EUROPEAN UNION RISK MANAGEMENT PLAN (RMP)

Bempedoic Acid 180 mg + Ezetimibe 10 mg

Fixed Dose Combination (FDC)

Indication: Hypercholesterolemia

Property of Daiichi-Sankyo Europe GmbH

Confidential

Qualified Person for Pharmacovigilance's (QPPV) Name:

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RMP version to be assessed as part of this application:

Data lock point for this RMP	20 Feb 2023	RMP Version number	5.0
Date of final sign off	26 Feb 2024		

Rationale for preparing an updated RMP:

This RMP update has been made to incorporate data from the CLEAR Outcomes Trial (Study 1002-043, A randomized, double-blind, placebo-controlled study to assess the effects of bempedoic acid on the occurrence of major cardiovascular events in patients with, or at high risk for, cardiovascular disease who are statin intolerant) into risk assessment and management for bempedoic acid.

Summary of significant changes in this RMP:

The new EU RMP was populated with content from the current bempedoic acid-ezetimibe EU RMP version 3.1 and certain sections were updated with data lock point 20 February 2023. The resulting version 4.0 has been submitted but not yet approved. Therefore, the following paragraphs of this version 5.0 describe the changes from the last approved bempedoic acid-ezetimibe EU RMP version 3.1:

Global – Deleted 'Myopathy with concomitant use of statins' and 'Gout' as important potential risks for bempedoic acid

Part I: Product Overview

Addition of proposed indication in the EEA

Part II: Safety Specification

SI - Addition of proposed indication

SI - Epidemiology section updated to reflect the new indication and target population

SIV.3 - Addition of data from the CLEAR Outcomes Trial (Study 1002-043)

SV.1 - Cumulative patient exposure from marketing experience updated till through DLP 20Feb2023

Part VI: Summary of the risk management plan

I - Addition of proposed indication

Appendix 7 - Updated list of references

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Explanation
ACL	adenosine triphosphate citrate lyase
ACSVL1	acyl-CoA synthetase 1
apo B	apolipoprotein B
ALT	alanine aminotransferase
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUCinf	area under the plasma concentration-time curve from time zero to infinity
BCRP	breast cancer-related protein
BUN	blood urea nitrogen
CABG	coronary artery bypass graft
CETP	cholesteryl ester transfer protein
CK	creatine kinase
Cmax	maximum plasma drug concentration
CP	Child-Pugh
CSR	clinical study report
CV	cardiovascular
CVD	cardiovascular disease
CYP	cytochrome P450
DALY	disability-adjusted life-years
DBP	diastolic blood pressure
ECG	electrocardiogram
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EPAR	European Public Assessment Report
ESP15228	active keto-metabolite of ETC-1002
ESRD	end-stage renal disease
ETC-1002	analyte of bempedoic acid measured in plasma, urine, or feces
ETC-1002-CoA	ETC-1002-coenzyme A
FDC	fixed dose combination
HbA_{1c}	glycosylated hemoglobin
HMG-CoA	3-hydroxy-3-methyl-glutaryl-coenzyme A
hsCRP	high-sensitivity C-reactive protein
IMP	investigational medicinal product

Abbreviation	Explanation
LDL-C	low-density lipoprotein cholesterol
LMT	lipid-modifying therapy
MACE	major adverse cardiovascular event
MI	myocardial infarction
MRHD	maximum recommended human dose
NOAEL	no-observed-adverse-effect level
non-HDL-C	non-high-density lipoprotein cholesterol
NSAID	nonsteroidal anti-inflammatory drugs
OAT	organic anion transporter
Oat	OAT ortholog in nonhuman species
OATP	organic anion transporting polypeptide
OR	odds ratio
PBRER	Periodic Benefit-Risk Evaluation Report
PCI	percutaneous coronary intervention
PCSK9	proprotein convertase subtilisin kexin type 9
PIL	Patient information leaflet
PK	pharmacokinetics
PPAR	peroxisome proliferator-activated receptor
QD	once daily
RBC	red blood cell
RMP	risk management plan
SBP	systolic blood pressure
SmPC	Summary of Product Characteristics
t½	terminal elimination half-life
T2DM	Type 2 diabetes mellitus
TB	total bilirubin
TC	total cholesterol
TGs	triglycerides
UGT	uridine 5´-diphospho-glucuronosyltransferase
UK	United Kingdom
ULN	upper limit of normal
US	United States

PART I: PRODUCT OVERVIEW

The following table (Table Part I.1) presents an overview of the combination product bempedoic acid-ezetimibe with product characteristics, indications and dosage.

Table Part I.1 – Product(s) Overview

Active substances (INN or common name)	Bempedoic acid + ezetimibe
Pharmacotherapeutic group(s) (ATC Code)	C10BA10
Marketing authorization Holder	Daiichi Sankyo Europe GmbH
Medicinal products to which this RMP refers	Bempedoic acid – ezetimibe 180mg/10mg film-coated tablets Ezetrol® (ezetimibe)
Invented name in the European Economic Area (EEA)	Nustendi®
Marketing authorization procedure	Centralised
Brief description of the product	Fixed dose combination (FDC) of bempedoic acid 180 mg + ezetimibe 10 mg, film-coated tablet
Bempedoic acid:	
Chemical class:	Adenosine triphosphate (ATP)-citrate lyase (ACL) inhibitor
Summary of mode of action:	Bempedoic acid is an ACL inhibitor that lowers low-density lipoprotein cholesterol (LDL-C) by inhibition of cholesterol synthesis in the liver. ACL is an enzyme upstream of 3-hydroxy-3-methyl- glutaryl-coenzyme A (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. ACSVL1 is expressed primarily in the liver and not in skeletal muscle. 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 receptors. Additionally, inhibition of ACL by ETC-1002-CoA results in a concomitant suppression of hepatic fatty acid biosynthesis.
Important information about its composition	Small synthetically derived molecule with no novel excipients

Ezetimibe	
Chemical class:	Cholesterol absorption inhibitor
Summary of mode of action:	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. 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.
Important information about its composition	Small synthetically derived molecule with no novel excipients
Hyperlink to the Product Information	Summary of Product Characteristics https://www.ema.europa.eu/en/documents/product-information/nustendi-epar-product-information_en
Indication in the EEA Current:	The bempedoic acid 180 mg + ezetimibe 10 mg FDC is indicated in adults with primary hypercholesterolemia (heterozygous familial and nonfamilial) or mixed dyslipidemia, as an adjunct to diet: • in combination with a statin in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin in addition to ezetimibe • alone in patients who are either statin-intolerant or for whom a statin is contraindicated, and are unable to reach LDL-C goals with ezetimibe alone • in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without statin
Proposed additional indication:	The bempedoic acid 180 mg + ezetimibe 10 mg FDC is indicated in adults with established or at high risk for atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors: • in patients on a maximum tolerated dose of a statin, and not adequately controlled with additional ezetimibe treatment or, • in patients who are either statin-intolerant, or for whom a statin is contraindicated, and not adequately controlled with ezetimibe treatment or, • in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets.
Dosage in the EEA Current:	Bempedoic acid 180 mg + ezetimibe 10 mg once daily

Pharmaceutical form(s) and strengths Current:	Film-coated tablet containing 180 mg of bempedoic acid and 10 mg of ezetimibe
Will the product be subject to additional monitoring in the European Union?	Yes

PART II: SAFETY SPECIFICATION

SI Epidemiology of the Indication and Target Population

The approved indication for the bempedoic 180 mg + ezetimibe 10 mg FDC is:

- The bempedoic acid + ezetimibe FDC is indicated in adults with primary hypercholesterolemia (heterozygous familial and nonfamilial) or mixed dyslipidemia, as an adjunct to diet:
  - in combination with a statin in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin in addition to ezetimibe
  - alone in patients who are either statin-intolerant or for whom a statin is contraindicated, and are unable to reach LDL-C goals with ezetimibe alone
  - in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets with or without statin

The proposed indication for the bempedoic acid 180 mg + ezetimibe 10 mg FDC is:

- The bempedoic acid + ezetimibe FDC is indicated in adults with established or at high risk for atherosclerotic cardiovascular disease to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors:
  - in patients on a maximum tolerated dose of a statin, and not adequately controlled with additional ezetimibe treatment or,
  - in patients who are either statin-intolerant, or for whom a statin is contraindicated, and not adequately controlled with ezetimibe treatment or,
  - in patients already being treated with the combination of bempedoic acid and ezetimibe as separate tablets.

The epidemiology of primary hypercholesterolemia, mixed dyslipidemia and cardiovascular disease is summarized in Table 1.

Table 1: Summary of Epidemiology of Primary Hypercholesterolemia,Mixed Dyslipidemia and Cardiovascular disease

Incidence/Prevalence
Hypercholesterolemia Hypercholesterolemia, or high cholesterol, is the presence of high levels of cholesterol in the blood. Primary hypercholesterolemia includes both familial hypercholesterolemia (inherited genetic abnormality) and nonfamilial forms. The prevalence of hypercholesterolemia is 63.4%, 59.0%, 49.8%, and 53.9% in the United Kingdom (UK), Finland, Croatia, and the Czech Republic, respectively (Barquera et al, 2015(5)). The global prevalence of heterozygous familial hypercholesterolemia (HeFH), an autosomal dominant disorder inherited from one parent, is estimated to be 1 in 250 (Sjouke et al, 2015(50)). In a meta-analysis, prevalence of HeFH across Europe tended to be lower but certain regions within Denmark, Spain, and Finland have reported higher prevalence statistics (Benn et al, 2012(8); Kontula et al, 1992(38); Zamora et al, 2017(57)). The accumulation of LDL particles in the artery wall is a central element in the initiation and progression of atherosclerosis. This linear relationship between cholesterol levels and risk of CV disease has been shown in populations worldwide (Verschuren et al, 1995(55)). Based on the Royal College of General Practitioners Research and Surveillance Centre (RCGP RSC) database, the prevalence of cardiovascular disease (CVD) or hypertension in adults in the UK in 2016 was 21.3%. The annual age- and gender-adjusted incidence rate was 22.1/10,000 for coronary artery disease (CAD), 6.0/10,000 for peripheral arterial disease (PAD), and 12.3/10,000 for congestive cardiac failure (Hinton et al, 2018(32)). Lowering LDL-C has been accepted as a validated surrogate endpoint of CV events by clinicians and regulatory authorities for many years (Cannon et al, 2002(14); Jacobson et al, 2014(35)). Nearly one-third of deaths worldwide were found to be associated with underlying CVD in 2013 (Benjamin et al, 2017(7)), and CVD causes more than half of all deaths across the European Region (World Health Organization, 2018(56)). *Mixed Dyslipidemia* Dyslipidemias, including isolated high LDL-C or mixed dyslipidemia, such as those seen in diabetes (hypertriglyceridemia, high LDL-C, or low HDL-C) correlate with a significant risk of CV and cerebrovascular disease worldwide. Evidence supporting a causal relationship between lipid profile abnormalities and the risk of CAD is overwhelming, confirming that hypercholesterolemia is an independent risk factor for CVD (Carr and Brunzell, 2004(16); Isomaa et al, 2001(34); Gordon et al, 1989(27)). In addition, hypertriglyceridemia and mixed dyslipidemias have been associated with the aggregation of metabolic risk factors, such as hypertension (Onat et al, 2005(45)) and obesity (Brown et al, 2000(11)). Dyslipidemia has been closely linked to the pathophysiology of CVD and is a key independent modifiable risk factor for CVD (Grundy, 1997(29); Haffner, 1999(30)). A study investigating different lipids in statin-treated patients at high CV risk in clinical practice in Germany found that despite statin treatment, LDL-C goals were not attained in 58.1%, elevated total cholesterol (TC) was found in 66.6%, low HDL-C in 22.7%, and elevated TG in 47.3 % (Gitt et al, 2010(26)). In a similar study in France >70% of the patients had elevated LDL-C despite being on lipid-lowering therapy. Among those who did not reach the LDL-C goal, 38.7% had dyslipidemias with low HDL-C, elevated TGs, or both (Van Ganse et al, 2007(54)). *Cardiovascular disease* Globally, CVD is the leading cause of morbidity and mortality (World Health Organization, 2021). Nearly one-third of deaths worldwide were found to be associated with underlying CVD in 2019. Currently, over 120 million adults in the US have some form of CVD (Centers for Disease Control, 2019) and heart disease is the leading cause of death, responsible for approximately 1 in 4 deaths each year. In Europe, there were 19.9 million new cases of CVD in 2017 (Timmis et al, 2020 (63)), accounting for 39% of all deaths in men and 46% of all deaths in women (Townsend et al, 2021 (64)). Atherosclerotic CVD, which includes coronary heart disease (CHD), cerebrovascular disease, and peripheral artery disease, is the most common form of CVD; ischemic heart disease and ischemic stroke jointly account for more than half of all CVD deaths (Arnett et al, 2019 (65); Roth et al, 2020 (66)). Atherosclerosis is a disease initiated and driven by the accumulation of cholesterol rich lipoproteins (primarily low-density lipoprotein [LDL]) within the intimal region of the artery wall and the chronic inflammatory response to the presence of these modified lipoproteins (Barquera et al, 2015 (67)). Because of the central role of LDL

Incidence/Prevalence
particle accumulation in the initiation and progression of atherosclerosis, there are significant associations between elevations in LDL-C and ASCVD events (Ference et al, 2017 (68); Borén et al, 2020 (69)). Evidence for the direct correlation between LDL-C and CVD comes from 4 different categories of studies: preclinical studies, epidemiological studies, genetic studies, and interventional studies (Kannel et al, 1971 (70); Stamler et al, 1986 (71); Chen et al, 1991 (72); Taylor et al, 2004 (73); Zadelaar et al, 2007 (74); Feig, 2014 (75)). Statins are the cornerstone of LDL-C lowering; many patients do not reach guideline-recommended LDL-C goals on statin therapy and there is a large unmet need for safe and effective non-statin lipid-lowering drugs (Mitchell et al, 2016 (62)). Furthermore, adherence to statin therapy remains a considerable challenge that contributes to a failure to achieve LDL-C goals in significant numbers of patients, increasing the risk of cardiovascular morbidity and mortality (Stroes et, 2015 (76)) highlighting the unmet need for LDL-C lowering nonstatin therapies that are safe and effective in patients who need additional therapeutic options.

Table 1: Epidemiology of Primary Hypercholesterolemia, Mixed Dyslipidemia and Cardiovascular disease (Continued)

Demographic Characteristics and Risk Factors for the Disease
Modifiable risk factors for hypercholesterolemia and CVD include a diet high in saturated or trans fats, physical inactivity, smoking, and obesity (Mozaffarian et al, 2016(42)). Secondary causes of elevated LDL-C include diseases such as biliary obstruction, chronic kidney disease, blood pressure, and hypothyroidism (Mozaffarian et al, 2016(42)). Medications such as diuretics, cyclosporine, and glucocorticoids can also contribute to elevated LDL-C levels (Stone et al, 2014(52)). A high proportion of patients with metabolic syndrome, obesity, or type 2 diabetes mellitus (T2DM) have complex lipid abnormalities (dyslipidemia) that are not restricted to elevated LDL-C or TC levels, but often comprise reduced levels of HDL-C and/or elevated TGs (Snow et al, 2004(51); American Diabetes Association [ADA], 20042)). Data related to the role of race and sex in the development of hypercholesterolemia have been conflicting; however, some risk factors may be more prevalent in specific ethnic groups, such as obesity in non-Hispanic blacks, and thus an increased incidence of hypercholesterolemia within that population (Ogden et al, 2014(43)). In a meta-analysis in which European studies predominated, prevalence of HeFH did not differ based on gender, and HeFH was slightly less prevalent in Europe and Asia than in North American or Australasia (Akioyamen et al, 2017(1)). The risk assessment system for risk of CVD, Systemic Coronary Risk Estimation (SCORE), uses higher age, male sex, smoking, high systolic blood pressure, and increased TC as risk factors for CVD. High risk is always postulated for patients with diabetes, chronic kidney disease, familial hypercholesterolemia, and earlier CV events (Conroy et al, 2003(21); Catapano et al, 2017(17)). A study investigating different lipids in statin-treated patients at high CV risk in clinical practice in Germany showed in the multivariate logistic regression model, non-attainment of target LDL-C levels was predicted by hypertension (odds ratio [OR], 1.4), current smoking (OR 1.3), sedentary lifestyle (OR 1.3), and female gender (OR 1.3) (Gitt et al, 2010(26)). On the other hand, a reduced risk for missing LDL-C targets was noted in the presence of ischemic heart disease (OR 0.6), diabetes (0.5), higher statin doses, ezetimibe treatment, or specialist care, respectively. In a similar study in France it was shown that compared with having a normal lipid profile, each additional CV risk factor increased the likelihood of the following types of dyslipidemias: low HDL-C and/or elevated TGs, but normal LDL-C OR, 1.36; 95% CI, 1.03-1.79); elevated LDL-C and TGs, but normal HDL-C (OR, 1.58; 95% CI, 1.24-2.02); and all 3 lipid abnormalities (OR, 1.54; 95% CI, 1.10-2.14) (Van Ganse et al, 2007(54)). Patients with diabetes had a similarly increased risk of mixed dyslipidemias, whereas patients with a history of CHD did not. In summary, patients with a greater number of nonlipid CV risk factors or with diabetes had a significantly increased risk of mixed dyslipidemias involving elevated TGs and/or low HDL-C in addition to elevated LDL-C.

Table 1: Epidemiology of Primary Hypercholesterolemia, Mixed Dyslipidemia and Cardiovascular disease (Continued)

Main Existing Treatment Options
Treatment options for hypercholesterolemia include modification of diet and lifestyle. Drug treatments include HMG Co-A reductase inhibitors (statins), a selective cholesterol absorption inhibitor (ezetimibe), bile acid sequestrants (eg, cholestyramine), fibric acid derivatives (gemfibrozil, fenofibrate, or clofibrate), omega-3 fatty acids, niacin, and proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors (evolocumab and alirocumab). Currently, HMG-CoA reductase inhibitions (statins) are the standard of care for dyslipidemias and are used by over 80 million patients worldwide to reduce elevated LDL-C. A 1 mmol/L (38.7 mg/dL) reduction in LDL-C with statin therapy was associated with a 22% reduction in the 5-year incidence of major coronary events, revascularizations, and ischemic strokes (Baigent et al, 2010(4)). An important barrier to statin adherence is tolerability, which can lead patients to stop statin therapy or reduce the dose. Muscle complaints, which encompass a range of conditions from mild muscle pain or discomfort to rare but life-threatening rhabdomyolysis, represent a major cause of statin discontinuation in clinical practice (Joy and Hegele, 2009(37)). Other manifestations include elevated liver enzymes, gastric upset, diarrhea, constipation, rash, headache, dizziness, mental confusion, forgetfulness, or erectile dysfunction (Eckel, 2010(22)). In the Prediction of Muscular Risk in Observational Conditions (PRIMO) survey of 7924 patients with hypercholesterolemia receiving high-dose statin therapy in an outpatient setting in France, muscular symptoms were reported by 11% of patients (Bruckert et al, 2005(12)). Results of a simulation model using data from a large US claims database showed that 31% of patients with atherosclerotic cardiovascular disease (ASCVD) were unable to achieve an LDL-C of less than 70 mg/dL (1.8 mmol/L) 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(15)). 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. The 2019 European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) Guidelines for the Management of Dyslipidaemias suggests staggered treatment goals based on baseline LDL-C levels and CVD risk, with targets of ≥50% LDL-C reduction from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) for patients at **very-high risk in primary or secondary prevention,** ≥50% LDL-C reduction from baseline and an LDL-C goal of <1.8 mmol/L (<70 mg/dL) for patients at high risk, <2.6 mmol/L (<100 mg/dL) for patients at moderate risk, and <3.0 mmol/L (<116 mg/dL) for patients at low risk. Non-HDL-C secondary goals are <2.2, 2.6, and 3.4 mmol/L (<85, 100, and 130 mg/dL) for very-high-, high-, and moderate-risk people, respectively (Catapano et al, 2017(17)). Several previous observational studies, such as the Dyslipidemia International Study (DYSIS), DYSIS II and the EUROASPIRE surveys, which were conducted over several decades (1995–2018), have shown that lipid management in patients with higher CV risk remains suboptimal. More recently, the DA VINCI study (2017–2018) has shown that the majority of lipid lowering therapy in Europe is monotherapy, mainly comprising of moderate and high-intensity statin (51.8% and 27.6%, respectively), with only 33% of patients attaining the 2019 ESC/EAS guideline LDL-C goals. Findings from the baseline data of the SANTORINI study were similar, suggesting that the gap between clinical guidelines and clinical practice for lipid management across Europe not only persists but widen with the new guidelines seemingly out of reach with monotherapy (Ray et al, 2023 (58), Ray et al, 2021 (59)). The EAS Task Force recognizes that the new LDL-C goals for high and very-high-risk patients with dyslipidaemia are even more demanding than previously; indeed, in real-world practice only about one-third attain LDL-C goal. Therefore, combination lipid lowering therapy should become the standard of care for these patients. The 2019 ESC/EAS guidelines also underline the need for combination therapy to achieve LDL-C goals as early as possible (Averna et al, 2021 (60), Masana et al, 2020 (61)).

Natural History of the Condition, Including Mortality and Morbidity
Hypercholesterolemia is a leading cause of atherosclerosis and CVD (Barquera et al, 2015(5); Lipids Research Clinics Program [LRCP], 1984(40); Oliver et al, 1978(44)) and CVD is the leading cause of death among Europeans, Americans, and other populations around the world (World Health Organization, 2018(56)). The global age- standardized mortality rate associated with elevated cholesterol ≥190 mg/dL was 1.7% in 2010, and in Europe the 2010 age-standardized mortality rate was 3.0%, 3.5%, 3.5%, and 4.1% in the UK, Finland, Croatia, and the Czech Republic, respectively (Barquera et al, 2015(5)). In the global population, health loss due to nonfatal disability from CV and circulatory diseases was 4470.9 disability-adjusted life-years (DALY) per 100,000 inhabitants in 2010, and in Europe in 2010, the same statistic was 2406.2, 2800.3, 4326.4, and 4035.9 DALY in the UK, Finland, Croatia, and the Czech Republic, respectively (Barquera et al, 2015(5)).
Important Comorbidities
Important comorbidities include diabetes (Centers for Disease Control and Prevention [CDC], 2017(19)), hypertension (Ferrara et al, 2002(25)), obesity (Gostynski et al, 2004(28)), hypothyroidism (Rizos et al, 2011(47)), kidney disease (Tsimihodimos et al, 2011(53)), and Cushing's disease (Arnaldi et al, 2010(3)).

SII Nonclinical Part of the Safety Specification

Important nonclinical safety findings are summarized for bempedoic acid in Table 2. No new nonclinical data were generated for ezetimibe.

Table 2: Important Safety Findings From Nonclinical Studies of Bempedoic Acid

Finding	Relevance to Human Usage
Acute and Repeat-Dose Toxicity Studies	
Bempedoic acid administration was associated with adaptive changes that were not associated with functional impairment in liver in mice, rats, and monkeys. At higher doses, adverse changes consisting primarily of single-cell necrosis were observed. In all 3 species, reversible dose-related increases in liver weight, hepatocellular hypertrophy, and increased vacuolation/fat accumulation were observed. As anticipated, these effects were more pronounced in mice and rats than in monkeys. In the 3- and 6-month rat studies, increases in liver enzymes and single-cell necrosis were observed at ≥30 mg/kg/day with associated exposures at ≥1.7 × the exposure in humans at 180 mg/day. In contrast to findings in rodents, no overt hepatic toxicity was observed in monkeys given single doses up to 2000 mg/kg or repeat doses up to 60 mg/kg/day for up to 12 months. The systemic exposure in the 12-month study at 60 mg/kg/day was ≤14 × the exposure in humans at 180 mg/day.	Such findings are common in laboratory animals given compounds that alter lipid metabolism or induce drug-metabolizing enzymes and are generally considered an adaptive response as they are directly attributable to and are secondary to liver weight changes. No safety concern was identified based on clinical data. Because statins have been associated with liver enzyme elevations, hepatic enzymes were evaluated in Phase 3 studies based on a predefined list of preferred terms and associated laboratory parameters (Module 2.7.4- BA, Section 2.1.4.2.4). Reversible elevations in hepatic enzymes were observed with bempedoic acid that were not associated with clinical symptoms (Section SVII.1.1). The rate of hepatic elevations in the bempedoic acid group was within the range of hepatic enzyme elevations reported for statins and ezetimibe. Rates of transaminase elevations >5 × upper limit of normal (ULN) were similar between the bempedoic acid and placebo groups and there were no elevations in bilirubin or cases of Hy's Law. Hepatic enzyme elevations are considered to represent an adverse reaction for bempedoic acid, but as they do not appear to be a risk to patients, they are not considered an important potential or important identified risk for bempedoic acid.
In rodents, bempedoic acid caused mild peroxisome proliferator-activated receptor (PPAR) α-related adaptive effects, ie, increased liver weights, and induction of peroxisomes and peroxisomal enzymes.	No important risk was identified based on clinical data. The mechanism for PPARα-related effects is specific to rodents; therefore, these effects were not anticipated in humans and did not occur in clinical studies.
Nonclinical studies with bempedoic acid showed minimal to mild decreases in hemoglobin and hematocrit. Mild, reversible decreases ≤15% were observed in red blood cell (RBC) parameters in subchronic mice, chronic rat, and subchronic monkey studies. There were no changes in RBC parameters in chronic monkey studies.	No important risk was identified based on clinical data (Module 2.7.4-BA, Section 2.1.4.2.9). Modest consistent decreases (2.0% to 2.5%) in mean hemoglobin levels were observed in clinical studies; however, no meaningful clinical manifestations in terms of significant, large drops in hemoglobin, were observed compared with placebo during shorter term (12- to 24-week) and chronic (52-week) treatment with bempedoic acid alone and added on to ezetimibe and/or maximally tolerated statins in Phase 3 studies (Section SVII.1.1).

Table 2: Important Safety Findings From Nonclinical Studies of Bempedoic Acid (Continued)

Finding	Relevance to Human Usage
Acute and Repeat-Dose Toxicity Studies (continued)	
Increases in urea nitrogen and creatinine associated with renal tubular degeneration and necrosis were seen in rat and monkey species receiving high doses of bempedoic acid (>14 × the range of exposures intended for clinical studies) (Module 2.4). Reversible changes in markers of renal effects in both species were observed in the absence of morphology of adverse renal effects in pivotal chronic studies at exposures at 9 × and 14 × exposure in humans at 180 mg/day, in rats and monkeys respectively.	In Phase 3 clinical studies, renal disorders were evaluated based on a predefined list of preferred terms and associated laboratory parameters. (Module 2.7.4-BA, Section 2.1.4.2.7). Small mean increases in creatinine and blood urea nitrogen (BUN) occurred with bempedoic acid. The increases occurred within the first month, remained stable with continued therapy, and returned to baseline levels after the discontinuation of bempedoic acid. Blood urea increased and blood creatinine increased were identified as adverse reactions. Increased creatinine, however, appears to represent a drug-endogenous substrate interaction rather than an indication of worsening renal function (Section SVII.1.1). In general, the incidence of renal adverse events, including acute kidney injury and renal impairment, were balanced between treatment groups. Increased creatinine and BUN are not considered safety concerns for bempedoic acid, and no renal-related change considered to represent an adverse reaction to bempedoic acid.
The mechanism leading to lethality in nonclinical species is sustained and severely decreased blood glucose (hypoglycemia) resulting from sustained high dose bempedoic acid exposure (>15 × the range of exposures intended for clinical studies. Hypoglycemia in monkeys was reversible with oral glucose supplement and cessation of dosing.	No important risk was identified based on clinical data. In clinical studies, bempedoic acid had no adverse effects on glycemic control (Module 2.7.4-BA, Section 2.1.4.2.2; Module 2.7.4-BA, Section 5.1.6.3). No safety concern associated with hypoglycemia or metabolic acidosis was identified during shorter term (12- to 24-week) and chronic (52-week) treatment with bempedoic acid administered alone and added on to ezetimibe and/or maximally tolerated statins in Phase 3 studies. In the Overall Phase 3 Pool, hypoglycemia was reported in 1.7% and 2.1% of patients in the bempedoic acid and placebo groups, respectively

Table 2: Important Safety Findings From Nonclinical Studies of Bempedoic Acid (Continued)

Finding	Relevance to Human Usage
Repeat-Dose Toxicity Studies in Combination With Statins	
In a 13-week combination toxicology study, treatment with bempedoic acid (up to 60 mg/kg/day, which approximates 16 × the exposure at the maximum recommended human dose [MRHD] of 180 mg/day) in combination with atorvastatin (at 40 mg/kg/day, approximately 9 × the exposure at the MRHD of 80 mg/day) resulted in moribundity and mortality in cynomolgus monkeys. Morbidity in these animals was consistent with known toxicological effects of atorvastatin above maximum tolerated dose in monkeys (kidney, liver, and gastrointestinal tract) and was likely aggravated by toxicological effects of bempedoic acid previously observed above maximum tolerated dose in monkeys (kidney, hypoglycemia). Dosing was terminated on Day 6. A definitive 13-week combination toxicology study in cynomolgus monkeys showed no adverse findings with the combination of atorvastatin at 5 mg/kg/day (approximates the exposure equivalent to the MRHD) and bempedoic acid at 20 mg/kg/day (approximately 3 × the exposure at the MRHD).	Clinical data from two 52-week Phase 3 trials involving over 3000 patients demonstrate that bempedoic acid in combination with maximally tolerated statins (including approximately 2000 patients on high intensity doses of statins) is well-tolerated with chronic use and do not indicate any adverse events or safety concerns related to target organ toxicities or hypoglycemia observed in cynomolgus monkeys (Module 2.7.4-BA, Section 2.1.4.2.2).
Reproductive and Developmental Toxicity	
Bempedoic acid was not teratogenic or toxic to embryos or fetuses in pregnant rabbits at doses up to 80 mg/kg/day or 12 × the systemic exposure in humans at 180 mg. Pregnant rats given bempedoic acid at 10, 30, and 60 mg/kg/day during organogenesis had decreased numbers of viable fetuses and reduced fetal body weight at ≥ 30 mg/kg/day or 4 × the systemic exposure in humans at 180 mg. An increased incidence of fetal skeletal findings (bent scapula and ribs) was observed at all doses, at exposures below the systemic exposure in humans at 180 mg. In a pre- and post-natal development study, pregnant rats administered bempedoic acid at 5, 10, 20 and 30 mg/kg/day throughout pregnancy and lactation had adverse maternal effects at ≥ 20 mg/kg/day and reductions in numbers of live pups and pup survival, pup growth and learning and memory at ≥10 mg/kg/day, with maternal exposures at 10 mg/kg/day, less than the exposure in humans at 180 mg.	There are no data available on use of bempedoic acid in pregnant women. Bempedoic acid is contraindicated in women who are or may become pregnant. Because bempedoic acid decreases cholesterol synthesis and possibly the synthesis of other cholesterol derivatives needed for normal fetal development, bempedoic acid may cause fetal harm when administered to pregnant women. Bempedoic acid should be discontinued prior to conception or as soon as pregnancy is recognized. Atherosclerosis is a chronic process, and ordinarily discontinuation of lipid-lowering medicinal products during pregnancy should have little impact on the long- term risk associated with primary hypercholesterolemia.

Table 2: Important Safety Findings From Nonclinical Studies of Bempedoic Acid (Continued)

Finding	Relevance to Human Usage
Reproductive and Developmental Toxicity (continued)	
In a study of juvenile rats treated from Postnatal Day (PND) 15 (~2-year-old infant) to PND 78 (adult) with recovery assessment on PND 132, the no-observed-adverse-effect level (NOAEL) dose was 10 mg/kg/day, which was the top dose evaluated for physical and behavioral development. The corresponding systemic exposures were less than clinical exposure at the 180 mg dose.	The safety and efficacy of bempedoic acid in children aged less than 18 years have not yet been established.
Genotoxicity	
The standard battery of genotoxicity studies have not identified a mutagenic or clastogenic potential of bempedoic acid.	There is no genotoxic potential. No important risk was identified based on clinical data.
Carcinogenicity	
In full lifetime carcinogenicity studies in rodents, bempedoic acid increased the incidence of hepatocellular and thyroid gland follicular tumors in male rats and hepatocellular tumors in male mice.	Bempedoic acid is noncarcinogenic in 2 rodent species. In full lifetime carcinogenicity studies in rodents, bempedoic acid increased the incidence of hepatocellular and thyroid gland follicular tumors in male rats and hepatocellular tumors in male mice. Because these are common tumors observed in rodent life-time bioassays and the mechanism for tumorigenesis is secondary to a rodent-specific PPAR-α activation pathway that does not mechanistically exist in humans, these tumors are not considered to translate to human risk.
Bempedoic acid did not affect heart rate, blood pressure (systolic, diastolic, mean arterial), or electrocardiogram (ECG) parameters (QRS duration, or PR, RR, or QT intervals) in telemetered monkeys given single doses of 10, 30, or 100 mg/kg in an escalating dose fashion, with 1 week between doses. Bempedoic acid had no significant effects in the human ether-à-go- go-related gene (hERG) assay at concentrations up to 300 μM (103 μg/mL). Bempedoic acid did not have any significant effects on arousal/activity, autonomic, neuromuscular, or physiological functions evaluated in rats given single oral doses of bempedoic acid at 10, 30, or 100 mg/kg in a central nervous system (CNS) safety pharmacology study. Bempedoic acid did not affect respiratory rate, tidal volume, or minute volume in rats given single oral doses of bempedoic acid at 10, 30, or 100 mg/kg in a pulmonary safety pharmacology study.	No clinically relevant effects on CV function/ECG, QTc prolongation, respiratory effects, or neurobehavioral/cognitive effects were seen in humans. No important risk was identified based on clinical data.

SIII Clinical Trial Exposure

SIII.1 Clinical Trial Exposure to the Fixed Dose Combination

Clinical trial exposure to the FDC is summarized overall in Table 3, by sex in Table 4, by age group in Table 5, and by ethnic origin in Table 6.

Table 3: Summary of Exposure to the Bempedoic Acid 180 mg + Ezetimibe 10 mg Fixed Dose Combination in Completed Clinical Studies

	Number of Persons
Phase 1 studies in healthy subjects	
Study 1002FDC-034	23[a]
Study 1002FDC-055	17
Phase 2 Study 1002FDC-058 in patients with T2DM and elevated LDL-C	81
Phase 3 Study 1002FDC-053 in patients with hyperlipidemiabb	86
Total	207

CSR = clinical study report; FDC = fixed dose combination
Source: Study 1002FDC-034 CSR, Listing 16.2.4.1, Listing 16.2.5.1; Study 1002FDC-053 CSR, Table 14.1.2.2a;
Study 1002FDC-055 CSR, Table 14.1.1, Study 1002FDC-058 CSR, Table 14.1.2.1.
[a] Number of subjects who received FDC monolayer formulation (to-be-marketed product). One additional subject received the FDC bilayer formulation but not the FDC monolayer formulation; that subject is not counted here.
[b] Excluding sites with suspect data (1028, 1058, and 1068).

Table 4: Summary of Exposure to the Bempedoic Acid 180 mg + Ezetimibe 10 mg Fixed Dose Combination by Sex in Completed Clinical Studies

Sex	Male	Female
Phase 1 studies in healthy subjects		
Study 1002FDC-034	16[a]	7
Study 1002FDC-055	6	11
Phase 2 Study 1002FDC-058 in patients with T2DM and elevated LDL-C	45	42
Phase 3 Study 1002FDC-053 in patients with hyperlipidemia[b]	42	44
Total	109	98

CSR = clinical study report; FDC = fixed dose combination
Source: Study 1002FDC-034 CSR, Listing 16.2.4.1, Listing 16.2.5.1; Study 1002FDC-055 CSR, Table 14.1.2.2a;
Study 1002FDC-053 CSR, Table 14.1.2.1, Study 1002FDC-058 CSR, Table 14.1.2.1.
[a]0 One additional male subject received the FDC bilayer formulation but not the FDC monolayer formulation; that subject is not counted here.
[b] Excluding sites with suspect data (1028, 1058, and 1068).

Table 5: Exposure to the Bempedoic Acid 180 mg + Ezetimibe 10 mg Fixed Dose Combination by Age Group in Completed Clinical Studies

	Age Group (y)		
	<65	**65 to <75**	**≥75**
Phase 1 studies in healthy subjects			
Study 1002FDC-034	23[a]	0	0
Study 1002FDC-055	17	0	0
Phase 2 Study 1002FDC-058 in patients with T2DM and elevated LDL-C	53	24	4
Phase 3 Study 1002FDC-053 in patients with hyperlipidemia[b]	51	25	10
Total	144	49	14

CSR = clinical study report; FDC = fixed dose combination
[a] One additional subject in this age group received the FDC bilayer formulation but not the FDC monolayer formulation; that subject is not counted here.
[b] Excluding sites with suspect data (1028, 1058, and 1068).
Source: Study 1002FDC-034 CSR, Listing 16.2.4.1, Listing 16.2.5.1; Study 1002FDC-055 CSR, Table 14.1.2; Study 1002FDC-053 CSR, Table 14.1.2.2a; Study 1002FDC-058 CSR, Table 14.1.2.1.

Table 6: Exposure to the Bempedoic Acid 180 mg + Ezetimibe 10 mg Fixed Dose Combination by Ethnic origin in Completed Clinical Studies

	White	**Black**	**Other**
Phase 1 studies in healthy subjects			
Study 1002FDC-034	16	7[a]	0
Study 1002FDC-055	4	13	0
Phase 2 Study 1002FDC-058	61	15	5
Phase 3 Study 1002FDC-053 in patients with hyperlipidemia[b]	67	16	3
Total	148	51	8

CSR = clinical study report; FDC = fixed dose combination
[a] One additional Black subject received the FDC bilayer formulation but not the FDC monolayer formulation; that subject is not counted here.
[b] Excluding sites with suspect data (1028, 1058, and 1068).
Source: Study 1002FDC-034 CSR, Listing 16.2.4.1, Listing 16.2.5.1; Study 1002FDC-055 CSR, Table 14.1.2; Study 1002FDC-053 CSR, Table 14.1.2.2a; Study 1002FDC-058 CSR, Table 14.1.2.1.

SIII.2 Clinical Trial Exposure to the Bempedoic Acid 180 mg and Ezetimibe 10 mg Coadministered as Individual Tablets

Clinical trial exposure to bempedoic acid 180 mg and ezetimibe 10 mg coadministered as individual tablets is summarized overall in Table 7, by sex in Table 8, by age group in Table 9, and by race in Table 10. In Phase 3 studies, exposure to bempedoic acid 180 mg + ezetimibe 10 mg as individual tablets was calculated by sex, age group, and race for Study 1002-048 but not for other Phase 3 studies. Exposure to bempedoic acid 180 mg + ezetimibe 10 mg as individual tablets was not calculated by age group for Phase 2 Study 1002-008.

Table 7: Summary of Exposure to Bempedoic Acid 180 mg and Ezetimibe 10 mg Coadministered as Individual Tablets in Completed Clinical Studies in Healthy Subjects or Patients with Hyperlipidemia (Safety Population)

	Number of Persons
Phase 1 studies	
Study 1002FDC-034	22
Study 1002FDC-049	38[a]
Total Phase 1	60
Phase 2 study in patients with hyperlipidemia	
Study 1002-008	24
Phase 3 study in patient with hyperlipidemia	
Study 1002-048	181
Phase 3 study pools	
High-Risk/Long-Term Pool[b]	2009
No or Low-Dose Statin Pool[c]	415

CSR = clinical study report; LMT = lipid-modifying therapy

[a] The Safety Population in this study included 40 subjects. Two subjects received study medication but did not receive ezetimibe and bempedoic acid tablets concurrently.

[b] Studies 1002-040 and 1002-047. Stable LMT included a maximally tolerated statin. Statin regimens other than daily dosing, including very low doses, were allowed; in Study 1002-047, maximally tolerated statin may also mean no statin.

[c] Studies 1002-046 and 1002-048. Patients in this pool had a documented history of statin intolerance and were using no or ≤ the lowest approved starting dose of a statin.

Source: Study 1002-034 CSR, Section 12.1; Study 1002FDC-049 CSR, Table 14.1.2, Listing 16.2.5.1;
Study 1002-008 CSR, Table 14.1.2.1, Table 14.1.7.1; Study 1002-048, Table 14.1.1.4, ISS Table 2.1, ISS Table 2.2

Table 8: Exposure to Bempedoic Acid 180 mg and Ezetimibe 10 mg Coadministered as Individual Tablets by Sex, Completed Clinical Studies

Sex	**Male**	**Female**
Phase 1 studies in healthy subjects		
Study 1002FDC-034	16	6
Study 1002FDC-049	18	20
Phase 1 total	35	26
Phase 2 study in patients with hyperlipidemia		
Study 1002-008	11	13
Phase 3 study in patients with hyperlipidemiaa		
Study 1002-048	72	109
Phase 3 study pools		
High-Risk/Long-Term Poolb	1427	582
No or Low-Dose Statin Poolc	173	242

CSR = clinical study report; LMT = lipid-modifying therapy
[a] Concurrent exposure to bempedoic acid and ezetimibe was not calculated by sex in the other Phase 3 studies.
[b] Studies 1002-040 and 1002-047. Stable LMT included a maximally tolerated statin. Statin regimens other than daily dosing, including very low doses, were allowed; in Study 1002-047, maximally tolerated statin may also mean no statin.
[c] Studies 1002-046 and 1002-048. Patients in this pool had a documented history of statin intolerance and were using no or ≤the lowest approved starting dose of a statin.
Source: Study 1002-034 CSR, Section 12.1, Table 14.1.2, Listing 16.2.4.1; Study 1002-048 CSR, Table 14.1.2.1.a;
Study 1002FDC-049 CSR, Table 14.1.2, Listing 16.2.5.1; ISS Table 2.1, ISS Table 2.2

Table 9: Exposure to Bempedoic Acid 180 mg and Ezetimibe 10 mg Coadministered as Individual Tablets by Age Group, Completed Clinical Studies

Sex	Age Group (y)		
	<65	65 to <75	≥75
Phase 1 studies in healthy subjects			
Study 1002FDC-049	38	0	0
Study 1002FDC-034	22	0	0
Phase 2 studies in patients with hyperlipidemiaa			
Study 1002-008	25	14	4
Phase 3 study in patients with hyperlipidemia			
Study 1002-048	81	73	27
Phase 3 study pools			
High-Risk/Long-Term Poolb	871	826	312
No or Low-Dose Statin Poolc	178	175	62

CSR = clinical study report; LMT = lipid-modifying therapy
[a] Concurrent exposure to bempedoic acid and ezetimibe was not calculated by age group in Study 1002-008.
[b] Studies 1002-040 and 1002-047. Stable LMT included a maximally tolerated statin. Statin regimens other than daily dosing, including very low doses, were allowed; in Study 1002-047, maximally tolerated statin may also mean no statin.
[c] Studies 1002-046 and 1002-048. Patients in this pool had a documented history of statin intolerance and were using no or ≤the lowest approved starting dose of a statin.
Source: Study 1002FDC-034, Section 12.1, Table 14.1.2, Listing 16.2.4.1; Study 1002-048 CSR, Table 14.1.2.1.a; Study 1002FDC-049 CSR, Table 14.1.2, Listing 16.2.5.1, ISS Table 2.1, ISS Table 2.2

Table 10. Exposure to Bempedoic Acid 180 mg and Ezetimibe 10 mg Coadministered as Individual Tablets by Ethnic origin , Completed Clinical Studies

	White	Black	Other
Phase 1 studies in healthy subjects			
Study 1002FDC-034	15	7	0
Study 1002FDC-049	31	4	3
Phase 2 study in patients with hyperlipidemia			
Study 1002-008	22	2	0
Phase 3 study in patients with hyperlipidemia			
Study 1002-048a	165	11	5
Phase 3 study pools			
High-Risk/Long-Term Poolb	1913	66	30
No or Low-Dose Statin Poolc	376	27	12

CSR = clinical study report; LMT = lipid-modifying therapy

[a] Concurrent exposure to bempedoic acid and ezetimibe was not calculated by age group in the other Phase 3 studies.

[b] Studies 1002-040 and 1002-047. Stable LMT included a maximally tolerated statin. Statin regimens other than daily dosing, including very low doses, were allowed; in Study 1002-047, maximally tolerated statin may also mean no statin.

[c] Studies 1002-046 and 1002-048. Patients in this pool had a documented history of statin intolerance and were using no or ≤ the lowest approved starting dose of a statin.

Source: Study 1002FDC-034, Section 12.1, Table 14.1.2, Listing 16.2.4.1; Study 1002-048 CSR, Table 14.1.2.1.a; Study 1002FDC-049 CSR, Table 14.1.2, Listing 16.2.5.1, ISS Table 2.1, ISS Table 2.2

SIV Populations Not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Important exclusion criteria in the pivotal Phase 3 study for the FDC, Study 1002FDC-053, are summarized in Table 11.

Table 11. Exclusion Criteria From Pivotal Phase 3 Clinical Study 1002FDC-053

Exclusion Criterion	Reason for Exclusion	Considered Missing Information?	
		Yes/ No	If No, Rationale
Baseline Disease			
Body mass index >40 kg/m^2	Morbid obesity may be associated with significantly unstable health conditions; thus, these patients were excluded due to potential impact on safety assessments.	No	No impact on safety or efficacy of bempedoic acid anticipated.
Hypertension: Uncontrolled hypertension (resting systolic blood pressure (SBP) ≥160 mm Hg and resting diastolic blood pressure (DBP) ≥100 mm Hg)	Patients with significantly unstable health status were excluded as this can impact assessment of drug safety and efficacy.	No	No impact on safety or efficacy of bempedoic acid anticipated. In a Phase 2 study conducted in 143 subjects with hypertension (mean sitting SBP ≥140 and ≤180 mm Hg and DBP ≥90 and ≤110 mm Hg), bempedoic acid appeared to be safe and well tolerated.
TGs: Total fasting TGs ≥5.6 mmol/L at screening	TGs at these elevated levels affect the accuracy of the calculation of LDL-C using the Friedewald equation.	No	No impact on safety or efficacy of bempedoic acid anticipated.

Exclusion Criterion	Reason for Exclusion	Considered Missing Information?	
		Yes/ No	If No, Rationale
Diabetes: Glycosylated hemoglobin (HbA_{1c}) ≥10% at screening	Poorly controlled diabetes has the ability to influence lipid levels including TGs and ultimately calculated LDL.	No	No impact on safety or efficacy of bempedoic acid anticipated.

Exclusion Criterion	Reason for Exclusion	Considered Missing Information?	
		Yes/ No	If No, Rationale
Baseline Disease (continued)			
Certain heart conditions: Any of the following within 3 months prior to screening or between screening and randomization visits: myocardial infarction (MI), unstable angina leading to hospitalization, uncontrolled symptomatic cardiac arrhythmia; coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), carotid surgery or stenting; cerebrovascular accident (CVA); transient ischemic attack; endovascular procedure or surgical intervention for peripheral vascular disease (PVD), or plans to undergo a major surgical or interventional procedure (eg, PCI, CABG, carotid or peripheral revascularization)	Patients with significantly unstable health status were excluded as this can impact assessment of drug safety and efficacy.	No	No impact on safety or efficacy of bempedoic acid anticipated.
Thyroid: Uncontrolled hypothyroidism, including thyroid-stimulating hormone (TSH) >1.5 × ULN at screening	Changes in thyroid hormone may cause secondary hyperlipidemia that can independently impact LDL-C levels.	No	No impact on safety or efficacy of bempedoic acid anticipated.

Exclusion Criterion	Reason for Exclusion	Considered Missing Information?	
		Yes/ No	If No, Rationale
Baseline Disease (continued)			
Liver function: Liver disease or dysfunction at screening, including positive serology for hepatitis B surface antigen (HBsAg) or hepatitis C antibodies (HCV-AB); alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2 × ULN; and/or total bilirubin (TB) ≥1.2[a] × ULN at screening	Existing liver disease can interfere with the assessment of safety in clinical trials.	No	While patients with hepatic impairment were excluded from Phase 3 clinical studies, patients with mild or moderate hepatic impairment were studied in a Phase 1 study (1002-032). Patients with severe hepatic impairment were not studied. No specific risk can be identified in these patients with hepatic impairment based on the data available. The SmPC states that no dose adjustment is necessary in patients with mild hepatic impairment (Child Pugh A). Treatment with the bempedoic acid + ezetimibe FDC is not recommended in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment due to the unknown effects of the increased exposure to ezetimibe.
Renal function: Renal dysfunction or nephritic syndrome or a history of nephritis, including estimated glomerular filtration rate (eGFR) <30 mL/min/ 1.73 m^2 at screening[b]	Severe renal dysfunction can interfere with the overall assessment of drug. A separate Phase 1 study conducted in patients with varying degrees of renal dysfunction was completed to understand this patient population.	Yes	Use in patients with end-stage renal disease (ESRD) on dialysis is considered missing information.
Gastrointestinal: Gastrointestinal conditions or procedures (including weight loss surgery; eg, Lap-Band® or gastric bypass) that might affect drug absorption	These conditions can impact drug absorption and thus may interfere with assessment of efficacy and safety.	No	No impact on safety of bempedoic acid anticipated.
CK: Unexplained[c] creatine kinase (CK) >3 × ULN at screening up to randomization	Including patients with unexplained CK measurements could impact the ability to assess muscle safety and tolerability.	No	No impact on safety or efficacy of bempedoic acid anticipated.

Exclusion Criterion	Reason for Exclusion	Considered Missing Information?	
		Yes/ No	If No, Rationale
Baseline Disease (continued)			
Drug/alcohol abuse: Any history of abuse of drugs, alcohol, amphetamine and derivatives, or cocaine within the last 2 years	Alcohol or substance abuse problems may confound safety assessments.	No	No impact on safety or efficacy of bempedoic acid anticipated.
Prior and Concomitant Medications			
New use of corticosteroids or planned dose changes during the study	Steroids are known to impact lipid levels.	No	No impact on safety or efficacy of bempedoic acid anticipated.
Planned use of mipomersen during the study	Mipomersen is a lipid-lowering therapy with a long half-life.	No	No impact on safety or efficacy of bempedoic acid anticipated.

Exclusion Criterion	Reason for Exclusion	Considered Missing Information?	
		Yes/ No	If No, Rationale
Prior and Concomitant Medications (continued)			
Recent use or a plan to use any of the following during the study: red yeast rice-containing products, lomitapide or apheresis therapy, PCSK9 inhibitors, or cholesteryl ester transfer protein (CETP) inhibitors within 12 months prior to screening.	Red yeast rice is a dietary supplement that may contain a chemical that is similar to statins and thus should not be taken with background statin. CETP inhibitors are investigational and some are known to have a very long half- life. Apheresis and PCSK9i were excluded based on the short duration of treatment and the careful planning of administration required around lipid assessments. PCSK9 inhibitors, particularly if administered monthly, can introduce fluctuations in LDL-C during the dosing interval that can greatly confound measures of efficacy. Lomitapide and mipomersen are indicated only in patients with homozygous FH and may impact liver monitoring. Probenecid and cyclosporine were avoided due to potential drug-drug/pharmacokinetic (PK) effects on the study drug.	No	No impact on safety or efficacy of bempedoic acid anticipated. Phase 2 Study 1002-039 compared the efficacy and safety of bempedoic acid vs placebo as add-on to evolocumab therapy. In this study, bempedoic acid was safe and well-tolerated with a safety profile similar to that observed for placebo. In Phase 1 Study 1002-031, administration of a single dose of bempedoic acid to healthy subjects receiving probenecid 500 mg twice daily at steady state resulted in 1.7-fold and 1.9-fold increases in ETC-1002 (parent compound) and ESP15228 (active metabolite) area under the plasma concentration-time curve from time zero to infinity (AUCinf), respectively, and 1.2-fold and 1.5-fold increases in ETC-1002 and ESP15228 maximum observed plasma concentration (Cmax), respectively, consistent with a weak drug-drug interaction (1.25- to <2-fold increase). Mean terminal elimination half-life (t½) was prolonged by approximately 8 and 15 hours for ETC-1002 and ESP15228, respectively, during probenecid treatment due to a 41% reduction in clearance, whereas volume of distribution was similar between treatments. The increase in mean ETC-1002 and ESP15228 exposure observed during coadministration with probenecid is considered unlikely to be clinically meaningful.

Exclusion Criterion	Reason for Exclusion	Considered Missing Information?	
		Yes/ No	If No, Rationale
Prior and Concomitant Medications (continued)			
Use of fibrates, niacin and derivatives, bile acid sequestrants, or ezetimibe within 5 weeks prior to screening or plan to use during the study	Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis; a lithogenic risk associated with the therapeutic use of Ezetrol cannot be ruled out (Ezetrol®, 2018(23)). Dosing should occur either ≥ 2 hours before or ≥ 4 hours after administration of a bile acid sequestrant. Ezetimibe is one of the compounds under study.	No	No impact on safety or efficacy of bempedoic acid anticipated.
Planned initiation of or changes to hormone replacement, thyroid replacement, diabetes medications, or obesity medications or omega-3 fatty acids	These drugs can impact lipid levels.	No	No impact on safety or efficacy of bempedoic acid anticipated.
Recent use of simvastatin ≥40 mg per day	This dose level of simvastatin was excluded in due to potential concern for drug-drug interactions.	No	When bempedoic acid is coadministered with simvastatin, simvastatin dose should be limited to 20 mg/day.

a If TB was ≥1.2 × ULN, a reflex indirect (unconjugated) bilirubin was obtained. and if the result was consistent with Gilbert's disease the patient could be enrolled in the study.
b Using the Modification of Diet in Renal Disease (MDRD) formula.
c Not associated with recent trauma or physically strenuous activity.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development programs for bempedoic acid and for the FDC are unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

Ezetimibe10 mg has been available for treatment of hyperlipidemia as Ezetrol® since 2003 when it was approved using the Mutual Recognition Procedure; thus, the safety of this component of the FDC is well understood. Rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure are likely to have been identified during this period. The objective literature review of pre- and postmarketing safety data for ezetimibe did not yield information changing the safety profile of ezetimibe as presented in the current labelling language (Module 2.5-Ezetimibe).

SIV.3 Limitations in Respect to Populations Typically Underrepresented in Clinical Trial Development Programs

Exposure of special populations included or not included in the clinical development program is described in Table 12.

Table 12. Exposure to Bempedoic Acid in Special Populations Included or Not Included in the Clinical Development Programs for Bempedoic Acid and the Fixed Dose Combination

Type of Special Population	Exposure	
	Bempedoic Acid	**Fixed Dose Combination**
Pregnant women	Not included in the clinical development program	Not included in the clinical development program
Lactating women	Not included in the clinical development program	Not included in the clinical development program
Subjects with hepatic impairment	Otherwise healthy subjects with mild (Child-Pugh [CP] Class A) or moderate (CP Class B) hepatic impairment were included a Phase 1 study of bempedoic acid PK in subjects with mild or moderate hepatic impairment (Study 1002-032). Patients with severe impairment (CP Class C) were not included. Sixteen patients (8 CP Class A, 8 CP Class B) received single doses of bempedoic acid.	Not included in the clinical development program
Subjects with renal impairment	A total of 18 otherwise healthy subjects with renal impairment, including 5 subjects with severe renal impairment, received single doses of bempedoic acid in Phase 1 Study 1002-023. In addition, 7678 patients with renal impairment at baseline were included in Phase 3 clinical studies (mild impairment, N = 5861, moderate impairment, N = 1797, severe impairment, N = 20). Patients with ESRD and patients undergoing dialysis were not studied.	Not included in the clinical development program
Patients with CV impairment	The Phase 3 clinical trial program included 2085 patients with ASCVD. Additionally, 4897 secondary prevention patients (documented CVD history) in the CLEAR Outcomes Trial (Study 1002-043) received bempedoic acid.	In Phase 3 Study 1002FDC-053, 53 patients who received the FDC had ASCVD and/or HeFH.
Patients with disease severity different from inclusion criteria in clinical studies	Not applicable.	Not included in the clinical development program
Populations with relevant different ethnic origins	In Phase 3 studies, 250 Black patients 481 other non-White patients received bempedoic acid.	In Phase 3 Study 1002FDC-053, 16 Black patients and 3 other non-White patients received the FDC.

Type of Special Population	Exposure	
	Bempedoic Acid	**Fixed Dose Combination**
Subpopulations carrying relevant genetic polymorphism	In Phase 3 studies, 80 patients with HeFH received bempedoic acid.	Patients with HeFH were eligible to participate in Study 1002FDC-053. The number of patients with HeFH in that study was not determined.

SV Post-authorization Experience

SV.1 Post-authorization Exposure

Bempedoic acid-ezetimibe fixed dose combination is currently authorized in the United States of America (USA), European Union (EU), Switzerland and the United Kingdom (UK). It is currently being marketed in the USA by Esperion and in Europe by Daichi Sankyo Europe. These data are national level prescription data (Rx), essentially prescriptions dispensed through pharmacies in the US and from supply chain figures in Europe.

SV.1.1 Method used to calculate exposure

Due to the recommended dose of Bempedoic acid/FDC for the treatment of hypercholesterolemia in adults being 180 mg/10mg per day the following calculation for exposure is used:

Total Sum in milligrams

180mg/10mg day X number of days on the market

Patient-Year exposed

Total mg / (Defined Daily Dose X 365)

The post-marketing cumulative patient exposure data is presented in Table 13 below.

Table 13. Cumulative patient exposure from marketing experience

Bempedoic acid/FDC	**Total mg**	**Patients exposed***	**Patient-Year exposed**
Period from 21-Feb-2020 to 20-Feb-2023			
Esperion Therapeutics, Inc USA**	2,349,637,740	71,792	35,763
DS*** Europe	3,886,280,820	119,819	59,152
DS UK	196,882,560	6010	2,997
DS Switzerland	36,648,360	1118	558

*Calculation patients: 1 Patient = 180 mg/10mg per day
**License partner in the USA.
***DS = Daiichi Sankyo

SVI Additional EU Requirements for the Safety Specification

SVI.1 Potential for Misuse for Illegal Purposes

Bempedoic acid has no potential for abuse as it is not associated with abuse-related activity and is not active in the CNS.

Results of nonclinical studies indicate that bempedoic acid has low potential for adverse CNS effects and abuse potential. In an in vitro assay, bempedoic acid at twice the steady-state human C_{max} at 180 mg/day did not bind to central nervous system (CNS) receptors associated with abuse potential (dopamine, serotonin, gamma-aminobutyric acid [GABA], opioid, and cannabinoid receptors; calcium, sodium, potassium and chloride ion channels; or norepinephrine, dopamine and serotonin transporter targets) (Module 2.6.2, Section 3.1.1, RR 1002-100-009). In a CNS safety pharmacology study in rats, bempedoic acid did not have any physiologically significant acute or residual effects on arousal/activity, autonomic, neuromuscular, or physiological functions in rats administered single oral doses up to 100 mg/kg, with exposures up to 18-fold higher than in humans at 180 mg/day (Module 2.6.2, Section 4.2.1, RR 1002-500-005). Similarly, there were no clinical observations of autonomic effects such as salivation, or CNS effects including tremors, convulsions, reactivity to handling, or bizarre behavior in monkeys administered single oral doses up to 100 mg/kg, with exposures up to 15 × exposure in humans at 180 mg/day (Module 2.6.2, Section 4.2.3, RR 1002-500-004). In toxicology studies up to 12 months duration, there were no findings indicative of abuse-related potential in rats or monkeys at respective exposures up to 9-fold or 14-fold higher than those in humans at 180 mg/day. Physical dependence and withdrawal behaviors were not observed in rats or monkeys during recovery phases of single-dose or repeat-dose toxicity studies.

Clinical experience in 3627 subjects/patients treated with bempedoic acid showed no evidence that bempedoic acid produces abuse-related psychoactive effects, such as mood or cognitive changes, in patients administered bempedoic acid at doses of 180 mg/day for up to 52 weeks. In Phase 2 clinical studies in which 766 patients received bempedoic acid, bempedoic acid did not produce abuse-related psychoactive effects, such as mood or cognitive changes or withdrawal symptoms, at doses of 180 mg for up to 12 weeks. In Phase 3 Study 1002-040, in which 1487 patients received bempedoic acid, bempedoic acid did not produce abuse-related psychoactive effects, such as mood or cognitive changes, at doses of 180 mg for up to 52 weeks based on a search of Nervous System Disorders and Psychiatric Disorders system organ classes as well as all preferred terms in the Medical Dictionary for Regulatory Activities (MedDRA) Standard Medical Query (SMQ) of Drug Abuse, Dependence and Withdrawal. Pooled Phase 3 data are consistent with these results.

In summary, neither nonclinical nor clinical data indicate have demonstrated abuse potential of bempedoic acid.

Ezetimibe10 mg has been available for treatment of hyperlipidemia as Ezetrol® since 2003 in the European Union (EU) and no drug abuse or misuse has been observed.

SVII Identified and Potential Risks

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

SVII.1.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns: Bempedoic Acid

Risks of bempedoic acid not considered important for inclusion in the list of safety concerns in the RMP are summarized in Table 14.

Table 14: Risks Not Considered Important for Inclusion in the List of Safety Concerns: Bempedoic Acid

Risk	Justification for Not including as Important Identified or Potential Risk	Relevant Section in Module 2.7.4-BA
Hepatic enzyme elevations	Statins have been associated with mild-to-moderate serum aminotransferase elevations during therapy that are typically transient, asymptomatic, and may resolve even with continuation without dose adjustment (Jose, 2016(36); Catapano et al, 2016(18)). Bempedoic acid shares a similar mechanism of action to statins in that both are hepatically acting drugs that inhibit key enzymes in the cholesterol synthetic pathway and ultimately upregulate LDL receptors. Nonclinical studies have demonstrated only minor effects of bempedoic acid on the liver of rats and mice (Module 2.6.6, Section 10.2). Because statins have been associated with liver enzyme elevations, particular attention was paid to evaluation of hepatic enzymes in Phase 2 and Phase 3 studies. Hepatic enzyme elevations were evaluated based on a prespecified list of adverse event preferred terms and associated laboratory parameters. Administration of bempedoic acid resulted in slight elevations in ALT and AST in Phase 3 studies. In pooled Phase 3 placebo-controlled studies, the incidence of repeated and confirmed ALT and/or AST elevations >3 × ULN was 0.7% in the bempedoic acid group and 0.3% in the placebo group; and the incidence of AST and or AST >5 × ULN was 0.2% of patients in each treatment groups. Among those patients who had repeated and confirmed elevations >3 × ULN who came back for a follow-up visit, levels returned to <3 × ULN, regardless of whether the patient discontinued investigational medicinal product (IMP) or continued study treatment. Analyses of adverse event terms related to hepatic enzyme elevations yielded similar results. The incidence of repeated and confirmed elevations in ALT and/or AST is within range of aminotransaminase elevations >3 × ULN reported for statins. These results appear to be consistent with prior clinical experience with statins and were not associated with any other adverse events. No patient in the bempedoic acid group had total bilirubin >2 × ULN and no patient in either treatment group met the criteria for potential Hy's Law. Prespecified adverse events in this category were primarily associated with elevations in transaminases. These reversible elevations in hepatic enzymes, which were not associated with clinical symptoms, are considered to represent an adverse reaction for bempedoic acid, but as they do not appear to be a risk to patients, elevated hepatic enzymes are not considered an important potential or important identified risk for bempedoic acid.	Section 2.1.4.2.4

Table 14: Risks Not Considered Important for Inclusion in the List of Safety Concerns: Bempedoic Acid (Continued)

Risk	Justification for Not including as Important Identified or Potential Risk	Relevant Section in Module 2.7.4-BA
Decreased hemoglobin	Nonclinical studies with bempedoic acid showed lower levels of hemoglobin and hematocrit (Module 2.4, Section 4.2.5). Mild decreases ≤15% were observed in red blood cell parameters in subchronic mice, chronic rat, and subchronic monkey studies. There were no changes in red blood cell parameters in chronic monkey studies. Mild changes in red blood cell parameters were reversible in the recovery period in all species at all doses. There were no effects on hematopoietic tissue associated with decreased erythropoiesis, no evidence of hemodilution, and no findings consistent with blood loss in studies with bempedoic acid alone. In Phase 1 and Phase 2 clinical studies, small mean decreases in hemoglobin were reported in subjects/patients who received bempedoic acid. Changes in hemoglobin were closely monitored in Phase 3 studies. There were no clinically meaningful changes from baseline in hematology parameters. Generally at any given visit, the mean hemoglobin for bempedoic acid was 2.0 to 2.5 percentage points lower than the mean for placebo at any given visit in pooled Phase 3 placebo-controlled studies. Similar changes were observed in red blood cell count and hematocrit. No changes in other hematological measures (eg, mean corpuscular hemoglobin concentration [MCHC], mean corpuscular volume [MCV]) occurred. These changes were evident by Weeks 4 to 8, remained constant, and were reversible upon discontinuation of bempedoic acid. Maximum postbaseline shifts from normal to low hemoglobin levels occurred in 1.4% of patients in the bempedoic acid group compared with 0.4% of patients in the placebo group. Maximum postbaseline shifts from normal to low hematocrit occurred in 0.5% of patients in the bempedoic acid group compared with <0.1% of patients in the placebo group. While decreased hemoglobin and anemia are considered adverse reactions potentially associated with bempedoic acid, reductions in hemoglobin were mild/modest with no meaningful clinical manifestations in terms of significant anemia. Therefore, decreased hemoglobin and anemia are not considered important potential or important identified risks.	Section 2.1.4.2.9

Table 14: Risks Not Considered Important for Inclusion in the List of Safety Concerns: Bempedoic Acid (Continued)

Risk	Justification for Not including as Important Identified or Potential Risk	Relevant Section in Module 2.7.4-BA
Blood creatinine increased and blood urea increased	In repeat-dose studies in rats and monkeys, bempedoic acid demonstrated mild to moderate, reversible increases in blood urea nitrogen (BUN) and creatinine at doses that were not associated with morphologic renal changes. Renal toxicity characterized by renal tubular vacuolation, degeneration, and necrosis were noted in both species at exposures >14 × the range of exposures intended for clinical studies. Nonclinical studies have also demonstrated nephrotoxic effects on tubular cells with other lipid-modifying agents (Module 2.6.6, Section 3). In Phase 1 and 2 studies, minimal mean increases in creatinine were reported in subjects/patients who received bempedoic acid. In Phase 3 clinical studies, renal disorders were evaluated based on a prespecified list of adverse event preferred terms and associated laboratory parameters. In pooled Phase 3 placebo-controlled studies, small mean increases in creatinine (2.6% to 5.6%) and BUN levels (12.0% to 14.0%) levels occurred with bempedoic acid treatment within the first 4 weeks of treatment. Mean change from baseline in creatinine did not increase with duration of treatment, regardless of baseline eGFR, and mean values for both parameters returned to baseline levels by the time of the first laboratory assessment after the discontinuation of bempedoic acid. In general in pooled Phase 3 placebo-controlled studies, the incidence of renal adverse events, including acute kidney injury and renal impairment, were balanced between treatment groups. The preferred term of renal failure showed an imbalance between treatment groups (0.8% bempedoic acid, 0.2% placebo). A wide range of verbatim terms were reported for this preferred term. None of the events of renal failure were serious, and only 1 case led to discontinuation of IMP. A close examination of these adverse events revealed that these events reflected modest creatinine increases and not true renal failure. No prerenal cause was identified for the increases in creatinine and BUN. Observations in renal-associated laboratory values suggest that the observed minor elevations in serum creatinine represent a drug-endogenous substrate interaction rather than an indication of worsening renal function. These changes are likely related to mild inhibition of bempedoic acid on the renal transport protein organic anion transporter 2 (OAT2), known to be involved in the secretion of creatinine (Shen et al, 2017; Lepist et al, 2014). Data from in vitro studies characterized bempedoic acid as a weak inhibitor of OAT2-mediated uptake of creatinine, suggesting that BA inhibition of OAT2 could be contributing to minor elevations of serum creatinine observed clinically. These changes in serum creatinine were not considered clinically meaningful. Examination of renal adverse events and shifts in renal function category appear to be driven by the observed changes in creatinine and eGFR (estimated using creatinine levels). Increased creatinine and BUN were identified as adverse reactions, but the changes were not considered clinically meaningful. No renal-related change is considered to represent an adverse reaction to bempedoic acid.	Section 2.1.4.2.7

SVII.1.1.2 Risks Not Considered Important for Inclusion in the List of Safety Concerns: Ezetimibe

Risks of ezetimibe not considered important for inclusion in the list of safety concerns in the RMP are summarized in Table 15.

Table 15: Risks Not Considered Important for Inclusion in the List of Safety Concerns: Ezetimibe

Risk	Justification for Not including as Important Identified or Potential Risk	Relevant Section in Module 2
Abnormal liver function	The IMPROVE-IT study demonstrated that the addition of ezetimibe to simvastatin did not increase the rates of elevated liver enzymes to a level >3 × ULN (Cannon et al, 2015(13)). In the study, 18,144 patients with CHD and ACS event history were randomized to receive ezetimibe/simvastatin 10/40 mg daily (N = 9067) or simvastatin 40 mg daily (N = 9077). During a median follow-up of 6.0 years, the incidence of consecutive elevations of transaminases (≥3 × ULN) was 2.5% for ezetimibe/simvastatin and 2.3% for simvastatin.	Module 2.5-Ezetimibe, Section 5.1.3
Drug interaction with warfarin, other coumarin anticoagulants, or fluindione	Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of 12 healthy subjects (Bauer et al, 2001(6)); however, there have been postmarketing reports of increased international normalized ratio (INR) in patients who had ezetimibe added to warfarin or fluindione (Ezetrol, 2018(23)). The Summary of Product Characteristics (SmPC) states that if the FDC is added to warfarin, another coumarin anticoagulant, or fluindione, INR should be appropriately monitored.	Module 2.5-Ezetimibe, Section 3.3
Drug interactions with cyclosporine	In a study of 8 postrenal transplant patients with creatinine clearance of >50 mL/min on a stable dose of cyclosporine, a single 10 mg dose of ezetimibe resulted in a 3.4-fold (range 2.3- to 7.9-fold) increase in the mean area under the plasma concentration-time curve (AUC) for total ezetimibe compared with healthy subjects receiving ezetimibe alone in another study (N = 17) (Bergman et al, 2006b(10)). In a 2-period crossover study in 12 healthy subjects, administration of ezetimibe 20 mg once daily (QD) for 8 days with a single 100 mg dose of cyclosporine on Day 7 resulted in a mean 15% increase in cyclosporine AUC (range 10% decrease to 51% increase) compared with a single 100 mg dose of cyclosporine alone (Bergman et al, 2006a(9)). A controlled study on the effect of coadministered ezetimibe on cyclosporine exposure in renal transplant patients has not been conducted. Caution should be exercised when initiating ezetimibe in the setting of cyclosporine. Cyclosporine concentrations should be monitored in patients receiving ezetimibe and cyclosporine.	Module 2.5-Ezetimibe, Section 3.3

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

SVII.1.2.1 Risks Considered Important for Inclusion in the List of Safety Concerns: Bempedoic Acid

Important identified risks, important potential risks, and missing information to be included in the list of safety concerns are summarized in Table 16.

Table 16: Risks Considered Important for Inclusion in the List of Safety Concerns: Bempedoic Acid

Risk	Evidence	Relevant Section in Module 2.7.4-BA
Important Identified Risk		
Not applicable		
Important Potential Risks		
Not applicable		
Missing Information		
Use in patients with severe renal impairment and patients with ESRD receiving dialysis	Patients with severe renal impairment (defined as eGFR <30 mL/min/1.73 m2) and patients with ESRD receiving dialysis have not been studied (Module SVII.3.2).	Section 5.1.4

SVII.1.2.2 Risks Considered Important for Inclusion in the List of Safety: Ezetimibe

No important identified risks, important potential risks, or missing information for ezetimibe are included in the list of safety concerns. The risks of ezetimibe are well characterized.

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

There are no newly identified or reclassified safety concerns since the last RMP version 3.1. Following completion of the CVOT, deleted 'Myopathy with concomitant use of statins' & 'Gout' as important potential risks of bempedoic acid. Clinical evidence (including clinical trial and post marketing data) support that current risk minimization measures addressing these safety concerns are sufficient.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

SVII3.1.1 Important Identified and Important Potential Risks for Bempedoic Acid

There are no important identified risks or important potential risks for bempedoic acid.

SVII.3.1.1 Important Identified and Important Potential Risks for Ezetimibe

There are no important identified risks or important potential risks for ezetimibe.

SVII.3.2 Presentation of Missing Information

SVII.3.2.1 Presentation of Missing Information for Bempedoic Acid

Details for missing information for bempedoic acid are presented Table 17.

Table 17: Missing Information for Bempedoic Acid: Use in Patients With Severe Renal Impairment and Patients With End-Stage Renal Disease Receiving Dialysis

Evidence source and strength of evidence	The PK of bempedoic acid was investigated in subjects with renal impairment in Phase 1 Study 1002-023. In addition, 1894 patients with renal impairment at baseline (1532 mild, 359 moderate, 3 severe) received bempedoic acid in Phase 3 studies. Exposure to bempedoic acid was assessed in a population PK analysis of Phase 3 study data, and adverse events were analyzed in by baseline eGFR category. The collective data demonstrate that renal impairment has a significant direct effect on bempedoic acid exposure with increasing degree of renal impairment (Module 2.7.2-BA, Section 3.4.4). Based on the population PK analyses, patients with moderate renal impairment are predicted to have 1.56-fold higher bempedoic acid AUC at steady state than subjects with normal renal function. In simulations using the studied population that incorporated other covariates (eg, sex, age, weight, etc), patients with mild or moderate renal impairment in the studied population were estimated to have a bempedoic acid steady-state mean AUC fold increase of 1.37 and 1.86, respectively, compared with subjects with normal renal function. These data were consistent with the effects observed in the intense sampling renal impairment PK study in 24 subjects, where an approximate 2-fold increase in the AUC was observed in subjects with moderate renal impairment when compared with subjects with normal renal function. No dose adjustment is recommended based on the observed PK alteration in mild and in moderate renal impairment. As expected, in Phase 3 studies the overall rate of adverse events increases with increasing renal impairment in both the bempedoic acid and placebo treatment groups in Phase 3 studies. The overall pattern seen when bempedoic acid is compared with placebo is generally consistent within the different eGFR subgroups. Any differences appear to be driven by the overall bempedoic acid vs placebo differences rather than by renal function at baseline. There are limited data in severe renal impairment (N = 5) where a 2.4-fold increase in AUC was observed. Patients with ESRD and patients undergoing dialysis were not studied.
Population in need of further characterization	There are no adequate, well-controlled studies in patients with severe renal impairment or in patients with ESRD receiving dialysis.

SVII.3.2.2 Presentation of Missing Information for Ezetimibe

There is no missing information for ezetimibe.

SVIII Summary of the Safety Concerns

A summary of the safety concerns is provided in Table 18.

Table 18: Summary of the Safety Concerns: Bempedoic Acid-Ezetimibe Fixed Dose Combination

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

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities are planned for all safety concerns.

Specific Adverse Reaction Follow-up Questionnaires

A targeted postmarketing questionnaire has been implemented to follow up patients with renal insufficiency, particularly patients with severe renal impairment or with ESRD receiving dialysis (see 0). The analysis of these data will be provided in the Periodic Benefit-Risk Evaluation Report (PBRER).

Other Forms of Routine Pharmacovigilance Activities

None planned.

III.2 Additional Pharmacovigilance Activities

Additional pharmacovigilance activities are detailed in Table 19.

Table 19: Safety Studies

Study No.	Study 1002-071
Short Title	Effects of ESRD and ESRD requiring dialysis on the PK of bempedoic acid
Rationale and Study Objectives	Primary objectives: • 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 Secondary objectives: • To evaluate the safety and tolerability of a single dose of bempedoic acid 180 mg in subjects with normal renal function, ESRD, and ESRD requiring dialysis. Safety concern addressed: use in patients with severe renal impairment and in patients with ESRD receiving dialysis (note: only part of the safety concern, patients with severe ESRD and ESRD requiring dialysis, is addressed by this study)
Study Design	This will be a Phase 1, open-label, single-dose, parallel-group study in 8 subjects with normal renal function, 8 subjects with ESRD, and 8 subjects with ESRD undergoing dialysis. All subjects will receive a single dose of bempedoic acid 180 mg. Serial blood samples will be collected from predose through 408 hours postdose. Urine and dialysate samples will also be collected.

Table 19: Safety Studies (continued)

Study Population	Subjects with normal renal function (eGFR ≥90 mL/min), subjects with ESRD (eGFR <15 mL/min), and subjects with ESRD (eGFR <15 mL/min) requiring dialysis.	
Milestones	Study status:	Planned
	Protocol final:	Completed
	Study completion:	Q4 2023
	Final CSR:	Q2 2024

III.3 Summary Table of Additional Pharmacovigilance Activities

Ongoing and planned pharmacovigilance activities are summarized in Table 20.

Table 20: Ongoing and Planned Pharmacovigilance Activities

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

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

No post-authorization efficacy studies have been imposed as a condition of marketing authorization.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1 Routine Risk Minimization Measures

Routine risk minimization measures are summarized in Table 21.

Table 21: Routine Risk Minimization Activities for the Bempedoic Acid + Ezetimibe Fixed Dose Combination

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks	
Not applicable	
Important Potential Risks	
Not applicable	
Missing Information	
Use in patients with severe renal impairment and patients with ESRD receiving dialysis (bempedoic acid)	SmPC Sections 4.4 and 5.2 PIL Section 2

V.2 Additional Risk Minimization Measures

Routine risk minimization activities as measures in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of Risk Minimization Measures

Risk minimization measures and pharmacovigilance activities are summarized in Table 22.

Table 22: Summary of Risk Minimization Measures and Pharmacovigilance Activities

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

Table 22: Summary of Risk Minimization Measures and Pharmacovigilance Activities (Continued)

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing Information (continued)		
Use in patients with severe renal impairment and patients with ESRD receiving dialysis (bempedoic acid)	Routine risk minimization measures: SmPC Section 4.2 and 5.2 PIL Section 2 Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: A targeted follow-up questionnaire for patients with renal insufficiency, particularly for patients with severe renal impairment or with ESRD receiving dialysis. Analysis of results will be provided in the PBRER.
		Upcoming additional pharmacovigilance activities:
		Study 1002-071, effects of ESRD and ESRD requiring dialysis on the PK of bempedoic acid (note: only part of the safety concern, patients with severe ESRD and ESRD requiring dialysis,is addressed by this study)

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Nustendi (Bempedoic acid/Ezetimibe)

This is a summary of the risk management plan (RMP) for Nustendi. There are no important identified risks or important potential risks for bempedoic acid. The RMP details how more information will be obtained about Nustendi's risks and uncertainties (missing information).

Nustendi's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Nustendi should be used.

This summary of the RMP for Nustendi should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Nustendi's RMP.

I. The Medicine and What It Is Used For

Nustendi is authorized for treatment of primary hypercholesterolemia in adults, as an adjunct to diet and is being proposed as a treatment for reducing cardiovascular risk in adults with established or at high risk for atherosclerotic cardiovascular disease by lowering LDL-C levels, as an adjunct to correction of other risk factors (see proposed SmPC for the full indication). It contains bempedoic acid as the active substance and it is given by mouth.

Further information about the evaluation of Nustendi’s benefits can be found in Nustendi’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage https://www.ema.europa.eu/en/documents/product-information/nustendi-epar-product-information_en

II. Risks Associated With the Medicine and Activities to Minimize or Further Characterize the Risks

There are no important identified risks or important potential risks for Nustendi. Routine risk minimization measures and pharmacovigilance activities are planned for all safety concerns.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine’s packaging
- The authorized pack size—the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly
- The medicine’s legal status—the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PBRER assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Nustendi is not yet available, it is listed under "missing information" below.

II.A List of Important Risks and Missing Information

Important risks of Nustendi are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Nustendi. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Identified and Potential Risks and Missing Information	
Important identified risk	Not applicable
Important potential risks	Not applicable
Missing information	Use in patients with severe renal impairment and patients with end-stage renal disease receiving dialysis

II.B Summary of Important Risks

Not applciable

Missing information: Use in Patients With Severe Renal Impairment and Patients With End-Stage Renal Disease Receiving Dialysis	
Risk minimization measures	Routine risk minimization measures SmPC Sections 4.4 and 5.2 PL Section 2 Additional risk minimization measures None
Additional pharmacovigilance activities	Phase 1, open-label, single-dose, parallel-group study to evaluate the effects of ESRD and ESRD requiring dialysis on the PK of bempedoic acid. See Section II.C of this summary for an overview of the postauthorization development plan.

II.C. Post-authorization Development Plan

II.C.1 Studies That Are Conditions of the Marketing Authorization

There are no studies that are conditions of the marketing authorization or specific obligation for Nustendi.

II.C.2 Other Studies in Post-authorization Development Plan

Short Title	Effects of ESRD and ESRD requiring dialysis on the PK of bempedoic acid (study 1002-071)
Purpose of the Study	Primary objectives: • 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 Secondary objectives: • To evaluate the safety and tolerability of a single dose of bempedoic acid 180 mg in subjects with normal renal function, ESRD, and ESRD requiring dialysis. Safety concern addressed: use in patients with severe renal impairment and in patients with ESRD receiving dialysis (note: only part of the safety concern, patients with severe ESRD and ESRD requiring dialysis, is addressed by this study)

PART VII: ANNEXES

TABLE OF CONTENTS

APPENDIX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

A renal insufficiency follow-up questionnaire has been developed to obtain additional information on patients with renal insufficiency (including patients with severe renal impairment and patients with ESRD receiving dialysis) in the postmarketing setting. Analysis of results will be provided in the PBRER.

ssion for Innovation,
mpassion for Patients.™

Daiichi Sankyo

Follow-up Questionnaire
- RENAL INSUFFICIENCY-

Daiichi Sankyo case ARGUS #:		**Date:**	
Reporter details			
Reporter Type		**Name:**	
☐ Health Care Professional		☐ Other (please specify)	
E-mail:		**Phone:**	
Fax:		**Signature:**	
Patient Demographics			
Initials:		Birth Date or Age:	
Gender:		Race/Ethnicity:	
Weight:		Height:	
BMI kg/m2:			
Company's Suspect Drug			
Name:		Lot Number:	
Start date:		Stop date:	
Dose:		Indication:	
Route of administration:		Dosage form:	
Last dose of drug prior to onset:		Frequency:	
Adverse Event Details (if present)			
Primary diagnosis of reported adverse event:			
Start date of event:		Stop date of event:	
Seriousness	☐ Hospitalization (new or prolonged) ☐ Permanent disability ☐ Life-threatening (immediate risk of death)		

	☐ Patient died (indicate cause & date of death) ☐ Congenital anomaly ☐ Other e.g. medically important event Please specify:_____		
Severity	☐ Mild	☐ Moderate	☐ Severe
Treatment with com. suspect drug discontinued due to adverse event?	☐ Yes / ☐ No	Date of the drug discontinuation	
Event resolved after discontinuation?	☐ Yes / ☐ No	Treatment with com. suspect drug restarted?	☐ Yes / ☐ No
Date of treatment with com. suspect drug restarted		Adverse Event reoccurred?	☐ Yes / ☐ No
Causality assessment to the drug	☐ Related	☐ Not related	
Rationale for causality assessment			
Adverse Event Outcome			
☐ Recovered/Resolved	☐ Recovered/Resolved with Sequelae	☐ Recovering/Resolving	
☐ Not Recovered/Not Resolved/Ongoing	☐ Fatal (if conducted, please provide copy of post-mortem report)	☐ Unknown	
Other, please describe:			
Narrative/AE description (please include details of AE, investigations, test results, event treatment including medication, outcome(s)			

Relevant Medical History			
Renal Insufficiency Diagnosis date (DD/MM/YYYY)	☐ Acute _____	☐ Acute on chronic _____	☐ Chronic _____
Chronic Kidney Disease (CKD)	☐ Stage 1 with normal or high GFR (GFR > 90 mL/min)	☐ Stage 2 Mild CKD (GFR = 60-89 mL/min)	☐ Stage 3A Moderate CKD (GFR = 45-59 mL/min)
	☐ Stage 3B Moderate CKD (GFR = 30-44 mL/min)	☐ Stage 4 Severe CKD (GFR = 15-29 mL/min)	☐ Stage 5 End Stage CKD (GFR <15 mL/min)
Dialysis	☐ Yes Please specify number of days per week	☐ No	
Other Medical History			
☐ Type 1 Diabetes Mellitus	☐ Type 2 Diabetes Mellitus	☐ Hypertension	☐ Glomerulonephritis
☐ Interstitial Nephritis	☐ Polycystic kidney disease	☐ Recurrent pyelonephritis	☐ Gout
☐ Liver failure	☐ Dehydration	☐ Smoking, specify packs per day/month ____	☐ Vesicoureteral reflux
☐ Family history of kidney disease, specify	☐ Cardiovascular disease (e.g. stroke, myocardial infarction), specify	☐ Urological conditions (e.g. obstruction of the urinary tract, kidney stones, enlarged prostate & some cancers), specify	
☐ Other(s), please specify:			

Relevant Laboratory Data			
Test	**Normal Range (including Units)**	**Baseline Value (including Units and Date)**	**Latest Value (including Units and Date)**
Creatinine			
GFR			

PO4			
Urea			
Electrolytes e.g. potassium			
Hemoglobin			
Cystatin C			
HbA1C			
Urinalysis qualitative and microscopic			

Imaging and Procedures		
Procedure	**Date** (DD/MM/YYYY)	**Result**
Renal ultrasound		
CT		
MRI		
Voiding cystourethrogram (VCUG)		
Renal Biopsy (with diagnosis)		

Serology/Studies		
Other Serology/Study	**Date**	**Results**
ANA serology test		
Antiphospholipid antibodies:		
Rheumatoid Factor		
Histone antibody:		
Anti-Neutrophil Cytoplasmic Antibodies		
Anti-Nucleosome Autoantibodies		
Anti-dsDNA		
Anti-PLA2R		
Anti-THSD7A		
Anti-Glomerular Basement Membrane (GBM)		
Other		

Relevant Concomitant Medications (including OTC and herbal supplements) within 2 months of adverse event				
Drug Name*	**Indication**	**Daily Dosage and route**	**Start Date** (DD/MM/YYYY)	**Stop Date or continued** (DD/MM/YYYY)
☐ Other contributing medications/conditions:				
Please provide outputs from electronic records if available				

*Please provide both brand name and generic. Also add designation "suspect" (as applicable) if adverse event is causally **unrelated** to Bempedoic Acid in section Adverse event details above

APPENDIX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

Not applicable.