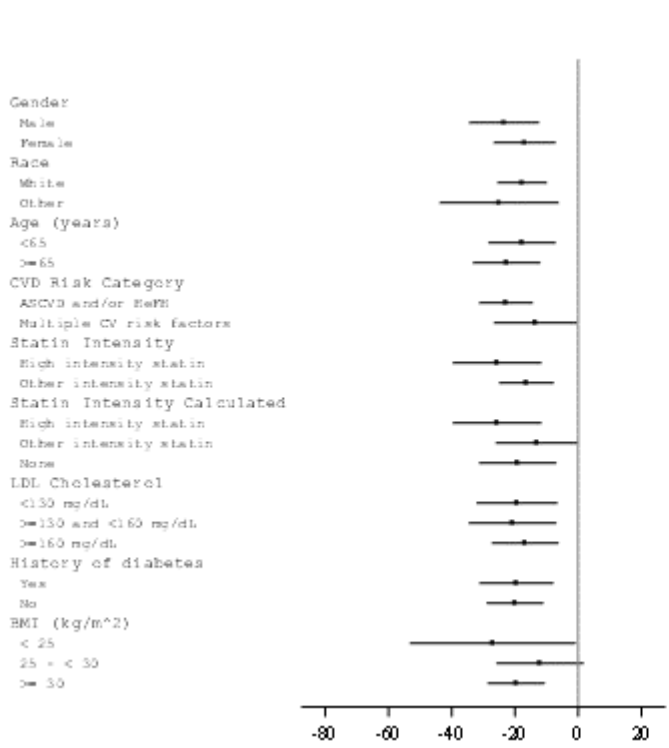
Results for percent change from baseline in Low Density Lipoprotein Cholesterol (LDL C) at Week 12 excluding three sites, were comparable to the results from the overall population as shown below in Figure :20, Figure :21 and Figure :22.

Figure :22: Forest Plot for Statistical Analysis Comparing the Fixed-dose Combination with Placebo on Percent Change from Baseline in Low-density Lipoprotein Cholesterol (Full Analysis Set, Excluding Three Sites)



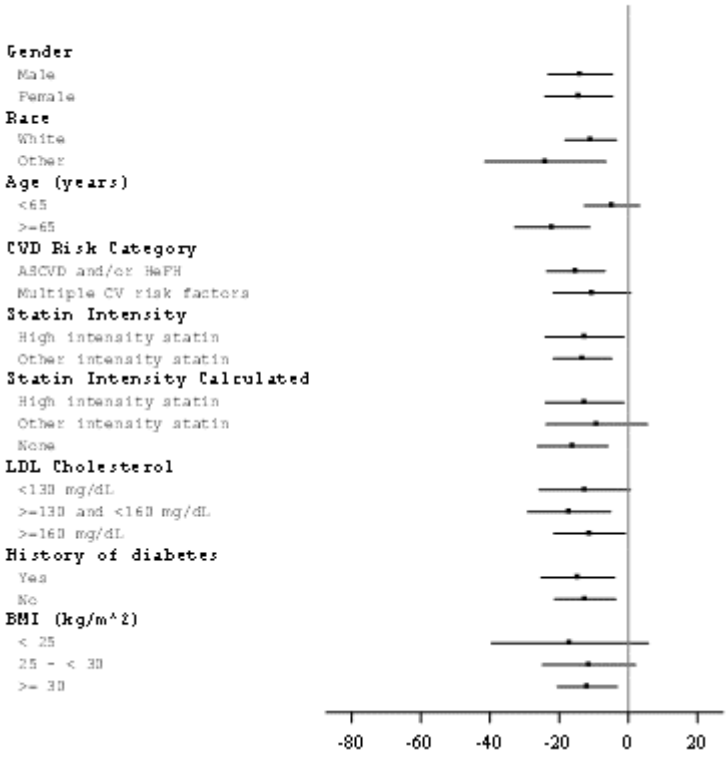
	BA 180 mg + EZE 10 mg FDC	Placebo	LS Mean Difference (95% CI)	P-Value
Gender				
Male	40	23	-40.41 (-52.74,-28.08)	<0.001
Female	43	17	-39.76 (-52.31,-27.22)	<0.001
Race				
White	64	33	-37.86 (-47.70,-28.02)	<0.001
Other	19	7	-44.56 (-65.62,-23.50)	<0.001
Age (years)				
<65	48	20	-37.61 (-50.31,-24.90)	<0.001
>=65	35	20	-41.59 (-54.65,-28.53)	<0.001
CVD Risk Category				
ASCVD and/or HeFH	50	26	-40.41 (-51.80,-29.02)	<0.001
Multiple CV risk factors	33	14	-37.23 (-51.66,-22.80)	<0.001
Statin Intensity				
High intensity statin	30	16	-45.12 (-62.73,-27.50)	<0.001
Other intensity statin	53	24	-35.32 (-44.51,-26.13)	<0.001
Statin Intensity Calculated				
High intensity statin	30	16	-45.12 (-62.73,-27.50)	<0.001
Other intensity statin	20	11	-31.04 (-45.71,-16.37)	<0.001
None	33	13	-39.23 (-51.73,-26.73)	<0.001
LDL Cholesterol				
<130 mg/dL	29	13	-28.91 (-42.51,-15.30)	<0.001
>=130 and <160 mg/dL	23	9	-52.25 (-78.73,-25.76)	0.001
>=160 mg/dL	31	18	-39.30 (-51.77,-26.83)	<0.001
History of diabetes				
Yes	34	17	-33.84 (-49.59,-18.09)	<0.001
No	49	23	-42.50 (-52.71,-32.28)	<0.001
BMI (kg/m^2)				
< 25	13	3	-36.91 (-53.43,-20.38)	<0.001
25 - < 30	18	16	-41.39 (-59.55,-23.23)	<0.001
>= 30	52	21	-35.55 (-46.01,-25.09)	<0.001

Figure :23: Forest Plot for Statistical Analysis Comparing the Fixed-dose Combination with Bempedoic Acid on Percent Change from Baseline in Low-density Lipoprotein Cholesterol (Full Analysis Set, Excluding Three Sites)



	BA 180 mg + EZE 10 mg FDC	BA 180 mg	LS Mean Difference (95% CI)	P-Value
Gender				
Male	40	37	-23.42 (-34.33,-12.52)	<0.001
Female	43	45	-16.94 (-26.60,-7.28)	<0.001
Race				
White	64	65	-17.73 (-25.43,-10.04)	<0.001
Other	19	17	-25.02 (-43.67,-6.37)	0.010
Age (years)				
<65	48	39	-17.75 (-28.23,-7.27)	0.001
>=65	35	43	-22.64 (-33.18,-12.11)	<0.001
CVD Risk Category				
ASCVD and/or HeFH	50	54	-22.87 (-31.22,-14.52)	<0.001
Multiple CV risk factors	33	28	-13.57 (-26.54,-0.60)	0.041
Statin Intensity				
High intensity statin	30	26	-25.66 (-39.56,-11.77)	<0.001
Other intensity statin	53	56	-16.42 (-24.90,-7.93)	<0.001
Statin Intensity Calculated				
High intensity statin	30	26	-25.66 (-39.56,-11.77)	<0.001
Other intensity statin	20	29	-13.08 (-25.89,-0.27)	0.046
None	33	27	-19.17 (-31.24,-7.09)	0.002
LDL Cholesterol				
<130 mg/dL	29	38	-19.38 (-32.01,-6.75)	0.003
>=130 and <160 mg/dL	23	21	-20.77 (-34.43,-7.12)	0.004
>=160 mg/dL	31	23	-16.83 (-27.23,-6.43)	0.002
History of diabetes				
Yes	34	41	-19.54 (-31.09,-7.99)	0.001
No	49	41	-19.98 (-28.82,-11.15)	<0.001
BMI (kg/m^2)				
< 25	13	13	-27.02 (-53.06,-0.98)	0.043
25 - < 30	18	26	-12.12 (-25.76,1.53)	0.080
>= 30	52	43	-19.61 (-28.52,-10.69)	<0.001

Figure :24: Forest Plot for Statistical Analysis Comparing the Fixed-dose Combination with Ezetimibe on Percent Change from Baseline in Low-density Lipoprotein Cholesterol (Full Analysis Set, Excluding Three Sites)



	BA 180 mg + EZE 10 mg FDC	EZE 10 mg	LS Mean Difference (95% CI)	P-Value
Gender				
Male	40	40	-13.92 (-23.26,-4.57)	0.004
Female	43	40	-14.32 (-24.11,-4.53)	0.005
Race				
White	64	67	-10.87 (-18.31,-3.42)	0.005
Other	19	13	-23.96 (-41.48,-6.44)	0.010
Age (years)				
<65	48	35	-4.74 (-12.76,3.27)	0.243
>=65	35	45	-22.00 (-32.88,-11.11)	<0.001
CVD Risk Category				
ASCVD and/or HeFH	50	49	-15.22 (-23.65,-6.80)	<0.001
Multiple CV risk factors	33	31	-10.47 (-21.71,0.76)	0.067
Statin Intensity				
High intensity statin	30	26	-12.62 (-24.01,-1.23)	0.031
Other intensity statin	53	54	-13.23 (-21.69,-4.78)	0.002
Statin Intensity Calculated				
High intensity statin	30	26	-12.62 (-24.01,-1.23)	0.031
Other intensity statin	20	24	-9.12 (-23.76,5.52)	0.215
None	33	30	-16.07 (-26.26,-5.88)	0.003
LDL Cholesterol				
<130 mg/dL	29	29	-12.58 (-25.80,0.63)	0.062
>=130 and <160 mg/dL	23	27	-17.11 (-29.10,-5.13)	0.006
>=160 mg/dL	31	24	-11.20 (-21.53,-0.86)	0.034
History of diabetes				
Yes	34	39	-14.60 (-25.24,-3.95)	0.008
No	49	41	-12.50 (-21.38,-3.61)	0.006
BMI (kg/m^2)				
< 25	13	13	-16.94 (-39.64,5.77)	0.137
25 - < 30	18	28	-11.39 (-24.85,2.08)	0.094
>= 30	52	39	-11.88 (-20.59,-3.18)	0.008

Summary of main efficacy results FDC

Table 36 summarise the efficacy results from one of 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 36. : Summary of efficacy for study 1002FDC-053 (sensitivity analysis, excluding three sites)

Title: A Randomized, Double-Blind, Parallel Group Study to Evaluate the Efficacy and Safety of Bempedoic Acid 180 mg + Ezetimibe 10 mg Fixed Dose Combination Compared to Bempedoic Acid, Ezetimibe, and Placebo Alone in Patients Treated with Maximally Tolerated Statin Therapy			
Study identifier	1002FDC-053		
Design	Randomized, multicenter, double-blind, placebo-controlled study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 weeks 2 weeks (screening period) not applicable
Hypothesis	Superiority of FDC over the monocomponents or placebo		
Treatments groups	FDC		Bempedoic Acid 180 mg + Ezetimibe 10 mg FDC. 12 weeks, n= 85 out of 108
	Bempedoic Acid		Bempedoic Acid 180 mg. 12 weeks, n= 88 out of 110
	Ezetimibe		Ezetimibe 10 mg. 12 weeks, n= 86 out of 109
	Placebo		Placebo. 12 weeks, n= 41 out of 55
Endpoints and definitions	Co-Primary endpoint	% change from baseline to week 12 in LDL-C	Percent change from baseline to Week 12 in LDL-C for the FDC versus placebo, FDC versus ezetimibe and FDC versus bempedoic acid
	Secondary endpoint	% change from baseline to week 12 in non-HDL	Percent change from baseline to Week 12 in non-HDL for the FDC versus placebo, FDC versus ezetimibe and FDC versus bempedoic acid
		% change from baseline to week 12 in apo B	Percent change from baseline to Week 12 in apo B for the FDC versus placebo, FDC versus ezetimibe and FDC versus bempedoic acid
		% change from baseline to week 12 in TC	Percent change from baseline to Week 12 TC for the FDC versus placebo, FDC versus ezetimibe and FDC versus bempedoic acid
Database lock	Not provided		
Results and Analysis			

Analysis description	**Primary Analysis**				
Analysis population and time point	Intent to treat (Full analysis set) in patients at high CV risk on maximally tolerated statin therapy				
Descriptive statistics and estimate variability	Treatment group	FDC	Bempedoic Acid	Ezetimibe	Placebo
	Number of subject	85	88	86	41
	% change from baseline to week 12 in LDL-C (LS mean (SE))	-36.2 (2.56)	-17.2 (2.52)	-23.2 (2.18)	+1.8 (3.49)
Comparison groups	FDC vs Placebo	**Comparison groups**		**FDC vs Placebo**	
		Difference (FDC-placebo) (LS mean)		-38.0	
		95%CI		-46.5, -29.6	
		P-value		<0.001	
		Comparison groups		**FDC vs bempedoic acid**	
		Difference (FDC-bempedoic acid) (LS mean)		-19.0	
		95%CI		-26.1, -11.9	
		P-value		<0.001	
		Comparison groups		**FDC vs ezetimibe**	
		Difference (FDC-ezetimibe) (LS mean)		-13.1	
		95%CI		-19.7, -6.5	
		P-value		0.001	
Notes	<free text>				
Analysis description	**Secondary analysis**				
Analysis population and time point description	Intent to treat (Full analysis set) in patients at high CV risk on maximally tolerated statin therapy				
Descriptive statistics and estimate variability	Treatment group	FDC	Bempedoic Acid	Ezetimibe	Placebo
	% change from baseline to week 12 in non-HDL (LS mean (SE))	-31.9 (2.23)	-14.1 (2.17)	-19.9 (2.05)	+1.8 (3.28)
		Difference(FDC-placebo)			-33.7
		95%CI			-43.9, -23.4
		P-value			<0.001
		Difference (FDC-bempedoic acid)	-17.8		
		95%CI	-25.1, -10.5		
		P-value	<0.001		
		Difference (FDC-ezetimibe)		-12.1	

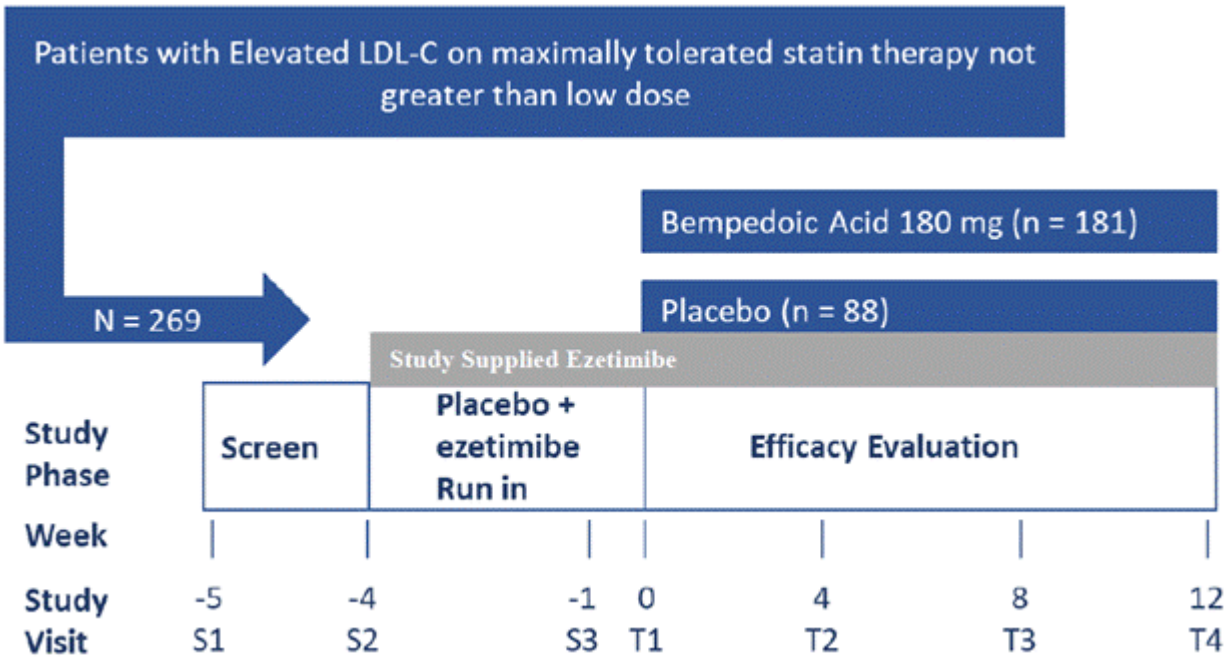
		95%CI		-19.1, -5.0	
		P-value		<0.001	
	% change from baseline to week 12 in apo B (LS mean (SE))	-24.6 (2.38)	-11.8 (2.18)	-15.3 (1.97)	+5.5 (2.97)
		Difference(FDC-placebo)			-30.1
		95%CI			-39.9, -20.3
		P-value			<0.001
		Difference (FDC-bempedoic acid)	-12.8		
		95%CI	-20.3, -5.3		
		P-value	<0.001		
		Difference (FDC-ezetimibe)		-9.3	
		95%CI		-16.5, -2.1	
		P-value		0.003	
	% change from baseline to week 12 in TC (LS mean (SSE))	-26.4 (1.90)	-12.1 (1.83)	-16.0 (1.59)	+0.7 (2.46)
		Difference(FDC-placebo)			-27.1
		95%CI			-35.1, -19.1
		P-value			<0.001
		Difference (FDC-bempedoic acid)	-14.2		
		95%CI	-25.1, -10.5		
		P-value	<0.001		
		Difference (FDC-ezetimibe)		-10.4	
		95%CI		-16.1, -4.6	
		P-value		<0.001	

Non-responder study 1002-048 (statin intolerance)

Study 1002-048: 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 (1002-048) (EudraCT No. 2016-004084-39, ClinicalTrials.gov No. NCT03001076).

Methods

Figure 25. 1002-048 Study Design



Screening period

Patients on low-dose or less than low-dose statin therapy (including patients unable to tolerate a statin at any dose) and who required additional LDL-C lowering were eligible for screening.

Patients started screening at Week -5, approximately 5 weeks prior to randomization. Patients must have had LDL-C of ≥100 mg/dL (or ≥120 mg/dL if not on ezetimibe). 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 returned to the clinical site at Week -4 to begin treatment with study-supplied ezetimibe and single-blind placebo.

Placebo and Ezetimibe Run-in Period

Patients were treated in the single-blind, placebo run-in period with study-supplied and labelled ezetimibe and placebo at Week -4 (Day -28 to ±3 days). If a patient was already taking ezetimibe, they stopped taking their personal supply of ezetimibe and began taking study-supplied ezetimibe. Patients were assessed to determine if they still met all enrollment criteria. At Week -1, patients returned (Day -7 to ±3 days) for continued determination of enrollment criteria.

Lipid sample collection

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

In this study, 2 committees monitored data during study conduct. An unblinded independent data monitoring committee monitored accumulating patient safety and efficacy data until the last patient completed study treatment.

Study Participants

Patients were required to have a fasting LDL-C ≥100 mg/dL (2.6 mmol/L) when already on ezetimibe on stable background LMT (≥4 weeks prior to screening), or LDL-C ≥120 mg/dL (3.1 mmol/L) on stable background LMT (≥4 weeks prior to screening) when not on ezetimibe, 5 weeks before randomization. All patients had to have had fasting LDL-C ≥70 mg/dL (1.8 mmol/L) 1 week before randomisation.

Patients could have received stable (≥4 weeks prior to screening) background statin dose that did not exceed low-dose statin therapy. Patients had to have reported attempting statin therapy and 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.

Relevant other exclusion criteria

TGs ≥500 mg/dL (5.6 mmol/L), eGFR (MDRD) <30 mL/min/1.73 m2, 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

Patients were randomized 2:1 to receive bempedoic acid 180 mg or placebo QD. Study-supplied ezetimibe was started at week -4.

Objectives

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 primary endpoint was the percent change from baseline to week 12 in LDL-C.

The secondary outcomes were percent change from baseline to Week 12 in non-HDL-C, TC, apo B, hsCRP, TGs and HDL-C

Sample size

The estimated sample size of 150 randomized patients in the bempedoic acid group and 75 randomized patients in the placebo group 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 (masking)

Patients were randomized 2:1 to bempedoic acid or matching placebo using an interactive web response system (IWRS).

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

For study 048, The primary efficacy endpoint was analyzed using analysis of covariance (ANCOVA), with treatment group as a factor and baseline LDL-C as a covariate. The ANCOVA was performed using the FAS, with patients included in their randomized treatment group regardless of the treatment they actually received. To account for the likelihood of unequal variances between the treatment groups, the robust variance estimator was used to allow estimating the residual variances separately between the treatment groups. Model assumptions for performing ANCOVA were assessed and if the assumptions were severely violated, non-parametric method was considered.

Multiplicity due to the multiple endpoints was handled by testing the endpoints in a stepdown approach.

Missing data was primarily handled using a pattern mixture model. Patients with missing lipid data that also discontinued study medication had their data imputed using placebo based imputation. Patients with missing data who were still taking study medication had data imputed using active arm imputation. Sensitivity analyses were performed using observed cases only, using on-treatment, completer and observed data analysis.

Results

Participant flow

A total of 616 patients signed ICDs and participated in some portion of the 5-week screening period that included placebo and ezetimibe run-in. Of the 616 patients who entered screening, 269 patients were randomized. The patients disposition is provided in the table below.

Table 37. Patient Disposition

	Placebo (N = 88)	**Bempedoic Acid (N = 181)**
Randomized	88	181
Completed study	81 (92.0)	176 (97.2)
Withdrew from study[a]	7 (8.0)	5 (2.8)
Adverse event	3 (3.4)	3 (1.7)
Withdrawal by patient	2 (2.3)	0
Protocol Deviation	0	0
Sponsor decision	1 (1.1)	0
Physician decision	0	0
Lost to Follow-up	0	2 (1.1)
Death	0	0
Other	1 (1.1)	0
Completed IMP	79 (89.8)	164 (90.6)
Discontinuation of IMP	8 (9.1)	17 (9.4)
Adverse event	5 (5.7)	13 (7.2)
Withdrawal by patient	2 (2.3)	0

Patient decision	0	1 (0.6)
Sponsor decision	0	0
Physician decision	0	1 (0.6)
Protocol deviation	0	0
Lost to follow-up	0	2 (1.1)
Death	0	0
Other	1 (1.1)	0

Baseline data

Table 38. Demographic Characteristics in Bempedoic Acid Study 1002 048 (Full Analysis Set)

	Placebo (N = 88)[1.]	**Bempedoic Acid (N = 181)**	**Total (N = 269)**
Age (years)			
Mean (SD)	63.7 (11.32)	63.8 (10.77)	63.8 (10.93)
Median	66.0	66.0	66.0
Gender, n (%)			
Male	32 (36.4)	72 (39.8)	104 (38.7)
Female	56 (63.6)	109 (60.2)	165 (61.3)
Race, n (%)			
Asian	1 (1.1)	3 (1.7)	4 (1.5)
Black or African American	10 (11.4)	11 (6.1)	21 (7.8)
Native Hawaiian or other Pacific Islander	0	2 (1.1)	2 (0.7)
White	75 (85.2)	165 (91.2)	240 (89.2)
Multiple	2 (2.3)	0	2 (0.7)
Ethnicity, n (%)			
Hispanic or Latino	23 (26.1)	43 (23.8)	66 (24.5)
Not Hispanic or Latino	65 (73.9)	138 (76.2)	203 (75.5)
Region, n (%)			
United States	67 (76.1)	136 (75.1)	203 (75.5)
Canada	6 (6.8)	11 (6.1)	17 (6.3)
European Union	15 (17.0)	34 (18.8)	49 (18.2)
History of hypertension			
Yes	48 (54.5)	109 (60.2)	
eGFR category at baseline (mL/min/1.73m^2)			
≥ 90	17 (19.3)	45 (24.9)	
60- < 90	57 (64.8)	110 (60.8)	
30- < 60	14 (15.9)	25 (13.8)	
15- < 30	0	1 (0.6)	
History of diabetes			

	Placebo (N = 88)1.	Bempedoic Acid (N = 181)	Total (N = 269)
Yes	17 (19.3)	35 (19.3)	
Tobacco Use			
Current	12 (13.6)	21 (11.6)	
Former	22 (25.0)	48 (26.5)	

Table 39. Other baseline characteristics study 048

	Placebo (N = 88)	Bempedoic Acid (N = 181)	Total (N = 269)
LDL-C (mg/dL)			
Mean (SD)	123.02 (27.197)	129.77 (30.871)	127.56 (29.838)
Median	118.50	127.00	124.00
Minimum, maximum	66.5, 204.5	54.0, 268.5	54.0, 268.5
Non-HDL-C (mg/dL)			
Mean (SD)	151.55 (32.734)	162.41 (35.413)	158.85 (34.874)
Median	146.00	158.50	156.50
Minimum, maximum	80.5, 244.5	83.0, 319.5	80.5, 319.5
Triglycerides (mg/dL)			
Mean (SD)	143.39 (61.932)	166.93 (75.683)	159.23 (72.213)
Median	135.50	153.00	146.00
Minimum, maximum	55.0, 371.5	50.0, 460.0	50.0, 460.0

HDL-C (mg/dL)			
Mean (SD)	57.07 (21.319)	55.84 (16.326)	56.24 (18.080)
Median	53.25	54.00	54.00
Minimum, maximum	34.5, 227.0	9.5, 112.5	9.5, 227.0
Apolipoprotein B (mg/dL)			
Mean (SD)	115.8 (23.47)	123.3 (26.48)	120.9 (25.75)
Median	115.0	121.5	119.0
Minimum, maximum	60, 181	68, 232	60, 232
hsCRP (mg/L)			
Mean (SD)	3.428 (3.3066)	3.699 (4.8781)	3.612 (4.4268)
Median	2.260	2.205	2.215
Minimum, maximum	0.13, 14.37	0.22, 39.20	0.13, 39.20
Total cholesterol (mg/dL)			
Mean (SD)	208.62 (35.712)	218.24 (35.883)	215.09 (36.045)
Median	203.75	215.00	211.00
Minimum, maximum	125.0, 356.0	125.5, 357.0	125.0, 357.0
Background LMT, n (%)			
Statins[a]	25 (28.4)	59 (32.6)	84 (31.2)
Other[b]	63 (71.6)	122 (67.4)	185 (68.8)
BMI (kg/m^2)			
Mean (SD)	30.45 (5.787)	29.52 (4.740)	29.83 (5.114)

Table 40. 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)

Numbers analysed

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

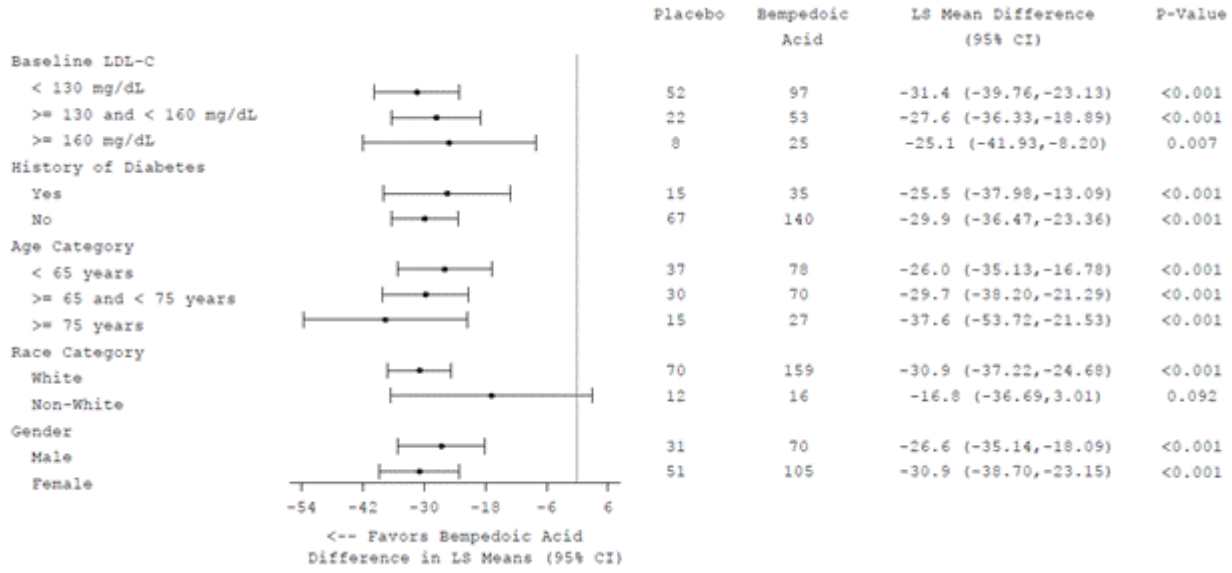
Outcomes and estimation

Reduction from baseline in LDL-C for bempedoic acid versus placebo was -23.5% vs 5.0%, respectively, which was significantly different (p < 0.001). The absolute difference from placebo was -0.93 mmol/L at Week 12.

Ancillary analyses

Subgroup analyses are provided in Figure 24 below.

Figure 26. Forest Plot of Percent Change from Baseline to Week 12 in LDL-C by Subgroups (Full Analysis Set)



The sensitivity analysis using an on-treatment approach (FAS) was performed for the primary endpoint; the difference in LS means between bempedoic acid and placebo was -31.49% (p <0.001). In the Completer Analysis Set, all patients were required to comply with protocol-defined treatment of double-blind IMP and ezetimibe, as well as having a non-missing LDL-C value at Week 12. The difference in LS means between bempedoic acid and placebo was -31.28% (p <0.001). The third sensitivity analysis included observed data only with no imputation for missing data (assumed missing completely at random). The difference in LS means between bempedoic acid and placebo was -29.31% (p <0.001).

Summary of main efficacy results

The summary of main efficacy results is already presented in **Table 27** (page 101). These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

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

Not performed

Clinical studies in special populations

Table 41. Summary of Patients by Age Group Category and Study (Safety Population)

Study Treatment Group	Age <65 n (%)	Age 65 to <75 n (%)	Age 75 to <85 n (%)	Age ≥85 n (%)
Study 1002FDC-053 (Excluding Three Sites)				
FDC	50 (58.8)	25 (29.4)	10 (11.8)	0
Bempedoic Acid	42 (47.7)	30 (34.1)	14 (15.9)	2 (2.3)
Ezetimibe	38 (44.2)	35 (40.7)	12 (14.0)	1 (1.2)
Placebo	21 (51.2)	10 (24.4)	7 (17.1)	3 (7.3)
Study 1002FDC-053 (All Sites)				
FDC	57 (53.3)	37 (34.6)	12 (11.2)	1 (0.9)
Bempedoic Acid	51 (46.4)	40 (36.4)	16 (14.5)	3 (2.7)
Ezetimibe	48 (44.0)	46 (42.2)	14 (12.8)	1 (0.9)
Placebo	27 (49.1)	13 (23.6)	12 (21.8)	3 (5.5)
Study 1002-048				
Bempedoic Acid	81 (44.8)	73 (40.3)	26 (14.4)	1 (0.6)
Placebo	40 (46.0)	31 (35.6)	13 (14.9)	3 (3.4)

Supportive studies bempedoic acid monocomponent

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 42).

Table 42. 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
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

Supportive studies FCMP

Phase 2 study 1002-008

Study 1002-008 was a randomized, double-blind, active-controlled, parallel-group study. Patients were stratified 1:1 by history of statin intolerance and were randomized 4:4:4:1:1 to receive bempedoic acid 120 mg, bempedoic acid 180 mg, ezetimibe 10 mg, bempedoic acid 120 mg + ezetimibe 10 mg, or bempedoic acid 180 mg + ezetimibe 10 mg QD for 12 weeks. Treatment effects are presented in the Table 43. Mean reduction was greatest in those patients who received combination therapy compared with either monotherapy.

Table 43. Study 1002-008: Percent Change from Baseline to Week 12 in LDL-C (mITT)

	Ezetimibe 10 mg (N=98)	Bempedoic Acid 120 mg (N=97)	Bempedoic Acid 180 mg (N=99)	Bempedoic Acid 120 mg + Ezetimibe 10 mg (N=24)	Bempedoic Acid 180 mg + Ezetimibe 10 mg (N=22)
Mean (SD) baseline	165.00 (25.15)	164.25 (27.75)	165.98 (23.58)	161.13 (26.12)	163.86 (26.50)
Mean (SD) Week 12	129.18 (20.11)	118.75 (29.51)	115.11 (25.20)	91.63 (29.13)	85.55 (21.25)
Percent change from baseline, n	98	97	99	24	22
Mean (SD)	-21.23 (9.36)	-27.42 (14.51)	-30.25 (13.82)	-42.73 (18.58)	-47.65 (11.06)
LS Means (SE)	-21.22 (1.309)	-27.47 (1.316)	-30.13 (1.303)	-43.08 (2.647)	-47.70 (2.764)

	Ezetimibe 10 mg (N=98)	Bempedoic Acid 120 mg (N=97)	Bempedoic Acid 180 mg (N=99)	Bempedoic Acid 120 mg + Ezetimibe 10 mg (N=24)	Bempedoic Acid 180 mg + Ezetimibe 10 mg (N=22)
Difference (BA – ezetimibe) of LS Means (SE)	-	-6.25 (1.856)	-8.91 (1.847)	-21.86 (2.953)	-26.48 (3.059)
Difference of LS Means 95% CI	-	(-9.90, -2.60)	(-12.54, -5.28)	(-27.67, -16.05)	(-32.50, -20.46)
P value	-	0.0008	<0.0001	<0.0001	<0.0001

Pooled phase 3 studies post-hoc ezetimibe subgroup in patients with background statin therapy (selected patient on ezetimibe background therapy from studies 040 and 047)

The 4 pivotal phase 3 studies as part of the bempedoic acid monotherapy MAA (Studies 1002-047, 1002-040, 1002-046, and 1002-048) were double-blind, placebo-controlled, randomized, parallel-group, multicenter studies with bempedoic acid 180 mg per day in 3621 adult patients at risk for CV events with primary hyperlipidemia when used alone and in combination with HMG-CoA reductase inhibitors (statins) and/or other stable lipid-modifying therapy, including ezetimibe and PCSK9 inhibitors. Data from these studies included coadminstration with ezetimibe. Study 048 is discussed separately as bempedoic acid was compared to placebo on a study supplied background therapy of ezetimibe in statin intolerant patients.

In the 2 Phase 3, 52-week studies (1002-040 and 1002-047), patients on maximally tolerated statin could continue their other LMTs, including ezetimibe. Of the 2010 patients randomized to bempedoic acid in these studies, 150 patients reported ezetimibe background therapy; of the 999 patients randomized to placebo, 76 patients were also on ezetimibe background therapy. In post hoc subgroup analyses by ezetimibe use at baseline, the mean reduction from baseline to Week 12 in LDL-C for bempedoic acid compared with placebo was -16.2% vs -2.8%, respectively (p <0.001) in patients taking ezetimibe, and -16.7% vs 2.1%, respectively (p <0.001) in patients not taking ezetimibe.

2.5.4. Discussion on clinical efficacy

Design and conduct of clinical studies

Bempedoic acid as monocomponent

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 was less clear. Patients had to have attempted one statin treatment and were 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) was 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.

Ezetimibe

Literature data identified relevant placebo controlled randomised studies investigating the lipid lowering effect of ezetimibe as monotherapy, in combination with statins, and investigating the effect on CV outcomes.

FCMP

Factorial design study on top of statins (study1002FDC-053)

A 4-arm factorial design study was performed comparing the FCMP with bempedoic acid alone, ezetimibe alone, and placebo added on to stable maximally-tolerated statin therapy. Patients with high CV risk eligible for lipid lowering treatment were included.

The general design of double-blind, placebo-controlled, randomized, parallel-group should allow for an adequate evaluation of the bempedoic acid with or without ezetimibe treatment effect on LD-C reduction. The 2:2:2:1 randomisation as applied in this study is acceptable to optimise exposure to the investigational products. The primary endpoint of percent change in LDL-C from baseline to Week 12 can be acceptable to evaluate the maximum and stable change in LDL-C lowering effect of bempedoic acid with ezetimibe compared to the monocomponents. Other parameters of the lipid profile (non-HDL-C, TC, apoB, TG, HDL-C) will also be evaluated as secondary endpoints, which is considered relevant and supported. The relevance of evaluation of hsCRP as secondary endpoint is considered of less importance as the clinical implication is less clear. A 2 week screening period is appropriate, as patients had to be stable on statin therapy already for at least 4 weeks prior screening. This study is only performed in the US which could limit interpretation for the EU situation. To establish baseline LDL-C levels based on week -1 and 0, or -2 and 0 is appropriate. Lipid sample collection by a centralised laboratory is appropriate and according to current study standards.

Identification of patients eligible for lipid lowering therapy was based on the combination of CV risk classification and LDL-C level in accord with treatment guidelines for learned societies. Patients were included at screening when they had established CV disease and or HeFH and ≥100 mg/dL (2.6 mmol/L), or when they had multiple CV risk factors and LDL-C ≥130 mg/dL (3.4 mmol/L), despite being on maximum statin therapy. Although, commonly in clinical practice such patients would not start to be treated with a combination of two lipid lowering drugs rather with a single lipid lowering drug additional treatment to statins. General exclusion criteria are acceptable to optimize study adherence and reduce potential dropouts, to comply with inclusion criteria, reduce potential tolerability issues with background medication, and exclude any possible relevant confounding.

Sample size was calculated to provide sufficient power to observe a difference of 13% on the percent change from baseline in LDL-C for the FCMP versus ezetimibe or bempedoic acid and a difference of 33% versus placebo. This difference is considered clinically relevant. In general, the statistical analysis plans are considered acceptable. However, the sensitivity analyses are considered optimistic, as they rely on on-treatment data.

Study in statin intolerant patients as add-on to ezetimibe (study 1002-048)

A randomized controlled phase 3 study in statin intolerant patients was performed to compare bempedoic acid with placebo as add-on therapy to ezetimibe.

The general design of double-blind, placebo-controlled, randomized, parallel-group should allow for an adequate evaluation of the bempedoic acid with ezetimibe treatment effect on LD-C reduction. The 2:1

randomisation as applied in this study is acceptable to optimise exposure to the investigational product. The primary endpoint of percent change in LDL-C from baseline to Week 12 can be acceptable to evaluate the maximum and stable change in LDL-C lowering effect of bempedoic acid with ezetimibe compared to the monocomponents. Other parameters of the lipid profile (non-HDL-C, TC, apoB, TG, HDL-C) will also be evaluated as secondary endpoints, which is considered relevant and supported. The relevance of evaluation of hsCRP as secondary endpoint is considered of less importance as the clinical implication is less clear. The 4-week placebo or ezetimibe run-in period is relatively short but acceptable to stabilise for study supplied ezetimibe therapy. To establish baseline LDL-C levels based on week -1 and 0, or -2 and 0 is appropriate. Lipid sample collection by a centralised laboratory is appropriate and according to current study standards.

The screening inclusion was meeting the definition of hypercholesterolemia, with ≥ 100 mg/dL in patients taking ezetimibe (≥4 weeks prior to screening), and ≥ 120 mg/dL in patients not taking ezetimibe (≥4 weeks prior to screening), 5 weeks before randomization. After the placebo and ezetimibe run-in of 4 weeks. Identification of patients eligible for randomization was based on LDL-C level LDL-C ≥70 mg/dL (1.8 mmol/L) at baseline without any CV risk level requirement.

General exclusion criteria are acceptable to optimize study adherence and reduce potential dropouts, to comply with inclusion criteria, reduce potential tolerability issues with background medication, and exclude any possible relevant confounding.

Sample sizes for 048 study were calculated to provide at least 95% power to observe a difference of 15% on the percent change from baseline in LDL-C. This difference is considered clinically relevant. In general, the statistical analysis plans for the studies are considered acceptable. However, the sensitivity analyses are considered optimistic, as they rely on on-treatment data.

Efficacy data and additional analyses

Bempedoic acid as monocomponent

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

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 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.

Ezetimibe

The efficacy of ezetimibe has sufficiently been described based on literature data including relevant placebo controlled randomised studies investigating the lipid lowering effect of ezetimibe as monotherapy, in combination with statins, and investigating the effect on CV outcomes.

FCMP

Factorial design study on top of statins (study 1002FDC-053)

An acceptable proportion of patients completed the study (95-96%) and completed the study period on study drug (87-90%). The primarily reason for study drug discontinuation was AEs (3.6%-9.2%). In general, disposition was approximately comparable between treatment groups allowing for an acceptable comparison between treatment groups. In the sensitivity analysis excluding 3 sites, a lower number of patients were included in each treatment group (approximately 20% of the patients), although dispositions were fairly similar. This should allow for a reasonably acceptable comparison between treatment groups for efficacy and safety.

The study population is at high or very high CV risk with approximately 62% with ASCVD and/ or HeFH and represents a Caucasian population at relative increased age (mean age range 62 to 65 years; Caucasian 85% to 90%). About half of the patients had diabetes (40-50%). The patient can be identified to be hypercholesterolemic with LDL-C baseline levels of mean 150 mg/dL (3.8 mmol/L). Despite that patients needed to be on maximum tolerated statin therapy, 25 to 30% did not use any statin, and only 30% used high intensity statin. The sensitivity patient population was not substantially different from the whole study population, except that the proportion of Latino was lower. The Asian population was underrepresented (1%). Randomisation was reasonably successful considering the size of the study.

The FCMP of bempedoic acid with ezetimibe demonstrated a significant difference in LDL-C reduction to be substantial in comparison to placebo (-29.0%; p<0.001), and only moderate in comparison to ezetimibe (-10.5%; p<0.001) and bempedoic acid (-13.8%; p<0.001). The post-hoc sensitivity

analyses excluding the three sites yielded comparable results as the whole study population with significant differences of -38.0%, -13.1%, and -19.0%. Mean absolute changes according to each treatment group were -1.3, -0.70, -0.87, and -0.13 mmol/L, with an LDL-C <70 mg/dL at Week 12 of 27.6%, 9.7%, 7.8%, 1.9%, respectively, assessed as exploratory endpoint. Significant reductions were also obtained for other lipids assessed as secondary endpoint including non-HDL-C (-25.4%, -10.9%, -12.3%), TC (-20.6%, -9.1%, -9.8%), apoB (-21.7%, -6.9%, -8.4%). The effects on hsCRP were less clear (-37.2%, -19.0%, -7.2%, last difference non-significant p=0.321).

Within subgroups of gender, race, age, CV risk category, statin intensity, LDL-C baseline level, history of diabetes, and BMI, an approximately similar beneficial treatment effect of the FCMP in comparison to placebo, BA and EZE was observed. Slight differences could be due to the small number of patients within each subgroup).

Study in statin intolerant patients as add-on to ezetimibe (study 1002-048)

A large number of patients completed the study, with more patients in the BA group (97%) than the placebo group (92%). Patients who completed the study on study drug was more balanced (90.6% vs 89.8%). AEs were the main reason for drug discontinuation and slightly higher for BA (7.2%) vs PLB (5.7%).

The study population represents primarily a Caucasian population (85-91%) at relative increased age (mean age 64 years) with more female than male patients (61-63%). CV risk estimation was performed post-hoc and identified 24% to have ASCVD. Other CV risk factors mentioned is hypertension (60 vs 54%), diabetes (19%) and tobacco use (11-13% current and 25-26% former). In this study, 27-32% used statins. The patient can be identified to be hypercholesterolemic with LDL-C baseline levels of mean 127 mg/dL (3.3 mmol/L). The Asian population was underrepresented (1.5%). Randomisation was reasonably successful considering the size of the study.

Bempedoic acid demonstrated a significantly larger reduction in LDL-C in comparison to placebo on a background of ezetimibe therapy (-23.46% vs 4.99%; -28.35%, p<0.001) with an absolute reduction of 0.94 mmol/L. Sensitivity analysis using observed cases and an on-treatment approach supported the primary analysis but are considered optimistic. Significant reductions were also obtained for other lipids assessed as secondary endpoint including non-HDL-C (-23.56%), TC (-17.99%), apoB (-19.32%), and hsCRP (-32.5% vs 2.09%).

Approximately similarly treatment effects were observed for the comparison of bempedoic acid vs placebo on top of ezetimibe within subgroups of LDL-C baseline level, history of diabetes, age, race and gender. Slight differences could be due to the small number of patients within each subgroup.

Supportive studies

The phase 2 study 1002-008 provided additional support for the additional efficacy of the combination of bempedoic acid 180 mg QD and ezetimibe (LDL-C difference from baseline -47.7%) in parallel comparison to ezetimibe (-21.2%) or bempedoic acid 180 mg QD (-27.5%), although the difference of the combination versus ezetimibe was only formally tested (p<0.0001). Of note, in this study, the effect of the combination is the sum of the effects of the individual components, in contrast to the FDMC study.

Further, in the 52-week phase 3 studies (1002-040 and 1002-047), as being part of the bempedoic acid monotherapy dossier as the pivotal studies, patients on maximally tolerated statin therapy provides additional support for the additional effect of bempedoic acid on top of ezetimibe therapy, although these data are not stratified and non-randomised for this ezetimibe subgroup; the LDL-C reduction was -13.4% (p <0.001) for bempedoic acid vs placebo in patients taking ezetimibe (n=217).

2.5.5. Conclusions on the clinical efficacy

Bempedoic acid monocomponent

Bempedoic acid has demonstrated the capacity to lower the LDL-C, although this effect was only moderate and declined with the highest doses of statin background 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.

Ezetimibe

Efficacy data for ezetimibe have sufficiently been described based on literature data.

FCMP

On top of statins

The lipid lowering treatment effect was consistently demonstrated for the FCMP of bempedoic acid and ezetimibe in comparison to the placebo and the monocomponents in the factorial design study on top of maximum tolerated statins, although the effect was only moderate when the FCMP was compared to ezetimibe or bempedoic acid. Apparently, the effect of the FCMP in the FCMP study was not the sum of the effects of the monocomponents, although this was observed in the phase 2 study. The lipid lowering treatment effect for the combination was further supported by the phase 3 studies of the bempedoic acid monocomponent dossier. Subgroup analyses generally showed a consistent effect.

Statin intolerance

The LDL-C lowering effect of bempedoic acid on top of ezetimibe background therapy observed in statin intolerant patients was substantially higher compared with the effect for the FCMP in comparison with ezetimibe which may be explained by the differences in statin background therapy between both studies (no or low dose statin therapy vs maximum tolerated statin therapy). This is also in line with the difference observed for the bempedoic acid treatment effect between "on top of statin" and "in statin intolerance". Subgroup analyses generally showed consistency in effect.

2.6. Clinical safety

2.6.1. Bempedoic acid as monocomponent

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 44.**

Table 44. 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
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 45.

Table 45. 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 46.

Table 46. 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)

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 (%)
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)
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 a 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 47. Infection and infestations, musculoskeletal and connective tissue disorders, and gastrointestinal disorders were the SOCs with highest frequencies.

Table 47. 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)

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 (%)
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)
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 48). 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 48. 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 49and Table 50 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 49. 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)
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)

	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 to Week 52	0.126 (2.341)	0.423 (2.147)	--	--	0.126 (2.341)	0.423 (2.147)

Table 50. 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)
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)

	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	0.002 (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 51). 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).

Table 51. 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						
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

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 53) was observed in low intensity statins (37.6% vs 23.7%), ~~which made up 6.1% of the population at baseline~~. No difference was found for muscular disorders in statin intolerance (11.3% vs 11.6%), see Table 52 and Table 53.

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 52. 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

Table 53. 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 54: 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)

Table 54: 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)**
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 55. 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**
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)

Table 55. 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 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 was 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 56.

Table 56. 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 comparable frequency (1.7% vs 2.1%), Table 57.

Table 57. 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 58.

Table 58. 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 was found for bempedoic acid (see Table 59).

Table 59. 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 60.

Table 60. 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 events and deaths

Serious adverse events

A summary of serious adverse events is provided below in Table 61. The number of serious adverse events were slightly higher (14.1% vs 13.3%) for bempedoic acid.

Table 61. 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 the phase 3 studies is provided in Table 62; 19 (0.8%) vs. 4 (0.3%). In the overall phase 2 pool, 1 patient died.

Table 62. 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	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 (%)
syndrome						
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
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	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 (%)
disorders						
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 63 and Table 64, and were lower for bempedoic acid (5.0% vs 5.7%).

Table 63. 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 64. 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)	29 (2.4)	57 (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 65.

Table 65. 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 66 and Table 67:

Table 66. 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 67. 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 Table 68. 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 68. 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 the phase 3 studies, Table 69.

Table 69. Overall Incidence of Adverse Events by Age, Placebo-Controlled Phase 3 Studies (Safety Analysis Set)

	18 < 65 years		65 < 75 years		≥ 75 years	
Pool	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 incidence of adverse events by sex for the Phase 3 pools is summarized in Table 70.

Table 70. 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 AES

In the Overall Phase 3 Pool, the most frequent adverse events that led to discontinuation of study drug are provided below in Table 71. 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 72 and Table 73.

Table 71. 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
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 72. 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 73. 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

2.6.2. Ezetimibe

Safety information is presented for ezetimibe monotherapy based on a meta-analysis covering 8 clinical trials and 2,722 patients (Pandor et al, 2009). Safety information on the combination of ezetimibe and statin therapy is presented based on the large IMPROVE-IT study (Cannon et al, 2015) including more than 18,000 patients. Further safety information is presented based on a meta-analysis of 27 additional double-blind, placebo-controlled or active comparator studies investigating statin monotherapy (atorvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin) versus ezetimibe combination therapy with a statin in more than 20,000 patients. Treatment durations were between 6 and 24 weeks. Thirteen studies evaluated first-line therapy and 14 studies evaluated second-line therapy (Toth et al, 2012). A further meta-analysis (partly overlapping with the above) covering 20 randomised studies investigated ezetimibe combination therapy with a statin (simvastatin, atorvastatin, rosuvastatin, lovastatin, pravastatin, fluvastatin) versus statin monotherapy in almost 15,000 patients treated for 6 to 12 weeks (Luo et al, 2015).

Adverse events

Pandor et al, 2009 present safety data of eight randomized, double-blind, placebo-controlled clinical trials (all 12 weeks). In total, 2,722 individuals were included in these studies. In the eight short-term studies, ezetimibe monotherapy was found to have a similar adverse event profile to placebo. Adverse events (any) ranged from 53–74% in the ezetimibe monotherapy groups and 54-72% in the placebo groups. Of these, 9–18% in the ezetimibe monotherapy group and 9-24% in the placebo group were considered treatment-related (mainly gastrointestinal adverse events or musculoskeletal disorders). Clinically important elevations in creatine phosphokinase (≥10 x upper limit of normal) and liver enzymes (alanine aminotransferase and aspartate aminotransferase ≥3 x upper limit of normal) were not influenced by treatment (<1% in both groups). Discontinuation rates were comparable between both arms and serious adverse events were rare and occurred with similar frequency in the ezetimibe monotherapy and placebo groups. No cases of hepatitis, jaundice, or other clinical signs of liver dysfunction were reported and no deaths were attributable to ezetimibe monotherapy in any of the included studies.

In the IMPROVE-IT study (Cannon et al, 2015), involving 18,144 patients treated with either ezetimibe/simvastatin 10/40 mg (n = 9067; of whom 6% were uptitrated to ezetimibe/simvastatin 10/80 mg) or simvastatin 40 mg (n = 9077; of whom 27% were uptitrated to simvastatin 80 mg), the safety profiles were similar during a median follow-up period of 6.0 years. Discontinuation rates due to adverse experiences were 10.6% for patients treated with ezetimibe/simvastatin and 10.1% for patients treated with simvastatin. The incidence of myopathy was 0.2% for ezetimibe/simvastatin and 0.1% for simvastatin, where myopathy was defined as unexplained muscle weakness or pain with a serum creatinine kinase (CK) ≥10 x upper limit of normal (ULN) or two consecutive observations of CK ≥5 and <10 x ULN. The incidence of rhabdomyolysis was 0.1% for ezetimibe/simvastatin and 0.2% for simvastatin, where rhabdomyolysis was defined as unexplained muscle weakness or pain with a serum CK ≥10 x ULN with evidence of renal injury, ≥5 x ULN and <10 x ULN on two consecutive occasions with evidence of renal injury or CK ≥10,000 IU/L without evidence of renal injury. The incidence of consecutive elevations of transaminases (≥3 x ULN) was 2.5% for ezetimibe/simvastatin and 2.3% for simvastatin. Gallbladder-related adverse effects were reported in 3.1% vs 3.5% of patients allocated to ezetimibe/simvastatin and simvastatin, respectively. The incidence of cholecystectomy hospitalisations was 1.5% in both treatment groups. Cancer (defined as any new malignancy) was diagnosed during the trial in 9.4% vs 9.5%, respectively.

In the meta-analysis conducted by Toth et al, 2012, study-level data were combined from 27 double-blind, placebo-controlled or active comparator studies conducted between 1999 and 2008 (Suhop et al, 2005; Davidson et al, 2002; Gaudiani et al, 2005; Feldman et al, 2004; Ballantyne et al, 2004; Stein et al, 2004; Bays et al, 2004; Pearson et al, 2005; Ballantyne et al, 2005; Catapano et al, 2006; Goldberg et al, 2006; Conard et al, 2008; Leiter et al, 2008; Robinson et al, 2009; Zieve et al, 2010; Kerzner et al, 2003; Melani et al, 2003; Ballantyne et al, 2003; Dobs et al, 2003; Brohet et al, 2005; Farnier et al, 2005; Cruz-Fandez et al, 2005; Barrios et al, 2005; Constance et al, 2007; Farnier et al, 2009; Gagne et al, 2002; Rodney et al, 2006). In these studies adult hypercholesterolemic patients were randomized to statin (atorvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin) or statin plus ezetimibe combination treatment for 6 to 24 weeks with a mean follow up duration of 9 weeks. Thirteen studies evaluated first-line therapy and 14 studies evaluated second-line therapy. A total of 34% of the patients had CHD at baseline. In the full cohort, the only significant difference between treatments was in consecutive AST or ALT elevations ≥ 3 x ULN. Although the incidence (0.35% vs. 0.56%, statin vs. statin / ezetimibe) was small in both treatment groups, there were significantly more reports of elevations in subjects treated with ezetimibe / statin therapy (p = 0.017). Otherwise, both treatments had generally similar tolerability and safety profiles, ie, there were no between-treatment differences in the proportion of subjects reporting at least 1 AE, drug-related AEs, serious AEs, serious drug-related AEs, discontinuations due to AEs, or CK elevations ≥ 10 x ULN.

Luo et al, 2015 conducted a meta-analysis of 20 randomised clinical trials (Ballantyne et al, 2003; Melani et al, 2003; Kerzner et al, 2003; Feldman et al, 2004; Bays et al, 2004; Goldberg et al, 2004; Cruz-Fernandez et al, 2005; Barrios et al, 2005; Ballantyne et al, 2005; Farnier et al, 2005; Catapano et al, 2006; Zubaid et al, 2008; Conard et al, 2008; Leiter et al, 2008; Robinson et al, 2009; Farnier et al, 2009; Foody et al, 2010; Averna et al, 2010; Bays et al, 2011; Hing Ling et al, 2012), that partly overlapped with the one from Toth et al, 2012; about 2,000 patients were considered in the 5 studies not included in the Toth et al, 2012 meta-analysis. The analysis included 14,856 patients >18 years of age diagnosed with hypercholesterolaemia, whose LDL-C levels were above NCEP ATP III guidelines. The studies included comparisons of safety of co-administation of ezetimibe and statins versus statin monotherapy and treatment durations between 6 and 12 weeks. The aim of the meta-analysis was to evaluate the evidence associated with the safety of co-administration of ezetimibe with statins.

A fixed-effects model was used for meta-analysis to assess the safety of combination therapy. In summary, co-administration of ezetimibe and statins did not result in significant increases in total adverse events compared with statin monotherapy (30% vs 29%, p = 0.34), serious adverse events (2% vs 1.6%, p = 0.81), treatment discontinuations (3.5% vs 2.9%, p = 0.22), gastrointestinal adverse events (5% vs 4%, p = 0.08), allergic reactions or rashes (0.9% vs 1.3%, p = 0.33), creatine kinase >10 × ULN (0.2% vs 0.2%, p = 0.86), alanine aminotransferase >3 × ULN (0.5% vs 0.4%, p = 0.96) and aspartate aminotransferase >3 × ULN (0.4% vs 0.4%, p = 0.58). In conclusion, the incidence of adverse events was similar between ezetimibe–statin combination therapy and statin monotherapy.

Adverse Events of Special Interest

In the Simvastatin and Ezetimibe for the Treatment of Aortic Stenosis (SEAS) study (Rossebø et al, 2008) cancer occurred more frequently in the ezetimibe/simvastatin group (105 versus 70, p = 0.01). The clinical relevance of this observation is uncertain as in the bigger SHARP trial (Baigent et al, 2011) the total number of patients with any incident cancer (438 in the ezetimibe/ simvastatin versus 439 placebo group) did not differ. In addition, in the IMPROVE-IT trial (Cannon et al, 2015) the total number of patients with any new malignancy (853 in the ezetimibe/simvastatin group versus 863 in the simvastatin group) did not differ significantly, and therefore, the finding of SEAS trial could not be confirmed by SHARP or IMPROVE-IT (see Peto et al, 2008 for a meta-analysis of the 2 trials compared to the SEAS trial). In the registry-based observational follow-up study of the original SEAS study

patient population, treatment with ezetimibe/simvastatin was not associated with an increased risk for cancer or mortality in the 21-month period after the completion of the original SEAS study (Green et al, 2014).

Alsheikh-Ali et al, 2009 investigated all adverse event reports listing "cancer" or "malignancy" filed with the FDA (July 2004 to March 2008) of patients taking ezetimibe or ezetimibe/simvastatin combination, and compared those to reports of patients taking simvastatin, atorvastatin, or rosuvastatin.

Prescriptions for all drugs totalled 559 million (approximately 52 and 55 million prescriptions of ezetimibe and ezetimibe/simvastatin, respectively), and cancer adverse event reports totalled 2334. There were 2.9 and 1.3 cancer-associated adverse event reports per million ezetimibe or ezetimibe/simvastatin prescriptions, respectively, compared to a range of 3.1 to 5.1 per million prescriptions for the other drugs. The proportions of reports listing cancer relative to all adverse event reports were 2.0% and 1.9% for ezetimibe and ezetimibe/simvastatin, respectively, compared to a range of 1.3% to 3.9% for the other drugs. In conclusion, this large-scale post-marketing analysis of reported adverse events does not support that ezetimibe or ezetimibe/simvastatin increase the risk of cancer.

Serious Adverse Events

Nußbaumer et al, 2016 conducted a meta-analysis of SAE reporting in 3 randomised (Feldman et al, 2004; Gaudiani et al, 2005; Cannon et al, 2015; Blazing et al, 2014), controlled trials including 19,068 patients. SAEs included death, life-threatening events and events resulting in hospitalisation, congenital anomaly or disability or permanent damage. Under ezetimibe-statin combination therapy, 38% of the 9628 patients experienced serious adverse events compared with 39% of the 9440 patients treated with statin monotherapy (RR 1.09 [0.77; 1.55]).

A further meta-analysis of 20 randomised clinical trials and 14,856 patients, Luo et al, 2015 found SAE reporting in 13 trials, with 76 events occurring in 3997 patients (2%) treated with ezetimibe and statins, compared with 69 events in 4301 patients (1.6%) treated with statins alone. This end point was not higher with combination therapy compared with statin monotherapy (95% CI, 0.75 – 1.45; p = 0.81).

Deaths

In the meta-analysis of clinical trials investigating ezetimibe monotherapy, no deaths were attributable to ezetimibe monotherapy in any of the included studies (Pandor et al, 2009).

For ezetimibe combination therapy studies, cardiovascular deaths were usually included in the efficacy analyses of clinical studies. None of the evaluated meta-analyses presented an analysis of deaths for ezetimibe combination therapy versus statin monotherapy.

In the IMPROVE-IT study, no differences between simvastatin monotherapy and combination treatment with simvastatin and ezetimibe were detected for deaths. Death from any cause was reported for 15.3% and 15.4% of patients receiving monotherapy and combination therapy, respectively. Hazard ratios (95% CI) for death from any cause, cardiovascular deaths, and CHD deaths were 0.99 (0.91–1.07), 1.00 (0.89–1.13), and 0.96 (0.84–1.09), respectively (Cannon et al, 2015).

Post marketing experience

The active substance ezetimibe is marketed since 2003. Product names are Ezetrol® or Zetia®.

With the exception of an investigation of malignancies during post-marketing treatment with ezetimibe/simvastatin combination vs. statin monotherapies (Alsheikh-Ali et al, 2009), no summaries of post-marketing safety data for ezetimibe treatment were found during the literature search for this clinical summary.

2.6.3. FCMP

In the pivotal FCMP study, 382 patients (2:2:2:1 ratio) received study drug for a median exposure of 84.0 days. Median exposure to IMP (excluding the three sites) was 84.0 days for the FDC, bempedoic acid, and ezetimibe treatment groups and 85.0 days for the placebo group.

In study pivotal study 1002-048 in statin intolerant patients, 268 patients (2:1 ratio) received study drug for a median exposure of 84.0 days.

In the supportive phase 2 study 1002-008, 24 patients received bempedoic acid 180 mg QD+ezetimibe (median 77.6 days), 99 patients ezetimibe (79.2 days) and 100 patients bempedoic acid 180 mg QD (77.7 days).

In the supportive phase 3 pool, 150 patients received bempedoic acid and 76 patients placebo on a background of ezetimibe. Exposure data are not available.

Adverse events

Overall safety profile

An overview of the overall safety profile for the pivotal studies is provided in Table 74 and Table 76.

Table 74. Overall Summary of Treatment-Emergent Adverse Events by Treatment in Phase 3 Study 1002FDC-053 (Safety Population)

Category	Bempedoic Acid 180 mg + Ezetimibe 10 mg FCMP (N = 107) n (%)	Bempedoic acid 180 mg (N = 110) n (%)	Ezetimibe 10 mg (N = 109) n (%)	Placebo (N = 55) n (%)
Total number of TEAEs	147	144	117	32
Patients with ≥1 TEAEs	63 (58.9)	68 (61.8)	58 (53.2)	24 (43.6)
Patients with ≥ 1 IMP-related TEAE	13 (12.1)	13 (11.8)	9 (8.3)	4 (7.3)
Patients with ≥ 1 serious TEAE	8 (7.5)	7 (6.4)	10 (9.2)	1 (1.8)
Patients with ≥ 1 IMP-related serious TEAE	0	0	0	0
Patients with a TEAE leading to death	0	0	0	0
Patients with a TEAE leading to discontinuation of IMP	7 (6.5)	9 (8.2)	10 (9.2)	2 (3.6)
Patients with TEAEs by highest severity				
Mild	31 (29.0)	42 (38.2)	35 (32.1)	16 (29.1)
Moderate	23 (21.5)	19 (17.3)	14 (12.8)	7 (12.7)
Severe	9 (8.4)	7 (6.4)	9 (8.3)	1 (1.8)

Table 75. Overall Summary of Treatment-Emergent Adverse Events by Treatment in Phase 3 Study 1002FDC-053 (Safety Population Excluding Three Sites)

Category	Bempedoic acid 180 mg + Ezetimibe 10 mg FDC (N = 85) n (%)	Bempedoic acid 180 mg (N = 88) n (%)	Ezetimibe 10 mg (N = 86) n (%)	Placebo (N = 41) n (%)
Total number of TEAEs	136	127	103	26
Patients with ≥1 TEAEs	53 (62.4)	58 (65.9)	47 (54.7)	18 (43.9)
Patients with ≥ 1 IMP-related TEAE	13 (15.3)	12 (13.6)	9 (10.5)	4 (9.8)
Patients with ≥ 1 serious TEAE	8 (9.4)	7 (8.0)	9 (10.5)	1 (2.4)
Patients with ≥ 1 IMP-related serious TEAE	0	0	0	0
Patients with a TEAE leading to death	0	0	0	0
Patients with a TEAE leading to discontinuation of IMP	7 (8.2)	9 (10.2)	10 (11.6)	2 (4.9)
Patients with TEAEs by highest severity				
Mild	21 (24.7)	32 (36.4)	25 (29.1)	11 (26.8)
Moderate	23 (27.1)	19 (21.6)	14 (16.3)	6 (14.6)

Category	Bempedoic acid 180 mg + Ezetimibe 10 mg FDC (N = 85) n (%)	Bempedoic acid 180 mg (N = 88) n (%)	Ezetimibe 10 mg (N = 86) n (%)	Placebo (N = 41) n (%)
Severe	9 (10.6)	7 (8.0)	8 (9.3)	1 (2.4)

Table 76. Overview of Treatment-Emergent Adverse Events in Bempedoic Acid Study 1002 048 (Safety Analysis Set)

	Placebo (N = 87) n (%)	Bempedoic Acid (N = 181) n (%)	Total (N = 268) n (%)
Total number of patients with ≥ 1 TEAE	39 (44.8)	88 (48.6)	127 (47.4)
Patients with ≥ 1 IMP-related TEAE	8 (9.2)	39 (21.5)	47 (17.5)
Patients with ≥ 1 serious TEAE	3 (3.4)	5 (2.8)	8 (3.0)
Patients with ≥ 1 IMP-related serious TEAE	0	0	0
Patients with a TEAE leading to discontinuation of IMP	5 (5.7)	11 (6.1)	16 (6.0)
Patients with a TEAE leading to discontinuation of ezetimibe	2 (2.3)	8 (4.4)	10 (3.7)
Patients with a TEAE leading to death	0	0	0
Patients with TEAEs by highest severity			
Mild	24 (27.6)	49 (27.1)	73 (27.2)
Moderate	10 (11.5)	33 (18.2)	43 (16.0)
Severe	5 (5.7)	6 (3.3)	11 (4.1)

The most common adverse events observed in the studies are mentioned below.

Table 77. Treatment-Emergent Adverse Event by Preferred Term Reported in ≥3% of Patients in Any Treatment Group in Phase 3 Study 1002FDC-053 (Safety Population)

Preferred Term	FCMP[a] (N = 107) n (%)	Bempedoic Acid 180 mg (N = 110) n (%)	Ezetimibe 10 mg (N = 109) n (%)	Placebo (N = 55) n (%)
Patients with ≥1 TEAE	63 (58.9)	68 (61.8)	58 (53.2)	24 (43.6)
Urinary tract infection	8 (7.5)	3 (2.7)	3 (2.8)	2 (3.6)
Nasopharyngitis	4 (3.7)	6 (5.5)	4 (3.7)	1 (1.8)
Constipation	4 (3.7)	0	2 (1.8)	0
Back pain	3 (2.8)	3 (2.7)	4 (3.7)	2 (3.6)
Hypertension	3 (2.8)	5 (4.5)	2 (1.8)	0
Muscle spasms	2 (1.9)	1 (0.9)	4 (3.7)	0
Myalgia	2 (1.9)	5 (4.5)	2 (1.8)	1 (1.8)
Headache	2 (1.9)	4 (3.6)	2 (1.8)	1 (1.8)
Arthralgia	1 (0.9)	4 (3.6)	4 (3.7)	2 (3.6)
Anaemia	1 (0.9)	2 (1.8)	1 (0.9)	2 (3.6)
Dyspnoea	0	0	1 (0.9)	2 (3.6)

Table 78. Treatment-Emergent Adverse Event by Preferred Term Reported in ≥3% of Patients in Any Treatment Group in Phase 3 Study 1002FDC-053 (Safety Population Excluding Three Sites)

Category	FDC[a] (N = 85) n (%)	Bempedoic acid180 mg (N = 88) n (%)	Ezetimibe 10 mg (N = 86) n (%)	Placebo (N = 41) n (%)
Patients with ≥1 TEAEs	53 (62.4)	58 (65.9)	47 (54.7)	18 (43.9)
Urinary tract infection	5 (5.9)	3 (3.4)	2 (2.3)	1 (2.4)
Nasopharyngitis	4 (4.7)	6 (6.8)	4 (4.7)	0
Constipation	4 (4.7)	0	2 (2.3)	0
Back pain	3 (3.5)	3 (3.4)	2 (2.3)	2 (4.9)
Fatigue	3 (3.5)	2 (2.3)	1 (1.2)	0
Upper respiratory tract infection	3 (3.5)	1 (1.1)	0	0
Blood creatinine increased	3 (3.5)	1 (1.1)	0	0
Blood uric acid increased	3 (3.5)	1 (1.1)	0	0
Bronchitis	3 (3.5)	0	3 (3.5)	0
Myalgia	2 (2.4)	5 (5.7)	2 (2.3)	1 (2.4)
Headache	2 (2.4)	3 (3.4)	1 (1.2)	1 (2.4)
Muscle spasms	2 (2.4)	1 (1.1)	4 (4.7)	0
Arthralgia	1 (1.2)	4 (4.5)	3 (3.5)	1 (2.4)
Hypertension	1 (1.2)	3 (3.4)	2 (2.3)	0

Category	FDC[a] (N = 85) n (%)	Bempedoic acid180 mg (N = 88) n (%)	Ezetimibe 10 mg (N = 86) n (%)	Placebo (N = 41) n (%)
Acute myocardial infarction	1 (1.2)	2 (2.3)	3 (3.5)	0
Dyspnoea	0	0	1 (1.2)	2 (4.9)
Back pain	3 (3.5)	3 (3.4)	2 (2.3)	2 (4.9)

Table 79. Treatment-emergent Adverse Events by Preferred Term Reported in ≥ 2% of Patients in Either Treatment Group in Bempedoic Acid Study 1002-048 (Safety Analysis Set)

Preferred Term	Placebo (N = 87) n (%)	Bempedoic Acid (N = 181) n (%)
Patients with ≥ 1 TEAE	39 (44.8)	88 (48.6)
Blood uric acid increased	2 (2.3)	14 (7.7)
Headache	3 (3.4)	8 (4.4)
Liver function test increased	0	7 (3.9)
Muscle spasms	3 (3.4)	6 (3.3)
Nausea	0	5 (2.8)
Sinusitis	0	5 (2.8)
Urinary tract infection	5 (5.7)	5 (2.8)
Glomerular filtration rate decreased	0	4 (2.2)
Nasopharyngitis	1 (1.1)	4 (2.2)
Myalgia	2 (2.3)	3 (1.7)
Diabetes mellitus	2 (2.3)	2 (1.1)
Vertigo	2 (2.3)	0
Vulvovaginal mycotic infection	2 (2.3)	0

In the phase 2 study 1002-008, constipation and nasopharyngitis were the most frequently reported adverse events in the bempedoic acid 180 mg + ezetimibe group (8.3%) and occurred more frequently than in other groups.

In the phase 3 ezetimibe subgroup analysis, the most frequently reported adverse event in each treatment group was nasopharyngitis (14.0% bempedoic acid, 6.6% placebo).

Adverse events of special interest

- Hypoglycemia/metabolic acidosis

In any of the pivotal studies the numbers were not larger than 1 patients and no metabolic acidosis was reported.

- New onset diabetes/hyperglycemia

In the FCMP study, the numbers of new onset diabetes was limited. In patients with a history of diabetes, laboratory abnormalities in glucose were more in the FCMP.

Table 80. Adverse Events of Special Interest by Preferred Term: New Onset or Worsening Diabetes in Phase 3 Study 1002FDC-053 (Safety Analysis Set)

AESI Category Preferred Term	FCMP (N = 107) n (%)	Bempedoic Acid (N = 110) n (%)	Ezetimibe (N = 109) n (%)	Placebo (N = 55) n (%)
New onset or worsening of diabetes mellitus	4 (3.7)	1 (0.9)	2 (1.8)	0
Blood glucose increased	1 (0.9)	0	0	0
Diabetes mellitus	0	1 (0.9)	2 (1.8)	0
Diabetes mellitus inadequate control	2 (1.9)	0	0	0
Glycosuria	1 (0.9)	0	0	0

Table 81. Adverse Events of Special Interest by Preferred Term: New Onset or Worsening Diabetes (Safety Analysis Set, Excluding Three Sites)

AESI Category Preferred Term	FCMP (N = 85) n (%)	Bempedoic Acid (N = 88) n (%)	Ezetimibe (N = 86) n (%)	Placebo (N = 41) n (%)
New onset or worsening of diabetes mellitus	4 (4.7)	1 (1.1)	2 (2.3)	0
Blood glucose increased	1 (1.2)	0	0	0
Diabetes mellitus	0	1 (1.1)	2 (2.3)	0
Diabetes mellitus inadequate control	2 (2.4)	0	0	0
Glycosuria	1 (1.2)	0	0	0

AESI = adverse event of special interest; FDC = fixed dose combination.

Note: Three sites were removed from this table.

Source: Study 1002FDC-053 CSR, Table 14.3.1.2.5a

Table 82. Laboratory Abnormalities: Fasting Glucose by Baseline Diabetes History in Phase 3 Study 1002FDC-053 (Safety Analysis Set)

Parameter Criteria	FCMP (N = 107) n (%)	Bempedoic Acid (N = 110) n (%)	Ezetimibe (N = 109) n (%)	Placebo (N = 55) n (%)
Fasting glucose in patients with a history of diabetes, n	48	62	61	24
≥126 mg/dL	34 (70.8)	33 (53.2)	36 (59.0)	13 (54.2)
≤50 mg/dL	0	0	0	0
Fasting glucose in patients with no history of diabetes, n	59	48	48	31
≥126 mg/dL	3 (5.1)	2 (4.2)	4 (8.3)	4 (12.9)
≤50 mg/dL	0	2 (4.2)	1 (2.1)	0

In study 1002-048, the numbers of new onset diabetes was limited. In patients with a history of diabetes, laboratory abnormalities in glucose were more in the bempedoic acid and ezetimibe combination.

Table 83. Adverse Events of Special Interest by Preferred Term: New Onset or Worsening of Diabetes in Bempedoic Acid Study 1002 048 (Safety Analysis Set)

AESI Category **Preferred Term**	**Placebo (N = 107) n (%)**	**Bempedoic Acid (N = 181) n (%)**	**Ezetimibe (N = 109) n (%)**	**Placebo (N = 55) n (%)**
Fasting glucose in patients with a history of diabetes mellitus	3 (3.4)	6 (3.3)	61	24
Diabetes mellitus	34 (70.8)	33 (53.2 (2.3)	36 (59.0)	13 (54.2 (1.1)
Impaired fasting glucose	0	2 (1.1)	0	0
Fasting glucose in patients with no history of diabetes, n	59	1 (0.6)	48	31
≥126 mg/dL	3 (5.1)	Type 2 diabetes mellitus	4 (8.3)	4 (12.9)
Diabetes mellitus inadequate control	0	2 (4.2)	1 (1.1)	0

Table 84. HbA1C by Baseline Diabetes History in Bempedoic Acid Study 1002 048 (Safety Analysis Set)

AESI Category **Preferred Term**	**Placebo (N = 87)** n (%)	**Bempedoic Acid (N = 181)** n (%)
New onset or worsening of diabetes mellitus	3 (3.4)	6 (3.3)
Diabetes mellitus	2 (2.3)	2 (1.1)
Impaired fasting glucose	0	2 (1.1)
≥126 mg/dL	12 (70.6)	19 (54.3)
Hyperglycaemia	0	1 (0.6)
HbA_{1C}		
≥6.5%	8 (47.1)	16 (45.7)
Patients with no history of diabetes mellitus	70	1 (0.6)
Fasting glucose		
Diabetes mellitus inadequate control	1 (1.4)	12 (8.2)
≤50 mg/dL	0	0
Hb_{A1C}		
≥6.5%	0	3 (2.1)

In the supportive phase 3 ezetimibe subgroup analysis, the percentage of patients who had new onset diabetes/hyperglycaemia adverse events was similar in patients who received ezetimibe background therapy in the bempedoic acid group (2.0%) and the placebo group (6.6%).

- Hepatic enzyme elevations

In the FCMP study, hepatic adverse events occurred in 2 patients (2.4%) in the FCMP group, 1 patient (1.1%) in the bempedoic acid group, and no patients in the ezetimibe or placebo groups. This was similar in the sensitivity analysis excluding the three sites.

Further, 2 patients (1.9%) in the FCMP group had an AST value >3 × upper limit of normal (ULN), neither of these patients demonstrated repeated and confirmed ALT and/or AST levels >3 × ULN that had increased from baseline. No patient had increased alanine aminotransferase (ALT) >3 × ULN or increased total bilirubin (TB) >2 × ULN, and there were no potential cases that met the criteria for Hy's Law.

In study 1002-048, hepatic events and liver enzyme abnormalities were more frequent in bempedoic acid plus ezetimibe, see tables below.

Table 85: Adverse Events of Special Interest by Preferred Term: Hepatic Events in .Bempedoic Acid Study 1002 048 (Safety Analysis Set)

AESI Category Preferred Term	**Placebo (N = 87) n (%)**	**Bempedoic Acid (N = 181) n (%)**
Liver function test increased	12 (70.6)	19 (54.3.9)
ALT increased	0	3 (1.7)
AST increased	8 (47.1)	16 (45.7)
LFT abnormal	1 (1.4)	12 (8.2 (1.1)
Hepatic enzyme increased	0	1 (0

In the supportive phase 2 study 1002-008, mild increases in AST and ALT were seen in the bempedoic acid groups.

In the supportive phase 3 ezetimibe subgroup analysis, hepatic enzyme elevation were higher for bempedoic acid (7 (4.7%) vs 1(1.3%)).

- Muscular disorders

In the FCMP study, muscular disorders were reported as indicated below. Further, 1 patient (0.9%) in the ezetimibe group had a single CK level >5 × ULN that was not confirmed upon repeat assessment. No patients in the FCMP, bempedoic acid, or placebo group had a CK level >5 × ULN and there were no incidences of CK > 10 × ULN.

Table 86. Adverse Events of Special Interest by Preferred Term: Muscular Disorders in Phase 3 Study 1002FDC-053 (Safety Analysis Set)

AESI Category Preferred Term	FCMP (N = 107) n (%)	Bempedoic Acid (N = 110) n (%)	Ezetimibe (N = 109) n (%)	Placebo (N = 55) n (%)
Muscular disorders	6 (5.6)	7 (6.4)	7 (6.4)	3 (5.5)
Muscle spasms	2 (1.9)	1 (0.9)	4 (3.7)	0
Muscular weakness	0	0	0	1 (1.8)
Myalgia	2 (1.9)	5 (4.5)	2 (1.8)	1 (1.8)
Pain in extremity	2 (1.9)	2 (1.8)	1 (0.9)	1 (1.8)

Table 87. Adverse Events of Special Interest by Preferred Term: Muscular Disorders (Safety Analysis Set, Excluding Three Sites)

AESI Category Preferred Term	FDC (N = 85) n (%)	Bempedoic Acid (N = 88) n (%)	Ezetimibe (N = 86) n (%)	Placebo (N = 41) n (%)
Muscular disorders	6 (7.1)	7 (8.0)	7 (8.1)	3 (7.3)
Muscle spasms	2 (2.4)	1 (1.1)	4 (4.7)	0
Muscular weakness	0	0	0	1 (2.4)
Myalgia	2 (2.4)	5 (5.7)	2 (2.3)	1 (2.4)
Pain in extremity	2 (2.4)	2 (2.3)	1 (1.2)	1 (2.4)

AESI = adverse event of special interest; FDC = fixed dose combination.
Source: Study 1002FDC-053 CSR, Table 14.3.1.2.5a

In study 1002-048, muscular disorders were reported as indicated below. One patient (0.6%) had a single postbaseline CK level >5 × ULN that was not confirmed upon repeat assessment, and no patient had an increase in CK >10 × ULN.

Table 88. Adverse Events of Special Interest by Preferred Term: Muscular Disorders in Bempedoic Acid Study 1002 048 (Safety Analysis Set)

AESI Category Preferred Term	Placebo (N = 87) n (%)	Bempedoic Acid (N = 181) n (%)
Muscular safety events	5 (5.7)	11 (6.1)
Muscle spasms	3 (3.4)	6 (3.3)
Myalgia	2 (2.3)	3 (1.7)
Muscular weakness	0	1 (0.6)
Pain in extremity	0	1 (0.6)

AESI Category Preferred Term	Placebo (N = 87) n (%)	Bempedoic Acid (N = 181) n (%)
Creatine kinase elevations	0	3 (1.7)
Blood creatine phosphokinase increased	0	3 (1.7)

In the supportive phase 2 study 1002-008, muscular disorders were reported in 6 patients (6.0%) in the bempedoic acid 180 mg group, 12 patients (12.1%) in the ezetimibe group, and 3 patients (12.5%) in the bempedoic acid 180 mg + ezetimibe group.

In the phase 3 ezetimibe subgroup analysis, muscular disorders were 23 (15.3%) for bempedoic acid and 11 (14.5%) for placebo.

- Neurocognitive disorders

No adverse events were reported in the pivotal studies.

- Renal disorders

In the FCMP study, renal disorder occurred overall in 4 (3.7%) patients in the FCMP group (3 blood creatinine increased, 1 acute kidney injury), and 2 (1.8%) of patients in the bempedoic acid group (2 blood creatinine increased), and no patients in the ezetimibe or placebo groups. The AKI event was considered mild and not related to treatment; treatment was continued and the patient recovered.

Table 89. Adverse Events of Special Interest by Preferred Term: Renal Events (Safety Analysis Set, Excluding Three Sites)

AESI Category System Organ Class Preferred Term	FDC (N = 85) n (%)	Bempedoic Acid (N = 88) n (%)	Ezetimibe (N = 86) n (%)	Placebo (N = 41) n (%)
Renal disorders	4 (4.7)	1 (1.1)	0	0
Investigations				
Blood creatinine increased	3 (3.5)	1 (1.1)	0	0
Renal and Urinary Disorders				
Acute kidney injury	1 (1.2)	0	0	0

AESI = adverse event of special interest; FDC = fixed dose combination.
Source: Study 1002FDC-053 CSR, Table 14.3.1.2.5a

Mean creatinine increased slightly postbaseline in the FCMP and bempedoic acid groups, with mean changes from +0.022 to +0.044 mg/dL (FCMP group) and +0.062 to +0.072 mg/dL (bempedoic acid group) by Week 4 and remained stable through Week 12. In the FCMP, bempedoic acid, and ezetimibe groups at all timepoints, a larger percentage of patients shifted to a worse eGFR category than to a better category. For example, at Week 12, 17 patients (16.2%) in the FCMP group shifted to a worse eGFR category and 7 patients (6.7%) shifted to a better eGFR category. In the bempedoic acid group, 18 patients (17.5%) shifted to a worse eGFR category and 8 patients (7.8%) shifted to a better eGFR category. In the ezetimibe group, 12 patients (11.7%) shifted to a worse eGFR category and 6 patients (5.8%) shifted to a better eGFR category. In the placebo group, the percentage of patients

who shifted to a worse eGFR category was generally similar to the percentage of patients who shifted to a better eGFR category.

In Study 1002-048, renal disorders occurred in 7 (3.9%) patients (4 GFR decrease, 3 blood creatininen increase, 2 renal failure, 1 renal impairment) in the bempedoic acid group, compared with 1 (1.1%) (renal failure) patient in the placebo group. Mean creatinine increased slightly postbaseline in the bempedoic acid group, with mean percent changes from 3.6% to 4.1%, compared with -0.11% to 1.1% in the placebo group. Shifts from normal to high (>ULN) creatinine levels occurred in a higher proportion of patients in the bempedoic acid group than in the placebo group (at Week 12: bempedoic acid, 10.8%; placebo, 6.1%)

In the supportive phase 3 ezetimibe subgroup analysis, renal disorders were 2 (1.3%) for bemepdoic acid and 1 (1.3%) for placebo.

- Uric acid increases/gout

Changes in uric acid are displayed in Table 90 and Table 91.

Table 90. Mean Percent Change from Baseline in Uric Acid at Week 12, Comparison of Results from the Initial Analysis and the Post Hoc Sensitivity Analysis

Analysis	FCMP	Bempedoic Acid	Ezetimibe	Placebo
Initial analysis, n	104	103	103	53
Mean % Change	+9.36%	+14.26%	+1.57%	-0.66%
Post hoc sensitivity analysis, n	82	82	80	40
Mean % Change	+11.83%	+16.14%	+1.49%	-1.32%

Table 91. Number (%) of Patients with Laboratory Abnormalities in Uric Acid in Study 1002FDC-053 (Safety Population)

Analyte Time Point	Number (%) of Patients with Laboratory Abnormalities			
	FCMP (N = 107) n (%)	Bempedoic Acid (N = 110) n (%)	Ezetimibe (N = 109) n (%)	Placebo (N = 55) n (%)
Uric acid				
Baseline	23 (21.5)	27 (24.5)	24 (22.0)	12 (21.8)
Week 4	***40 (37.4)***	***47 (42.7)***	19 (17.4)	9 (16.4)
Week 8	***41 (38.3)***	***41 (37.3)***	20 (18.3)	10 (18.2)
Week 12	***38 (35.5)***	***44 (40.0)***	27 (24.8)	10 (18.2)

Three patients (2.8%) in the FCMP group (treatment related) and 2 patients (1.8%) in the bempedoic acid group (not treatment related) had adverse events of blood uric acid increased. No event of gout were reported.

In study 1002-048, mean uric acid increased slightly increased in the bempedoic acid group, with mean percent changes from 8.3% to 9.8%, compared with -0.28% to -2.7% in the placebo group. Shifts from normal to high (>ULN) uric acid levels were for bempedoic acid 16.6% and placebo, 7.3% at week 12. A total of 14 patients (7.7%) in the bempedoic acid group had an adverse events of blood

uric acid increased (of which 10 [5.5%] treatment related compared with 2 patients (2.3%) in the placebo group (of which 1 [1.1%] treatment related).

In the supportive phase 2 study 1002-008, a mild increase in mean uric acid from baseline was seen with bempedoic acid treatment.

In the supportive phase 3 ezetimibe subgroup analysis, 2 patients (1.3%) in the bempedoic acid group and 1 patient (1.3%) in the placebo group had blood uric acid increased, and 3 (2.0%) vs none had gout.

- Hemoglobin decreased

In the FCMP study, mean hemoglobin decreased slightly from baseline in the FCMP and bempedoic acid groups, with mean changes of -0.04 to -0.29 g/dL (-0.20% to -2.02%) in the FCMP group, -0.13 to -0.30 g/dL (-0.92% to -2.04%) in the bempedoic acid group, and +0.03 to +0.06 g/dL (mean 0.32% to 0.60%) in placebo. One patient (0.9%) in the FCMP group and no patient in the placebo group had decreases in hemoglobin of at least 2 g/dL from baseline and none with decrease in hemoglobin to < 8 g/dL. One patient (0.9%) in the FCMP group and 2 patients (3.6%) in the placebo group had adverse events of anemia.

In study 1002-048, mean hemoglobin decreased slightly from baseline in the bempedoic acid group, -0.23 to -0.29 g/dL (-0.47% to 0.51 %) compared with mean increases of 0.06 to 0.07 g/dL (1.60% to 1.92%) in the placebo group, 8 patients (4.4%) vs none had decreases in hemoglobin of at least 2 g/dL from baseline and no adverse events of anemia were observed.

In the supportive phase 2 study 1002-008, a mild decrease in hemoglobin was seen with bempedoic acid treatment.

In the supportive phase 3 ezetimibe subgroup analysis, no patients in the bempedoic acid group and 1 (1.3%) patient in the placebo group had anaemia.

Serious adverse events and deaths

Serious adverse events

For the FCMP study, serious adverse events are provided in Table 92. None were considered treatment related.

Table 92. Treatment-Emergent Serious Adverse Events by Preferred Term (Safety Population)

Preferred Term	FCMP(1) (N = 107) n (%)	Bempedoic Acid 180 mg (N = 110) n (%)	Ezetimibe 10 mg (N = 109) n (%)	Placebo (N = 55) n (%)
Patients with treatment-emergent SAE	8 (7.5)	7 (6.4)	10 (9.2)	1 (1.8)
Acute myocardial infarction	1 (0.9)	2 (1.8)	3 (2.8)	0
Angina pectoris	1 (0.9)	0	0	0
Atrial fibrillation	1 (0.9)	0	0	0
Coronary artery disease	1 (0.9)	0	0	1 (1.8)
Myocardial ischaemia	1 (0.9)	0	0	0
Non-cardiac chest pain	1 (0.9)	0	0	0
Rhinovirus infection	1 (0.9)	0	0	0
Hemiparesis	1 (0.9)	0	0	0
Cardiac failure congestive	0	0	1 (0.9)	0
Myocardial infarction	0	1 (0.9)	0	1 (1.8)
Supraventricular tachycardia	0	1 (0.9)	0	0
Diverticulitis	0	1 (0.9)	0	0
Pneumonia	0	1 (0.9)	1 (0.9)	0
Coronary vascular graft stenosis	0	0	1 (0.9)	0
Limb injury	0	0	1 (0.9)	0
Ovarian cancer	0	0	1 (0.9)	0
Confusional state	0	1 (0.9)	0	0
Renal artery occlusion	0	0	1 (0.9)	0
Chronic obstructive pulmonary disease	0	1 (0.9)	0	0
Chronic respiratory failure	0	0	1 (0.9)	0
Pulmonary fibrosis	0	0	1 (0.9)[b]	0
Staphylococcal bacteraemia	0	0	1 (0.9)[b]	0
Respiratory failure	0	0	1 (0.9)	0
Deep vein thrombosis	0	0	1 (0.9)	0

Table 93. Treatment-Emergent Serious Adverse Events by Preferred Term in Phase 3 Study 1002FDC-053 (Safety Population Excluding Three Sites)

Preferred Term	FDC[a] (N = 85) n (%)	Bempedoic Acid 180 mg (N = 88) n (%)	Ezetimibe 10 mg (N = 86) n (%)	Placebo (N = 41) n (%)
Patients with treatment-emergent serious adverse event	8 (9.4)	7 (8.0)	9 (9.5)	1 (2.4)
Acute myocardial infarction	1 (1.2)	2 (2.3)	3 (3.5)	0

Preferred Term	FDC[a] (N = 85) n (%)	Bempedoic Acid 180 mg (N = 88) n (%)	Ezetimibe 10 mg (N = 86) n (%)	Placebo (N = 41) n (%)
Angina pectoris	1 (1.2)	0	0	0
Atrial fibrillation	1 (1.2)	0	0	0
Coronary artery disease	1 (1.2)	0	0	1 (2.4)
Myocardial infarction	0	1 (1.1)	0	1 (2.4)
Myocardial ischaemia	1 (1.2)	0	0	0
Supraventricular tachycardia	0	1 (1.1)	0	0
Non-cardiac chest pain	1 (1.2)	0	0	0
Diverticulitis	0	1 (1.1)	0	0
Pneumonia	0	1 (1.1)	1 (1.2)	0
Rhinovirus infection	1 (1.2)	0	0	0
Coronary vascular graft stenosis	0	0	1 (1.2)	0
Limb injury	0	0	1 (1.2)	0
Ovarian cancer	0	0	1 (1.2)	0
Hemiparesis	1 (1.2)	0	0	0
Confusional state	0	1 (1.1)	0	0
Renal artery occlusion	0	0	1 (1.2)	0
Chronic obstructive pulmonary disease	0	1 (1.1)	0	0
Chronic respiratory failure	0	0	1 (1.2)	0
Respiratory failure	0	0	1 (1.2)	0
Deep vein thrombosis	0	0	1 (1.2)	0

For study 1002-048, serious adverse event are provided in Table 94. None were considered treatment related.

Table 94. Serious Treatment-Emergent Adverse Events by Preferred Term in Bempedoic Acid Study 1002 048 (Safety Analysis Set)

Preferred Term	Placebo (N = 87) n (%)	Bempedoic Acid (N = 181) n (%)
Patients with ≥ 1 serious adverse event	3 (3.4)	5 (2.8)
Bronchitis	0	1 (0.6)
Dysuria	0	1 (0.6)
Hepatic cancer	0	1 (0.6)
Intestinal obstruction	0	1 (0.6)
Osteoarthritis	0	1 (0.6)
Syncope	0	1 (0.6)
Breast cancer	1 (1.1)	0
Pneumonia bacterial	1 (1.1)	0
Poisoning deliberate	1 (1.1)	0
Subdural hematoma	1 (1.1)	0

In the supportive phase 3 ezetimibe subgroup analysis, serious adverse event were 11.3% for bempedoic acid, placebo 13.2%. The most common serious adverse event was angina pectoris (1.3% bempedoic acid, 1.3% placebo).

Deaths

No patients died in the pivotal studies. One patient died in the phase 2 study 1002-008, and one patient on ezetimibe background therapy died in the supportive phase 3 study pool.

MACE events

These were not adjudicated in the pivotal studies.

MACE analyses were also not conducted for the subgroup of patients who received ezetimibe in the bempedoic phase 3 studies,. In the overall phase 3 pool, the analysis of 3-, 4-, and 5-component MACE demonstrated HRs, analyzed with and without hospitalization for heart failure, yielded HR of 0.85-1.03 with upper limits of the 95% confidence interval ranging from 1.271 to 1.577. These findings have also been discussed in the bempedoic acid monocomponent MAA.

Laboratory findings

Specific laboratory findings have already been discussed under specific adverse events. Vital signs, including mean heart rate, systolic and diastolic blood pressure were essentially unchanged.

Safety in special populations

For the FCMP study, the safety in special population or according to subgroups is provided below.

Table 95. Overall Summary of Treatment-Emergent Adverse Events by Intrinsic Factor Subgroup and Treatment in Phase 3 Study 1002FDC-053 (Safety Population)

Intrinsic Factor Category	**Bempedoic acid 180 mg + Ezetimibe 10 mg FCMP (N = 107)**	**Bempedoic acid 180 mg (N = 110)**	**Ezetimibe 10 mg (N = 109)**	**Placebo (N = 55)**
Gender				
Males				
N	50	45	52	33
Patients with TEAEs	28 (56.0)	26 (57.8)	27 (51.9)	13 (39.4)
Patients with Serious TEAEs	3 (6.0)	3 (6.7)	7 (13.5)	1 (3.0)
Females				
N	57	65	57	22
Patients with TEAEs	35 (61.4)	42 (64.6)	31 (54.4)	11 (50.0)
Patients with Serious TEAEs	5 (8.8)	4 (6.2)	3 (5.3)	0

Intrinsic Factor Category	Bempedoic acid 180 mg + Ezetimibe 10 mg FCMP (N = 107)	Bempedoic acid 180 mg (N = 110)	Ezetimibe 10 mg (N = 109)	Placebo (N = 55)
Age group				
<65 years				
N	57	51	48	27
Patients with TEAEs	35 (61.4)	31 (60.8)	22 (45.8)	11 (40.7)
Patients with Serious TEAEs	6 (10.5)	2 (3.9)	3 (6.3)	1 (3.7)
≥65 years				
N	50	59	61	28
Patients with TEAEs	28 (56.0)	37 (62.7)	36 (59.0)	13 (46.4)
Patients with Serious TEAEs	2 (4.0)	5 (8.5)	7 (11.5)	0
Race				
White				
N	84	90	91	48
Patients with TEAEs	52 (61.9)	58 (64.4)	49 (53.8)	21 (43.8)
Patients with Serious TEAEs	5 (6.0)	6 (6.7)	9 (9.9)	1 (2.1)
Other race				
N	23	20	18	7
Patients with TEAEs	11 (47.8)	10 (50.0)	9 (50.0)	3 (42.9)
Patients with Serious TEAEs	3 (13.0)	1 (5.0)	1 (5.6)	0
CVD Risk Category				
ASCVD and/or HeFH,				
N	60	68	60	32
Patients with TEAEs	36 (60.0)	47 (69.1)	38 (63.3)	16 (50.0)
Patients with Serious TEAEs	7 (11.7)	6 (8.8)	10 (16.7)	1 (3.1)
Multiple CV risk factors				
N	47	42	49	23
Patients with TEAEs	27 (57.4)	21 (50.0)	20 (40.8)	8 (34.8)
Patients with Serious TEAEs	1 (2.1)	1 (2.4)	0	0
History of Diabetes				
Yes				
N	48	62	61	24
Patients with TEAEs	26 (54.2)	36 (58.1)	31 (50.8)	10 (41.7)
Patients with Serious TEAEs	3 (6.3)	5 (8.1)	6 (9.8)	0
No				
N	59	48	48	31
Patients with TEAEs	37 (62.7)	32 (66.7)	27 (56.3)	14 (45.2)
Patients with Serious TEAEs	5 (8.5)	2 (4.2)	4 (8.3)	1 (3.2)

Intrinsic Factor Category	Bempedoic acid 180 mg + Ezetimibe 10 mg FCMP (N = 107)	Bempedoic acid 180 mg (N = 110)	Ezetimibe 10 mg (N = 109)	Placebo (N = 55)
BMI				
<25 kg/m^2				
N	13	16	13	6
Patients with TEAEs	8 (61.5)	13 (81.3)	6 (46.2)	4 (66.7)
Patients with Serious TEAEs	0	1 (6.3)	0	0
25 to <30 kg/m^2				
N	27	38	37	22
Patients with TEAEs	14 (51.9)	17 (44.7)	24 (64.9)	10 (45.5)
Patients with Serious TEAEs	3 (11.1)	2 (5.3)	4 (10.8)	1 (4.5)
≥30 kg/m^2				
N	67	56	59	27
Patients with TEAEs	41 (61.2)	38 (67.9)	28 (47.5)	10 (37.0)
Patients with Serious TEAEs	5 (7.5)	4 (7.1)	6 (10.2)	0

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

See discussion on concomitant use with statins.

Discontinuation due to AES

In the FCMP study, 7 patients (6.5%), 9 patients (8.2%), 10 patients (9.2%), and 2 patients (3.6%) in the FCMP, bempedoic acid, ezetimibe, and placebo groups, discontinued due to an adverse event. In the FCMP study excluding the 3 sites, 7 patients (8.2%), 9 patients (10.2%), 10 patients (11.6%), and 2 patients (4.9%) in the FCMP, bempedoic acid, ezetimibe, and placebo groups, discontinued due to an adverse event.

In study 1002-048, 6.1% of bempedoic acid and 5.7% of placebo discontinued due to an adverse event.

Post marketing experience

N/A

2.6.4. Discussion on clinical safety

Bempedoic acid monocomponent

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 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.

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 in patients 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. 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.

Ezetimibe

The (known) safety profile of ezetimibe has sufficiently been described based on a summary of the published data.

FCMP

General comments

The factorial design study 1002FDC-053 compares the safety of the FCMP with the monocomponents and placebo treatment and is therefore of relevance. Also, study 048 is of relevance as the safety of the combination of bempedoic acid and ezetimibe are compared to ezetimibe in a randomised fashion in statin intolerant patients. Further, data on the phase 2 study 1002-008 could be of relevance as the combination of bempedoic acid and ezetimibe is compared to monocomponents, although the data are more limited than the phase 3 studies.

The post-hoc analyses of the phase 3 pool in patients treated on top of statin use is of less relevance as data are from a subgroup of patients on a background treatment that included ezetimibe which are in principle not randomised. However, these data could provide some insight in longer term use with the combination. The post-hoc analyses of the phase 3 pool in statin intolerant patients is not relevant as this mainly represents the data of the 048 study, with little data on study 046 as very few patients on ezetimibe were included in this study. These data should be separately presented. The data in the phase I studies are of limited relevance due to the single-dose administration and in healthy volunteers.

Factorial design study on top of statins (study 1002FDC-053)

The overall exposure comparing the FCMP of bempedoic acid and ezetimibe with the monocomponents and placebo in a randomised fashion are limited both in terms of follow-up with 12 weeks as in terms of numbers, since the exposure is limited to 107 FCMP treated patients, 110 bempedoic acid patients, 109 ezetimibe patients and 55 placebo patients with a mean exposure of 80 days in each group. This was 85 FCMP treated patients, 88 bempedoic acid patients, 86 ezetimibe patients and 41 placebo patients excluding the three sites.

Despite the limited number of patients, a slightly higher incidence of AEs and treatment related AEs was observed for FCMP (62.4%, 15.3%) and BA (65.9%, 13.6%) in comparison to EZE (54.7%, 10.5%) or PLB (43.9%, 9.8%). No substantial differences in serious AEs (except versus placebo) and discontinuations due to AEs were observed, although data were limited to draw meaningful conclusions. The sensitivity analysis excluding the three sites provided a similar pattern. Furthermore, the study is too small to differentiate for any possible patterns on individual AEs. Urinary tract infection (5.9%, 3.4%, 2.3%, 2.4%), nasopharyngitis (4.7%, 6.8%, 4.7%, 0%), constipation (4.7%, 0, 2.3%, 0), back pain (3.5%, 3.4%, 2.3%, 4.9%) and hypertension (3.5%, 5.7%, 2.3%, 0) were the most frequently observed AEs.

Relative low proportions of patients discontinued treatment due to AEs (7 (8.2%) FCMP, 9 (10.2%) BA, 10 (11.6%) EZE, and 2 (4.9%) PLB), without any clear differences between study groups except for placebo. Absolute numbers on a single AE level ranged from 1 to 3 not allowing for any conclusions.

Also limited numbers of serious AEs were observed with 8 patients (9.4%) in FCMP, 7 (8.0%) in BA, 10 (9.5%) in EZE, and 1 patient (2.4%) in PLB; all occurred at similar frequency across the treatment groups (except for placebo). None were considered related to study medication. Most of these serious AEs were cardiac disorders (14) and infections and infestations (4). Most of the AEs reported only 1 on a single level definition of the AEs not allowing to observe any particular pattern.

Specific attention has been given to reporting on known adverse events from treatment with statins including new-onset diabetes/hyperglycaemia, 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. In general, the numbers according to single adverse events definitions were limited complicating interpretation of the data.

For new-onset diabetes, very limited data reported a slightly higher incidence of new-onset or worsening of DM with the FCMP (4 (4.7%) FCMP, 1 (1.1%) BA, 2 (2.3%) EZE and 0 PLB), not allowing for any conclusions. A comparable pattern could be observed for fasting glucose in patients with a history of diabetes but not for patients without a history of diabetes. For hepatic abnormalities, 3 hepatic events occurred (2 (2.4%) in the FCMP and 1 (1.1%) in the BA group). In contrast to an increased frequency of muscular disorders with bempedoic acid when given on top of statins, these were reported with approximately similar frequency between treatment groups in this study, although numbers were limited (6 (7.1%) FCMP, 7 (8.0%) BA, 7 (8.1%) EZE, and 3 (7.3%) PLB). Renal disorders were slightly higher for FCMP and BA, although numbers were very limited (4 (4.7%) FCMP, 2 (1.1%) BA, 0 EZE, and 0 PLB). The mean creatinine levels slightly increased during the start of therapy for FCMP and BA compared to EZE and PLB. Moreover, more patients shifted to a worse eGFR category (17 (16%) FCMP, 18 (17%) BA, 12 (11.7%) EZE, 3 (5.4%) PLB). A slightly higher mean change in uric acid levels was observed (approximately 0.5 mg/dL) resulting in slightly higher mean % change for FCMP (11.8%) and BA (16.1%) versus EZE (1.5%) and PLB (-1.3%) and higher abnormal uric acid levels from 4 weeks onward (40 (37%), 47 (42%), 19 (17%) and 9 (16%)) with 3 patients (3.5%) in the FCMP group and 1 patient (1.1%) in the bempedoic acid group experienced adverse events of blood uric acid increased of which 2 events in the FCMP were considered treatment related. No AEs of gout were reported. Furthermore, no events of neurocognitive disorders were reported.

Mean haemoglobin decreased slightly with the FCMP (-0.31 g /dL) and BA (-0.28) compared to EZE (-0.11) and PLB (0.15) at week 12. AEs of haemoglobin decreased and anaemia were very limited.

No meaningful differences in vital signs, including hypertension, were observed in this study.

A slightly higher incidence of AEs was found for females than for males across all the treatment groups. Only data for the difference between < and >65 years of age have been provided, not indicating substantial differences in AE frequency between these categories. Data on the age categories according to <65 years, 65-74, 75-84 and >85 years of age have been provided but are too limited to draw meaningful conclusions.

Study in statin intolerant patients as add-on to ezetimibe (study 1002-048)

In study 048 in statin intolerant patients, the exposure is rather limited, as 181 patients were exposed to the combination of bempedoic acid and ezetimibe and 87 patients on ezetimibe in a randomised fashion for 12 weeks.

A (slightly) higher incidence of AEs and treatment related AEs with BA (48.6%, 21.5%) versus placebo (44.8%, 9.2%) was observed, while numbers in serious AEs (total 8) and discontinuation due to AEs (10) were too limited to draw any meaningful conclusions. Although numbers were limited, a higher incidence of blood uric increased (14 (7.7%) vs 2 (2.3%)), headache (8 (4.4%) vs 3 (3.4%)), and liver

function test increased (7 (3.9%) vs 0) were most frequently observed and higher for BA versus PLB. These were also reported most frequently and with a higher incidence for BA as treatment related AEs.

Relative low proportions of patients discontinued treatment due to AEs and comparable between BA and PLB (11 (6.1%) vs 5 (5.7%)). Absolute numbers on a single AE level were not larger than 1, not allowing for any conclusions.

Five patients (2.8%) in BA and 3 patients (3.4%) in PLB experienced serious AEs, limiting interpretation for any potential treatment difference. None were considered related to study medication. No deaths were reported.

With regard to AEs of specific interest, no differences were found for new-onset or worsening DM (6 (3.3%) BA vs 3 (3.4%) PLB), but this was based on very limited data. Some difference could be observed for high levels of fasting glucose ≥126 mg/dL in patients with a history of diabetes (19 (54%) vs 12 (70%) but this was in contrast to patients without a history of diabetes (12 (8.2%) vs 1 (1.4%)), while HbA_{1C} was comparable. A higher percentage of 13 (7.2%) hepatic events in BA vs 0 in PLB occurred, all which can be notified as liver enzyme elevations, 5 with > 3 x ULN in ALT, 1 >5 x ULN in ALT and 5 > 3 x ULN in AST and none with potential Hy's law. For muscular disorders, a slightly higher incidence for BA was observed compared to PLB (11(6.1%) vs 5 (5.7%)) and CK increases (3 (1.7%) vs 0). For renal disorders, a slightly higher incidence for BA was observed (7(3.9%) vs 1 (1.1%)), but numbers were very limited. The mean creatinine levels slightly increased during the start of therapy for BA compared to PLB. Likewise, more patients shifted from mild to moderate eGFR category (19 (11%) BA, 5 (6.2%) PLB at week 12). Increases in uric acid were observed for BA vs PLB (0.54 mg/dL vs -0.28 mg/dL), shifts in uric acid, and AEs of blood uric acid increased (10 (5.5%) vs 2 (2.3%)), however, no gout AEs were reported. Furthermore, no events of neurocognitive disorders were reported.

No meaningful differences in vital signs, including hypertension, were observed in this study.

Safety data according to subgroups do not show meaningful differences.

Phase 2 study 1002-008 and post-hoc analysis of the phase 3 pool

Although data are limited, the phase 2 study 1002-008 could be of relevance as the combination of bempedoic acid 180 mg and ezetimibe 10 mgQD were received by 24 patients compared to 100 patients on bempedoic acid 180 mg QD and 99 patients on ezetimibe 10 mg treated for approximately 78 days. For longer term exposure, only data of 150 bempedoic acid treated patients and 76 placebo patients in the subgroup of patients with background ezetimibe use are available from the post-hoc analyses of the 52 weeks phase 3 pool in patients treated on top of statin use. Further, some patients in the 24 weeks 046 study in statin intolerant patients used ezetimibe as background therapy resulting in 34 patients treated with bempedoic acid with ezetimibe background therapy and 15 patients on ezetimibe background therapy. Specific data on this 046 study according to ezetimibe use are too limited to draw conclusions on. Further, these subgroups were not randomised, therefore the comparison of these data should be taken with caution.

In the phase 2 study, a higher incidence of AEs and treatment related AEs with BA/EZE (70.8%, 41.7%) was observed in comparison to BA (55.0%, 18.0%) as well as EZE (53.5%, 19.2%), although only 24 patients were treated with the combination including the dose of 180 mg QD. Contrasting results were observed for the post-hoc ezetimibe subgroup data of pooled phase 3 studies in patients with background statin therapy showing less AEs with BA (78.7%) versus placebo (90.8%), and similar incidence in treatment related AEs (24.0% vs 23.7%). Also, discontinuation due to AEs was lower for BA (n=12, 8.0%) versus placebo (n=9, 11.8%), although numbers were limited.

In the phase 2 study, numbers were limited not allowing for any clear patterns in individual AEs. Constipation (2 (8.3%) BA/EZE, 1 (1.0%) BA and 1 (1.0%) EZE) and nasopharyngitis (2 (8.3%), 5 (5.0%) and 4 (4.0%)) were most frequently reported. In the ezetimibe subgroup data of pooled phase 3 studies in patients with background statin therapy the most frequently observed AEs observed to be higher for BA vs PLB (on a background of EZE) were nasopharyngitis (21 (14.0%) vs 5 (6.6%)), upper respiratory tract infection (5.3% vs 2.6%), bronchitis (4.0% vs 1.3%), gastroenteritis (2.7% vs 0) and blood CK increased (3.7% vs 0), although data for some of these AEs were also limited.

In the phase 2 study, relatively low proportions of patients discontinued treatment (1 (4.2%) BA/EZE, 6 (6.0%), 8 (8.1%) EZE) with relative low absolute numbers which do not allow for any conclusions. For the post-hoc ezetimibe subgroup data of pooled phase 3 studies in patients with background statin therapy, discontinuations rates due to AEs were relatively low and comparable (8.0% vs 11.0%).

The 4 cases of serious AEs in the phase 2 study are also too limited to draw any conclusions. For the post-hoc non-randomised data of pooled phase 3 studies in patients with background statin therapy, frequencies of serious AEs across treatment groups are comparable (11.3% BA, 13.2% PLB). The overall number of deaths was very limited with one in the phase 2 study and one in the ezetimibe subgroup of the phase 3 studies. Likewise, for these datasets it was not useful to analyse for MACE events.

With regards to AE of specific interest, for the ezetimibe subgroup data of pooled phase 3 studies in patients with background statin therapy, new onset diabetes was observed in 8 patients total. These data do not indicate a clear pattern for the risk of diabetes, although the number was too limited to allow for meaningful conclusions. In the phase 2 study 008, events of liver enzyme increases were very rare and observed in 10 patients in total across the different treatment groups. For the post-hoc ezetimibe subgroup data of pooled phase 3 studies in patients with background statin therapy, hepatic enzyme elevation were rarely noticed but with a higher incidence for BA (7 (4.7%) vs 1(1.3%)). In the phase 2 study, muscle related AEs were also slightly higher for BA/EZE (3(12.5%) vs BA (6 (6.0%)) but comparable to EZE (12 (12.1%)). For the post-hoc ezetimibe subgroup of pooled phase 3 studies in patients with background statin therapy, muscular disorders were only slightly higher for BA (23 (15.3%) vs 11 (14.5%)). Myalgia was mostly reported, but with a higher frequency in PLB (11 (7.3%) vs 9 (11.8%)). Across the different studies, no clear pattern of increased muscle related disorders for the bempedoic acid ezetimibe combination could be observed, although the limited numbers do not allow for meaningful conclusions. In the phase 2 study, renal disorders were not specifically investigated, and were very rarely observed. Also, for the post-hoc ezetimibe subgroup data of pooled phase 3 studies in patients with background statin therapy, renal disorders were very rare (n=3), not allowing for any conclusions. For the post-hoc ezetimibe subgroup data of pooled phase 3 studies in patients with background statin therapy, only 3 events of uric acid increase were observed. Very limited numbers of neurocognitive disorders were reported, only in the post-hoc ezetimibe subgroup data of pooled phase 3 studies (0.3% and 1.1% BA and PLB), not allowing for any firm conclusions.

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

2.6.5. Conclusions on the clinical safety

Bempedoic acid monocomponent

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.

Ezetimibe

The (known) safety profile of ezetimibe has sufficiently been described based on a summary of the published data.

FCMP

On top of statins

The clinical safety database of the combination of bempedoic acid and ezetimibe is limited in terms of the number of patients and follow up time, especially for the randomised data comparing the combination of bempedoic acid and ezetimibe to the monocomponents or placebo. Overall, (treatment related) adverse events were higher with the use of the combination or bempedoic acid in comparison to ezetimibe or placebo. Moreover, similar to the bempedoic acid component, specific bempedoic acid induced effects of increase in uric acid, increase in serum creatinine, slightly increased in frequency of renal disorders and increase in liver enzymes were observed. No other particular pattern in adverse events could be observed likely due to the limited database. Some non-randomised data on long term use of the combination of bempedoic acid and ezetimibe comes from the subgroup of ezetimibe background treated patients in the pivotal phase 3 studies of the monocomponent dossier. These data are generally in line with the observations of the FCMP study.

Statin intolerance

The clinical safety database of the combination of bempedoic acid and ezetimibe as compared to ezetimibe background therapy is also limited in terms of the number of patients and follow up time. Generally, these data generally display similar results as for the combined use of bempedoic acid and ezetimibe on top of statin therapy. Although, conclusions are generally difficult to draw based on the observed data. Therefore, reliance on the safety profile of bempedoic acid and ezetimibe monocomponents is also warranted.

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 with T2DM after	Gout	Final CSR	Q1 2020

	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 OAT2 substrates	Drug interactions with substrates of OAT2	Protocol final: Study completion: Final report:	Q2 2020 Q3 2020 Q4 2020

human hepatocytes Planned	whose primary clearance mechanism is hepatic in sandwich hepatocyte culture. The identified substrates are warfarin (R- and S-enantiomers) and naproxen.			
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 minimization 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 applicant compared the structure of bempedoic acid / ezetimibe with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers bempedoic acid / ezetimibe 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

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Nustendi (bempedoic acid / ezetimibe) 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.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. 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.

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 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. **Ezetimibe** localizes at the brush border of the small intestine and inhibits the absorption of cholesterol via the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in LDL receptors, resulting in clearance of cholesterol from the blood. This distinct mechanism is complementary to that of bempedoic acid.

The proposed indication for **bempedoic acid with ezetimibe fixed combination medicinal product (FCMP)** was the following:

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

- *in combination with a statin in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin alone,*

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

The FCMP contains ezetimibe and bempedoic acid. Ezetimibe 10 mg has been shown to reduce the frequency of cardiovascular events. The effect of bempedoic acid on cardiovascular morbidity and mortality has not been determined.

Elevated cholesterol as indicated by definitions of hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, is a risk factor for cardiovascular disease. **Lowering LDL-C** has been accepted as a **surrogate endpoint** for the reduction of CV events.

The proposed indication statement covered the three therapeutic scenarios described in the *"Guideline on clinical development of fixed combination medicinal products (EMA/CHMP/158268/2017)*":

- **''first line indication''** after statins
    - *in combination with a statin in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin alone;*
    - *alone in patients who are either statin-intolerant or for whom a statin is contraindicated*),
- **add-on indications** either to non-responders of bempedoic acid or ezetimibe
    - *in combination with a statin in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin in addition to bempedoic acid or ezetimibe;*
    - *alone in patients who are either statin-intolerant or for whom a statin is contraindicated, and are unable to reach LDL-C goals with bempedoic acid alone or ezetimibe alone*),
- **substitution indication**
    - *in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without statin*.

The Fixed Combination Medicinal Product (FCMP), administered as a single tablet, is intended to facilitate the correct use of the medicine in terms of daily dosing **to improve overall patient adherence**.

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) then 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 could provide additional LDL-C lowering and is 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). Moreover, ezetimibe is indicated in patients alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or in patients for whom a statin is not considered clinically appropriate or contraindicated. In clinical guidelines ezetimibe is recommended to be used as second-line therapy in association with statins when the therapeutic goal is not achieved at the maximal tolerated statin dose or in patients intolerant to statins or with contraindications to these drugs. 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.

Other available therapies could include **PCSK9 inhibitors** which have shown very effective LDL-C lowering effect 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). PCSK9 inhibitors have also demonstrated CV benefit in 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.

3.1.3. Main clinical studies

Bempedoic acid as monocomponent

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 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.

FCMP

The main studies in which the combination of bempedoic acid with ezetimibe was compared in a randomised fashion to the monocomponents were the following phase 3 studies:

On top of statins

- Study 1002FDC-053: A phase 3 factorial design pivotal 4-arm (2:2:2:1) Phase 3 (n=382), randomized, 12-week, controlled study comparing the Fixed Combination Medicinal Product (BA+ezetimibe) with bempedoic acid alone, ezetimibe alone, and placebo as add on to stable, maximally-tolerated statin therapy.

Statin intolerance

- Study 1002-048: a phase 3 randomized, controlled bempedoic acid study (n=269) that compared bempedoic acid with placebo as add-on therapy to ezetimibe (and no or no more than low doses of statins) for 12 weeks.

Pharmacokinetics

Study 1002FDC-034: a phase 1, randomised, open-label, single-dose, 3-period crossover study in healthy subjects including 6 treatment sequences in a 1:1:1:1:1:1 ratio, to compare the oral bioavailability of bempedoic acid and ezetimibe with two different formulations of the FCMP to the bioavailability of bempedoic acid and ezetimibe with 1 bempedoic acid 180 mg tablet and 1 ezetimibe 10 mg tablet coadministered.

3.2. Favourable effects

Bempedoic acid as monocomponent

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 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).

Ezetimibe

The efficacy of ezetimibe has been described based on literature data including relevant placebo controlled randomised studies investigating the lipid lowering effect of ezetimibe as monotherapy, in combination with statins, and investigating the effect on CV outcomes.

FCMP

Factorial data on top of statins

The FCMP of bempedoic acid and ezetimibe demonstrated a significant **reduction in LDL-C** in comparison to placebo (-38.0%), and a moderate reduction in comparison to ezetimibe (-13.1%) or bempedoic acid (-19.0%) in the primary analysis of mean percent change in LDL-C after 12 weeks of treatment in high CV risk patients with mean baseline LDL-C of 3.85 mmol/L **on top of statins** . This translated into 31.3%, 10.0%, 6.1%, and 0% of the patients meeting the LDL-C < 70 mg/dL treatment goal, in the BA+ezetimibe, ezetimibe, BA and placebo groups respectively. Efficacy was supported by significant and beneficial changes in other relevant parameters of the cholesterol profile, i.e. non-HDL-C (-33.7%, -12.1%, -17.8%), TC (-27.1%, -10.4%, -14.2%), and apoB (-30.1%, -9.3%, -12.8%).

The LDL-C effect of the FCMP of bempedoic acid with ezetimibe was consistent in **several subgroups** of gender, race, age, CV risk category, statin intensity, LDL-C baseline level, history of diabetes, and BMI in comparison to placebo, bempedoic acid and ezetimibe.

A small phase 2 study and data from the subgroup of patients on ezetimibe background therapy from other phase 3 studies in patients treated with maximum tolerated statin therapy provided additional support for these findings.

Add-on to ezetimibe in statin intolerance

For **statin intolerant** patients, bempedoic acid demonstrated a significant **reduction in LDL-C** in comparison to placebo (-29%) on top of study supplied ezetimibe treatment, in the primary analysis of mean percent change in LDL-C after 12 weeks of treatment in patients with mean baseline LDL-C of 3.3 mmol/L. Efficacy was supported by significant and beneficial changes in other relevant parameters of the cholesterol profile, i.e. non-HDL-C (-23.6%), TC (-18.0%), apoB (-19.3%). Also an effect on hsCRP was observed (-32.5% vs 2.09%).

The effect was consistent in **several subgroups** of gender, race, age, LDL-C baseline level, and history of diabetes.

3.3. Uncertainties and limitations about favourable effects

Bempedoic acid as monocomponent

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 effect has not been 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 induced **increase in exposure of AUC** (and Cmax) **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 **-**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, for these patients the impact of the pharmacokinetic interaction with statins may be higher. 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 on the contribution of statins to 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 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 statin background studies. 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 (4.9-6.2%), Asians (0-1.1%), and patients severe renal impairment (0-0.4%) were **underrepresented**.

FCMP

Pharmacokinetics

In the pivotal study **1002FDC-034**, bioequivalence between the FCMP and the mono components bempedoic acid and ezetimibe could not be demonstrated for ezetimibe. However, the clinical study 1002FDC-053 was considered as primary evidence. This study demonstrated a positive benefit/risk for the FDC. Therefore, it was agreed a clinical difference is not expected when switching from the monocomponents to the FDC.

Factorial data on top of statins

The LDL-C lowering effect of the FCMP of bempedoic acid and ezetimibe (-36.2%) appears not to be the sum of the effect observed of the monocomponents (ezetimibe (-23.2%) or bempedoic acid (-17.2%)) for the mean percent change from baseline in LDL-C after 12 weeks of treatment in the FCMP study. However, the phase 2 study data do show that the sum of the effect of the mono-components is

comparable to the effect of the FCMP (LDL-C difference from baseline -47.7%) vs ezetimibe (-21.2%) or bempedoic acid (-27.5%)).

Data on **longer term effect on LDL-C** of FCMP on top of statin therapy are not available as the study was only performed for 12 weeks.

In the factorial design study, 3 study sites were identified with GCP issues. These 3 study sites have been excluded in the FDC study due to potential GCP issues. Sensitivity analyses excluding these sites (81 of the 382 patients) resulted in fewer patients from Hispanic origin. A post-hoc sensitivity analyses excluding these sites yielded comparable results.

Sensitivity analysis using observed cases and an on-treatment approach supported the primary analysis.

Add-on to ezetimibe in statin intolerance

Data on **longer term effect on LDL-C** of BA on a background of ezetimibe therapy are not available as the study was only performed for 12 weeks.

Sensitivity analysis using observed cases and an on-treatment approach supported the primary analysis.

The LDL-C lowering effect of bempedoic acid on top of ezetimibe background therapy observed in statin intolerant patients was substantially higher compared with the effect for the FCMP in comparison with ezetimibe which may be explained by the differences in statin background therapy between both studies (no or low dose statin therapy vs maximum tolerated statin therapy). This is also in line with the difference observed between on top of statin and statin intolerance for the bempedoic acid treatment effect. Subgroup analyses generally showed consistency in effect.

3.4. Unfavourable effects

Bempedoic acid as monocomponent

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% respectively 51.5%, a **consistent and slightly higher frequency of serious adverse events** was observed; 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% respectively 76.7%, a **consistent and slightly higher frequency of serious adverse events** was observed; 16.0% respectively 15.2% 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 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, is increased when bempedoic acid is 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 was 7 (0.3%) vs 2 (0.2%) and > 10 x ULN was 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 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). 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.

Ezetimibe

The (known) safety profile of ezetimibe has been described based on a summary of the published data.

FCMP

Factorial data on top of statins

An appropriate number of patients have been evaluated to allow the assessment of **safety of the bempedoic acid monocomponent**. Further, the safety profile of ezetimibe is well known. However, the **overall exposure for the FCMP is limited** to 107 patients treated for 12 weeks (median exposure 80 days). For longer term exposure only data of 150 bempedoic acid treated patients and 76

placebo patients in the subgroup of patients with background ezetimibe treatment are available from the post-hoc analyses of the 52 weeks phase 3 pool in patients treated on top of statin use.

Despite the limited number of patients, a slightly **higher incidence of adverse events and treatment related adverse events** was observed for the FCMP (58.9%, 12.1%) and bempedoic acid (61.8%, 11.8%) in comparison to ezetimibe (53.2%, 8.3%) or placebo (43.6%, 7.3%). The sensitivity analysis excluding the three sites provided a similar pattern. The small phase 2 study supported these findings (BA/EZE (70.8%, 41.7%), BA (55.0%, 18.0%), EZE (53.5%, 19.2%)), while no such increase was found in the post-hoc ezetimibe subgroup data of pooled phase 3 studies in patients with background statin therapy (BA (78.7%, 24.0%) versus placebo (90.8%, 23.7%)).

A consistent increase in **liver enzymes** for treatment with bempedoic acid in combination with ezetimibe was observed, although this was based on limited data. For hepatic abnormalities, in the FCMP study 3 hepatic events occurred. For the post-hoc ezetimibe subgroup data of pooled phase 3 studies in patients with background statin therapy, hepatic enzyme elevation were rarely noticed but with a higher incidence for bempedoic acid than placebo (7 (4.7%) vs 1(1.3%)).

Add-on to ezetimibe in statin intolerance

The **overall exposure** for the combination of bempedoic acid as monocomponent when added to background of ezetimibe for 12 weeks in SI patients is limited (median exposure 80 days).

Despite the limited number of patients, a slightly **higher incidence of adverse events and treatment related adverse events** was observed for bempedoic acid plus ezetimibe (48.6%, 21.5%) versus ezetimibe (44.8%, 9.2%).

A consistent increase in **liver enzymes** for treatment with bempedoic acid in combination with ezetimibe is observed, although this was based on limited data. A higher percentage of 13 (7.2%) hepatic events in bempedoic acid vs 0 in placebo occurred, all which can be notified as liver enzyme elevations (5 with > 3 x ULN in ALT, 1 >5 x ULN in ALT and 5 > 3 x ULN in AST and none with potential Hy's law).

3.5. Uncertainties and limitations about unfavourable effects

Bempedoic acid as monocomponent

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 revasularisation. 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 **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 HbA_{1c} 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%)), renal impairment (2 (0.5%) vs 0).

There was a reversible increased 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** were 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.

On top of statins

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 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.

FCMP

Pharmacokinetics

In the pivotal study **1002FDC-034**, bioequivalence between the FCMP and the mono components bempedoic acid and ezetimibe could not be demonstrated for ezetimibe. However, the clinical study 1002FDC-053 was considered as primary evidence. This study demonstrated a positive benefit/risk for

the FDC. Therefore, it was agreed a clinical difference is not expected when switching from the monocomponents to the FDC.

Factorial data on top of statins

The study was limited to evaluate differences between treatment arms for **single term adverse events**. In the FCMP study, the most frequently observed adverse events for the FCMP (BA+ezetimibe), bempedoic acid, ezetimibe and placebo groups respectively were urinary tract infection (5.9%, 3.4%, 2.3%, 2.4%), nasopharyngitis (4.7%, 6.8%, 4.7%, 0%), constipation (4.7%, 0, 2.3%, 0), back pain (3.5%, 3.4%, 2.3%, 4.9%) and hypertension (3.5%, 5.7%, 2.3%, 0). These events were also reported most frequently and with a higher incidence as treatment related adverse events. In the ezetimibe subgroup data of pooled phase 3 studies in patients with background statin therapy, the most frequently observed adverse events observed to be higher for bempedoic acid versus placebo (on a background of ezetimibe) were nasopharyngitis (21 (14.0%) vs5 (6.6%)), upper respiratory tract infection (5.3% vs 2.6%), bronchitis (4.0% vs 1.3%), gastroenteritis (2.7% vs 0) and blood CK increased (3.7% vs 0).

The FCMP study was too small to provide meaningful conclusions of any patterns in **serious adverse events**. In the FCMP study this was 8 (9.4%) for the FCMP, 7 (8.0%) for bempedoic acid, 10 (9.5%) for ezetimibe, and 1 patient (2.4%) for placebo, mostly related to cardiac disorders (8) and none considered treatment related. For the post-hoc non-randomised data of pooled phase 3 studies in patients with background statin therapy, frequencies across treatment groups are comparable (11.3% bempedoic acid, 13.2% placebo). The number of **deaths** were very limited with one in the phase 2 study and one in the ezetimibe subgroup of the phase 3 studies. For these datasets it was not useful to analyse for MACE events.

Overall, relative low proportions of patients **discontinued treatment due to an adverse event**. Any difference in frequency could not be noticed possibly due to the limited numbers observed. In the FCMP this was 7 (8.2%) for the FCMP, 9 (10.2%) for bempedoic acid, 10 (11.6%) for ezetimibe, and 2 (4.9%) for placebo. For the phase 2 study and the post-hoc ezetimibe subgroup data of pooled phase 3 studies in patients with background statin therapy, comparable low rates were observed.

No clear pattern for risk of **diabetes** could be observed for the combined use of bempedoic acid with ezetimibe, although the numbers were too small to allow for meaningful conclusions. In the FCMP study very limited data reported a slightly higher incidence of new onset or worsening of diabetes mellitus (4 (4.7%) FCMP, 1 (1.1%) bempedoic acid, 2 (2.3%) ezetimibe and 0 placebo). Some difference could be observed for high levels of fasting glucose ≥126 mg/dL in patients with a history of diabetes (19 (54%) vs 12 (70%) in contrast to patients without a history of diabetes (12 (8.2%) vs 1 (1.4%)), while HbA_{1C} was comparable. For the ezetimibe subgroup data of pooled phase 3 studies in patients with background statin therapy, new onset diabetes was observed in 8 patients total.

In contrast to observation in the data of the monocomponent, no clear pattern of increased **muscle related disorders** for the bempedoic acid ezetimibe combination could be observed based on limited numbers. In the FCMP study, muscular disorders were reported with approximately similar frequency between treatment groups (6 (57.1%) FCMP, 7 (8.0%) bempedoic acid, 7 (8.1%) ezetimibe, and 3 (7.3%) placebo). In the phase 2 study, muscle related AEs were also slightly higher for bempedoic acid with ezetimibe (3(12.5%) vs bempedoic acid(6 (6.0%)) but comparable to ezetimibe (12 (12.1%). For the post-hoc ezetimibe subgroup of pooled phase 3 studies in patients with background statin therapy, this was only slightly higher for bempedoic acid (23 (15.3%) vs (11 (14.5%). Myalgia was mostly reported, but with a higher frequency in placebo (11 (7.3%) vs 9 (11.8%)).

Limited data showed a bempedoic acid induced increase in **serum creatinine** (with currently insufficient clarified mechanism of action) starting at beginning of therapy and slightly increased

frequency of **renal disorder** with the bempedoic acid with or without ezetimibe. The mean creatinine levels slightly increased during the start of therapy for the FCMP and bempedoic acid compared to ezetimibe and placebo. Moreover, more patients shifted to a worse eGFR category (17 (16%) FCMP, 18 (17%) BA, 12 (11.7%) EZE, unknown PLB). Renal disorders were slightly higher for the FCMP (4 (3.7%)) and bempedoic acid (2 (1.8%)) vs none in ezetimibe or placebo.

A bempedoic acid induced increase in **uric acid** (with currently insufficient clarified mechanism of action) was observed, in rare cases resulting in adverse events reported increased uric acid levels, but no adverse events of gout were reported, likely due to the limited database. A slightly higher mean change in **uric acid** levels was observed (approximately 0.5 mg/dL) resulting in slightly higher mean percent change (11.8% FCMP, 16.1% bempedoic acid) versus ezetimibe (1.5%) and placebo (-1.3%) and higher abnormal uric acid levels from 4 weeks onward (40 (37%), 47 (42%), 19 (17%) and 9 (16%)) with 3 patients (2.8%) in the FCMP group and 2 patients (1.8%) in the bempedoic acid group who experienced adverse events of blood uric acid increased (2 in FCMP treatment related). For the post-hoc ezetimibe subgroup data of pooled phase 3 studies in patients with background statin therapy, only 3 events of uric acid increase were observed.

Very limited numbers of **neurocognitive disorders** were reported, only in the post-hoc ezetimibe subgroup data of pooled phase 3 studies (0.3% and 1.1% bempedoic acid and placebo). This does not allow for any conclusions.

Mean **haemoglobin decreased** slightly with the FCMP (-0.31 g /dL) and bemepdoic (-0.28) compared to ezetimibe (-0.11) and placebo (0.15) at week 12. Adverse events of haemoglobin decreased and anaemia were very limited.

No meaningful differences in **vital signs**, including hypertension, were observed in the studies.

In the FCMP study, for the **subgroup** of gender, a slightly higher incidence of adverse events was found for females than for males. Only data for the difference between <>65 years of age have been provided, not indicating substantial differences in AE frequency between these categories. Data on the age categories according to <65 years, 65-74, 75-84 and >85 years of age are currently not available.

In the FCMP study, 3 study sites were identified with potential GCP issues. Sensitivity analyses excluding these sites did not substantially alter the safety findings.

Add-on to ezetimibe in statin intolerance

The add-on to ezetimibe non-responders study (study 048) in patients who are SI was limited to evaluate differences between treatment arms for **single term adverse events**. The most frequently observed adverse events that had a higher incidence in the bempedoic acid/ezetimibe combination than in the ezetimibe group were; blood uric increased (14 (7.7%) vs 2 (2.3%)), headache (8 (4.4%) vs 3 (3.4%)), and liver function test increased (7 (3.9%) vs 0). These events were also reported most frequently and with a higher incidence as treatment related adverse events.

The study was too small to provide meaningful conclusions of any patterns in **serious adverse events**. Numbers of serious adverse events were 8 (5 vs 3). No **deaths** were observed.

Overall, relative low proportions of patients **discontinued treatment due to an adverse event**. Any difference in frequency could not be noticed possibly due to the limited numbers observed. This was 11 (6.1%) for bempedoic acid and 5 (5.7%) for placebo.

No clear pattern for risk of **diabetes** could be observed for the combined use of bempedoic acid with ezetimibe, although the numbers were too small to allow for meaningful conclusions. No differences were found for new onset or worsening DM (6(3.3%) bempedoic acid vs 3 (3.4%) placebo).

A slightly higher incidence for bempedoic acid was observed for **muscle related disorders** (11(6.1%) vs 5 (5.7%)) and CK increases (3 (1.7%) vs 0), although data are limited to draw meaningful conclusions.

Limited data showed a bempedoic acid induced increase in **serum creatinine** starting at beginning of therapy and slightly increased frequency of **renal disorder** with the bempedoic acid. The mean creatinine levels slightly increased during the start of therapy for bempedoic acid compared to placebo. Also, more patients shifted from mild to moderate eGFR category (19 (11%) BA, 5 (6.2%) PLB at week 12). Further, a slightly higher incidence of renal disorders for bempedoic acid was observed (7(3.9%) vs 1 (1.1%)).

A bempedoic acid induced increase in **uric acid** was observed, in rare cases resulting in adverse events reported increased uric acid levels, but no adverse events of gout were reported, likely due to the limited database. Increases in uric acid were 0.54 mg/dL vs -0.28 mg/dL for bempedoic acid and placebo, shifts in uric acid and adverse events of blood uric acid increased were 14 (7.7%) vs 2 (2.3%).

No **neurocognitive disorders** were evaluated or reported.

Haemoglobin decreased was only observed in one patient**.**

No meaningful differences in **vital signs**, including hypertension, were observed.

Data according to **subgroups** do not show meaningful differences.

3.6. Effects Table

Table 96. 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	Statin intolerant pool [2]
		% (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]

Effect	Short Description	Unit	BA 180 mg	PLB	Uncertainties/ Strength of evidence	References
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%	1002-046 (no CV events in 1002-048)
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.	
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.	

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 97. Effects table bempedoic acid on top of statins (Studies 1002-047 (n=779) and1002-040 (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

Effect	Short Description	Unit	BA 180 mg	PLB	Uncertainties/ Strength of evidence	References
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	High risk/long-term pool [1]
ALT and/or AST > 3 x ULN		%	0.6 (13)	0.3 (3)		
Muscular disorders		% (n)	13.2 (265)	10.2 (102)		
Musculoskeletal and connective tissue disorders						
Low intensity statin		% (n)	37.6 (47)	23.7 (14)	Low intensity statin category showed the highest frequency of AEs.	
Moderate intensity statin		% (n)	24.7 (200)	24.0 (97)		
High intensity statin		% (n)	24.3 (248)	22.5 (114)		
Renal disorders		% (n)	2.9 (59)	1.3 (13)		
Renal failure		%	0.8 (16)	0.1 (1)	Creatinine increase evident by 4 weeks and stable during treatment, and is reversible.	
Uric acid elevations/gout		% (n)	4.8 (97)	1.5 (15)	Similar trajectory as creatinine. 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.	

Table 98. Effects Table for FCMP: study 1002FDC-053 (n=215). Factorial design on top of statins (excluding three sites)

Effect	Short Description	Unit	FCMP	comparator	Uncertainties/ Strength of evidence	References
Favourable Effects						
LDL-C lowering	Change from baseline to week 12 (LS mean (SE)) [primary endpoint]	% (SE)	FCMP: -36.2 (2.56)	PLB: +1.8 (3.49)	Difference: -38.0 95%CI: -46.5, -29.6 P<0.001	Study 1002FDC-053 (max. tolerated statins) [ITT Analysis]
				BA: -17.2 (2.52)	Difference: -19.0 95%CI: -26.1, -11.9 P<0.001	
				EZE: -23.2 (2.18)	Difference: -13.1 95%CI: -19.7, -6.5 P<0.001	
Unfavourable Effects						
Hepatic events		% (n)	FCMP: 2.4 (2)	PLB: 0 BA:1.1 (1) EZE: 0	Limited number of events not allowing for meaningful conclusions	Study 1002FDC-053 (max. tolerated statins)
Muscular disorders		% (n)	FCMP: 7.1 (6)	PLB: 7.3 (3) BA: 8.0 (7) EZE: 8.1 (7)	Limited number of events not allowing for meaningful conclusions	Study 1002FDC-053 (max. tolerated statins)
Renal disorders		% (n)	FCMP: 4.7 (4)	PLB: 0 BA: 1.1 (1) EZE: 0	Limited number of events not allowing for meaningful conclusions	Study 1002FDC-053 (max. tolerated statins)
Uric acid elevations/gout						
	Blood uric acid increased	% (n)	FCMP: 3.5 (3)	PLB: 0 BA: 1.1 (1) EZE: 0	There were no new onset of gout events reported	Study 1002FDC-053 (max. tolerated statins)
Decrease in hemoglobin						
	Hemoglobin decreased	% (n)	FCMP: 1.2 (1)	PLB: 0 BA: 2.3 (2) EZE: 0		Study 1002FDC-053 (max. tolerated statins)
	Anaemia	% (n)	FCMP: 1.2 (1)	PLB: 2.4 (1) BA: 2.3 (2) EZE: 1.2 (1)		Study 1002FDC-053 (max. tolerated statins)

Abbreviations: BA: bempedoic acid; EZE: ezetimibe; FCMP: Fixed Combination Medicinal Products; PLB: placebo
Notes:

Table 99. Effects Table for FCMP: Study 1002-048 (n=269). Add-on study to ezetimibe in statin intolerance

Effect	Short Description	Unit	BA+ Bkgd EZE QD	comparator	Uncertainties/ Strength of evidence	References
Favourable Effects						
LDL-C lowering	Change from baseline to week 12 (LS mean (SE)) [primary endpoint]	% (SE)	BA+ Bkgd EZE: -23.5 (1.95)	PLB + Bkgd EZE: 5.0 (2.30)	Difference: -28.5 95%CI: -34.4, -22.5 P<0.001	Study 1002-048 (no-or low-dose statins)
Unfavourable Effects						
Hepatic events		% (n)	BA+ Bkgd EZE: 7.2 (13)	PLB + Bkgd EZE: 0	Imbalance due to hepatic enzyme elevations	Study 1002-048 (no-or low-dose statins)
Muscular disorders		% (n)	BA+ Bkgd EZE: 6.1 (11)	PLB + Bkgd EZE: 5.7 (5)	Limited number of events not allowing for meaningful conclusions	Study 1002-048 (no-or low-dose statins)
Renal disorders		% (n)	BA+ Bkgd EZE: 3.9 (7)	PLB + Bkgd EZE: 1.1 (1)	Limited number of events not allowing for meaningful conclusions	Study 1002-048 (no-or low-dose statins)
Uric acid elevations/gout						
	Blood uric acid increased	% (n)	BA + Bkgd EZE: 7.7 (14)	PLB + Bkgd EZE: 2.3 (2)	There were no new onset of gout events reported	Study 1002-048 (no-or low-dose statins)
Decrease in hemoglobin						
	Hemoglobin decreased	% (n)	BA + Bkgd EZE: 0.6 (1)	PLB + Bkgd EZE: 0	The observed decreases did not result in anaemia adverse events	Study 1002-048 (no-or low-dose statins)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Bempedoic acid as monocomponent

Statin intolerance

Bempedoic acid used in patients with hypercholesterolaemia, mixed dyslipidaemia and in patients with heterozygous familial hypercholesterolemia who were SI has demonstrated a 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.

FCMP

Factorial data on top of statins

Bempedoic acid in combination with ezetimibe in patients with hypercholesterolemia or mixed dyslipidaemia at increased risk for CV events and treated with maximum tolerated statin dose has demonstrated a consistent reduction in LDL-C and other relevant lipid parameters which was substantial compared to placebo (statin background therapy) but only moderate in comparison to bempedoic acid or ezetimibe monotherapy. Despite that the LDL-C lowering effect of the combination was somewhat moderate when compared to bempedoic acid or ezetimibe monocomponents, these are considered to be clinically relevant because the reduction in the LDL-cholesterol is an important surrogate marker with potential benefits in terms of cardiovascular outcome. Analyses on MACE events based on the phase 3 studies for the single bempedoic acid component did not indicate any trend towards cardiovascular harm. However, currently the impact of the bempedoic acid monocomponent on cardiovascular risk reduction remains unknown, while this has been demonstrated for ezetimibe in the IMPROVE-IT study. Further, it is not expected that improvement on cardiovascular outcome will be evaluated for the combination and thus such data needs to be extrapolated from the effects observed with the monocomponents.

Further, the combination of bempedoic acid with ezetimibe on top of statin therapy showed an expected safety profile that is in line with adverse effects observed with bempedoic acid and/or ezetimibe, with relatively limited patients who discontinue FCMP treatment and who demonstrate serious adverse events. Although the safety database is still limited the FCMP patients seem to experience adverse events comparable in character, but slightly more, as patients using either ezetimibe or bempedoic acid alone. Due to the small database, a signal for an increased frequency of muscular disorders, most likely triggered by bempedoic acid induced increased exposure of statins, could not be observed but can be expected. This can be of concern in patients already treated with maximum tolerated statin therapy. A similar concern is applicable for treatment of bempedoic acid on top of maximum tolerated statins.

Add-on to ezetimibe in statin intolerance

In statin-intolerant patients, the addition of bempedoic acid to patients insufficiently responding to ezetimibe therapy to reach their target LDL-C level, shows a substantial reduction in LDL-C. In line

with the data of the studies, as displayed in the monocomponent dossier, the effect in SI patients was much larger than in patients treated on top of maximum tolerated statin therapy.

Within the study pool of statin-intolerant patients, very limited data are available on CV risk reduction, and thus information should be extrapolated from the MACE analyses within the pool of patients treated on top of statins, which demonstrated an absence of CV harm. The combination of bempedoic acid with ezetimibe in statin-intolerant patients displays an expected safety profile that is in line with adverse effects observed with the monocomponents bempedoic acid and/or ezetimibe Finally, for an intended lifelong treatment, a follow-up treatment period of 12 weeks in the randomised study can be considered very limited.

3.7.2. Balance of benefits and risks

Bempedoic acid as monocomponent

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 agreement 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 the 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% respectively 2% of the patients despite proven cardiovascular benefit and being indicated for a similar patient population as currently proposed. This may potentially limit 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 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 the 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.

FCMP

On top of statins

The LDL-C lowering effect of the combined use of bempedoic acid and ezetimibe in comparison to ezetimibe and bempedoic acid monocomponents is only moderate although of clinical relevance. The data are obtained from a factorial design study, lacking clear data on the additional effect of the combination in those patients not sufficiently responding on ezetimibe or bempedoic acid. Further, as discussed for the bempedoic acid monocomponent, similar safety issues apply to the combined use of the FCMP with statins although a clear pattern of increased muscle disorders could not be observed due to the limited database with the FCMP. The identified safety issues appear to be limited, not of specific concern and in line with the safety issues identified in the bempedoic acid monocomponent and known from ezetimibe. Although the efficacy data suggest that the balance of benefits of the FCMP outweighs the risks, there are several outstanding issues related to the available clinical data and the intended patient population to be treated with the FCMP.

Statin intolerance

The screening inclusion was meeting the definition of hypercholesterolemia, with ≥ 100 mg/dL in patients taking ezetimibe and ≥ 120 mg/dL in patients not taking ezetimibe. Identification of patients eligible for randomization was based on LDL-C level of ≥70 mg/dL (1.8 mmol/L) at baseline without any CV risk level requirement.

The LDL-C lowering effect of the combined use of bempedoic acid and ezetimibe in comparison to ezetimibe and bempedoic acid monocomponents is substantial and of clinical relevance. In the statin-intolerant population, insufficiently controlled with ezetimibe, a positive trade-off between benefit and risk of bempedoic acid has been demonstrated. Comparable safety issues can be identified for the combined use of bempedoic acid with ezetimibe as identified in the bempedoic acid and ezetimibe monocomponents. Similar to the use of the FCMP on top of statins, there is also a lack of cardiovascular outcome data for the combined use of bempedoic acid with ezetimibe in SI patients.

Finally, for an intended lifelong treatment, a follow-up treatment period of 12 weeks in the randomised studies and a treatment period of 52 weeks in the subgroup of patients treated with background ezetimibe therapy from the pivotal phase 3 studies of the bempedoic acid monocomponent can be considered limited. The impact of the bempedoic acid monocomponent on cardiovascular risk reduction remains unknown. A large outcome study in SI patients is currently ongoing and evaluates the CV effect of bempedoic acid.

3.7.3. Additional considerations on the benefit-risk balance

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

- Justification of the pharmacological and medicinal rationale for the combination. As both products (bempedoic acid and ezetimibe) have distinct but complementary mechanisms of action, the pharmacological rationale appears reasonable. Further, there is an unmet medical need to further lower LDL-C levels for those patients not able to reach the anticipated LDL-C goals with the maximum lipid lowering therapy. Also, it is reasonable to consider that an FCMP reduces pill burden and could improve the easiness of use.
- Establishment of the evidence base for the relevant contribution of all active substances to the desired therapeutic effect. The data from the factorial design study show that in patients who are insufficiently controlled with statin therapy, bempedoic acid alone, ezetimibe alone and the combination result in further reductions in LDL-C, with the FCMP resulting in the largest reductions overall. A similar study has not been performed in SI patients, but ezetimibe has previously shown to be efficacious in this population, and in study 1002-048 bempedoic acid was shown to reduce LDL-C further in SI patients that were insufficiently controlled by ezetimibe alone.
- Establishment of the evidence base for the positive benefit risk for the combination in the targeted population. In this respect, the several proposed indications should be discussed following the evidentiary requirements as outlined in the FCMP and lipid-modifying guidelines.

Treatment of insufficiently responding patients ('add-on indication')

On top of statins

The 'add-on' indication is defined as adding one component of the FCMP to patients not sufficiently responding to the other component of the FCMP (apart from other background therapy such as maximum tolerated statin therapy). As such, specific studies of the FCMP in patients who are on maximally tolerated statin doses and who do not sufficiently respond to ezetimibe or bempedoic acid have not been conducted. Only a factorial design study (on top of maximum tolerated statin therapy) has been submitted, which supports the contribution of the individual components and the combination to the therapeutic efficacy, but does not establish a positive benefit-risk of the FCMP in the claimed situations in patients not responding to either one of the FCMP monocomponents. Nevertheless, added benefit (and risk) of bempedoic acid in patients insufficiently controlled with ezetimibe has been shown in statin-intolerant patients. To support an 'add on' indication for the FCMP in patients on maximally tolerated statin doses and insufficiently responding to ezetimibe, data are present from the subset of 226 (7.5%) patients that were also taking ezetimibe, of whom 217 patients had a week 12 LDL-C measurement in studies 040 and 047 on top of statins. For these patients, mean percent reduction in LDL-C from baseline to Week 12 was -16.2% in patients receiving bempedoic acid compared with -

2.8% for placebo, with a difference from placebo of -13.4% (p <0.001), comparable to the overall efficacy findings in these studies. Because the safety profile of these patients subsets does not importantly differentiate between the FCMP and the monocomponents, although the data of the factorial design study are limited to 12 weeks of treatment, these data reasonably support the indication of combination with a statin in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin in addition to ezetimibe.

Statin intolerance

In the statin-intolerant population, added benefit (and risk) of bempedoic acid in patients insufficiently controlled with ezetimibe has been shown. These data, therefore, support an 'add on' indication for the FCMP in SI patients insufficiently responding to ezetimibe.

However, efficacy in terms of an 'add-on' indication of the FCMP in the context of a patient population not meeting treatment goals with bempedoic acid alone and in whom ezetimibe is added, has not been examined and was therefore not acceptable. An 'add-on' indication for the FCMP in patients non-responsive to bempedoic acid in SI patients is therefore currently not approvable. Further, current learned society guidelines recommend ezetimibe and bile acid sequestrants in SI patients. There are also no major or unique reasons to exclude patients from using ezetimibe.

Initial combination treatment

The proposed 'initial combination treatment" indication concerning a patient population unable to reach LDL-C goals with the maximum tolerated dose of a statin alone and the patient population either statin-intolerant or for whom a statin is contraindicated was considered not approvable. The added benefit in terms of reduction by lowering LDL-C by initial combining bempedoic acid with ezetimibe instead of following a sequential addition of the single lipid lowering product (preferably starting with ezetimibe) is likely to be limited and it is highly questionable whether this would translate into a difference in CV risk reduction. Sequential treatment allows the physician to evaluate the incremental contribution of each component, both in terms of efficacy as well as safety, and avoids the risk of overtreatment, especially knowing that the effect could be heterogeneous between patients and the effect needs to be monitored. Finally, although benefits on CV outcomes have been demonstrated for ezetimibe such impact is not established for bempedoic acid.

Switch in patients adequately controlled with two or more active substances used in combination ('substitution')

In principle, the factorial design study data in addition to the other clinical study data support the rationale for the combined use of the active substances and is considered sufficient for a substitution indication regarding patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without a statin.

3.8. Conclusions

The overall B/R of Nustendi 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 Nustendi is favourable in the following indication:

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

The 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

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

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) EMEA-002200-PIP01-17 on the granting of a (product-specific) waiver for the paediatric population from birth to less than 18 years of age.